Metabolic Heterogeneity and the Tumor Microenvironment in Clear Cell RCC

Cerise Tang, BS
Ed Reznik, PhD
A. Ari Hakimi, MD
ccRCC is Metabolically Driven, Genetically Heterogeneous, and Highly Immune Infiltrated

• What drives metabolic heterogeneity and how does it manifest within tumors?

• Do metabolic changes co-evolve alongside changes in the immune microenvironment?
Differential Expression of Fatty Acids, OXPHOS and ROS Define Universal Pattern of Intratumor Heterogeneity
Universal Pattern of Intratumor Heterogeneity May Compensate for Ferroptotic Susceptibility

Intratumor Heterogeneity Phenotypes:

- Elevated PUFA levels
- High levels of OXPHOS
- Enriched ROS levels
- High expression of cysteine
- High anti-oxidant expression
Highly Immune Infiltrated Tumor Regions are Associated With Increased NAD+ Metabolism

![Graphs showing the relationship between immune infiltration and NAD+ metabolism.](image)

- Marginal Explained Variance
- Nicotinamide Expression
- Myeloid Signature

**Key Points:**
- Glutathione, oxidized (GSSG), quinolinate, cysteine, 1-methyl-2-pyridone-5-carboxamide, nicotinamide are associated with increased NAD+ metabolism.
- The level of immune infiltration is significantly associated with NAD+ metabolism.
- Myeloid signature is depicted with markers like N-acetylcysteine, N-acetylaspartate (NAA), N-acetylglutamine, N-acetylaspartate (NAA), N-acetylaspartate (NAA).
Overarching Conclusions

• Within a single ccRCC tumor, there is a dominant heterogeneity program driven by PUFAs, cysteine accumulation and ROS tolerance.

• In ccRCC NAD+ metabolites (specifically quinolinate and nicotinamide) are associated with higher immune infiltration intratumorally.

• *Metabolic heterogeneity is pervasive in ccRCC and can be remodeled by the presence of immune cells.*
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