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Epigenetic regulation of oncogenes and tumor suppressors in chronic lymphocytic leukemia

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs Universitet kommer att offentligen försvaras i salen Kammaren, Sahlgrenska Universitetssjukhuset, fredagen den 24 november 2017, klockan 13.00

av Pradeep Kumar Kopparapu

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Avhandlingen baseras på följande delarbeten

I. **Kopparapu PK**, Miranda C, Fogelstrand L, Mishra K, Andersson PO, Kanduri C, Kanduri M. MCPH1 maintains long-term epigenetic silencing of ANGPT2 in chronic lymphocytic leukemia. FEBS J. 2015; 282 :1939-52

II. **Kopparapu PK**, Bhoi S, Mansouri L, Arabanian LS, Plevova K, Pospisilova S, Wasik AM, Croci GA, Sander B, Paulli M, Rosenquist R, Kanduri M. Epigenetic silencing of miR-26A1 in chronic lymphocytic leukemia and mantle cell lymphoma: Impact on EZH2 expression. Epigenetics. 2016; 11: 335-43.

III. **Kopparapu PK**, Morsy MHA, Kanduri C, Kanduri M. Gene-body hypermethylation controlled cryptic promoter and miR26A1-dependent EZH2 regulation of TET1 gene activity in chronic lymphocytic leukemia. Oncotorget. 2017; 8: 77595-608

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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 1 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 *miR26A*1 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

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