

## SUMMARY

T-cell acute lymphoblastic leukemia is a rare subtype of acute lymphoblastic leukemia, which is the most commonly diagnosed childhood cancer. From a clinical point of view, T-ALL is characterized by an aggressive course and a relatively high rate of primary resistance to treatment and relapse. The development of T-ALL occurs as a result of abnormalities in the maturation of T cell precursors. Activation of proto-oncogenes and inactivation of tumor suppressor genes leads to the inhibition of thymocyte differentiation, as well as to their uncontrolled proliferation and avoidance of apoptosis. Leukemogenesis processes can start at any stage of the complex process of T cell differentiation and can result from genetic and epigenetic aberrations. High immunophenotypic and (epi-)genetic heterogeneity is observed among patients with T-ALL, which, combined with the relatively low incidence of T-ALL, makes understanding the biology of this leukemia challenging.

Despite significant advances in understanding the biology of this disease, the role of epigenetic factors and the non-coding part of the genome remains elusive. Particularly noteworthy are miRNA molecules, i.e. short oligonucleotides which function as the negative regulators of gene expression. miRNAs are involved in many cellular processes, and their abnormal expression and dysfunction may contribute to the development and progression of cancer. The state of knowledge about the role of miRNAs in T-ALL leukemia at the time of the start of the research described in my doctoral dissertation showed only a fragment of the global regulatory network in which miRNAs are involved. Therefore, the aim of my study was to use next-generation sequencing to search for miRNAs abnormally expressed in T-ALL, to identify their target genes, to identify pathways and biological processes regulated by them, and to demonstrate the oncogenic or tumor suppressor effect of selected miRNAs in the T-ALL cell model *in vitro*.

This doctoral dissertation is a collection of five publications on the expression and role of miRNAs in T-ALL. The first one is a review of the scientific literature on the role of miRNA molecules in T-ALL leukemia, both in the context of their biological significance for the pathogenesis of this cancer, and their potential usefulness as diagnostic and prognostic biomarkers. The remaining four publications are original papers, the purpose of which was to identify miRNA molecules with abnormal expression in primary T-ALL cells (obtained from patients diagnosed with leukemia) and in T-ALL cell lines in relation to normal T cells, and to identify target genes regulated by selected miRNAs and to study the oncogenic or suppressor effect of these miRNA-mRNA interactions *in vitro*.

The results obtained within my doctoral thesis show that the tested miRNAs, which are abnormally expressed in samples of T-ALL patients, show oncogenic activity in T-ALL cell lines, which is reflected by the effect on proliferation, cell cycle and apoptosis of T-ALL cells. The phenotypic effect of the increased expression of hsa-miR-20b-5p and hsa-miR-363-3p is, at least in part, the result of silencing two important tumor suppressor genes, *PTEN* and *BIM*. Moreover, aberrant expression of hsa-miR-363-3p and impaired methylation of

promoter regions may be mechanisms of deregulation of JAK-STAT signaling pathways and potentially also other JAK-dependent pathways. Identification of these mechanisms may in the future contribute to the broadening of the criteria for inclusion of patients to the treatment options targeted at the JAK-STAT pathway.

The results obtained in this dissertation indicate the complexity and importance of miRNA-mRNA interactions in the deregulation of pathways and processes relevant to the biology of T-ALL, and thus the role of miRNAs in the pathogenesis of this leukemia.