P28 In vitro prostate tissue generation using induced pluripotent stem cells and rodent seminal vesicle mesenchyme

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Introduction & Objectives: Prostate cancer (PCa) is one of the leading causes of death among men in developed countries. Most PCa research heavily relies on models that do not completely incorporate the complexity and variability of the disease. Cell lines generally do not represent the genetic variability of the disease and may acquire genetic lesions following prolonged culturing. Primary cells are not readily available to all researchers and have a limited lifespan in culture. Rodent models are expensive to produce and do not entirely recapitulate human PCa due to differences in tumorigenesis and prostate anatomy between humans and rodents. Although these models continue to provide insight for the disease, the inherent limitations prevent a complete understanding of prostate cancer. Recently, prostate organoids have emerged as an alternative model that eliminates some of the disadvantages of current PCa models. Since cells for organoid generation can come directly from patients, this model can incorporate the genetic diversity of PCa. Patient-derived organoids could allow for high-throughput testing of therapies and predict individual patient response to specific drugs. However, the process of prostate organoid generation using primary prostate tissue is currently inefficient. The objective of this research is to produce prostate organoids using an alternative method, namely using patient-derived induced pluripotent stem cells as the starting material.

Materials & Methods: To produce prostate organoids, we used induced pluripotent stem cells (iPSCs). The iPSCs were first differentiated to definitive endoderm. The definitive endoderm was then co-cultured in 3D conditions with inductive seminal vesicle mesenchyme (SVM) isolated from rats, which is known to induce prostate differentiation in vivo. The culture was supplemented with Clevers organoid media to further mature and maintain prostate tissue. Organoids that formed were then harvested and assessed for prostate-specific markers using immunofluorescence techniques.

Results: Co-culturing of iPSCs and SVM cells produced spheroid formation early on, which continued to grow with prolonged culturing. Higher concentrations of SVM resulted in greater numbers of structures forming, though increasing iPSC concentrations diminished spheroid formation. When spheroids formed, cells that are thought to comprise the mesenchymal component, migrated toward the spheroids and interacted with the structure. We have confirmed that the spheroids are solely derived from the human iPSCs and not the rat SVM through human mitochondrial staining. Expression of the luminal epithelial marker CK8/18 and prostate-specific markers NKX3.1, AR, and PSA have also been confirmed. Current work is focused on optimising the generation of prostate organoids using this method by varying cell concentrations and changing co-culture duration.