Discovery of AID-dependent Epigenetic Mechanisms in Hematological Malignancies

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Abstract: Our goal is to discover and target epigenetic mechanisms that contribute to hematological malignancies. Our focus is activation-induced cytidine deaminase (AID), a gene that regulates cytosine methylation patterns. We hypothesize that AID controls the epigenetic landscape of hematopoietic stem/progenitor cells, and can impact cancer by regulating DNA methylation patterns, irrespective of mutator activity. Our preliminary data suggest that AID functions as a tumor promoter in lymphoma, and as a tumor suppressor in myeloid leukemia. Using mouse models of lymphoma and leukemia we will 1) Determine whether AID is required to maintain self-renewal and tumor repopulating properties of DLBCL and how this is linked to its effects on cytosine methylation, and 2) Discover mechanisms by which AID functions as a tumor suppressor through resistance to a leukemia stem cell phenotype. We have also developed a novel reprogramming assay using AID-null fibroblasts that revealed AID-dependent functions at two distinct transitional stages: first for maintaining a committed state, and secondarily for stabilizing a stem cell phenotype. We propose to use this tightly controlled in vitro system to model both the putative tumor promoter and tumor suppressor capacities of AID. Our experiments will map AID-dependent epigenetic programs and use enhanced computational methods to discover targetable pathways. To achieve our goals, we built a consortium of collaborative investigators with expertise in AID, lymphoma, leukemia, epigenetics, stem cell biology, and computational genomics. This project will reveal at the genome-wide level AID-dependent epigenetic mechanisms that impact lymphoma and leukemia and thereby identify novel therapeutic targets.