Molecular Characterization of the Tumor Microenvironment in Chromophobe Renal Cell Carcinoma (ChRCC) and Related Oncocytic Neoplasms

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Overview of Renal Oncocytic Neoplasms

Renal Oncocytoma (RO)
- Benign tumor
- Limited chromosomal abnormalities
- Mitochondrial defects → disruption of Golgi

Low-grade Oncocytic Tumor (LOT)
- Benign tumor
- Novel renal entity
- Eosinophilic renal tumors with “oncocytic” features

Chromophobe RCC (ChRCC)
- Malignant tumor
- Multiple chromosomal losses
- Mitochondrial molecular alterations

Benign

Malignant

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How do patients with metastatic ChRCC respond to IO-based regimens?

Poor survival outcomes to immunotherapy in ChRCC as compared to ccRCC

Why?
**Cohort Overview**

**Cohort:**
- 5 Tumor Samples (3 ChRCC, 1 LOT, 1 RO) + 4 Matched Normals
- scRNA-seq +/- scTCR-seq
- CD45 Quantification of ICs

### Table

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<th>ChRCC</th>
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### Sex
- Male
- NR

### Disease Extent
- Localized

### T-stage
- T2b
- T3a
- T1a

### Samples
- Tumor + Normal
- Tumor Only

### scRNA-seq
- Tumor and Normal
- Tumor Only

### scTCR-seq
- Tumor and Normal
- Tumor Only

### CD45 Infiltration
- Tumor Only
- None

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Cellular Populations
Renal Oncocytic Neoplasms

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Determinants of Response to ICIs

- Immune Infiltration
- Immune Exhaustion Profile
- Tumor Specificity
How immune-infiltrated are oncocytic tumors?

Poor infiltration of immune cells among renal oncocytic neoplasms
What is the exhaustion profile of renal oncocytic tumors?

Low expression of immune exhaustion markers in ChRCC vs. ccRCC

scRNA-seq
Do T-cells from oncocytic tumors recognize tumor antigens?

TCRs mapping to viral antigens ("bystander T-cells")

Low tumor specificity and higher proportion of viral-specific T-cells

Mapping of clonotypes (CDR3A+CDR3B) from scTCR-seq data to known epitopes (VDJdb)

NeoTCR8 signature (243 genes) is indicative of tumor specificity among CD8+ T-cells

Immune Infiltration
Immune Exhaustion Profile
Tumor Specificity
Conclusions

• Poor response among patients with ChRCC to IO-based regimens (vs. ccRCC)

• Characteristics of the TME in renal oncocytyic neoplasms:
  1. Low infiltration of immune cells
  2. Poor exhaustion profile
  3. Low tumor specificity (T-cells)

Potential implications for therapy: reinvigoration of the immune landscape in ChRCC (i.e. targeted cancer vaccines) to elicit IO response?