World Academy of Science, Engineering and Technology
International Journal of Bioengineering and Life Sciences
Vol:16, No:10, 2022

The Stem Cell Transcription Co-factor Znf521 Sustains Mll-af9 Fusion Protein In Acute Myeloid Leukemias By Altering The Gene Expression Landscape

Authors : Emanuela Chiarella, Annamaria Aloisio, Nisticò Clelia, Maria Mesuraca

Abstract : ZNF521 is a stem cell-associated transcription co-factor, that plays a crucial role in the homeostatic regulation of the stem cell compartment in the hematopoietic, osteo-adipogenic, and neural system. In normal hematopoiesis, primary human CD34+ hematopoietic stem cells display typically a high expression of ZNF521, while its mRNA levels rapidly decrease when these progenitors progress towards erythroid, granulocytic, or B-lymphoid differentiation. However, most acute myeloid leukemias (AMLs) and leukemia-initiating cells keep high ZNF521 expression. In particular, AMLs are often characterized by chromosomal translocations involving the Mixed Lineage Leukemia (MLL) gene, which MLL gene includes a variety of fusion oncogenes arisen from genes normally required during hematopoietic development; once they are fused, they promote epigenetic and transcription factor dysregulation. The chromosomal translocation t(9;11)(p21-22;q23), fusing the MLL gene with AF9 gene, results in a monocytic immune phenotype with an aggressive course, frequent relapses, and a short survival time. To better understand the dysfunctional transcriptional networks related to genetic aberrations, AML gene expression profile datasets were queried for ZNF521 expression and its correlations with specific gene rearrangements and mutations. The results showed that ZNF521 mRNA levels are associated with specific genetic aberrations: the highest expression levels were observed in AMLs involving t(11q23) MLL rearrangements in two distinct datasets (MILE and den Boer); elevated ZNF521 mRNA expression levels were also revealed in AMLs with t(7;12) or with internal rearrangements of chromosome 16. On the contrary, relatively low ZNF521 expression levels seemed to be associated with the t(8;21) translocation, that in turn is correlated with the AML1-ETO fusion gene or the t(15;17) translocation and in AMLs with FLT3-ITD, NPM1, or CEBPα double mutations. Invitro, we found that the enforced co-expression of ZNF521 in cord blood-derived CD34+ cells induced a significant proliferative advantage, improving MLL-AF9 effects on the induction of proliferation and the expansion of leukemic progenitor cells. Transcriptome profiling of CD34+ cells transduced with either MLL-AF9, ZNF521, or a combination of the two transgenes highlighted specific sets of up- or down-regulated genes that are involved in the leukemic phenotype, including those encoding transcription factors, epigenetic modulators, and cell cycle regulators as well as those engaged in the transport or uptake of nutrients. These data enhance the functional cooperation between ZNF521 and MA9, resulting in the development, maintenance, and clonal expansion of leukemic cells. Finally, silencing of ZNF521 in MLL-AF9-transformed primary CD34+ cells inhibited their proliferation and led to their extinction, as well as ZNF521 silencing in the MLL-AF9+ THP-1 cell line resulted in an impairment of their growth and clonogenicity. Taken together, our data highlight ZNF521 role in the control of self-renewal and in the immature compartment of malignant hematopoiesis, which, by altering the gene expression landscape, contributes to the development and/or maintenance of AML acting in concert with the MLL-AF9 fusion oncogene.

Keywords : AML, human zinc finger protein 521 (hZNF521), mixed lineage leukemia gene (MLL) AF9 (MLLT3 or LTG9), cord blood-derived hematopoietic stem cells (CB-CD34+)
Conference Title : ICBBMB 2022 : International Conference on Biochemistry, Bioinformatics and Molecular Biology
Conference Location : Rome, Italy
Conference Dates : October 13-14, 2022