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Hypermethylation of the GATA binding protein 4 (GATA4) promoter in Chinese pediatric acute myeloid leukemia

Li Zhi-Heng, Wang Na-Na, Xu Li-Xiao, Fang Fang, Li Yan-Hong, Li Yi-Ping, Xu Yun-Yun and **Pan Jian**
Children's Hospital of Soochow University, China

Background: Acute myeloid leukemia (AML) is the second-most common form of leukemia in children. Aberrant DNA methylation patterns are a characteristic feature of AML. GATA4 has been suggested to be a tumor suppressor gene regulated by promoter hypermethylation in various types of human cancers although the expression and promoter methylation of GATA4 in pediatric AML is still unclear.

Materials: Transcriptional expression levels of GATA4 were evaluated by semi-quantitative and real-time PCR. Methylation status was investigated by methylation-specific PCR (MSP) and bisulfate genomic sequencing (BGS). The prognostic significance of GATA4 expression and promoter methylation was assessed in 105 cases of Chinese pediatric acute myeloid leukemia patients with clinical follow-up records.

Results: MSP and BGS analysis showed that the GATA4 gene promoter is hypermethylated in AML cells, such as the HL-60 and MV4-11 human myeloid leukemia cell lines. 5-Aza treatment significantly upregulated GATA4 expression in HL-60 and MV4-11 cells. Aberrant methylation of GATA4 was observed in 15.0% (3/20) of the normal bone marrow control samples compared to 56.2% (59/105) of the pediatric AML sample. GATA4 transcript levels were significantly decreased in AML patients (33.06±70.94; P=0.011) compared to normal bone marrow/idiopathic thrombocytopenic purpura controls (116.76±105.39). GATA4 promoter methylation was correlated with patient leukocyte counts (WBC, white blood cells) (P=0.035) and minimal residual disease MRD (P=0.031). Kaplan-Meier survival analysis revealed significantly shorter overall survival times in patients with GATA4 promoter methylation (P=0.014).

Conclusion: Epigenetic inactivation of GATA4 by promoter hypermethylation was observed in both AML cell lines and pediatric AML samples; our study implicates GATA4 as a putative tumor suppressor gene in pediatric AML. In addition, our findings imply that GATA4 promoter methylation is correlated with WBC and MRD. Kaplan-Meier survival analysis revealed significantly shorter overall survival in pediatric AML with GATA4 promoter methylation. However, further research focusing on the mechanism of GATA4 in pediatric leukemia is required.

panjian2008@163.com