

APOBEC Mutagenesis in Bladder Cancer: Mechanisms and Therapeutic Opportunities

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Abstract: The cancer genome reflects the mutagenic processes that are active over the course of disease. These processes can be categorized by characteristic mutational signatures that are rooted in the dueling natures of DNA damage and repair. The APOBEC3 family of single-stranded DNA cytosine- to-uracil deaminases has recently emerged as a potent driver of cancer-associated mutagenesis and the second most frequent mutational signature in human cancer. APOBEC3-induced mutations most frequently appear dispersed throughout the genome, but can also cluster at chromothripsis-associated rearrangement breakpoints. APOBEC3 mutagenesis is prominent in bladder cancer, where it causes driver mutations and therapeutic resistance. Despite the ubiquity of the APOBEC3 mutational signature and its contributions to bladder cancer progression, there are major unanswered questions. The relationship between APOBEC3 mutation clusters, known as kataegis, and chromothripsis breakpoints is not understood. The identity of the APOBEC3 family member that drives mutagenesis in bladder cancer is unknown. We seek to obtain a mechanistic understanding of the relationship between APOBEC3 mutations and chromothripsis and to identify the APOBEC3s responsible for the accumulation of APOBEC3-signature mutations in bladder cancer. We will also develop novel approaches to assay APOBEC3 activity. Finally, we will identify therapeutic vulnerabilities associated with APOBEC3 activation in bladder cancer. We are bringing together complementary expertise in bladder cancer, APOBEC biology, and chromothripsis and therefore are uniquely positioned to successfully achieve these goals. We will leverage our collective expertise to determine how APOBEC3 mutagenesis shapes the bladder cancer genome and translate this knowledge into therapeutic advances.