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Study of alternative wilms tumor gene methylation as an epigenetic biomarker in acute myeloid leukemia

Reham Abo Elwafa, Magdy El-Bordiny, Ashraf Al-Ghandour and **Omneya Fayed**
Alexandria University, Egypt

Background: Overexpression of the Wilms tumor 1 gene (WT1) is implicated in the prognosis of acute myeloid leukemia (AML) with high expression predicting disease progression as well as being intensively studied as a potential molecular marker for minimal residual disease (MRD) and treatment response. Many different isoforms for WT1 are generated by alternative transcription initiation, mRNA splicing and alternative translation initiation. Recently, an alternative promoter incorporating a unique first exon, alternative WT1 transcript (AWT1) has been described. The AWT1 expression and the underlying epigenetic alterations associated with its expression in AML are still unknown.

Objectives: We studied the AWT1 gene specific methylation changes and its relation with other clinicopathological features. We also integrated the corresponding gene expression profile to explore the role of methylation in regulating gene expression.

Materials & Methods: Bisulfite PCR followed by pyrosequencing were done to determine the methylation status of AWT1 gene promotor CPG islands in 50 newly diagnosed AML patients and 50 healthy subjects as a control group. The level of AWT1 expression was assessed using RQ-PCR.

Results: AWT1 expression level was significantly higher in the AML patients in comparison to the control group ($P<0.001$) and it was surprising to find robust hypermethylation of the AWT1 promoter in AML patients compared to the controls ($P<0.001$). A statistically significant negative correlation between AWT1 expression and methylation level was found ($r=0.67$, $P<0.001$). At a cutoff value of 45.2% AWT1 promoter hypermethylation was found to be a highly specific marker for AML (specificity 95% and sensitivity 97.5%).

Conclusion: We described an expression methylation signature of the AWT1 that are promising markers for diagnosis and MRD assessment in AML.

rehamhalem@hotmail.com