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Defining the Role of Beta-Catenin Activation in Wilms Tumor

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TECHNICAL ABSTRACT

Background: Wilms tumor (WT) resembles the developing kidney, consisting of blastemal/nephron progenitor cells (NPCs) as well as immature epithelial and stromal cells, indicating a link between the dysregulation of normal development and tumorigenesis. Although all WT appear to derive from aberrant renal development, no unifying mechanism has been identified. While activating mutations in CTNNB1, the gene encoding beta-catenin, are found in approximately 15% of WTs, tumors without mutations in CTNNB1 frequently show signs of upregulated beta-catenin activity, suggesting this pathway may drive tumorigenesis. However, beta-catenin signaling is highly cell type- and context-dependent with multiple functions in different aspects of renal development, with little understood about its role in WT. While it has previously been assumed that blastema/NPCs act as a cancer stem cell, mouse models with activation of beta-catenin within the NPC lineage paradoxically show premature loss of the blastema, a phenotype opposite to WT. We and others have recently shown that signals from developing renal stroma somewhat surprisingly regulate NPCs, and loss of this regulation results in abnormally maintained nephron progenitors reminiscent of nephrogenic rests in WTs. This led us to the central hypothesis that aberrant signaling from the stroma, as mediated by activating mutations in beta-catenin, plays a critical role in Wilms tumorigenesis.

Hypothesis/Specific Aims: We hypothesize that beta-catenin activation in the stroma specifically (1) regulates stroma-to-nephron progenitor crosstalk, promoting a tumorigenic microenvironment, and/or (2) results in oncogenic potential of stromal cells, which will be tested through the following aims:

Aim 1. Determine how stromal beta-catenin inhibits nephron progenitor differentiation to identify potential signaling pathways perturbed in the WT microenvironment.

Aim 2. Evaluate human WT for cell lineage-specific beta-catenin mutations and localize the expression of stromal beta-catenin target genes using both directed and global gene profiling.

Aim 3. Determine cell-lineage effects of activating beta-catenin mutations (in the stroma, nephron progenitor cells, and potential common progenitors/early precursor cells) and assess their tumorigenic potential.

Study Design: To determine how beta-catenin contributes to tumor formation, we have generated mouse lines containing activating mutations of beta-catenin (Bcat-Exon3) in the NPCs and stromal populations. Preliminary analysis of mouse kidneys carrying activating mutations of beta-catenin specifically within stromal cells remarkably resemble WT at both the histological and molecular level. We propose to further characterize these mutants by identifying stromal targets of beta-catenin (Aim 1a), testing their ability to regulate nephron progenitor maintenance/differentiation (Aim 1b), and localizing the expression of identified beta-catenin target genes in human WT(Aim 2b). We will also perform global gene profiling of human WTs using nuclear single cell RNA seq (Aim 2c) in an effort to better characterize the spectrum of cell types in WT, specifically stroma. Additionally, we will assess the cell lineage effects of activating beta-catenin mutations (in the stroma, nephron progenitor cells, and potential common progenitors/early precursor cells) for WT-like phenotypes and assess the tumorigenic potential of these mutants, utilizing an organoid transplant assay that will allow us to evaluate the complex cross-talk regulating nephron proliferation and differentiation and how defects within the stromal microenvironment contribute to WT.

Personnel: My long-term career goal is to develop an independent research career studying translational applications of renal development research, specifically understanding cell fate determination and how signaling pathways critical to normal development are perturbed in cancers. Given my background in kidney development, pursuing the study of WT biology not only offers important translational/clinical implications, but also provides the opportunity for significant insight into mechanisms that govern normal development vs tumorigenesis. Under the mentorship of Dr. Thomas Carroll, an expert in the field of renal development with several ongoing projects examining kidney cancer, I will take full advantage of my experience in his lab and the environment at UTSW outlined in my career development plan to produce strong scientific work and establish expertise in the field of renal development and WT biology.

Impact: Overall, the experiments outlined in this proposal are aimed to better understand WT as a model linking developmental processes and tumorigenesis. Our findings may have applications to other embryonal tumors in which the microenvironment and/or beta-catenin activation may contribute to tumor formation and ultimately identify novel targets/pathways to advance precision medicine in the treatment of these cancers.

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