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POSTER ABSTRACTS

602.MYELOID ONCOGENESIS: BASIC

Pre-Existing Chromatin States Regulate KLF4 Binding to Eliminate Leukemia Stem Cells

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Transcription factors collaborate with chromatin's epigenetic states to regulate cell fate decisions. While recent in vitro work using cryo-EM (Sinha et al., Nature, 2023) suggested that histone modifications could regulate the activity of pioneer transcription factors, it was not clear whether these findings applied in vivo, or if chromatin states could influence transcription factor binding to affect cell fate. Our previous work (Liu et al., Leukemia,2014; Wang et al., Nat Commun,2019) showed that reprogramming factors (Oct4, Sox2, Klf4, and cMyc, collectively known as OSKM) selectively eliminated leukemia cells in vivo, with minimal impact on normal Hematopoietic Stem and Progenitor Cells (HSPCs). This suggested that cell fates induced by OSKM could be influenced by pre-existing chromatin states.
Building on this hypothesis, we profiled the pre-existing chromatin states of leukemia cells and HSPCs using MNase-ChIP-seq, ATAC-seq, and WGBS-seq. In our Tet-on-induced models, Klf4 activation resulted in the targeting of distinct gene sets and exhibited similar dynamic changes in chromatin accessibility, despite these regions sharing the same active chromatin state. Using machine learning algorithms, we identified H3K18ac –a feature of the active chromatin states preferred by Klf4– as a dominant factor influencing Klf4's genomic binding. We then altered H3K18ac through an enzymatically deficient SIRT7, which is an H3K18ac deacetylase, and examined where Klf4 binds. We observed an increase in Klf4 binding at sites where H3K18ac levels were elevated. This result suggested that Klf4 binding was influenced by changes in H3K18ac. We exposed human CD34+ cells, several leukemia cell lines, and samples from leukemia patients to ATPO-253. This small molecule, currently in phase 1 clinical trials, has been found to enhance the levels of the KLF4 protein. This treatment led to an increase in KLF4 protein levels and we observed activation of apoptosis genes in the tested leukemia cell lines that possessed high pre-existing H3K18ac levels. In addition, we observed a decline across all tested leukemia samples, while the population of CD34+ cells essentially remained stable.
In conclusion, our work demonstrated that pre-existing chromatin states, such as H3K18ac, regulate Klf4's genomic binding, thereby influencing distinct cell fates in leukemia cells and HSPCs. This opens potential avenues for clinical applications in targeted leukemia cell clearance using KLF4 or ATPO-253.

Disclosures No relevant conflicts of interest to declare.

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