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Streszczenie w języku angielskim

A fusion of the *breakpoint cluster region* (*BCR*) and *V-abl Abelson murine leukemia viral oncogene homolog 1* (*ABL1*) genes (*BCR-ABL1*) is a result of translocation between chromosomes 9 and 22. It causes formation of the aberrant Philadelphia chromosome (Ph), encoding BCR-ABL1, a constitutively active tyrosine kinase. BCR-ABL1 is the hallmark and main oncodriver of chronic myeloid leukemia (CML). Even though CML historically had a poor outcome, the introduction of tyrosine kinase inhibitors (TKIs) made it a maintainable and mostly treatable disease. Apart from CML, Ph is also found in a subset of another leukemia type, B cell acute lymphoblastic leukemia (B-ALL). This leukemia is a common pediatric malignancy, characterized by the accumulation of immature lymphocytes, but it also occurs in adults. It is mainly treated with chemotherapy, but in a substantial fraction of patients, it returns as a difficult to cure, chemotherapy-resistant disease, therefore novel therapeutic approaches are urgently needed. Philadelphia chromosome-positive B-ALL (Ph^+ B-ALL) is one of the high-risk subtypes of B-ALL. Even though CML responds very well to treatment with TKIs, Ph^+ B-ALL has a relatively poor survival prognosis, with approximately 50% of cases relapsing post initial treatment. For this reason, the search for novel Ph^+ B-ALL targets is of utmost importance.

One of the hallmarks of cancer is the dysregulation of redox homeostasis caused by elevated levels of reactive oxygen species (ROS). To counteract the effects of ROS accumulation and prevent cell death, malignant cells upregulate elements of antioxidant machinery. Recent studies have shown increased levels of ROS and increased expression of the thioredoxin (TXN) family antioxidant enzymes in BALL cell lines and primary cells. Particular dysregulation of redox homeostasis was observed in Ph^+ BALL.

The main aim of the presented thesis was to assess the TXN system as a therapeutic target in Ph-positive (Ph^+) leukemias. Another objective was to propose potential drug combination and to test it in *in vitro* cell models of Ph^+ leukemias.

Initial experiments showed that the inhibition of the TXN system with either auranofin (AUR) or adenanthin (ADE) caused increased cell death in lymphoid Ph^+ cell lines and sensitized them to TKIs. Moreover, increased expression of peroxiredoxin 1 (PRDX1), one of the TXN

system elements, was found in lymphoid Ph^+ cell lines and primary cells in comparison to myeloid CML cells. CRISPR-Cas9 mediated knockout of PRDX1 significantly reduced lymphoid, but not myeloid, Ph^+ cells' proliferation and sensitized them to TKIs. These results strongly indicated that PRDX1 plays a lineage-specific role in Ph^+ leukemias. RNAseq analysis of genome-wide changes in imatinib -induced gene expression patterns in lymphoid Ph^+ cell line upon PRDX1 knockout revealed dysregulation of some genes and pathways crucial to cell maintenance and survival, further verifying PRDX1 key role in lymphoid Ph^+ cells. Moreover, no significant changes in ROS levels and endoplasmic reticulum stress upon PRDX1 knockout were identified. Further investigations of the mechanism of cell death triggered by imatinib in PRDX1-deficient cells led to the recognition of increased DNA damage and non-homologous end joining (NHEJ) as a vulnerability of lymphoid Ph^+ cells. A triple combination of TKIs, NHEJ, and TXN system inhibitors showed promising responses in both lymphoid Ph^+ cell lines and patient-derived Ph^+ B-ALL primary cells.

In summary, the role of PRDX1 in Ph^+ cells was shown to be associated with cell survival, resistance to therapy, and maintenance of genomic integrity in a lymphoid-specific manner. Moreover, the TXN system was identified as a new therapeutic target in Ph^+ B-ALL, the inhibition of which enhanced the effectiveness of standard therapy. NHEJ was also discovered as a previously unknown vulnerability in Ph^+ B-ALL and should be further investigated. Overall, these studies uncover novel potential targets that can contribute to the improvement of the effectiveness of Ph^+ B-ALL therapy in the future.