Establishment of pre-clinical models for the discovery of new mitochondrial biomarkers of high-risk prostate cancer

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Abstract

Background: Prostate cancer (PCa) is generally an indolent disease. However, a significant percentage may progress to a more aggressive phenotype with metastatic potential and which may be lethal. Currently, it is difficult to accurately identify those at greatest risk of PCa-specific morbidity and mortality where actionable measures would improve survival rates. Our center serves a vulnerable community of predominantly African American (AA) men, who are amongst the highest-risk population groups disproportionally affected by PCa. Our goal is to identify and validate molecular changes linked to aggressive PCa and poor prognosis in high-risk groups by developing appropriate pre-clinical models that would enable functional experimentation in the high-risk disease context.

Methods: We have established a robust human PCa patient tissue procurement protocol for the collection of biopsy and prostatectomy samples. Utilizing a recently developed protocol for tissue processing and development of patient-derived organoid (PDO) models we performed pre-clinical characterization studies. To assess the conservation of phenotypic and molecular features of the PDOs to their corresponding primary tissue, we performed immunohistochemical, gene expression and copy number alteration (CNA) analyses.

Results: We found that the PDOs maintained benign or tumor histological features in long-term cultures, evident by the presence or absence of cancer markers both at the protein and gene expression level. Low passage whole genome sequencing confirmed the conservation of high CNA tumor fraction in the tumor tissues and their PDOs. Preliminary gene expression profiling identified promising candidates significantly upregulated in tumor vs benign PDOs of high-risk patients, including known molecular pathways of tumor initiation, hypoxia and redox deregulation.

Conclusions: Our preliminary studies provide a strong basis for the establishment of a unique patient-derived pre-clinical biobank, which can be used to identify and functionally validate new biomarkers of high-risk prostate cancer; ultimately assessing their clinical relevance for prostate cancer disparities.

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