Mitochondrial Metabolic Reprogramming Orchestrates Tumor–Immune Crosstalk and Dictates Disease Outcomes in Primary Prostate Cancer

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Background:
Metabolic reprogramming is recognized as a hallmark of cancer, with mitochondria serving as the central hub of bioenergetics, biosynthesis, and redox signaling. Prostate cancer, an androgen driven malignancy, exhibits profound metabolic alterations. Yet the systematic characterization and clinical implications of mitochondrial metabolism in this disease remain largely undefined.

Methods:
We curated a 40-gene mitochondrial metabolic network encompassing the tricarboxylic acid (TCA) cycle, oxidative phosphorylation, fatty acid oxidation, and mitochondrial biogenesis. Using the TCGA prostate cancer cohort, we integrated transcriptomic, somatic mutation, copy-number variation (CNV), DNA methylation, and clinical data. Gene set variation analysis (GSVA), survival modeling, and immune deconvolution were applied to delineate the molecular and immunological landscape of mitochondrial metabolism.

Results:
Alterations in the mitochondrial metabolic gene set were strongly associated with adverse clinical outcomes. Patients harboring gene set mutations exhibited significantly reduced disease-free interval (DFI) and progression-free survival (PFS) (log-rank $p = 0.010$ and 1.3×10^{-5}), with *Citrate Synthase (CS)* gene mutations exerting the most pronounced effect ($p = 2.5\times10^{-6}$). High GSVA-derived metabolic activity correlated with inferior disease-specific survival (DSS, $p = 0.008$). Immune profiling further revealed that mitochondrial dysregulation was coupled with marked remodeling of the tumor microenvironment, including altered infiltration of $CD4^+$ regulatory T cells, $CD8^+$ cytotoxic T cells, macrophages, and dendritic cells. Epigenetic analysis identified prognostic methylation signatures in key genes such as *Fumarate Hydratase* (*FH*), *Malate Dehydrogenase 1* (*MDH1*), and *aconitase 2* (*ACO2*), extending the clinical relevance of mitochondrial metabolism across cancer types.

Conclusions:
This integrative analysis provides the first comprehensive landscape of mitochondrial metabolic reprogramming in prostate cancer, uncovering its genomic underpinnings, immunological correlates, and clinical significance. Our findings highlight mitochondrial metabolism as both a driver of tumor–immune crosstalk and a promising biomarker for risk stratification, with potential implications for the development of metabolic targeting and combination immunotherapeutic strategies in prostate cancer.

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