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Genome-wide identification of regulatory variation in T-cell prolymphocytic leukemia

Huihuang Yan, Shulan Tian, Henan Zhang and **Wei Ding**
Mayo Clinic School of Medicine, USA

T-cell prolymphocytic leukemia (T-PLL) is a rare disease with a median survival of <1 year. T-PLL demonstrates poor response to conventional chemotherapy and inevitable relapse after immunotherapy due to resistance. Cytogenetic analysis, whole-exome and whole-genome sequencing have identified primary structural alterations in T-PLL, including inversions, translocations, and copy number variation. Recurrent somatic mutations were identified in genes encoding chromatin regulators and those in the JAK-STAT signaling pathway. Epigenetic mechanism defines cell type-specific transcriptional program, whose misregulation is implicated in disease susceptibility and progression. However, a lack of genome-wide epigenetic data has limited the mechanistic study of T-PLL carcinogenesis. Here, we used micrococcal nuclease digestion of linker DNA and sequencing of nucleosome-free DNA fragments (MNase-seq) to profile the open chromatin regions, i.e., gene regulatory regions such as promoters, enhancers and insulators, in T-PLL patients and age-matched healthy individuals. Samples were collected with written consent and approval from the institutional review board at Mayo Clinic. Clustering of normalized read density revealed distinct differences in chromatin accessibility, with both gains and losses of open chromatin regions in T-PLL relative to the normal controls. We also identified alterations of enhancers in T-PLL using histone H3 lysine 4 monomethylation (H3K4me1) and lysine 27 acetylation (H3K27ac) ChIP-seq. Our analysis provided insights into the epigenetic mechanisms that drive oncogenic activation in T-PLL.

Biography

Huihuang Yan is an Assistant Professor in the Division of Biomedical Statistics and Informatics, Department of Health Sciences Research at Mayo Clinic. He has received his PhD from the Chinese Academy of Agricultural Sciences in Genetics. As part of the Mayo Clinic Center for Individualized Medicine, his research primarily focuses on cancer genomics and epigenetics and the development of algorithms for analyzing next-generation sequencing data from patients. He has published 50 peer-reviewed articles.

Yan.Huihuang@mayo.edu

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