Mapping Mitochondrial interactions in prostate Cancer

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Introduction

Prostate cancer (PCa) demonstrates notable racial disparities, with African American men (AAM) experiencing a higher incidence and increased mortality rates compared to their European American (EAM) counterparts. While social determinants of health are key contributors to these disparities, underlying biological differences remain important drivers of disease severity and outcomes. Previous studies demonstrated that disrupted DNA damage repair mechanisms represent one such biological distinctions. In the current work, we aimed to explore the interplay between DNA damage and mitochondria.

Methods

We used a retrospective race-matched Genomic Resource Intelligent Discovery (GRID^{TM}) database (NCT02609269) (n=8,626), and the prospective VANDAAM study (NCT02723734) (n=243) to map pathways regulating DNA repair and Mitochondrial function.

Results

Using race-matched genomic datasets and patient-derived explants (PDEs), we first demonstrate that AAM tumors exhibit a distinct DNA damage response (DDR). Mitochondrial dysfunction emerges as a key feature, with reduced expression of electron transport chain (ETC) Complex I and III genes in AAM tumors. To further dissect the link between DNA damage and mitochondrial functionality, we chronically treated prostate cancer cells with DNA repair inhibiting agents followed by metabolic characterization and assessment of mitochondrial related functions. Interestingly, these cells demonstrate distinctive metabolic profiles and enhanced mitochondria-endoplasmic reticulum interaction which is reminiscent of ETC regulation.

Conclusion

Collectively, these findings highlight the link between DNA damage response and mitochondrial circuits. The study of mitochondrial dynamics may offer novel therapeutic strategies for overcoming racial disparities in PCa outcomes.

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Conflicts of Interest Disclosure Statement

Authors declare No conflict