Prognostic DNA methylation patterns in cytogenetically normal acute myeloid leukemia are predefined by stem cell chromatin marks

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Résumé en anglais	Cytogenetically normal acute myeloid leukemia (CN-AML) compose between 40% and 50% of all adult acute myeloid leukemia (AML) cases. In this clinically diverse group, molecular aberrations, such as FLT3-ITD, NPM1, and CEBPA mutations, recently have added to the prognostic accuracy. Aberrant DNA methylation is a hallmark of cancer, including AML. We investigated in total 118 CN-AML samples in a test and a validation cohort for genome-wide promoter DNA methylation with Illumina Methylation Bead arrays and compared them with normal myeloid precursors and global gene expression. IDH and NPM1 mutations were associated with different methylation patterns (P = .0004 and .04, respectively). Genome-wide methylation levels were elevated in IDH-mutated samples (P = .006). We observed a negative impact of DNA methylation on transcription. Genes targeted by Polycomb group (PcG) proteins and genes associated with bivalent histone marks in stem cells showed increased aberrant methylation in AML (P < .0001). Furthermore, high methylation levels of PcG target genes were independently associated with better progression-free survival (odds ratio = 0.47, P = .01) and overall survival (odds ratio = 0.36, P = .001). In summary, genome-wide methylation patterns show preferential methylation of PcG targets with prognostic impact in CN-AML.
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