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Unlocking the Human Relevance of a New Genetic Papillary Renal Cell Carcinoma Mouse Model

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TECHNICAL ABSTRACT

Background: Kidney cancer is the ninth most common cancer and accounts yearly for >14,000 American deaths. Papillary renal cell carcinoma (pRCC) is the second most common subtype of kidney cancer and is divided into two histological variants (I and II). The mutational landscape of pRCC is complex without a universal prevailing theme, but several pathways have emerged as potentially important drivers. Treatment options for advanced pRCC are often extrapolated from clear cell clinical trials due to patient accrual challenges, and outcomes are poor. Until now, no human relevant pRCC mouse models have existed. By combining MET activation and Pten loss with transposon mutagenesis, we have engineered a genetic mouse model that faithfully and reliably produces renal tumors histologically identical to human pRCC.

Hypothesis: Determining which molecular subtype(s) of pRCC this model recapitulates will be critical to unlocking its potential to provide insight into treatment for pRCC patients.

Specific Aims:

(1) Molecularly profile murine pRCC tumors. Banked tumor specimens will be reviewed in a blinded manner by an expert pathologist to determine histopathologic subtype. Tumor samples will then be molecularly analyzed using RNA-Seq and Reverse Phase Protein Arrays.

(2) Determine the human subtype specificity of murine pRCC tumors. We will establish the similarity between our pRCC mouse models and The Cancer Genome Atlas (TCGA) patient data at three levels: (1) identify and validate overlap of individual genes and proteins; (2) establish significant overlap of the gene signatures and the protein signatures, respectively, using ORA and GSEA; and (3) establish enrichment of similar pathways in the mouse model and TCGA for pRCC.

Study Design: The overall objective of this proposal is to determine the spectrum of molecular pRCC subtype(s) developed by a newly engineered mouse model. This model combines an activating allele of the MET proto-oncogene (M1248T) that has been identified in pRCC patients, a single allele loss of the tumor suppressor PTEN, and additional mutagenesis driven by the Sleeping Beauty transposon. Using two high-throughput molecular approaches, we will characterize the RNA (RNA-Seq) and protein (Reverse Phase Protein Array; RPPA) profiles of these tumors. To determine the molecular subtype(s) represented by these tumors, we will compare these profiles to human data from TCGA.

Innovation: This work is highly innovative on several fronts. First, we are utilizing a new and previously undescribed in vivo model of pRCC that combines pRCC-relevant mutations (METM1248T, PTEN-loss) with a transposon system to accelerate tumorigenesis. These mice, here described for the first time, develop spontaneous tumors with histologic features that closely mimic human pRCC. Molecular subtyping of these tumors is a key step to unlocking the human relevance potential of this model. pRCC is a diverse set of molecular subtypes in humans. Defining the molecular signatures of our mouse tumors will be critical for exploiting this exciting model to apply it to human disease.

Impact: Successful completion of this project will provide critical resources in the form of a molecularly subtyped genetic mouse model for papillary renal cell carcinoma. Currently, this resource does not exist, significantly limiting our ability to understand potential vulnerabilities for the disease in individual patients. Such a model could allow testing of hypotheses before moving on to costly and time-consuming human clinical trials for new strategies. Laboratory models (mouse and cell culture) have been the key to identifying and testing durable treatment options in other forms of cancer. In this project, we expect to deliver both mouse and cell culture-based models for molecular subtype-specific forms of papillary renal cell carcinoma relevant to human patients. We anticipate that the research community will exploit these models to identify tumor vulnerabilities and develop and test targeted therapeutics against each tumor molecular subtype that can one day provide more effective treatment for patients with papillary renal cell carcinoma.

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