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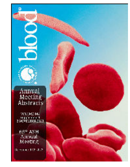

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Epigenetic Classification of Acute Myeloid Leukemia Revealed By Genome-Wide Chromatin Profiling

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Background

Acute myeloid leukemia (AML) is a clinically and molecularly heterogeneous disease and is predominantly defined by genetic abnormalities and morphology. However, many lines of evidence suggest the role of epigenetic alterations in the pathogenesis and the classification of AML, whereas no large-scale comprehensive analyses of both genetic and epigenetic alterations in AML have been reported.

Methods

We enrolled a total of 1,564 primary AML cases (524 from Japanese and 1,040 from Swedish cohorts), whose diagnostic samples were subjected to ATAC sequencing together with targeted capture sequencing using an in-house gene panel including 331 known AML driver genes and an additional 1,158-1,317 probes for copy number detection. We also performed

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RNA (N=1,398) and H3K27ac-targeted ChIP sequencing (N=80). Normal bone marrow samples from 25 donors as well as 15 remission samples were analyzed by ATAC-seq as a control.

Results

ATAC-seq revealed approximately 300,000 reproducible peaks in primary AML. Most peaks were found in gene-distal regions, and explained a large variance across samples. Among all peaks, 72% were not detected in control samples and thus, specific to AML. Analysis of the correlations between ATAC-seq accessibility and gene expression revealed a subset of regulatory elements that regulate nearby gene expression; 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 of the bulk AML samples by deconvolution analysis using ATAC-seq data. 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, suggesting bulk ATAC-seq of AML samples reflected the differentiation potential of leukemic cells.

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 four subgroups based on the varying degrees of ATAC signatures associated with HSC and monocytes. Each subgroup of *NPM1*-mutated AML showed different clinical characteristics such as white blood cell counts, age, and prognosis, and co-mutation pattern in *FLT3*, *DNMT3A*, and *IDH1*/ *IDH2* mutations. Gene ontology analysis revealed that the subgroup of *NPM1*-mutated AML with high HSC signature showed upregulated TGF-β signaling, while one with monocytic signature showed upregulated TNF-α signaling and interferon-γ response.

Next, we evaluated transcription factor (TF) binding sites in a genome-wide manner, using TF motifs and foot printing in upregulated ATAC-peaks in each subgroup and revealed distinct profiles of activated TFs in each epigenetic subgroup of *NPM1*-mutated AML. In the subgroup characterized by high 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, were more enriched in the subgroup showing high monocyte signature.

By developing a prediction model for these subgroups of *NPM1*-mutated AML based on the gene expression profile, we reproduced these subgroups and validated clinical and molecular features in an external Beat AML cohort. Utilizing ex vivo drug sensitivity dataset in the Beat AML, we identified candidate drugs showing subgroup-specific effectiveness such as panobinostat for *NPM1*-mutated AML with monocytic differentiation.

Finally, ChIP-seq analysis identified a number of super-enhancers in the vicinity of leukemia-related TFs and oncogenes.

Conclusion

Through comprehensive profiling of chromatin accessibility and gene mutations/expression in a large cohort of AML patients, we demonstrate the epigenetic heterogeneity and identify novel AML subgroups that had unique epigenetic and clinical features. Our findings highlight the role of epigenetic alterations in AML pathogenesis and impact on molecular classification of AML.

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