Defining Prostate Stem Cells: Clues to Improving Prostate Cancer Treatment

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Introduction
Prostate cancer is one of the leading causes of death in Australian men. Despite the clinical significance of this disease, our understanding of the cellular origins of prostate cancer and the cells within tumours that propagate growth and survival are relatively limited. Many laboratories have sought to isolate prostate stem cells to understand their hormone-dependent and -independent growth and differentiation, with the hope that this will ultimately lead to the development of new therapies for prostate cancer. Recent evidence supports the concept that there are multiple cells from which prostate cancer can arise, and that features of the molecular signature of normal stem cells can be detected in prostate cancer tissues. More importantly, there are regenerating cells within tumours that are resistant to hormonal therapy and continue to propagate tumour progression. One of the most important challenges in cancer biology is to understand the cell populations that drive tumour growth and how they can be effectively targeted.

Epithelial Stem Cells in the Prostate
The prostate gland is a relatively slow growing, androgen-dependent organ. In normal prostatic epithelium, there are three primary cell types: luminal secretory cells, the underlying basal support cells, and rare neuroendocrine cells (Fig. 1). Lineage tracing studies consistently demonstrate that prostate basal cells and luminal cells are independently sustained in adult mice, but may give rise to other cell types under certain conditions (1–3). The advances in 3D organoid culture have provided conditions under which multiple prostate cell types can survive and proliferate (4,5). Studies using this approach have provided further support of the existence of respective multipotent stem cells or progenitors within both the basal and luminal cell lineages (3,6,7). The discovery of multiple stem cells in normal tissue has expanded the intrigue surrounding the cell(s) of origin of prostate cancer.

Cells of Origin of Prostate Cancer
Prostate adenocarcinomas represent the vast majority of prostate cancer and are composed of cells with a luminal phenotype, largely devoid of basal cells. Thus it was long presumed that prostate cancer is derived from a luminal cell within the normal epithelium. However, it is clear that basal cells also can be genetically transformed to give rise to prostate tumours (3,8,9). In fact, comprehensive molecular studies on sorted populations of human prostate cancer cells showed that the transcriptional profiles of aggressive forms of prostate cancer share common features with human basal cells. Specifically, metastatic human prostate cancer cells showed an activation of stem-like genes specifically associated with a set of genes targeted by the E2F family of transcription factors (10). Nevertheless, a rate-limiting step for basal cells in the initiation of prostate cancer is that they must differentiate into luminal cells, demonstrating the importance of the luminal phenotype in prostate cancer progression.

As such, the recent focus in the field has been on subpopulations of luminal cells in the normal prostate gland that may contribute to cancer initiation and propagation. Luminal cells have been traditionally regarded as terminally differentiated cells with secretory functions and thus were unlikely to possess stem/progenitor activity. However, a recent study identified a distinct population of luminal epithelial progenitor cells in mice, marked by Sca-1 expression, that can propagate multilineage organoids in culture and in an in vivo prostate regeneration assay (11). Importantly, this luminal cell population can survive androgen deprivation, one of the hallmarks of prostatic stem cells. The study provides new evidence that a Sca1+ fraction of prostatic luminal cells may be the preferred cell of origin of prostate cancer, although an equivalent human population is yet to be identified.

Stem/Progenitor Cells in Prostate Cancer
Androgen-deprivation therapy is the mainstay treatment for advanced prostate cancer and relies on the exquisite sensitivity of the prostate to androgens. Clinically, most tumours respond and up to 95% of the cancer bulk is removed. However, tumour regrowth is inevitable, leading to a lethal form of the disease referred to as castration-resistant prostate cancer (Fig. 1). The scientific goal is to identify the prostate cancer cells that survive androgen-deprivation therapy, because this population offers the potential for disease progression. The ability to eliminate these cells therapeutically will lead to increased survival for men with prostate cancer.

Using a human patient-derived xenograft model (12), our laboratory identified a subpopulation of luminal prostate cancer cells that survive androgen withdrawal in vivo (13). The subset of human cancer cells that survive in the androgen-depleted environment show stem-like features including expression of the stem cell markers Oct-4, Sox2, NANOG and ALDH1, as well as the ability to actively repopulate tumours upon androgen readministration. The demonstration that a population of ‘castrate-tolerant’ cancer cells pre-exist in hormone-dependent prostate cancer, prior to hormonal treatment, was a major discovery. The finding now provides an opportunity to determine the mechanisms by which they survive and continue to propagate tumour progression.
Complementary studies in a Pten/TP53-null mouse model of prostate cancer revealed a luminal progenitor population in prostate tumours (14). Agarwal and colleagues used organoid cultures to demonstrate tumour-initiating activity that exists in both the luminal and basal fractions. Using FACS cell sorting strategies, two distinct PROM1+ mouse luminal progenitors were identified; a minor population within mouse tumours that gives rise to multilineage organoids (multipotent progenitors) and a major population producing luminal-only organoids (luminal committed progenitors). Similar to the findings from castration of human patient-derived xenografts, a significant proportion of mouse luminal progenitor cells survived in vivo castration. A comparison of the molecular features that are shared between human and mouse luminal progenitor cells within tumours may reveal key signalling pathways that offer new therapeutic potential.

A major advance in the field was the adaptation of the mouse 3D organoid culture technique to human prostate cancer tissues. Gao and colleagues successfully established long-term (more than six months) cultures of patient-derived prostate tumour organoids from dissociated cells taken from metastatic biopsy specimens and circulating tumour cells (4). This technique is relatively efficient for advanced castrate-resistant metastatic prostate cancer specimens, where continuously propagated organoid lines were established from metastatic biopsies at a rate of 15%–20%. Whilst this method has proven successful for advanced tumours, adaptation to organ-confined, hormone-dependent tumours is yet to be optimised. Nonetheless, the approach will provide a reliable in vitro culture system for high throughput drug screening of clinical samples with significant molecular and phenotypic heterogeneity. Advances in fractionating cell populations from within tumours will also generate new knowledge about the role of stem cells in propagating prostate cancer, and provide a new approach for testing novel therapeutic agents.

Conclusions and Future Directions

The prostate epithelial hierarchy is complex, with multiple stem/progenitor cells residing in both the basal and luminal lineages. The nature of the perturbations in these stem cells remains largely unknown, and therefore the implications for disease are still not clear. Despite the best efforts of researchers, the molecular profiles of prostate epithelial stem cells have not been definitively characterised at the single cell level. In prostate cancer, there is an advanced castrate-resistant metastatic prostate cancer.

Fig. 1. In the normal prostate gland, the epithelium is composed of luminal secretory cells (blue), basal cells (red) and rare neuroendocrine cells (green). Multipotent stem cells have been reported in basal and luminal populations. In addition, each of these populations has the potential to give rise to prostate adenocarcinomas, thereby acting as cells of origin of prostate cancer. Recent advances in studying human prostate cancer using patient-derived xenografts or patient-derived organoids have revealed key subpopulations of cancer cells that can propagate tumours in vivo and in vitro. Using these approaches, a subset of prostate cancer cells (red nuclei) have been identified that are therapy resistant (i.e. survive androgen withdrawal therapy) and repopulate tumours given growth stimuli. These ‘castrate-tolerant’ prostate cancer cells are the focus of new therapeutic targets that may be effective in preventing progression to lethal prostate cancer.
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important subpopulation of tumour cells that can survive androgen withdrawal and potentially lead to incurable prostate cancer. Until now, a deeper understanding of the biology of these castrate-tolerant cells has been hindered by a lack of biomarkers and cell surface markers that can be used to prospectively isolate them from human prostate cancer tissue and potentially apply them to novel platforms such as patient-derived organoids. Whether or not the cells that survive castration are bona fide stem cells that exist within tumours, or a transient population that is induced in response to androgen withdrawal is yet to be determined. Nonetheless, this subpopulation of cancer cells should be considered as a cellular target for prostate cancer therapeutics, perhaps in combination with androgen-deprivation therapy to maximise the control of cancer progression.

References