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Identifying Novel Epigenetic Dependencies in Pre-leukemic Hematopoietic Stem Cells

Emily Haussler
Washington University in St. Louis

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Mentors: Grant Challen and Elizabeth Ostrander

The DNA methylation modifying enzymes DNMT3A and TET2 are essential for proper differentiation of hematopoietic stem cells and are frequently found to be mutated in a range of blood cancers. Although their functions in regulating DNA methylation have been characterized, a specific connection between methylation patterns and altered gene expression has not been established to explain the observed disease phenotype. We hypothesize that DNMT3A- and TET2-mutant HSCs are dependent on other epigenetic regulators to corrupt normal hematopoietic pathways. If this is the case, inhibition of the chromatin modifiers on which driver mutations DNMT3A and TET2 depend could represent a novel therapeutic strategy for reducing the propagation of pre-leukemic HSC populations and preventing the onset of a range of blood cancers. To test this hypothesis, we employed a CRISPR-Cas9 based negative selection screen on cells derived from DNMT3A-null and TET2-null HSCs, targeting 180 chromatin modifying genes, using three to six sgRNA "guides" per gene. Results were obtained from three independent screens, and those genes showing significant fold depletion over time in DNMT3A-null or TET2-null cells were selected for further investigation as potential therapeutic targets. Specifically, *Brd2* and *Zmynd8* are being considered for future directions. Ultimately, we conclude that our negative selection CRISPR screen is optimized to detect those genes potentially showing an epigenetic dependence with DNMT3A and TET2 in hematopoiesis, and that further functional studies *in vivo* are needed to draw definite conclusions about their roles.