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Genomic and Functional Analysis of Translocation Renal Cell Carcinoma

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TECHNICAL ABSTRACT

Background: Translocation renal cell carcinoma (TRCC) is a rare and aggressive type of non-clear cell renal cell carcinoma (RCC) that represents 1%-5% of sporadic RCC in adults. Currently, there are no treatments that are specifically targeted to TRCC, and the treatments approved for clear-cell RCC may be less effective in patients with TRCC. Limited genomic and functional studies have revealed that TRCC is molecularly distinct from clear-cell RCC, and these differences likely underlie differing responses to treatment in these two histologies. Nonetheless, a comprehensive genomic and functional characterization of TRCC has not yet been performed. Most cases of TRCC are characterized by in-frame fusions between the transcription factor TFE3 and any one of several different partner genes (TFE3-TRCC). Intriguingly, many TFE3 fusion partners have roles in RNA splicing, raising the question of whether perturbation of alternative splicing is a hallmark of disease pathogenesis.

FY18 KCRP Areas of Emphasis: We will address the following areas of emphasis: genetic, chromatin and gene regulation, mechanism of response and resistance, and rare kidney cancers. Specifically, Aim 1 will define the genetic landscape of this disease; Aim 2 will determine how TFE3 fusions alter the chromatin landscape and gene expression program; Aim 3 will identify novel therapeutic vulnerabilities of TRCC, which may provide insight into mechanisms of intrinsic resistance to therapy. Overall, TRCC represents a rare, non-clear cell kidney cancer.

Hypothesis/Objective: We hypothesize that TFE3-TRCC may represent a "spliceopathy," whereby endogenous transcriptional and splicing complexes are rewired by TFE3 fusions, leading to a decoupling of the normally co-regulated processes of transcription and splicing, and to the expression of an oncogenic transcriptional program. We propose genomic, biochemical, and functional genetic studies to achieve the dual objectives of testing this hypothesis and of performing a comprehensive genomic and functional characterization of this rare disease.

Specific Aims: (1) To perform linked-read whole genome sequencing and transcriptome sequencing on a cohort of tumor-normal pairs from patients with TFE3-TRCC. (2) To characterize the protein interactomes, genomic occupancy, and RNA-binding sites of TFE3 fusions and to determine how these differ from those of wild type TFE3 or TFE3 partners. (3) To uncover novel therapeutic vulnerabilities of TFE3-TRCC via genome-scale functional genetic CRISPR/Cas9 screening.

Study Design: Aim 1 will involve linked-read whole genome sequencing and transcriptome sequencing of 25-30 tumor-normal pairs of TFE3-TRCC. We will define the genetic and transcriptomic landscape of TFE3-TRCC and identify genetic events that correlate to particular transcriptional or splicing features. In Aim 2, we will perform immunoprecipitation and mass-spectrometry (IP-MS), chromatin immunoprecipitation and sequencing (ChIP-Seq), and enhanced cross linking and immunoprecipitation with sequencing (eCLIP-Seq) of TFE3 fusions in three TFE3-TRCC cell lines. In doing so, we will identify protein, DNA, and RNA interactors of TFE3 fusions and compare these to interactors of wild type TFE3 and wild type TFE3 fusion partners. In Aim 3, we will perform genome-scale CRISPR/Cas9 essentiality screening on three TFE3-TRCC cell lines that contain distinct TFE3 fusions. We will compare essential genes identified in this context to candidate vulnerabilities identified via the prior screening of clear-cell RCC lines in order to identify genetic targets that may be unique to TFE3-TRCC.

Innovation: This work will result in extensive biochemical and functional profiling of TFE3-TRCC using multiple orthogonal data types. We will employ a range of cutting-edge technologies, including linked-read whole genome sequencing, genome-/transcriptome-/proteome-wide biochemical profiling, and genome-scale functional genetic screening. This work will significantly advance our understanding of the pathways that drive TFE3-TRCC and will provide valuable resources to the kidney cancer research community.

Impact: The proposed work is consistent with the KCRP vision of eliminating kidney cancer, as it seeks to perform comprehensive molecular characterization of TFE3-TRCC, a rare and poorly studied subtype of kidney cancer. In the short-term, this work will generate valuable datasets for the kidney cancer research community, including (1) whole genome and transcriptome sequencing of a large TFE3-TRCC cohort; (2) comprehensive molecular profiling of TFE3 fusions including their protein interacting partners and the sites to which they bind in the genome and transcriptome; (3) genetic vulnerabilities of TFE3-TRCC cell lines as determined via unbiased genome-scale CRISPR/Cas9 screening. Over the long-term, this work will be foundational for novel diagnostic and therapeutic hypotheses in TRCC and may form the basis for the clinical development of drugs against novel therapeutic targets in this rare kidney cancer subtype.

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