Identification of transcriptional determinants of asparaginase sensitivity in leukemias

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Abstract: Cancer cells frequently become addicted to certain nutrient sources due to oncogenic alterations. Restricting the uptake or usage of nutrients has the potential to disrupt cancer cell proliferation without affecting normal cells, thus providing a powerful intervention point for the development of targeted therapies. A well-known example of exploiting nutrient addiction for therapeutic gain involves the asparagine auxotrophy of leukemias. Asparaginase, which selectively depletes asparagine from serum, kills asparagine-dependent leukemia cells and is a first line chemotherapeutic agent. However, the precise mechanisms underlying the asparaginase response of leukemic cells and whether there are other cancer types dependent on particular amino acids remain poorly understood. Using a combination of a DNA barcoding competition assay we developed and a transcription based CRISPR screen, we identified ZBTB1 as an essential transcription factor for resistance to asparaginase therapy of leukemias. Building upon this preliminary data, we will first determine the precise mechanism by which ZBTB1 enables Acute Lymphoblastic Leukemias (ALLs) to survive under asparaginase treatment. As ZBTB1 loss sensitizes ALLs to asparaginase, we will next understand the clinical significance of ZBTB1 in ALLs as well as other lymphoid and myeloid malignancies as both a prognostic and therapeutic target. Finally, given the success of our DNA barcoding strategy, we would like to map other amino acid dependencies of blood cancer cells systematically.