Abstract: P424

Title: LANDSCAPE OF CHROMATIN ACCESSIBILITY IN ACUTE MYELOID LEUKEMIA

Abstract Type: Poster Presentation

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Background:

Acute myeloid leukemia (AML) is a clinically and molecularly heterogeneous disease, which is predominantly defined by genetic abnormalities and morphology. However, it still remains unclear whether epigenetic information may improve the current understanding of the pathogenesis and classification of AML due to the lack of large-scale and comprehensive epigenetic studies.

Aims:

We elucidate the epigenetic landscape and its implication for the pathogenesis of AML by genome-wide profiling of chromatin accessibility in addition to gene mutations and transcription in a large cohort of AML patients.

Methods:

We performed ATAC-seq and targeted-capture sequencing of myeloid driver genes in 448 primary AML samples. RNA-seq and H3K27ac ChIP-seq were also performed in 316 and 30 samples, respectively. In addition, normal bone marrow samples from 25 donors as well as 15 remission samples were also analyzed by ATAC-seq as a control.

Results:

ATAC-seq revealed approximately 190,000 reproducible peaks. Most peaks were found in gene-distal regions, explaining a large variance across samples. Among all peaks, 72% were not detected in control samples and considered AML-specific. Analysis of the correlations between ATAC-seq accessibility and gene expression revealed that each peak was linked to a median of 1 gene (0–31), while each gene was associated with a median of 11 peaks (0–110). We next estimated the cellular composition by deconvolution analysis of the ATAC data from bulk samples. The predominance of hematopoietic stem cell (HSC), monocyte, and erythroid signatures was associated with French-American-British (FAB) subtypes of minimal differentiation/without maturation subtypes (M0/M1), myelomonocytic/monoblastic/monocytic subtypes (M4/M5), and erythroid subtype (M6), respectively. The ATAC-based clustering identified 11 distinct epigenetic subgroups, including three well-known genetic classes defined by gene fusions, such as *PML::RARA*, *RUNX1::RUNX1T1*, and *CBFB::MYH11*. By contrast, some genetic classes defined by a single mutation, such as *NPM1* or *CEBPA* mutation, were further classified into multiple distinct epigenetic subgroups. For example, the *NPM1*-mutated subtype was separated into three subgroups with distinct clinical and molecular features, based on the unique ATAC signatures associated with HSC, monocytes, and mixed HSC and monocytes. By developing a prediction model of these distinct subtypes of *NPM1*-mutated AML based on the gene expression profile, we largely reproduced these subtypes and validated clinical and genetic features in the Beat AML cohort. Next, we evaluated transcription factor (TF) bindings in a genome-wide manner, using foot printing and motif analysis. This revealed distinct profiles of activated TFs in epigenetic subgroups of *NPM1*-mutated AML. In the subtype of *NPM1*-mutated AML characterized by HSC signature, HSC-related TFs that belong to MECOM, HOX, and RUNX families, were more active. By contrast, other TFs, such as IRF, CEBP, and JUN/FOS families of TFs, were more enriched in the subtype showing monocyte signature. Finally, combined with ChIP-seq, we identified a number of super-enhancers in the vicinity of leukemia-related oncogenes.

Summary/Conclusion:

Through the large-scale and comprehensive profiling of chromatin accessibility as well as profiling of mutations and gene expression, we demonstrate the epigenetic heterogeneity and the utility of epigenetics to advance the classification of AML.

Keywords: Leukemia, Acute myeloid leukemia, Epigenetic, Chromatin