EPIGENETIC REGULATION OF THE NON-CANONICAL WNT PATHWAY IN ACUTE MYELOID LEUKEMIA.


Abstract

Wnt5a is a member of the Wnt family of proteins that signals through the non-canonical Wnt/Ca(2+) pathway to suppress cyclin D1. Deregulation of this pathway has been found in animal models suggesting that it acts as tumour suppressor in acute myeloid leukemia (AML). Although DNA methylation is the main mechanism of regulation of the canonical Wnt pathway in AML, the role of WNT5A abnormalities has never been evaluated in this clinical setting. The methylation status of WNT5A promoter-exon 1 was analyzed by methylation-specific PCR and sequencing in eleven AML-derived cell lines and 252 AML patients. We observed WNT5A hypermethylation in seven cell lines and in 43% (107/252) of AML patients. WNT5A methylation was associated with decreased WNT5A expression (P < 0.001) that was restored after exposure to 5-Aza-2'-deoxycytidine. Moreover, WNT5A hypermethylation correlated with upregulation of CYCLIN D1 expression (P < 0.001). Relapse (15% vs 37%, P < 0.001) and mortality (61% vs 79%, P = 0.004) rates were lower for patients in the non-methylated group. Disease-free survival and overall survival at 6 and 7 years, respectively, were 60% and 27% for unmethylated patients and 20% and 0% for hypermethylated patients (P = 0.0001 and P = 0.04, respectively). Interestingly, significant differences were also observed when the analysis was carried out according to cytogenetic risk groups. We demonstrate that WNT5A, a putative tumor suppressor gene in AML, is silenced by methylation in this disease and that this epigenetic event is associated with upregulation of CYCLIN D1 expression and confers poor prognosis in patients with AML.

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