Abstract

HOX gene expression is tightly regulated during hematopoiesis and it is gradually decreased during the differentiation of hematopoietic cells. By contrast in case of leukemic blasts the expression of *HOX* genes is often disrupted and dysregulated. Especially in acute myeloid leukemia (AML) different expression of *HOX* genes was described between different subtypes classified according to cytogenetics and molecular genetics. In this study, the cohort of childhood AML patients were screened for *HOX* gene expression and based on these valuesdivided into five clusters using unsupervised hierarchical clustering characterized mainly by presence or absence of the typical molecular aberrations. *HOX* gene expression was also tested in the healthy counterpart of hematologic cells equivalent to the particular morphological stages of leukemic cells. Based on these results, *HOX* gene expression directly or indirectly participate in leukemogenesis and it not only copies the developmental/morphological stage in which the hematopoietic cell was stopped during differentiation. It this thesis/study it was concluded that the *HOX* gene expression is dependent on the presence of specific molecular aberration. In the second part of our study, we investigated the *HOX* gene transcription regulation in AML patients with *PML-RARα* fusion gene with the overall lowest expression of *HOX* genes. We determined that the presence of *FLT3/ITD* mutation usually connected with the high expression of *HOX* genes had no effect on the level of *HOX* genes in PML-RARα positive cases which means that the HOX gene expression profile is dependent mainly on *PML-RARα* fusion genes In PML-RARα positive patients the low expression of *HOX* genes was associated with low expression of histone demethylases (JMJD3 and UTX) and high expression of DNA methyltransferases. We showed using ATRA, causing degradation of PML-RARα fusion protein, and JMJD3 specific inhibitor that *HOX* gene expression is regulated by PML-RARα/JMJD3. Using chromatin immunoprecipitation (ChIP) and ChIP followed by next-generation sequencing we identified *HOX* genes, which are regulated by PML-RARα/JMJD3 pathway. Furthermore, we observed the synergistic apoptotic effect of ATRA a JMJD3 specific inhibitor on ATRA-sensitive but also on ATRA-resistant cell lines. This apoptotic effect shows potential future therapeutic usage in PML-RARα ATRA-resistant patients.