New approach to model genetically defined hormone-naïve castration-sensitive human prostate cancer

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Background: Understanding how disease-initiating factors influence dependence on androgen receptor (AR) signaling in human AR+ hormone-naïve, castration-sensitive cells is of utmost importance. However, nearly all genetically defined human prostate cancer initiating models arise from the transformation of basal cells, which lack endogenous AR or exhibit low AR signaling. An ideal model to define the influence of disease initiating driver genes in AR-signaling dependent cells would arise from the transformation of human epithelial cells expressing endogenous AR.

Methods: To date, we have established a growing set of human AR+ organoid models, some of which express one or more defined driver genes. Oncogene-expressing organoids can be continuously propagated in 3D culture for over a year without losing endogenous AR expression. Importantly, transformed organoids exhibit reliance on AR for growth, even after extended culture. Finally, the addition of secondary driver genes modulates response to AR blockade.

Results: We devised a new strategy to retain non-malignant AR+ hormone-naïve, castration-sensitive cells in 3D organoid culture from naïve human patient tissue in order to engineer them with defined driver genes and model disease initiation. We used proliferation assays and immunoblots to define our models in response to androgen receptor targeted therapies.

Conclusions: In conclusion, through improved methodology, by retaining AR+ human cells for cancer initiation in a defined genetic system, we are beginning to understand the factors that regulate castration-sensitive prostate cancer and the transition toward castration-resistance.

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