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Functionally Characterizing the Enhancer Cistrome in Advanced Human Kidney Cancer

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TECHNICAL ABSTRACT

Background: Metastatic clear cell renal cell carcinoma (ccRCC) is a condition that is fatal in the majority of cases. The centrality of chromatin remodeling in ccRCC pathogenesis renders it an ideal tumor type in which to study epigenetics. Using chromatin immunoprecipitation followed by high throughput sequencing (ChIP-seq) in human ccRCC specimens, we charted the histone 3 lysine 27 acetylation (H3K27Ac) cistrome – the universe of all sites in the genome harboring active enhancers, regulatory sites that are able to enact the transcriptional programs of distal genes. We demonstrated that enhancer landscape is significantly and consistently re- programmed during kidney tumorigenesis.

In our recent work in prostate cancer epigenetics, we observed that the active enhancer cistrome undergoes significant alterations during the transition to the metastatic state. Interrogation of the differential H3K27Ac sites led to the identification of one of the first described functionally relevant enhancers of the androgen receptor in prostate cancer. Our work to date provides strong evidence that studying the cancer epigenome across disease states in vivo will reveal important insights into mechanisms of metastasis. We therefore aim to apply this strategy to the study of ccRCC, analyzing the enhancer cistrome in human tissue to identify drivers of metastatic kidney cancer. Completion of the novel experiments outlined in this proposal will directly address a FY18 KCRP Areas of Emphasis: Chromatin and Gene Regulation.

Hypothesis: We hypothesize that aberrant epigenetic signaling underlies ccRCC progression. We further postulate that characterizing changes in epigenetic programs will lead to new targets for cancer therapy.

Specific Aims:

(Aim 1) To characterize the genome-wide landscape of open chromatin and active regulatory elements and their connections to target genes in the progression from localized to metastatic ccRCC.

*Perform ChIP-seq for histone 3 lysine 27 acetylation (H3K27Ac) to identify differential regions of active enhancers from primary vs. metastatic ccRCC samples.

*Correlate ChIP-seq findings with gene expression changes detected by RNA-seq.

*Systematically annotate the genome-wide landscape of chromatin interactions and determine regulatory networks within metastatic RCC cells, using HiChIP.

(Aim 2) To perform epigenome-wide CRISPR-based screens across the epigenome to identify the functional relevance of regulatory elements associated with ccRCC in model systems.

*Use CRISPR/Cas9 technology to suppress enhancer activity at sites identified in our preliminary H3K27Ac data from primary ccRCC.

*Use CRISPR/Cas9 technology to suppress enhancer activity at sites identified in our preliminary H3K27Ac data at sites associated with metastatic progression discovered in Aim 1.

Study Design: Aim 1 will systematically characterize the active enhancer landscape (using H3K27ac ChIP-seq) during the progression from localized to metastatic ccRCC in clinically relevant samples. Aim 2 will leverage our experience performing HiChIP, a method for identifying biologically meaningful chromatin-chromatin interactions genome-wide. This will allow us to identify enhancer/gene networks present in metastatic ccRCC. Using the powerful tools of genome editing, Aim 3 will identify functionally relevant regulatory elements by performing genome-wide CRISPR screens. Using cell line models, the screen will identify non-coding elements that influence progression to metastasis. Notably, the team has deep expertise for the clinical and scientific aspects of each aim and they have successfully conducted and/or published prior studies using the methods outlined in this proposal.

Innovation: While in the current era there has been a focus on genetic sequencing and somatic alterations in the exome, there is increasing appreciation of the importance of the non-coding portion of the genome. The proposal will specifically identify functional enhancers, non-coding drivers of progression to lethal ccRCC. Completion of this study will yield the largest catalog to date of gene regulatory elements in metastatic ccRCC.

Impact: By identifying elements driving ccRCC progression, the results of this project will present new targets for therapeutic intervention. The completion of the above aims will also identify a pattern of epigenetic features, specimens, that can serve as marker for aggressive disease.

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