Epigenetic Control of DNA Transposition in Embryonal Cancers

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Abstract: Half of the human genome originates from mobile DNA elements whose significance in cancer remains almost completely unexplored. This knowledge gap represents an important problem because many human cancers, and most childhood tumors in particular, exhibit a dearth of gene mutations, preventing understanding of their molecular causes and development of improved therapies. The Kentsis laboratory recently discovered active endogenous human DNA transposases in human embryonal tumors, whose expression is sufficient to transform human cells. We have now defined the mechanism of DNA transposition, which involves precise excision of inverted terminal repeat transposons and their insertion into euchromatic genomic loci (Henssen et al, 2015). We hypothesize that endogenous DNA transposition causes genomic and epigenomic dysregulation of oncogenic molecular pathways. The objective of this proposal is to investigate the previously hidden mechanisms by which DNA transposons promote cellular transformation by leveraging our complementary expertise in genomics, epigenomics, and cancer biology. First, we will use recently developed sequence analysis and transposon mapping approaches developed in the Mason laboratory to define endogenous transposons in primary and genetically-engineered embryonal tumors, including the first ever use of long-read single-molecule sequencing of pediatric tumor genomes. Second, we will investigate the alternative model that DNA transposons promote transformation epigenetically by altering chromatin state and regulation, using integrated ChIP-seq and transposase-seq technologies (Bernstein). Finally, we will determine the factors required for transposase transformation using proteomics and functional genomic approaches (Kentsis). Most immediately, this research project is expected to catalyze the discovery of elusive mechanisms of embryonal tumor pathogenesis that can serve as targets of rational therapies. In the long-term, we will establish essential tools for studying DNA transposition and defining the relationship between chromatin-mediated cell fate specification and structural genomic variation, with broad implications for a variety of human cancers.