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 values divided 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.