Dissecting metabolic alterations of clear cell renal cell carcinomas one cell at a time

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Background

- Sporadic Clear cell renal cell carcinoma (ccRCC) is the most common type of kidney cancer, representing 70% of all renal cell carcinoma cases.
- Molecularly is characterized by alterations in the short arm of chromosome 3, in particular alterations in the VHL gene.
- Metabolic alterations have been described affecting the tumors due to the pseudohypoxia environment.

Findings

- Figure 1. Uniform Manifold Approximation Projection (UMAP) of normal adjacent and tumor cells organized using a weighted nearest neighbor analysis integrating snRNA-seq and snATAC-seq.
- Figure 2. Upregulated metabolic pathways in normal and tumor cells.
- Figure 3. Metabolic shifts across different cell types.

Data and Methods

- Samples were collected between 1994 and 2009.
- Tumors were split for pathology and biobank at the time of collection.
- Biobanked samples were mechanically and enzymatically dissociated at the time of collection, and stored at -80 Celsius until processing.
- Cell were rapidly thawed, debris and non-viable cells were removed.
- 10Xmultiome protocol was used to measure single-nuclei RNA-seq and ATAC-seq.
- scMetabolism was used to infer dysregulated metabolic pathways.

References


Summary of Findings

- The mean age at diagnosis was 61.7 yrs (SD: 12.5), 67% being stages I/II.
- 79,804 tumor and 5,967 normal-adjacent cells were analyzed. 34,318 were classified as epithelial cells from the nephron (juxtaglomerular, glomeruli, renal tubules), 5,947 as collecting ducts cells, 18,959 as immune cells, 13,445 as endothelial cells, and 13,112 as other stroma cells.

Discussion and Future Directions

- Cell-specific metabolic shifts were observed between tumor and normal adjacent samples that cannot be explained only by sample heterogeneity or cell lineages.
- Oxidative phosphorylation and TCA cycle modifications were observed in tumor endothelia and cells resembling distal tubules and collecting ducts.
- Glutamine/glutamate expression increased in lymphoid, endothelial, and stromal cells.
- Fatty acid biosynthesis increased in myeloid and reduced in lymphoid, collecting ducts-like, and nephron loop-like cells.
- Glycolysis increased in glomeruli-like, nephron loops-like, collecting ducts-like and endothelial.
- Oxidative phosphorylation and TCA cycle genes decreased in distal tubules-like, collecting ducts-like, and endothelial.
- Further dissecting these findings will provide additional therapeutic avenues for newer targets, such as glutaminase inhibitors and combinations with current therapies.

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