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**Rola indukowanych przez estradiol mikroRNA w patogenezie
raka endometrium**

**Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki medyczne**

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3. Klaudia Klicka, Tomasz M. Grzywa, Aleksandra Mielniczuk, Alicja Klinke, Paweł K. Włodarski. The role of miR-200 family in the regulation of hallmarks of cancer. *Front. Oncol.* 12:965231. doi: 10.3389/fonc.2022.965231
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4. Klaudia Klicka, Tomasz M. Grzywa, Alicja Klinke, Aleksandra Mielniczuk, Jarosław Wejman, Joanna Ostrowska, Agata Gondek, Paweł K. Włodarski. Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients. *Sci Rep.* 2022 Nov 5;12(1):18824. doi: 10.1038/s41598-022-22306-w.
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Wykaz stosowanych skrótów

FIGO- ang. *The International Federation of Gynecology and Obstetrics*

PRISMA- ang. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

LCM- laserowa mikrodyssekcja, ang. *Laser Capture Microdissection*

qPCR- ang. *Quantitative Polymerase Chain Reaction*

FFPE- tkanka utrwalona w formalinie i zatopiona w parafinie, ang. *Formalin-Fixed Paraffin-Embedded*

TCGA – ang. *The Cancer Genome Atlas*

TGFβ- transformujący czynnik β, ang. *Transforming Growth Factor β*

MMRd- ang. *Mismatch Repair Deficiency*

NSMP- ang. *No Specific Molecular Profile*

LVSI- naciekanie przestrzeni limfatycznej, ang. *Lymphovascular Space Invasion*

DGCR8- ang. *DiGeorge Critical Region 8*

RISC- ang. *RNA-induced Silencing Complex*

ZEB- ang. *zinc-finger E-box binding homeobox*

EMT- przejście nabłonkowo- mezenchymalne, ang. *Epithelial-Mesenchymal Transition*

Streszczenie w języku polskim

Rak endometrium jest najczęstszym nowotworem żeńskich dróg rodnych i czwartym najczęstszym nowotworem u kobiet. Jest diagnozowany głównie u pacjentek po menopauzie. W związku z rosnącym występowaniem otyłości w populacji, nowotwór ten jest coraz częściej rozpoznawany. Wśród czynników ryzyka wyróżniamy m.in. zespół metaboliczny, zaburzenia miesiączkowania i nie zrównoważoną terapię estrogenową. Historycznie wyróżniano dwa typy raka endometrium- typ I (gruczolakorak endometrioidalny, zależny od estrogenów) i typ II (gruczolakorak nieendometrialny - najczęściej rak surowiczy, niezależny od hiperestrogenizmu), który charakteryzuje się gorszym rokowaniem. Obecnie w diagnostyce istotną rolę pełnią badania molekularne, których wyniki uwzględnione są w najnowszej klasyfikacji FIGO 2023 raka endometrium.

MikroRNA to krótkie niekodujące cząsteczki RNA, których mechanizm działania polega na post-transkrypcyjnej regulacji ekspresji genów poprzez wyciszenie translacji lub degradację mRNA. Poprzez ten wpływ biorą udział w patogenezie wielu chorób, w tym nowotworów. W komórkach nowotworowych mogą pełnić rolę inhibitorów transformacji nowotworowej i progresji choroby lub cząsteczek stymulujących te procesy (nazywanych onkomiRami). Ekspresja mikroRNA jest regulowana wieloma czynnikami. Wcześniejsze badania wykazały wpływ estrogenów na ekspresję mikroRNA i transformację nowotworową w raku piersi. Głównym celem niniejszej pracy doktorskiej, złożonej z cyklu trzech artykułów przeglądowych i dwóch prac oryginalnych, było zbadanie roli indukowanych przez estradiol mikroRNA w patogenezie raka endometrium.

Pierwszym artykułem wchodzącym w skład cyklu publikacji jest praca przeglądowa pt. „*Regulators at Every Step-How microRNAs Drive Tumor Cell Invasiveness and Metastasis*”, która została opublikowana w czasopiśmie *Cancers*. W artykule szczegółowo omówiono mechanizm działania oraz rolę cząsteczek mikroRNA jako inhibitorów lub promotorów poszczególnych etapów progresji nowotworów. Opisano wpływ mikroRNA na migrację komórek nowotworowych, miejscową inwazję, proces przejścia nabłonkowo-mezenchymalnego, angiogenezę oraz przerzutowanie. W tabelach uporządkowano dotychczas zebrane dane dotyczące roli poszczególnych cząsteczek mikroRNA i wiążących je, docelowych mRNA w wymienionych procesach. Ponadto omówiono potencjalne zastosowanie mikroRNA jako biomarkerów nowotworów, a nawet jako czynników terapeutycznych.

Drugim artykułem wchodzącym w skład cyklu jest przegląd systematyczny pt. „*The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis-A Systematic Review*”. Praca przygotowana wg wytycznych PRISMA poddaje analizie 163 artykułów, które spełniły kryteria włączenia. W pracy zebrano dane dotyczące ekspresji 106 cząsteczek mikroRNA i ich roli w regulacji inwazyjności i migracji komórek raka endometrium *in vitro* oraz wzrostu guza i tworzenia przerzutów w badaniach *in vivo*. Spośród nich 63 cząsteczki mikroRNA pełniły funkcję inhibitorów, a 38 sprzyjały rozwojowi raka endometrium. Usystematyzowano również dane dotyczące mechanizmu działania mikroRNA w komórkach raka endometrium oraz ich wpływu na różne szlaki sygnałowe. Podsumowano korelację ekspresji poszczególnych mikroRNA z parametrami klinicznymi pacjentów. Badanie to wykazało złożoność procesów, w jakie zaangażowane są mikroRNA w patogenezie raka endometrium oraz zidentyfikowało dalsze kierunki badań nad mikroRNA.

Szczególną grupą cząsteczek mikroRNA jest rodzina mikroRNA-200, w skład której wchodzi mikroRNA-200a, mikroRNA-200b, mikroRNA-200c, mikroRNA-141, oraz mikroRNA-429. Regulują one wszystkie cechy nowotworów opisane przez Hanahana i Weinberga, co omówiono w trzeciej publikacji wchodzącej w skład cyklu pt. „*The role of miR-200 family in the regulation of hallmarks of cancer*”. Rodzina mikroRNA-200 pełni funkcję onkomikroRNA jak i inhibitorów proliferacji, wzrostu guza, migracji, inwazji i angiogenezy w różnych typach nowotworów, uwzględniając raka endometrium.

Przeprowadzony przegląd literatury stanowił podstawę do badań oryginalnych, których wyniki zostały zebrane w dwóch manuskryptach. Artykuł pt. „*Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients*” został opublikowany w czasopiśmie *Scientific Reports*. Celem tego badania była ocena ekspresji wybranych 16 miRNA w obu typach raka endometrium i zdrowym endometrium. W badaniu wzięło udział 45 pacjentek: 18 pacjentek z rakiem endometrium typu I, 12 z rakiem endometrium typu II i 15 ze zdrowym endometrium (grupa kontrolna). Przy zastosowaniu metody laserowej mikrodyssekcji (LCM) wyizolowano komórki nowotworowe oraz zdrowe tkanki endometrium z preparatów histologicznych. Z tych tkanek wyizolowano RNA, a ekspresję wybranych miRNA określono ilościowo za pomocą metody qPCR w czasie rzeczywistym. Ekspresja miR-23b, miR-125b-5p, miR-199a-3p, miR-221-3p i miR-451a była obniżona w tkankach raka endometrium w porównaniu do zdrowego endometrium. Natomiast ekspresja miR-34a-5p i miR-146-5p była wyższa

w raku endometrium typu I w porównaniu do raka endometrium typu II. Analiza bazy danych The Cancer Genome Atlas (TCGA) potwierdziła obniżoną ekspresję miR-23b, miR-125b-5p i miR-199a-3p w tkankach raka endometrium w porównaniu do zdrowych tkanek. Zmniejszona ekspresja miR-23b wiązała się z krótszym przeżyciem pacjentów chorych na raka endometrium.

Artykuł pt. „*Estradiol induces global changes in miRNA expression in endometrial cancer cells and upregulates oncogenic miR-182*” został opublikowany jako preprint w *bioRxiv*. Celem tego badania była ocena roli osi miRNA-estrogen w komórkach raka endometrium. W badaniu wykorzystano modelową linię komórkową raka endometrium Ishikawa, która jest zależna od estrogenów. Komórki inkubowano z estradiolem, a następnie wyizolowano z nich RNA. Zastosowano mikromacierze, aby zidentyfikować miRNA indukowane estradiolem w komórkach raka endometrium. Następnie wykorzystano tkanki pochodzące od 45 pacjentów (18 pacjentek z rakiem endometrium typu I, 12 z rakiem endometrium typu II, 15 pacjentek ze zdrowym endometrium), które zostały pocięte przy zastosowaniu LCM. Ekspresję wybranych miRNA i regulowanych przez nie mRNA oceniono przy użyciu metody qPCR w czasie rzeczywistym. Komórki Ishikawa zostały transfekowane miRNA-mimetykiem, inhibitorem miRNA (anty-miRNA) i ich kontrolami. Zidentyfikowano 66 miRNA, których ekspresja była zwiększona po inkubacji komórek raka endometrium z estradiolem. Spośród nich, poziom ekspresji miR-182 był podwyższony w tkankach raka endometrium typu I w porównaniu do zdrowego endometrium. Badania funkcjonalne wykazały, że miR-182 pełnił funkcję onkomiRNA w raku endometrium, ponieważ jego zwiększona ekspresja promowała proliferację komórek raka endometrium, a zmniejszona ekspresja miR-182 była związana z hamowaniem proliferacji komórek nowotworowych. Hamowanie miR-182 zwiększyło ekspresję SMAD4, ważnego elementu szlaku sygnałowego TGF β , co może być potencjalnym mechanizmem działania tego mikroRNA.

Podsumowując, wyniki przeprowadzonych badań wskazują na ważną rolę mikroRNA w patogenezie raka endometrium, w tym cząsteczek mikroRNA indukowanych przez estradiol. W związku z tym mikroRNA mogą stać się obiecującymi biomarkerami choroby. Potencjalnie mikroRNA mogą być zastosowane w celach leczniczych, lecz ich zastosowanie kliniczne wymaga wielu dalszych badań translacyjnych.

Streszczenie w języku angielskim

The role of estradiol-induced microRNAs in the pathogenesis of endometrial cancer

Endometrial cancer is the most common cancer of the female reproductive tract and the fourth most common cancer in women. It is diagnosed mainly in postmenopausal patients. Due to the increasing prevalence of obesity in the population, this cancer is increasingly being diagnosed. Risk factors include metabolic syndrome, menstrual disorders and unbalanced estrogen therapy. Historically, two types of endometrial cancer were distinguished - type I endometrioid adenocarcinoma (estrogen-dependent) and type II (non-endometrioid adenocarcinoma, most often serous, independent of hyperestrogenism), which is characterized by a worse prognosis. Currently, molecular tests play an important role in diagnostics, the results of which are included in the latest FIGO 2023 classification of endometrial cancer.

MicroRNAs are short non-coding RNA molecules whose mechanism of action is the post-transcriptional regulation of gene expression by silencing translation or degradation of mRNA. By affecting their targets, they participate in the pathogenesis of many diseases, including cancers. In cancer cells, they can act as tumor suppressors or oncomiRs. MicroRNA expression is regulated by multiple factors. Previous studies have shown the influence of estrogens on microRNA expression and neoplastic transformation in breast cancer. The aim of the presented doctoral thesis, consisting of a series of three review articles and two original papers, was to investigate the role of estradiol-induced microRNAs in the pathogenesis of endometrial cancer.

The first article in the series is a review article entitled *"Regulators at Every Step-How microRNAs Drive Tumor Cell Invasiveness and Metastasis"*, published in *Cancers*. The article discusses in detail the mechanism of action and the role of microRNA molecules as inhibitors or promoters of each stage of cancer progression. It describes the influence of microRNAs on cancer cell migration, local invasion, epithelial-mesenchymal transition, angiogenesis, and distant metastasis. The tables summarize and organize the existing data on the role of individual microRNA molecules and their target mRNAs in the above-mentioned processes. In addition, the potential use of microRNAs as cancer biomarkers and therapeutic agents is discussed.

The second article in the series is a systematic review entitled *"The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis-A Systematic Review"*,

which was published in *Cancers*. The manuscript, prepared according to PRISMA guidelines, analyses 163 articles that met the inclusion criteria. The paper collected data on the expression of 106 microRNA molecules and their role in the regulation of endometrial cancer cell invasiveness and migration *in vitro*, as well as tumor growth and metastasis in *in vivo* studies. Of these, 63 microRNA molecules acted as inhibitors, and 38 promoted the development of endometrial cancer. Data on the mechanisms of action of microRNAs in endometrial cancer cells, their targets and their effect on various signaling pathways were also organized. Moreover, the study summarized the correlation of the expression of individual microRNAs with clinical parameters of patients. This study showed the complexity of the processes in which microRNAs are involved in the pathogenesis of endometrial cancer.

A special group of microRNA molecules is the microRNA-200 family, which includes microRNA-200a, microRNA-200b, microRNA-200c, microRNA-141, and microRNA-429. They regulate all hallmarks of cancer described by Hanahan and Weinberg, as discussed in the third publication entitled "*The role of miR-200 family in the regulation of hallmarks of cancer*". The microRNA-200 family can act as oncomiRs and as inhibitors of proliferation, tumor growth, migration, invasion, and angiogenesis in various types of cancer, including endometrial cancer.

The literature review was the basis for the original research, whose results were collected in two manuscripts. The article entitled "*Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients*" was published in *Scientific Reports* journal. The aim of this study was to evaluate the expression level of a panel of 16 miRNAs in both types of endometrial cancer and healthy endometrium. A total of 45 patients participated in the study: 18 patients with type 1 endometrial cancer, 12 patients with type 2 endometrial cancer, and 15 patients with healthy endometrium as controls. Using the laser microdissection method (LCM), tumor tissues and healthy endometrial tissues were dissected from FFPE slides. RNA was isolated from the tissues, and the expression of selected miRNAs was determined using real-time qPCR. The expression levels of miR-23b, miR-125b-5p, miR-199a-3p, miR-221-3p, and miR-451a were decreased in endometrial cancer compared to healthy endometrium. The expression of miR-34a-5p and miR-146-5p was increased in type I endometrial cancer compared to type II endometrial cancer. Analysis of The Cancer Genome Atlas (TCGA) database confirmed the decreased

expression levels of miR-23b, miR-125b-5p, and miR-199a-3p in EC. Reduced expression of miR-23b was associated with poorer survival of endometrial cancer patients.

The article "*Estradiol induces global changes in miRNA expression in endometrial cancer cells and upregulates oncogenic miR-182*" has been published as a preprint in *bioRxiv*. The aim of this study was to evaluate the role of the miRNA-estrogen axis in endometrial cancer cells. The study used the Ishikawa endometrial cancer cell line, which is estrogen-dependent. Cells were incubated with estradiol and then RNA was isolated. A microarray method was used to identify estradiol-induced miRNAs in endometrial cancer cells. Then, tissues from 45 patients (18 patients with type I endometrial cancer, 12 patients with type II endometrial cancer, and 15 patients with healthy endometrium) were cut using LCM. The expression of selected miRNAs and their targets was assessed using RT-qPCR. Ishikawa cells were transfected with miRNA-mimic, miRNA inhibitor (anti-miRNA), and corresponding controls. We identified 66 miRNAs whose expression was upregulated after incubation of endometrial cancer cells with estradiol. Among them, the expression level of miR-182 was increased in type I endometrial cancer tissues compared with healthy endometrium. Additionally, miR-182 acted as an oncomiR in endometrial cancer, as its increased expression promoted endometrial cancer cells proliferation, and decreased miR-182 expression was associated with inhibition of cancer cell proliferation. Inhibition of miR-182 increased the expression of SMAD4, an important member of the TGF β signaling pathway, which may be a potential mechanism of action of this microRNA.

In summary, the results of the conducted studies indicate an important role of microRNAs in the pathogenesis of endometrial cancer, including estradiol-induced microRNAs. Therefore, microRNAs may become promising biomarkers of the disease. Potentially, microRNAs can be used for therapeutic purposes, but their clinical application requires further translational studies.

Wstęp

Rak endometrium (rak trzonu macicy) jest najczęstszym nowotworem żeńskich dróg rodnych, czwartym najczęstszym nowotworem u kobiet i piątym pod względem śmiertelności [1]. Najczęściej chorują kobiety w okresie pomenopauzalnym, ze szczytem zachorowania około 60 roku życia [2]. Najczęstszym objawem choroby jest krwawienie po menopauzie. U młodszych pacjentek mogą występować obfite, przedłużające się miesiączki, a także krwawienia międzymiesiączkowe. W bardziej zaawansowanej chorobie pojawia się ból brzucha, zaburzenia czynności jelit i układu moczowego [2].

Główne czynniki ryzyka zachorowania na raka endometrium są związane z nie zrównoważoną przez progesteron ekspozycją na estrogen, który stymuluje komórki endometrium do proliferacji [3]. Są to m.in. otyłość, cukrzyca, cykle bezowulacyjne, wczesna menarche, późna menopauza, bezdzietność, stosowanie estrogenowej hormonalnej terapii zastępczej [4]. Pod wpływem estrogenów dochodzi do hiperplazji endometrium bez atypii lub z atypią, która stanowi podłoże do rozwoju nowotworu [5].

Diagnoza opiera się na badaniu histopatologicznym wyskrobin w jamy macicy lub macicy po histerektomii [6]. Historycznie wyróżniano dwa typy raka endometrium [7]. Typ I, zależny od estrogenów gruczołowy rak endometrioidny, jest najczęściej diagnozowany i charakteryzuje się lepszym rokowaniem. Typ 2 to gruczolakorak nieendometrialny - najczęściej rak surowiczy, niezależny od hiperestrogenizmu. Obecnie stosowana jest molekularna klasyfikacja raka endometrium [8]. Wyróżniono w niej cztery grupy raka endometrium. Pierwsza grupa to nowotwory z mutacją genu POLE, które charakteryzują się dobrym rokowaniem. Drugą grupę stanowią nowotwory z deficytem naprawy niesparowanych zasad (MMRd), trzecią z mutacją TP53. Ostatnią grupę stanowią niesklasyfikowane pod względem molekularnym nowotwory (NSMP). Najnowsza klasyfikacja FIGO 2023, oceniająca zaawansowanie raka endometrium, uwzględnia wynik badania molekularnego, a także naciekanie przestrzeni limfatycznej (LVSI) [9].

Leczenie choroby zależy od jej zaawansowania. Leczenie chirurgiczne polega na radykalnej histerektomii z usunięciem przydatków i biopsją węzłów biodrowo-zasłonowych. Stosuje się także brachyterapię, teleradioterapię i chemioterapię u pacjentów z rakiem endometrium [10]. Głównymi czynnikami prognostycznymi są stadium zaawansowania choroby, typ histologiczny, naciekanie przestrzeni limfatycznej (LVSI), a także podtyp molekularny [11, 12]. W związku z rosnącą liczbą przypadków, wysoką

śmiertelnością i coraz wcześniejszym pojawianiem się choroby, rak endometrium stanowi ważny klinicznie problem [13].

MikroRNA to krótkie, jednoniciowe, niekodujące cząsteczki RNA [14]. Po raz pierwszy zostały one opisane w 1993r. przez Lee jako krótkie cząsteczki RNA, które regulują ekspresję białka lin-14 w *Caenorhabditis elegans* [15]. Biogeneza mikroRNA w komórce jest wieloetapowa. W pierwszym etapie cząsteczki pri-mikroRNA są transkrybowane w jądrze komórki przez polimerazę RNA II. Z jednej cząsteczki pri-mikroRNA może powstać jedna lub grupa cząsteczek mikroRNA. Następnie cząsteczka pri-mikroRNA jest cięta przez kompleks zwany Microprocessor, który składa się z enzymu DROSHA i czynnika DGCR8. W ten sposób powstaje pre-mikroRNA, które jest transportowane do cytoplazmy przez eksportynę 5, gdzie ulega dalszym przemianom przez enzym Dicer. Przy udziale białek Argonaute z mikroRNA powstaje kompleks RISC (*RNA-induced silencing complex*), który wpływa na ekspresję genów post-transkrypcyjnie [16].

Dotychczas opisano tysiące cząsteczek mikroRNA. Ich mechanizm działania polega na zahamowaniu translacji lub degradacji mRNA poprzez wiązanie się cząsteczki mikroRNA do komplementarnych sekwencji w docelowym mRNA [16]. Pojedyncza cząsteczka mikroRNA może wiązać się z wieloma różnymi mRNA i przez to kontrolować wiele różnych procesów [17]. Cząsteczki mikroRNA pełnią ważną rolę w patogenezie wielu chorób, w tym także nowotworów [18]. W komórkach nowotworowych mogą pełnić rolę inhibitorów transformacji nowotworowej (supresorów) lub onkomirów (cząsteczek promujących transformację nowotworową i progresję choroby), wpływając na różne ich cechy poprzez regulację ważnych szlaków sygnałowych [18]. Opisano dotychczas rolę mikroRNA m. in. w regulacji proliferacji, inwazyjności, różnicowania, apoptozy angiogenezy i wielu innych [19]. MikroRNA są stabilne i możliwe jest oznaczenie ich ekspresji w świeżo mrożonych tkankach, preparatach histologicznych FFPE oraz płynach ustrojowych, takich jak surowica, ślina i mocz [20, 21]. W związku z tym poszukuje się ich zastosowania jako biomarkerów diagnostycznych i prognostycznych [22, 23]. Dostępne są już komercyjne testy wykorzystujące mikroRNA jako biomarker diagnostyczny [24]. Trwają również badania nad zastosowaniem mikroRNA jako opcji terapeutycznej [25].

Dotychczas opisywany był związek szlaków sygnałowych estrogenów z cząsteczkami mikroRNA. Natomiast większość badań była przeprowadzana w modelu raka piersi [26, 27]. W raku endometrium zbadano rolę onkomirów mikroRNA-107-5p, mikroRNA205

i mikroRNA 222-3p, które wpływają na receptory estrogenowe i w ten sposób promują progresję nowotworu [28-30]. Istnieją także doniesienia naukowe dotyczące roli indukowanych przez estradiol mikroRNA- 181c i mikroRNA-200c w modelu raka endometrium [31, 32].

Niniejsza praca doktorska stanowi cykl pięciu publikacji opisujących rolę cząsteczek mikroRNA w patogenezie nowotworów, ze szczególnym uwzględnieniem roli indukowanych przez estradiol mikroRNA w rozwoju raka endometrium. Sumaryczna wartość współczynnika oddziaływania (ang. *impact factor*) czasopism, w których opublikowano artykuły wynosi 22,514, a całkowita liczba punktów MEiN to 520.

Pierwszym etapem pracy doktorskiej było zebranie dotychczasowej wiedzy na temat roli mikroRNA w patogenezie nowotworów, w tym raka endometrium. W artykule pt. „*Regulators at Every Step-How microRNAs Drive Tumor Cell Invasiveness and Metastasis*” opisano rolę mikroRNA jako inhibitorów i promotorów inwazyjności i przerzutów komórek nowotworowych [33]. W pracy szczegółowo opisano wpływ mikroRNA na kolejne etapy progresji nowotworu, w tym na wzrost pierwotnego guza, miejscową inwazję, migrację, proces przejścia nabłonkowo-mezenchymalnego, angiogenezę i tworzenie guzów przerzutowych. W obszernych tabelach zebrano dane na temat poszczególnych cząsteczek mikroRNA wraz z ich docelowymi mRNA i efektem działania w komórce nowotworowej. W artykule przedyskutowano także rolę mikroRNA jako biomarkerów nowotworowych. Dzięki temu, że są one stabilne w różnych płynach ustrojowych, świeżo pobranych tkankach, a także w materiale FFPE, są one obiecującym markerem diagnostycznym i prognostycznym [34]. Istnieją doniesienia na temat korelacji pomiędzy poziomem ekspresji mikroRNA w surowicy a obecnością przerzutów do węzłów chłonnych i odległych przerzutów [35]. W artykule omówiono również możliwość zastosowania mikroRNA jako czynników terapeutycznych. Pierwsze badanie kliniczne zbadało MRX34, liposomalny mimetyk mikroRNA-34, w nowotworach litych. Badanie I fazy potwierdziło skuteczność działania przeciwnowotworowego i wykazało akceptowalne bezpieczeństwo przy stosowaniu z premedykacją deksametazonem u pacjentów z różnymi nowotworami litymi w zaawansowanym stadium [36]. Jednak dalsze badania zostały przerwane z powodu poważnych zdarzeń niepożądanych (NCT01829971, NCT02862145) [37]. Głównym ograniczeniem dotyczącym zastosowania mikroRNA w terapii nowotworów jest złożoność oddziaływań pomiędzy mikroRNA a mRNA, gdyż jedna cząsteczka mikroRNA może mieć wiele docelowych mRNA.

Dodatkowym wyzwaniem jest dostarczenie terapeutycznego mikroRNA do guza z ograniczeniem toksyczności dla tkanek zdrowych. Stąd też konieczne są dalsze badania w tym zakresie.

Drugim artykułem przeglądowym jest praca pt. „*The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis—A Systematic Review*” [38]. Jest to przegląd systematyczny literatury dotyczący złożonej roli mikroRNA w patogenezie raka endometrium ze szczególnym uwzględnieniem danych dotyczących zmienionej ekspresji mikroRNA w tkankach i liniach komórkowych raka endometrium, a także ich roli w regulacji inwazji, przerzutów oraz wpływu na wyniki leczenia pacjentów. Artykuł został przygotowany wg wytycznych PRISMA. Spośród 379 artykułów wyszukanych w bazach PubMed, Embase i Scopus, 163 prace spełniły kryteria włączenia. Zidentyfikowano 106 cząsteczek mikroRNA, których ekspresja jest zmieniona w tkankach raka endometrium, w tym 63 to supresory, 38 to onkomiry, a dane dotyczące ekspresji 5 mikroRNA były niezgodne. W artykule podzielono cząsteczki mikroRNA na te, które wpływają na inwazyjność, migrację, wzrost guza i przerzuty raka endometrium. Zebrano szczegółowe dane dotyczące celów poszczególnych cząsteczek mikroRNA, a także procesów komórkowych, w których biorą udział. Szczegółowo omówiono rolę jaką mikroRNA pełnią w komórkach raka endometrium poprzez wpływ na proces przejścia nabłonkowo-mezenchymalnego, cykl komórkowy, czynniki wzrostu, cytoskielet, epigenetykę, hormony, szlak sygnałowy PI3K/AKT, apoptozę, macierz pozakomórkową, szlak sygnałowy JAK-STAT, czynniki adhezyjne, angiogenezę, szlak sygnałowy cAMP, i inne. Zebrano również dane dotyczące korelacji ekspresji poszczególnych mikroRNA w surowicy z parametrami klinicznymi pacjentów, w tym z inwazją miometrium i obecnością przerzutów do węzłów chłonnych. Badanie to ukazało złożoność procesów, w jakie zaangażowane są mikroRNA w patogenezie raka endometrium.

W artykule przeglądowym pt. „*The role of miR-200 family in the regulation of hallmarks of cancer*”, opublikowanym w czasopiśmie *Frontiers in Oncology*, opisano rolę rodziny mikroRNA-200, w skład której wchodzi cząsteczki mikroRNA-200a, -200b, -200c, -141, i -429. [39]. Jest to rodzina mikroRNA, która pełni głównie rolę supresorową w komórkach nowotworowych poprzez wpływ na *zinc-finger E-box binding homeobox* (ZEB) i zahamowanie procesu przejścia nabłonkowo-mezenchymalnego (EMT) [40]. W artykule omówiono rolę mikroRNA-200 w regulacji wszystkich cech nowotworów opisanych przez Hannahana i Weinberga, ang. *hallmarks of cancer*. W aktualnej wersji wyróżniamy 14 cech

charakterystycznych dla nowotworów, są to: stała aktywacja szlaków sygnałowych odpowiedzialnych za proliferację, brak reakcji na inhibitory wzrostu guza, nieśmiertelność replikacyjna, aktywacja inwazji i przerzutowania, zaburzenie apoptozy, indukowanie angiogenezy, „unikanie” nadzoru przez układ odpornościowy, utrzymywanie zapalenia promującego nowotworzenie, niestabilność genomu i mutacje, przeprogramowanie metabolizmu komórkowego, odblokowanie plastyczności fenotypowej, zaburzenie mikrobiomu, niemutacyjne przeprogramowanie epigenetyczne i senescencja komórkowa [41]. W artykule zebrano dane literaturowe na temat poziomu ekspresji rodziny mikroRNA-200 w tkankach różnych typów nowotworów oraz w płynach ustrojowych. Poziom ekspresji cząsteczek z rodziny mikroRNA-200 jest podwyższony w tkankach raka endometrium w porównaniu do zdrowej tkanki [42, 43]. Dodatkowo poziomy mikroRNA-200a i mikroRNA-141 są podwyższone w surowicy pacjentów chorych na raka endometrium [43]. Omówiono również ważną rolę mikroRNA-200 w regulacji oporności na leczenie.

Przeprowadzony przegląd literatury stanowił podstawę do badań oryginalnych, których wyniki zostały zebrane w dwóch manuskryptach. Pierwszym z nich jest praca pt. *„Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients”* opublikowana w czasopiśmie *Scientific Reports* [44]. Głównym celem pracy było lepsze poznanie patogenezy raka endometrium poprzez ocenę ekspresji panelu mikroRNA, które pełnią ważną rolę w rozwoju nowotworów. W badaniu wzięło udział 30 pacjentek chorych na raka endometrium. Wśród nich u 18 zdiagnozowano raka endometrium typu I, a u 12 z nich raka surowiczego endometrium (typu II). Kontrolę stanowiło 15 pacjentów operowanych z innych powodów, m.in. z powodu mięśniaków macicy, a ich endometrium oceniono jako zdrowe w badaniu histopatologicznym. Przy zastosowaniu techniki LCM z preparatów FFPE precyzyjnie wycięto tylko komórki nowotworowe i zdrowe endometrium, co umożliwiło dalszą analizę bez zaburzenia wyników wynikających z obecności nienowotworowych tkanek otaczających [45]. W tak przygotowanym materiale oceniono poziom ekspresji panelu 16 cząsteczek mikroRNA: mikroRNA-21, mikroRNA-23b, mikroRNA-34a-5p, mikroRNA-96-5p, mikroRNA-134-5p, mikroRNA-146-5p, mikroRNA-150-5p, mikroRNA-181b-5p, mikroRNA-199a-3p, mikroRNA-200b-3p, mikroRNA-211-3p, mikroRNA-221-3p, mikroRNA-410-3p i mikroRNA-451a. Badanie wykazało obniżony poziom ekspresji cząsteczek mikroRNA-23b, mikroRNA-125b-5p, mikroRNA-199a-3p, mikroRNA-221-3p i mikroRNA-451a w tkankach raka

endometrium w porównaniu do zdrowej tkanki. Dodatkowo, poziom ekspresji mikroRNA-34a-5p i mikroRNA-146-5p był wyższy w tkankach raka endometrium endometrioidalnego w porównaniu do surowiczego raka endometrium. W celu potwierdzenia tych danych przeprowadzono analizę 418 tkanek raka endometrium zebranych w TCGA wykorzystując bazę danych OncomiR [46]. Potwierdzono istotne statystycznie obniżenie poziomu ekspresji mikroRNA-23b, mikroRNA-125b-5p, mikroRNA-199a-3p i mikroRNA-221-3p w tkankach raka endometrium w porównaniu do zdrowej tkanki. Dodatkowo, obniżona ekspresja mikroRNA-23b korelowała z gorszym przeżyciem pacjentów, co sprawdzono przy zastosowaniu OncoLnc [47]. W kolejnym etapie przeprowadzono badania *in vitro* w celu oceny roli jaką pełni mikroRNA-23b w komórkach raka endometrium. W tym celu komórki linii Ishikawa transfekowano syntetycznymi mimetykiem i inhibitorem mikroRNA-23b oraz ich kontrolami, a następnie przeprowadzono test proliferacji komórkowej. Zaobserwowano zahamowanie proliferacji komórek raka endometrium po transfekcji syntetycznym mikroRNA-23b. Natomiast zastosowanie inhibitora mikroRNA-23b powodowało zwiększoną proliferację komórek linii Ishikawa. W związku z tym mikroRNA-23b pełni rolę supresora w komórkach raka endometrium. Następnie wykonano analizę bazy danych ENCORI w celu identyfikacji mechanizmu działania mikroRNA-23b [48]. Pokazano, że mikroRNA-23b reguluje kluczowe szlaki komórkowe, m.in. szlak sygnałowy p53, szlak sygnałowy Wnt, szlak sygnałowy mTOR, cykl komórkowy, cytoskielet. Badanie to wskazało cząsteczki mikroRNA, które potencjalnie mogą służyć jako biomarkery choroby, w szczególności mikroRNA-23b. Natomiast głównym ograniczeniem pracy była liczba analizowanych preparatów. Stąd też konieczne są dalsze badania dotyczące zastosowania klinicznego badanych mikroRNA.

Głównym celem projektu doktorskiego było zbadanie roli indukowanych przez estradiol mikroRNA w raku endometrium. Wyniki przeprowadzonych w tym celu badań zebrano w manuskrypcie pt. „*Estradiol induces global changes in miRNA expression in endometrial cancer cells and upregulates oncogenic miR-182*” opublikowanym jako preprint w bioRxiv. W pracy wykorzystano linię raka endometrium Ishikawa, która charakteryzuje się obecnością receptorów estrogenowych [49]. Aby zbadać poziom ekspresji cząsteczek mikroRNA zastosowano szerokospektralną metodę mikromacierzy. W ten sposób oceniono poziom ekspresji 754 cząsteczek mikroRNA w komórkach raka endometrium, które były uprzednio inkubowane z estradiolem przez 48 godzin. Spośród nich wybrano 26 mikroRNA, których ekspresja wzrosła najbardziej pod wpływem estradiolu. Poziom

ekspresji wybranych mikroRNA zbadano w tkankach FFPE pochodzących od 30 pacjentów z rakiem endometrium (18 pacjentów z rakiem endometrium typu I, 12 pacjentów z rakiem endometrium typu II) i od 15 pacjentów ze zdrowym endometrium. Tkanki zostały wcześniej przygotowane przy zastosowaniu LCM. Zaobserwowano zwiększony poziom ekspresji mikroRNA-182 w tkankach raka endometrium typu I w porównaniu do zdrowego endometrium, obniżony poziom ekspresji mikroRNA-27b w tkankach raka endometrium typu II w porównaniu do zdrowego endometrium oraz obniżony poziom ekspresji mikroRNA-140 w tkankach raka endometrium typu I i typu II w porównaniu do zdrowego endometrium. Do badań funkcjonalnych *in vitro* wybrano mikroRNA-182. Komórki raka endometrium linii Ishikawa były tranfekowane synetycznymi mimetykiem i inhibitorem mikroRNA-182 oraz ich odpowiadającymi kontrolami. Zaobserwowano, że zwiększony poziom mikroRNA-182 powodował zwiększenie proliferacji komórek nowotworowych, a obniżenie poziomu mikroRNA-182 prowadziło do zahamowania proliferacji komórek Ishikawa. Badanie to pokazało, że mikroRNA-182 pełni rolę oncomiRNA w komórkach raka endometrium. Kolejnym etapem było ustalenie mechanizmu działania mikroRNA-182 w raku endometrium. W tym celu z transfekowanych komórek wyizolowano RNA, a następnie przy zastosowaniu RT-qPCR zbadano poziom ekspresji wybranych na podstawie literatury targetów. Oceniono rolę mikroRNA-182 w regulacji kluczowych szlaków sygnałowych odpowiadających m.in. za proces przejścia nabłonkowo-mezenchymalnego, apoptozę i proliferację komórek raka endometrium. Zaobserwowano, że zahamowanie mikroRNA-182 prowadzi do zwiększonej ekspresji SMAD4, który jest elementem szlaku TGFβ [50]. Natomiast konieczne są dalsze badania dotyczące bezpośredniego punktu uchwytu mikroRNA-182 i jego mechanizmu działania.

Podsumowując, w pracy doktorskiej zidentyfikowano mikroRNA, które są indukowane przez estradiol w komórkach raka endometrium metodą mikromacierzy. W obu pracach oryginalnych łącznie zbadano poziom ekspresji 42 cząsteczek mikroRNA z wykorzystaniem 30 preparatów FFPE od pacjentów chorych na raka endometrium i 15 pacjentów ze zdrowym endometrium. Rola wybranych mikroRNA została zbadana w testach *in vitro*.

W pracy doktorskiej pokazano, że mikroRNA-23b, którego ekspresja była obniżona w tkankach raka endometrium, pełni rolę supresora proliferacji komórek raka endometrium w badaniach *in vitro*, a poziom jego ekspresji koreluje z przeżyciem pacjentek z rakiem

endometrium. Natomiast indukowany przez estradiol w komórkach raka endometrium mikroRNA-182 pełni rolę onkomiRNA i stymuluje proliferację komórek raka endometrium w badaniach *in vitro*, a poziom jego ekspresji koreluje z poziomem ekspresji ważnego czynnika sygnałowego SMAD4. Głównymi ograniczeniami badania była mała liczba pacjentów włączonych do badania oraz brak danych klinicznych dotyczących pacjentów, co uniemożliwiło korelację wyników badań m. in. z czasem przeżycia pacjentów i innymi parametrami. Konieczne są także dalsze badania dotyczące mechanizmu działania mikroRNA-23b i mikroRNA-182.

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Założenia i cel pracy

Dotychczas opisywana była rola cząsteczek mikroRNA w patogenezie wielu nowotworów. Istniały także doniesienia naukowe na temat wpływu estradiolu na ekspresję mikroRNA w komórkach nowotworowych. Jednak rola regulacji mikroRNA przez estradiol była słabo zbadana w modelu raka endometrium. Stąd też konieczne były badania nad rolą estradiolu w regulacji ekspresji cząsteczek mikroRNA oraz ich roli w patogenezie raka endometrium i potencjalnej roli jako biomarkerów.

Głównym celem projektu było zbadanie osi estradiol- mikroRNA w komórkach raka endometrium, określenie poziomu ekspresji cząsteczek mikroRNA w tkankach raka endometrium i zdrowego endometrium, a następnie określenie ich wpływu na komórki raka endometrium w badaniach *in vitro* oraz poznanie mechanizmu oddziaływania na komórki nowotworowe.

Poszczególne cele pracy doktorskiej to:

- Przegląd literatury na temat roli mikroRNA w regulacji migracji, inwazyjności i przerzutów komórek nowotworowych;
- Przegląd systematyczny literatury na temat roli mikroRNA w regulacji inwazyjności i przerzuto komórek raka endometrium;
- Przegląd literatury na temat wpływu rodziny mikroRNA-200 na różne cechy nowotworów zaproponowane przez Hanahana i Weinberga;
- Identyfikacja indukowanych przez estradiol cząsteczek mikroRNA w komórkach raka endometrium;
- Zbadanie poziomu ekspresji cząsteczek mikroRNA w tkankach surowiczego i endometrioidnego raka endometrium oraz w tkankach zdrowego endometrium;
- Zbadanie wpływu poszczególnych cząsteczek mikroRNA na komórki raka endometrium w badaniach *in vitro*;
- Określenie roli mikroRNA jako biomarkerów w modelu raka endometrium;
- Zbadanie mechanizmu działania mikroRNA w komórkach raka endometrium.

Regulators at Every Step—How microRNAs Drive Tumor Cell Invasiveness and Metastasis



cancers



Review

Regulators at Every Step—How microRNAs Drive Tumor Cell Invasiveness and Metastasis

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Simple Summary: Tumor cell invasiveness and metastasis are key processes in cancer progression and are composed of many steps. All of them are regulated by multiple microRNAs that either promote or suppress tumor progression. Multiple studies demonstrated that microRNAs target the mRNAs of multiple genes involved in the regulation of cell motility, local invasion, and metastatic niche formation. Thus, microRNAs are promising biomarkers and therapeutic targets in oncology.

Abstract: Tumor cell invasiveness and metastasis are the main causes of mortality in cancer. Tumor progression is composed of many steps, including primary tumor growth, local invasion, intravasation, survival in the circulation, pre-metastatic niche formation, and metastasis. All these steps are strictly controlled by microRNAs (miRNAs), small non-coding RNA that regulate gene expression at the post-transcriptional level. miRNAs can act as oncomiRs that promote tumor cell invasion and metastasis or as tumor suppressor miRNAs that inhibit tumor progression. These miRNAs regulate the actin cytoskeleton, the expression of extracellular matrix (ECM) receptors including integrins and ECM-remodeling enzymes comprising matrix metalloproteinases (MMPs), and regulate epithelial–mesenchymal transition (EMT), hence modulating cell migration and invasiveness. Moreover, miRNAs regulate angiogenesis, the formation of a pre-metastatic niche, and metastasis. Thus, miRNAs are biomarkers of metastases as well as promising targets of therapy. In this review, we comprehensively describe the role of various miRNAs in tumor cell migration, invasion, and metastasis.

Keywords: miRNA; tumor invasiveness; metastasis; cell migration; epithelial–mesenchymal transition; tumor suppressor miR; oncomiR

1. Introduction

Tumor cell invasiveness is one of the hallmarks of cancer defined by Hanahan and Weinberg [1]. During oncogenesis, tumor cells acquire invasive potential, followed by the expansive growth and invasion of adjacent tissues and basement membrane. Tumor invasiveness is regarded as a heterogeneous and multistep process [2]. It is accompanied by angiogenesis, intravasation, and metastasis into the secondary site [3]. Initial steps in metastasis are completed very effectively, whereas the latest steps are very inefficient and are limiting for cancer progression [4]. Only 0.01% of cells that enter the circulation will successfully colonize distant sites [5]. Nonetheless, over 90% of the mortality due to cancer is attributable to metastases [6].

In 1993, Lee et al. described for the first time small RNA molecules encoded by the *lin-4* gene regulating the expression of protein *lin-14* in *Caenorhabditis elegans* [7]. Further studies revealed that microRNAs (miRNAs, miRs) are short single-stranded non-coding RNAs that regulate gene expression post-transcriptionally (Figure 1) [8]. Pri-miRNAs are transcribed in the nucleus by RNA polymerase II. Then, pri-miRNAs are cut by a protein complex consisting of Drosha and DGCR8. In the next step, pre-miRNA is exported to the cytoplasm and then cut by Dicer near the loop to form the miRNA duplex [9]. Cooperating with Argonaute proteins, miRNA creates an RNA-induced silencing complex (RISC) that targets mRNA and regulates genes the expression post-transcriptionally [10,11].

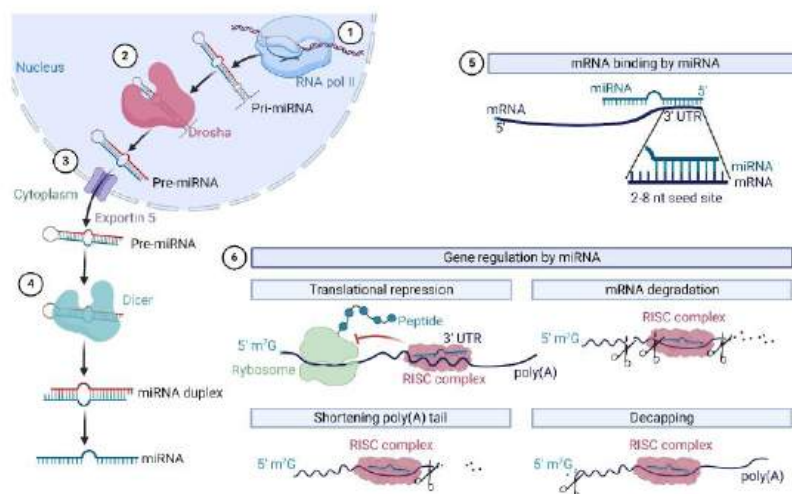


Figure 1. MiRNAs biogenesis and the mechanism of mRNA regulation. The crucial steps in microRNAs biogenesis include (1) transcription by RNA polymerase II; (2) the processing of pri-miRNA by ribonuclease Drosha; (3) transport into the cytoplasm by Exportin 5; and (4) the maturation of miRNA. The mechanism of miRNA action includes binding to the seed site of mRNA (5) and gene regulation by the RNA-induced silencing complex (RISC) complex (6) by translational repression, mRNA degradation, shortening poly(A) tail and the removal of 5' 7-methylguanylate cap.

The mechanism of this regulation involves the direct silencing of mRNA by the inhibition of the translation or destabilization of mRNA achieved by a shortening poly(A) tail, 5'-to-3' exonucleolytic decay, and decapping [11]. MiRNAs bind to complementary sequences in the 3' untranslated region (UTR) of target mRNA [9]. It has been identified that over 60% of human protein-coding genes harbor conserved miRNA target sites [12]. By targeting multiple mRNAs, miRNAs are involved in the regulation of a wide range of cellular processes including cell proliferation, differentiation, and apoptosis. Thus, the dysregulation of miRNAs is involved in the pathogenesis of many diseases, including cancer [13].

MiRNAs may play opposite roles in cancer after being either oncomiRs or tumor suppressor miRs (Table 1) [14]. The complexity of their effects makes them key regulators of all hallmarks of cancer [15]. MiRNAs may affect (promote or suppress) cancer cell proliferation, genomic instability [16], and apoptosis [17]. Moreover, miRNAs regulate tumor cell metabolism [18], angiogenesis [19], and cancer immune escape [20]. MiRNAs may either regulate gene expression in the cell or can be released outside the cell leading to the regulation of gene expression in adjacent cells. Therefore, miRNAs are not only key regulators of cancer cells but also of the complex regulatory network of the tumor microenvironment [21–23].

Table 1. Role of miRNAs in cancer progression.

miRNA	Cancer Type	Target	Role in Vitro	Role in Vivo	Ref.
miR-9	Breast cancer	CDH1	↑ cell migration and invasiveness	↑ tumor invasion and metastasis ↑ angiogenesis	[24]
miR-10b	Breast cancer	HOXD10	↑ cell migration and invasiveness	↑ tumor invasion and metastasis	[25]
miR-17-5p	Colorectal cancer	PTEN, P130	↑ cell migration and invasiveness	↑ tumor growth	[26,27]
miR-19b	Breast cancer	TP53	↑ cell migration and invasiveness, cell cycle progression	↑ tumor growth and metastasis	[28]
miR-21	Colorectal cancer	Pdcd4	↑ cell invasiveness	↑ intravasation and metastasis	[29]
miR-135b	Lung cancer	LZTS1, Hippo pathway	↑ cell migration and invasiveness	↑ tumor growth and metastasis	[30]
miR-181a	Breast cancer	Bim	↑ cell migration and invasiveness ↓ anoikis	↑ tumor growth and metastasis	[31]
miR-214	Melanoma	TEAP2C, ITGA3	↑ cell migration and invasiveness	↑ extravasation and metastasis	[32]
miR-211	Colorectal cancer	CHD5	↑ cells proliferation and migration	↑ tumor growth	[33]
miR-223	Gastric cancer	EPB41L3	↑ cells motility and invasiveness	↑ metastasis	[34]
miR-34a	Neuroblastoma	MAP3K9	↑ induction of cell cycle arrest and apoptosis	↓ tumor growth	[35]
miR-137	Colorectal cancer	FMNL2	↓ cells proliferation and invasion	↓ metastasis	[36]
miR-192	Colon cancer	Bcl-2, ZEB2	↑ apoptosis	↓ metastasis	[37]
miR-375	Liver cancer	AEG-1	↓ cell growth and invasiveness	↓ tumor growth	[38]
miR-874	Non-small cell lung cancer	MMP-2, uPA	↓ cells invasiveness	↓ tumor growth	[39]
let-7	Lung cancer	KRAS	↓ cell proliferation	↓ tumor growth	[40]

↑—increase, ↓—decrease.

MiRNAs expression is often aberrated in cancers and results in the dysregulation of gene expression. The pan-cancer analysis revealed a global downregulation of tumor suppressors by miRNAs in cancer cells [41]. Many oncogenes, including MYC, were reported to upregulate oncomiRs [9]. Moreover, oncogenes repress the expression of tumor suppressor miRNAs [42]. Mutations in proteins involved in miRNAs biogenesis and maturation, e.g., Drosha or Dicer, lead to the dysregulation of the expression of tumor suppressor miRs or oncomiRs resulting in cancer progression [9]. A study of Merritt et al. showed that the majority of ovarian tumor specimens had decreased Dicer or Drosha mRNA which affects miRNA expression [43]. Dicer is also downregulated by miRNAs, including miR-103/107 [44]. Moreover, epigenetic changes in miRNA promoters affect miRNA expression in cancer tissue [45].

MiRNAs have been reported to regulate every step of cancer progression. They promote or suppress primary tumor growth, local invasion, as well as metastasis (Figure 2). In this review, we aim to comprehensively review the role of miRNAs in the progression from a benign tumor to an invasive metastatic cancer.

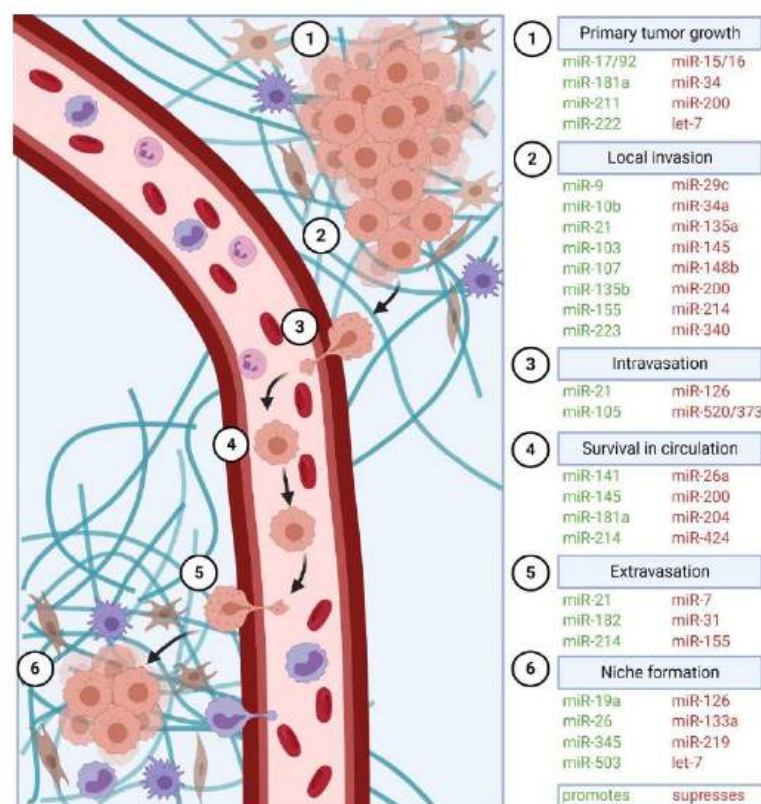


Figure 2. Regulation of cancer progression by miRNAs. Cancer progression involves several crucial steps, including (1) primary tumor growth, (2) migration and local invasion, (3) intravasation, (4) survival in the circulation, (5) extravasation, and (6) pre-metastatic niche formation (stromal cells, brown), recruitment of tumor-promoting immune cells (violet) and metastasis. Multiple miRNAs regulate each of these steps, and thus, act as either oncomiRs (promote cancer progression) or tumor suppressor miRs (suppress cancer progression).

2.1. Step 1: Polarization of the Cytoskeleton and Formation of the Leading Protrusion

Cell migration is initiated by the changes in the cell cytoskeleton that result in the formation of the protrusions of the cell membrane. These actin-based structures are termed filopodia, lamellipodia, invadopodia, and podosomes, based on their characters [48]. Despite being regulated mostly on posttranslational levels, multiple miRNAs regulate the reorganization and polarization of the cytoskeleton. The majority of miRNAs targeting the mRNA of cytoskeleton-regulating proteins are tumor suppressors and are downregulated in cancer. The overexpression of those miRNAs affects cytoskeleton remodeling and decreases cell migration and invasiveness. The first step of tumor cell invasion is the formation of the leading edge protrusion, which is controlled mainly by the members of the Rho family of small GTPases, Cdc42 and Rac [2]. Cdc42 is a direct target of miR-133 [49], miR-186 [50], miR-195 [51] and miR-330 [52]. Moreover, Cdc42 is targeted also by miR-137 which inhibits cell invasiveness [53]. Importantly, the expression of miR-137 gradually decreases during cancer progression due to epigenetic silencing at an early stage [54,55]. Cdc42 cooperates with Rac to promote cell invasiveness [56]. RAC1 is targeted by miR-142-3p and miR-145, leading to suppressed cell migration and invasiveness [57,58]. Moreover, miR-124 affects the subcellular localization of RAC1 [59]. MiRNAs regulate not only small GTPases but also their regulators, including guanine nucleotide exchange factors (RhoGEFs), GTPase-activating proteins (RhoGAPs), GDP dissociation inhibitors (RhoGDIs), and guanine nucleotide exchange modifiers (GEMs) [2,60].

Multiple miRNAs have been identified as crucial regulators of the actin cytoskeleton in cancer cells by direct targeting multiple cytoskeleton-associated proteins (Table 2). The reduced expression of miR-138, which targets RhoC and ROCK2, is associated with enhanced metastatic potential in oral squamous cell carcinomas [61]. The overexpression of miR-138 decreases tumor cell migration and invasiveness. Likewise, overexpression of miR-124 targeting ROCK1, a major downstream effector of RhoA and RhoC family members [62], results in the decreased length and number of actin fibers in cells as well as a reduction in long and thin protrusions on the cell surface [63]. Increased let-7b or miR-142-3p expression inhibits the formation of lamellipodia and filopodia which leads to the persistent stabilization of stress fibers [64,65]. MiR-145 promotes actin cytoskeleton rearrangements and cortical actin distribution, but it also reduces actin stress fiber and filopodia formation [66]. Thus, by targeting regulators of the actin cytoskeleton, miRNAs can potentially affect cancer cell migration and invasiveness.

Table 2. Direct regulation of actin cytoskeleton by miRNAs in cancer cells.

Target	Role	miRNA	Role	Ref.
RhoC	Promotes reorganization of the actin cytoskeleton and regulates cell shape and motility.	miR-93, miR-106b, miR-138, miR-372, miR-493, miR-509	Decreases migration and invasiveness, reorganization of the stress fibers.	[67–73]
CDC42	Transduces signals to the actin cytoskeleton, promotes the formation of filopodia.	miR-133, miR-137, miR-186, miR-195, miR-330	Decreases cell migration and invasiveness.	[49–53,74]
RAC1	Regulates reorganization of the actin cytoskeleton, promotes the formation of lamellipodia.	miR-142-3p, miR-145	Decreases cell migration and invasiveness.	[57,58]
RHOA	Regulates cell adhesion and migration, provides contractile force by the formation of stress fibers.	miR-31, miR-122, miR-133a-3p, miR-146a, miR-200b, miR-340-5p	Decreases cell migration.	[75–80]
PHACTR1	Binds actin and regulates the reorganization of the actin cytoskeleton.	miR-584	Decreases expression leads to the induction of migration.	[81]
TKS5	Regulates actin cytoskeleton and invadopodia formation.	miR-200c	Decreases invasiveness.	[82]
MYLK	Regulates the phosphorylation of myosin light chains.	miR-155, miR-200c	Decreases invasiveness and ability to form invadopodia.	[82,83]
ROCK1	Regulates actinomyosin cytoskeleton.	miR-124, miR-145, miR-148b, miR-199a, miR-335, miR-340, miR-584, miR-1280	Decreases cells migration and invasiveness.	[63,84–89]
ROCK2	Regulates actinomyosin cytoskeleton.	miR-124, miR-130a, miR-135a, miR-138, miR-139, miR-144, miR-185, miR-4529-5p	Decreases cells migration and invasiveness.	[90–97]
PHOD1	Regulates actin cytoskeleton.	miR-200c	Decreases migration and invasiveness.	[98]

Table 2. Cont.

Target	Role	miRNA	Role	Ref.
PPM1F	Regulates actin cytoskeleton.	miR-149, miR-200c, miR-490, miR-590	Decreases migration and invasiveness.	[98–101]
WAVE3	Regulates actin cytoskeleton.	miR-31, miR-200	Decreases invasiveness.	[102,103]
PAK1	Regulates cell motility and cytoskeletal remodeling.	Let-7, miR-7, miR-26a, miR-26b, miR-98, miR-145, miR-485, miR-494,	Decreases migration and invasiveness.	[64,103–109]
DIAPH2	Regulates microtubule attachment to kinetochores.	Let-7, miR-10b	Decreases migration and invasiveness.	[64,110]
RDX	Regulates of membrane domains through interaction with the cytoskeleton and transmembrane proteins.	Let-7, miR-31, miR-200b, miR-409	Decreases migration and invasiveness.	[64,111,112]
PAK2	Regulates of cell motility and cytoskeletal remodeling.	miR-7, miR-23b, miR-137, miR-216a, miR-455, miR-4779,	Decreases migration and invasiveness, cytoskeleton remodeling.	[113–117]
CFL1	Binds actin and regulates cell proliferation and migration.	miR-342	Decreases invasion and migration.	[118]
TWFT	Binds actin and promotes EMT.	miR-30c, miR-142, miR-486	Decreases stress fibers F-actin formation.	[119–121]
PFN1	Binds actin and inhibits cells proliferation, migration, invasion and EMT.	miR-19a-3p, miR-182, miR-299-3p, miR-330-3p,	Increases migration and invasiveness.	[122–126]
FSCN1	Stabilizes actin filaments in invadopodia.	miR-24, miR-133a, miR-133b, miR-145, miR-200b, miR-326, miR-429, miR-539, miR-663	Decreases invasiveness.	[127–135]
WASL	Regulates actin polymerization.	miR-142-3p, miR-148a	Decreases invasiveness, reduced number of membrane protrusions.	[65,136]

2.2. Step 2: Formation of Focalized Clusters by Recruitment and Adhesion of Cell Surface Receptors to ECM

The second step in the tumor invasion is the activation of signaling pathways that control the tumor cells cytoskeleton as well as the cell-to-cell and cell-to-matrix interactions [2]. Extracellular matrix (ECM) is a key component of the tumor microenvironment [137]. ECM constituents serve as co-receptors, ligands, and signal presenters. Mechanocoupling between the cytoskeleton and ECM is crucial for the initiation of cell migration. For instance, miR-25-3p decreases adhesion to collagens I, II, and IV as to fibronectin, laminin, and tenascin [138]. Cancer cells sense ECM components and their mechanical properties by multiple adhesion and signal-transducing receptors, including integrins, syndecans, or CD44.

2.2.1. Integrins

The main mechanosensors and cell adhesion receptors for ECM are integrins, a family of 24 transmembrane proteins [139]. These heterodimeric $\alpha\beta$ receptors bind either ECM proteins or membrane proteins on other cells. The activation of integrins by ligand binding leads to the formation of adhesome, which regulates multiple processes including cell proliferation, survival, differentiation, and migration [140]. Downstream integrin effectors include cytoskeletal adaptor proteins talin, paxillin, and kindlin as well as small GTPases Rac and Rho, that regulate cell protrusion and rear contraction [2]. Thus, the role of integrins goes far beyond only ECM–cell interaction. Moreover, the interaction between integrins and growth factor receptors regulates tumor growth and metastasis [141]. Importantly, the expression of a specific integrin determines the target organs for metastases [142]. Multiple studies reported disturbed integrins expression in cancer, thus, they are a promising target of therapy [143].

Integrin subunits are targeted by multiple miRNAs (Table 3). For instance, miR-31 directly targets integrins $\alpha 2$, $\alpha 5$, αV , and $\beta 3$ leading to the inhibition of cell spreading in a ligand-dependent manner [144]. Moreover, miR-142-3p targeting integrin αV substantially decreases tumor cell invasiveness [65]. In addition to the direct targeting of integrin-coding mRNA, miRNAs may indirectly affect integrin levels. For example, miR-375 decreases HuD mRNA stability and translation and leads to a reduced expression of N-cadherin, RhoA, NCAM1, and integrin $\alpha 1$ [145].

Table 3. The direct regulation of integrin subunits by miRNAs in cancer cells.

Integrin	Protein Name	Synonyms [146]	miRNA	Ref.
ITGA1	$\alpha 1$	CD49a	miR-375	[145]
ITGA2	$\alpha 2$	CD49b, $\alpha 2$ subunit of very late antigen 2 (VLA-2)	miR-31	[144]
ITGA2B	αIIb	GTA, CD41, GP2B, HPA3, CD41b, GPIIb	miR-122	[147]
ITGA3	$\alpha 3$	CD49c, $\alpha 3$ subunit of VLA-3	miR-199 family	[148]
ITGA4	$\alpha 4$	CD49d, $\alpha 4$ subunit of VLA-4	miR-30a	[149]
ITGA5	$\alpha 5$	CD49e, fibronectin receptor alpha	miR-25-3p, miR-26a, miR-31, miR-92, miR-142-3p, miR-148b, miR-149	[65,84,138,144,150]
ITGA6	$\alpha 6$	CD49f, ITGA6B	miR-25, miR-29s, miR-143-3p	[151–153]
ITGA7	$\alpha 7$		nd	
ITGA8	$\alpha 8$		nd	

Table 3. Cont.

Integrin	Protein Name	Synonyms [146]	miRNA	Ref.
ITGA9	$\alpha 9$		miR-296-3p	[154]
ITGA10	$\alpha 10$		miR-34a	[155]
ITGA11	$\alpha 11$		miR-148a	[136]
ITGAD	αD		nd	
ITGAE	αE	CD103, human mucosal lymphocyte antigen 1 α	nd	
ITGAL	αL	CD11a (p180), lymphocyte function-associated antigen 1 (LFA-1) α subunit	miR-126	[156]
ITGAM	αM	Mac-1, CD11b, complement receptor 3 (CR3) subunit	miR-124 miR-223	[157,158]
ITGAV	αV	CD51, MSK8, vitronectin receptor α (VNR α)	miR-25, miR-31, miR-92, miR-142-3p	[65,144,151,159]
ITGAX	αX	CD11c, CR4 subunit	miR-142	[160]
ITGB1	$\beta 1$	Fibronectin receptor β , CD29, MDF2, MSK12	miR-29b, miR-29c, miR-31, miR-124 miR-130b, miR-149 miR-183, miR-338-3p, miR-451	[144,161–167]
ITGB2	$\beta 2$	Leukocyte cell adhesion molecule, CD18, CR3 subunit, CR4 subunit	miR-1, miR-133a	[168]
ITGB3	$\beta 3$	CD61; GP3A; GPIIb, platelet glycoprotein IIIa	miR-31, miR-150	[144,169]
ITGB4	$\beta 4$	CD104	miR-29a, miR-184	[170]
ITGB5	$\beta 5$		miR-185	[171]
ITGB6	$\beta 6$		miR-17/20a	[172]
ITGB7	$\beta 7$		nd	
ITGB8	$\beta 8$		let-7, miR-93 miR-145, miR-148a	[64,136,173]

nd—no data.

2.2.2. Podoplanin

Podoplanin is a transmembrane glycoprotein that mediates the degradation of ECM via controlling the stability of invadopodia [174]. Moreover, podoplanin binds the ERM (ezrin, radixin, moesin) protein family to enhance RhoA activity and cell invasiveness [175]. MiR-363 targets podoplanin, leading to the inhibition of cell migration and invasion, thus its level is downregulated in metastatic squamous cell carcinoma [176]. Similarly, podoplanin is also a target of miR-29b and miR-125a that are downregulated in glioblastoma [177].

2.2.3. CD44

CD44 is a cell-surface glycoprotein that mediates cell–cell interactions and cell adhesion. CD44 binds to hyaluronic acid and with low affinity to heparan sulfate, fibronectin, and collagen [178,179]. It is overexpressed in several cell types, including cancer stem cells [180]. The level of CD44 is

strongly regulated by miR-34a, which is a key negative regulator of prostate cancer stem cells [181]. MiR-34a, via targeting CD44, also suppresses angiogenesis [182]. Moreover, CD44 is targeted by miR-199a in ovarian cancer cells and so it suppresses the invasiveness, tumorigenicity, and multidrug resistance [183]. On the other side, the interaction of the CD44 with hyaluronan promotes miR-21 expression leading to the increased expression of anti-apoptotic proteins Bcl-2 and inhibitors of the apoptosis family of proteins (IAPs) [184] as well as increased cell migration and invasiveness [185]. Similarly, CD44–hyaluronan interaction induces the expression of miR-10b, which upregulates RhoA and RhoC resulting in the cytoskeleton activation and increased tumor cell invasiveness [186].

2.2.4. Syndecan-1

Another protein mediating cell–ECM adhesion is syndecan-1 (CD138). It is a heparan sulfate proteoglycan and one of the regulators of integrin function that is involved in the differentiation of tumor cells [187,188]. Syndecan-1 is targeted by miR-10b which promotes cancer cell motility and invasiveness [188].

2.2.5. Focal Adhesion Kinase (FAK)

FAK is a crucial component of the focal adhesion complex and functions as an integrator to control cell migration. FAK transduces extracellular stimuli into intracellular signaling, inducing the reorganization of the cytoskeleton. FAK has been identified as a target of tumor-suppressor miR-7, which inhibits EMT and metastasis [189,190]. Similarly, miR-138 and miR-135 target FAK and inhibit tumor cells invasiveness [191].

2.2.6. Production of ECM

MiRNAs are important modulators of major ECM components expression. MiR-200c targets fibronectin [192]. MiR-29c, which is downregulated in tumor cells, targets mRNA encoding ECM proteins, including collagens I, III, IV, and XV as well as laminin, and osteonectin [193]. Moreover, some miRNAs were reported to regulate collagen maturation, including miR-122 that targets prolyl 4-hydroxylase subunit alpha-1 (P4HA1) [194]. Two tumor suppressor miRNAs, miR-26 and miR-29 target lysyl oxidase-like 2 (LOXL-2), which is a collagen-modifying enzyme, crucial for tissue remodeling and metastasis [195].

2.2.7. Cadherins

In addition to cell–ECM interactions, tumor cells have dysregulated the expression of cell-to-cell adhesion proteins, including cadherins. Changes in the expression of cadherins promote or inhibit cell migration and invasiveness. MiR-9 targets E-cadherin resulting in the activation of β -catenin signaling [24]. Inhibiting miR-9 leads to the inhibition of metastasis formation [24]. Similarly, miR-720 targets E-cadherin and promotes metastasis [196]. Conversely, miR-96 upregulates E-cadherin expression by direct binding, which leads to the enhanced cell-to-cell adhesion [197].

2.2.8. JAM-A

Junctional adhesion molecule A (JAM-A) is a cell–cell adhesion protein and a key regulator of cell migration and invasion [198]. JAM-A has been identified as a direct target of miR-145, which finds its expression downregulated in cancer [66]. An increase in the miR-145 level leads to the inhibition of cell motility and invasiveness [66].

2.3. Step 3: Local Proteolysis of ECM

The proteolysis and remodeling of ECM are crucial for the invasiveness of the cancer cell. Moreover, ECM is a signal reservoir due to the binding of growth factors, sequestering them, and preventing their free diffusion [137]. The degradation of ECM releases growth factors, chemokines, and angiogenic

factors, that promote tumor growth, invasiveness, and metastasis [199]. The main enzymes that generate paths for migrating cells are matrix metalloproteinases (MMPs) [200,201]. MMPs are a family of zinc-dependent endopeptidases that degrade all components of ECM. The formation of the invadopodia that promotes the degradation of ECM by the presentation of MMP-14 and secretion of MMP-2 and MMP-9 is a fundamental event during tumor cell invasion [202].

Multiple miRNAs have been identified as directly targeting MMP mRNA. These miRNAs are tumor suppressors and potentially decrease tumor cell invasiveness. For instance, the overexpression of miR-874 targeting MMP-2 decreases tumor cells' invasiveness in vitro as well as decreases tumor growth in vivo [39]. Moreover, downregulated in metastatic cancer miR-29c targets MMP-2 and integrin $\beta 1$ [203]. The loss of miR-29c increases cell proliferation, adhesion to ECM, as well as migration, and invasiveness [203]. Importantly, miRNAs can also target components of transcription factors regulating MMP expression. Tumor suppressor miR-34a has been identified to target Fra-1 [204,205], a component of activator protein 1 (AP-1) necessary for MMP-1 expression [206]. On the other site, many oncomiRs target negative regulators of MMPs, increasing their expression and activity. A well described oncomiR-21 targets RECK, a membrane-anchored MMP inhibitor, and TIMP3, a tissue inhibitor of MMP activity [207]. The inhibition of miR-21 results in the downregulation of MMP activities and reduced the motility and invasiveness of tumor cells [207].

In addition to MMPs, disintegrin and metalloprotease domains with thrombospondins motifs (ADAMTSs) are important metalloproteases with a complex role in tumor biology [208]. Many of them were reported to be controlled by miRNAs. MiR-140, with a reduced expression in cancer, decreases ADAMTS5, and inhibits cell migration and invasiveness [209]. On the contrary, upregulated miR-365 promotes cell invasion by targeting ADAMTS1 [210]. MiR-221-3p targets ADAMTS6 [211]. Thus, miRNAs are crucial in the regulation of ECM proteolysis (Table 4).

Table 4. Direct regulation of matrix metalloproteinases (MMPs) by miRNAs in cancer cells.

MMP	Role	Role in Cancer	miRNA	Ref.
Collagenases				
MMP-1	Degradation of collagen types I, II, III, V, IX and fibrillary collagen	Initial invasion, metastasis	miR-222, miR-361-5p	[212,213]
MMP-8	Degradation of collagen types I, II, III, V, IX and fibrillary collagen	Inhibits invasion and metastasis	miR-539, miR-2682-3p	[214]
MMP-13	Degradation of collagens types I, II, III, V, IX and fibrillary collagen	Tumor growth, invasion	miR-125b, miR-148a, miR-188-5p	[215,216]
Matrilysins				
MMP-7	Proteolysis of fibronectin, collagen type IV, laminin, elastin, entactin, osteopontin, and cartilage proteoglycan aggregates	Invasive potential, proliferation, anti-apoptotic	miR-143, miR-489, miR-543	[217,218]
MMP-26	Degradation of collagen type IV, fibronectin, fibrinogen, casein, vitronectin, and others	Activates MMP-9	nd	
Metalloelastase				
MMP-12	Degradation of elastin	Protective inhibition of tumor growth	nd	
Stromelysins				
MMP-3	Degradation of collagen types II, III, IV, IX, and X, proteoglycans, fibronectin, laminin, and elastin	Invasion, metastasis, EMT, angiogenesis	miR-17, miR-152	[219,220]
MMP-10	Degradation of proteoglycans and fibronectin	Invasion, migration, tumor growth	nd	
MMP-11	Degradation of alpha-1 antitrypsin	Early tumor invasion	miR-125a-5p, miR-145, miR-192	[221–223]

Table 4. Cont.

MMP	Role	Role in Cancer	miRNA	Ref.
Gelatinases				
MMP-2	Degradation of type IV collagen	Degradation of ECM	miR-29b, miR-29c, miR-106b, miR-874	[39,203,224,225]
MMP-9	Degradation of type IV collagen	Degradation of ECM	miR-29b, miR-183, miR-491-5p	[226–228]
Enamelysin				
MMP-20	Tooth-specific MMP		nd	
Membrane-Type				
MMP-14	Degradation of fibronectin, collagen, and gelatin	Activation of other MMPs	miR-9, miR-22, miR-337-3p	[229–231]
MMP-15		EMT, angiogenesis	miR-608	[232]
MMP-16		Invasion, metastasis	miR-132, miR-146a, miR-146b, miR-215, miR-328-3p	[233–237]
MMP-17		Angiogenesis, metastasis	nd	
MMP-24		Migration, metastasis	nd	
MMP-25		Tumor growth	nd	
Others				
MMP-19		Tumor growth, adhesion, metastasis	miR-16, miR-193b-3p, miR-637	[238–240]
Inhibitors of metalloproteinase				
TIMP1	Inhibition of MMP-14 -16, -19, -24 and ADAM10	Inhibition of cancer growth and metastasis	miR-182, miR-1293	[241,242]
TIMP2	Inhibition of all MMPs and ADAM12	Inhibition of cancer growth and metastasis	miR-205-5p	[243]
TIMP3	Inhibition of all MMPs and ADAM10, 12, 17, 28 and 33; ADAMTS-1, -4, and -5, ADAMTS-2	Inhibition of tumor growth, angiogenesis, and invasion	miR-21, miR-103, miR-181b, miR-191	[244–247]
TIMP4	Inhibition of most MMPs and ADAM17d, -28, and -33	Inhibition of angiogenesis, and invasion, promotion of apoptosis	miR-558	[248]
RECK	Inhibition of MMP-9	Inhibition of metastasis	miR-7, miR-21, miR-222	[207,249–251]

nd—no data.

2.4. Step 4: Cell Contraction by Actomyosin, Myosin II Activation by the Small GTPase Rho and Step 5: Rotation of the Adhesive Bonds on the Trailing Edge

Actomyosin is the primary source of force in mammalian cells. Actin filaments are highly plastic and change dynamically in the cell. Actin polymerization and depolymerization are regulated mainly by the Ras homologue (Rho) superfamily of small GTPases [252], that are involved in the control of cell cytoskeleton organization, thus cell motility [253]. MiR-21 targets tropomyosin 1, an actin-binding protein and a putative tumor suppressor [254]. The administration of the miR-21 inhibitor substantially decreases tumor growth [255]. The regulation of the latest stages of invasive cell migration that includes cell contraction and rear-end retraction is similar to the regulation of the first step (Figure 3, Table 1).

Taken together, miRNAs create a complex network of interactions to regulate cell invasiveness (Table 5). The loss of miRNAs suppressing invasiveness is a crucial step during oncogenesis that allows local invasion and metastasis. On the other site, the upregulation of miRNAs promoting invasiveness accelerates cancer progression by increasing cell motility, invasion, and metastasis.

Table 5. MiRNAs regulating cancer cell invasiveness and their direct targets.

miRNAs Promoting Invasiveness			miRNAs Suppressing Invasiveness		
miRNA	Targets	Ref.	miRNA	Targets	Ref.
miR-9	SOX7, CDH1, α -catenin	[24,256–258]	miR-10b	IGF-1R, HOXA-3, FGF13	[259–261]
miR-10b	TP53, PAX6, NOTCH1, HOXD10, TIP30, KLF4, HOXB3	[259,262–265]	miR-29c	CDK6, ITGB1, TIAM1, Collagens, Laminin γ 1	[193,266–268]
miR-21	PDCD4, maspin, HBP1, LZTFL1, KLF5	[185,269–272]	miR-34a	SATB2, BCL-2, HNF4 α , Snail, MMP9, MMP14, Notch1	[273–278]
miR-103	DAPK, KLF4, OLFM4, LATS2, PTEN	[279–282]	miR-135a	ROCK1, Smo, ERK α	[283–285]
miR-107	TPM1, DAPK, KLF4	[279,286]	miR-145	PAK4, ROCK1, MMP11, Rab27a, MUC1, MMP16, N-cadherin, ZEB2, Ets1, KLF4	[88,287–293]
miR-135b	NR3C2, LZTSL1, APC, FOXO1, ST6GALNAC2, RECK, EVI5	[30,71,294–297]	miR-148b	WNT1, MTA2, ROCK1, Dock6	[298–301]
miR-155	DOCK-1, SDCBP, ANXA-2, CLDN-1, NDFIP1, SOCS1, TP53INP1, BCL6	[302–306]	miR-200	Foxf2, Ftl1, BMP4, Onecut2, LIMK1, BMI-1, E2F3	[307–311]
miR-223	PAX6, hFBXW7, EPB41L3	[34,312,313]	miR-214	JAG1, ROCK1, CDC25B, ARL2, GALNT7, MKK3, JAK1	[314–320]
miR-424	CADM1, SMAD7	[321,322]	miR-340	NT5E, EphA3, SIRT7, NF- κ B1, RhoA, ROCK1, JAK1	[85,323–328]

3. Epithelial–Mesenchymal Transition (EMT)

Epithelial–mesenchymal transition (EMT) is a process that is crucial for embryogenesis, wound healing but also malignant progression. EMT leads to the changes in cell–cell and cell–ECM interactions, that allow the migration of epithelial cells and confer them to the mesenchymal phenotype [329]. The process can be reversed and it is called a mesenchymal–epithelial transition (MET) and is associated with the colonization of distant organs and the formation of metastases [330]. The most important steps are changes in the cell polarity, cytoskeleton and adhesion to other cells and the basement membrane (Figure 4). This allows cells to invade local structures and migrate to distant localizations. Moreover, by undergoing an EMT, carcinoma cells can acquire stem-like cell capabilities such as unlimited self-renewal [331]. EMT is characterized by the downregulation of E-cadherin and the upregulation of N-cadherin and proteases including matrix metalloproteinases such as MMP2 and MMP9 [332]. The most important transcription factors initiating EMT are SNAIL, TWIST, and ZEB. EMT transcription factors regulate the expression of multiple miRNAs [333]. One of the targets of ZEB1 is miR-34a, which regulates multiple properties of tumor cells, including cell migration and invasiveness [333].

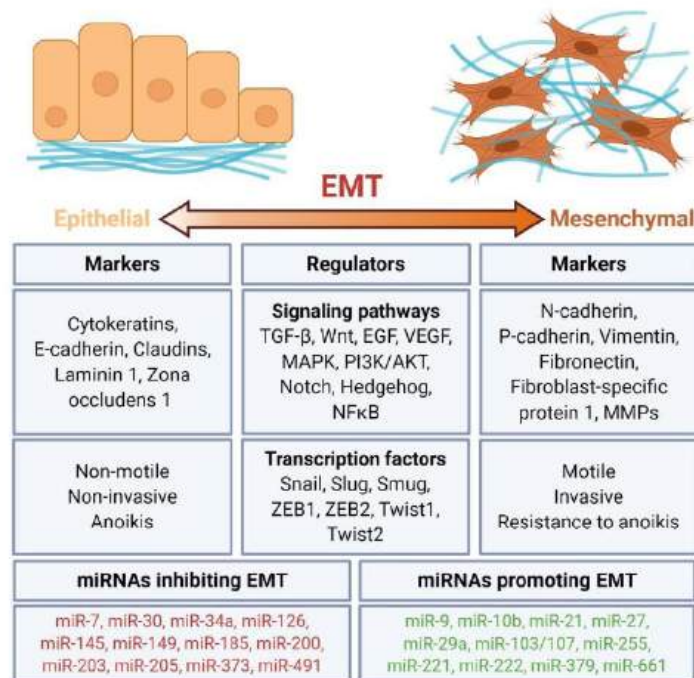


Figure 4. Regulation of epithelial–mesenchymal transition (EMT) by miRNAs. EMT is a process of the acquisition of the mesenchymal features, including motility, invasiveness, and resistance to anoikis of epithelial cells. It is regulated by multiple signaling pathways and transcription factors. Several miRNAs have been identified as either inhibiting or promoting EMT.

All components of EMT signaling pathways are regulated by miRNAs post-transcriptionally [332] (Table 6). In general, EMT is promoted by oncomiRs and inhibited by tumor suppressor miRNAs (Figure 4). A group of oncomiRs called pro-EMT miRNAs promote EMT, tumor cell invasiveness, migration, and metastasis. For example, miR-9 and miR-92a bind to CDH1 which encodes E-cadherin [334]. MiR-10a promotes tumor cell migration and invasion by regulating EMT [335]. In cancer, the maturation of miR-10a is accelerated by XRN2, which leads to increased EMT and metastasis [336]. On the other side, the most important negative regulators of EMT are the miRNA-200 family members. MiR-200s target central regulators of EMT, ZEB1, and ZEB2 [337]. Similarly, miR-22 inhibits EMT via targeting EMT inducer SNAIL and ECM-remodeling MMP14, leading to the suppressed tumor growth, dissemination, and metastasis [231]. MiR-122 triggers a reverse process to EMT, mesenchymal–epithelial transition (MET), and causes cytoskeleton disruption, enhances cell adhesion, and inhibits the migration and invasiveness of cancer cells [80]. A similar effect was exerted by miR-200 family members that induced MET in cancer cell lines [338]. The transformation of the growth factor- β (TGF- β) pathway is key signaling inducing EMT. Moreover, TGF- β controls other processes crucial for cancer progression including tumor cell proliferation and invasion. It was shown TGF- β regulates miRNAs expression but is also a target of miRNAs. Several miRNAs were described to be implicated in TGF- β -mediated EMT [339]. Among them, the miR-34 and miR-200 family seem to play the most important role as they form two negative feedback loops with transcription factors involved in EMT. MiR-34 participates with SNAIL1 with the first negative feedback loop and controls the initiation of the EMT process. TGF- β downregulates members of the miR-200 family by the

methylation of their promoters and forms an autocrine TGF- β /miR-200b feedback loop. Thus, TGF- β induces EMT by miR-200/ZEB interaction [340]. TGF- β downregulates the expression of miR-584, a negative regulator of PHACTR1 (phosphatase and actin regulator 1), which in turn leads to actin rearrangement and cancer cell migration [81]. Moreover, TGF- β regulates miRNAs targeting adhesion genes [138].

Another crucial signaling pathway for tumor cell invasiveness and metastasis is Wnt/ β -catenin. β -catenin-dependent canonical Wnt signaling regulates cell proliferation as well as the development and promotion of EMT, tumor cell invasiveness, and metastasis [341,342]. In the absence of Wnt, β -catenin forms a complex with the tumor suppressor adenomatous polyposis coli gene product (APC), glycogen synthase kinase 3 (GSK3), Axin, and casein kinase 1 (CK1) and is phosphorylated by CK1 and GSK3, which leads to the constant proteasomal degradation of β -catenin. After stimulation with the Wnt ligand, axin is recruited to the membrane complex of the Frizzled (Fz) receptor, low-density lipoprotein receptor-related protein 5 (LRP5) or LRP6 and the scaffolding protein Dishevelled (Dvl), which inhibits the phosphorylation of β -catenin, leading to its stabilization and accumulation in the nucleus [343]. Canonical Wnt signaling is regulated by multiple miRNAs. Wnt1 ligand is targeted by miR-122 [298], miR-148a [344], miR-148b [345], miR-152 [346], miR-329 [347]. Similarly, β -catenin is a target of multiple tumor suppressor miRNAs including miR-33a [348], miR-214 [349], miR-200c [350], miR-320a [351]. WWOX, a β -catenin inhibitor, is targeted by an oncogene, miR-153 [352]. The systemic administration of the miR-153 inhibitor suppressed the development of hepatocellular carcinoma in mice, while tumor cells with upregulated miR-153 expression exhibited increased growth [352]. The expression of miR-374a promotes cell migration and invasiveness by targeting crucial negative regulators of Wnt/ β -catenin, including WIF1, PTEN, and WNT5A [353]. Moreover, other components of the Wnt signaling pathway are regulated by miRNAs, including Frizzled-7 by miR-27a [354], LRP6 by miR-202 [355] and miR-432 [356], axin 2 by miR-107 [357], and axin 2 and GSK β by miR-1246 [358]. Altogether, miRNAs are important regulators of EMT and may either promote or suppress it by targeting different factors (Table 6).

Table 6. Direct regulation of EMT signaling by miRNAs.

Target	miRNAs	Ref.
TGF- β 1	miR-99a, miR-99b, miR-744	[359,360]
TGFBR2	miR-17 family, miR-21, miR-204, miR-211, miR-373, miR-520	[361–365]
ZEB1	miR-200 family, miR-205	[366,367]
ZEB2	miR-132, miR-138, miR-154, miR-200 family, miR-205, miR-215	[367–371]
Twist1	let-7d, miR-33a, miR-145a-5p, miR-151-5p, miR-214, miR-580	[372–375]
Twist2	miR-138, miR-215	[376,377]
Notch	miR-23b, miR-30a, miR-34a, miR-206	[131,378–380]
Snail1	miR-22, miR-34a, miR-137, miR-182	[231,276,381]
Snail2	miR-30a, miR-124, miR-203, miR-204, miR-211	[362,382–384]
EZH2	miR-138	[368]
Slug	miR-1, miR-30a, miR-124, miR-506, miR-630, miR-590-3p	[385–390]
N-cadherin	miR-145, miR-194	[391,392]
Vimentin	miR-30c	[393]
Fibronectin	miR-1, miR-139, miR-200c, miR-432	[394–397]
E-Cadherin	miR-10b, miR-22, miR-23b, miR-25, miR-92a, miR-221, miR-720,	[196,398–403]
ZO-1	miR-103	[404]
Claudins	miR-98 (claudin-1), miR-146-5p (claudin-12), miR-421 (claudin-11), miR-488 (claudin-2), miR-155 (claudin-1)	[405–409]

4. Angiogenesis

4.1. Regulation of Angiogenesis by miRNA

Angiogenesis is a process of blood vessel creation. Tumor angiogenesis is classified as one of the hallmarks of cancer [410]. MiRNAs create a regulatory network that controls angiogenesis [411]. MiRNAs target multiple components of the angiogenesis regulatory pathway (Table 7). The tumor cell secretes miRNAs in exosomes to promote the angiogenesis of microvessel endothelial cells [412]. Moreover, multiple miRNAs either promote or inhibit endothelial cell proliferation, migration, and tube formation [408]. MiR-93 produced by glioblastoma cells promotes endothelial cell spreading, growth, migration, and tube formation, stimulating blood vessel formation and supporting tumor growth in vivo [173]. On the other hand, tumor suppressor miRNAs, like the miR-200 family suppress angiogenesis through multiple mechanisms, including targeting IL-8 and CXCL1. Moreover, tumor suppressor miRNAs inhibit crucial signaling pathways including PI3K/AKT, mTOR, and IGF1R pathways to inhibit angiogenesis. Targeting the miRNA-dependent regulation of angiogenesis seems to be a promising therapeutic approach [19]. Noteworthy, MMPs and the tissue inhibitors of metalloproteinases (TIMPs) are crucial for the ECM remodeling and angiogenesis [200], and their regulation by miRNAs was described above.

Table 7. The direct regulation of the angiogenesis pathway by miRNA.

Target	miRNA	Ref.
VEGF	miR-20b, miR-27b, miR-29b, miR-93, miR-126, miR-128, miR-140-5p, miR-195, miR-203, miR-205, miR-497, miR-503, miR-638,	[51,245,413–424]
VEGFR	miR-378a, miR-497	[425]
NRP1	miR-141, miR-338	[426,427]
TSP-1	miR-19a, miR-182, miR-467	[428–430]
FGF	miR-503, miR-5582-5p	[421,431]
HDGF	miR-139, miR-195, miR-214, miR-497, miR-511, miR-873, miR-939	[432–438]
Angiogenin	miR-204	[363]
PDGF	miR-29a	[439]
HIF1a	miR-20b, miR-33a, miR-107, miR-135b, miR-519c	[440–443]
HIF2a	miR-145	[58]
VHL	miR-21, miR-155, miR-222	[444–446]
STAT3	miR-125a, miR-411, miR-544, miR-874, miR-1299	[447–451]
Bmi-1	miR-16, miR-132, miR-183, miR-200c, miR-203, miR-218	[452–457]
E2F3	miR-194-5p, miR-200c, miR-217, miR-432, miR-449a	[311,458–461]
NF90	miR-590-5p	[462]

4.2. Vascular Endothelial Growth Factor-A (VEGF-A)

VEGF family members are growth factors that play a key role in angiogenesis. They bind to tyrosine kinase cell receptors, VEGFR-1, VEGFR-2, and VEGFR-3. Among them, VEGFR-2 is the most pro-angiogenic receptor [463]. Both, VEGF and VEGFR are regulated by miRNAs in cancer tissues. MiR-140-5p targets VEGF-A and suppresses angiogenesis and cell invasion [413]. Moreover, miR-205 and miR-497 bind directly to VEGF [414,415]. Expression of miR-140-5p, miR-205, and miR-497 targeting VEGF are substantially downregulated in cancer. VEGFR is targeted by miR-378a which acts as a suppressor of cell proliferation and invasion [425]. Furthermore, miR-497 via targeting VEGF suppresses cell proliferation and invasion and inhibits key signaling pathways as MEK/ERK and p38/MAPK [464].

4.3. *Thrombospondin-1 (TSP-1)*

TSP-1 is a known antioncogenic factor that controls many cellular processes. It influences cell proliferation, invasion, and migration. It functions as a ligand of CD47 [465]. MiR-467 binds to TSP-1 and promotes tumor angiogenesis and thus increases tumor growth. The expression of miR-467 is upregulated in tumor cells [428].

4.4. *Platelet-Derived Growth Factor (PDGF)*

PDGF, a member of the receptor tyrosine kinases family, is a growth factor involved in angiogenesis, cell proliferation, and migration. MiR-29a targets PDGFC and PDGFA and thus acts as a tumor suppressor [439]. Moreover, PDGF induces the expression of miRNAs, including miR-221, which regulates PDGF-induced EMT and cell migration [466].

4.5. *Hypoxia-Inducible Factor 1 Alpha (HIF1 α)*

HIF-1 α is a transcription factor that regulates angiogenesis, cell proliferation, and invasion. In normoxia, the proline residues of HIF-1 α are hydroxylated, which is recognized by Hippel-Lindau tumor-suppressor protein (VHL) leading to the degradation in the proteasome [467]. HIF-1 α accumulates in the cell under hypoxic conditions. Despite being regulated mainly by posttranslational modification, HIF-1 α is also a target of several miRNAs, including miR-20b and miR-107 (Table 7).

VHL is described as a tumor suppressor gene and its inactivation may regulate cancer development and progression [467]. VHL is directly targeted by miR-21 in pancreatic cancer. The inhibition of miR-21 causes the suppression of tumor cell invasiveness via the HIF-1/VEGF pathway and the downregulating of MMP-2 and MMP-9 [445]. Moreover, miR-155 creates a signaling pathway with VHL/HIF/VEGF and regulates angiogenesis and the aggressive malignant phenotype of cancer cells [446].

5. Chemokines and Growth Factors

The mobilization of tumor cells from tissue-fixed state to migrating cells is regulated by multiple factors, including extracellular chemokines and growth factors. Several chemokines, CXCL12, CXCL10, CXCL11, CCL21, and CCL25 were identified as crucial in the induction of cell invasion [2,468]. CXCL12, which promotes invasiveness as well as the recruitment of monocytes to the tumor microenvironment, is a target of miR-342 [469]. The upregulation of miR-342 leads to the inhibition of tumor growth in vivo [469]. Moreover, the receptor for CXCL12, CXCR4, is targeted by miR-613, which suppresses cell invasiveness [470]. MiR-34a downregulates CXCL10 leading to a decrease in cell migration and invasiveness [471]. CCR7, a receptor for CCL21, promotes invasiveness and metastasis as well as regulates actin polymerization and pseudopodia formation is a target of Let-7a [472–474]. Moreover, CXCL11, which promotes cell migration, is a target of miR-144 [468,475,476]. Activation of the CXCL12/CXCR4 axis activates RhoA signaling, which regulates actin cytoskeleton and cell motility. This effect is mediated by the upregulation of lncRNA XIST, which acts as a sponge for miR-133a-3p, preventing RhoA downregulation, and promoting tumor cell invasion [76].

MiRNAs are important regulators of all crucial signaling pathways in cancer cells. They regulate the transduction of signaling from the growth factor receptors, including epidermal growth factor receptor (EGFR) [477], and regulate the MAPK signaling pathway [478,479], PI3K/Akt [480], p53 signaling [481], and JAK/STAT pathway [482]. For instance, SOCS2, a negative regulator of the JAK/STAT pathway, is targeted by multiple miRNAs including miR-196a, miR-196b, and miR-194 that promote cell migration, invasion, cell proliferation, and EMT [483,484].

6. Intravasation, Systemic Circulation, and Extravasation

After the local invasion, the tumor begins to grow. A fast increase in the cell number eventually leads to the dissemination of cancer cells to distant sites. Tumor dissemination occurs in early lesions as

well as in mid- or late-stage tumors [485]. Cancer cells emigrate from the primary tumor to secondary sites via blood vessels, lymphatic vessels, interstitial fluid, and nerves [485–487]. Most miRNAs regulate multiple steps of metastasis, conferring tumor cells the ability to spread. For instance, miR-182, markedly overexpressed in metastatic cancer, targets four metastasis-suppressing genes [242]. The inhibition of miR-182 decreases cell migration and invasiveness as well as decreases the rate of tumor cells' intravasation and metastasis to the lungs [242]. The first and critical step for metastasis is intravasation. To do this, tumor cells have to overcome the barrier of the basement membrane and the wall of the vessel.

6.1. Intravasation

Tumor cells secrete miR-105, which targets ZO-1, the tight junction protein-1 in endothelial cells. The exosome-mediated transfer of miR-105 from cancer cells destroys the integrity of endothelial monolayers, which enable intravasation [488]. Additionally, miR-181a disrupts the endothelial barrier by targeting Kruppel-like factor 6 (KL-F6), leading to the decreased expression of ZO-1, occluding, and claudin-5, which results in blood–tumor barrier permeability [489]. Tumor cells intravasation is also promoted by miR-21, which targets tumor suppressor Pdc4 [29].

6.2. Systemic Circulation

Most of the tumor cells in the circulation are either killed by immune cells or die in the process called anoikis [490,491]. Natural killer (NK) cells are the main immune cells eliminating circulating tumor cells, thus suppressing metastasis. Circulating tumor cells use multiple mechanisms to escape from NK, including coating with platelets [492] and alterations in the expression of MHC molecules, NK cell ligand, and immune-checkpoints [490]. Importantly, miR-296-3p, which is overexpressed in metastatic cells, targets ICAM-1, rendering resistance to NK cells lysis in vasculature [491]. Moreover, Dicer-generated miR-222 and miR-339 suppress ICAM-1 on tumor cells, leading to the decreased susceptibility to cytotoxic T-cells cytotoxicity [490,491,493]. ICAM-1 is also a target of miR-296-3p, which enables invasiveness, intravasation, and enhances the survival of NK-resistant circulating tumor cells [491].

Anoikis is a form of programmed cell death induced by the loss of contact with the ECM or with other cells [494]. Anoikis depends on the activation of caspase and downstream pathways that includes the intrinsic and extrinsic apoptotic pathways [494]. Many miRNAs have been identified as crucial in the promotion or prevention of anoikis. MiR-141 enhances anoikis resistance and metastasis by targeting KLF12 [495]. Similarly, miR-214 promotes cell survival contributing to the enhanced metastasis of melanoma cells [32].

6.3. Extravasation

The extravasation of tumor cells determines their metastatic potential. Tumor cells were found to secrete extracellular vesicles (EVs) loaded with multiple miRNAs that are transferred to endothelial cells leading to changes in vascular permeability. Tumor-derived exosomes containing miR-181c are capable of destructing the blood–brain barrier by the dysregulation of the actin cytoskeleton via targeting PDPK1 [496]. Similarly, exosomal miR-25-3p promotes vascular permeability and angiogenesis by targeting KLF2 and KLF4, regulating tight junction proteins [497]. Moreover, miR-214 has been identified as crucial in the promotion of metastasis by an enhancement of extravasation [498]. On the other side, p38 activated by IL-1 β promotes the expression of miR-31, which targets E-selectin [499]. This in turn leads to the decreased adhesion to the endothelium and inhibited transendothelial migration of tumor cells [499]. Similarly, tumor-suppressors miR-148b as well as miR-155 inhibit metastasis formation by affecting extravasation and survival [84,500].

7. Metastatic Colonization

The last stage of tumor invasion is the colonization of the secondary site. Metastasis to the sentinel lymph node is the most common and the most reliable factor for survival predicting in patients with different types of cancer [501]. Furthermore, tumor cells exit lymphatics, enabling systemic dissemination [502]. Tumor cells modulate premetastatic niches to enable the settlement and metastasis growth in tumor-draining lymph nodes or distant organs [5,142,501]. MiRNAs regulate this process either directly in tumor cells, promoting their migration, invasiveness, and survival or by affecting other cells in the premetastatic niches.

Tumor cells secrete multiple factors that reach distant sites via body fluids—blood, lymph, and interstitial fluid. The pro-metastatic secretome includes pro-angiogenic VEGF, PLGF, immunomodulating TGF- β , and S100 family proteins [142]. Moreover, tumors secrete extracellular vesicles that contain multiple proteins and miRNAs to prepare premetastatic niches [142,503]. It makes the tissue microenvironment supportive and receptive for the colonization by the metastatic tumor cell, according to the seed and soil hypothesis [504–506]. Premetastatic niche formation includes ECM remodeling, angiogenesis [507], and immune cell education towards a pro-metastatic phenotype [503]. All these processes are regulated by miRNAs in EVs. Secreted miRNAs, including miR-105-5p, miR-21-5p, miR-139-5p, regulate ECM remodeling by increasing the expression of MMPs in fibroblasts, as well as stimulate their proliferation creating a premetastatic niche [508]. Moreover, miR-122 in tumor-secreted extracellular vesicles reprograms the metabolism of stromal cells favoring a premetastatic microenvironment [509,510]. An exceptional pro-angiogenic and pro-metastatic role has been attributed to cancer stem cell (CSC)-released EVs containing miRNAs that regulate crucial biological processes [507,508].

Additionally, it seems that the secretion of tumor-suppressor miRNAs in the exosome is one of the mechanisms for decreasing their levels. Tumor cells secrete tumor-suppressors, including miR-23b, miR-224, and miR-921, which inhibit cell invasiveness, anoikis, angiogenesis, and metastasis [511]. Tumor suppressor miRNAs, miR-26, and miR-29, by targeting LOXL2, suppress tumor metastasis and the recruitment of myeloid cells to the metastatic site [195]. Moreover, miR-203 acts as a tumor suppressor miR and quells cancer cell proliferation and invasion [512]. However, miR-203 in exosome secreted by tumor cells promotes the polarization of monocytes into tumor-associated macrophages, thus supporting metastatic niche formation [512].

8. Tumor–Stroma Interactions

8.1. Cancer-Associated Fibroblasts (CAFs–Tumor Cells Interactions)

Tumor cells and non-cancerous stromal cells interact with each other. Importantly, tumor invasiveness and metastasis greatly depend on stromal cells. Among the crucial stromal cells that induce ECM remodeling and enable cancer cell invasion are cancer-associated fibroblasts (CAFs) [513]. Cancer cells acquire migratory properties by the interaction between integrin $\alpha 5 \beta 1$ and fibronectin on the surface of CAFs, which enables migration through the ECM [514]. Tumor cells dysregulate miRNAs expression in resident fibroblasts favoring their polarization into tumor-promoting CAFs [515,516]. Many miRNAs have been identified as regulating CAF activation, including the miR-31, miR-214, miR-155 [515], and miR-200 family [517]. MiR-200s regulate collagen contraction by CAFs as well as trigger ECM remodeling, invasion, and tumor metastasis [517]. Similarly, miR-222 regulates CAFs' reprogramming and its overexpression promotes fibroblast-induced cancer cell migration and invasiveness [518].

Moreover, also stromal cells secrete exosomes that regulate tumor cells. For instance, astrocytes secrete exosomes that contain miR-345 targeting KISS1, upregulate autophagy and promote brain invasion [519]. Additionally, astrocytes-derived exosomes contain miRNAs targeting PTEN, leading to its loss in brain metastasis [520].

Bones are a frequent location of solid tumors metastases. Tumor cells secrete factors that dysregulate miRNA expression in osteoclast, favoring bone metastasis and osteolysis [521]. Moreover, cancer-derived miRNA-218 decreases the production of type I collagen by directly targeting Col1a1 in preosteoblasts [522].

8.2. Immune Cells–Tumor Cells Interactions

MiRNAs are also important regulators of immune cells in the tumor microenvironment [22,523]. Tumor cells secrete miRNAs to directly suppress the antitumor response. The high expression of miR-424 in tumors decreases T-cell activation [524]. Similarly, a high level of miR-23a and miR-29a impairs the antitumor activity of cytotoxic T lymphocytes [525,526]. MiR-10b upregulated in tumor cells suppresses NK-mediated killing of tumor cells via targeting stress-induced cell surface molecule MICB [527].

In addition to directly suppressing antitumor immunity, miRNAs induce the polarization of immune cells [528]. Tumor cells as well as tumor-associated stromal cells secrete miRNAs that hijack immune cells to polarize them into immunosuppressive, tumor-promoting cells. MiRNAs may be secreted in extracellular vesicles, in the complexes with RNA-binding proteins including AGO2 and nucleophosmin, with lipoproteins, or by the direct exchange between cell via gap junctions [23,529]. In addition to directly suppressing antitumor immunity, miRNAs induce the polarization of immune cells [530]. Among others, cancer cells secrete miR-1246, which is delivered to macrophages and triggers the increased activity of TGF- β and an anti-inflammatory phenotype [530]. Similar effects are exerted by tumor-secreted miR-21 [531], miR-22-3p [532] and miR-203 [512]. Moreover, tumor-associated macrophages secrete miR-223 that promotes the invasiveness of tumor cells [533].

MiRNAs are also involved in the regulation of immune cell recruitment into the tumor microenvironment. MiR-155 enables the infiltration of innate immune cells and the suppression of antitumor immunity [534]. MiR-494 regulates the accumulation of myeloid-derived suppressor cells (MDSCs) and the inhibition of the miR-494 suppressed tumor growth and metastasis [535]. Moreover, miR-494 promotes arginase expression in MDSCs [535], which is crucial for the suppression of antitumor immunity [536]. Elevated TGF- β suppresses miR-34a which targets CCL22. Increased CCL22 production recruits regulatory T cells, which creates an immunosuppressive microenvironment and favors the colonization of tumor cells [537]. On the other hand, TGF- β promotes miR-155 and miR-21 expression in myeloid cells favoring polarization into immunosuppressive MDSCs [538].

9. miRNAs as Biomarkers in Cancer

Due to the dysregulated pattern of miRNA expression in cancer, miRNAs arose as promising biomarkers [539,540]. MiRNA profiling is feasible because of the stability of miRNAs and their presence in different body fluids, fresh frozen tissues, and even routinely collected formalin-fixed paraffin-embedded (FFPE) tumor tissue [541]. Multiple miRNAs have been identified as diagnostic or prognostic biomarkers [542,543]. Moreover, several miRNAs have been reported as an important prognostic marker of lymph node metastasis and distant organ metastasis (Table 8). MiR-21 which inhibits apoptosis [184] and potently promotes invasiveness (Table 5), correlates with the lymph node metastasis in many types of cancer [544], including breast cancer [545] and pancreatic ductal adenocarcinoma [546]. Similarly, miR-10b increases tumor cell migration, and invasiveness is a biomarker of distant metastasis in colorectal cancer [547]. Furthermore, as miRNAs regulate tumor cells' response to the therapy [548], there are promising tools to monitor anticancer treatment.

Table 8. MiRNAs as biomarkers of metastasis.

miRNA	Cancer	Type of Tissue	Mirna Level	Lymph Node Metastasis	Distant Metastasis	Ref.
miR-203	Colorectal	Serum	High	OR 2.9; 95%CI 1.4–6.1; $p = 0.0035$	OR 5.3; 95%CI 2.4–11.5; $p < 0.0001$	[549]
miR-885-5p	Colorectal	Serum	High	OR 3.0; 95%CI 1.3–7.2; $p = 0.0116$	OR 3.1; 95%CI 1.0–10.0; $p = 0.0456$	[547]
miR-19a	Various carcinomas	Serum and tissue	High	OR 0.564; 95%CI 0.346–0.921	nd	[550]
miR-20a	Cervical	Serum	High	OR 1.552; 95%CI 1.137–2.118	nd	[551]
miR-21	Breast	Serum and tissue	High	OR 2.36; 95%CI 1.04–4.78; $p = 0.03$	nd	[545]
miR-21	Pancreatic ductal adenocarcinoma	Serum and tissue	High	OR 1.45; 95%CI 1.02–2.06; $p = 0.038$		[546]
miR-122-5p	Colorectal	Serum	High	OR 1.621; 95%CI 1.255–2.092; $p = 0.0002$	nd	[552]
miR-146b-5p	Colorectal	Serum	High	OR 2.096; 95%CI 1.594–2.756; $p < 0.0001$	nd	[552]
miR-186-5	Colorectal	Serum	High	OR 2.910; 95%CI 1.810–4.678; $p < 0.0001$	nd	[552]
miR-193a-5p	Colorectal	Serum	High	OR 0.656; 95%CI 0.577–0.774; $p < 0.0001$	nd	[552]
let-7i	Colorectal	Tissue	Low	nd	OR 5.5; 95%CI 1.1–26.8; $p = 0.0334$	[547]
miR-10b	Colorectal	Tissue	High	nd	OR 4.9; 95%CI 1.2–19.7; $p = 0.0248$	[547]
miR-29a	Colorectal	Serum	High	nd	OR 3.500; 95%CI 1.274–9.617; $p < 0.05$	[553]

OR—odds ratio, 95%CI—95% confidence interval, nd—no data.

10. Challenges for the Use of miRNAs in Clinical Oncology

MiRNAs seem to have the potential for therapeutic use [554–556]. However, the first clinical trials did not live up to expectations. The first trial tested the miR-34a-based compound—MRX34—in several types of cancer. X34 is a liposomal miR-34a-mimic that entered the phase I study. MiR-34a is a tumor suppressor miRNA which targets several genes from the different oncogenic pathway. The results confirmed antitumor actions and showed acceptable safety when used twice a week in patients with different solid tumors in the advanced stadium [557]. However, further studies were terminated due to serious adverse events (NCT01829971, NCT02862145) [558]. Other compounds tested in clinical trials involved TargomiRs, targeted minicells containing miR-16 family (NCT02369198, NCT03713320) [559,560], and cobomarsen, an oligonucleotide inhibitor of miR-155 (NCT03837457, NCT02580552) [561].

Despite great expectations, only a few miRNA-based therapies were tested in clinical trials and did not achieve satisfactory effects. There are several crucial challenges for the use of miRNAs in oncology that limit their efficacy (Figure 5). The most important biological feature of miRNAs that leads to unpredictable results as well as putative multiple side-effects is the complexity of miRNAs–targets network. That is, numerous pathways are affected, hence any miRNA-based therapy will always have diverse effects depending on the initial expression of their targets. Moreover, miRNA off-targets on mismatched targets must be taken into account [562].

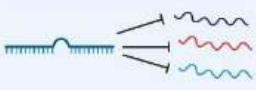
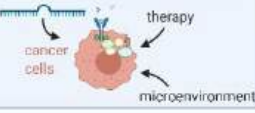
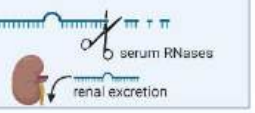
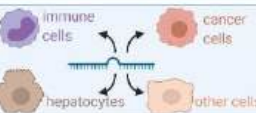
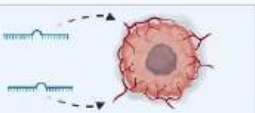
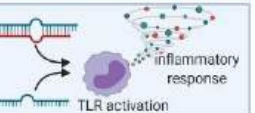
Challenges for the use of miRNAs in clinical oncology			
Biological feature	Multiple targets of a single miRNA	Complex miRNAs-targets network	Degradation and clearance in the circulation
			
	• Multiple side-effects • Unpredictable results • Reduced therapeutic effects • Interactions with drugs • Unwanted on-target effects	• Multiple side-effects • Unpredictable results • Low efficacy	• Requirement of high doses and multiple administrations • Chemical modification of administration as complexes • Possible renal damage
Strategy	• Comprehensive research on miRNA-mRNA regulatory network	• Comprehensive research on miRNA-mRNA regulatory network	• Chemical modifications • Delivery routes
Biological feature	Unspecific delivery	Limited <i>in vivo</i> tumor penetration	Activation of immune cells
			
	• Multiple side-effects • Low efficacy • Unpredictable effects • Interaction with drugs	• Low efficacy • Lack of therapeutic effects • Requires intratumoral injection	• Immune-related side effects • Toxicity • Unpredictable effects
Strategy	• Targeted delivery • Adequate delivery routes	• Targeted delivery • Adequate delivery routes	• Targeted delivery • Combined immunosuppression

Figure 5. Challenges for the use of miRNAs in clinical oncology. Biological features of miRNAs include multiple targets, the complexity of the miRNAs–mRNAs network, the degradation by RNases and clearance in the circulation via renal excretion, unspecific delivery—not only to their destination, but also to healthy unaffected tissue including hepatocytes, limited *in vivo* tumor penetration and the activation of immune cells. This leads to a lack of therapy efficiency and there is a need for further comprehensive research on the miRNA–mRNA network and miRNAs’ delivery methods to overcome them.

MiRNAs act as modulators of the levels of multiple rather than only strong post transcriptional repressors [563]. However, many targets of miRNAs remain unknown as most studies focus on simple miRNA–target axes. Importantly, the upregulation of a single miRNA affects the global regulation of gene expression by endogenous miRNAs [564]. Therefore, comprehensive studies on miRNA–mRNA interactions with the use of high-throughput methods are required.

Recent advances provided reliable models to investigate the complex role of miRNAs in cancer [565], since the role of miRNA depends on the context and may be modulated by the tumor microenvironment or therapy. Thus, miRNAs must be tested in *in vivo* preclinical studies in different models, since single miRNA may act as either oncomiR or tumor-suppressor miR, even in similar tumor types. Xenograft models of human tumor-derived cells in immune deficient mice are the most reliable to evaluate the *in vivo* potential of miRNAs as well as their therapeutic potential [565].

Importantly, regardless of their relatively high stability, unmodified miRNAs administered to the circulation are degraded quickly by serum RNases [566]. Thus, chemical modifications are required to

increase miRNA stability, providing their longer half-life time and higher therapeutic efficacy [567,568]. Another major limitation of miRNAs therapy, common to almost all types of gene therapy, is the targeted delivery of oligonucleotides to cancer cells. Unmodified miRNAs poorly penetrate the cell membrane. Therefore, delivery vehicles are required. Currently, different types of vectors are being tested for miRNA delivery, including inorganic materials, lipid-based nanocarriers, cell-derived membrane vesicles and viral vectors [568].

miRNA delivery is limited by several factors including limited tumor penetration and unavoidable yet undesired delivery to healthy tissues, including immune cells and hepatocytes. Over 60% of lipid-conjugated miRNAs are accumulated in the liver [569]. This leads to multiple side effects, unpredictable results, interactions with other drugs, low therapy efficiency or a lack of therapeutic effects. Intratumor injections, targeted delivery, or adequate delivery routes may overcome these obstacles. The more targeted delivery of miRNAs to the tumor increases the amount of miRNA that reach destination cells [570]. A tumor targeting antibody-guided nanoparticles with miR-34a effectively reached the metastasis of melanoma, which increased the amount of absorbed miRNA in tumor cells [571,572]. A similar approach was tested in patient-derived xenografts of pancreatic ductal adenocarcinoma. Tumor-penetrating nanocomplexes targeting cell surface proteins carrying anti-miR oligonucleotides inhibiting identified oncomiRs, which potently suppressed tumor growth [573].

The administration of high doses of miRNAs also increases a high risk of immune cell activation. Exogenous single-stranded RNAs and double-stranded duplexes are recognized by Toll-like receptors (TLRs), triggering the expression of pro-inflammatory cytokines, including interferons (IFNs) [574,575]. Indeed, the first-in-human clinical trial of miRNA therapy was closed early due to serious immune-related adverse effects that resulted in patients deaths [558].

Considering all the aforementioned limitations, despite a huge progress in our understanding of miRNA engagement in cancer, before successfully entering clinical medicine, more comprehensive studies are required. Not only on the mechanisms of miRNAs action, but also on the safety and specificity of miRNAs delivery.

11. Conclusions

In recent years, significant progress has been made in understanding the role of miRNAs in orchestrating cancer progression. Molecular studies enabled the identification of tumor suppressor genes and oncogenes as direct targets of miRNAs. Multiple reports described the role of miRNAs in promoting or suppressing tumor cell proliferation, migration, invasiveness, and metastasis. Moreover, miRNAs are important players in chemoresistance and tumor immune evasion. Importantly, the function of miRNAs is tissue specific as well as context dependent. Single miRNA may act as oncomiR that promotes tumor cell invasiveness and metastasis in one type of cancer but in another type of tumor it can act as a suppressor miR [14]. Some oncomiRs are specific biomarkers and their inhibition seems to be a promising therapeutic approach. However, due to fact that a single miRNA can target multiple mRNAs, further research and careful data analysis are necessary.

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The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis—A Systematic Review



Systematic Review

The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis—A Systematic Review

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Simple Summary: Endometrial cancer (EC) is one of the most frequent cancers with increasing annual death rates. Therefore, it is of great clinical importance to understand the mechanisms of endometrial cancer invasiveness and metastasis. miRNAs are small single-stranded RNAs that regulate gene expression. They were discovered to play a role in all steps of cancer development. This study aimed at conducting a systematic review of the role of miRNAs in endometrial cancer invasiveness and metastasis. The collected data demonstrate that miRNAs regulate EC invasiveness and metastasis by different targets. miRNAs seem to be potential candidates for diagnostic and prognostic biomarkers, as well as possible therapeutic targets.



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Abstract: Endometrial cancer (EC) is the most common genital cancer in women with increasing death rates. miRNAs are short non-coding RNAs that regulate gene expression on the post-transcriptional levels. Multiple studies demonstrated a fundamental role of miRNAs in the regulation of carcinogenesis. This systematic review is a comprehensive overview of the role of miRNAs in the regulation of cancer cell invasiveness and metastasis in EC. The literature was searched for studies investigating the role of miRNAs in the regulation of invasiveness and metastasis in EC. We explored PubMed, Embase, and Scopus using the following keywords: miRNA, metastasis, invasiveness, endometrial cancer. Data were collected from 163 articles that described the expression and role of 106 miRNAs in the regulation of EC invasiveness and metastasis out of which 63 were tumor suppressor miRNAs, and 38 were oncomiRNAs. Five miRNAs had a discordant role in different studies. Moreover, we identified 66 miRNAs whose expression in tumor tissue or concentration in serum correlated with at least one clinical parameter. These findings suggest a crucial role of miRNAs in the regulation of EC invasiveness and metastasis and present them as potential prognostic factors for patients with EC.

Keywords: endometrial cancer; miRNAs; metastasis; invasiveness; migration; biomarker

1. Introduction

Endometrial cancer (EC) accounts for the most frequent cancers with growing incidence rates [1,2]. The outcome depends on the progression of the disease and applied treatment [3,4]. That makes effective management of EC risk factors, early diagnosis, and effective therapy strategies of EC the clinically important challenges. There are two most common EC staging classifications, TNM and The International Federation of Gynecology and Obstetrics (FIGO) that differentiate endometrial cancer tumors according to the depth of invasion and presence of metastases (Figure 1) [5]. Furthermore, there is a FIGO grading based on the level of glandular differentiation. A higher grade is associated with a non-glandular, non-squamous growth [6].

Endometrial cancer staging and histological grading

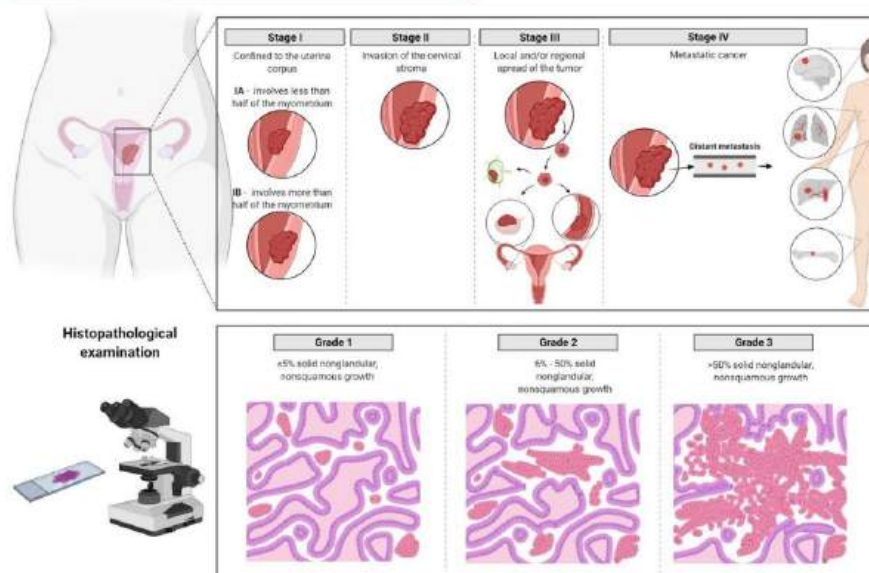


Figure 1. Federation of Gynecology and Obstetrics (FIGO) staging and histological grading of endometrial cancer. Figure was created using [Biorender.com](https://www.biorender.com/).

MiRNAs are small non-coding single-stranded molecules that regulate all hallmarks of cancer by influencing gene expression post-transcriptionally. The formation of miRNAs begins in the nucleus where polymerase II (Pol II) transcribes pri-miRNA. The pri-miRNA is cropped by the DROSHA complex and exported by exportin 5 to the cytoplasm where mature single-stranded miRNAs arise with the participation of DICER and Argonaute 2 (AGO2) [7,8]. During carcinogenesis, the profile of miRNAs expression undergoes a substantial dysregulation [9,10]. It is a result of multiple changes, including amplification and deletion of miRNA genes or dysregulation of epigenetics [9]. Moreover, miRNAs expression is dysregulated in cancer as an effect of defects in miRNA biogenesis machinery, including DICER and DROSHA [11].

MiRNAs take part in all steps of tumor cell invasiveness and metastasis including migration, local invasion, epithelial–mesenchymal transition (EMT), and systemic circulation [12]. The same miRNAs may play opposite roles in different tumors, promoting tumor growth (oncomiRNAs) or acting as tumor suppressor miRNAs [13]. By targeting 3′ untranslated region (UTR) of multiple mRNAs they regulate all hallmarks of cancer defined by Hanahan and Weinberg, including proliferation, invasion, angiogenesis, as well as they influence cancer cells chemoresistance [12,14–17].

This systematic review aims to highlight the complex role of miRNAs in regulating endometrial cancer invasion and metastasis. We focus on the aberrant expression of different miRNAs in endometrial cancer tissues and cell lines and their role in the regulation of tumor invasion, metastasis, and patients’ outcomes.

2. Materials and Methods

2.1. Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used to ensure reporting transparency (Figure 2). Two reviewers (KK and TMG) collected, screened, and performed an independent assessment of the quality of the studies.

Discrepancies were discussed and resolved by consensus. The literature systematic search was undertaken using MEDLINE (PubMed), Embase, and Scopus (9 March 2021) with the terms ('microRNA' OR 'miRNA') AND ('metastasis' OR 'invasiveness') AND ('endometrial cancer' OR 'endometrial carcinoma'). Duplicates were deleted. The references of the found studies were reviewed to find other records.

Search strategy and study selection

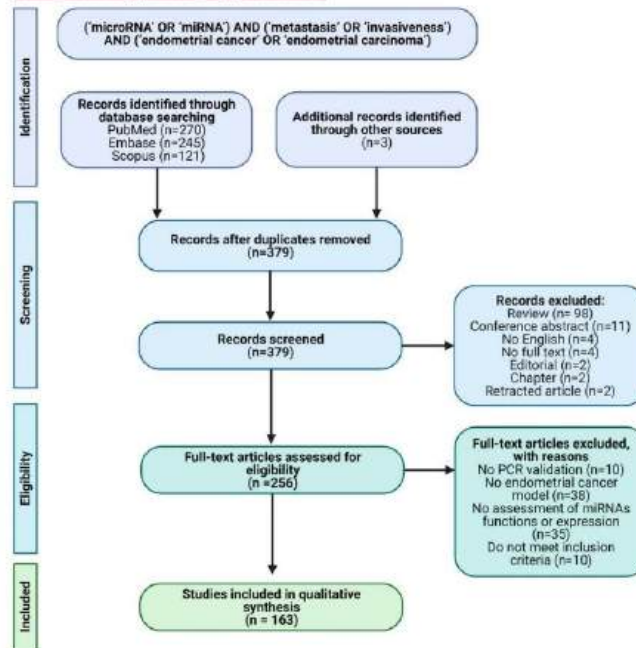


Figure 2. PRISMA flow-chart diagram of study selection. n = number of articles. Figure was created using [Biorender.com](https://www.biorender.com).

2.2. Inclusion and Exclusion Criteria

The articles were included if they answered the PICO question (Table 1). The studies with the assessment of miRNA expression levels and the role of miRNAs in endometrial cancer cell invasion, migration, or outcome were allowed. We assessed only original articles written in English with full-text available. Review articles, chapters, conference abstracts, and retracted articles were excluded. Full texts were assessed for eligibility. We excluded articles that did not meet inclusion criteria, articles with no assessment of miRNAs function or expression in the endometrial cancer model, and no validation with RT-qPCR (real-time quantitative PCR) of miRNA expression.

Table 1. PICO question form.

Domain	Inclusion Criteria
Patients (P)	Patients with endometrial cancer or endometrial cancer cells
Interventions (I)	Differentially expressed miRNAs
Comparators (C)	Non-neoplastic endometrium or cells
Outcomes (O)	Tumor invasiveness or metastasis

2.3. Data Extraction

The data extracted from the revised full-texts were the levels of expression of miRNAs in human tissues, human serum, and cell lines, the role of miRNAs in the regulation of migration, invasion, and EMT in vitro, as well as tumor growth and metastasis in vivo, the outcomes of patients, the overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), FIGO stage, histological grade, myometrial invasion, and lymph node metastases.

3. Results

The detailed results of the literature search are presented in Figure 2. The search strategy provided a total of 270 records in the PubMed database, 245 in the Embase, 121 in the Scopus database, and three records identified through other sources. In total, 379 records remained after the removal of duplicated articles. Out of 379, 123 records were excluded with reasons (no validation by RT-qPCR, no EC model, no assessment of miRNA functions or expression, or records that do not meet inclusion criteria). A total of 256 full-text articles were assessed for eligibility. Finally, data were collected from 163 articles demonstrating the role of miRNA in the regulation of EC invasiveness or metastasis.

3.1. MiRNAs Dysregulation in Endometrial Cancer

Our search identified 115 articles that revealed 106 miRNAs regulating invasiveness and metastasis that are dysregulated in EC, which was confirmed by RT-qPCR (Table 2) [18–132]. In total, 33 miRNAs were confirmed to be dysregulated by at least two studies. Most of them (63) are tumor suppressors and are downregulated in EC, while 38 are oncomiRNAs upregulated in cancer tissue. Five miRNAs have discordant expression levels in different studies.

Table 2. Dysregulation of expression of invasiveness-associated miRNAs in endometrial cancer.

MiRNA	Human Tissue	Cell Line	Circulating miRNA	Ref.	MiRNA	Human Tissue	Cell Line	Circulating miRNA	Ref.
let-7b	↓	↓	n/d	[41]	miR-10b *	↑	n/d	↑	[118,129]
miR-1	↓	↓	n/d	[97]	miR-21	↑	n/d	n/d	[57,75,107]
miR-10b *	↓	n/d	n/d	[38,78]	miR-27	↑	n/d	↑	[60]
miR-20a-5p	↓	↓	n/d	[40]	miR-34a *	↑	n/d	n/d	[61]
miR-20b-5p	↓	↓	n/d	[116]	miR-93	↑	n/d	n/d	[27]
miR-22	↓	↓	n/d	[77,121]	miR-93-5p	↑	↑	n/d	[95,105]
miR-23a	↓	n/d	↓	[118,128]	miR-95	↑	n/d	↑	[110]
miR-26a	n/d	n/d	↓	[42]	miR-99a	n/d	n/d	↑	[76]
miR-29a-5p	↓	↓	n/d	[44]	miR-100	n/d	n/d	↑	[76]
miR-29b	↓	n/d	↓	[24,38,81]	miR-106a	↑	↑	n/d	[73]
miR-30c	↓	n/d	n/d	[96]	miR-107-5p	↑	↑	n/d	[19]
miR-34	↓	n/d	n/d	[57]	miR-130b *	↑	n/d	n/d	[122]
miR-34a *	↓	n/d	n/d	[34]	miR-141	↑	n/d	↑	[35,47,77]
miR-34b	↓	n/d	n/d	[38,39,101]	miR-145	↑	n/d	n/d	[21]
miR-34c	↓	n/d	n/d	[43,123]	miR-146a	↑	n/d	n/d	[114]
miR-99a	↓	n/d	n/d	[51,76]	miR-148b	↑	n/d	n/d	[57]
miR-100	↓	n/d	n/d	[76]	miR-181a	↑	n/d	n/d	[37]
miR-101	↓	↓	n/d	[38,46,56,106,119]	miR-182	↑	n/d	n/d	[30,47,48,77]
miR-124	↓	n/d	n/d	[33,50,99]	miR-183	↑	n/d	n/d	[30,48,62,77,92]
miR-125	↓	n/d	n/d	[57]	miR-192	↑	n/d	n/d	[30]
miR-125b	↓	n/d	n/d	[63,104]	miR-194	↑	n/d	n/d	[30]
miR-126	↓	n/d	n/d	[109,120]	miR-200a	↑	n/d	↑	[35,48,77,102]
miR-130b *	↓	n/d	n/d	[32]	miR-200b	↑	n/d	n/d	[31,77,102]
miR-133a	↓	↓	n/d	[38,97]	miR-200c	↑	↑	n/d	[26,47,48,53,77]
miR-133b	↓	n/d	n/d	[38]	miR-203	↑	n/d	↑	[77]
miR-136	↓	n/d	n/d	[65]	miR-205*	↑	n/d	n/d	[29,30,35,38,47,48,59,68,77,78,89,91]
miR-139-5p	↓	n/d	n/d	[54]	miR-210	↑	n/d	n/d	[100]
miR-142	↓	n/d	n/d	[69]	miR-218 *	↑	n/d	n/d	[30]
miR-143	↓	↓	↓	[22]	miR-222-3p	↑	↑	n/d	[47,52]
miR-144-3p	↓	↓	n/d	[85]	miR-301	↑	n/d	n/d	[57]
miR-152	↓	n/d	n/d	[38]	miR-373	↑	↑	n/d	[49,99]
miR-183-5p	↓	n/d	n/d	[98]	miR-429	↑	n/d	n/d	[77,102]
miR-184	↓	n/d	n/d	[28]	miR-449	↑	n/d	n/d	[30]
miR-195	↓	↓	n/d	[78,108]	miR-449a	n/d	n/d	↑	[77]
miR-196a	↓	n/d	n/d	[23]	miR-486-5p	↑	n/d	↑	[112]

Table 2. *Cont.*

MIRNA	Human Tissue	Cell Line	Circulating miRNA	Ref.	MIRNA	Human Tissue	Cell Line	Circulating miRNA	Ref.
miR-199a-3p	↓	n/d	n/d	[90]	miR-494-3p	↑	n/d	n/d	[117]
miR-199a/b-3p	↓	n/d	n/d	[93]	miR-499	↑	n/d	n/d	[78]
miR-202	↓	n/d	n/d	[25,94]	miR-522	↑	↑	n/d	[132]
miR-204	↓	n/d	n/d	[18,30]	miR-544a	↑	↑	n/d	[111]
miR-205	n/d	n/d	↓	[110,118]	miR-652	↑	n/d	n/d	[72]
miR-206	↓	↓	n/d	[124]	miR-940	↑	↑	n/d	[115]
miR-214-3p	↓	↓	n/d	[36,82]	miR-1202	↑	n/d	n/d	[23]
miR-218	↓	↓	n/d	[125]	miR-1228	n/d	n/d	↑	[77]
miR-219-5p	↓	n/d	n/d	[87]					
miR-301b	n/d	n/d	↓	[77]					
miR-302a-5p	↓	n/d	n/d	[126]					
miR-302c-3p	↓	n/d	n/d	[67]					
miR-320a	↓	n/d	n/d	[103]					
miR-326	↓	↓	n/d	[55]					
miR-340-5p	↓	n/d	n/d	[103]					
miR-361	↓	↓	n/d	[41]					
miR-363	↓	↓	n/d	[83]					
miR-365	↓	↓	n/d	[80]					
miR-367-3p	↓	n/d	n/d	[126]					
miR-372	↓	n/d	n/d	[130]					
miR-381	↓	↓	n/d	[79]					
miR-424	↓	↓	n/d	[34,58,66]					
miR-449a	↓	n/d	n/d	[127]					
miR-490-3p	↓	n/d	n/d	[64,70]					
miR-499a	↓	↓	n/d	[45]					
miR-505	↓	n/d	n/d	[131]					
miR-513	↓	n/d	n/d	[34]					
miR-543	↓	↓	n/d	[20]					
miR-548c	↓	n/d	n/d	[71]					
miR-589-5p	↓	n/d	n/d	[86]					
miR-646	↓	↓	n/d	[113]					
miR-873	↓	↓	n/d	[84]					
miR-1271-5p	↓	↓	n/d	[74,88]					

↓—downregulated in endometrial cancer compared to normal cells, ↑—upregulated in endometrial cancer compared to normal cells, n/d—no data, *—inconsistent data of miRNAs expression.

3.2. MiRNAs Regulating Endometrial Cancer (EC) Invasiveness and Metastasis

Further, we collected data from articles investigating the role of miRNAs in the regulation of EC invasiveness and metastasis. We identified 132 articles demonstrating the role of 97 miRNAs in the regulation of migration, invasiveness, and EMT of endometrial cancer cell lines in vitro [18–28,30–34,36,39–46,49–56,58,62–74,79,80,82,83,85–88,91–98,100–103,105–109,111–117,119,121–131,133–173]. From them, 69 miRNAs act as tumor-suppressor miRNAs and 26 are oncomiRNAs, and two miRNAs (miR-130b and miR-200c) have an unclear role due to inconsistent data (Figure 3).

Included studies involved established EC cell lines, including Ishikawa, HEC-1A, HEC-1B, HHUA, AN3CA, ECC-1, RL-95-2, KLE, SPAC-1-L, HEC-50, HOUA-I, and JEC cell line (EC cell lines have been reviewed by Van Nyen et al. [174]). Transient upregulation of a given miRNA with synthetic miRNA or downregulation with complementary anti-miRNA revealed regulation of tumor cell migration and invasiveness in vitro assays by 97 miRNAs. Further, luciferase reporter assays confirmed direct binding of 102 targets by miRNAs regulating invasiveness of EC cells creating a complex regulatory network. Tumor-suppressor miRNAs that are downregulated in EC were identified to bind 77 targets, including some of the well-known oncogenes. OncomiRNAs were identified to promote EC cell migration and invasiveness by binding 25 targets.

Moreover, 35 studies investigated the role of miRNAs in the regulation of tumor growth and EC metastasis in vivo in murine models [18,19,24,36,41,42,44,45,49,51–53,56,62,69,70,72,73,92,93,101,111,117,119,122,126,128,136,137,144,145,151,157,160,166]. Eight miRNAs were identified as oncomiRNAs in vivo (miR-106a, miR-107-5p, miR-130b, miR-183, miR-222-3p, miR-494-3p, miR-544a, and miR-652) and 27 as tumor suppressor miRNAs (miR-23a, miR-23b, miR-26a, miR-29a-5p, miR-29b, miR-34a, miR-34b, miR-99a, miR-101, miR-129, miR-142, miR-148b, miR-194, miR-199a/b-5p, miR-200c, miR-204, miR-214-3p, miR-302a-5p, miR-326, miR-361, miR-367-3p, miR-372, miR-449a, miR-490-3p, miR-499a,

miR-505, and miR-1827). All but miR-148b and miR-652 were found to regulate primary tumor growth. Moreover, miR-29b, miR-148b, miR-194, miR-199a/b-5p and miR-214-3p were identified to suppress tumor metastasis while miR-652 were found to promote this process. Most of the studies used xenograft assays with human HEC-1B or Ishikawa EC cell lines in immunocompromised mice (Table 3).

The regulation of invasiveness by miRNAs

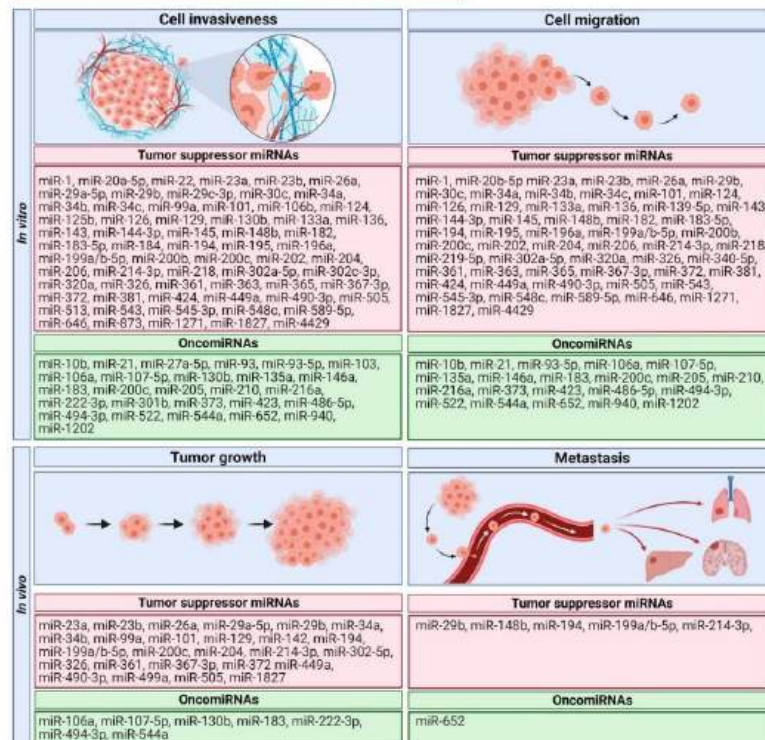


Figure 3. miRNAs regulating cell invasiveness and cell migration in vitro as well as tumor growth, and metastasis in vivo. Figure was created using [Biorender.com](#).

Table 3. The role of miRNAs in invasion and metastasis in vitro and in vivo.

miRNA	Target ¹	Migration	Invasion	EMT	Tumor Growth In Vivo	Metastasis In Vivo	Ref.
miR-1	PDE7A	↓	↓	n/d	n/d	n/d	[97]
miR-20a-5p	STAT3	n/d	↓	↓	n/d	n/d	[40]
miR-20b-5p	H19	↓	n/d	n/d	n/d	n/d	[116]
miR-22	ERα	n/d	↓	n/d	n/d	n/d	[121,156]
miR-23a	SIX1	↓	↓	n/d	↓	n/d	[128]
miR-23b	MACC1	↓	↓	n/d	↓	n/d	[137]
miR-26a	EZH2	↓	↓	↓	↓	n/d	[42]
miR-29a-5p	TPX2	n/d	↓	n/d	↓	n/d	[44]
miR-29b	VEGFA, PTEN	↓	↓	n/d	↓	↓	[24,150]

Table 3. *Cont.*

MiRNA	Target ¹	Migration	Invasion	EMT	Tumor Growth In Vivo	Metastasis In Vivo	Ref.
miR-29c-3p	KDM5B	n/d	↓	n/d	n/d	n/d	[154]
miR-30c	MTA-1	↓	↓	n/d	n/d	n/d	[96,173]
miR-34a	Notch1, L1CAM, MMSET	↓	↓	↓	↓	n/d	[34,166,170]
miR-34b	n/d	↓	↓	n/d	↓	n/d	[39,101]
miR-34c	IL-6R	↓	↓	n/d	n/d	n/d	[43,123]
miR-99a	AKT1, mTOR	n/d	↓	n/d	↓	n/d	[51]
	COX-2, EZH2,						
miR-101	MCL-1, FOS, mTOR	↓	↓	↓	↓	n/d	[46,56,106, 119]
miR-106b	TWIST1	n/d	↓	↓	n/d	n/d	[140]
miR-124	STAT3, IQGAP1, ITGB3	↓	↓	↓	n/d	n/d	[33,50,167]
miR-125b	ERBB2	n/d	↓	n/d	n/d	n/d	[63,161]
miR-126	IRS1	↓	↓	n/d	n/d	n/d	[109]
miR-129	GSK-3β	↓	↓	n/d	↓	n/d	[136]
miR-130b*	ZEB1	n/d	↓	↓	n/d	n/d	[32]
miR-133a	PDE7A	↓	↓	n/d	n/d	n/d	[97]
miR-136	HMGA2	↓	↓	n/d	n/d	n/d	[65]
miR-139-5p	HOXA10	↓	n/d	n/d	n/d	n/d	[54]
miR-142	CCND1	n/d	n/d	n/d	↓	n/d	[69]
miR-143	MAPK1	↓	↓	n/d	n/d	n/d	[22]
miR-144-3p	EZH2	↓	↓	n/d	n/d	n/d	[85]
miR-145	SOX11	↓	↓	n/d	n/d	n/d	[21]
miR-148b	DNMT1	↓	↓	n/d	n/d	↓	[151]
miR-182	FOXO1	↓	↓	n/d	n/d	n/d	[142,163]
miR-183-5p	Ezrin	↓	↓	↓	n/d	n/d	[98]
miR-184	CDC25A	n/d	↓	n/d	n/d	n/d	[28]
miR-194	BMI-1, Sox3	↓	↓	↓	↓	↓	[141,145]
miR-195	SOX4, GPER	↓	↓	↓	n/d	n/d	[108,139]
miR-196a	n/d	↓	↓	n/d	n/d	n/d	[23]
miR-199a/b-5p	FAM83B	↓	↓	↓	↓	↓	[93]
	TIMP2, PTEN,						
miR-200b	ZEB2	↓	↓	n/d	n/d	n/d	[31,102,133]
	TUBB3, BMI-1,						
miR-200c *	MSN, FN1, TrkB, ARHGAP19, LEPR	↓	↓	↓	↓	n/d	[138,146,152]
miR-202	FGF2, TIMD4	↓	↓	↓	n/d	n/d	[25,94]
miR-204	TrkB, FOXC1	↓	↓	n/d	↓	n/d	[18,30]
miR-206	HDAC6, ERα	↓	↓	n/d	n/d	n/d	[124,168]
miR-214-3p	TWIST1, HMGA1	↓	↓	↓	↓	↓	[36,82]
miR-218	ADD2	↓	↓	n/d	n/d	n/d	[125]
miR-219-5p	COX-2	↓	n/d	n/d	n/d	n/d	[87]
miR-302a-5p	HMGA2	↓	↓	n/d	↓	n/d	[126]
miR-302c-3p	ZFX, YKL-40	n/d	↓	n/d	n/d	n/d	[67]
miR-320a	eIF4E	↓	↓	↓	n/d	n/d	[103]
miR-326	TWIST1, GPR91	↓	↓	↓	↓	n/d	[55,144]
miR-340-5p	eIF4E	↓	n/d	↓	n/d	n/d	[103]
miR-361	TWIST, STAT3	↓	↓	n/d	↓	n/d	[41,169]
miR-363	SOX4	↓	↓	n/d	n/d	n/d	[83]
miR-365	EZH2, FOS	↓	↓	↓	n/d	n/d	[80]
miR-367-3p	HMGA2	↓	↓	n/d	↓	n/d	[126]
miR-372	RhoC	↓	↓	n/d	↓	n/d	[130]

Table 3. *Cont.*

MiRNA	Target ¹	Migration	Invasion	EMT	Tumor Growth In Vivo	Metastasis In Vivo	Ref.
miR-381	IGF-1R, E2F3	↓	↓	n/d	n/d	n/d	[79,148]
miR-424	IGF-1R, E2F6, MMSET	↓	↓	↓	n/d	n/d	[34,58,66]
miR-449a	NDRG1, SRC, MET	↓	↓	n/d	↓	n/d	[127,143,147, 160,172]
miR-490-3p	TGFα, SP1	↓	↓	n/d	↓	n/d	[64,70]
miR-499a	VAV3	n/d	n/d	n/d	↓	n/d	[45]
miR-505	TGFα	↓	↓	n/d	↓	n/d	[131]
miR-513	MMSET	n/d	↓	↓	n/d	n/d	[34]
miR-543	FAK, TWIST1	↓	↓	n/d	n/d	n/d	[20]
miR-545-3p	VEGF	↓	↓	n/d	n/d	n/d	[165]
miR-548c	TWIST	↓	↓	n/d	n/d	n/d	[71]
miR-589-5p	TRIP6	↓	↓	n/d	n/d	n/d	[86]
miR-646	NPM1	↓	↓	n/d	n/d	n/d	[113,155]
miR-873	HDGF	n/d	↓	n/d	n/d	n/d	[84]
miR-1271	LDHA, CTNND1	↓	↓	n/d	n/d	n/d	[74,88]
miR-1827	TPPP3	↓	↓	n/d	↓	n/d	[157]
miR-4429	SNHG12	↓	↓	n/d	n/d	n/d	[134]
miR-10b	HOXB3	↑	↑	n/d	n/d	n/d	[129]
miR-21	n/d	↑	↑	n/d	n/d	n/d	[107]
miR-27a-5p	SMAD4	n/d	↑	n/d	n/d	n/d	[135]
miR-93	FOXA1	n/d	↑	↑	n/d	n/d	[27]
miR-93-5p	ZBTB7A	↑	↑	n/d	n/d	n/d	[95,105]
miR-103	TIMP3	n/d	↑	n/d	n/d	n/d	[164]
miR-106a	BCL2L1	↑	↑	n/d	↑	n/d	[73]
miR-107-5p	ERα	↑	↑	n/d	↑	n/d	[19]
miR-130b *	DICER1, BHLHE40/41	n/d	↑	↑	↑	n/d	[122,171]
miR-135a	PTEN	↑	↑	n/d	n/d	n/d	[159]
miR-146a	n/d	↑	↑	n/d	n/d	n/d	[114]
miR-183	CPEB1, MMP-9, FOXO1	↑	↑	↑	↑	n/d	[62,92,142]
miR-200a	FOXA2, PTEN	n/d	n/d	↑	n/d	n/d	[102,158]
miR-200c *	PTENP1, PTEN, MALAT1	↑	↑	↑	n/d	n/d	[26,53]
miR-205	ESRRG, PTEN	↑	↑	↑	n/d	n/d	[68,91,149]
miR-210	NFIX	↑	↑	n/d	n/d	n/d	[100]
miR-216a	PD-L1	↑	↑	n/d	n/d	n/d	[162]
miR-222-3p	ERα	n/d	↑	n/d	↑	n/d	[52]
miR-301b	BHLHE40/41	n/d	↑	↑	n/d	n/d	[171]
miR-373	LATS2	↑	↑	n/d	n/d	n/d	[49]
miR-423	n/d	↑	↑	n/d	n/d	n/d	[153]
miR-486-5p	MARK1	↑	↑	n/d	n/d	n/d	[112]
miR-494-3p	PTEN	↑	↑	n/d	↑	n/d	[117]
miR-522	MAOB	↑	↑	n/d	n/d	n/d	[132]
miR-544a	RECK	↑	↑	n/d	↑	n/d	[111]
miR-652	RORA	↑	↑	n/d	n/d	↑	[72]
miR-940	MRV11	↑	↑	n/d	n/d	n/d	[115]
miR-1202	n/d	↑	↑	n/d	n/d	n/d	[23]

¹—direct binding confirmed by luciferase assay, ↓—downregulated in endometrial cancer compared to normal cells, ↑—upregulated in endometrial cancer compared to normal cells, n/d—no data, EMT—epithelial-mesenchymal transition. *—inconsistent data of miRNAs role.

We categorized miRNAs' targets into 15 groups based on their biological function in cancer (Figure 4). Tumor suppressor miRNAs that inhibit cell invasiveness and migration and were downregulated in EC (Table 2) were found to target regulators of EMT (5 targets, 12 miRNAs), growth factor signaling (14 targets, 18 miRNAs), cell cycle (9 targets, 10 miR-

NAs), cytoskeleton (10 targets, 10 miRNAs), hormone signaling (3 targets, 4 miRNAs), phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling (3 targets, 5 miRNAs), epigenetic regulators (10 targets, 16 miRNAs). Moreover, tumor suppressor miRNAs were identified to target regulators of signaling pathways (7 targets, 7 miRNAs), extracellular matrix (ECM) remodeling (2 targets, 2 miRNAs), adhesion molecules (3 targets, 3 miRNAs), angiogenesis pathway (2 targets, 3 miRNAs), Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathway (1 target, 3 miRNAs), apoptosis (2 targets, 2 miRNAs), cyclic adenosine monophosphate (cAMP) signaling (1 target, 2 miRNAs), and various other miRNAs (7 targets, 9 miRNAs). On the contrary, oncomiRNAs that were upregulated in EC target regulators of EMT (4 targets, 5 miRNAs), hormone signaling (3 targets, 4 miRNAs), ECM remodeling (3 targets, 3 miRNAs), PI3K/AKT signaling (2 targets, 6 miRNAs), cell cycle (2 targets, 2 miRNAs), cytoskeleton regulators (1 target, 1 miRNA), apoptosis (1 target, 1 miRNA), and others (8 targets, 8 miRNAs).

Pathways regulated by invasion-associated miRNA

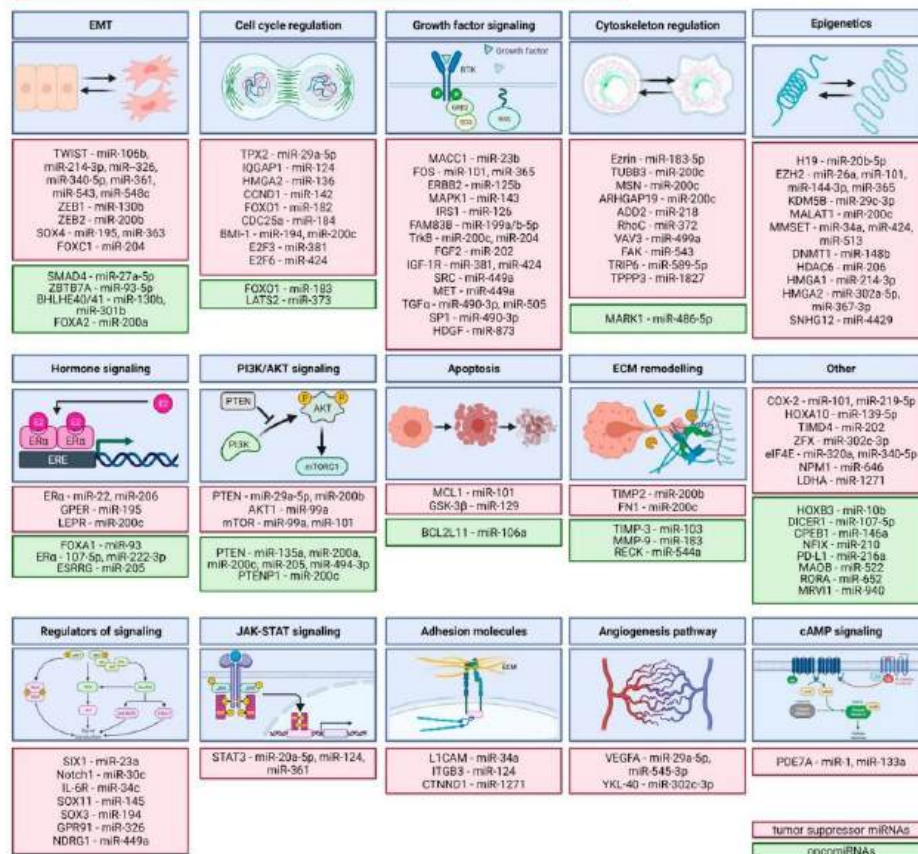


Figure 4. Direct targets of invasion-regulating miRNAs. cAMP—Cyclic Adenosine Monophosphate, EMT—epithelial-mesenchymal transition, ECM—extracellular matrix, JAK-STAT—Janus Kinase/Signal Transducers and Activators of Transcription, PI3K/AKT—Phosphatidylinositol 3-Kinase/Protein Kinase B. Figure was created using [Biorender.com](https://www.biorender.com/).

3.3. Relationship between miRNA Expression and Clinical Parameters

Further, we collected data from articles investigating the association between the expression of invasion-related miRNAs in tumor tissue and clinical parameters, including OS, DFS, PFS, FIGO stage, histological grade, myometrial invasion, and lymph node metastases. We identified 51 articles that correlated upregulated expression of 25 miRNAs and downregulated expression of 41 miRNAs with at least one clinical parameter (Table 4) [18,19,24,25,28,29,32,34,37,38,41,44,49,51,52,56–58,60,69–71,76–79,81,84,95,99,100,108,110,111,115,117,120,122,130–132,147,154,160,175–181].

Table 4. The correlation of miRNA expression and clinical parameters.

MiRNA	Expression	OS	DFS or PFS	FIGO Stage	Histological Grade	Myometrial Invasion	Lymph Node Metastases	Ref.
miR-10a	Upregulation	n/d	n/d	n/d	n/d	n/d	↑	[29]
miR-27a	Upregulation	n/d	n/d	↑	n/d	n/d	n/d	[60]
miR-30c-3p	Upregulation	n/d	n/d	n/d	n/d	n/d	↑a	[178]
miR-34a *	Upregulation	n/d	n/d	n/d	n/d	n/d	↑	[29]
miR-93-5p	Upregulation	↓	n/d	↑	n/d	n/d	↑	[95]
miR-95	Upregulation	↓	n/d	↑	n/d	n/d	↑	[29,110]
miR-107-5p	Upregulation	n/d	n/d	↑	n/d	↑	↑	[19]
miR-130b	Upregulation	↑	n/d	↑	n/d	↑	n/d	[32,122]
miR-181a	Upregulation	n/d	n/d	↑	n/d	n/d	n/d	[37]
miR-192	Upregulation	n/d	n/d	n/d	n/d	n/d	↑a	[178]
miR-194	Upregulation	n/d	n/d	n/d	n/d	n/d	↑a	[178]
miR-199a	Upregulation	↑	↑	n/d	n/d	n/d	n/d	[177]
miR-200a	Upregulation	n/d	n/d	↑	n/d	n/d	n/d	[29]
miR-203	Upregulation	n/d	n/d	n/d	n/d	n/d	↑a	[178]
miR-205	Upregulation	↓	n/d	n/d	n/d	n/d	n/d	[29]
miR-210	Upregulation	n/d	n/d	↑	↑	n/d	↑	[100,178]
miR-222-3p	Upregulation	n/d	n/d	↑	↑	n/d	↑	[52]
miR-301	Upregulation	↓	n/d	↑	↑	↑	↑	[57,178]
miR-345	Upregulation	n/d	n/d	n/d	n/d	n/d	↑a	[178]
miR-373	Upregulation	↓	n/d	↑	↑	↑	↑	[49,99]
miR-494-3p	Upregulation	↓	n/d	n/d	n/d	n/d	n/d	[117]
miR-499	Upregulation	n/d	n/d	↑	↑	n/d	n/d	[78]
miR-522	Upregulation	↓	n/d	n/d	↑	n/d	n/d	[132]
miR-544a	Upregulation	↓	n/d	n/d	n/d	n/d	n/d	[111]
miR-940	Upregulation	↓	n/d	n/d	↑	n/d	n/d	[115]
miR-10b	Downregulation	↓	n/d	n/d	n/d	n/d	n/d	[38]
miR-29b	Downregulation	↓	↓	↑	n/d	n/d	↑	[24,38,81]
miR-29a-5p	Downregulation	n/d	n/d	↑	↑	↑	↑	[44]
miR-29c	Downregulation	↓	n/d	n/d	n/d	n/d	n/d	[154]
miR-34a *	Downregulation	↓	n/d	↑	↑	↑	↑	[34,175]
miR-34b-5p	Downregulation	n/d	n/d	n/d	n/d	n/d	↑	[176]
miR-34c-3p	Downregulation	n/d	n/d	n/d	n/d	n/d	↑	[176]
miR-34c-5p	Downregulation	n/d	n/d	n/d	n/d	n/d	↑	[176]
miR-100	Downregulation	↓	n/d	n/d	n/d	n/d	n/d	[76]
miR-101	Downregulation	↓	n/d	n/d	↑	↑	↑	[38,56,175]
miR-124	Downregulation	↓	n/d	↑	↑	↑	↑	[99]
miR-125b	Downregulation	n/d	n/d	n/d	↑	↑	n/d	[175]
miR-126	Downregulation	n/d	n/d	↑	↑	n/d	n/d	[120]
miR-139-5p	Downregulation	↓	n/d	n/d	n/d	n/d	n/d	[38]
miR-141	Downregulation	↓	↓	n/d	n/d	n/d	n/d	[77]
miR-142	Downregulation	↓	n/d	n/d	↑	↑	n/d	[69,175]
miR-152	Downregulation	↓	n/d	n/d	n/d	n/d	n/d	[58]
miR-184	Downregulation	↓	n/d	n/d	n/d	n/d	↑	[28,176]
miR-194	Downregulation	↓	n/d	↑	n/d	n/d	n/d	[180]
miR-195	Downregulation	n/d	n/d	↑	n/d	n/d	↑a	[108]
miR-202	Downregulation	↓	n/d	↑	n/d	n/d	↑	[25]
miR-203	Downregulation	↓	↓	n/d	n/d	n/d	n/d	[77]
miR-204	Downregulation	n/d	n/d	↑	n/d	n/d	↑	[18]
miR-301b	Downregulation	↓	↓	n/d	n/d	n/d	n/d	[77]
miR-361	Downregulation	n/d	n/d	n/d	↑	n/d	n/d	[41]
miR-372	Downregulation	n/d	n/d	n/d	n/d	n/d	↑	[130]
miR-375	Downregulation	n/d	n/d	n/d	n/d	n/d	↑	[176]
miR-381	Downregulation	n/d	n/d	↑	n/d	↑	↑	[79]

Table 4. *Cont.*

MiRNA	Expression	OS	DFS or PFS	FIGO Stage	Histological Grade	Myometrial Invasion	Lymph Node Metastases	Ref.
miR-424	Downregulation	↓	n/d	↑	↑	n/d	↑	[34,58]
miR-429	Downregulation	n/d	↓	n/d	n/d	n/d	n/d	[77]
miR-449a	Downregulation	↓	n/d	↑	↑	n/d	↑	[147,160]
miR-455-5p	Downregulation	↓	n/d	n/d	n/d	n/d	n/d	[38]
miR-490-3p	Downregulation	n/d	n/d	↑	↑	↑	↑	[70]
miR-497	Downregulation	n/d	n/d	↑	↑	n/d	n/d	[179]
miR-505	Downregulation	n/d	n/d	↑	n/d	n/d	↑	[131]
miR-513	Downregulation	↓	n/d	n/d	n/d	n/d	n/d	[34]
miR-548c	Downregulation	↓	n/d	n/d	n/d	n/d	n/d	[71]
miR-873	Downregulation	n/d	n/d	↑	↑	n/d	n/d	[84]
miR-99a	Downregulation	n/d	n/d	↑	↑	n/d	n/d	[51]
miR-200 family	Downregulation	n/d	n/d	n/d	↑	n/d	n/d	[181]
miR-1228	Downregulation	n/d	↓	n/d	n/d	n/d	n/d	[77]

↓—decreased, ↑—increased, n/d—no data, a—lympho-vascular invasion, *—inconsistent data of miRNAs expression and clinical parameters, OS—overall survival, DFS—disease-free survival, PFS—progression-free survival, FIGO stage—The International Federation of Gynecology and Obstetrics staging classification.

Increased levels of nine miRNAs, miR-93-5p, miR-95, miR-205, miR-301, miR-373, miR-494-3p, miR-522, miR-544a and miR-940 in tumor tissue as well as decreased levels of 22 miRNAs, miR-10b, miR-29b, miR-29c, miR-34a, miR-100, miR-101, miR-124, miR-139-5p, miR-141, miR-142, miR-152, miR-184, miR-194, miR-202, miR-203, miR-301b, miR-424, miR-449a, miR-455-5p, miR-497, miR-513, and miR-548c were correlated with a shorter OS (Table 4). On the contrary, upregulated expression of miR-130b and miR-199a was associated with a longer OS in ECs. Upregulation of four miRNAs, miR-107-5p, miR-130b, miR-301, miR-373 as well as downregulation of eight miRNAs, miR-29a-5p, miR-34a, miR-101, miR-124, miR-125b, miR-142, miR-381, miR-490-3p, were associated with the invasion of the myometrium. We identified nine upregulated miRNAs and 17 downregulated miRNAs that correlated with lymph node metastases. Moreover, an increase of miR-30c-3p, miR-192, miR-194, miR-203, miR-345 and a decrease of miR-195 were associated with lymphovascular invasion (Table 4).

4. Discussion

Tumor expansion and progression are enabled by coordinated dysregulation of various mechanisms. The process of tumor invasion and metastasis is composed of several steps, including primary tumor growth, migration, local invasion, intravasation, survival in the circulation, extravasation, and pre-metastatic niche formation. All of these steps are regulated by a variety of different miRNAs [12].

In this work, we provide a comprehensive overview of miRNAs that are dysregulated in EC and contribute to tumor progression. We identified 106 dysregulated miRNAs through a systematic literature review. Small RNA-seq analysis revealed that 239 out of 359 detected miRNAs are dysregulated in EC compared to healthy adjacent endometrial tissue [182]. Further, analysis of miRNA-seq data from The Cancer Genome Atlas (TCGA) database expanded the list of dysregulated miRNAs to 531 [179]. Previous systematic reviews identified, respectively, 106 miRNAs [183], 261 miRNAs [184], 310 miRNAs [185] dysregulated in ECs. However, these studies included also many miRNAs detected by high throughput methods, including microarrays and small RNA-seq, without confirmation by the RT-qPCR method that is a gold standard for miRNAs analysis [186]. Moreover, in contrast to previous reviews, we included only miRNAs with a confirmed role in the regulation of EC cell migration, invasiveness, and metastasis in vitro and/or in vivo.

4.1. Regulatory Network of Invasion-Associated miRNAs

MiRNAs orchestrate tumor invasion and metastasis by targeting various mRNAs. Complex regulation of multiple signaling pathways, including PI3K/AKT [187], and cellular processes, including EMT and cytoskeleton remodeling [188], by miRNAs enable the control of the invasiveness and metastasis of cancer cells. We classified targets of miRNAs into 15 categories based on their function. Notably, multiple miRNAs target

regulators of multiple cellular processes and create a complex network of interactions. Hence, they have been assigned to a given category based on their best-described function in the EC (Figure 4).

4.1.1. Epithelial–Mesenchymal Transition (EMT)

One of the most important processes in the myometrial invasion of EC is an EMT [188]. EMT enables the acquisition of the mesenchymal-like features from the epithelial cells and occurs physiologically during embryonic development and tissue regeneration [189]. EMT is characterized by the loss of adherent junctions, downregulation of epithelial markers (cytokeratins and E-cadherin) but upregulation of mesenchymal markers, including N-cadherin, vimentin, and fibronectin [12,189]. EMT is regulated by multiple signaling pathways, including Transforming Growth Factor β (TGF- β)/SMAD signaling, Wnt pathway, and PI3K/AKT, and is orchestrated by Snail, Slug, Smug, SRY-Box Transcription Factor 1 (SOX1), Forkhead Box C1 (FOXC1), Zinc Finger E-Box Binding Homeobox 1/Zinc Finger E-Box Binding Homeobox 2 (ZEB1/ZEB2), and Twist-related protein 1/Twist-related protein 2 (TWIST1/TWIST2) transcription factors [190,191].

We identified 20 suppressors of this process in EC cells (miR-20a-5p, miR-26a, miR-34a, miR-101, miR-106b, miR-124, miR-130b, miR-183-5p, miR-194, miR-195, miR-199a/b-5p, miR-200c, miR-202, miR-214-3p, miR-320a, miR-326, miR-340-5p, miR-365, miR-424, and miR-513) and seven oncomiRNAs that stimulate cells transition (miR-93, miR-130b, miR-183, miR-200a, miR-200c, miR-205, and miR-301b) (Table 3). Moreover, we identified microRNAs that target nine regulators of EMT, including TWIST, ZEB1/ZEB2, SRY-Box Transcription Factor 4 (SOX4), FOXC1, SMAD4, Zinc Finger and BTB Domain Containing 7A (ZBTB7A), Basic helix-loop-helix transcription factors e40/41 (BHLHE40/41), and Forkhead Box A2 (FOXA2). TWIST, a crucial transcription factor regulating EMT, was identified as a target of several miRNAs in this study (miR-106b, miR-214-3p, miR-326, miR-340-5p, miR-361, miR-543, and miR-548c). Similarly, ZEB1 and ZEB2 transcription factors were identified to be targets of miR-130b and miR-200b, respectively (Figure 4).

4.1.2. Cell Cycle

The cell cycle is regulated by several protein checkpoints including cyclins, cyclin-dependent kinases (CDKs), and their inhibitors (CKI), that may be inactivated or mutated in cancer cells that lead to uncontrolled proliferation and thus to the progression of cancer [192,193]. There are several I–III phases clinical trials of the application of CKI in EC [194]. MiRNAs are described to control the expression of genes related to the cell cycle [195]. In this systematic review, we summarize tumor suppressor miRNAs (miR-29a-5p, miR-124, miR-136, miR-142, miR-182, miR-184, miR-194, miR-200c, miR-381, miR-424) and their targets (TPX2 Microtubule Nucleation Factor (TPX2), IQ Motif Containing GTPase Activating Protein 1 (IQGAP1), High Mobility Group AT-Hook 2 (HMGA2), C-terminal Cyclin D1 (CCND1), Forkhead Box O1 (FOXO1), Cell division cycle 25a (CDC25a), B-lymphoma Moloney murine leukemia virus insertion region-1 (BMI-1), Transcription Factor 3 (E2F3), and E2F Transcription Factor 6 (E2F6)) and oncomiRNAs (miR-183 and miR-373) and their targets (FOXO1 and Large Tumor Suppressor Kinase 2 (LATS2)) involved in cell-cycle regulation. HMGA2 is an oncogene upregulated in several cancers that stimulates proliferation and invasion. HMGA2 is targeted in ECs by tumor suppressor miR-136 [65]. CCND1 activates cyclin-dependent kinase (CDK)4/6 and thus stimulates proliferation, migration, and invasion of cells [196]. In this study, CCND1 was found to be targeted by miR-142 [69].

4.1.3. Growth Factors and Regulators of Signaling

Overactivation of growth factors signaling is crucial in tumor development and progression. Thus, inhibitors of signaling pathways are currently under investigation in EC patients [197]. In this study, we identified multiple growth factors and regulators of signaling that promote EC cell invasion and were targets of different miRNAs. MiRNAs (miR-23b, miR-101, miR-125b, miR-126, miR-143, miR-199a/b-5p, miR-200c, miR-202,

miR-204, miR-365, miR-381, miR-424, miR-449a, miR-490-3p, miR-505, and miR-873) that target growth factors (Metastasis-associated in colon cancer protein 1 (MACC1), Fos Proto-Oncogene (FOS), Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2), Mitogen-Activated Protein Kinase (MAPK1), Insulin Receptor Substrate 1 (IRS1), Family With Sequence Similarity 83 Member B (FAM83B), Tropomyosin receptor kinase B (TrkB), Fibroblast growth factor 2 (FGF2), Insulin-like growth factor 1 (IGF-1R), SRC Proto-Oncogene (SRC), MET Proto-Oncogene (MET), Transforming Growth Factor Alpha (TGF α), Sp1 Transcription Factor (SP1), and Hepatoma-derived Growth Factor (HDGF)) decrease migration, invasion, and EMT in vitro and tumor growth and metastases in vivo, as well as correlate with EC stage, grade, and patients outcome. TGF α promotes the progression of cancer by increasing proliferation and differentiation. In our study, miR-490-3p and miR-505 target TGF α and act as tumor suppressor miRNAs [27,70].

Additionally, several tumor-suppressing miRNAs (miR-23a, miR-30c, miR-34c, miR-145, miR-194, miR-326, and miR-449a) target regulators of signaling (SIX Homeobox 1 (SIX1), Notch homolog 1 (Notch1), Interleukin 6 Receptor (IL-6R), SRY-Box Transcription Factor 11 (SOX11), SRY-Box Transcription Factor 3 (SOX3), G protein-coupled receptor 91 (GPR91), and N-Myc Downstream Regulated 1 (NDRG1)). Notch1 is associated with EMT, metastases, and poor prognosis in different cancers including EC [198,199]. MiR-30c targets Notch1 and decreases migration and invasion, however, it is associated with increased lymphovascular invasion in EC patients [96,164,178].

4.1.4. Cytoskeleton Regulation

The polarization of the cytoskeleton and formation of the leading protrusion initiate cell migration [200]. During this process, the cell cytoskeleton undergoes dynamic changes that are regulated by multiple factors interacting with actin microfilaments or tubulin [201]. We identified eight tumor suppressor miRNAs (miR-183-5p, miR-200c, miR-218, miR-372, miR-499a, miR-543, miR-589-5p, and miR-1827) that target regulators of the cytoskeleton (Ezrin, Tubulin Beta 3 Class III (TUBB3), moesin (MSN), Rho GTPase activating protein 19 (ARHGAP19), adducin 2 (ADD2), Ras Homolog Family Member C (RhoC), Vav Guanine Nucleotide Exchange Factor 3 (VAV3), Focal adhesion kinase (FAK), Thyroid Hormone Receptor Interactor 6 (TRIP6), Tubulin Polymerization Promoting Protein Family Member 3 (TPPP3)) and inhibits EC cell migration and invasiveness. Ezrin, which overexpression in EC is related to poor prognosis [202], is targeted by downregulated miR-183-5p. Moreover, a well-described tumor suppressor miR-200c [203] targets TUBB3, MSN, and ARHGAP19, which regulate multiple cytoskeletal-related events. On the contrary, miR-486-5p was found to promote EC cell invasiveness by targeting Microtubule affinity regulating kinase 1 (MARK1) [112], a tumor suppressor in several types of cancer [112,204,205].

4.1.5. Epigenetics

Gene expression is modified by multiple epigenetic mechanisms, including DNA methylation, histone acetylation and methylation, and non-coding RNAs. Dysregulation of these mechanisms in cancer affects a variety of cellular responses [206]. We selected 16 tumor suppressor miRNAs (miR-20b, miR-26a, miR-29c-3p, miR-34a, miR-101, miR-144-3p, miR-148b, miR-200c, miR-206, miR-214-3p, miR-302a-5p, miR-365, miR-367-3p, miR-424, miR-513, miR-4429) that targeted 10 regulators, including Enhancer of Zeste Homolog 2 (EZH2), Lysine Demethylase 5B (KDM5B), Multiple Myeloma SET Domain (MMSET), Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1), DNA methyltransferase 1 (DNMT1), Histone Deacetylase 6 (HDAC6), High Mobility Group AT-Hook 1 (HMGA1), High Mobility Group AT-Hook 2 (HMGA2), Small Nucleolar RNA Host Gene 12 (SNHG12), and H19 Imprinted Maternally Expressed Transcript (H19). EZH2 is the enzymatic catalytic subunit of the polycomb-repressive complex 2 (PRC2) that represses transcription of multiple genes, including tumor-suppressors [207]. It is overexpressed in many types of cancer, including EC [208], and is correlated with decreased

DPS and OS [209]. EZH2 is targeted by miR-26a and miR-101, which are downregulated in EC [42,46].

Importantly, epigenetic alterations affect miRNAs profile in EC [185]. It was found that loci of genes coding oncomiRNAs miR-130a/b, miR-182, miR-200b, miR-208a, miR-222, miR-625 are hypo-methylated in EC while genes of tumor-suppressor miRNAs miR-34b, miR-124a-1, miR-124a-2, miR-124a-3, miR-129-2, miR-137, miR-152, miR-638, miR-663 are hyper-methylated [185].

4.1.6. Hormone Signaling

Dysregulation of hormone signaling is one of the most important factors in EC development. From them, estrogen seems to be crucial in EC pathogenesis. Estrogen binds to estrogen receptors (ER) or G protein-coupled estrogen receptor 1 (GPER1) to regulate gene transcription and to promote cancer cell pathways [210–212]. Estrogen signaling and miRNAs are in complex interaction since estrogen modulates miRNAs expression but also miRNAs target their receptors [213]. In this study, we identified miRNAs that suppress EC progression via binding to estrogen receptors. MiR-22 and miR-206 target ER what inhibits EC cell invasion and migration [121,156,168]. Moreover, miR-195 targets GPER1 and inhibits EC migration, invasion, and EMT in vitro [139]. On the other hand, miR-107-5p and miR-222-3p targeting ERα and miR-205 targeting Estrogen Related Receptor Gamma (ESRRG) act as oncomiRNAs by enhancing migration, invasion in vitro or/and tumor growth in vivo [19,52,68].

4.1.7. Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K/AKT) Pathways

Estrogen stimulates the PI3K/Akt pathway, one of the most important pathways responsible for EC proliferation, migration, invasion, and EMT [210]. The activation of this oncogenic pathway is regulated by PTEN, a well-known tumor suppressor potentially downregulated in EC [214]. Our study highlights oncomiRNAs (miR-135a, miR-200a, miR-200c, miR-205, and miR-494-3p) and tumor suppressor miRNAs (miR-29a-5p, miR-99a, miR-101, and miR-200b) that target members of this pathway.

4.1.8. Apoptosis

Apoptosis is a process of programmed cell death via the activation of different pathways [215]. Novel therapies targeting apoptosis inhibit B-cell lymphoma-2 (Bcl-2), induced Myeloid Leukemia Cell Differentiation Protein 1 (MCL-1), or target the P53 pathway [216]. In this study, we identified tumor suppressor miRs and oncomiRNAs that target mRNAs of proteins involved in the regulation of apoptosis. Tumor suppressor miR-101 that targets MCL-1, a protein belonging to the Bcl-2 family that inhibits apoptosis, inhibits migration, invasion, and EMT in vitro and tumor growth in vivo, and influences patient survival. Moreover, we recognized invasion-suppressing miR-129 that targets Glycogen synthase kinase-3β (GSK3β), a serine/threonine-protein kinase that inhibits apoptosis via NF-κB activation [217]. MiR-106a targets proapoptotic Bcl-2-like protein 11 (BCL2L1) and acts as oncomiRNA and stimulates migration, invasion in vitro, and tumor growth in vivo [218].

4.1.9. Extracellular Matrix (ECM) Remodeling

Remodeling of ECM is crucial for a cancer cell to initiate an invasion of adjacent tissues. Among multiple factors regulating this process, the most important are Matrix Metalloproteinases (MMPs) and their inhibitors Tissue Inhibitors of Metalloproteinases (TIMPs). MMPs degrade collagen, fibrinogen, fibronectin (FN1), and others and in this way enable tumor cells to invade [12]. In this study, miR-200b targets TIMP-2, miR-200c targets FN1 and both miRNAs act as tumor suppressor miRNAs. On the other hand, miR-103 targets TIMP-3 and stimulates invasion. Moreover, oncomiRNA miR-183 targets MMP-9 and miR-544a targets Reversion Inducing Cysteine Rich Protein with Kazal Motifs (RECK). These results show the complexity of the regulatory processes involved in ECM remodeling.

One target may be regulated by several miRNAs, as well as miRNAs may have a role in the regulation of invasion by different mRNAs [219].

4.1.10. Janus Kinase/Signal Transducers and Activators of Transcription (JAK-STAT) Signaling

JAK-STAT pathway is a known regulator of tumor progression [220]. JAK-STAT pathway is dysregulated in endometrial cancer cells what leads to increased proliferation [221]. In this study, we identified three miRNAs (miR-20a-5p, miR-124, and miR-361) that target STAT3. MiR-20a-5p inhibits invasion and EMT [40]. MiR-124 decreases migration, invasion, and EMT in vitro and is associated with patients' outcomes [50,99]. Conversely, miR-361 inhibits migration and invasion in vitro and tumor growth in vivo, as well as is negatively correlated with histological grade [169].

4.1.11. Adhesion Molecules

Tumor cell migration and invasiveness strictly depend on the cell adhesion molecules, which include cadherins, integrins, selectins, Ig-superfamily Cell Adhesion Molecules (CAMs), and others [12,222,223]. We identified three tumor suppressor miRNAs (miR-34a, miR-124, and miR-1271) that target three adhesion molecules (L1 Cell Adhesion Molecule (L1CAM), Integrin Subunit Beta 3 (ITGB3), Catenin Delta 1 (CTNND1)). L1CAM is primarily a regulator of nervous system development [224]. However, further studies demonstrated its role in the regulation of tumor progression [225]. In EC patients, L1CAM is an important prognostic factor and an independent predictor of poor survival [226–228]. Upregulation of L1CAM in EC is at least in part caused by the downregulation of L1CAM-targeting tumor suppressor miR-34a.

4.1.12. Angiogenesis

Angiogenesis is one of the hallmarks of cancer according to Hanahan and Weinberg [14] playing a crucial role in the progression of EC. One of the most important proangiogenic factors is the Vascular Endothelial Growth Factor (VEGF) [229]. VEGF is often targeted in novel therapies including anti-VEGF antibody (bevacizumab), VEGF trap (aflibercept), or Tyrosine Kinase Inhibitors (TKI). Therapy with bevacizumab was approved by FDA in different tumors including colorectal cancer and is currently tested in EC [229,230]. An increased number of clinical trials are assessing the efficacy of that novel therapies in monotherapy as well as in a combination with other applied therapies but still lacks a personalized approach [229]. In this study, we found two miRNAs (miR-29a-5p and miR-545-3p) that target VEGF and thus influence EC progression.

4.1.13. Cyclic Adenosine Monophosphate (cAMP) Signaling

cAMP pathways are described to inhibit the invasion of cancer [231,232]. cAMP promotes apoptosis and decreases tumor growth [233]. The cAMP-specific phosphodiesterase 7A (PDE7A) hydrolyzes cAMP [97]. MiR-1 and miR-133a target PDE7A which leads to the inhibition of EC cell migration and invasion in vitro.

4.2. The Role of miRNAs in EC Diagnosis and Management

There is a great clinical interest in the determination of biomarkers for the diagnosis and management of EC, especially to enable individualized cancer care in the light of genomic classification [234]. Despite the identification of many prognostic biomarkers in EC [235,236], none of them are routinely used for diagnostic or prognostic purposes. Recent systematic reviews and meta-analyses revealed the clinical utility for the use of miRNAs as biomarkers in a variety of cancer, including bladder cancer [237], prostate cancer [238], ovarian cancer [239], and breast cancer [240], which makes miRNAs promising candidate for biomarkers in EC (Figure 5).

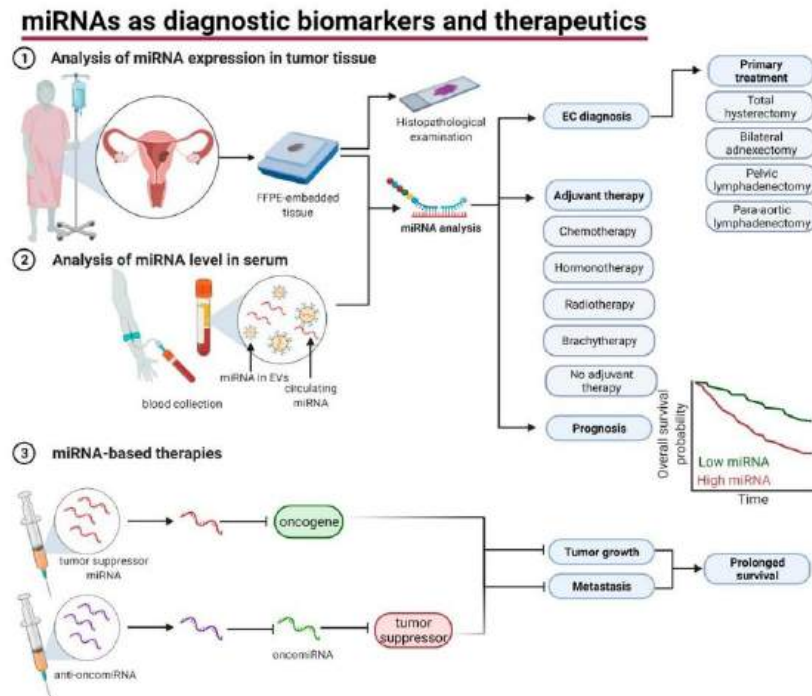


Figure 5. miRNAs as diagnostic biomarkers and therapeutics. miRNAs are promising biomarkers that can be analyzed either from tumor tissue (1) or from blood obtained from EC patients (2). miRNAs may support EC diagnosis and indicate primary and adjuvant treatment. Moreover, their expression is an important prognostic factor. miRNA-based therapies that include tumor suppressor miRNAs and anti-oncomiRNAs are currently tested in preclinical and clinical trials (3). EVs—extracellular vesicles, FFPE—formalin-fixed, paraffin-embedded. Figure was created using [Biorender.com](#).

Importantly, dysregulation of miRNAs expression can be also detected in plasma or serum (Figure 5). It was identified that the concentration of 19 miRNAs is increased in EC patients and the concentration of 10 miRNAs is decreased compared to healthy women [184]. Exploring publications we found that the concentration of six miRNAs was decreased and the concentration of 11 miRNAs was higher in EC patients and five from them (miR-27, miR-29b, miR-95, miR-203, and miR-449a) were associated with tumor myometrial invasion or lymph node metastases [60,77,81,110].

MiRNAs are also promising therapeutics in clinical oncology. Among described in this study miRNAs regulating tumor invasiveness, the effectiveness and safety of miR-34 have been tested in clinical trials. Despite the good efficacy of MRX34 (the liposome-miR-34 complex) in intravenous administration with dexamethasone premedication, the clinical trial was terminated due to severe adverse events including deaths [241,242]. One of the challenges with using miRNAs or their inhibitors in clinical practice is finding the correct route of administration because of their toxicity, limited stability, and low penetrance to target cells. Several delivery strategies have been developed including local delivery, viral delivery, lipid-based and polymer-based vectors [243]. So far, despite numerous preclinical studies and clinical trials none of the miRNA-based therapeutics have complied with expectations [243–245].

Some limitations should be acknowledged in this systematic review. First, to minimize the rate of false-positive results, we excluded studies that did not confirm the expression of miRNAs by RT-qPCR. Thus, we excluded studies that performed only global miRNA

profiling. It may introduce selection bias and cause exclusion of relevant miRNAs as well as limits the number of comparable results. Second, most of the studies did not distinguish types of EC in the analyzed cohort or focus on EC type I which may introduce bias. Indeed, some studies demonstrate the differences in the miRNA profile in different types of EC [246,247]. Third, the included studies present heterogeneity in sample types (fresh frozen or formalin-fixed, paraffin-embedded (FFPE) tissues), types of controls, and heterogeneity of study group. Fourth, a small number of miRNAs were assessed by at least two independent studies. Moreover, most of the studies that assessed the correlation of miRNA level and clinical parameters relied on a small group of patients and many of the included articles did not report relevant statistical parameters. Therefore, a meta-analysis could not be performed. Despite these limitations, our article is the first systematic review that comprehensively discusses data regarding the role of miRNAs in EC invasiveness and metastasis.

5. Conclusions

In this systematic review, we comprehensively reviewed miRNAs that are crucial regulators of EC invasiveness and metastasis. Extensive research revealed a complex regulatory network of tumor suppressors and oncomiRNAs that orchestrate tumor progression. Identified miRNAs control EC cell migration, invasion, and EMT in vitro, as well as tumor growth and lymph node metastases in vivo. These miRNAs regulate EC by targeting various members of pathways involved in diverse steps of cancer progression. That makes miRNAs promising candidates for diagnostic and prognostic biomarkers and potential therapeutic targets. Nonetheless, miRNAs that can be useful in clinical practice remain to be identified yet. Further large translational and clinical studies are needed to assess the clinical utility of miRNAs.

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The role of miR-200 family in the regulation of hallmarks of cancer



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The role of miR-200 family in the regulation of hallmarks of cancer

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MiRNAs are short non-coding RNAs that regulate gene expression post-transcriptionally contributing to the development of different diseases including cancer. The miR-200 family consists of five members, miR-200a, miR-200b, miR-200c, miR-141, and miR-429. Their expression is dysregulated in cancer tissue and their level is altered in the body fluids of cancer patients. Moreover, the levels of miR-200 family members correlate with clinical parameters such as cancer patients' survival which makes them potentially useful as diagnostic and prognostic biomarkers. MiRNAs can act as either oncomiRs or tumor suppressor miRNAs depending on the target genes and their role in the regulation of key oncogenic signaling pathways. In most types of cancer, the miR-200 family acts as tumor suppressor miRNA and regulates all features of cancer. In this review, we summarized the expression pattern of the miR-200 family in different types of cancer and their potential utility as biomarkers. Moreover, we comprehensively described the role of miR-200 family members in the regulation of all hallmarks of cancer proposed by Hanahan and Weinberg with the focus on the epithelial-mesenchymal transition, invasiveness, and metastasis of tumor cells.

KEYWORDS

miR-200, miR-200 family, miRNA, hallmarks of cancer, tumor progression, invasiveness, metastasis

Introduction

MiRNAs (microRNAs, miRs) are small non-coding RNAs that regulate gene expression at the post-transcriptional level. They were discovered in 1993, when Lee et al. described an antisense RNA-RNA interaction between *lin-4* transcripts complementary to the 3' untranslated region (UTR) of *lin-14* mRNA in

Caenorhabditis elegans (1). Over the past 30 years, miRNAs have become the subject of intense research, including in the field of cancer research (2, 3). So far over 2000 human miRNAs have been described (4, 5). Numerous studies have focused on the role of miRNAs in cancer development *in vitro* and *in vivo*, as well as their potential use as diagnostic and prognostic biomarkers and therapeutic agents (6, 7).

MiRNA biogenesis is a multistep process resulting in the formation of mature single-stranded miRNA (8). It begins in the nucleus where pri-miRNA is transcribed with RNA polymerase II. MiRNAs may be monocistronic (encoded individually) or polycistronic (encoded in clusters). In the next step, pre-miRNA is generated with the participation of the Drosha complex (microprocessor) and transported to the cytoplasm where it is further processed by the Dicer complex to miRNA duplex. Only one strand of the miRNA duplex (mature miRNA) forms the miRNA-induced silencing complex (RISC) (9–11).

MiRNAs bind with their seed region to complementary sequences in the 3' UTR of mRNAs (12). The seed region is a sequence of 2–7 nucleotides at the 5' end of the miRNA that is responsible for mRNA binding (13). That leads to the degradation of mRNA or inhibition of protein translation (14). One miRNA may target several mRNAs, as well as an individual mRNA may be regulated by numerous miRNAs. There are several bioinformatic tools (e.g. TargetScan, Starbase) that enable the prediction of the targets of miRNAs *in silico*, but the result must be validated experimentally (15). Thus, miRNAs form a complex miRNA-mRNA regulatory network that influences key

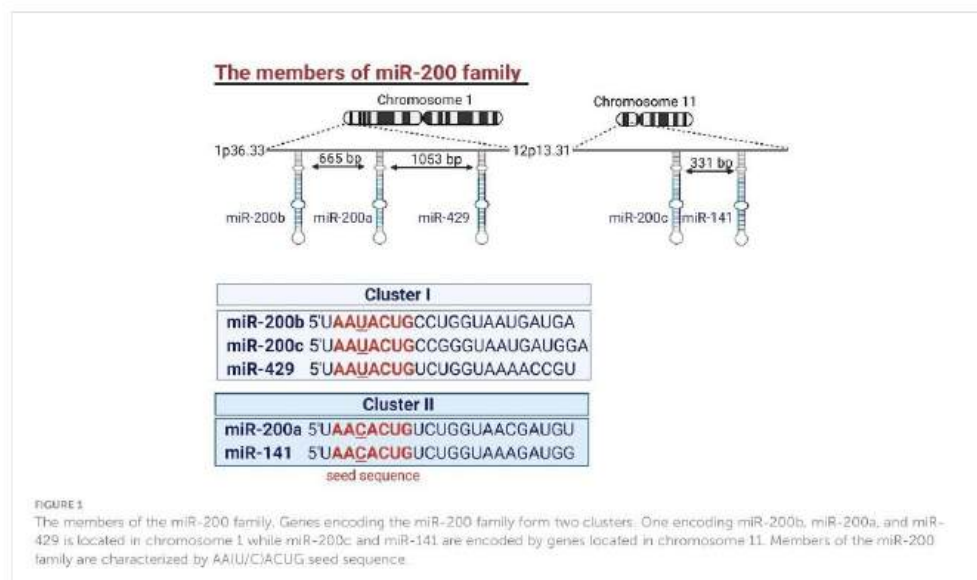
pathways in cells and controls all biological processes including carcinogenesis (2, 12).

The miR-200 family consists of five members, miR-200a, miR-200b, miR-200c, miR-141, and miR-429. They are divided into two clusters based on their seed sequence. miR-200b, miR-200a, and miR-429 (cluster I) are located on chromosome 1 and have a common seed sequence (AAUACUG). While miR-200c and miR-141 belong to cluster II and are located on chromosome 11. Their seed sequence (AACACUG) differs only by one nucleotide from the seed sequence of cluster I (Figure 1) (16). Hence the members of the miR-200 family can theoretically target similar mRNAs (13). This review aims to comprehensively describe the role of the miR-200 family members in regulating all hallmarks of cancer.

Expression of miR-200 family in cancer

Dysregulation of the expression of miRNAs in cancer

MiRNA expression is often dysregulated in cancer cells. New technologies such as high-throughput RNA sequencing enable to profile miRNAs expression (17). Several studies showed the general repression of miRNAs in cancer tissues since the majority of them are tumor suppressors (18–20). One of the miRNA families that suppress cancer development and



progression is the miR-200 family which is known for targeting zinc-finger E-box binding homeobox (ZEB) and inhibiting epithelial-mesenchymal transition (EMT) (21). In contrast, miR-21 is a well-known oncomiR that targets mainly tumor suppressors (22). Notably, the individual miRNA expression and functions in cancer cells may be tissue-specific and differ between different tumor types (23).

Mechanisms of miRNAs dysregulation in cancer

The mechanisms of miRNAs expression regulation are complex and multistep (24). They may be divided into transcriptional mechanisms such as the influence of transcription factors, DNA methylation, and histone modifications (25). All of them control pri-miRNA transcription. Among numerous transcription factors that regulate miRNAs expression are p53, ZEB, Myc, and hormone receptors, including estrogen receptors (26). The next mechanism regulating miRNAs expression is DNA promoter methylation. Hypermethylation was associated with decreased

expression of miRNAs, while hypomethylation caused the upregulation of miRNAs expression (27). Furthermore, there are posttranscriptional mechanisms that regulate miRNA expression by the regulation of pri-miRNA and pre-miRNA processing (26). The genes involved in miRNAs biogenesis, including DICER, are frequently dysregulated in cancer (28, 29). Downregulation of DICER is a prediction of poor prognosis for overall and progression-free survival (30).

Expression of miR-200 family

In our review, we collected articles that determined the expression of miR-200 family members in 25 cancer types in the tumor tissue compared to corresponding healthy tissue using the RT-qPCR (real-time quantitative PCR) method (Table 1). MiR-200 family members were downregulated in 10 types of cancer and upregulated in 2 cancer types. In 12 types of cancer individual members of the miR-200 family had different levels of expression (Table 1). MiRNAs from both miR-200b/miR-200a/miR-429 and miR200c/miR-141 clusters are expressed together as two different polycistronic pri-miRNA transcripts (133).

TABLE 1 The expression of miR-200 family members in different types of cancer compared to the healthy tissue.

Cancer	miR-200a expression	miR-200b expression	miR-200c expression	miR-141 expression	miR-429 expression	Ref.
Acute myeloid leukemia	↓	↓	n/d	n/d	↓	(31)
Acute lymphoblastic leukemia	n/d	n/d	n/d	↓	↑	(32, 33)
Bladder cancer	↓/↑	↑	↓/↑	↑	↑	(34–41)
Breast cancer	↓/↑	↓/↑	↓/↑	↓/↑	n/d	(42, 43)
Cervical carcinoma	↓	↓	↓/↑	↑	↓	(44–50)
Cholangiocarcinoma	↓	↓	↓	n/d	n/d	(51, 52)
Colorectal cancer	↑	↑	↑	↑	↑/↓	(53–59)
Endometrial cancer	↑	↑	↑	↑	↑	(60, 61)
Esophageal carcinoma	↓/↑	↓	↓	↓	↓	(62–70)
Gastric cancer	↓/↑	↓/↑	↓/↑	↓	↓/↑	(71–76)
Glioma	↓	↓	↓	↓	↑/↓	(77–83)
Head and neck carcinoma	↓	n/d	n/d	↓	n/d	(84–86)
Liver cancer	↓	↓	↓	↓	↓	(87–91)
Melanoma	↓	↓	↓	↓	↓	(92–94)
Nephroblastoma	↓	↓	↓	↓	↓	(95–98)
Neuroblastoma	↓	n/d	n/d	n/d	n/d	(99)
Non-small cell lung cancer	↓	↓	↓	↑/↓	↑	(100)
Oral squamous cell carcinoma	↓	↓	↓	↓	↓	(101, 102)
Osteosarcoma	↓	↓	↓	↓	↓	(103–107)
Ovarian cancer	↑	↑	↑	↑	n/d	(108–113)
Pancreatic cancer	↑	↑	↓	↑/↓	↓	(114–118)
Prostate cancer	↓/↑	↑	↓	↑	n/d	(119–122)
Renal cell carcinoma	↓	↓	↓	↓	↓	(123–128)
Small cell lung carcinoma	n/d	n/d	n/d	n/d	n/d	n/d
Thyroid cancer	↓/↑	↓/↑	↓/↑	↓/↑	↓/↑	(129–132)

↓ - downregulated expression; ↑ - upregulated expression; n/d - no data.

Therefore, they have a similar pattern of expression (up- or downregulation) in most cancer types. The expression of the miR-200 family is regulated by different mechanisms, including DNA methylation. miR-200b, miR-200c, and miR-141 were described as epigenetically silenced by DNA methylation in breast cancer (134). Moreover, the miR-200b/miR-200a/miR-429 cluster was repressed in the mechanism of histone modifications in this model (135).

miRNAs in body fluids

Circulating miRNAs can be detected in various body fluids including serum, saliva, and urine. Thus, they are promising diagnostic and prognostic biomarkers. MiR-200 family members have been detected in different body fluids and were dysregulated in 18 cancer types (Table 2). The level of miR-200 family members in serum was increased in 7 cancer types and decreased in serum in 3 cancer types. There are inconsistent data concerning serum miRNAs expression in bladder cancer, prostate cancer, and non-small lung carcinoma. Notably, the expression patterns of miR-200

family members in cancer tissue are consistent with their level in body fluids only in 5 cancer types. The observation is consistent with the studies that demonstrate that the miRNAs expression profiles of patients' serum and cancer tissue are different (194, 195). Importantly, the levels of miR-200 family in different types of body fluids vary in cancer patients and may not correlate (196).

MiRNAs may be loaded into small vesicles, including exosomes. Exosomal miRNAs are distributed to body fluids where they play important role in the pathogenesis of cancer by regulating all hallmarks of cancer (197). The level of exosomal miR-200 family members may serve as prognostic or diagnostic markers in various tumor types. The level of exosomal miR-200 is upregulated in ovarian cancer patients' serum (198) and in pleural effusion of patients diagnosed with lung adenocarcinoma (199). Moreover, the level of exosomal miR-200 correlates with the invasiveness of ovarian cancer (200). Exosomal miR-200b and miR-200c may serve as independent prognostic factors in pancreatic ductal adenocarcinoma as they correlate with overall survival of patients (180). Lower expression of exosomal miR-200c and miR-141 is associated with longer overall survival of colon cancer patients (201). Moreover, miR-200 family members

TABLE 2 The level of miR-200 family members in the serum, urine or saliva of patients with different types of cancer.

Cancer	miR-200a level	miR-200b level	miR-200c level	miR-141 level	miR-429 level	Ref.
Acute myeloid leukemia	n/d	n/d	n/d	n/d	n/d	n/d
Acute lymphoblastic leukemia	n/d	n/d	n/d	n/d	n/d	n/d
Bladder cancer	↓ (urine)	↓ (urine)	↓ (urine)	↑/↓ (urine)	↓ (urine)	(136–139)
Breast cancer	n/d	n/d	↓	n/d	n/d	(140, 141)
Cervical carcinoma	↑	n/d	↑	↓	n/d	(48, 142, 143)
Cholangiocarcinoma	↑	↑	↑	↑	n/d	(144)
Colorectal cancer	n/d	↑	↑	↑	n/d	(145–150)
Endometrial cancer	↑	n/d	n/d	↑	n/d	(61)
Esophageal carcinoma	n/d	n/d	↑	n/d	n/d	(151, 152)
Gastric cancer	↑	n/d	↑	↓	n/d	(153–158)
Glioma	↓	n/d	n/d	n/d	n/d	(81)
Head and neck carcinoma	n/d	n/d	n/d	n/d	n/d	n/d
Liver cancer	↓	n/d	n/d	n/d	↑	(159–162)
Melanoma	n/d	n/d	↓	n/d	n/d	(163)
Nephroblastoma	n/d	n/d	n/d	n/d	n/d	n/d
Neuroblastoma	n/d	n/d	n/d	n/d	n/d	n/d
Non-small cell lung cancer	n/d	↑/↓	n/d	↑	↑/↓	(164–169)
Oral squamous cell carcinoma	↓ (saliva)	↑	n/d	n/d	n/d	(170, 171)
Osteosarcoma	n/d	n/d	n/d	n/d	n/d	n/d
Ovarian cancer	↑	↑	↑	↑	↑	(172–178)
Pancreatic cancer	↑	↑	↑	n/d	n/d	(179, 180)
Prostate cancer	↑	↑/↓	↑/↓	↑	n/d	(181–189)
Renal cell carcinoma	↓	n/d	n/d	↓	↑	(190–192)
Small cell lung carcinoma	n/d	n/d	n/d	↑	n/d	(193)
Thyroid cancer	n/d	n/d	n/d	n/d	n/d	n/d

↓ - decreased level; ↑ - increased level; n/d - no data. Arrows refer to serum miRNA level unless otherwise indicated.

may play role as biomarker of cholangiocarcinoma, in particular miR-200a/c correlates with tumor stage (144).

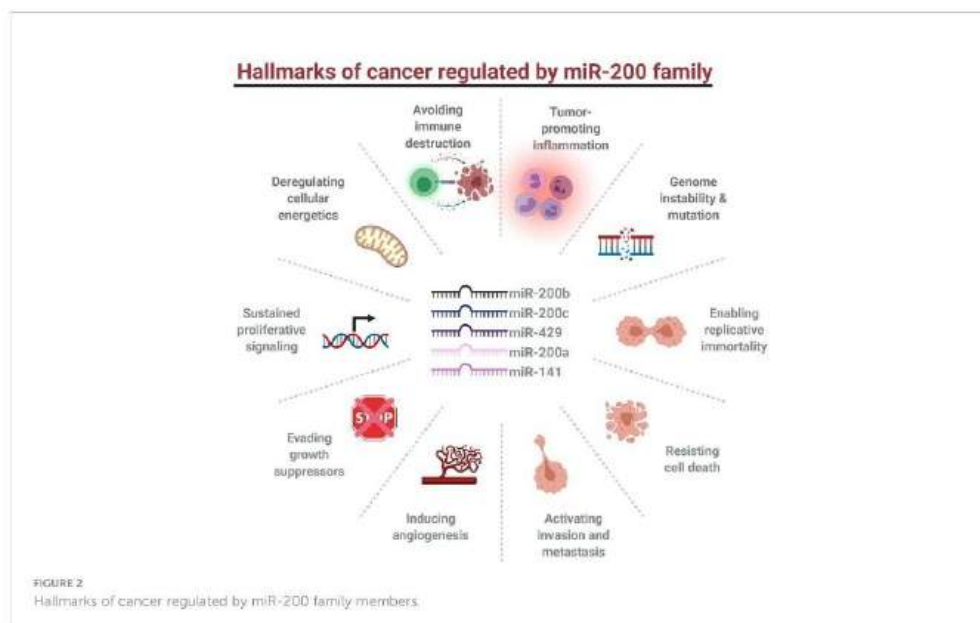
miRNAs as diagnostic and prognostic biomarkers

miRNAs may not only serve as diagnostic biomarkers that enable to distinguish between cancer and healthy tissue but also their levels correlate with clinical parameters and thus may have potential prognostic value (202). The combination of miRNAs may discriminate cancerous from healthy tissues with high accuracy (203, 204). The meta-analysis shows that miR-200c expression has a moderate diagnostic value in gastric cancer (205) and miR-141 may be a diagnostic marker of colorectal cancer (206). Notably, a meta-analysis of 58 articles with 8107 cancer patients revealed that in general higher expression of miR-200 family members is associated with worse survival (207, 208). Moreover, miR-200a expression was associated with unfavorable prognosis in breast cancer patients, and miR-429 correlated with shorter survival in liver cancer patients (207). Higher miR-200c expression was correlated with shorter overall survival in gastric cancer and non-small cell lung carcinoma (205, 209). However, in another meta-analysis, the expression of miR-200 family members was associated with a better prognosis in bladder cancer as it correlated with longer overall survival, recurrence-free survival,

and cancer-specific survival (210). Moreover, miR-200c correlated with a better prognosis in ovarian cancer (211). Notably, it was found that serum miR-200c may be used as a marker of colorectal cancer tumor recurrence after surgery (147). Similarly, urine miR-200a was identified as marker the recurrence of non-muscle-invasive bladder cancer (137). In addition to miRNAs in the body fluids, it was found that the level of miR-141 in prostate cancer tissue may be associated with the tumor recurrence (212). Thus, more prospective clinical trials are required to determine the utility of miR-200 family members as biomarkers.

Hallmarks of cancer

Hallmarks of cancer have been first described in 2000 (213). In the updated version of their review, 14 features of human tumor development were proposed: sustaining proliferative signaling, evading tumor growth suppressors, enabling replicative immortality, activating invasion and metastasis, resisting cell death, inducing angiogenesis, avoiding immune destruction, tumor-promoting inflammation, genome instability & mutation, enabling replicative immortality, sustaining proliferative signaling, evading growth suppressors, and resisting cell death (214). All of them are regulated by miRNAs, including miR-200 family members (Figure 2) (215, 216).



Regulation of cell proliferation by miR-200 family

The proliferation of cancer cells is one of the most important hallmarks of cancer. It is sustained by growth factors, constitutive activation of oncogenic signaling pathways, evading growth repressors like p53 or RB, and enabled replicative immortality (217). Proliferation is regulated by numerous pathways including PI3K/AKT, MEK/ERK, JAK/STAT, and β -Catenin/Wnt signaling, and by cell cycle regulators such as cyclin-dependent kinases (CDKs). The members of those pathways are regulated by miRNAs that may either promote or inhibit cancer cell proliferation. MiR-200 family has different effects on tumor cell proliferation *in vitro* depending on the cancer type (Table 3). Based on our literature review, miR-200a increases the proliferation of 5 cancer types and inhibits the proliferation of 13 cancer types, and there are inconsistent results concerning colorectal cancer, non-small cell lung cancer, and renal cell carcinoma. *In vivo*, miR-200a inhibits tumor growth of gastric cancer, glioma, melanoma, neuroblastoma, and prostate cancer. Furthermore, miR-200b stimulates the proliferation of 4 cancer types, and inhibits 13 cancer types, and there are inconsistent results concerning colorectal and non-small cell lung, and ovarian cell carcinoma. *In vivo* studies show miR-200b increases tumor growth of cervical and ovarian cancer and decreases tumor growth of breast cancer, glioma, head and neck cancer, non-small lung cancer, prostate cancer, and thyroid cancer. MiR-200c acts as oncomiR in 3 cancer types and as tumor suppressor miR in 13 cancer types and there are inconsistent results concerning colorectal, endometrial, and renal cell carcinoma. It decreases tumor growth *in vivo* of 9 cancer types *in vivo* and increases tumor growth of head and neck carcinoma. Moreover, miR-141 increases the proliferation of 6 cancer types, and decreases in 12 cancer types, and there are discrepancies regarding the role of miR-141 in the regulation of colorectal, non-small cell lung, and ovarian carcinoma cell proliferation. *In vivo*, miR-141 acts mainly as tumor suppressor miR and inhibits the tumor growth of numerous cancer types including colorectal, gastric, and pancreatic cancer. miR-141 increases the tumor growth of cervical and non-small cell lung cancer. Furthermore, it increases the proliferation of 5 and decreases the proliferation of 14 cancer types. *In vivo*, miR-429 inhibits tumor growth of 7 cancer types and increases tumor growth of bladder cancer only. Based on that information, miR-200 family members are suppressive miRNAs in most cancer types, however, they might also stimulate the proliferation of some types of cancer cells.

MiR-200 family members exert their effects by targeting several mRNAs associated with cancer cell proliferation. MiR-200a targets Cyclin-Dependent Kinase 6 (CDK6) in melanoma and thus causes cell-cycle arrest and decreases cancer cell

proliferation (93). MiR-429 targets p27Kip1, an inhibitor of the cell cycle, and its overexpression promotes the proliferation of prostate cancer cells (311). Furthermore, the miR-200 family targets the members of key pathways regulating cancer cell proliferation. PI3K/AKT pathway promotes proliferation, migration, invasion, and EMT (epithelial-mesenchymal transition) (313). AKT1/2 is targeted by miR-200c in osteosarcoma (105), and by miR-429 in melanoma (306) and renal cell carcinoma (312). Downregulation of AKT1/2 by miRNAs inhibits cancer cell proliferation *in vitro* and tumor growth *in vivo*. Moreover, the miR-200 family targets PTEN, a key suppressor of the PI3K/AKT pathway (314). It is targeted by miR-200a in endometrial cancer (223) and esophageal carcinoma (70), miR-200b in endometrial cancer (223), miR-200c in endometrial cancer (273) and head and neck carcinoma (276), and miR-429 in non-small cell lung cancer (308) resulting in increased of cancer cells proliferation *in vitro*.

The second most important pathway regulating cell proliferation is MEK/ERK pathway. KRAS which activates MEK/ERK is targeted by miR-200c in breast cancer. MiR-200c thus has an inhibitory effect on breast cancer cell proliferation and tumor growth (265). Moreover, miR-200b targets p70S6K1 and inhibits lung cancer cell proliferation *in vitro* and tumor growth *in vivo* (256). Whereas, miR-429 targets RAB23 in esophageal and liver carcinomas resulting in the suppression of cell proliferation, migration, and invasion (69, 305). On the contrary, MEK/ERK inhibitor Ras Association Domain Family Member 2 (RASSF2) is targeted by miR-200a, miR-200c, miR-141 in colorectal cancer, and Ras Association Domain-Containing Protein 8 (RASSF8) by miR-429 in non-small lung carcinoma which results in increased proliferation (56, 308). Similarly, other signaling pathways regulating cell proliferation are targeted by miRNAs. MiR-200a binds STAT4 in bladder and liver cancer and decreases cell proliferation *in vitro* (162, 218). In esophageal carcinoma, however, miR-200a acts as oncomiR and targets APC, an inhibitor of β -Catenin/Wnt signaling (70).

Regulation of cell migration and invasiveness by miR-200 family

Cancer cell migration and invasion are multistep processes that involve cytoskeleton remodeling, interaction with extracellular matrix (ECM), and then its digestion. All these steps are regulated by miRNAs that suppress or promote cancer progression (7).

In this study, we summarized the knowledge about miR-200 family regulation of cancer cell migration and invasion *in vitro* (Table 4). MiR-200 family members suppress cell migration and invasiveness in most types of cancer. MiR-200a increases the migration of 2 cancer types and the invasion of 3 cancer types and it decreases the migration of

TABLE 3 The role of the miR-200 family in proliferation and tumor growth.

miRNAs	Cancer	Target	Cell proliferation <i>in vitro</i>	Tumor growth <i>in vivo</i>	Ref.
miR-200a	Acute myeloid leu-kemia	n/d	n/d	n/d	n/d
	Acute lymphoblastic leukemia	n/d	n/d	n/d	n/d
	Bladder cancer	STAT4	↓	n/d	(218)
	Breast cancer	TFAM	↓	n/d	(219)
	Cervical cancer	EGLN1	↑	n/d	(220)
	Cholangiocarcinoma	n/d	↓	n/d	(52)
	Colorectal cancer	FOXA1, RASSF2	↓/↑	n/d	(56, 221, 222)
	Endometrial cancer	PTEN	↑	n/d	(60, 223)
	Esophageal carcinoma	CTNBN1, CDH1, APC, PTEN, CTNNA1, CRMP1 and SOD2	↑	n/d	(70, 224)
	Gastric cancer	n/d	↓	↓	(225)
	Glioma	FOXA1, SIM2-s	↓	↓	(83, 226)
	Head and neck carcinoma	CD47	↓	n/d	(86)
	Liver cancer	STAT4, FOXA2	↓	n/d	(161, 162, 227)
	Melanoma	CDK6, GOLM1	↓	↓	(93, 228)
	Nephroblastoma	n/d	n/d	n/d	n/d
	Neuroblastoma	AP-2γ	↓	↓	(99)
	Non-small cell lung cancer	RHPN2	↑/↓	n/d	(229, 230)
	Oral squamous cell carcinoma	n/d	n/d	n/d	n/d
	Osteosarcoma	ZEB1	↓	n/d	(104)
	Ovarian cancer	PDCH9	↑	n/d	(111, 113)
	Pancreatic cancer	DEK	↓	n/d	(231, 232)
	Prostate cancer	BRD4	↓	↓	(233, 234)
	Renal cell carcinoma	CBL, SIRT1, SPAG9, TGFβ2	↓/↑	n/d	(124, 126, 127, 235, 236)
	Small cell lung carcinoma	n/d	n/d	n/d	n/d
	Thyroid cancer	FOXA1	↓	n/d	(130)
miR-200b	Acute myeloid leu-kemia	n/d	↓	n/d	(237)
	Acute lymphoblastic leukemia	n/d	n/d	n/d	n/d
	Bladder cancer	FSCN1	↓	n/d	(238)
	Breast cancer	IKBKB, FUT4, radixin, SPI	↓	↓	(239–242)
	Cervical cancer	FOXG1	↑	↑	(243)
	Cholangiocarcinoma	n/d	↑	n/d	(244)
	Colorectal cancer	RECK, TUBB3, Wnt1	↑/↓	n/d	(245–247)
	Endometrial cancer	PTEN	↑	n/d	(60, 223)
	Esophageal carcinoma	n/d	n/d	n/d	n/d
	Gastric cancer	ZEB2	↓	n/d	(248)
	Glioma	CD133, CREB1, ERK5	↓	↓	(249–251)
	Head and neck carcinoma	Notch1	↓	↓	(252)
	Liver cancer	HMGB3	↓	n/d	(90)
	Melanoma	n/d	↓	n/d	(253)
	Nephroblastoma	IKK-β	↓	n/d	(98)
	Neuroblastoma	n/d	n/d	n/d	n/d
	Non-small cell lung cancer	ABCA1, p70S6K1, RhoE	↑/↓	↓	(254–256)
		Kindlin-2, ZEB2	↓	n/d	(257)

(Continued)

TABLE 3 Continued

miRNAs	Cancer	Target	Cell proliferation <i>in vitro</i>	Tumor growth <i>in vivo</i>	Ref.
miR-200c	Oral squamous cell carcinoma				
	Osteosarcoma	ZEB1	↓	n/d	
	Ovarian cancer	ATAD2, ING5	↑/↓	↑	(258, 259)
	Pancreatic cancer	n/d	n/d	n/d	n/d
	Prostate cancer	n/d	↓	↓	(233, 260–262)
	Renal cell carcinoma	n/d	↑	n/d	(124)
	Small cell lung carcinoma	n/d	n/d	n/d	n/d
	Thyroid cancer	RAP1B	↓	↓	(132)
	Acute myeloid leu-kemia	n/d	n/d	n/d	n/d
	Acute lymphoblastic leukemia	n/d	n/d	n/d	n/d
	Bladder cancer	BMI-1, E2F3, LDHA	↓	n/d	(36, 263)
	Breast cancer	BMI-1, KRAS, PDE7B, XIAP	↓	↓	(264–269)
	Cervical cancer	MAP4K4	↓	n/d	(270)
	Cholangiocarcinoma	n/d	n/d	n/d	n/d
	Colorectal cancer	CDK2, RASSF2	↑/↓	n/d	(56, 271)
	Endometrial cancer	PTEN, PTENP1, MALAT1	↑/↓	↓	(60, 272, 273)
	Esophageal carcinoma	n/d	n/d	n/d	n/d
	Gastric cancer	EDNRA, FN1	↓	n/d	(274, 275)
	Glioma	MSN	↓	↓	(79)
	Head and neck carcinoma	PTEN	↑	↑	(276)
	Liver cancer	MAD2L1	↓	n/d	(88)
	Melanoma	n/d	↓	↓	(277)
	Nephroblastoma	FRS2, IKK-β	↓	n/d	(97, 98, 278)
	Neuroblastoma	n/d	n/d	n/d	n/d
	Non-small cell lung cancer	LDHA	↓	↓	(279, 280)
	Oral squamous cell carcinoma	n/d	↓	n/d	(102)
miR-141	Osteosarcoma	AKT2	↓	↓	(105)
	Ovarian cancer	n/d	↑	↓	(281, 282)
	Pancreatic cancer	n/d	↑	n/d	(283)
	Prostate cancer	AMACR, ZEB2	↓	↓	(122, 284, 285)
	Renal cell carcinoma	SLC6A1	↑/↓	n/d	(124, 128)
	Small cell lung carcinoma	n/d	n/d	n/d	n/d
	Thyroid cancer	RAP1B	↓	↓	(132)
	Acute myeloid leu-kemia	RAB32	↓	↓	(286)
	Acute lymphoblastic leukemia	TRAF5	↓	n/d	(51)
	Bladder cancer	n/d	n/d	n/d	n/d
	Breast cancer	ANP32E, HMGB1	↓	↓	(287, 288)
	Cervical cancer	FOXA2	↑	↑	(289)
	Cholangiocarcinoma	n/d	↑	n/d	(244)
	Colorectal cancer	PHLPP2, RASSF2	↑/↓	↓	(56, 58, 290, 291)
	Endometrial cancer	n/d	↑	n/d	(60)
	Esophageal carcinoma	n/d	↓	n/d	(67)
	Gastric cancer	YAP1, TAZ	↓	↓	(75, 292)
	Glioma	SKA2	↓	↓	(77)

(Continued)

TABLE 3 Continued

miRNAs	Cancer	Target	Cell proliferation <i>in vitro</i>	Tumor growth <i>in vivo</i>	Ref.
miR-429	Head and neck carcinoma	EGFR	↓	↓	(85)
	Liver cancer	TGFBRI	↓	n/d	(91)
	Melanoma	n/d	n/d	n/d	n/d
	Nephroblastoma	n/d	n/d	n/d	n/d
	Neuroblastoma	FUS	↓	↓	(293)
	Non-small cell lung cancer	HOXC13, KLF9	↑/↓	↑	(193, 294, 295)
	Oral squamous cell carcinoma	n/d	n/d	n/d	n/d
	Osteosarcoma	GLI2	↓	n/d	(106, 296)
	Ovarian cancer	n/d	↑/↓	n/d	(112, 297)
	Pancreatic cancer	MAP4K4	↓	↓	(298)
	Prostate cancer	KLF9, RUNX1	↑	n/d	(299, 300)
	Renal cell carcinoma	n/d	↑	n/d	(124)
	Small cell lung carcinoma	n/d	n/d	n/d	n/d
	Thyroid cancer	IRS2	↓	↓	(129)
	Acute myeloid leukemia	n/d	n/d	n/d	n/d
	Acute lymphoblastic leukemia	n/d	n/d	n/d	n/d
	Bladder cancer	CDKN2B	↑	↑	(39)
	Breast cancer	FN1	↓	n/d	(301)
	Cervical cancer	IKK-β, ZEB1	↓	↓	(46, 302)
	Cholangiocarcinoma	n/d	n/d	n/d	n/d
	Colorectal cancer	HMGB3, Onecut2	↓	↓	(55, 59)
	Endometrial cancer	n/d	↑	n/d	(60)
	Esophageal carcinoma	Bcl-2, SP1, Slug, RAB23	↓	↓	(65, 68, 69)
	Gastric cancer	FSCN1, c-MYC	↓	↓	(71, 74, 303)
	Glioma	SOX2	↓	n/d	(82)
	Head and neck carcinoma	n/d	↓	n/d	(304)
	Liver cancer	RAB23	↓	n/d	(305)
	Melanoma	AKT1	n/d	↓	(306)
	Nephroblastoma	c-MYC, IKK-β	↓	n/d	(96, 98)
	Neuroblastoma	IKK-β	↓	↓	(307)
	Non-small cell lung cancer	DLC-1, PTEN, RASSF8, TIMP2	↑	n/d	(308, 309)
	Oral squamous cell carcinoma	ZEB1	↓	n/d	(310)
	Osteosarcoma	ZEB1, HOXA9	↓	n/d	(103, 107)
	Ovarian cancer	n/d	n/d	n/d	n/d
	Pancreatic cancer	NT-3	↓	n/d	(117)
	Prostate cancer	p27Kip1	↑	n/d	(311)
	Renal cell carcinoma	AKT1	↑	↓	(124, 312)
	Small cell lung carcinoma	n/d	n/d	n/d	n/d
	Thyroid cancer	ZEB1	↓	n/d	(131)

↓ - suppression by miRNA; ↑ - promotion by miRNA; n/d - no data.

12 and invasion of 13 cancer types. MiR-200b increases the migration of renal cell cancer and decreases the migration of 16 cancer types and invasion of 15 cancer types. Furthermore, miR-200c promotes the migration and invasion of head and neck carcinoma. On the other hand, miR-200c inhibits the

migration of 15 and invasion of 13 types of cancers. MiR-141 decreases the migration of 13 types of cancer cells and invasion of 13 cancer types. However, it increases the migration of bladder and renal cell carcinoma, and it stimulates the invasion of bladder, cervical, and non-small

TABLE 4 Members of the miR-200 family regulating cancer cell migration and invasion.

miRNAs	Cancer	Target	Cell migration <i>in vitro</i>	Cell invasion <i>in vitro</i>	Ref.
miR-200a	Acute myeloid leukemia	n/d	n/d	n/d	n/d
	Acute lymphoblastic leukemia	n/d	n/d	n/d	n/d
	Bladder cancer	DICER	n/d	↑	(41)
	Breast cancer	ELK3, EPHA2	↓	↓	(315, 316)
	Cervical cancer	n/d	n/d	n/d	n/d
	Cholangiocarcinoma	n/d	n/d	↓	(52)
	Colorectal cancer	FOXA1	↓	↓	(221, 222)
	Endometrial cancer	n/d	n/d	n/d	n/d
	Esophageal carcinoma	CTNNA1, CDH1, APC, PTEN, CTNNA1 and SOD2	↑	↑	(70)
	Gastric cancer	n/d	↓	↓	(225)
	Glioma	FOXA1, SIM2-s	↓	↓	(83, 226)
	Head and neck carcinoma	CD47	↓	↓	(86)
	Liver cancer	STAT4, Foxa2	↓	↓	(161, 162, 227)
	Melanoma	GOLM1	↓	↓	(228)
	Nephroblastoma	n/d	n/d	n/d	n/d
	Neuroblastoma	n/d	n/d	n/d	n/d
	Non-small cell lung cancer	HGF	↓	↓	(100)
	Oral squamous cell carcinoma	n/d	n/d	n/d	n/d
	Osteosarcoma	ZEB1	↓	n/d	(104)
	Ovarian cancer	PDCH9	↑	↑	(111, 113)
	Pancreatic cancer	DEK	↓	↓	(231, 232, 317)
	Prostate cancer	n/d	n/d	↓	(233)
	Renal cell carcinoma	TGFβ2	↓	↓	(235)
	Small cell lung carcinoma	n/d	n/d	n/d	n/d
	Thyroid cancer	FOXA1	↓	↓	(130)
miR-200b	Acute myeloid leukemia	n/d	n/d	↓	(237)
	Acute lymphoblastic leukemia	n/d	n/d	n/d	n/d
	Bladder cancer	FSCN1	↓	↓	(238)
	Breast cancer	IKKB, FUT4, PKGα, radixin	↓	↓	(240–242, 318, 319)
	Cervical cancer	FoxG1, RhoE	↓/↑	↓/↑	(45, 243, 320)
	Cholangiocarcinoma	SUZ12 and ROCK2	↓	↓	(51)
	Colorectal cancer	TUBB3	↓	↓	(247)
	Endometrial cancer	TIMP2	↓	n/d	(321)
	Esophageal carcinoma	Kindlin-2	↓	↓	(322)
	Gastric cancer	ZEB2	↓	↓	(248)
	Glioma	CD133, ERK5	↓	↓	(250, 251)
	Head and neck carcinoma	Notch1	↓	↓	(252)
	Liver cancer	HMGB3	↓	n/d	(90)
	Melanoma	n/d	↓	↓	(253)
	Nephroblastoma	IKK-β	↓	↓	(98)
	Neuroblastoma	n/d	n/d	n/d	n/d
	Non-small cell lung cancer	ABCA1, p70S6K1, RhoE, TGFγ	↑/↓	↑/↓	(255, 256, 323, 324)

(Continued)

TABLE 4 Continued

miRNAs	Cancer	Target	Cell migration <i>in vitro</i>	Cell invasion <i>in vitro</i>	Ref.
miR-200c	Oral squamous cell carcinoma	Kindlin-2, ZEB2	↓	↓	(257)
	Osteosarcoma	ZEB1	↓	↓	
	Ovarian cancer	n/d	n/d	n/d	n/d
	Pancreatic cancer	n/d	n/d	n/d	n/d
	Prostate cancer	n/d	↓	↓	(233, 261, 262)
	Renal cell carcinoma	n/d	↑	n/d	(124)
	Small cell lung carcinoma	n/d	n/d	n/d	n/d
	Thyroid cancer	RAP1B	↓	↓	(132, 325)
	Acute myeloid leukemia	n/d	n/d	n/d	n/d
	Acute lymphoblastic leukemia	n/d	n/d	n/d	n/d
	Bladder cancer	BMJ-1, E2F3, LDHA, RECK	↑/↓	↑/↓	(36, 38, 263)
	Breast cancer	n/d	↓	↓	(267, 268, 326)
	Cervical cancer	MAP4K4	↓	n/d	(270)
	Cholangiocarcinoma	SUZ12 and ROCK2	↓	↓	(51)
	Colorectal cancer	n/d	↓	↓	(327)
	Endometrial cancer	PTEN, PTENP1	↑/↓	↑/↓	(272, 328, 273)
	Esophageal carcinoma	n/d	n/d	n/d	n/d
	Gastric cancer	EDNRA, FN1	↓	↓	(274, 275)
	Glioma	MSN	↓	↓	(79)
	Head and neck carcinoma	PTEN	↑	↑	(276)
	Liver cancer	MAD2L1	↓	↓	(88)
	Melanoma	n/d	↓	n/d	(277)
	Nephroblastoma	FRS2, IKK-β	↓	↓	(97, 98)
	Neuroblastoma	n/d	n/d	n/d	n/d
	Non-small cell lung cancer	LDHA	↓	n/d	(280)
	Oral squamous cell carcinoma	ZEB1	↓	↓	(329)
miR-141	Osteosarcoma	AKT2	↓	n/d	(105)
	Ovarian cancer	n/d	↓	↓	(281, 282)
	Pancreatic cancer	n/d	n/d	↓	(283, 330)
	Prostate cancer	AMACR, ZEB2	↓	↓	(122, 284, 285)
	Renal cell carcinoma	SLC6A1	↑/↓	↓	(124, 128)
	Small cell lung carcinoma	n/d	n/d	n/d	n/d
	Thyroid cancer	RAP1B	↓	↓	(132)
	Acute myeloid leukemia	n/d	n/d	n/d	n/d
	Acute lymphoblastic leukemia	n/d	n/d	n/d	n/d
	Bladder cancer	n/d	n/d	n/d	n/d
	Breast cancer	ANP32E, ZEB1/2	↓	↓	(287, 331)
	Cervical cancer	FOXA2	n/d	↑	(289)
	Cholangiocarcinoma	n/d	n/d	n/d	n/d
	Colorectal cancer	EGFR	↓	↓	(332)
	Endometrial cancer	n/d	n/d	n/d	n/d
	Esophageal carcinoma	n/d	↓	↓	(67)
	Gastric cancer	TAZ	↓	↓	(292)
	Glioma	SKA2	↓	↓	(77)

(Continued)

TABLE 4 Continued

miRNAs	Cancer	Target	Cell migration <i>in vitro</i>	Cell invasion <i>in vitro</i>	Ref.
miR-429	Head and neck carcinoma	EGFR	↓	↓	(85)
	Liver cancer	TGFBR1	↓	↓	(91)
	Melanoma	n/d	n/d	n/d	n/d
	Nephroblastoma	n/d	n/d	n/d	n/d
	Neuroblastoma	FUS	↓	↓	(293)
	Non-small cell lung cancer	KLF9	n/d	↑	(295)
	Oral squamous cell carcinoma	n/d	n/d	n/d	n/d
	Osteosarcoma	FUS	↓	↓	(296)
	Ovarian cancer	n/d	↓	↓	(297)
	Pancreatic cancer	MAP4K4, TM4SF1	↓	↓	(298, 333)
	Prostate cancer	RUNX1	↓	↓	(300)
	Renal cell carcinoma	n/d	↑	n/d	(124)
	Small cell lung carcinoma	n/d	n/d	n/d	n/d
	Thyroid cancer	IRS2	↓	↓	(129)
	Acute myeloid leukemia	n/d	n/d	n/d	n/d
	Acute lymphoblastic leukemia	n/d	n/d	n/d	n/d
	Bladder cancer	n/d	↓	↓	(334)
	Breast cancer	FN1	↓	↓	(301)
	Cervical cancer	ZEB1	↓	↓	(302)
	Cholangiocarcinoma	n/d	n/d	n/d	n/d
	Colorectal cancer	Onecut2, PAK6	↓	↓	(55, 335)
	Endometrial cancer	n/d	n/d	n/d	n/d
	Esophageal carcinoma	Bcl-2, Slug, SP1	↓	↓	(65, 68)
	Gastric cancer	Sp1, Notch1	↓	↓	(336, 337)
	Glioma	BMK1, SOX2	↓	↓	(82, 338)
	Head and neck carcinoma	n/d	↓	↓	(304)
	Liver cancer	CRKL, RAB23	↓	↓	(89, 305)
	Melanoma	LIMK1	↓	↓	(94)
	Nephroblastoma	IKK-β	↓	↓	(98)
	Neuroblastoma	IKKβ	↓	↓	(307)
	Non-small cell lung cancer	PTEN, RASSF8, TTF1γ and TIMP2	↑	↑	(308, 323)
	Oral squamous cell carcinoma	n/d	n/d	n/d	n/d
	Osteosarcoma	ZEB1, HOXA9	↓	↓	(103, 107)
	Ovarian cancer	p15PAF	↓	n/d	(339)
	Pancreatic cancer	NT-3	n/d	↓	(117)
	Prostate cancer	n/d	n/d	n/d	n/d
	Renal cell carcinoma	n/d	↑	n/d	(124)
	Small cell lung carcinoma	n/d	n/d	n/d	n/d
	Thyroid cancer	ZEB1	↓	↓	(131)

↓ - suppression by miRNA; ↑ - promotion by miRNA; n/d - no data.

lung cancer. Likewise, miR-429 decreases the migration and invasion of 15 cancer types, while it increases the migration of renal cell carcinoma and migration and invasion of non-small lung carcinoma.

The epithelial-mesenchymal process (EMT) is one of the crucial cellular processes in cancer cell invasion. During this process, epithelial cells gain mesenchymal capabilities including migration. The regulation of EMT is complex and is modulated

by numerous signaling pathways including TGF β and Wnt/ β -catenin and transcription factors such as Snail, Slug, ZEB1/2, and TWIST1/2 (7, 340). MiR-200 family is a well-known regulator of EMT because of targeting ZEB1 and ZEB2 (341) which are key inducers of this process (342). ZEB1/2 is targeted by miR-200a [osteosarcoma (104)], 200b [gastric cancer, oral squamous cell carcinoma, osteosarcoma (248, 257)], miR-200c [oral squamous cell carcinoma, prostate cancer (285, 329)], miR-141 [breast cancer (331)], and miR-429 [cervical cancer, osteosarcoma, thyroid cancer (103, 131, 302)]. Moreover, the miR-200 family targets other regulators of EMT. MiR-200a targets TGF β 2 in renal cell carcinoma and inhibits the invasion and migration of cancer cells (235). MiR-141 suppresses liver cancer cell invasion and migration by targeting TGF β R1 (91). Moreover, miR-429 targets Slug, a transcription factor that belongs to the Snail family and activates EMT. Thus, miR-429 inhibits the migration and invasion of esophageal cancer cells (68). On the contrary, miR-200a targets Catenin Beta 1 (CTNNB1), the member of the Wnt/ β -catenin pathway, and promotes the invasion and migration of esophageal cancer cells (70).

Cytoskeleton remodeling is a vital step in cells motility. It leads to the formation of cell membrane protrusions, then to cell contraction and retraction of rear-end (343). Moesin and radixin belong to ERM (ezrin-radixin-moesin) protein family that is responsible for cytoskeleton structure and cell migration (344). MiR-200c targets moesin in glioma (79) and miR-200b targets radixin in breast cancer cells (242). By targeting them, miR-200b and miR-200c suppress cancer progression (70). Fascin 1 (FSCN1) is an actin-bundling protein involved in the formation of protrusions. It is targeted by miR-200b leading to the decrease of cancer cell migration and invasion in bladder cancer (238). RhoE is a member of Ras superfamily and is responsible for actin reorganization. Both, miR-200b and miR-200c are described to target RhoE and inhibit the invasion of non-small cell lung cancer cells (344). Kindlin-2 is another protein involved in extracellular matrix regulation. It is reported to be directly targeted by miR-200b in esophageal carcinoma and in oral squamous cell carcinoma which causes the inhibition of cancer cell migration and invasion (79). TUBB3 (Tubulin Beta 3 Class III), a main cytoskeletal microtubule protein engaged in various processes including cancer invasion and migration, is targeted by miR-200b in colorectal cancer leading to the suppression of migration and invasion of cancer cells (247).

The ECM proteolysis and interactions with the cancer cell cytoskeleton play a crucial role in the migration and invasion of tumor cells (345). MiRNA-200c targets fibronectin (FN1), the component of the extracellular matrix, in gastric cancer cells and acts as a suppressor of invasion and migration (274). On the contrary, miR-200 family members also promote cancer progression by targeting the inhibitors of metalloproteinases that digest ECM. miR-200c targets RECK in bladder cancer (38), whereas TIMP2 is targeted by miR-200b in endometrial cancer

cells (66, 257). Moreover, miR-200a regulates cell-to-cell adhesion by targeting CDH1 (cadherin 1) (70).

Regulation of apoptosis by miR-200 family

Apoptosis is so-called programmed cell death, essential for maintaining tissue homeostasis. The mechanism of apoptosis is complex and involves several steps. Each of these steps can be impaired, thus leading to carcinogenesis (346). The major role in apoptosis belongs to caspases, which may be both initiators and executioners of apoptosis (347). Numerous studies have reported the influence of miRNAs on the regulation of both the intrinsic and the extrinsic apoptosis pathways (348).

The miR-200 family members act mainly as apoptosis promoters (Table 5). miR-200a promotes apoptosis in 6 cancer types and inhibits apoptosis only in cervical cancer. There are discordant results concerning the role of miR-200a in the regulation of non-small cell lung cancer. MiR-200b promotes apoptosis in 5 cancer types and miR-200c promotes apoptosis in 6 cancer types. miR-141 promotes apoptosis in 6 cancer types, and inhibits apoptosis in pancreatic cancer, but its role in prostate cancer is inconsistent. miR-429 promotes apoptosis in 9 cancer types and inhibits apoptosis only in colorectal cancer.

MiR-200a enhances TRAIL-triggered apoptosis in gastric cancer cells by targeting TNF α -induced protein 3 (A20) (349). Moreover, miR-200a shows pro-apoptotic activity in the human hepatocellular carcinoma cell line (227). In Wilms tumor cells, miR-200a promotes apoptosis by targeting CDC7 (350). Similarly, miR-200a can promote apoptosis in prostate cancer cells through BRD4/AR signaling pathway (234), by directly targeting SIRT1 (236) or by targeting Sperm-associated antigen 9 (SPAG9) (100). The last-mentioned protein, SPAG9, is an oncogene protein that regulates renal cell carcinoma progression. Accordingly, its regulation by miR-200 also has a stimulatory effect on apoptosis in renal cell carcinoma (126). Moreover, miR-200a has been shown to promote apoptosis of renal cell carcinoma cells by targeting CBL (127). Furthermore, by targeting FOXA1, miR-200a also promotes cell apoptosis in anaplastic thyroid carcinoma (130). In contrast, miR-200a suppresses apoptosis and promotes the proliferation of cervical cancer cells by targeting EGLN1 (220). In the case of NSCLC, miR-200 demonstrates a two-fold action. It promotes apoptosis by downregulation of the hepatocyte growth factor (HGF) (100).

MiR-200b has been shown to have pro-apoptotic effects among all the studied types of cancer. In breast cancer, miR-200b induces apoptosis and inhibits cell proliferation by directly targeting Sp1 (239). Moreover, high expression of miR-200b appeared to be an independent prognostic factor for patients with breast cancer (239). Moreover, miR-200b-3p shows pro-apoptotic effects in colorectal cancer by inactivating the Wnt/ β -

TABLE 5 Members of the miR-200 family regulating apoptosis.

miRNAs	Cancer	Target	Apoptosis <i>in vitro</i>	Ref.
miR-200a	Cervical cancer	EGLN1	↓	(220)
	Gastric cancer	A20	↑	(349)
	Liver cancer	n/d	↑	(227)
	Nephroblastoma	CDG7	↑	(350)
	Non-small cell lung cancer	HGF, RHPN2	↓/↑	(100, 351)
	Prostate cancer	BRD4, SIRT1, SPAG9	↑	(126, 234, 236)
	Renal cell carcinoma	CBL, SPAG9	↑	(126, 127)
miR-200b	Thyroid cancer	FOXA1	↑	(130)
	Acute myeloid leukemia	n/d	↑	(237)
	Breast cancer	Sp1	↑	(239)
	Colorectal cancer	TU883, Wnt1	↑	(246, 247)
	Oral squamous cell carcinoma	CDK2, PAF	↑	(352)
miR-200c	Ovarian cancer	ATAD2	↑	(259)
	Breast cancer	XIAP	↑	(264)
	Colorectal cancer	CDK2	↑	(271)
	Gastric cancer	EDNRA	↑	(275)
	Liver carcinoma	MAD2L1	↑	(88)
miR-141	Nephroblastoma	n/d	↑	(278)
	Non-small cell lung cancer	n/d	↑	(279)
	Acute lymphoblastic leukemia	TRAF5	↑	(32)
	Colorectal cancer	EGFR	↑	(332)
	Gastric cancer	YAP1	↑	(75)
miR-429	Head and neck carcinoma	EGFR	↑	(85)
	Osteosarcoma	GLI2	↑	(106)
	Pancreatic cancer	MAP4K4	↓	(298)
	Prostate cancer	KLF9	↓/↑	(299, 300)
	Thyroid cancer	IRS2	↑	(129)
miR-200b	Gastric carcinoma	Bcl-2	↑	(303, 353)
	Glioblastoma	Bcl-2	↑	
	Nephroblastoma	c-MYC	↑	(96)
	Colorectal cancer	HMG3	↑	(59)
	Osteosarcoma	ZEB1	↑	(103)
	Glioblastoma	SOX2	↑	(82)
	Esophageal carcinoma	Bcl-2, SP1	↑	(65)
	Thyroid cancer	ZEB1	↑	(131)
	Colorectal cancer	SOX2	↓	(53)
	Cervical carcinoma	IKKb	↑	(46)

↓ - suppression by miRNA; ↑ - promotion by miRNA; n/d - no data

catenin signaling pathway (246). Likewise, the same occurs in esophageal squamous cell carcinoma where miR-200b also modulates the Wnt/β-catenin signaling pathway by targeting CDK2 and PAF. Therefore, by inducing cell cycle arrest and apoptosis, miR-200b alleviates cancer cell growth (246). In ovarian cancer, miR-200b significantly increases the apoptosis rate of the cancer cells by targeting ATAD2 and regulating PI3K/AKT signaling pathway (259). miR-200b inhibited cancer growth and induced cell apoptosis in the oxaliplatin-resistant colorectal cancer cells through suppression of βIII-tubulin protein expression (247).

MiR-200c also has a pro-apoptotic effect in all studied types of cancer. In triple-negative breast cancer cells, microRNA-200c was found to downregulate XIAP expression and thus suppress proliferation and promote apoptosis of cancer (264). In gastric cancer, miR-200c promotes apoptosis of the tumor cells by downregulation of endothelin receptor A (EDNRA) expression (275). Similarly, in human hepatocellular carcinoma miR-200c induces apoptosis *via* suppressing MAD2L1 (88). Overexpression of miR-200c has been proven to promote apoptosis in Wilms tumors *via* downregulation of the Akt/GLUT1 signaling pathway (278). Furthermore, the high

expression of miR-200c was also reported to enhance apoptosis in lung cancer tissues, where it caused activation of the JNK signaling pathway and upregulation of an ER stress-related protein, RECK.

MiR-141 demonstrates apoptosis-promoting activity in the majority of cancer types. However, miR-141 appears to modulate apoptosis in a bidirectional manner in prostate cancer. miR-141 induces prostate cancer cell apoptosis *via* targeting Runt-related transcription factor 1 (RUNX1) (300). However, another study reported that miR141 significantly reduced cell apoptosis, thus appearing to be a novel oncogene miRNA, which promotes prostate tumorigenesis *via* suppressing a key transcription factor kruppel-like factor-9 (KLF9) (299). Therefore, it remains to define the role that miR-141 plays in the apoptosis of prostate cancer cells. In T-cell acute lymphoblastic leukemia cells the upregulation of miR-141-3p significantly decreased cancer cell proliferation and promoted its apoptosis by direct targeting tumor necrosis factor receptor-associated factor 5 (TRAF5) (32). Furthermore, among colorectal cancer cells, miR-141- has been proven to reduce cell growth and induce apoptosis and differentiation of colorectal cancer cells by targeting EGFR (332). Similarly, in head and neck squamous cell carcinoma, where miR-141, also by suppressing EGFR signaling, inhibits tumor growth, and promotes apoptosis in cancer (85). Moreover, in pancreatic cancer cells, miR-141 acts as a tumor suppressor by targeting MAP4K4, which knockdown inhibits cell proliferation and induces G1 arrest and apoptosis (298). Moreover, since insulin receptor substrate 2 (IRS2), a known oncogene, was confirmed to be a direct target of miR-141, its overexpression blocks cell proliferation and induces cell apoptosis of thyroid cancer (129).

MiR-429 acts in a pro-apoptotic manner in the majority of cancer types. In colorectal cancer, miR-429 has been demonstrated to exert a two-fold effect. By mediating high mobility group box 3 (HMGB3) miR-429 promotes apoptosis in colorectal cancer cells (59). However, directly targeting SOX2 may prevent cell death (53). Therefore, it is unclear whether

miR-429 plays an oncogenic or tumor-suppressive role in colorectal cancer. Remarkably, SOX2 is also directly targeted by miR-429 in glioblastoma multiforme, but in this cancer downregulation of SOX2 inhibits cell proliferation and induces apoptosis (82). Moreover, in glioblastoma miR-429 induces apoptosis also by targeting Bcl-2. Furthermore, downregulation of Bcl-2 by miR-429 induces apoptosis in gastric carcinoma (303, 353). In both types of cancers, overexpression of miR-429 inhibits Bcl-2-mediated cell survival (303, 353). In esophageal carcinoma upregulation of miR-429, by targeting both Bcl-2 and SP1, promotes apoptosis in cancer cells (65). Another direct target for miR-429 is ZEB1 which inhibition results in the induction of apoptosis in osteosarcoma (103) and thyroid cancer cells (131). Moreover, miR-429 enhances apoptosis in nephroblastoma, by targeting c-myc (96) and also in cervical carcinoma, through the NF- κ B pathway by targeting IKK β (46).

Regulation of angiogenesis by miR-200 family

Angiogenesis is the process of formation of new capillaries from a pre-existing vasculature, which is a crucial factor affecting tumor formation, progression, and metastasis (217). Malignant tumors create an environment that favors the predominance of proangiogenic factors over antiangiogenic factors, resulting in inappropriate vessel growth towards the neoplastic lesion. Many proangiogenic and antiangiogenic agents have been identified. They may be secreted by endothelial cells, tumor cells, or by the surrounding stroma. MiRNAs may target genes involved in angiogenesis, but on the other hand, their expression can be modulated *via* pro-angiogenic or anti-angiogenic factors (354).

miR-200 family members act both as angiogenesis inhibitors and promoters (Table 6). miR-200a, miR-200b and miR-429

TABLE 6 Regulation of angiogenesis by miR-200 family members.

miRNAs	Cancer	Target	Angiogenesis	Ref.
miR-200a	n/d	n/d	↓	(355)
miR-200b	n/d	n/d	↓	(355)
	Prostate cancer	n/d	↓	(261)
miR-200c	n/d	n/d	↓	(355)
	Pancreatic cancer	n/d	↑	(356)
miR-141	Small cell lung cancer	KLF12	↑	(193)
	Ovarian cancer	n/d	↑	(357)
	n/d	CXCL12 β , GAB1, GATA6, NRP1, TGF β 2	↓	(355)
miR-429	n/d	n/d	↓	(355)

↓ - suppression by miRNA; ↑ - promotion by miRNA; n/d - no data.

inhibit angiogenesis. miR-200c is described as an angiogenesis inhibitor, but it promotes angiogenesis in pancreatic cancer. Similarly, miR-141 is described to inhibit angiogenesis, but it also promotes angiogenesis in small-cell lung cancer and ovarian cancer.

In 2011, Chan et al. first described the effect of miR-200b on the suppression of angiogenesis, thus identifying the first member of the miR-200 family to have an inhibitory effect on this process (358). Several years after this finding, it was confirmed that all members of the miR-200 family suppress angiogenesis (193). In prostate cancer cells, miR-200b reverses the angiogenic switch (261). Nevertheless, some members of the miR-200 family, more specifically miR-200c and miR-141, may demonstrate pro-angiogenic effects as well. For instance, increased expression of miR-200c in pancreatic cancer endothelial cells is observed and its inhibition significantly reduces cancer cell migration and angiogenesis, confirming the pro-angiogenic effects of miR-200c in pancreatic cancer (356). MiR-141 is another member of the miR-200 family that, in addition to its anti-angiogenic effects (355), also demonstrates angiogenesis-promoting activity in ovarian cancer. The ovarian cancer-secreted miR141-3p promotes endothelial cell angiogenesis by activating the JAK/STAT3 and NF- κ B signaling pathways (357). Likewise, in small cell lung cancer (SCLC), miR-141 promotes angiogenesis via the KLF12 pathway (193).

Regulation of drug resistance by miR-200 family

Drug resistance in cancer cells, resulting in reduced or no response to the administered therapy and poorer overall survival of cancer patients is a limiting factor for this treatment approach. Furthermore, residual cancer cells surviving therapy gradually divide, thereby initiating recurrence of the disease, often having worse responses to treatment and a poorer prognosis. Chemoresistance can develop through various mechanisms, such as gene mutation, DNA methylation, and histone modification (359). Numerous studies focus on identifying and understanding the role that miRNAs play in the development of chemotherapy resistance. Members of the miR-200 family appear to be critical of this phenomenon. Depending on cancer and the miR-200 family member, the underlying mechanism and the effect they have on modulating the resistance are different.

miR-200 family members reduce drug resistance in most cases (Table 7). miR-200a enhances drug resistance in breast and liver cancer, and it reduces drug resistance in glioma. miR-200b reduces drug resistance in 7 cancer types. miR-200c reduces drug resistance in 7 cancer types but it enhances chemoresistance in esophageal carcinoma. miR-141 increases drug resistance in breast cancer and glioma and it decreases drug resistance in neuroblastoma, colorectal and pancreatic cancer. miR-141

increases the resistance to cisplatin in non-small cell lung cancer and ovarian cancer. However, it reduces the resistance to other drugs in those cancer types. miR-429 reduces drug resistance in colorectal and ovarian cancers and increases drug resistance in endometrial cancer.

MiR-200a demonstrates various effects on the modulation of drug resistance among different types of cancer. In breast cancer cells, Mir-200a, via antagonizing TP53INP1 and YAP1, contributes to increased resistance to chemotherapeutics (360). Moreover, inhibition of miR-200a enhances gemcitabine chemosensitivity in cancer cells (360). In human hepatocellular carcinoma, miR-200a-3p targets dual-specificity phosphatase 6 (DUSP6) to augment cancer cell resistance to 5-fluorouracil, doxorubicin, and cisplatin (361). In contrast, miR-200a has opposite effects on drug resistance in glioma. Moreover, downregulation of miR-200a is associated with decreased chemotherapeutic treatment efficacy (81).

MiR-200b appears to reduce the chemoresistance of all cancers. In cholangiocarcinoma, it was demonstrated that miR-200b, as well as miR-200c, reduces resistance to chemotherapeutics by directly targeting SUZ12 and ROCK2 (51). The same effect, but in a different mechanism, was reported with miR-200b-3p in colorectal cancer, where, via targeting TUBB3, it reduced resistance to oxaliplatin and promoted apoptosis and growth inhibition in resistant cancer cells (247). In bladder cancer cells, methylation of miR-200b was associated with resistance of this cancer to cisplatin (134). Moreover, it was suggested that epigenetic silencing of miR-200b might be a marker of cisplatin resistance in this tumor. In addition, miR-200b seems to play an essential role in the response of non-small lung cancer to treatment. It has been evidenced that induction of miR-200b, but also miR-141, increased sensitivity to nintedanib in nintedanib-resistant cells (365). Moreover, miR-200b increases the chemosensitivity of the docetaxel-resistant lung cancer cells by directly targeting autophagy-associated gene 12 (ATG12) (364). A further study revealed that expression of miR-200b, by direct targeting SUZ12 and through histone deacetylase 1/Sp1/miR-200b signaling pathway might lead to the formation of chemoresistant phenotype in docetaxel-resistant cancer cells. Moreover, histone deacetylase-mediated silencing of miR-200b increased chemoresistance in lung adenocarcinoma cells (254, 363). Furthermore, miR-200b in lung cancer cells inhibits chemoresistance and increased sensitivity to cisplatin via targeting p70S6K1 (256). This miRNA was also found to reverse the chemoresistance of docetaxel-resistant lung adenocarcinoma cells via targeting E2F3 (362). Moreover, also in small cell lung cancer, miR-200b reduces drug resistance namely by modulating ZEB2, which in small cell lung cancer leads to multidrug resistance of the tumor (366). By regulating B-cell-specific Moloney murine leukemia virus insertion site 1 (Bmi-1), miR-200b has been shown to enhance the chemosensitivity of prostate cancer cells to docetaxel (262).

TABLE 7 Regulation of drug resistance by miR-200 family members.

miRNAs	Cancer	Target	Drug resistance	Ref.
miR-200a	Breast cancer	TP53MNP1	↑	(360)
	Glioma	n/d	↓	(81)
	Liver cancer	DUSP6	↑	(361)
miR-200b	Bladder cancer	n/d	↓	(134)
	Cholangiocarcinoma	SUZ12 and ROCK2	↓	(51)
	Colorectal cancer	TUBB3	↓	(247)
	Non-small cell lung cancer	ATG12, E2F3, p70S6K1, SUZ12	↓	(254, 256, 362–365)
	Prostate cancer	n/d	↓	(262)
	Small cell lung cancer	ZEB2	↓	(366)
	Ovarian cancer	DNMT3A/DNMT3B	↓	(367)
	Breast cancer		↓	(368)
miR-200c	Gastric carcinoma	ZEB2	↓	(369)
	Melanoma	n/d	↓	(277)
	Osteosarcoma	AKT2	↓	(105)
	Ovarian cancer	DNMT3A/DNMT3B	↓	(367)
	Pancreatic cancer	n/d	↓	(330)
	Cholangiocarcinoma	SUZ12 and ROCK2	↓	(51)
	Esophageal carcinoma	n/d	↑	(370)
	Colorectal cancer	EGFR	↓	(291)
	Breast cancer	EIF4E	↑	(371)
miR-141	Glioma	TP53	↑	(372)
	Neuroblastoma	FUS	↓	(293)
	Non-small cell lung cancer	PDCD4	↑/↓	(365, 373)
	Ovarian cancer	KEAP1	↑/↓	(374, 375)
	Pancreatic cancer	MAP4K4	↓	(298)
	Colorectal cancer	DUSP4	↓	(376)
miR-429	Endometrial cancer	n/d	↑	(60)
	Ovarian cancer	ZEB1	↓	(377)

↓ - suppression by miRNA; ↑ - promotion by miRNA; n/d - no data.

Besides, in ovarian cancer, miR-200b and miR-200c have been reported to be able to reverse cisplatin resistance by directly targeting DNMT3A/DNMT3B (367).

In most cases, miR-200c decreases drug resistance. In breast cancer, miR-200c increases sensitivity to chemotherapy as well as sensitizes HER2+ cancer cells to trastuzumab (368). Moreover, miR-200c, by directly targeting and thus downregulating ZEB2, increases the sensitivity of gastric cancer tissues to cisplatin (369). In melanoma cells, overexpression of miR-200c significantly reduces resistance to chemotherapy *via* downregulation of Bmi-1 (277). This miRNA was also revealed to enhance osteosarcoma chemosensitivity to cisplatin by targeting AKT2 (105). In pancreatic cells, miR-200c sensitizes cancer cells to chemotherapy (330). In contrast, overexpression of miR-200c in esophageal cancer induces chemoresistance to cisplatin by activation of the Akt signaling pathway (370).

Similarly, miR-141 has been reported to have significant effects on the modulation of drug resistance. In neuroblastoma cells, miR-141 increases cancer cell sensitivity to cisplatin

(293). Also in pancreatic cancer, miR-141, by directly targeting MAP4K4, increases the chemosensitivity of the cancer cells (298). However, in breast cancer upregulation of miR-141 has been found to exacerbate docetaxel resistance of cancer cells (371). In non-small cell lung carcinoma, the function of miR-141 is more complex as, on the one hand, it increases sensitivity to nintedanib in nintedanib-resistant cancer cells (365), but on the other hand, *via* upregulation of PDCD4, it reverses cisplatin resistance (373). Moreover, in ovarian cancer, the action of miR-141 is also bidirectional. Transfection with inhibitors of miR141, as well as of inhibitors of miR-200c, in ovarian cancer cell lines induced cell resistance to paclitaxel and carboplatin (375); however, it has been described that expression of miR-141, *via* regulating KEAP1, can increase resistance to cisplatin chemotherapy in ovarian cancer cells (374). In glioma cells, miR-141 renders resistance to temozolomide therapy by targeting TP53 (372).

The last member of the miR-200 family is miR-429, whose effect on the modulation of drug resistance has been observed in

colorectal, endometrial, and ovarian cancers. In colorectal cancer, overexpression of miR-429 has been found to target DUSP4, block the JNK pathway, and thereby increase cancer cell sensitivity to nintedanib (376). Also in ovarian cancer, overexpression of miR-429 appears to sensitize cancer cells to cisplatin by targeting ZEB1 (377). However, in endometrial cancer, the effect of miR-429 on drug resistance of this tumor is the opposite, as transfection with anti-miR-429 increased the cytotoxic effect of cisplatin in cancer cells, thus improving treatment efficacy (60).

Regulation of immune response by miR-200 family

Tumor cells evade immune response via multiple mechanisms. Programmed Cell Death Protein 1 (PD-1) and its ligand, PD-L1, are key immune checkpoint molecules suppressing anti-tumor immune response (378). Several miRNAs were identified to regulate the PD-1/PD-L1 axis, including miR-200 (379). By targeting PD-L1, miR-200 enhances CD8⁺ cytotoxic T-cells activity in the tumor microenvironment and regulates the metastatic potential of tumor cells (379). Moreover, PD-L1 is targeted by miR-429 in gastric cancer (380).

MiR-200 family regulates also myeloid cells in the tumor microenvironment. MiR-200c by targeting PTEN and FOG2 induces the expansion and enhances the immunoregulatory properties of myeloid-derived suppressor cells (MDSCs) (381). It induces, among others, the expression of arginase 1, a key immunoregulatory enzyme of MDSCs (382), potentiating suppressive effects on T-cells (381). Moreover, miR-200c suppresses the expression of multiple cytokines by tumor-associated macrophages (383). Restoration of miR-200c upregulates cytokines and promotes M1 polarization of macrophages (383). Notably, cytokines suppressed by miR-200c predict favorable survival of TNBC patients (383). Similarly, miR-200a promotes phagocytosis of tumor cells by macrophages by targeting CD47, a “do not eat me” signal protein overexpressed in tumor cells (86). Nonetheless, more research is required to dissect the role of the miR-200 family in the antitumor immune response as well as patients’ response to immunotherapy.

Genome instability and mutations

Various miRNAs regulate the expression of DNA damage proteins leading to genomic instability (384). However, little is known regarding the role of the miR-200 family in the regulation of genomic instability and mutations. It was demonstrated that miR-200a regulates DNA repair in aging keratinocytes (385),

nonetheless, its role in genome instability in cancer requires further studies.

Novel hallmarks of cancer

Recently, five emerging hallmarks of cancer have been suggested, including dysregulation of cellular energetic, unlocking phenotypic plasticity, dysregulation of the microbiome, nonmutational epigenetic reprogramming, and senescence (214). Despite little being known about the role of the miR-200 family in novel hallmarks of cancer, some studies suggested that they may be important regulators of these features.

MiRNAs, including the miR-200 family, are involved in the reprogramming of cancer cell metabolism. For instance, miR-200b suppresses lactate dehydrogenase A which suppresses glycolysis leading to the inhibited proliferation and invasion of glioma cells (386). Moreover, miR-200b/miR-200c regulates EMT differentiation and proliferation by modulation of metabolic properties of colorectal cancer cells (387). Notably, the miR-200 family also regulates the cellular senescence of cancer cells. It was demonstrated that suppression or loss of the miR-200 family in cancer cells induces morphological changes, cell cycle arrest, and induces cell senescence (388).

Recently, more and more studies have stated that the multifactorial impact of polymorphic microbiomes on cancer regulation is linked to their bidirectional interference with miRNAs in which those two factors interact resulting in apoptosis or proliferation of tumor cells (389, 390). A prominent example is an ovarian cancer where tissue-specific bacteria, *L. lactis*, seem to be in control of miR-200b and TLR-4 downregulation, which is connected to the progression of ovarian cancer (389). Another example of miRNA-microbiome interaction is exosomal miR-200c which was identified as a tumor suppressor of colorectal cancer cells, but only after it came in contact with lipopolysaccharide (LPS) that is a component of the bacterial outer membrane (391). Nonetheless, more research is required to determine the role of the miR-200 family in the regulation of these hallmarks of cancer.

Conclusions

Members of the miR-200 family are crucial regulators of hallmarks of cancer. Several studies described alterations in their expression in human tumors and determined their utility as biomarkers in cancer. Our literature review summarized known functions and biological targets of the miR-200 family in different types of cancer. Furthermore, it identified gaps and limitations in current knowledge indicating the directions of further research. More studies are necessary to determine the role of members of the miR-200 family in the regulation of recently added hallmarks of cancer. Additionally, preclinical

studies are required to determine the therapeutic potential of the miR-200 family.

Author contributions

KK and TG are co-first authors. All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Conflict of interest

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Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients

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Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients

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Endometrial cancer (EC) is one of the most common types of cancer of the female reproductive system. EC is classified into two types (EC1 and EC2). MiRNAs are single-stranded RNA molecules that regulate gene expression posttranscriptionally. They have aberrant expression profiles in cancer, including EC. This study aimed to assess the level of expression of a panel of 16 miRNAs in both types of EC and healthy endometrium (HE). A total of 45 patients were enrolled into the study, 18 patients diagnosed with EC1, 12 diagnosed with EC2, and 15 HE controls. Tumor tissues or healthy endometrial tissues were dissected from archival formalin-fixed paraffin-embedded (FFPE) using laser capture microdissection (LCM). RNA was isolated from collected material and the expression of selected miRNAs was determined using the real-time qPCR. We found that miR-23b, miR-125b-5p, miR-199a-3p, miR-221-3p, and miR-451a were downregulated in EC in comparison to HE. Moreover, the expression of miR-34a-5p and miR-146-5p was higher in EC1 compared to EC2. Analysis of The Cancer Genome Atlas (TCGA) database confirmed decreased levels of miR-23b, miR-125b-5p, and miR-199a-3p in EC. Decreased miR-23b expression was associated with worse survival of EC patients.

Endometrial cancer (EC) arises from the epithelial lining of the uterus (endometrium) and is the most common cancer of the female reproductive system in the USA¹. It is estimated that 65,950 new cases will be diagnosed in 2022, representing 3.5% of all new cancer cases in the USA, and the disease will be fatal to 12,550 patients, which is equivalent to 2.1% of all cancer deaths². The incidence and mortality are steadily increasing in the population which is associated with many factors, including the growing prevalence of obesity—one of the major risk factors for the development of the EC³. The 5-year relative survival is estimated at 81.1%⁴. EC can be classified based on two different classification systems. The traditional classification proposed in 1981 by Bokhman⁵, divides EC into two types, where type 1 of EC (EC1) is defined as an estrogen-dependent tumor associated with endometrial hyperplasia, and type 2 of EC (EC2) as an estrogen-independent tumor which is associated with endometrial atrophy. Another classification of EC divides tumors based on the histopathological characteristics, where EC can be categorized into endometrioid carcinoma, serous carcinoma, clear-cell adenocarcinoma, carcinosarcoma, and other types⁶. The Cancer Genome Atlas Research Network (TCGA) analysis revealed that EC can be classified based on their molecular features which enable better stratification of EC patients⁷.

MiRNAs (microRNAs) are endogenous, small single-stranded non-coding RNA molecules that regulate gene expression at the posttranscriptional level⁸. They play a significant role in a broad range of biological processes such as cellular proliferation, differentiation, and apoptosis^{9–12}. The biogenesis of miRNAs involves multiple steps that occur at each step of the synthesis of the functional molecule^{9,11}. The expression of miRNAs is controlled by numerous transcription factors, two of which, p53 and c-Myc, appear to play a key role in this process¹⁰. The dysregulation of miRNAs may result in the initiation of carcinogenesis, which can affect all hallmarks of cancer as defined by Hanahan and Weinberg¹³, including replicative immortality, proliferative signaling, immune evasion, deactivation of growth suppressors, or inducing angiogenesis^{10,14}. Notably, miRNAs can act as both: oncogenes or tumor suppressors, as dictated by their target genes¹⁵. Over the past decade, a body of evidence of dysregulation of miRNA expression in a variety of cancer types has been described. The focus on this subject by

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numerous research groups, including our, resulted in reports on the role of miRNAs as cancer biomarkers, as well as markers of cancer invasiveness and metastasis^{12,16–19}.

This study aimed to further characterize the pathogenesis of EC by determining the level of miRNAs typically involved in cancer development. The study was conducted on microdissected tissue samples of both types of EC: EC1 and EC2 and the healthy endometrial tissue.

Results

In this study, we enrolled 30 primary EC patients, previously untreated, and 15 control patients with healthy endometrium (HE) operated due to other gynecological pathologies (leiomyoma). The endometrium of these patients was histopathologically confirmed to be normal. To ensure that material obtained for miRNAs expression analysis contained only EC or HE tissue, we used Laser Capture Microdissection (LCM) to precisely dissect only specific fragments of tissue. From each FFPE sample of EC, only tumor tissue was dissected using LCM. In HE samples, only glandular endometrial tissue was dissected (Fig. 1). From the collected material we have determined the level of: miR-21-3p, miR-23b, miR-34a-5p, miR-96-5p, miR-125b-5p, miR-134-5p, miR-146-5p, miR-150-5p, miR-181b-5p, miR-182-5p, miR-199a-3p, miR-200b-3p, miR-211-3p, miR-221-3p, miR-410-3p, and miR-451a.

miR-23b, miR-125b-5p, miR-199a-3p, miR-221-3p, and miR-451a are downregulated in EC. The analysis of 16 miRNAs revealed that the levels of expression of certain miRNAs were significantly downregulated in EC compared to HE. miR-23b was downregulated 4.54 times, (Fig. 2a, $p < 0.0001$), miR-125b-5p was downregulated 7.15 times (Fig. 2b, $p = 0.0005$), miR-199a-3p was downregulated 11.11 times (Fig. 2c, $p < 0.0001$), miR-221-3p was downregulated 4.54 times, (Fig. 2d, $p = 0.0029$), and miR-451a was downregulated 17.24 times (Fig. 2e, $p < 0.0001$). In contrast, there were no statistically significant differences between the expression of miR-21-3p, miR-34a-5p, miR-96-5p, miR-134-5p, miR-146-5p, miR-150-5p, miR-181b-5p, miR-182-5p, miR-200b-3p, miR-211-3p, and miR-410-3p in EC compared to HE (Fig. 3a–k, $p > 0.05$).

miR-34a-5p and miR-146-5p are upregulated in EC1 compared to EC2. Next, we analyzed the differences in miRNAs expression profiles between EC1 and EC2. Out of 30 EC samples used in this study, 18 samples were EC1 type and 12 samples were EC2. The expression of two miRNAs was upregulated in EC1 compared to EC2. These were miR-34a-5p (Fig. 4a, upregulated 5.43 times, $p = 0.031$) and miR-146-5p (Fig. 4b, upregulated 3.50 times, $p = 0.0479$). There was no differences in expression of miR-21-3p, miR-23b, miR-96-5p, miR-125b-5p, miR-134-5p, miR-150-5p, miR-181b-5p, miR-182-5p, miR-199a-3p, miR-200b-3p, miR-211-3p, miR-221-3p, miR-410-3p, and miR-451a between EC1 and EC2 specimens (Fig. 5a–n, $p > 0.05$).

miR-23b, miR-125b-5p, miR-199a-3p, miR-221-3p are downregulated in TCGA cohort. To confirm our findings, we analyzed the expression of investigated miRNAs in The Cancer Genome Atlas (TCGA) on the cohort of 418 EC tissues and 32 HE controls using OncomiR database²⁰. The levels of miR-23b (Fig. 6a, downregulated 1.87 times, $p < 0.0001$), miR-125b-5p (Fig. 6b, downregulated 2.34 times, $p < 0.0001$), miR-199a-3p (Fig. 6c, downregulated 1.26 times, $p = 0.0067$), and miR-221-3p (Fig. 6d, downregulated 1.45 times, $p = 0.0110$) were significantly downregulated in EC compared to HE. There were no differences in expression levels of miR-451a in EC compared to HE (Fig. 6e, $p > 0.05$).

Decreased miR-23b expression is associated with worse survival. Further, we checked whether the expression of downregulated miRNAs in the EC tissue correlated with the survival of patients. We analyzed the patients' survival and miRNAs level in TCGA EC cohort using OncoLnc²¹. We found that worse survival was associated only with decreased expression of miR-23b (Fig. 7a, $p = 0.0203$). The decreased expressions of miR-125-5p, miR-199a-3p, miR-221-3p, or miR-451a were not correlated with the survival of EC patients (Fig. 7b–e, $p > 0.05$).

miR-23b suppresses the proliferation of EC cells. Decreased expression of miR-23b in EC tissue suggests its role as tumor-suppressor miRNA. To determine whether miR-23b may act as a tumor-suppressor, we transfected Ishikawa EC cells with synthetic mimic miR-23b, anti miR-23b (inhibitor of miR-23b), and corresponding scramble control and performed a proliferation assay. We observed that upregulation of miR-23b with mimic miR-23b potently suppressed the proliferation of Ishikawa cells (Fig. 8, $p = 0.0065$). Conversely, inhibition of miR-23b with anti miR-23b upregulated the proliferation of Ishikawa cells (Fig. 8, $p = 0.0226$). It suggests that miR-23b is a tumor suppressor miRNA in EC. Further, we analyzed The Encyclopedia of RNA Interactomes (ENCORI)²² to identify the enriched KEGG pathways of miR-23b targets (Table 1)^{23–25}. It revealed that miR-23b regulates crucial pathways in cancer, including P53 signaling pathway, Wnt signaling pathway, mTOR pathway, cell cycle, and pathways regulating the actin cytoskeleton.

Discussion

Aberrant expression of miRNAs has been observed in many types of cancers, including EC^{12,26–28}. Our recent systematic review revealed that miRNAs are crucial regulators of EC progression¹⁶. By analyzing 115 articles, we identified 106 dysregulated miRNAs involved in the modulation of the EC invasiveness and metastasis. They regulate not only EC cells invasion and migration but also influence metastasis and tumor growth. Moreover, the expression of several miRNAs was correlated with clinical parameters of EC patients¹⁶. In this study, we analyzed the expression of 16 miRNAs with a well-established role in tumor tissues of EC1 and EC2 as well as in healthy

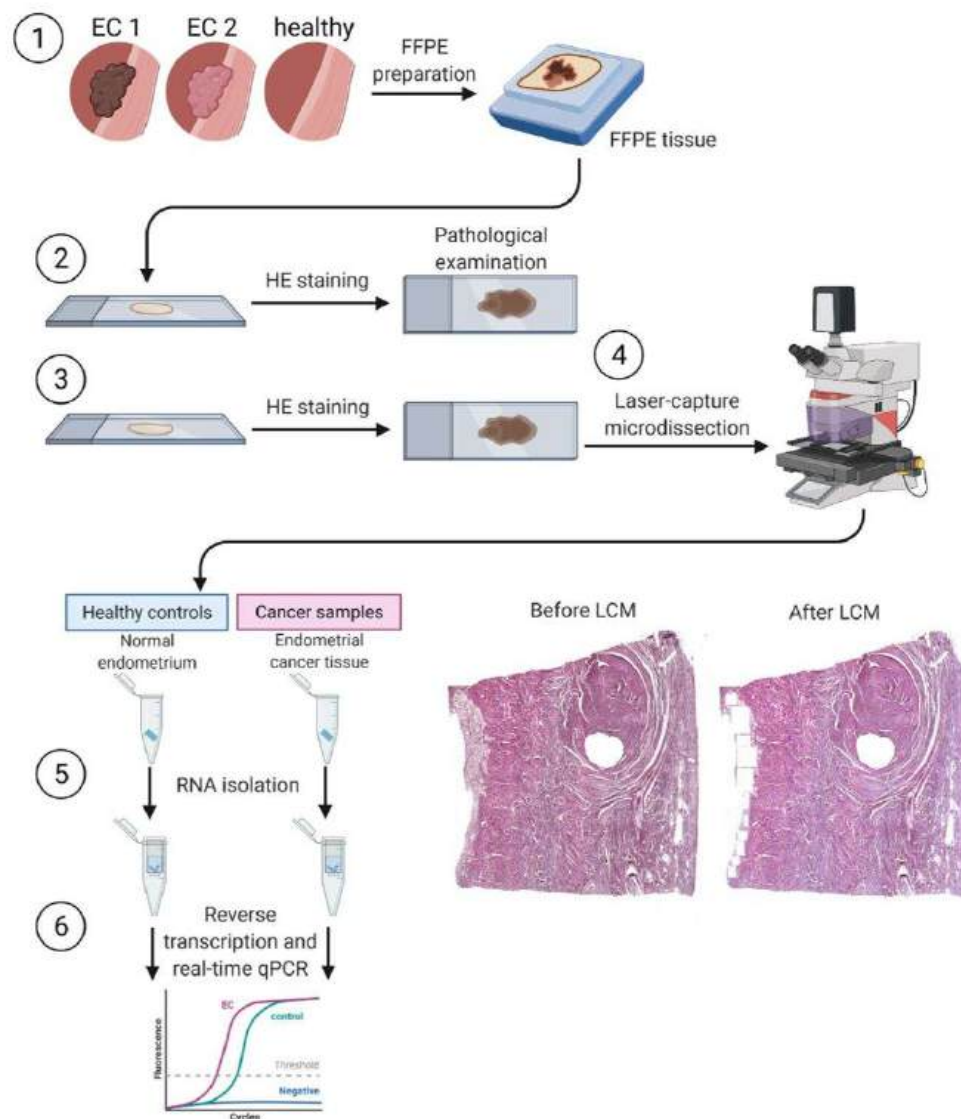


Figure 1. Schematic representation of the study design. (1) Formalin-fixed paraffin-embedded (FFPE) samples were prepared from endometrial cancer type 1 (EC1) and type 2 (EC2) tumors and healthy endometrium. (2) FFPE specimens were hematoxylin and eosin stained for pathological examination. (3) FFPE specimens were hematoxylin and eosin stained and (4) subjected to laser-capture microdissection (LCM). Microscopic scans of slides before LCM (left) and after LCM (right) with dissected cancer tissue. (5) RNA was isolated from the collected tissue of endometrial cancer and healthy endometrium. (6) After reverse transcription, the expression of selected miRNAs was assessed using real-time qPCR method. Created using Biorender.com.

endometrium¹². We identified five miRNAs, miR-23b, miR-125b-5p, miR-199a-3p, miR-221-3p, and miR-451a, that are downregulated in EC compared to HE.

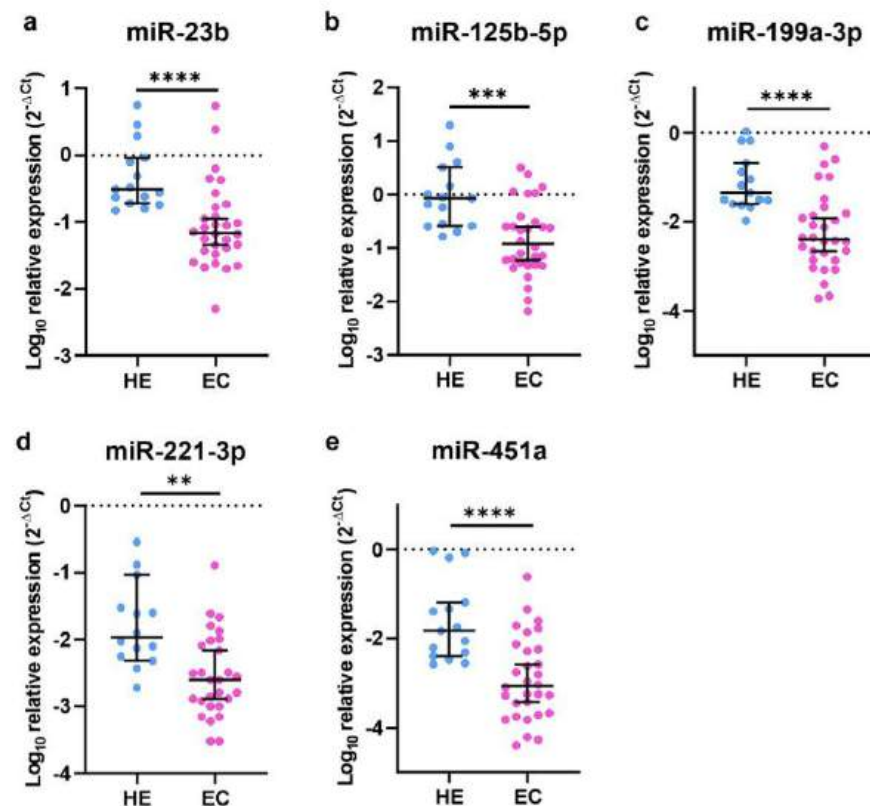


Figure 2. miR-23b, miR-125b-5p, miR-199a-3p, miR-221-3p, and miR-451a are downregulated in EC. The expression of miR-23b (a) and miR-125b-5p (b), miR-199a-3p (c), miR-221-3p (d), and miR-451a (e) in dissected tumor tissue of EC1 and EC2 ($p < 0.0001$, $p = 0.0005$, $p < 0.0001$, $p = 0.0029$, $p < 0.0001$, respectively). P -values were calculated using the Mann-Whitney test.

MiR-23b plays contrary roles in different types of cancer but is a tumor suppressor miRNA in EC^{29,30}. MiR-23b targets metastasis-associated in colon cancer-1 (MACC1) inhibiting EC cells proliferation, invasion, and migration. Moreover, miR-23b suppresses EC metastasis *in vivo* in a murine model³⁰. The expression of miR-23b was downregulated in EC-derived cell lines compared to the normal fallopian epithelial cells. It is also downregulated in FFPE EC tissues in the miRNA-profiling study³¹. Moreover, the expression of miR-23b was lower in grade 3 EC1 compared to grade 1 tumors³². We found that miR-23b is downregulated in EC tissues compared to HE regardless of the EC type. Additionally, analysis of the TCGA cohort revealed that decreased expression of miR-23b was correlated with the poor survival of EC patients. Upregulation of miR-23b in Ishikawa EC cells suppressed their proliferation while its inhibition potentially upregulated it. Analysis of enriched pathways of miR-23b targets revealed that it regulates key signaling pathways in EC. Further studies are required to dissect the role of miR-23b as tumor suppressor miRNA in EC.

MiR-125b-5p expression was downregulated in EC tissue in our study which was confirmed in the TCGA cohort. In EC, miR-125b-5p acts as a tumor suppressor miRNA and inhibits invasion of EC cells by directly targeting protooncogene ERBB2³³. However, the expression of miR-125b-5p was not correlated with patients' survival, even though the decreased level of miR-125b-5p was found to be associated with higher histological grade and myometrial invasion³⁴.

MiR-199a-3p is another miRNA that was downregulated in EC compared to HE^{35,36}. Also, the increased level of miR-199a-3p was associated with better progression-free survival and overall survival of EC patients³⁷, however, it was not the case for TCGA cohort patients.

Moreover, we found that miR-221-3p and miR-451a were downregulated in EC tissue compared to HE regardless of EC type. Notably, miR-221-3p was confirmed to be downregulated in the TCGA cohort of EC patients. Of note, miR-221 was identified as an oncomiRNA in other types of cancer, including breast cancer and liver

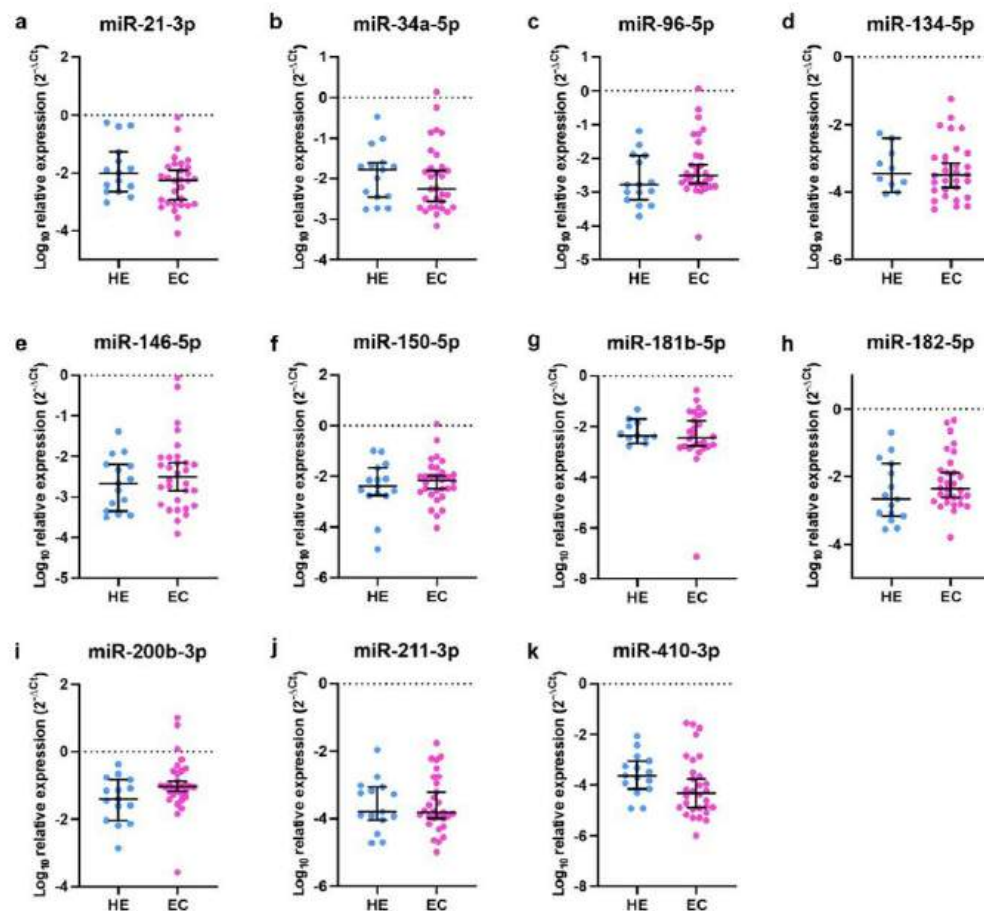


Figure 3. Homogeneous expression of selected miRNAs in EC and HE tissues. The expression of miR-21-3p (a), miR-34a-5p (b), miR-96-5p (c), miR-134-5p (d), miR-146-5p (e), miR-150-5p (f), miR-181b-5p (g), miR-182-5p (h), miR-200b-3p (i), miR-211-3p (j), and miR-410-3p (k). *P*-values were calculated using Mann-Whitney test, *p* > 0.05.

cancer³⁸. Its overexpression promotes tumor cell migration, invasiveness, and proliferation³⁸. Our results suggest that the role of miR-221 is not critical for tumor growth in EC since its expression is decreased in this pathology. This is contrary to published data on other cancers, where miR-221 and miR-451a both act as tumor suppressor miRNAs, including ovarian cancer and cervical cancer³⁹.

Further, we found that the expression of the majority of analyzed miRNAs was very similar in both types of EC. Only miR-34a-5p and miR-146-5p levels differed between both types, namely the expression of miR-34a-5p and miR-146-5p was upregulated in EC1 compared to EC2. There are discordant data concerning the level of expression of miR-34a-5p in EC compared to HE^{40,41}. Nonetheless, miR-34a-5p was identified to act as tumor suppressor miRNA in EC. It targets Notch1, L1CAM, MMSET and thus inhibits EC cells migration, invasion, and EMT in vitro as well as tumor growth *in vivo*^{41–43}. There are no studies regarding the role or the level of expression of miR-146-5p in EC. However, the expression of miR-146-5p was increased by estrogen in the plasma of rats with prostate cancer⁴⁴, which may suggest that upregulation of miR-146-5p may be related to estrogens in EC1. Notably, currently most of the studies on miRNA expression in EC are based on classical classification into two types. However, there is an effort to include molecular classification of EC patients in clinical practice⁷. Therefore, studies are required to determine the profile of miRNAs expression in different types of EC.

As miRNAs reveal different expression patterns in healthy and cancerous tissues, they have great potential to be diagnostically and prognostically valuable biomarkers as well as potential therapeutic targets⁴⁵. So far, a

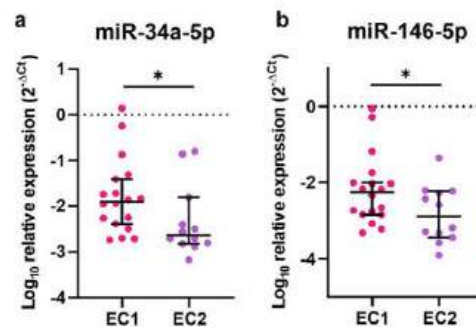


Figure 4. miR-34a and miR-146-5p are decreased in EC2 compared to EC1. The expression of miR-34a-5p (a) and miR-146-5p (b) in dissected tumor tissue of EC1 and EC2 ($p = 0.031$, $p = 0.0479$, respectively). P -values were calculated with Mann–Whitney.

variety of miRNAs with different expression patterns in normal and malignant endometrial tissue have been identified^{46,47}. MiRNAs expression can be determined in FFPE tissues and this evaluation could be performed in addition to the standard histopathological examination⁴⁸. Moreover, using laser capture microdissection (LCM) it is possible to precisely dissect only tumor tissue without contamination of non-malignant cells surrounding tumor^{46,47,49,50}. In this study, we dissected only neoplastic tissues or glandular healthy endometrium, so the analyses were not disturbed by adjacent tissues. The main limitation of our study is a low number of specimens of EC tissue and a lack of complete clinical data of included patients. For this reason, we were unable to correlate the expression of analyzed miRNAs with e.g. survival of our patients. Therefore, further studies are required to assess the clinical relevance of studied miRNAs in EC, especially the role of miR-23b as a prognostic biomarker.

Conclusions

In this study, we found that miR-23b, miR-125b-5p, miR-199a-3p, miR-221-3p, and miR-451a were downregulated in endometrial cancer compared to healthy endometrium. Additionally, the expression of miR-34a-5p and miR-146-5p were higher in EC1 than in EC2. Decreased miR-23b expression is associated with worse survival of EC patients. There is a need for further studies assessing the potential clinical use of described miRNAs as biomarkers.

Materials and methods

Patients tissue. A total of 45 patients were enrolled into the study, 18 patients diagnosed with EC1, 12 diagnosed with EC2, and 15 HE controls. Tumor tissues or healthy endometrial tissues were dissected from archival formalin-fixed paraffin-embedded (FFPE) using laser capture microdissection (LCM). The FFPE samples have been obtained from the Department of Pathology, Medical Center of Postgraduate Education, Warsaw, Poland. Patients data are presented in Table 2. The study was conducted following the Declaration of Helsinki and was approved by the Bioethical Committee Medical University of Warsaw (AKBE/78/2021, 17 May 2021). The patient's consent was waived due to the performed anonymization and retrospective character of the study.

Hematoxylin and Eosin Staining. Resected tumors were formalin-fixed and paraffin-embedded according to the standard protocol in the tissue processor. Thereafter the samples were cut on microtome and hematoxylin and eosin-stained for the pathologist examination.

All samples were cut with a microtome to 10 μ m slices and were mounted on glass slides with a drop of UltraPure DNase/RNase-free water. Then, samples were incubated in a fume hood at 56 °C for one hour to increase slices' adherence. Mounted slices were hematoxylin and eosin-stained according to the standard protocol in a set of stains, alcohol solutions, and xylene. Slides were immediately subjected to LCM.

Laser capture microdissection. Stained and dehydrated sections of EC or HE were subjected to LCM-aided dissection of regions containing only neoplastic tissues or glandular healthy endometrium. Approximately 10 mm² of each region was marked to dissect with LCM system (PALM Robo, Zeiss, Germany). These regions were selected by a board-certified pathologist. Each LCM was preceded by optimization of LCP energy and spot distance to provide a full dissection of marked areas. LCM was performed under the following conditions: LCP energy—80–90, LCP spot distance—25 μ m, magnification—5 $\times$, tissue collected in 20 μ l of Digestion Buffer (Norgen Biotek) in 500 μ l sterile PCR-tube cap. Caps were sealed back with tubes, centrifuged briefly, and placed on wet ice until further steps^{49–52}.

RNA isolation and RT-qPCR. Norgen Biotek FFPE RNA/DNA Purification Plus Kit was used for RNA isolation according to the manufacturer guidelines. RNA was eluted with 30 μ l ultrapure, molecular-grade water,

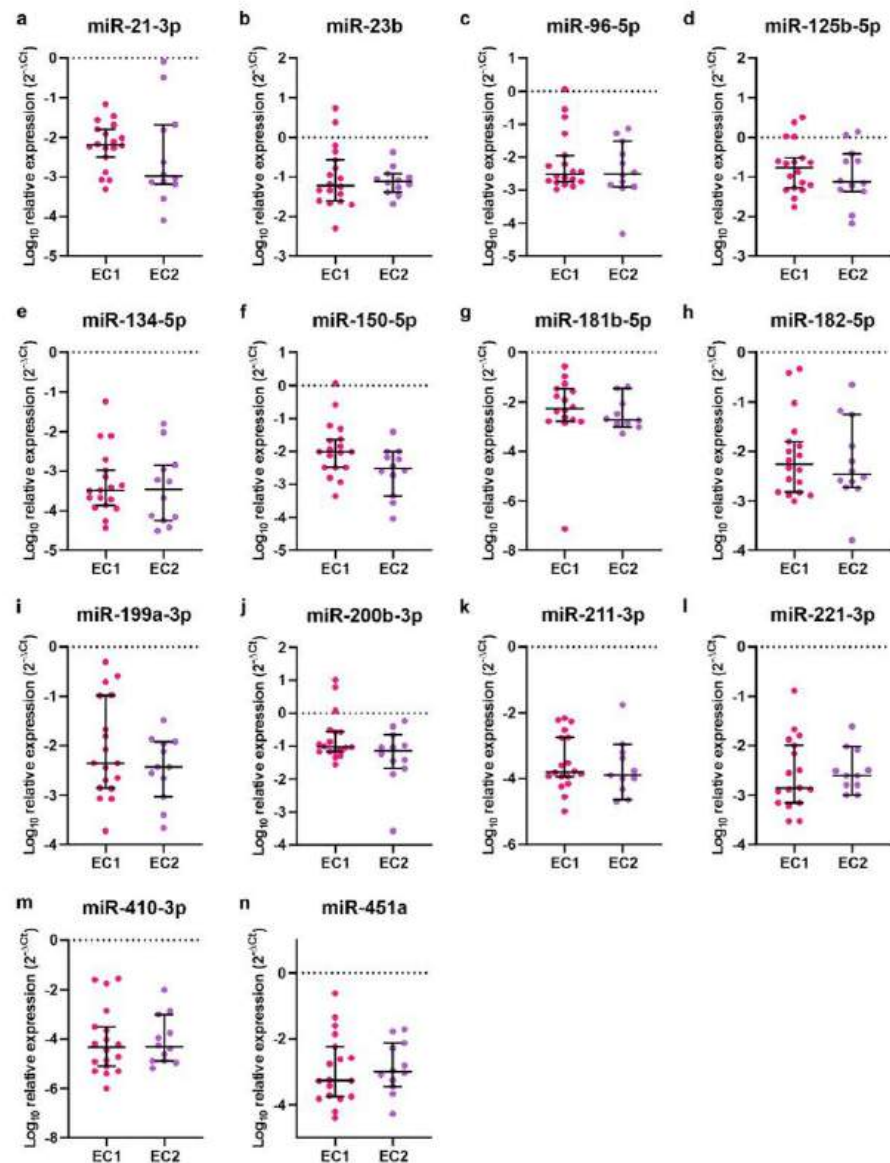


Figure 5. Homogeneous expression of selected miRNAs in EC1 and EC2 tumor tissues. The expression of miR-21-3p (a), miR-23b (b), miR-96-5p (c), miR-125b-5p (d), miR-134-5p (e), miR-150-5p (f), miR-181b-5p (g), miR-182-5p (h), miR-199a-3p (i), miR-200b-3p (j), miR-211-3p (k), miR-221-3p (l), miR-410-3p (m), and miR-451a (n). *P*-values were calculated using Mann–Whitney test, *p* > 0.05.

and stored at -80°C until the next steps. The purity and quantity of isolated RNA were assessed by the absorbance measurements at wavelengths of 260/280 nm using the NanoDrop2000 spectrophotometer (Thermo Fisher Scientific). Samples with 260/280 ratios between 1.8 and 2.1 were used for further analysis. RNA was then sub-

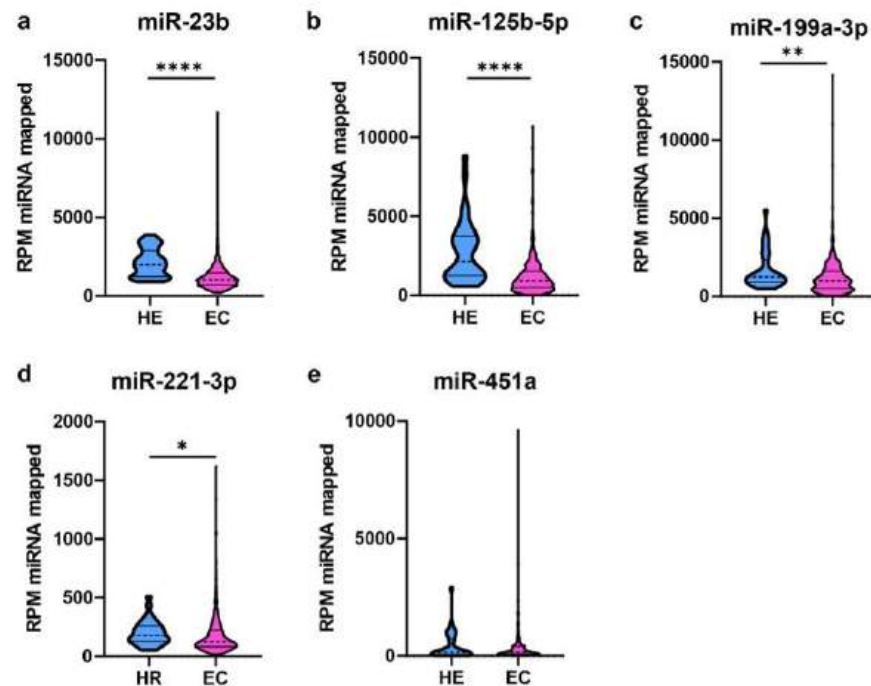


Figure 6. Downregulation of miR-23b, miR-199a, and miR-221 in TCGA cohort. Analysis of TCGA Uterine Corpus Endometrial Carcinoma (EC) cohort using OncomiR database²⁰. The level of miR-23b (a), miR-125b-3p (b), miR-199a (c), miR-221 (d), and miR-451a (e) presented as reads per million (RPM) miRNAs mapped. Healthy endometrial tissues (HE, n = 32), EC tissues (n = 418). Median indicated as dashed line; quartiles indicated as solid lines. ($p < 0.0001$, $p < 0.0001$, $p = 0.0067$, $p = 0.0110$, respectively) P -values were calculated using Mann–Whitney test.

jected to reverse transcription using Mir-X miRNA FirstStrand Synthesis (Takara, Clontech) followed by real-time qPCR using SYBR qRT-PCR (Thermo Fisher Scientific). Primers sequences used in the study are presented in Table 3. U6 (Takara, Clontech) was used as an endogenous control for the analysis of microRNA expression. The $2^{-\Delta\Delta Ct}$ method was used to calculate relative expression using the mean Ct values of target genes and the control.

Bioinformatical analysis. Analysis of TCGA database of Uterine Corpus Endometrial Carcinoma (EC) cohort was performed using OncomiR database²⁰. Analysis of the association of the miRNAs expression and EC patients' survival from the TCGA cohort (n = 533) was performed using OncoLnc²¹. Patients were divided based on miRNA level low: high 75:25. Analysis of enriched signaling pathways was performed using starBase²².

Proliferation assay. EC Ishikawa cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with heat-inactivated 10% (v/v) fetal bovine serum (FBS, Gibco), 100 U/ml penicillin and 100 µg/ml streptomycin (Sigma-Aldrich) at 37 °C in an atmosphere of 5% CO₂ in the air. Cells were tested for Mycoplasma contamination using PCR technique and were confirmed to be negative.

All transfections were performed using DharmaFECT (ThermoFisher) according to the manufacturer's protocol. miR-23b mimic (assay ID: MC12931), anti miR-23b (assay ID: MH12931), mimic miR-scramble (miR-scr, miRNA Mimic Negative Control, catalog number: 4464058), and anti miR-scramble (anti-miR scr, miRNA Inhibitor, Negative Control, catalog number: 4464078) were obtained from Invitrogen mirVan (Thermo Fisher Scientific). miRs were used at a final concentration of 50 nM. The efficiency of the transfection was determined by RT-qPCR method. For proliferation assay, 1×10^5 cells/well were seeded in 12-well plates 24 h after transfection and were incubated for 48 h. Then, cells were fixed with 4% PFA and stained with 0.1% crystal violet. Cells were photographed using Nikon Ti-U. The photos were analyzed using ImageJ (National Institutes of Health, Bethesda MD, USA) and ColonyArea plugin³³.

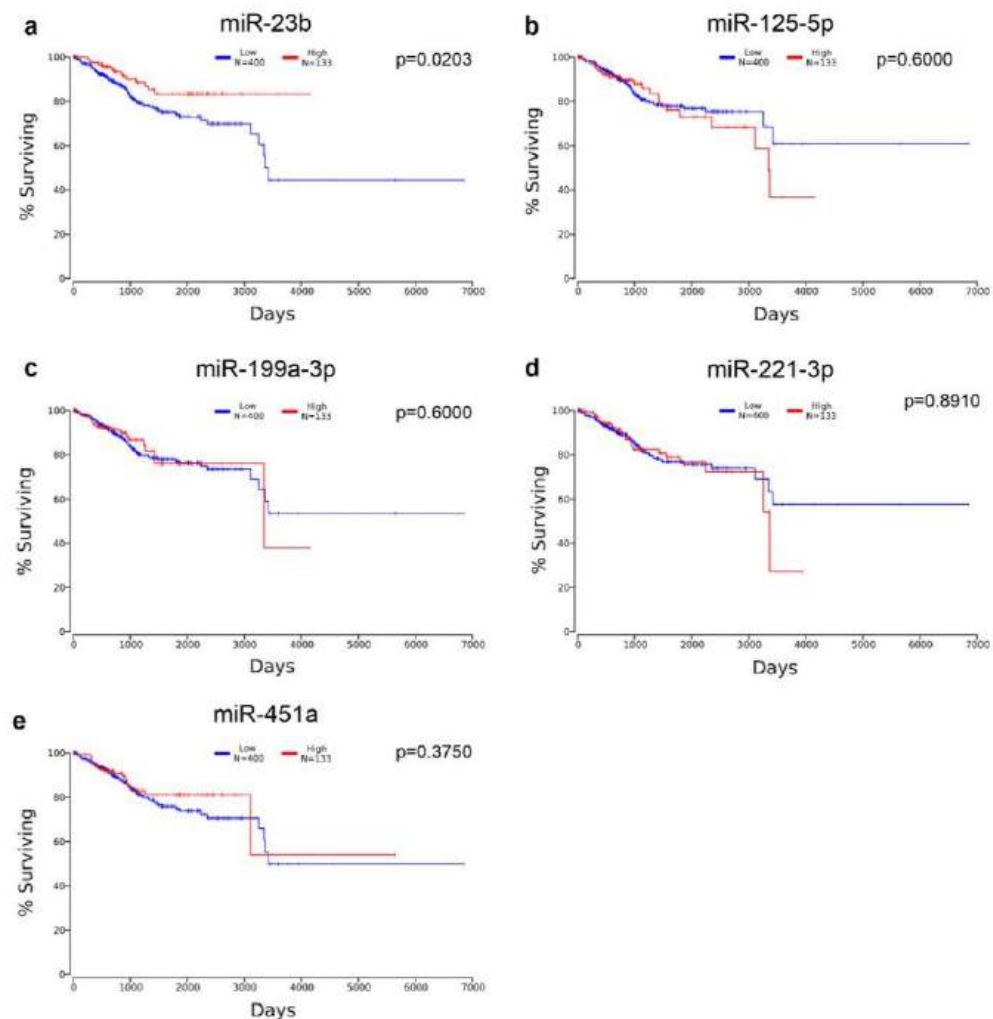


Figure 7. Decreased miR-23b expression is associated with worse survival of EC patients. Survival of EC patients based on the miR-23b (a), miR-125b-5p (b), miR-199a-3p (c), miR-221-3p (d), miR-451a (e) expression in TCGA cohort (n = 533) data using OncoLnc²¹. Patients were divided based on miRNA level low:high 75:25. Logrank P-value presented in the graphs.

Data processing and analysis. Data were collected and processed with Excel 2016 (Microsoft, USA). Statistical analyses were conducted with GraphPad Prism 8.4.3 (GraphPad Software Inc.) using the Mann-Whitney and log-rank tests. Data distribution was tested using the Shapiro-Wilk test. All values in Figs. 2, 3, 4 and 5 are represented as median and 95% CI. Data in Fig. 6 is presented as a violin plot with the median indicated as dashed line and quartiles indicated as solid lines. Data in Fig. 7 is presented as a Kaplan-Meier plot. A p value of < 0.05 was considered statistically significant.

Data availability

The data that support the findings of this study are available from T.M.G. or K.K. upon reasonable request. Data from TCGA <https://www.cancer.gov/tcga> are publicly available.

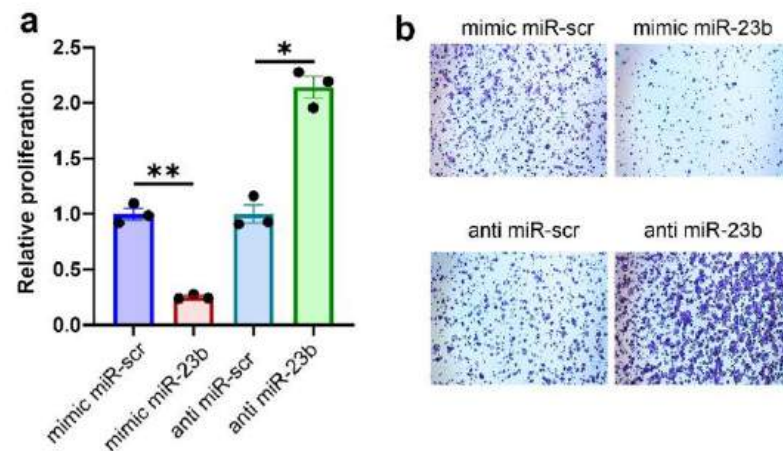


Figure 8. miR-23b suppresses proliferation of EC cells. (a) The relative proliferation of mimic miR-23b- and anti miR-23b-transfected Ishikawa cells compared to corresponding control miR-scr- (miR-scr)-transfected cells (n = 3). (b) Representative photos of proliferation assay. P-values were calculated using paired T test (**p = 0.006, *p = 0.0226).

Pathway name	log10 (pval)	log10 (FDR)
KEGG_Endocytosis	-5.60057	-3.429
KEGG_Pathways_In_Cancer	-4.6286	-3.0622
KEGG_Focal_Adhesion	-4.47	-2.6644
KEGG_Renal_Cell_Carcinoma	-4.8815	-2.43253
KEGG_Adherens_Junction	-3.95195	-2.39324
KEGG_Ubiquitin_Mediated_Proteolysis	-3.9785	-2.1833
KEGG_Neurotrophin_Signaling_Pathway	-3.40911	-2.05452
KEGG_Tight_Junction	-3.45378	-2.0412
KEGG_Chronic_Myeloid_Leukemia	-3.32173	-2.01829
KEGG_ErbB_Signaling_Pathway	-3.1505	-1.89282
KEGG_Fc_Gamma_R_Mediated_Phagocytosis	-3.01252	-1.79624
KEGG_Snare_Interactions_In_Vesicular_Transport	-2.90603	-1.7623
KEGG_P53_Signaling_Pathway	-2.91993	-1.74143
KEGG_Pancreatic_Cancer	-2.82496	-1.71341
KEGG_Phosphatidylinositol_Signaling_System	-2.65879	-1.5772
KEGG_Axon_Guidance	-2.60006	-1.57283
KEGG_Valine_Leucine_And_Isoleucine_Degradation	-2.62381	-1.57026
KEGG_Wnt_Signaling_Pathway	-2.37947	-1.48352
KEGG_Small_Cell_Lung_Cancer	-2.36051	-1.48305
KEGG_Cell_Cycle	-2.3871	-1.47184
KEGG_Insulin_Signaling_Pathway	-2.39269	-1.45723
KEGG_Inositol_Phosphate_Metabolism	-2.40479	-1.44814
KEGG_Regulation_Of_Actin_Cytoskeleton	-2.41013	-1.43121
KEGG_Colonrectal_Cancer	-2.42489	-1.42249
KEGG_Mitochondrial_Pathway	-2.20486	-1.34512

Table 1. The Enrichment Analysis of hsa-miR-23b Targets in KEGG Pathways²².

ID	Age	Type of EC/ HE	Grading	TNM
101	53	Endometrioid EC (EC1)	G2	pT3b N0
102	66	Endometrioid EC (EC1)	G1	pT1b N0
103	60	Endometrioid EC (EC1)	G3	pT1a N1
104	46	Endometrioid EC (EC1)	G1	pT1a N0
105	60	Endometrioid EC (EC1)	G1	pT2 N0
106	70	Endometrioid EC (EC1)	G1	pT1a N0
107	63	Endometrioid EC (EC1)	G2	pT2 N0
108	68	Endometrioid EC (EC1)	G1	pT1b Nx
109	64	Endometrioid EC (EC1)	G1	pT3b N0
110	79	Endometrioid EC (EC1)	G2	pT1b N0
111	57	Endometrioid EC (EC1)	G1	pT1a N0
112	65	Endometrioid EC (EC1)	G1	pT3b N0
113	64	Endometrioid EC (EC1)	G1	pT1a N0
114	52	Endometrioid EC (EC1)	G2	pT2 N0
115	62	Endometrioid EC (EC1)	G2	pT3a N0
116	68	Endometrioid EC (EC1)	G1	pT1b N1
117	71	Endometrioid EC (EC1)	G2	pT1a N0
118	61	Endometrioid EC (EC1)	G1	pT1a N0
119	64	Serous EC (EC2)	High grade	pT3a N0
120	84	Serous EC (EC2)	n/a	pT1a N0
121	80	Serous EC (EC2)	High grade	pT3b N1a
122	79	Serous EC (EC2) + Endometrioid EC (EC1)	High grade + G1	pT3c N0 + pT1a N0
123	68	Serous EC (EC2)	High grade	pT3b N0
124	64	Serous EC (EC2)	High grade	pT1b N1
125	78	Serous EC (EC2)	High grade	pT1b Nx
126	73	Serous EC (EC2)	n/a	pT3b N1
127	84	Serous EC (EC2)	High grade	pT1a N0
128	69	Serous EC (EC2)	High grade	pT2 N1a
129	78	Serous EC (EC2)	High grade	pT3b N2
130	66	Serous EC (EC2)	High grade	pT3b N2
131	23	HE	n/a	n/a
132	46	HE	n/a	n/a
133	44	HE	n/a	n/a
134	41	HE	n/a	n/a
135	49	HE	n/a	n/a
136	50	HE	n/a	n/a
137	48	HE	n/a	n/a
138	55	HE	n/a	n/a
139	37	HE	n/a	n/a
140	51	HE	n/a	n/a
141	46	HE	n/a	n/a
142	52	HE	n/a	n/a
143	51	HE	n/a	n/a
144	47	HE	n/a	n/a
145	50	HE	n/a	n/a

Table 2. The histopathological and clinical data of patients.

miRNA	Sequence
hsa-miR-21-3p	5'-CAACACCAGTCGATGGGCTGT-3'
hsa-miR-23b	5'-ATCACATTGCCAGGATTACC-3'
hsa-miR-34a-5p	5'-TGGCAGTGTCTTAGCTGGTTGT-3'
hsa-miR-96-5p	5'-TTTGGCACTAGCACATTTTGCT-3'
hsa-miR-125b-5p	5'-TCCTGAGACCTAACTGTGA-3'
hsa-miR-134-5p	5'-TGTGACTGGTTGACAGAGGGG-5'
hsa-miR-146-5p	5'-TGAGAACTGAATTCATGGGTT-5'
hsa-miR-150-5p	5'-TCTCCCAACCTGTACAGTG-3'
hsa-miR-181b-5p	5'-AACATTTCATGCTGCTGGTGGGT-3'
hsa-miR-182-5p	5'-TTTGGCAATGGTAGAAGTACACT-3'
hsa-miR-199a-3p	5'-ACAGTAGTCTGCACATTGGTTA-3'
hsa-miR-200b-3p	5'-TAATACTGCCTGGTAATGATGA-3'
hsa-miR-211-3p	5'-GCAGGGACAGCAAAGGGGTGC-3'
hsa-miR-221-3p	5'-AGCTACATTGCTGCTGGGTTTC-3'
hsa-miR-410-3p	5'-AATATAACACAGATGGCTGT-3'
hsa-miR-451a	5'-AAACCGTTACATTACTGAGTT-3'

Table 3. List of primers sequences.

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Author contributions

K.K. acquired funding, planned and conducted the experiments, analyzed the results, and wrote the manuscript. T.M.G. conceived the experiments, conducted the experiments, analyzed the results, prepared figures, supervised the study, and wrote the manuscript. A.K. collected and analyzed clinical data of the patients. A.M. wrote the manuscript. J.W. and J.O. performed collected and provided HE and EC samples and performed histopathological analysis of the samples. A.G. participated in the experiments. P.K.W. acquire funding and supervised the study. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Estradiol induces global changes in miRNA expression in endometrial cancer cells and upregulates oncogenic miR-182

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1 Estradiol induces global changes in miRNA expression in endometrial cancer 2 cells and upregulates oncogenic miR-182

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16 ABSTRACT

17 Endometrial cancer (EC) occurs mainly in perimenopausal age. Risk factors are associated with
18 unopposed estrogen stimulation of the endometrium. There are two main types of EC, EC1 and EC2.
19 The pathogenesis of EC1 is estrogen-dependent. MiRNAs are small RNAs that regulate gene expression
20 posttranscriptionally. They are induced by estrogens in different hormone-dependent neoplasias
21 including breast cancer. However, little is known regarding their role in EC. Thus, this study aims to
22 assess the role of the miRNA-estrogen axis in endometrial cancer cells. Estrogen-dependent endometrial
23 cancer cell line Ishikawa was used in the study. Cells were incubated with estradiol, followed by RNA
24 isolation. We used the microarray method to identify estradiol-induced miRNAs in EC cells. Then, we
25 analyzed tissues derived from 45 patients (18 EC1, 12 EC2, and 15 healthy endometrium (HE)) that
26 were cut using the Laser Capture Microdissection method. The expression of selected miRNAs and their
27 targets was assessed using the RT-qPCR method. Ishikawa cells were transfected with miRNA mimic,
28 miRNA inhibitor (anti-miRNA), and their scrambled controls. We identified 66 estrogen-upregulated
29 miRNAs in endometrial cancer cells. Out of them, miR-182 was upregulated in EC1 compared to HE.
30 We found that miR-182 is an oncomiR in EC since its increased expression promoted the proliferation
31 of EC cells and decreased expression of miR-182 was associated with the inhibition of cancer cell
32 proliferation. Moreover, miR-182 inhibition upregulated SMAD4 expression. Our study allowed us to
33 better understand the role of estrogen in the pathogenesis of EC.
34
35
36

37 Keywords:

38 Endometrial cancer, miRNA, biomarkers, miR-182, estrogen

39 **Introduction**

40 Endometrial cancer (EC) is one of the most frequent cancers in women of perimenopausal age with
 41 growing incidence rates (Crosbie, Kitson et al. 2022). The first symptom is usually abnormal vaginal
 42 bleeding. There are no screening programs for early EC diagnosis (Crosbie, Kitson et al. 2022).
 43 Diagnosis is based on a transvaginal ultrasound scan and endometrial biopsy. Obesity is one of the most
 44 important risk factors of EC due to the estrogenic stimulation of endometrium unopposed by
 45 progesterone which leads to its proliferation (Crosbie, Kitson et al. 2022). Risk factors include other
 46 situations in which exposure to estrogens is prolonged, such as early menarche, late menopause, cycles
 47 without ovulations, and exogenous intake of estrogens (Nees, Heublein et al. 2022). Some genetic
 48 factors are also associated with the predisposition to endometrial cancer including Cowden syndrome
 49 or Lynch syndrome (Shai, Segev et al. 2014, Dominguez-Valentin, Sampson et al. 2020).
 50 Endometrial cancer is divided into two types 1 and 2. EC1 is an estrogen-dependent EC that is
 51 characterized by a better outcome. Whereas type 2 is rare but associated with a worse prognosis (Henley,
 52 Ward et al. 2020). EC2 is responsible for 40% of deaths in the EC population even though it represents
 53 only 10-20% of EC cases (Setiawan, Yang et al. 2013). Recently proposed classification of EC is based
 54 on its molecular characteristics. There are four types of EC, ultramutated (POLE-mutant), hypermutated
 55 (mismatch repair deficient), copy number-high (p53-abnormal), and copy number-low, each
 56 characterized by different prognosis for patients (Crosbie, Kitson et al. 2022).
 57 MiRNAs are small non-coding molecules that emerge as promising biomarkers of EC (Hutt, Tailor et
 58 al. 2019). They regulate the pathogenesis of different diseases by targeting the mRNAs of members of
 59 various cellular pathways (Grzywa, Klicka et al. 2019, Grzywa, Klicka et al. 2020). The expression of
 60 numerous miRNAs is dysregulated in EC tissues and their expression is correlated with patients'
 61 outcomes (Klicka, Grzywa et al. 2022). Moreover, they regulate different cell signaling pathways in EC
 62 cells and thus they can inhibit (tumor suppressor miRNA) or promote cancer invasiveness and metastasis
 63 (oncomiRs) (Grzywa, Klicka et al. 2020, Klicka, Grzywa et al. 2021). Previous studies revealed that
 64 estrogens can induce expression of oncomiRs in breast cancer (Nagpal, Ahmad et al. 2013). Nonetheless,
 65 little is known regarding the role of the estrogens-miRNAs axis in EC. Hence, the aim of this study was
 66 to assess the role of the estrogen-induced miRNAs in EC.

67 **Materials and Methods**

68 **Cell culture and treatment**

69 Ishikawa cell line, estrogen and progesterone receptors-positive endometrial adenocarcinoma was used
 70 in this study. Cell line was purchased from Sigma-Aldrich. Cells were cultured in standard conditions
 71 (5% CO₂, humidified atmosphere, 37°C) using recommended Dulbecco's Modified Eagle's Medium
 72 (DMEM, Gibco, USA) containing 10% fetal bovine serum (FBS, Hyclone) according to the guidelines.

To evaluate the role of estradiol in endometrial cancer in vitro, cells were incubated with 17β -estradiol 10^{-8} M (Sigma, USA) for 48 hours.

RNA isolation, reverse transcription, and microarrays

RNA was isolated from cells incubated with estradiol and controls using RNeasy Mini Kit (Qiagen). Isolated RNA was eluted in 30 μ l of ultrapure water and then stored in -80°C . The RNA purity and quantity were evaluated using NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA). cDNA was synthesized using Megaplex™ RT Primers, Human Pool Set v3.0 (ThermoFisher) and TaqMan™ MicroRNA Reverse Transcription Kit (ThermoFisher). Real-time PCR mix was prepared using TaqMan® Universal PCR Master Mix, No AmpErase UNG. The 100 μ l aliquot was added to each port of TaqMan™ Array Human MicroRNA A+B Cards Set v3.0. The reactions were conducted using ViiA™ 7 Real-Time PCR System in universal cycling conditions ($95^{\circ}\text{C}/10$ min, then $95^{\circ}\text{C}/15$ sec, $60^{\circ}\text{C}/60$ sec for 40 cycles). All reactions were performed according to the manufacturer's protocols. Cycle threshold (Ct) values were used to analyze 754 human microRNAs. The expression of miRNAs selected in this step was subsequently assessed in EC tissues.

Tissue specimens

In this study, we collected tissues of 30 patients diagnosed with endometrial cancer (EC) consisting of 18 type I EC and 12 type II EC, as well as 15 patients with healthy endometrium. Archival, formalin-fixed, paraffin-embedded (FFPE) tissues were obtained from the Department of Pathology, Medical Center of Postgraduate Education, Warsaw, Poland, and assessed there by a pathologist. Medical data such as a pathological description of collected tissues of endometrial cancer and healthy endometrium was received in anonymized form (Table 1).

Table 1. The histopathological and clinical data of patients

ID	Age	Type of EC/ HE	Grading	TNM
101	53	Endometrioid EC (EC1)	G2	pT3b N0
102	66	Endometrioid EC (EC1)	G1	pT1b N0
103	60	Endometrioid EC (EC1)	G3	pT1a N1
104	46	Endometrioid EC (EC1)	G1	pT1a N0
105	60	Endometrioid EC (EC1)	G1	pT2 N0
106	70	Endometrioid EC (EC1)	G1	pT1a N0
107	63	Endometrioid EC (EC1)	G2	pT2 N0
108	68	Endometrioid EC (EC1)	G1	pT1b Nx
109	64	Endometrioid EC (EC1)	G1	pT3b N0
110	79	Endometrioid EC (EC1)	G2	pT1b N0
111	57	Endometrioid EC (EC1)	G1	pT1a N0
112	65	Endometrioid EC (EC1)	G1	pT3b N0
113	64	Endometrioid EC (EC1)	G1	pT1a N0
114	52	Endometrioid EC (EC1)	G2	pT2 N0

115	62	Endometrioid EC (EC1)	G2	pT3a N0
116	68	Endometrioid EC (EC1)	G1	pT1b N1
117	71	Endometrioid EC (EC1)	G2	pT1a N0
118	61	Endometrioid EC (EC1)	G1	pT1a N0
119	64	Serous EC (EC2)	High grade	pT3a N0
120	84	Serous EC (EC2)	n/a	pT1a N0
121	80	Serous EC (EC2)	High grade	pT3b N1a
122	79	Serous EC (EC2) + Endometrioid EC (EC1)	High grade + G1	pT3c N0 + pT1a N0
123	68	Serous EC (EC2)	High grade	pT3b N0
124	64	Serous EC (EC2)	High grade	pT1b N1
125	78	Serous EC (EC2)	High grade	pT1b Nx
126	73	Serous EC (EC2)	n/a	pT3b N1
127	84	Serous EC (EC2)	High grade	pT1a N0
128	69	Serous EC (EC2)	High grade	pT2 N1a
129	78	Serous EC (EC2)	High grade	pT3b N2
130	66	Serous EC (EC2)	High grade	pT3b N2
131	23	HE	n/a	n/a
132	46	HE	n/a	n/a
133	44	HE	n/a	n/a
134	41	HE	n/a	n/a
135	49	HE	n/a	n/a
136	50	HE	n/a	n/a
137	48	HE	n/a	n/a
138	55	HE	n/a	n/a
139	37	HE	n/a	n/a
140	51	HE	n/a	n/a
141	46	HE	n/a	n/a
142	52	HE	n/a	n/a
143	51	HE	n/a	n/a
144	47	HE	n/a	n/a
145	50	HE	n/a	n/a

95

96 Preparation of archival samples for laser capture microdissection (LCM)

97 All FFPE samples were cut to 10 µm sections using a microtome and mounted on glass slides
98 (SuperFrost Ultra Plus, Menzel Gläser) with a drop of DNase/RNase-free water. To increase adherence
99 of slides, samples were incubated for an hour in a fume hood at 56 °C. Next, mounted tissue slices were
100 hematoxylin and eosin stained according to the standard protocol in a set of stains, alcohol solutions,
101 and xylene. Slides were subjected to LCM immediately after staining.

102 Laser capture microdissection

103 LCM was performed using Zeiss PALM MicroBeam, Germany. Fragments of endometrial cancer tissue
104 or healthy endometrium were cut out from the whole slide to avoid bias resulting from surrounding non-

glandular tissues. The cut-out regions were marked before by a pathologist. Approximately 10mm² of each section was cut and catapulted to the cap with 20 µl of Digestion Buffer.

RNA isolation from tissue, reverse transcription, and real-time quantitative polymerase chain reaction (RT-qPCR)

RNA from the dissected fragment of tissue was isolated using RNAasy Mini Kit (Qiagen) following the manufacturer's protocols. RNA was eluted in 30 µl of ultrapure water and stored at -80°C until the next steps. The quality of extracted RNA was assessed using NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA). Then, reverse transcription was conducted using Mir-X™ miRNA FirstStrand Synthesis Kit. Real-time qPCR was performed with Power SYBR™ Green PCR Master Mix (Thermo Fisher Scientific) and primers of miR-15a, -16, -27b, -28-3p, -29c, -31#, -92a, -106a, -106b, -129, -129-3p, -130a, -140, -140-3p, -141, -150, -152, -182, -192, -198, -200c, -215, -335, -496, -517c, -590-3p, and -656 (Table 2). U6 expression was used as normalization between samples. All reactions was performed in triplicates using ViiA 7 Real-Time PCR System (Thermo Fisher, USA). The $2^{-\Delta\Delta C_t}$ method was used to assess relative expression in analyzed tissues using the mean Ct values of selected microRNAs and U6.

Table 2. List of miRNAs' primers sequences

miRNA	Sequence
hsa-miR-15a	UAGCAGCACAUAAUGGUUUGUG
hsa-miR-16	UAGCAGCACGUAAAUAUUGGCG
hsa-miR-27b	UUCACAGUGGCUAAGUUCUGC
hsa-miR-28-3p	CACUAGAUUGUGAGCUCCUGGA
hsa-miR-29c	UAGCACCAUUUGAAAUCGGUUA
hsa-miR-31#	UGCUAUGCCAACAUAUUGCCAU
hsa-miR-92a	UAUUGCACUUGUCCCGGCCUGU
hsa-miR-106a	AAAAGUGCUUACAGUGCAGGUAG
hsa-miR-106b	UAAAGUGCUGACAGUGCAGAU
hsa-miR-129-3p	AAGCCCUUACCCCAAAAAGCAU
hsa-miR-130a	CAGUGCAAUGUAAAAGGGCAU
hsa-miR-140	CAGUGGUUUUACCCUAUGGUAG
hsa-miR-140-3p	UACCACAGGGUAGAACCACGG
hsa-miR-141	UAAACACUGUCUGGUAAGAUGG
hsa-miR-150	UCUCCCAACCCUUGUACCAGUG
hsa-miR-152	UCAGUGCAUGACAGAACUUGG
hsa-miR-182	UUUGGCAAUGGUAGAACUCACACU
hsa-miR-192	CUGACCUAUGAAUUGACAGCC
hsa-miR-198	GGUCCAGAGGGGAGAUAGGUUC
hsa-miR-200c	UAAUACUGCCGGGUAUUGAUGGA
hsa-miR-215	AUGACCUAUGAAUUGACAGAC
hsa-miR-335	UCAAGAGCAAUAACGAAAAAUGU
hsa-miR-496	UGAGUAUUACAUGGCCAAUCUC

hsa-miR-517c	AUCGUGCAUCCUUUUAGAGUGU
hsa-miR-590-3p	UAAUUUUUAUGUAUAAGCUAGU
hsa-miR-656	AAUAUUUAACAGUCAACCUCU

122
123

124 Transfection

125 Transfection of Ishikawa was performed using DharmaFECT 1 siRNA Transfection Reagent according
126 to the manufacturer's protocol. Endometrial cancer cells were transfected with synthetic miR-mimic-
127 182 and anti-miR-182, and their controls, miR-scrambled and anti-miR-scrambled obtained from
128 Invitrogen™ mirVana™ (Thermo Fisher Scientific). The efficiency of transfection was assessed using
129 the real-time qPCR method. Cells were then subjected to in vitro functional studies.

130 Proliferation assay

131 For proliferation assay, 1×10^5 cells/well were seeded in 12-well plates 24 h after transfection and were
132 incubated for 48. Cells were then fixed with 4% paraformaldehyde, stained with 0.1% crystal violet, and
133 photographed. The photos were analyzed using the ImageJ ColonyArea plugin (National Institutes of
134 Health, Bethesda MD, USA) (Guzmán, Bagga et al. 2014).

135 RNA isolation from cells, reverse transcription, and qRT-PCR

136 Total RNA was isolated from cells 24 h after transfection with miR-182 mimic, anti- miR-182 and their
137 controls. Isolation was performed using RNAasy Mini Kit (Qiagen) according to the protocol. Then,
138 RNA was reverse transcribed using Mir-X™ miRNA FirstStrand Synthesis Kit. Real-time qPCR was
139 performed using Power SYBR™ Green PCR Master Mix (Thermo Fisher Scientific). The primer
140 sequences of BCL6, CDH1-R, CDH2-R, COX2, ERα, ESRR1, EZH2, FN1, FOS, FOXA1, MARK-1,
141 MCL-1, MMP9, NOTCH, PDL1, PFN, PTEN, RECK, SMAD4, SNAIL, TIM2, TIMP3, TP53, TWIST,
142 VIM, ZBTB4 and ZEB1 are listed in Table 3. GAPDH was used as an endogenous control. The 2⁻
143 $\Delta\Delta C_t$ method was used to calculate relative expression.

144 **Table 3. List of targets' primers sequences**

Target	Forward	Reverse
BCL6	CATGCAGAGATGTGCCCTCCACA	TCAGAGAAGCGGCAGTCACACT
COX2	CGGTGAAACTCTGGCTAGACAG	GCAAACCGTAGATGCTCAGGGA
ERα	GCTTACTGACCAACCTGGCAGA	GGATCTCTAGCCAGGCACATTC
ESRR1	CACCACACTCTGTGACTTGGCT	ATGCACTCTGGAGGAGGCTCAT
EZH2	GACCTCTGTCTTACTTGTGGAGC	CGTCAGATGGTGCCAGCAATAG

FN1	ACAACACCGAGGTGACTGAG	GGACACAACGATGCTTCCTG
FOS	GCCTCTCTTACTACCACTCACC	AGATGGCAGTGACCGTGGAAT
FOXA1	CGCTTCGCACAGGGCTGGAT	TGCTGACCGGGACGGAGGAG
MARK-1	TGCTCACCTGAAGGTCCAGAGA	CTTCCACACTGTTAGCCTGAGG
MCL-1	CCAAGAAAGCTGCATCGAACCAT	CAGCACATTCTGATGCCACCT
MMP9	TTCCAAACCTTTGAGGGCGA	CAAAGGCGTCGTCAATCACC
NOTCH	GGTGAAGTCTCTGAGGAGATC	GGATTGCAGTCGTCCACGTTGA
PDL1	TGCCGACTACAAGCGAATTACTG	CTGCTTGTCAGATGACTTCGG
PFN	CATCGTGGGCTACAAGGACTCG	CCAAGTGTGAGCCATTACGT
PTEN	TCCACAAACAGAACAAGATGCTA	CGATTTCTTGATCACATAGACTTCC
RECK	AATCCTTGCCCTGCCAATGAGC	GCACCTGGATTAGTGCCCTTG
SMAD4	CTACCAGCACTGCCAACCTTCC	CCTGATGCTATCTGCAACAGTCC
SNAIL	TGCCCTCAAGATGCACATCCGA	GGGACAGGAGAAGGGCTTCTC
TIM2	ACCCTCTGTGACTTCATCGTGC	GGAGATGTAGCACGGGATCATG
TIMP3	TACCGAGGCTTCACCAAGATGC	CATCTTGCCATCATAGACGCGAC
TP53	CCTCAGCATCTTATCCGAGTGG	TGGATGGTGGTACAGTCAGAGC
TWIST	GCCAGGTACATCGACTTCCTCT	TCCATCCTCCAGACCGAGAAGG
VIM	AGGCAAAGCAGGAGTCCACTGA	ATCTGGCGTTCCAGGGACTCAT
ZEB1	GGCATAACCTACTCAACTACGG	TGGGCGGTGTAGAATCAGAGTC
ZBTB4	TACACTCGTGGCGGAGGAAGTA	CTCCCAACAGAAGATGCACTGG

145

146 Data processing and analysis

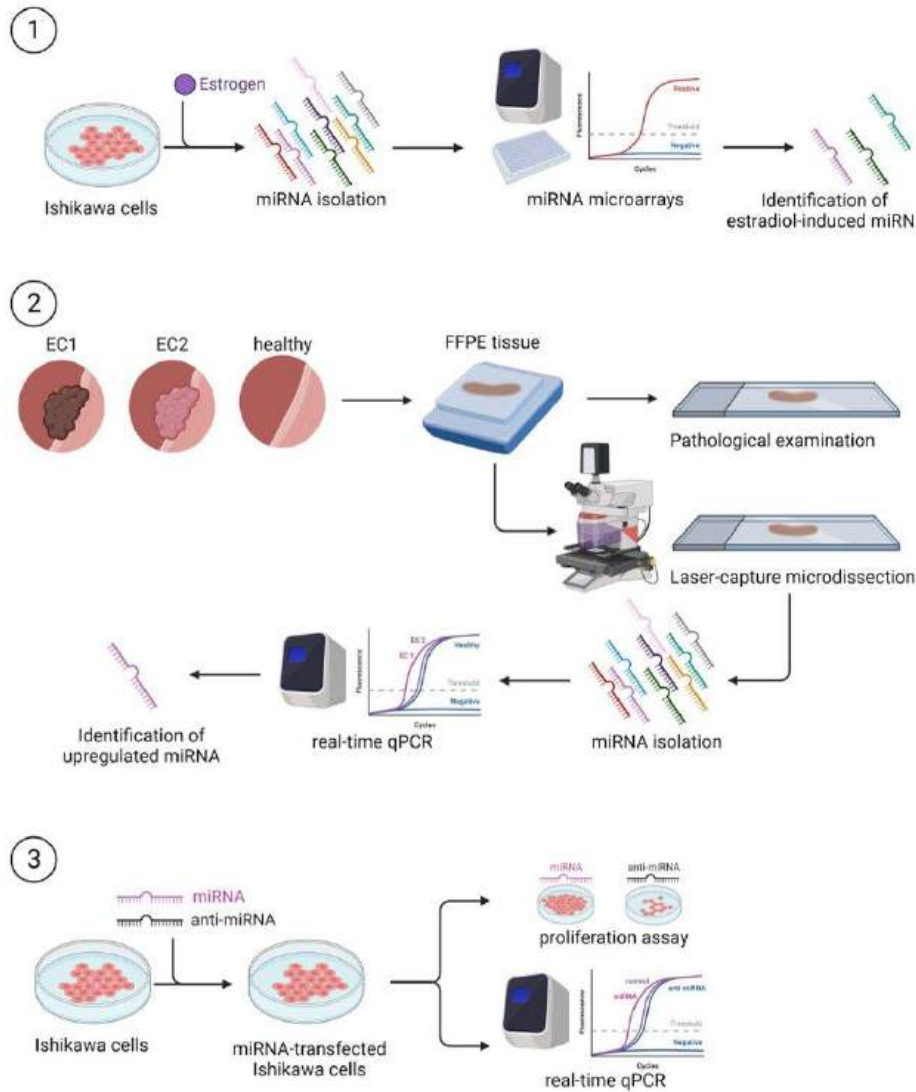
147 All experiments were conducted according to the protocol in triplicates. GraphPad Prism 9.1 (GraphPad
148 Software Inc.) was used for statistical analyses using the Kruskal-Wallis and paired t-test. A p-value
149 lower than 0.05 was considered statistically significant. The figures were generated using Biorender.
150 The Bioethical Committee of the Medical University of Warsaw declares (AKBE/78/2021) that the
151 study is not considered a medical experiment under the Act of 5 December 1996 about the professions
152 of doctor and dentist.

153

154 Results

155 Estradiol induces global changes in miRNA expression in endometrial cancer cells

156 To assess the role of the estrogen-miRNAs axis in EC (Fig. 1), we chose an Ishikawa endometrial cancer
 157 cell line that is characterized by the expression of estrogen receptors (Johnson, Maleki-Dizaji et al.
 158 2007). These cells respond to estradiol stimulation with an increased proliferation (Supplementary Fig.
 159 1). To determine a global profile of miRNA expression, we utilized the microarray method. We assessed
 160 the level of expression of a panel of 754 human miRNAs in Ishikawa cells that were incubated with
 161 estradiol for 48 hours. We detected 416 miRNAs in total and 66 miRNAs were upregulated in estradiol-
 162 treated Ishikawa cells. From them, we selected 26 miRNAs whose expression was most strongly
 163 upregulated by estradiol in EC cells (miR-15a, miR-16, miR-27b, miR-28-3p, miR-29c, miR-31#, miR-
 164 92a, miR-106a, miR-106b, miR-129-3p, miR-130a, miR-140, miR-140-3p, miR-141, miR-150, miR-
 165 152, miR-182, miR-192, miR-198, miR-200c, miR-215, miR-335, miR-496, miR-517c, miR-590-3p,
 166 and miR-656) (Table 4).



167

168 **Fig. 1 Study design diagram.** (1) Ishikawa EC cells were incubated with estradiol. RNA was isolated.
169 Estradiol-induced miRNAs were identified using the microarray method. (2) Selected regions of FFPE
170 tissues of EC1, EC2 and HE were dissected. MiRNAs were isolated and their expression was assessed
171 using RT-qPCR method. (3) Ishikawa EC cells were transfected with miRNA-mimic and its inhibitor
172 and subjected to proliferation assay and RT-qPCR to find its target.

173

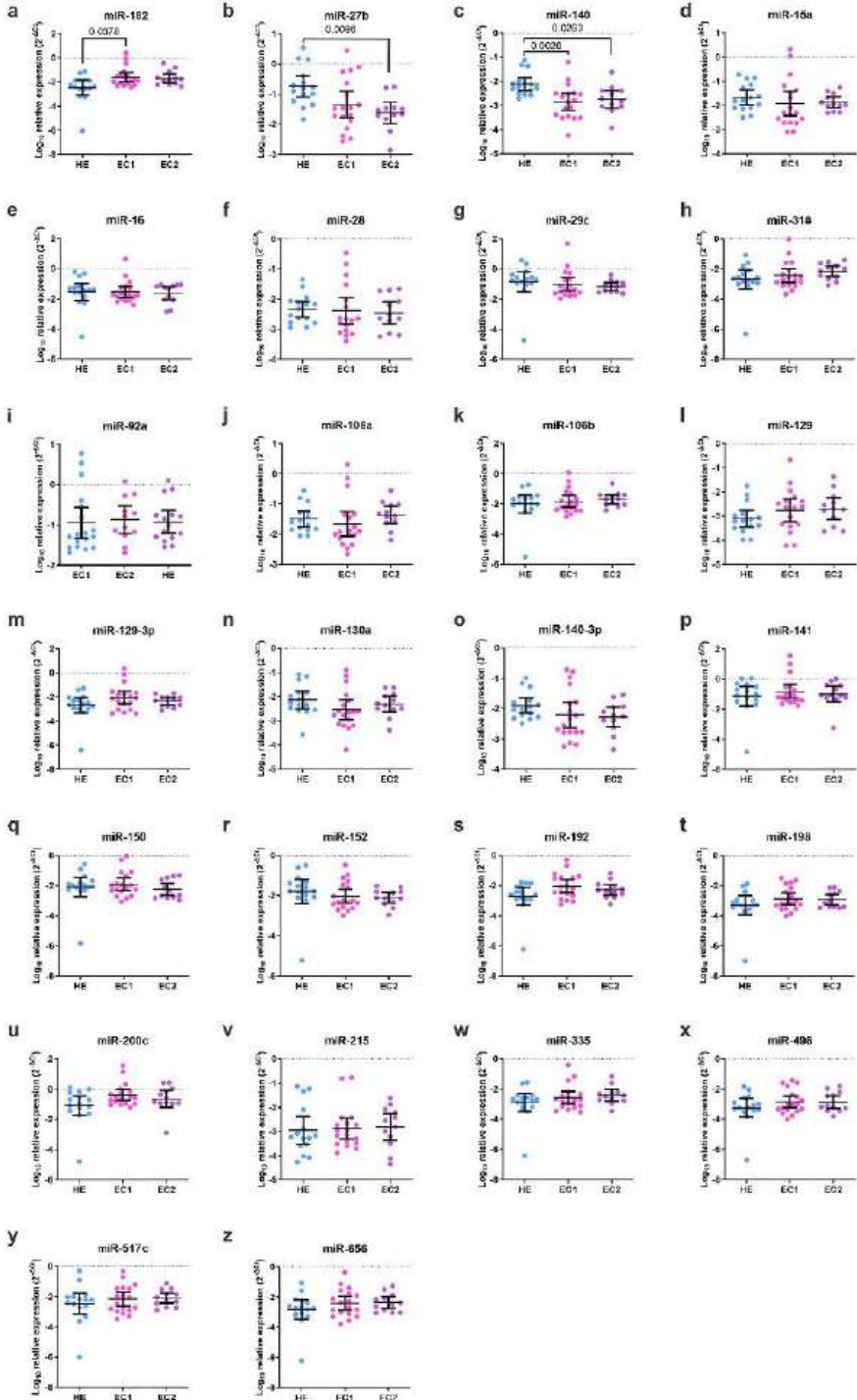
174 **Table 4. Relative expression of selected miRNAs which expression was most strongly induced by**
175 **estradiol in EC cells.** Ishikawa EC cells were incubated with estradiol. The expression of miRNAs was
176 assessed using microarray method. $R = 2^{-\Delta\Delta Ct}$. The experiments were conducted in triplicates.
177

miRNA	R1	R2	R3
hsa-miR-15a	2,467880839	1,057148936	1,521061477
hsa-miR-16	1,038336523	1,13145572	1,579074587
hsa-miR-27b	1,608005906	1,102	1,883
hsa-miR-28-3p	1,256379062	1,216873893	2,101005552
hsa-miR-29c	1,260741828	1,121304206	2,170577526
hsa-miR-31#	2,321803776	6,03526599	5,412045038
hsa-miR-92a	1,029734961	1,019017726	1,615611437
hsa-miR-106a	1,086187165	1,195139224	1,31228322
hsa-miR-106b	1,675129604	1,929	1,225
mmu-miR-129-3p	2,95318864	12,136	58,895
hsa-miR-130a	1,524431298	1,020431937	2,056341445
mmu-miR-140	1,835626692	1,06819722	1,622343006
hsa-miR-140-3p	1,252900716	1,072649364	2,269036844
hsa-miR-141	1,0899575	1,191830424	2,280072983
hsa-miR-150	4,820805576	1,522222892	4,039225975
hsa-miR-152	2,786151833	1,033957689	1,513699148
hsa-miR-182	1,441201201	1,412428573	3,600208353
hsa-miR-192	4,017432428	1,989184912	2,086489757
hsa-miR-198	4,311754235	2,155733029	4,783538936
hsa-miR-200c	1,5457141	1,455161307	2,19783108
hsa-miR-215	1,483776178	2,503898738	1,083786101
hsa-miR-335	2,846667552	2,760977007	2,631852852
mmu-miR-496	3,134579781	7,444528801	4,503593272
hsa-miR-517c	3,610684897	2,193413999	3,810761257
hsa-miR-590-3P	2,809368102	16,273	15,902
hsa-miR-656	3,3040759	2,133788754	3,65830464

178
179 **MiR-182 is upregulated in endometrial cancer type I**

180 To further confirm which miRNAs may be upregulated by estradiol in human EC, we analyzed tissues
181 derived from 30 patients diagnosed with EC (18 EC1 and 12 EC2 samples) and 15 patients with healthy
182 endometrium (HE) operated because of other reasons e.g., leiomyoma. We used the Laser Capture
183 Microdissection method to isolate and selectively measure the expression of 26 miRNAs in cancer
184 tissue. The results of the analyses revealed aberrant expression levels of three miRNAs. Notably, the
185 expression of miR-182 was upregulated in EC1 compared to HE (Fig. 2a). MiR-27b expression was
186 decreased in EC2 compared to HE (Fig. 2b) while the expression of miR-140 was decreased in both
187 EC1 and EC2 compared to HE (Fig. 2c). There were no differences between the expression of miR-15a
188 (Fig. 2d), miR-16 (Fig. 2e), miR-28-3p (Fig. 2f), miR-29c (Fig. 2g), miR-31# (Fig. 2h), miR-92a (Fig.
189 2i), miR-106a (Fig. 2j), miR-106b (Fig. 2k), miR-129 (Fig. 2l), miR-129-3p (Fig. 2m), miR-130a (Fig.
190 2n), miR-140-3p (Fig. 2o), miR-141 (Fig. 2p), miR-150 (Fig. 2q), miR-152 (Fig. 2r), miR-192 (Fig. 2s),
191 miR-198 (Fig. 2t), miR-200c (Fig. 2u), miR-215 (Fig. 2v), miR-335 (Fig. 2w), miR-496 (Fig. 2x), miR-

192 517c (Fig. 2y) and miR-656 (Fig. 2z) in EC1, EC2 and HE. The expression of miR-590-3p was too low
193 to detect (data not shown). Thus, we selected miRNA-182 for further *in vitro* studies.
194



195

Fig. 2 MiR-182 is upregulated in EC1 compared to HE. The expression of a) miR-182, b) miR-15a, c) miR-16, d) miR-27b, e) miR-28-3p, f) miR-29c, g) miR-31#, h) miR-92a, i) miR-106a, j) miR-106b, k) miR-129, l) miR-129-3p, m) miR-130a, n) miR-140, o) miR-140-3p, p) miR-141, q) miR-150, r) miR-152, s) miR-192, t) miR-198, u) miR-200c, v) miR-215, w) miR-335, x) miR-496, y) miR-517c, and z) miR-656 in dissected tissue of EC1, EC2 and HE. U6 was used as an endogenous control. *P*-values were calculated using the Kruskal-Wallis test. **p*<0.05

MiR-182 acts as an oncomiR in endometrial cancer

Our microarray results and increased expression of miR-182 in EC1 tissues compared to HE suggest miR-182 is induced by estrogens and may have a role in the pathogenesis of EC. To check that hypothesis we performed a proliferation assay. Ishikawa cells were transfected with a synthetic miR-182 mimic or miR-182 inhibitor (anti-miR-182) and their corresponding controls. We found that an increased level of miR-182 significantly enhanced the proliferation of Ishikawa cells (Fig. 3a), whereas inhibition of miR-182 resulted in an inhibition of the proliferation of EC cells (Fig. 3b). These studies revealed that miR-182 acts as an oncomiRs in EC.

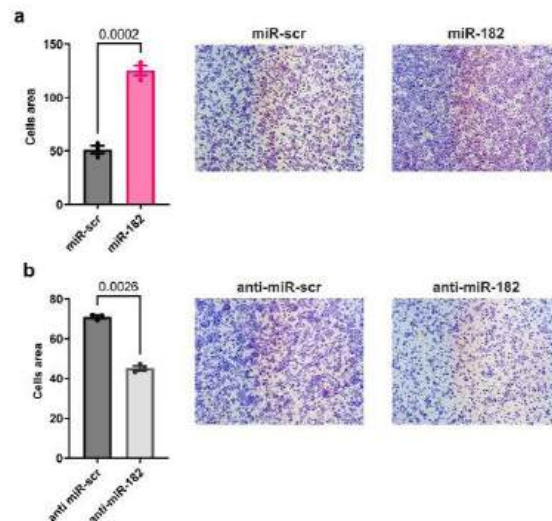


Fig. 3 MiR-182 acts as oncomiRNA in EC cells. (a) The proliferation of mimic miR-182-transfected Ishikawa cells compared to control miR-scramble (miR-scr)-transfected cells and representative photos, *p*=0.0002. (b) The proliferation of anti-miR-182-transfected Ishikawa cells compared to control anti-miR-scr-transfected cells and representative photos, *p*=0.0026.

Inhibition of miR-182 upregulates SMAD4 expression

218 Further, we sought to determine the mechanism of action of miRNA-182 in EC cells. We checked the
 219 role miRNA-182 plays in regulating the main oncogenic pathways in EC cells. For this purpose,
 220 Ishikawa cells were transfected with miR-182 mimic and its inhibitor. After 48 hours, the RNA was
 221 isolated, and then the expression of the targets selected based on the literature data was assessed. We
 222 determined the influence of miR-182 modulation on the expression of key proteins regulating epithelial-
 223 to-mesenchymal transition (EMT), apoptosis, and proliferation in EC (Grzywa, Klicka et al. 2020). We
 224 found that the inhibition of miR-182 in EC cells leads to the upregulated SMAD4 expression, which is
 225 an important member of TGF β signaling (Fig. 4a) (Zhao, Mishra et al. 2018). We did not observe any
 226 influence of miR-182 on the expression of BCL2 (Fig. 4b), COX2 (Fig. 4c), ER α (Fig. 4d), ESRR1 (Fig.
 227 4e), EZH2 (Fig. 4f), FN1 (Fig. 4g), FOS (Fig. 4h), FOXA1 (Fig. 4i), MARK1 (Fig. 4j), MCL1 (Fig. 4k),
 228 MMP9 (Fig. 4l), NOTCH (Fig. 4m), PDL1 (Fig. 4n), PFN (Fig. 4o), PTEN (Fig. 4p), RECK (Fig. 4q),
 229 TIM2 (Fig. 4r), TIMP3 (Fig. 4s), TP53 (Fig. 4t), TWIST (Fig. 4u), VIM (Fig. 4v), ZBTB4 (Fig. 4w),
 230 ZEB1 (Fig. 4y).

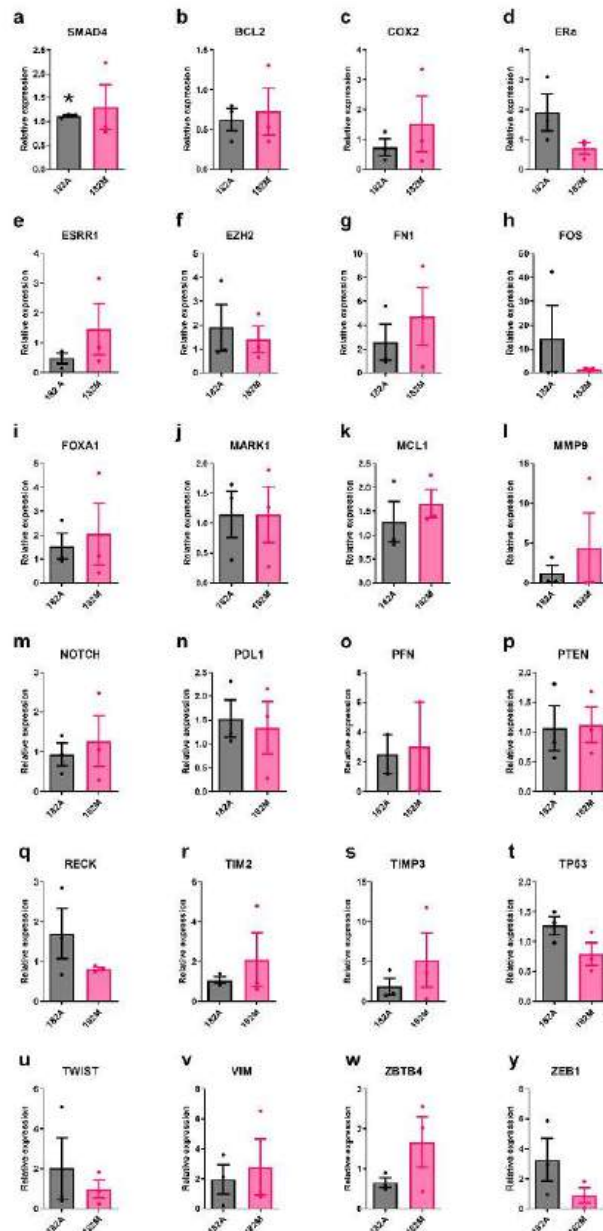


Fig.4 Inhibition of miR-182 upregulates SMAD4 expression. The relative expression of a) SMAD4, b) BCL2, c) COX2, d) ERα, e) ESRR1, f) EZH2, g) FN1, h) FOS, i) FOXA1, j) MARK1, k) MCL1, l) MMP9, m) NOTCH, n) PDL1, o) PFN, p) PTEN, q) RECK, r) TIM2, s) TIMP3, t) TP53, u) TWIST, v) VIM, w) ZBTB4, and y) ZEB1 in mimic miR-182 (182M) and anti-miR-182 (182a)-transfected

236 Ishikawa cells compared to control miR-scramble-transfected Ishikawa cells. GAPDH was used as an
237 endogenous control. *p=0.03.

238

239 Discussion

240 This study demonstrated the global changes in miRNA expression induced by estradiol in EC cells.
241 MiRNAs were described to have a crucial role in the pathogenesis of EC (Klicka, Grzywa et al. 2021).
242 MiRNAs target mRNAs involved in the EMT process, cell cycle signaling, growth factor signaling,
243 epigenetics, hormone signaling, and others (Klicka, Grzywa et al. 2021). Notably, the expression of
244 various miRNAs was correlated with clinical parameters of patients with EC suggesting their potential
245 as diagnostic and prognostic biomarkers (Klicka, Grzywa et al. 2021).

246 Some data in the literature already described the relationship between estrogens and miRNAs, but they
247 were focused on breast cancer cells (Nagpal, Ahmad et al. 2013). Estrogen increases the proliferation of
248 cancer cells, induces mostly oncomiRs, and represses tumor suppressor miRNAs (Cochrane, Cittelly et
249 al. 2011). In the EC cell line rat model, estrogen was described to increase the expression of miR-181c
250 and miR-200c (Zierau, Helle et al. 2018). These miRNAs target PTEN which regulates the PI3K-Akt
251 axis, the key oncogenic pathway in EC cells (Chen, Zhang et al. 2018). Moreover, high expression of
252 ERα was associated with overexpression of miR-200 (Indumati, Apurva et al. 2023). In this study, we
253 detected 416 miRNAs, among which 66 were upregulated in Ishikawa EC cells incubated with estrogen.
254 Out of them we chose 26 miRNAs and checked their expression in EC1, EC2 compared to HE (Table
255 4). The expression of miR-27b, miR-140, and miR-182 was changed in EC tissue.

256 Previous studies reported upregulated expression of miRNA-106a, miR-141, miR-182, miR-192, and
257 miR-200c in EC human tissues. MiR-106a was described to act as an oncomiRNA promoting EC cell
258 proliferation, invasion, and tumor growth by targeting BCL2L1 (Tang, Li et al. 2017). Upregulated
259 expression of miR-141 in EC was associated with positive ER status, however, its expression is not
260 statistically significantly correlated with clinical features (Dong, Si et al. 2015). Upregulated expression
261 of miRNA-192 was associated with lymphovascular invasion (Lee, Ratner et al. 2014). MiR-200c
262 expression was described to be upregulated in EC tissues however its role in EC is unclear (Klicka,
263 Grzywa et al. 2021). The expression of miRNA-152 was downregulated in EC (Klicka, Grzywa et al.
264 2021). However, our study did not confirm these changes, excluding the role of these miRNAs as
265 biomarkers of EC.

266 In our study, miR-182 was induced by estradiol in the EC cell line and upregulated in EC 1 compared
267 to HE. MiR-182 was described to be upregulated in EC compared to HE tissue in both proliferative and
268 secretory phases (Lee, Choi et al. 2012, Nishijima, Inoue et al. 2022) and in EC cell lines compared to
269 human normal endometrial epithelial cells (Guo, Liao et al. 2013). Moreover, inhibition of miR-182
270 increased apoptosis of EC cells [18]. MiR-182 targets directly transcription elongation factor A-like 7

(TCEAL7). Inhibition of miR-182 decreased the proliferation of EC cells by downregulating NFκB-p65, cyclin D1, and c-Myc (Guo, Liao et al. 2013). Moreover, miR-182 directly binds to FOXO1 and FoxF2 and thus promotes proliferation, invasion, and migration (Fang, Sang et al. 2018, Yao, Kong et al. 2019). MiR-182 was described as a promising biomarker for the survival of EC patients (Wang, Zhong et al. 2015) as well as a possible therapeutic agent (Sameti, Tohidast et al. 2023). In our study, miR-182 increased the proliferation of EC cells which is consistent with literature data. Moreover, inhibition of miR-182 increased SMAD4 expression. The TGF-β/Smad pathway is one of the most important pathways in EC pathogenesis. These broad effects of miR-182 may be potentiated by its upregulation by estrogen in EC. SMAD4 is a known tumor suppressor in numerous cancer types (Zhao, Mishra et al. 2018). It interacts with key signaling pathways including MAPK, PI3K/Akt, and WNT/β-catenin (Zhao, Mishra et al. 2018). Thus, it influences the main processes in cancer cells, among them the EMT process in which cancer cells acquire the ability to migrate (Chen, Chiang et al. 2021). Downregulation of SMAD4 in EC causes repression of junction and adhesion complex genes leading to the increased motility of cancer cells (Lin, Kost et al. 2020). Moreover, lower expression of SMAD4 correlates with higher grading and worse prognosis of EC patients (Mhawech-Fauceglia, Kesterson et al. 2011). The TGF-β pathway members are described as targets of miRNAs in EC. SMAD4 is targeted by miR-27a-5p in EC which resulted in an inhibition of invasion and migration of EC cells (Che, Jian et al. 2020). Similarly, in other types of cancers, SMAD4 is a target of different miRNAs which promote cancer development (Zeng, Zhu et al. 2017, Zhou, Zhang et al. 2020). In ovarian cancer, SMAD4 is targeted by miR-145-5p and causes enhanced proliferation of cancer cells (Zhou, Zhang et al. 2020). It was reported that miR-205 targets SMAD4 in lung cancer resulting in increased growth of cancer cells *in vitro* and in *in vivo* studies (Zeng, Zhu et al. 2017). The main limitation of the study is the small study group and lack of data concerning the outcome of patients, so the results of our study cannot be correlated with the patient's prognosis. There is a need for further studies assessing the mechanism of action of estradiol-induced miRNAs in EC *in vitro*, as well as their association with clinical features of patients.

297 Conclusions

298 In this study, we found that miR-182 is induced by estrogen in the EC cell line. Its expression was
299 upregulated in tissue of EC I compared to healthy endometrium. *In vitro* studies revealed that miR-182
300 increased the proliferation of EC cells. Inhibition of miR-182 in EC resulted in increased expression of
301 SMAD4. Additional studies are needed to assess the mechanism of action of miR-182, its role in EC in
302 *in vivo* studies, and its potential clinical use as a biomarker.

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310 Author Contributions

311 K.K. acquired funding, planned and conducted the experiments, analyzed the results, and wrote the
312 manuscript. T.M.G. planned and conducted the experiments, analyzed the results, prepared figures,
313 supervised the study, and wrote the manuscript. J.W. and J.O. performed collected and provided HE and
314 EC samples and performed histopathological analysis of the samples. P.K.W. acquire funding and
315 supervised the study. All authors have read and agreed to the published version of the manuscript.

316 Data Availability Statement

317 The data that support the findings of this study are available from T.M.G. or P.K.W. upon reasonable
318 request. Data from TCGA are publicly available.

319 Competing Interests Statement

320 The authors declare no conflict of interest.

321 322 References

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Podsumowanie i wnioski

W pracy doktorskiej zebrano i usystematyzowano dotychczasową wiedzę dotyczącą roli mikroRNA w regulacji inwazyjności i przerzutów komórek nowotworowych, ze szczególnym uwzględnieniem ich roli w modelu raka endometrium. Wyniki przeprowadzonych badań oryginalnych wykazały szczególną rolę osi estradiol-mikroRNA w patogenezie raka endometrium. Mogą one posłużyć jako podstawa do dalszych badań nad rolą mikroRNA jako biomarkerów raka endometrium- zarówno jako wczesnego markera choroby, jak i jej czynnika prognostycznego.

Szczegółowe wyniki badań w ramach pracy doktorskiej:

- Estradiol wpływa na globalną zmianę poziomu ekspresji cząsteczek mikroRNA w komórkach raka endometrium;
- Ekspresja miR-23b, miR-125-b-5p, miR-140, miR-199a-3p, miR-221-3p i miR-451a jest obniżona w tkankach raka endometrium w porównaniu do zdrowego endometrium;
- Ekspresja miR-34a-5p i miR-146-5p jest wyższa w tkankach raka endometrium typu I w porównaniu do raka endometrium typu II;
- Ekspresja miR-182 jest podwyższona w tkankach raka endometrium typu I w porównaniu do zdrowego endometrium;
- Ekspresja miR-27b jest obniżona w tkankach raka endometrium typu II w porównaniu do zdrowego endometrium;
- Obniżona ekspresja miR-23b jest związana z gorszym rokowaniem u pacjentów;
- MiR-23b hamuje proliferację komórek raka endometrium linii Ishikawa;
- MiR-182 zwiększa proliferację komórek raka endometrium linii Ishikawa;
- Zahamowanie miR-182 powoduje zwiększenie ekspresji SMAD4, który jest członkiem szlaku sygnałowego TGF β .

Oświadczenie Komisji Bioetycznej



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AKBE/ 78 / 2021

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OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 17 maja 2021 r. przyjęła do wiadomości informację na temat badania pt. "MikroRNA regulacja inwazyjności komórek raka endometrium."

Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21 ust. 1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U. z 2018 r. poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust. 1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz

Oświadczenia współautorów publikacji

Warszawa, 22.10.2023r.

Dr n. med. i n. o zdr. Tomasz M. Grzywa

OŚWIADCZENIE

Jako współautor pracy pt. "Regulators at Every Step—How microRNAs Drive Tumor Cell Invasiveness and Metastasis" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja. Mój udział procentowy w przygotowaniu publikacji określam jako 40%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 40%, obejmował on przygotowanie oryginalnego manuskryptu i jego edycja.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.


(podpis oświadczającego)

Warszawa, 15.04.2025r.

Lek. Klaudia Klicka

OŚWIADCZENIE

Jako współautor pracy pt. "Regulators at Every Step-How microRNAs Drive Tumor Cell Invasiveness and Metastasis" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie oryginalnego manuskryptu i jego edycja.

Mój udział procentowy w przygotowaniu publikacji określam jako 40%.

Klaudia Klicka

(podpis oświadczającego)

Warszawa, 29.03.2025r.

Prof. dr hab. n. med. Paweł Włodarski

OŚWIADCZENIE

Jako współautor pracy pt. "Regulators at Every Step-How microRNAs Drive Tumor Cell Invasiveness and Metastasis" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: edycja oryginalnego manuskryptu. Mój udział procentowy w przygotowaniu publikacji określłam jako 20%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określłam jako 40%, obejmował on przygotowanie oryginalnego manuskryptu i jego edycja.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.



(podpis oświadczającego)

Warszawa, 15.04.2025r.

Lek. Klaudia Klicka

OŚWIADCZENIE

Jako współautor pracy pt. "The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis-A Systematic Review" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja.

Mój udział procentowy w przygotowaniu publikacji określam jako 35%.

.....Klaudia.....Klicka

(podpis oświadczającego)

Warszawa, 22.10.2023r.

Dr n. med. i n. o zdr. Tomasz M. Grzywa

OŚWIADCZENIE

Jako współautor pracy pt. "The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis-A Systematic Review" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja, przygotowanie rycin do artykułu. Mój udział procentowy w przygotowaniu publikacji określam jako 35%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 35%, obejmował on: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.


(podpis oświadczającego)

Warszawa, 12.10.2023r.

Lek. Alicja Klinke

OŚWIADCZENIE

Jako współautor pracy pt. "The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis-A Systematic Review" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: uczestnictwo w przygotowaniu oryginalnego manuskryptu i jego edycji. Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 35%, obejmował on: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.


(podpis oświadczającego)

Warszawa, 12.10.2023r.

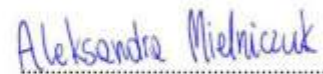
Lek. Aleksandra Mielniczuk

OŚWIADCZENIE

Jako współautor pracy pt. "The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis-A Systematic Review" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: uczestnictwo w przygotowaniu oryginalnego manuskryptu i jego edycji. Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 35%, obejmował on: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.



(podpis oświadczającego)

Warszawa, 15.04.2025r.

Prof. dr hab. n. med. Paweł K. Włodarski

OŚWIADCZENIE

Jako współautor pracy pt. "The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis-A Systematic Review" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: edycja oryginalnego manuskryptu, nadzorowanie prac zespołu badawczego. Mój udział procentowy w przygotowaniu publikacji określam jako 20%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 35%, obejmował on: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.



(podpis oświadczającego)

Warszawa, 15.04.2025r.

Lek. Klaudia Klicka

OŚWIADCZENIE

Jako współautor pracy pt. "The role of miR-200 family in the regulation of hallmarks of cancer" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja.

Mój udział procentowy w przygotowaniu publikacji określám jako 30%.

.....Klaudia Klicka
(podpis oświadczającego)

Warszawa, 22.10.2023r.

Dr n. med. i n. o zdr. Tomasz M. Grzywa

OŚWIADCZENIE

Jako współautor pracy pt. "The role of miR-200 family in the regulation of hallmarks of cancer" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja, przygotowanie rycin do artykułu. Mój udział procentowy w przygotowaniu publikacji określam jako 30%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 30%, obejmował on: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.


(podpis oświadczającego)

Warszawa, 12.10.2023r.

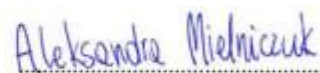
Lek. Aleksandra Mielniczuk

OŚWIADCZENIE

Jako współautor pracy pt. "The role of miR-200 family in the regulation of hallmarks of cancer" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: uczestnictwo w przygotowaniu oryginalnego manuskryptu i jego edycji. Mój udział procentowy w przygotowaniu publikacji określam jako 15%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 30%, obejmował on: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.



(podpis oświadczającego)

Warszawa, 12.10.2023r.

Lek. Alicja Klinke

OŚWIADCZENIE

Jako współautor pracy pt. "The role of miR-200 family in the regulation of hallmarks of cancer" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: uczestnictwo w przygotowaniu oryginalnego manuskryptu i jego edycji. Mój udział procentowy w przygotowaniu publikacji określłam jako 5%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określłam jako 30%, obejmował on: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.


.....
(podpis oświadczającego)

Warszawa, 15.04.2025r.

Prof. dr hab. n. med. Paweł K. Włodarski

OŚWIADCZENIE

Jako współautor pracy pt. "The role of miR-200 family in the regulation of hallmarks of cancer" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: edycja oryginalnego manuskryptu, nadzorowanie prac zespołu badawczego. Mój udział procentowy w przygotowaniu publikacji określam jako 20%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 30%, obejmował on: przygotowanie koncepcji pracy, przygotowanie oryginalnego manuskryptu i jego edycja.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.



(podpis oświadczającego)

Warszawa, 29.03.2025r.

Lek. Klaudia Klicka

OŚWIADCZENIE

Jako współautor pracy pt. "Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zapewnienie finansowania badań, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określłam jako 30%.

Klaudia Klicka

(podpis oświadczającego)

Warszawa, 22.10.2023r.

Dr n. med. i n. o zdr. Tomasz M. Grzywa

OŚWIADCZENIE

Jako współautor pracy pt. "Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przygotowanie koncepcji pracy, wykonanie eksperymentów, analiza wyników badań, przygotowanie rycin do artykułu, nadzór nad przebiegiem prac badawczych, przygotowanie oryginalnego manuskryptu. Mój udział procentowy w przygotowaniu publikacji określam jako 30%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 30%, obejmował on: zapewnienie finansowania badań, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.


(podpis oświadczającego)

Warszawa, 12.10.2023r.

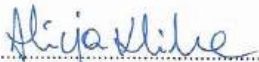
Lek. Alicja Klinke

OŚWIADCZENIE

Jako współautor pracy pt. "Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zebranie i analiza danych klinicznych pacjentów. Mój udział procentowy w przygotowaniu publikacji określłam jako 8%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określłam jako 30%, obejmował on: zapewnienie finansowania badań, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.


(podpis oświadczającego)

Warszawa, 12.10.2023r.

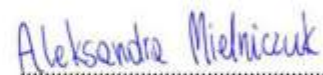
Lek. Aleksandra Mielniczuk

OŚWIADCZENIE

Jako współautor pracy pt. "Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: uczestniczenie w przygotowaniu oryginalnego manuskryptu. Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 30%, obejmował on: zapewnienie finansowania badań, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.



(podpis oświadczającego)

Warszawa, 29.03.2025r.

Dr n. med. Jarosław Wejman

OŚWIADCZENIE

Jako współautor pracy pt. "Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zebranie preparatów histopatologicznych tkanek zdrowego endometrium i raka endometrium, badanie histopatologiczne preparatów. Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 30%, obejmował on: zapewnienie finansowania badań, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.



(podpis oświadczającego)

Warszawa, 29.03.2025r.

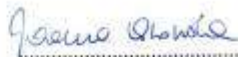
Lek. Joanna Ostrowska

OŚWIADCZENIE

Jako współautor pracy pt. "Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zebranie preparatów histopatologicznych tkanek zdrowego endometrium i raka endometrium, badanie histopatologiczne preparatów. Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 30%, obejmował on: zapewnienie finansowania badań, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.



(podpis oświadczającego)

Warszawa, 29.03.2025r.

Dr n. rol. Agata Gondek

OŚWIADCZENIE

Jako współautor pracy pt. "Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: udział w wykonywaniu eksperymentów. Mój udział procentowy w przygotowaniu publikacji określam jako 2%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 30%, obejmował on: zapewnienie finansowania badań, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.

.....A. Gondek.....
(podpis oświadczającego)

Warszawa, 29.03.2025r.

Prof. dr hab. n. med. Paweł Włodarski

OŚWIADCZENIE

Jako współautor pracy pt. "Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zapewnienie finansowania badań oraz nadzór nad przebiegiem prac badawczych. Mój udział procentowy w przygotowaniu publikacji określam jako 15%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 30%, obejmował on: zapewnienie finansowania badań, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.



.....
(podpis oświadczającego)

Warszawa, 15.04.2025r.

Lek. Klaudia Klicka

OŚWIADCZENIE

Jako współautor pracy pt. "Estradiol induces global changes in miRNA expression in endometrial cancer cells and upregulates oncogenic miR-182" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zapewnienie finansowania projektu, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 50%.

Klaudia Klicka
(podpis oświadczającego)

Warszawa, 22.10.2023r.

Dr n. med. i n. o zdr. Tomasz M. Grzywa

OŚWIADCZENIE

Jako współautor pracy pt. "Estradiol induces global changes in miRNA expression in endometrial cancer cells and upregulates oncogenic miR-182" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie rycin do artykułu, nadzór nad przebiegiem prac badawczych, przygotowanie oryginalnego manuskryptu. Mój udział procentowy w przygotowaniu publikacji określám jako 35%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określám jako 50%, obejmował on zapewnienie finansowania projektu, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.


(podpis oświadczającego)

Warszawa, 29.03.2025r.

Dr n. med. Jarosław Wejman

OŚWIADCZENIE

Jako współautor pracy pt. "Estradiol induces global changes in miRNA expression in endometrial cancer cells and upregulates oncogenic miR-182" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zebranie preparatów histopatologicznych tkanek zdrowego endometrium i raka endometrium, badanie histopatologiczne preparatów. Mój udział procentowy w przygotowaniu publikacji określam jako 3%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 50%, obejmował on zapewnienie finansowania projektu, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.


(podpis oświadczającego)

Warszawa, 29.03.2025r.

Lek. Joanna Ostrowska

OŚWIADCZENIE

Jako współautor pracy pt. "Estradiol induces global changes in miRNA expression in endometrial cancer cells and upregulates oncogenic miR-182" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zebranie preparatów histopatologicznych tkanek zdrowego endometrium i raka endometrium, badanie histopatologiczne preparatów. Mój udział procentowy w przygotowaniu publikacji określam jako 2%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 50%, obejmował on zapewnienie finansowania projektu, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.


.....
(podpis oświadczającego)

Warszawa, 29.03.2025r.

Prof. dr hab. n. med. Paweł Włodarski

OŚWIADCZENIE

Jako współautor pracy pt. "Estradiol induces global changes in miRNA expression in endometrial cancer cells and upregulates oncogenic miR-182" oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zapewnienie finansowania projektu, nadzór nad przebiegiem prac badawczych. Mój udział procentowy w przygotowaniu publikacji określam jako 10%.

Wkład lek. Klaudii Klickiej w powstawanie publikacji określam jako 50%, obejmował on zapewnienie finansowania projektu, zaplanowanie i wykonanie eksperymentów, analiza wyników badań, przygotowanie oryginalnego manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Klaudii Klickiej.



(podpis oświadczającego)

Analiza bibliometryczna dorobku



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BIBLIOTEKA UCZELNIANA

Nr referencyjny
BIBG/Punktacja/170/2025/JL

Warszawa, 01.04.2025

Sz. Pani
Klaudia Klicka

ANALIZA BIBLIOMETRYCZNA PUBLIKACJI PANI KLAUDII KLICKIEJ, WCHODZĄCYCH W SKŁAD CYKLU PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

LP	OPIS	IF	MNIŚW	NAJWYŻSZY KWARTYL*
1	Klicka K [korespondencyjny], Grzywa T, Klinke A, Mielniczuk A, Wejman J, Ostrowska J, Gondek A, Włodarski P. Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients. Scientific Reports. 2022;12:1-14. <i>Rodzaj pracy: praca oryginalna</i>	4,600	140	Q2
2	Klicka K [korespondencyjny], Grzywa T, Mielniczuk A, Klinke A, Włodarski P. The role of miR-200 family in the regulation of hallmarks of cancer. Frontiers in Oncology. 2022;12:1-28. <i>Rodzaj pracy: praca poglądowa</i>	4,700	100	Q2
3	Klicka K, Grzywa T, Klinke A, Mielniczuk A, Włodarski P. The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis—A Systematic Review. Cancers. 2021;13(14):1-26. <i>Rodzaj pracy: przegląd systematyczny</i>	6,575	140	Q1
4	Grzywa T, Klicka K [równorzędny pierwszy autor], Włodarski P. Regulators at Every Step—How microRNAs Drive Tumor Cell Invasiveness and Metastasis. Cancers. 2020;12(12):1-54. <i>Rodzaj pracy: praca poglądowa</i>	6,639	140	Q1
Łącznie:		22,514	520	-

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biblioteka@wum.edu.pl

KSIĄŻKI	
LP	OPIS
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ROZDZIAŁY	
LP	OPIS
1.	-

* Kwartył z roku publikacji, według Impact Factor.

Kierownik
Oddziału Innowacji Naukowej

mgr Anna Ajdukiewicz-Tarkowska



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Nr referencyjny
BIBG/Punktacja/ 19/2025/JL

Warszawa, 01.04.2025

Sz. Pani
Klaudia Klicka

ANALIZA BIBLIOMETRYCZNA CAŁOKSZTAŁTU DOROBKU PUBLIKACYJNEGO
PANI KLAUDII KLIKIEJ,
W POSTĘPOWANIU O NADANIE STOPNIA NAUKOWEGO DOKTORA

LP	OPIS	IF	MNISW	NAJWYŻSZY KWARTYL*
I. Artykuły opublikowane w czasopismach naukowych lub w recenzowanych materiałach z konferencji międzynarodowych ujętych w aktualnym wykazie MNISW [1].				
1	Walasik I, Klicka K [równorzędny pierwszy autor], Grzywa T, Szymusik I, Włodarski P, Wielgoś M, Pietrzak B, Ludwin A. Circulating miR-3613-5p but not miR-125b-5p, miR-199a-3p, and miR-451a are biomarkers of endometriosis. Reproductive Biology. 2023;23(4):1-8. <i>Rodzaj pracy: praca oryginalna</i>	2,500	140	Q3
2	Klicka K [korespondencyjny], Grzywa T, Klinke A, Mielniczuk A, Wejman J, Ostrowska J, Gondek A, Włodarski P. Decreased expression of miR-23b is associated with poor survival of endometrial cancer patients. Scientific Reports. 2022;12:1-14. <i>Rodzaj pracy: praca oryginalna</i>	4,600	140	Q2
3	Klicka K [korespondencyjny], Grzywa T, Mielniczuk A, Klinke A, Włodarski P. The role of miR-200 family in the regulation of hallmarks of cancer. Frontiers in Oncology. 2022;12:1-28. <i>Rodzaj pracy: praca poglądowa</i>	4,700	100	Q2
4	Grzywa T, Koppolu A, Paskal W, Klicka K, Rydzanicz M, Wejman J, Płoski R, Włodarski P. Higher Mutation Burden in High Proliferation Compartments of Heterogeneous Melanoma Tumors. International Journal of Molecular Sciences. 2021;22(8):1-17. <i>Rodzaj pracy: praca oryginalna</i>	6,208	140	Q1

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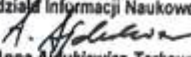
5	Grzywa T, Sosnowska A, Rydzynska Z, Łazniewski M, Plewczyński D, Klicka K, Małecka-Gieldowska M, Rodziewicz-Lurzyńska A, Ciepiela O, Justyniarska M, Pomper P, Grzybowski M, Błaszczyk R, Węgrzynowicz M, Tomaszewska A, Basak G, Gołab J, Nowis D. Potent but transient immunosuppression of T-cells is a general feature of CD71+ erythroid cells. <i>Communications Biology</i> . 2021;4(1):1-19. <i>Rodzaj pracy: praca oryginalna</i>	6,548	20	Q1
6	Klicka K, Grzywa T, Klinke A, Mielniczuk A, Włodarski P. The Role of miRNAs in the Regulation of Endometrial Cancer Invasiveness and Metastasis—A Systematic Review. <i>Cancers</i> . 2021;13(14):1-26. <i>Rodzaj pracy: przegląd systematyczny</i>	6,575	140	Q1
7	Pełka K, Klicka K, Grzywa T, Gondek A, Marczevska J, Garbicz F, Szczepaniak K, Paskal W, Włodarski P. miR-96-5p, miR-134-5p, miR-181b-5p and miR-200b-3p heterogenous expression in sites of prostate cancer versus benign prostate hyperplasia-archival samples study. <i>Histochemistry and Cell Biology</i> . 2021;155(3):423-433. <i>Rodzaj pracy: praca oryginalna</i>	2,531	100	Q2
8	Grzywa T, Klicka K [równorzędny pierwszy autor], Włodarski P. Regulators at Every Step-How microRNAs Drive Tumor Cell Invasiveness and Metastasis. <i>Cancers</i> . 2020;12(12):1-54. <i>Rodzaj pracy: praca poglądowa</i>	6,639	140	Q1
9	Grzywa T, Klicka K, Paskal W, Dudkiewicz J, Wejman J, Pyżlak M, Włodarski P. miR-410-3p is induced by vemurafenib via ER stress and contributes to resistance to BRAF inhibitor in melanoma. <i>PLoS One</i> . 2020;15(6):1-15. <i>Rodzaj pracy: praca oryginalna</i>	3,240	100	Q2
10	Grzywa T, Klicka K [równorzędny pierwszy autor], Rak B, Mehlich D, Garbicz F, Zieliński G, Maksymowicz M, Sajjad E, Włodarski P. Lineage-dependent role of miR-410-3p as oncomiR in gonadotroph and corticotroph pituitary adenomas or tumor suppressor miR in somatotroph adenomas via MAPK, PTEN/AKT, and STAT3 signaling pathways. <i>Endocrine</i> . 2019;65(3):646-655. <i>Rodzaj pracy: praca oryginalna</i>	3,235	100	Q3
11	Rudnicka E, Kruszevska J, Klicka K, Kowalczyk J, Grymowicz M, Skórska J, Pięta W, Smolareczyk R. Premature ovarian insufficiency - aetiopathology, epidemiology, and diagnostic evaluation. <i>Przegląd Menopauzalny</i> . 2018;17(3):105-108. <i>Rodzaj pracy: praca poglądowa</i>	-	15	-
Łącznie:		46,776	1135	-
II. Artykuły opublikowane przed 1.01.2019 r. w czasopiśmie MNISW z dnia 25.01.2017 r., o ile czasopismo uzyskało co najmniej 10 pkt.				
Łącznie:		-	-	-

III. Pozostałe artykuły.			
Łącznie:		-	-
Łącznie (cz. I-III):		46,776	1135
IV. Monografie naukowe/rozdziały w monografiach wydane przez wydawnictwa ujęte w wykazie MEIN [2] lub jednostki organizacyjne podmiotów, których wydawnictwa są ujęte w tym wykazie.			
12	Szlufik S, Kosowska A, Klicka K, Józwiak J. Rola aktywacji receptorów estrogenowych i szlaków Erk/Akt w etiologii glejaków. W: Postępy w Badaniach Biomedycznych - wybrane zagadnienia. Wyd. I. Praca zbiorowa pod red. Biały Ł [redaktor], Młynarczuk-Biały I [redaktor]. Lublin: Wydawnictwo Naukowe TYGIEL Sp. z o. o., 2018. Str.: 35-42.		
V. Pozostałe monografie lub rozdziały w monografiach.			
VI. Patenty.			

* Kwartył z roku publikacji, według Impact Factor.

[1]. Wykaz sporządzony zgodnie z przepisami wydanymi na podstawie art. 267 ust. 2 pkt 2 lit. b Ustawy z dnia 20 lipca 2018 r. - Prawo o szkolnictwie wyższym i nauce (Dz. U. z 2022 r., poz. 574 z późn. zm.). Wykaz stanowi załącznik do komunikatu MNiSW z 5 stycznia 2024 r. w sprawie wykazu czasopism naukowych i recenzowanych materiałów z konferencji międzynarodowych.

[2]. Wykaz sporządzony zgodnie z przepisami wydanymi na podstawie art. 267 ust. 2 pkt 2 lit. a Ustawy z dnia 20 lipca 2018 r. - Prawo o szkolnictwie wyższym i nauce (Dz. U. z 2022 r., poz. 574 z późn. zm.). Wykaz ogłoszony komunikatem MEiN z dnia 22 lipca 2021 r. w sprawie wykazu wydawnictw publikujących recenzowane monografie naukowe.

Kierownik
Oddziału Informacji Naukowej

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