Epigenetic regulation of oncogenes and tumor suppressors in chronic lymphocytic leukemia

Avhandlingen baseras på följande delarbeten


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Abstract

DNA methylation is one of the well-known epigenetic modifications. Aberrant DNA methylation has been shown to have a major role in tumorigenesis and is associated with tumor aggressiveness and inferior outcome in various cancer types. Chronic lymphocytic leukemia (CLL) is the most common adult leukemia characterized by the accumulation and clonal expansion of long-lived neoplastic B-lymphocytes. It is clinically and biologically a very heterogeneous disease. The specific aim of study I is to investigate the role of the tumor suppressor gene, Microcephalin (MCPH1) in regulating the expression of the Angiopoietin gene (ANGPT2) in CLL. We showed that MCPH1 negatively regulates ANGPT2 gene, which is overlapping with MCPH1 in opposite direction through a novel mechanism. MCPH1 physically binds to the ANGPT2 promoter and recruits the DNA methylation machinery for subsequent silencing of ANGPT2. Study II is mainly focused on epigenetic silencing of miR26A1 microRNA and its impact on Enhancer of zeste homolog 2 (EZH2) in CLL and mantle cell lymphoma (MCL). We showed that miR26A1 acts as a tumor suppressor and epigenetically silenced in CLL, which is required for maintaining high levels of EZH2, resulting in poor overall survival. Finally, in study III we analyzed the mechanisms behind Ten-eleven-translocation 1 (TET1) deregulation in CLL. Here we characterized mechanisms that control TET1 gene activity at the transcriptional level. Overall, we proposed a model by which the TET1 gene activation in CLL depends on miR26A1 regulated EZH2 binding at the TET1 promoter and silencing of a novel cryptic promoter through gene-body hypermethylation. In conclusion, these three studies deepen our knowledge in understanding the functional role of DNA methylation controlled tumor-related genes in CLL, resulting in the identification of potential prognostic biomarkers and target for therapy.

Keywords: DNA methylation, epigenetic modifications, CLL, MCPH1, ANGPT2, EZH2, miR26A1, TET1, MCL, tumor suppressor, gene-body, expression, prognostic biomarkers