Patient-derived hormone naive prostate cancer organoids to test responsiveness to therapy

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Background: Genome sequencing and expression profiling have revealed the clonal heterogeneity within hormone naïve prostate cancer (HNPC) foci and across prostate cancer (PCa) patients. This heterogeneity translates into variegated responses to the same therapies. Androgen deprivation therapy (ADT) despite its effectiveness increases clonal heterogeneity, allows seeding between sites, and causes progression to castration resistant PCa (CRPC). Currently, therapies used to prevent progression to CRPC are examined in cell lines and mouse models, however, these models fail to mimic the complexities of human PCa, lack microenvironmental regulation and cause incongruity between preclinical and clinical studies. Recently, 3D culture of patient-derived cells has been used to model CRPC metastasis and generate mouse and human benign prostate organoids. Here, we utilized a novel organoid technology encompassing 3D culture of epithelial PCa cells with microenviromental stromal growth factors to generate and maintain HNPC organoids from both localized and metastatic HNPC and examine these organoids' responsiveness to therapy. These tissues were harvested from metastatic HNPC patients undergoing cytoreductive prostatectomy (clinicaltrial.gov#NCT02458716).

Methods: Cells from histopathologically-mapped foci from radical prostatectomy and metastatic lymph node specimens were isolated. Utilizing two-stage 3D cultures of epithelial cells with stromal derived growth factors, we generated normal and HNPC organoids with a high success rate. We are analyzing the genomic and phosphoproteomic profiles of organoids compared to corresponding original FFPE tissues, and examining biological responsiveness of organoids to ADT, AR-directed agents, PI3K-directed and docetaxel.

Results: Normal and HNPC organoid pairs were derived from 26 of 29 cases primary PC's. Analysis of a subset of these cases indicates that the organoids recreate the morphologic features of the parental tumor foci (self-organized glands with central E-Cad$^+$ cells, peripheral Vimentin$^+$ cells and a surrounding thick basement membrane), express AR and PSA. More importantly, the organoids shared some of the most prevalent genomic alterations associated with PC including TMRSS2-Erg, PTEN, RB and CHD1, and overexpression of Erg, BMI-1 and AR-Vs. Proliferation, cell viability and organoid-forming potential was variable in response to treatment and correlated with pathway activity determined by IHC in FFPE tissues.

Conclusions: We have established a systematic approach to derive 3D organoid cultures from HNPC tumor foci in the primary and LN metastasis. We have preliminary evidence that these organoids mirror the genomic alterations of the PCa foci in the patient and are biologically responsive to a variety of agents targeting key pathways of progression. To provide proof of concept, genomic profiling of a larger cohort of organoid cultures and parental PC foci to establish identity, as well as assessment of the biologic response to ongoing treatments in the patient is in progress. We expect to refine this system to test personalized treatments options for men with lethal metastatic HNPC.

Conflict of Interest: None

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