Streszczenie w języku angielskim

Introduction: Papillary renal cell carcinoma (pRCC) is the second most common subtype of renal cell carcinoma (RCC), after clear cell RCC (ccRCC). It presents distinct histological and molecular characteristics compared to the more prevalent ccRCC. Despite therapeutic advances in ccRCC, the prognosis for pRCC, particularly in advanced stages, remains unsatisfactory. Growing evidence suggests that the sympathetic nervous system and β-adrenergic signaling are involved in tumor development and progression. The β_2-adrenergic receptor (β_2-AR) subtype is thought to play a key role in cancer pathophysiology. In various tumors, β_2-AR signaling has been shown to regulate proliferation, angiogenesis, migration, and invasion of cancer cells, as well as to influence cancer stem cell (CSC) phenotypes and modulate the immune system. However, the role of β-adrenergic signaling in RCC, especially in pRCC, remains unclear. Given the widespread use of β-AR-targeting drugs in cardiovascular diseases, understanding their potential impact on RCC holds significant clinical relevance.

Aims: The first aim of this study was to assess *ADRB2* gene expression across the main RCC subtypes and investigate its relationship with clinicopathological features and prognosis in pRCC patients (Part I). The second aim was to evaluate the effects of β_2-AR agonists and antagonists on cancer cell viability and the expression of genes associated with the CSC phenotype and angiogenesis (Part II).

Materials and Methods: *ADRB2* gene expression was analyzed using transcriptomic and clinical data of pRCC patients from The Cancer Genome Atlas (TCGA). The experimental part involved RCC cell lines derived from pRCC (Caki-2 and ACHN) and ccRCC (Caki-1, 786-O). qRT-PCR was used to compare *ADRB2* expression between pRCC and ccRCC cell lines. pRCC-derived cells were treated with salbutamol (a selective β_2-AR agonist) and ICI-118,551 (a selective β_2-AR antagonist) at varying concentrations, followed by viability assessment. Gene expression of CSC markers (*POU5F1* and *NES*) and angiogenesis-related genes (*VEGF-A* and *FLT1*) was also evaluated using qRT-PCR in cell lines treatet with ICI-118,551 and salbutamol.

Results: TCGA data analysis revealed that lower *ADRB2* expression levels in pRCC patients were associated with more frequent lymph node metastases, higher clinical stage at diagnosis, and shorter overall (OS) and progression-free survival (PFS). In vitro, treatment with the β_2-AR antagonist ICI-118,551 at 100 μM significantly reduced cell viability in both pRCC lines

(Caki-2 and ACHN). Lower concentrations (0.1–10 μM) also decreased ACHN cell viability. ICI-118,551 altered CSC gene expression, increasing *POU5F1* and decreasing *NES* (significantly in Caki-2). It also led to reduced *VEGF-A* expression (in the metastatic pRCC line) and compensatory upregulation of *VEGFR1* (*FLT1*) in both cell lines. Salbutamol did not affect cell viability or gene expression related to CSCs and angiogenesis.

Conclusions: High *ADRB2* expression is an unfavorable prognostic factor in pRCC, associated with lymph node involvement, distant metastases, and worse OS and PFS. β_2-AR blockade via the selective antagonist ICI-118,551 reduces pRCC cell viability, downregulates angiogenesis-related genes, and may induce selection of CSC-like cells.

Summary: This doctoral study demonstrates that β_2-AR plays a role in pRCC pathogenesis. Considering the widespread use of β-blockers and the higher incidence of RCC in hypertensive patients treated with such drugs, further preclinical and clinical research into β-adrenergic signaling in RCC may have clinical implications.