PD16-03

UNDERSTANDING THE MOLECULAR CHARACTERISTICS AND VULNERABILITIES OF SARCOMATOID/RHABDOID RENAL CELL CARCINOMAS THROUGH INTEGRATIVE HISTOLOGICAL AND SPATIAL GENOMICS APPROACHES

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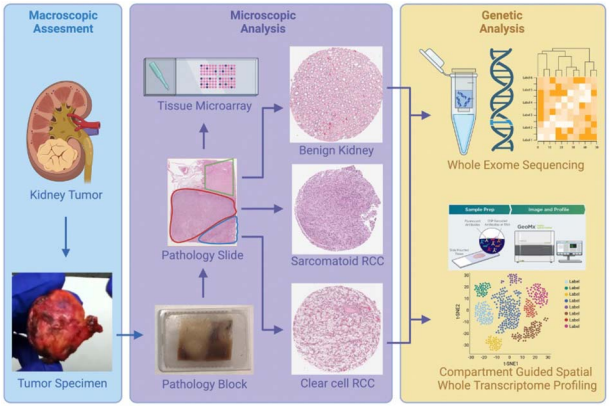
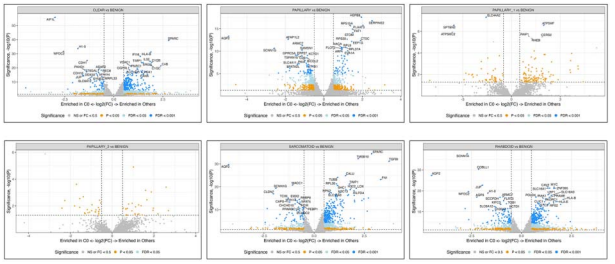
INTRODUCTION AND OBJECTIVE: Genomic and immune analyses in S/R RCC have been limited to bulk tumor analysis and thus lack cellular resolution and spatial perspective. Herein, we use in situ Whole Transcriptome Profiling (WTP) to define molecular differences between tumor regions with and without S/R features, aiming at identifying molecular markers of S/R tumors that could lead to better diagnosis or treatments.

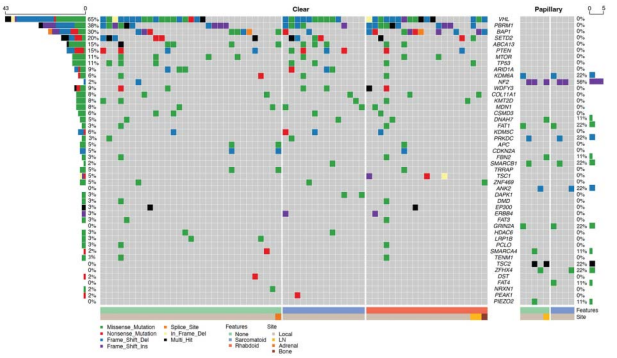
METHODS: All patients who underwent surgical excision of RCC at the MUHC between 2010 and 2020 were screened by a uropathologist, and histologically defined regions of S/R, ccRCC, papillary, chromophobe RCC, and benign kidney were selected to construct tissue microarrays (TMAs). Whole-exome sequencing (WES) and Compartment-Guided Spatial WTP were applied for gene and transcriptome analysis (Figure 1).

RESULTS: A cohort of 56 RCC patients and their TMAs, consisting of 403 cores representing patient-matched tumor areas with and without S/R features. For WES, 47 patients were used to identify copy number variations (CNVs) analysis. Four hundred cores of 55 patients were used for WTP and 5 groups of clustered with 2000 highly variable genes (HVGs) were constructed. The most variable genes of each tumor type were identified by using digital spatial transcriptome profiling (Figure 2). Whole-exome sequencing was used to identify mutational patterns of tumor cells using a list of specific genes of interest (Figure 3).

CONCLUSIONS: According to current and ongoing results, WES, and compartment-guided WTP should be used to generate an unprecedented resolution to the molecular and genomic characteristics of S/R RCC tumors and tumor microenvironment.







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PD16-04

SPATIAL ANALYSIS OF PRIMARY AND METASTATIC LESIONS IN SARCOMATOID RENAL CELL CARCINOMA REVEALS INSIGHT TO TUMOR BIOLOGY AND IMMUNE MICROENVIRONMENT

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INTRODUCTION AND OBJECTIVE: Sarcomatoid renal cell carcinoma (sRCC) is a dedifferentiation process that can occur in any kidney tumor, most commonly clear cell RCC (ccRCC). sRCC tumors have a high rate of metastasis. It is unknown whether metastatic lesions initiate from ccRCC or sRCC cells. Our prior work identified the ability to detect cells in a transition state from ccRCC to sRCC which was associated with dense macrophage and CD8 T-cell infiltrate. We hypothesized that clear cells in an early stage of transition to sRCC have more metastatic potential than fully mesenchymal sRCC cells. Here, we use spatial single cell transcriptomics and multiplex immunofluorescent staining to explore the tumor cell biology and corresponding immune microenvironment in matched primary and metastatic sRCC lesions.

METHODS: Single cell spatial transcriptomics via NanoString's CosMx platform was performed on 6 specimens from two patients with matched primary and metastatic lesions. Fields of view were selected based on histology, selecting regions of ccRCC, “transition” (areas spatially between clear cell and sarcomatoid areas with an intermediate morphologic appearance), and sRCC. Unsupervised clustering was used to identify cell types which were mapped to spatial location. Immunoflourescent staining of 18 markers was performed on an adjacent cut of the same specimens and immune infiltrate was quantified via the Canopy CellScape platform.

RESULTS: Unique tumor cell states were identified in ccRCC and sRCC areas. Transition areas were comprised largely of sRCC cell states with some component of ccRCC, consistent with prior findings. Metastatic lesions were comprised predominantly of ccRCC cell states with high expression of stemness genes such as POU5F1. Primary lesions had high T-cell infiltrate with the majority comprised of memory T-cells while metastatic lesions and much higher effector T-cell infiltrate. Ongoing work includes spatial analysis of tumor cell/immune interactions.

CONCLUSIONS: These findings support the hypothesis that initial metastases in sRCC arise from clear cell RCC cells with stem-like properties, which may then progress to develop sarcomatoid features. The immune microenvironment varies from primary to metastatic lesions with a higher density of effector T-cells in metastases. Further exploration of these findings will have important implications for understanding sRCC biology and response to immunotherapy in primary versus metastatic lesions.

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