Abstract (English version):

Hematopoietic differentiation is highly ordered multistep process, where generation of terminal blood cells is dependent upon coordinated regulation of gene expression by key regulators: transcription factors and mikroRNAs.

PU.1 (Sfpi1) is a versatile hematopoetic transcription factor required for the proper generation of both myeloid and lymphoid lineages.

MikroRNAs represent a novel class of ~22 nucleotide long non-coding posttranscriptional regulators that inhibit expression of genes by blocking protein translation or by mRNA degradation.

In this PhD thesis I present research data documenting novel mechanisms of regulation and function of two oncogenic mikroRNAs, miR-17-92 cluster and miR-155 and myeloid transcriptional factors PU.1 upon macrophage differentiation of myeloid progenitors.

The miR-17-92 cluster (Oncomir1) encodes seven related mikroRNAs that regulate cell proliferation, apoptosis and development and is overexpressed in number of malignancies including myeloid leukemia. Presented PhD thesis documents novel macrophage specific regulatory mechanisms involving the oncogenic cluster miR-17-92. Using transgenic PU.1-/- myeloid progenitors we show that upon macrophage differentiation, the transcription factor PU.1 induces the secondary determinant, the transcription factor Egr2 which, in turn, directly represses miR-17-92 expression by causing substantial chromatin changes in miR-17-92 gene. These chromatin changes include the recruitment of the histone demethylase Jarid1b leading to histone H3 lysine K4 demethylation within the CpG island at the miR-17-92 promoter, leading to repression of miR-17-92 cluster expression. The downregulation step appears very important as the ectopic expression of miR-17-92 prevents macrophage differentiation.

Conversely this PhD thesis shows that Egr2 itself is targeted and inhibited by miR-17-92, indicating existence of a double negative feedback regulation between miR-17-92 and Egr2, where Egr2 negatively regulates miR-17-92 cluster in differentiating cells and, in turn, miR-17-92 cluster negatively regulates Egr2 in highly proliferating progenitor cells.

In addition to miR-17-92, we identified that PU.1 upregulate another oncogenic mikroRNA - miR-155 that is temporary induced in early stages of macrophage differentiation by mechanism involving histone acetylation.

The identified regulatory mechanisms of miR-17-92 cluster and miR-155 were found deregulated in acute myeloid leukemia (AML) patients that express elevated levels of miR-17-92 or miR-155 and simultaneously exhibited significantly downregulated levels of PU.1 and EGR2, compare to healthy controls.

This PhD thesis states collectively a novel view on miR-17-92 role in leukemia and differentiation exemplified by the PU.1-mediated repression of the miR-17-92 cluster by an Egr2/Jarid1b mediated H3K4 demethylation upon macrophage differentiation, mechanism whose deregulation may contribute to pathogenesis of acute myeloid leukemia and possibly other malignancies.