中文題目：單細胞分析急性骨髓性白血病獨特之表觀遺傳腫瘤微環境變化

英文題目：Utilizing single cell analysis to decipher the epigenetic perturbations in acute myeloid leukemia

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Background

Genetic mutations and epigenetic perturbations are both recognized as important mechanisms for leukemogenesis. While genetic mutations have been widely studied in acute myeloid leukemia (AML), the epigenetic landscape remains largely unknown. Beside, tumor heterogeneity presents a challenge to currently widely-used bulk cell analysis. Analysis of individual single cells from a heterogeneous population enables the reduction of biological noise and offers the ability to investigate and characterize rare cells. In this study, we aim to utilize single cell analysis platform to decipher the epigenetic perturbations in AML.

Methods

We collected primary bone marrow samples from 50 AML patients at initial diagnosis. Bone marrow samples from 5 healthy controls were also obtained during the stem cell harvest procedure. Mass cytometry (CyTOF) is a high dimensional single cell flow cytometry that allows simultaneous quantification of more than 50 cellular parameters. Epigenetic landscape profiling using cytometry by time-of-flight (EpiTOF) is a mass cytometry-based analytical platform focusing on epigenetic markers which could analyze the global levels of a broad array of histone modifications. By this method, we were able to directly measure the in vivo immunophenotypic, epigenetic and intracellular signaling properties of leukemia blasts and individual cell type in the microenvironment

Results

Our data revealed lineage-specific chromatin modification in hematopoietic cells. Myeloid cells were characterized by higher H3K36me3 than lymphoid cells. In contrast, myeloid cells were characterized by higher H3K27me3 than

myeloid cells. Compared to healthy controls, patients with AML were characterized by multiple upregulated chromatin modifiers and histone marks. More specifically, de-acetylation by Histone deacetylase and demethylation by LSD1 are the most notable events in patients with AML. M-MDSC and B cell showed the most prominent epigenetic changes than other cells in the bone marrow microenvironment.

Next we studied the correlation of epigenetic perturbations with AML risk groups. AML in favorable European LeukemiaNet category was associated with lower acetylation, lower PCAF, lower HDAC2, but higher H3K27me3, and Gfi1.

Conclusion

Dysregulated epigenetic mechanisms, charactered by upregulated chromatin modifiers and histone marks, have been demonstrated in patients with AML. Differential expression of epigenetic markers could partly explain the heterogamous nature and clinical outcome of AML.

Key words: acute myeloid leukemia, single cell analysis, epigenetics