Search Awards

Back to Search Results | Modify Search | New Search

The Pathogenesis and Therapy of Chromophobe Renal Cell Carcinoma: A Single-Cell RNA Sequencing Approach

Principal Investigator: HENSKE, ELIZABETH P
Institution Receiving Award: BRIGHAM AND WOMEN'S HOSPITAL, INC.
Program: KCRP
Proposal Number: KC180079
Award Number: W81XWH-19-1-0550
Funding Mechanism: Concept Award
Partnering Awards:
Award Amount: $133,830.00

View Public Abstract

TECHNICAL ABSTRACT

Background: Chromophobe renal cell carcinoma (RCC), the third most common subtype of RCC, represents ~5% of all RCC and is pathologically and genetically distinct from other subtypes. The incidence of metastatic spread of Chromophobe RCC (ChRCC) is lower than for clear cell RCC, but because there are currently no proven therapies for metastatic ChRCC, the prognosis for patients with metastatic ChRCC is estimated to be less favorable than for metastatic clear cell RCC. Single-cell RNA-Seq (scRNA-Seq) is a relatively new method for transcriptional investigation of single cells from a complex population, thereby enabling completely new insights into tumor heterogeneity and the tumor microenvironment, including immune cell populations and stromal cells. Single cell ATAC-Seq (scATAC-Seq), which assesses chromatin accessibility and reveals cell-cell epigenetic regulatory variation, can be used to investigate underlying mechanisms. We propose to investigate transcriptional heterogeneity and epigenetic regulation of ChRCC using scRNA-Seq and scATACSeq profiling.

Hypothesis/Objective: Our central hypothesis is that integrative profiling of single cell transcriptomics and chromatin accessibility will reveal novel pathogenic mechanisms in ChRCC, including pathogenic contributions from stromal and immune cell populations in ChRCC.

Specific Aims:

Aim 1: Determine the heterogeneity of individual tumor cells, stromal cells, and immune cells in ChRCC using scRNASeq.

Aim 2: Investigate role of epigenetic regulation in tumor heterogeneity using scATAC-Seq.

Aim 3: Determine levels of immune infiltration and clonal diversity using single cell T cell receptor (TCR) and B cell receptor (BCR) profiling.

Study Design: ScRNA-Seq will be performed on five freshly resected ChRCC specimens collected through collaboration with our RCC research team. Tumors will be from patients in whom pre-operative biopsy has demonstrated ChRCC. Complementary cell type annotation strategies will be employed for cell type identification: annotation by well-defined cell-type specific signature gene sets, and database-based approaches using R package SingleR. Density-based clustering and Non-Negative Matrix Factorization (NMF) will be used to interrogate transcriptional programs in tumor cells and in each of cell types identified in microenvironment. Immune-cell “exhaustion” markers (including PD-1, TIGIT, LAG3, TIM3, VISTA, CTLA-4) will be profiled. Tumor-associated macrophages and tumor-associated fibroblasts will be identified using marker genes and will be further stratified by transcriptional pattern. We will perform scATAC-Seq on the five tumors to reveal the landscape of chromatin regulatory variation. Bayesian network analysis of scRNA-Seq and single cell chromatin accessibility from the same sample will be used to identify candidate regulatory networks. Single cell TCR/BCR profiling will be performed, with integrative analysis of gene transcription, chromatin accessibility, and clonal diversity. Immune exhaustion mechanisms will be investigated by pathway/network analyses. Pairwise ligand-receptor correlation analysis will be used to reveal cell-cell crosstalk and identify cell populations that may be interacting with and/or suppressing immune cells.

Innovation: To our knowledge, this will be the first single cell interrogation of ChRCC, allowing integration of single cell transcriptomics, single cell epigenomics, and single cell immune profiling.

Back to Search Results

1077 Patchel Street
Fort Detrick, MD 21702-5024

(301) 619-7071

cdmrpwebmaster@webcdmrp.org (mailto:cdmrpwebmaster@webcdmrp.org)

About Us

The CDMRP originated in 1992 via a Congressional appropriation to foster novel approaches to biomedical research in response to the expressed needs of its stakeholders-the American public, the military, and Congress.

 (https://www.facebook.com/TheCDMRP)  (http://twitter.com/CDMRP) 

(https://www.youtube.com/user/CDMRP)  (/rss/funding_opportunities.xml)