Preclinical Prostate Cancer Research

Subjects: Oncology

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We address the challenges of using primary cultures and patient-derived xenografts to study prostate cancer. We describe emerging approaches using primary prostate epithelial cells and prostate organoids and their genetic manipulation for disease modelling. Furthermore, the use of human prostate-derived induced pluripotent stem cells (iPSCs) is highlighted as a promising complimentary approach. Finally, we discuss the manipulation of iPSCs to generate ‘avatars’ for drug disease testing. Specifically, we describe how a conceptual advance through the creation of living biobanks of "genetically engineered cancers" that contain patient-specific driver mutations hold promise for personalised medicine.

Keywords: prostate cancer ; induced pluripotent stem cells ; organoids ; patient-derived xenografts ; primary culture ; cell lines ; preclinical model

1. Introduction

One of the key issues hampering the development of effective treatments for prostate cancer is the lack of suitable, tractable, and patient-specific in vitro models that accurately recapitulate this disease.

2. Emerging Approaches

2.1. Transformation of Primary Prostate Cells

In a seminal paper, it was shown that primary benign human basal prostate epithelium can initiate prostate cancer in immune-deficient mice and that the derived tumours realistically recreate histology of in situ human prostate cancer[1]. This has been the basis for an interesting strategy to overcome some of the problems of primary prostate cancer culture, where researchers can now transform easier to grow benign prostate epithelium to generate prostate cancer organoids[2]. These studies lay the platform for a new paradigm, where benign cells are converted into “designer” cancers harbouring specific mutations of interest. These can be repeatedly generated whilst faithfully maintaining the genotypes of interest avoiding the ever evolving subclonal progressions affecting long term culture of primary derived cancers[3]. Despite the promise of this “tumour engineering” approach there are limitations to maintaining even benign prostate epithelial cultures and a more ready supply of cells to manipulate are ideally required. In this respect, the emergence of easy to expand and immortalised iPSCs and the ability to differentiate these in the tissue type of interest offers a new way forward.

2.2. Prostate iDOs

Recently, a high throughput model of generating human prostate organoids from iPSCs has also been described, involving co-culturing iPSCs with rodent urogenital sinus mesenchyme (UGM). This simple differentiation protocol results in glandular structures in vitro that faithfully mimic prostate tissue histology and express key prostate markers such as AR, prostate specific homeobox protein NKX3.1 and secretory prostate specific antigen (PSA)[4]. This approach built on previous data showing the generation of prostate tissue in xenograft studies from ESCs[5]. Differentiation from iPSCs avoids many ethical and regulatory restrictions relating to ESCs and enable greater access to organoid generation to groups worldwide culture[6][7]. Previous in vitro human prostate organoid approaches, from either tissue-derived cells or ESCs, do not recreate the full breadth of in situ prostate differentiation as they do not contain neuroendocrine cells particularly relevant in light of emerging data showing that neuroendocrine differentiation drives treatment-resistant prostate cancer[8][9][10]. Additionally, it would be of interest to determine whether following maturation of prostate iDOs there is a switch to a somatic stem cell mode of homeostasis, identified by the presence of DLK1-enriched basal stem cells, to sustain long-term culture[11]. High-throughput iPSC-derived human prostate tissue generation provides unparalleled scope for in vitro disease modelling and drug discovery without the constraints of tissue accessibility and long-standing difficulties associated with primary culture.

2.3. Genome Editing Technology and Precision Medicine

Genome editing technology has emerged as an extremely powerful tool that can greatly advance organoid-based research for the development of better targeted therapies[12]. CRISPR-Cas9 genome editing induces double-stranded DNA breaks at specific loci adjacent to a protospacer-adjacent motif (PAM) using a complementary single-guide RNA sequence (sgRNA) and Cas9 endonuclease[13]. DNA repair then takes place by either non-homologous end joining, resulting in insertions/deletions (INDELs) or homology-directed repair with a donor template. In 2013, Schwank et al. reported the first successful therapeutic CRISPR-Cas9 gene editing in human tissue, by correcting the CFTR locus in intestinal organoids from patients with cystic fibrosis (CF), making CF treatment a possible reality[14]. Since then, CRISPR-Cas9 has further been used to reproduce genetic mutations that occur in cancers including prostate cancer. In 2017, for the first time, the use of CRISPR/Cas9 to create endogenous gene fusions in organoids was reported[15]. Mouse prostate organoids were modified to carry the TMPRSS2-ERG fusion, a genetic alteration present in more than 50% of prostate cancers that leads to high ERG expression driven from the androgen-responsive promoter of the TMPRSS2 gene[15][16][17]. Previously this fusion had been modelled by artificial ERG overexpression and studied in human prostate cancer cell lines and mouse models, but this approach for the first time allows investigation of its effect in a wildtype background[15][18].

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