Modeling Spatial Ecology in Clear Cell Renal Cell Carcinoma Model: A Novel Tool to Support Drug Sequencing Decisions

Principal Investigator: MANLEY, BRANDON
Institution Receiving Award: H. LEE MOFFITT CANCER CENTER AND RESEARCH INSTITUTE, AT SOUTH FLORIDA, UNIVERSITY OF
Program: KCRP
Proposal Number: KC180036
Award Number: W81XWH-19-1-0655
Funding Mechanism: Concept Award
Partnering Awards:
Award Amount: $128,806.00

View Public Abstract

TECHNICAL ABSTRACT

Background: There are almost 64,000 new cases each year of renal cell carcinoma (RCC) in the U.S., with just over 30% of those patients presenting with metastatic RCC (mRCC). Clear cell RCC (ccRCC) accounts for approximately 70% of new RCC cases. The influx of multiple novel therapeutic options for mRCC has created treatment sequencing challenges. One aspect of the disease that is known to have biologic importance but has been understudied is the role of stromal architecture. Studies in other solid tumors have given insight into possible clinical associations between stromal cells like cancer-associated fibroblasts and their spatial proximity to tumor cells. Given the mechanism of action of many RCC drugs, study of the tumor stromal microenvironment (TSM) could help predict response or resistance to specific therapies and provide insight into relationships between tumor progression and treatment sequencing.

Hypothesis/Objectives: We hypothesize that the stromal architecture in ccRCC can predict response to the most common classes of systemic treatment, targeted therapy and immunotherapy. Aim 1: Characterize the TSM of ccRCC tumors through histological analyses using specific immunohistochemical stromal and proliferative markers, which will capture differences in stromal architecture among patients who responded to or progressed on specific classes of systemic therapies. Aim 2: Develop novel computational tools and in silico models that can be used to better predict tumor evolution by inputting analyses from Aim 1 on stromal architecture and proliferative markers. A scoring system built on spatial-ecology that can be applied to RCC in relationship to specific treatments will be used to estimate the most likely cancer-stromal cell interaction range. This will be tested to augment treatment response and clinical outcomes.

Study Design: This will be a retrospective two-cohort assessment of ccRCC surgical tissue samples before systemic treatment. Cohort 1: Targeted therapy (TT; n = 50) will be given to patients who received first-line sunitinib or pazopanib. Half of the patients will be “responders” who had > 9 months of progression-free survival (PFS) on TT and the other half will be “non-responders” who had < 6 months of PFS on TT. Cohort 2: Immunotherapy (IT; n = 50) patients who received first-line nivolumab or IL-2, will be stratified by PFS while on IT similar to cohort 1. Aim 1: Tumor samples from both cohorts will be obtained from formalin-fixed paraffin-embedded blocks. On two distinct regions of each tumor, immunohistochemical analyses will be performed using alpha-SMA (fibroblast marker), KI-67 (proliferative marker), and caspase-3 (apoptosis marker). The stained slides will be analyzed for the presence or absence of stain, intensity of staining, and spatial organization. Tissue segmentation and analyses will be done by Definiens Developer XD and Visiopharm software. Aim 2: Using extracted slide images, computational tools and in silico statistical models will be developed that will better predict the impact of cellular architecture on therapy response. A scoring system built on the spatial-ecology measure Ripley’s K function will be used. Cohorts will be randomly divided into training (40%), testing (40%), and validation (20%) sets, and the Anderson-Darling test and Kullback-Leibler divergence between sample distributions will be used to establish the most likely interaction-distance between stromal cells and tumor tissue.

Innovation: New tools are needed to help understand many of the complex interactions in the TSM. In recent years, mathematical modeling has demonstrated promising results in elucidating important dynamics in cancer research. These models allow for expansion of time scales (days, years) that are not possible using traditional in vivo experiments. Our study looks to develop a framework using in silico models that help to characterize the TSM in ccRCC.

Impact: At the completion of this project, first-of-their-kind models and characterizations of spatial ecology in ccRCC will have been generated. These models will serve as important foundations for the development of larger and more comprehensive applications in kidney cancer research.