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A comprehensive microarray-based DNA methylation study of 367 hematological neoplasms.

Martin-Subero JI, Ammerpohl O, Bibikova M, Wickham-Garcia E, Agirre X, Alvarez S, Brüggemann M, Bug S, Calasanz MJ, Deckert M, Dreyling M, Du MQ, Dürig J, Dyer MJ, Fan JB, Gesk S, Hansmann ML, Harder L, Hartmann S, Klapper W, Küppers R, Montesinos-Rongen M, Nagel I, Pott C, Richter J, Román-Gómez J, Seifert M, Stein H, Suela J, Trümper L, Vater I, Prosper F, Haferlach C, Cruz Cigudosa J, Siebert R.

Source

Institute of Human Genetics, Christian-Albrechts University, Kiel, Germany. jimartin@idibell.cat

Abstract

BACKGROUND: Alterations in the DNA methylation pattern are a hallmark of leukemias and lymphomas. However, most epigenetic studies in hematologic neoplasms (HNs) have focused either on the analysis of few candidate genes or many genes and few HN entities, and comprehensive studies are required.

METHODOLOGY/PRINCIPAL FINDINGS: Here, we report for the first time a microarray-based DNA methylation study of 767 genes in 367 HNs diagnosed with 16 of the most representative B-cell (n = 203), T-cell (n = 30), and myeloid (n = 134) neoplasias, as well as 37 samples from different cell types of the hematopoietic system. Using appropriate controls of B-, T-, or myeloid cellular origin, we identified a total of 220 genes hypermethylated in at least one HN entity. In general, promoter hypermethylation was more frequent in lymphoid malignancies than in myeloid malignancies, being germinal center mature B-cell lymphomas as well as B and T precursor lymphoid neoplasias those entities with highest frequency of gene-associated DNA hypermethylation. We also observed a significant correlation between the number of hypermethylated and hypomethylated genes in several mature B-cell neoplasias, but not in precursor B- and T-cell leukemias. Most of the genes becoming hypermethylated contained promoters with high CpG content, and a significant fraction of them are targets of the polycomb repressor complex. Interestingly, T-cell prolymphocytic leukemias show low levels of DNA hypermethylation and a comparatively large number of hypomethylated genes, many of them showing an increased gene expression.

CONCLUSIONS/SIGNIFICANCE: We have characterized the DNA methylation profile of a wide range of different HNs entities. As well as identifying genes showing aberrant DNA methylation in certain HN subtypes, we also detected six genes--DBC1, DIO3, FZD9, HS3ST2, MOS, and MYOD1--that were significantly hypermethylated in B-cell, T-cell, and myeloid malignancies. These might therefore play an important role in the development of different HNs.

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