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MLL3-Mediated Changes in Chromatin Structure During Hematopoiesis

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The MLL3 gene encodes an epigenetic regulator thought to play a role in hematopoietic differentiation. Recent experiments in the Druley Lab suggest that MLL3-deficient iPSCs fail to form hemogenic endothelium, resulting in a lack of definitive hematopoiesis in these cell lines and potentially explaining why rare nonsynonymous germline mutations in MLL3 are implicated in the development of infant leukemia. The assay for transposase-accessible chromatin (ATAC-seq) can localize the structural changes in chromatin that accompany this change in hematopoietic potential by identifying peaks of open chromatin.

ATAC-seq peaks were compared between umbilical cord blood CD34+ stem cells (UCB), wild-type CD34+ iPSC cells (WT), and CD34+ MLL3$^{-/-}$ iPSC cells (KO). ATAC-seq libraries were produced from 50,000 UCB, WT, and KO cells according to a modified ATAC-seq protocol (Semenkovich et al. *PNAS*, 2016). After Illumina sequencing, the reads were analyzed with the Kundaje Lab ATAC-seq pipeline to generate peak files of each sample. DiffBind was used to compare samples and identify regions of significant change between the negative controls and KO.

Comparison of UCB, WT, and KO samples has yielded a list of 4923 differentially-called peaks, 248 of which were found within 3kb of a promoter, often of another known epigenetic regulator. 64% of these promoter peaks were increased in the KO sample.

We conclude that MLL3-mediated changes in chromatin structure are widespread, often affecting the accessibility other epigenetic regulators in a way that correlates with their under- or over-expression in cancer. The focus of additional research will be to repeat these experiments and supplement ATAC-seq data with other epigenetic assays to provide a more complete view of the mechanisms of epigenetic regulation involved in hematopoiesis.