

Title: Human prostate chunkanoids give rise to AR+ cells to study cell-state dependent oncogenesis

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Background: Human prostate androgen receptor (AR)-positive luminal cells are understudied due to limitations in maintaining AR-dependent cells in vitro. Commonly used human prostate cancer models represent highly-mutated advanced disease states or rely on transformation of AR-low/negative basal cells with a combination of potent driver genes. Consequently, genetically defined models that retain AR expression and exhibit sensitivity to AR blockade remain limited. Such a system would be ideal to investigate the influence of disease initiating driver genes in AR-signaling dependent human prostate epithelial cells. In this study, we are defining how the epigenetic state of human prostate AR+ cells is shaped by distinct driver genes, as well as how cellular programs are reprogrammed during the transition from castration-sensitive to castration-resistant prostate cancer.

Methods: To date, we have established a growing set of patient-derived AR+ human prostate organoid models, engineered to express defined driver genes. Oncogene-expressing organoids can be continuously propagated in 3D culture for over a year without losing endogenous AR expression and reliance on AR-signaling for growth. We employed single-cell RNA sequencing to define oncogene-associated cell states and transcriptional programs. Proliferation assays and immunoblots have been used to define response to AR targeted therapies.

Results: This platform provides a malleable genetically defined system for studying PCa initiation and progression in AR+ hormone-naïve, castration-sensitive cells.

Conclusions: In conclusion, through improved methodology, we can now retain AR+ human prostate cells to investigate their response to disease-initiating driver genes, allowing us to understand for the first time how oncogenic-drivers reprogram AR dependent human prostate cells.

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