

Stem cell repertoire in the prostate epithelium

Abstract

Over the past two decades, the roles of stem cells have been studied in the contexts of developmental biology, tissue engineering, cancer therapy, neurodegenerative disorders and what not! Right since the discovery of prostate specific adult stem cells or stem-like cells in both stromal and epithelial compartments, their participation in prostate development and prostatic pathologies (like benign prostatic hyperplasia and prostate cancer) are being thoroughly investigated. The present mini-review summarizes the ins and outs of the histological organization of acinar prostate and prostate cancer, keeping the prostate-specific epithelial stem cells on the backdrop.

Keywords: prostate stem cell, adult stem cell, prostate cancer stem cell, targeted therapy

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Introduction

Based on the proliferative heterogeneity in both the human and mice prostate gland, a very small population of basal cells located on the basement membrane in the prostate glandular epithelium was recognized as prostate epithelial stem cells or prostate stem cells.¹ Mesenchymal stem cells are also present in the prostate stromal compartment. In this review, we invariably use prostate stem cells to indicate epithelial stem cells. Notwithstanding being few in number, they reserve the 'keystone' position among the prostatic epithelial cells owing to their potential for self-renewal and differentiation.^{2,3} With the growing popularity of the hierarchical model of solid tumorigenesis, prostate cancer stem cells are being suspected as a derivative of the resident stem cells because of a considerable overlap of the surface markers.⁴

Origin of cell lineages

Normal adult stem cells are characterized by their unusual ability to self-renew and the ability to differentiate into various other cell types as well.⁵ Mature prostatic epithelium is composed of luminal cells, basal cells, neuroendocrine cells, and transit-amplifying (TA) cells.³ Luminal cells are the most differentiated members of prostatic epithelium. They constitute the lining of glandular acini and secrete prostate specific antigen (PSA) and prostatic acid phosphatase (PAP).^{2,6} Basal cells are sandwiched between the secretory luminal cells and the underlying basement membrane. In a histological section they appear polygonal in shape with large irregular shaped nuclei. They lack secretory vesicles in their cytoplasm.³ TA cells that localize in both luminal and basal layers express both the basal and luminal cell surface markers.⁷ Highly specialized neuroendocrine cells possess less than 1% share of the total epithelial cell population and are characterized by the expression of neurotransmitters like serotonin, bombesin etc.^{8,9}

Scientists grew interest in adult stem cell (ASC) research since the discovery of hematopoietic stem cells and mesenchymal stem cells in bone marrow.^{10,11} Relatively undifferentiated cells that are found among the differentiated cells in a tissue or organ, can self-

renew themselves, and can differentiate into some or all of the major specialized cell types are called adult or somatic stem cells.⁵ Quest for such an ASC in prostate continued until only in 2008 the wonderful *in vivo* implantation experiment by Gao and colleagues identified a cell (Lin⁻/Sca-1⁺/CD133⁺/CD44⁺/CD117⁺) capable of generating a whole new prostate.¹² Not much before this experiment, in 2005 Long and Peehl groups separately identified a stem-like population in the basal layer as the responsible faculty for the development of prostatic epithelium.^{13,14} Lee *et al.*¹⁵ reported seven basal cell subpopulations among which p63⁺/K5⁺/K14⁻ cells show the highest stem-like phenotype.¹⁵ Goldstein *et al.*¹⁶ on the other hand, classified basal cell population into only basal cells and stem-like basal cells based on the differential expression of tumor-associated calcium signal transducer 2 (Trop2).¹⁶

Based on various experimental evidences, different models have been devised to explain the routes of differentiation of multipotent prostate stem cells into other epithelial cell types:

- Linear differentiation model,
- Bidirectional differentiation model, and
- Independent lineage model.^{3,17,18}

All these hypothetical models are schematically explained in Figure 1.

Prostate cancer

Since the discovery of cancer stem cells (CSCs) in the year 1997 by Bonnet and Dick in leukemia, they have been shown to exist in several other types of solid tumors including colon, breast, brain, and skin.^{19,20} Cancer stem cells hold a premier position in a tumor cell population in that they only possess the indefinite clonogenic ability and differentiation potential. Prominin 1 (CD133) expression characterizes the stem-like cells ($\alpha 2\beta 1$ and high clonogenic property) in adult human prostate.⁴ CD133 expression also marks the prostate cancer stem cells.²¹ Transcriptomic profiling data also exhibited that an elevated basal stem cell signature indicates the aggressiveness of prostate cancer.²² Flow cytometry and fluorescent

in situ hybridization localized prostate stem cell antigen (PSCA) expression in normal prostate to the basal cell epithelium, the putative stem cell compartment of the prostate. This surface marker was found to be over-expressed in prostatic intraepithelial neoplasia, and androgen-dependent and androgen-independent tumors.²³ Xin and his colleagues demonstrated that the murine prostate Sca-1+ stem cells

can give rise to prostatic intraepithelial lesions following 8-weeks of incubation in vivo.²⁴ Tumor tissue derived from normal prostate cells infected with lentivirus containing AKT has been shown to possess a big pool of Sca-1 marked cells. Similar phenomenon is also evident in tumors from transgenic murine model expressing the c-myc oncogene or having a conditional knockout of PTEN.²⁵

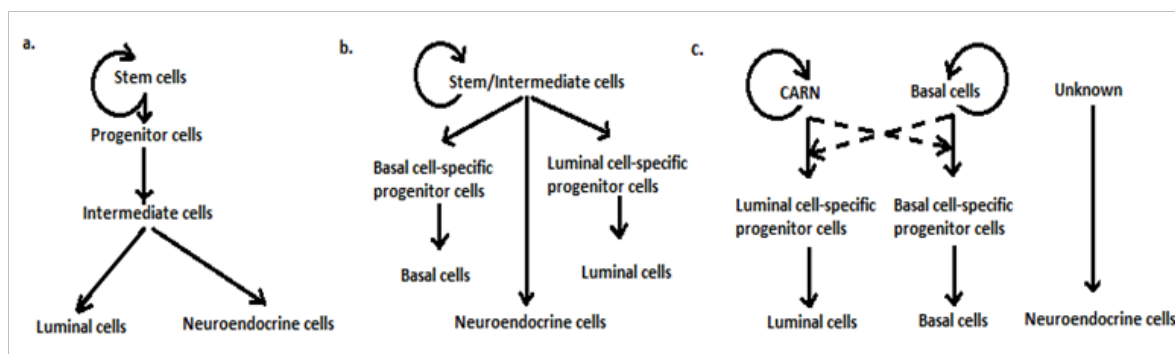


Figure 1 Schematic representation of three hypothetical models of prostate stem cell differentiation pathway. a: Linear differentiation model: multipotent stem cells are localized in the basal compartment. These cells differentiate into intermediate/TA cells which further become either luminal or neuroendocrine cells; b: Bidirectional differentiation model: According to this model, intermediate cells expressing both the basal and luminal cell markers are thought to have stem-like properties. These cells differentiate into basal or luminal cells via lineage-specific progenitors; c: Independent lineage model: As per this model, both the basal and luminal compartments reserve stem cells. Castrate-resistant Nkx3.1-expressing cells (CARN) and basal stem cells independently give rise to luminal and basal cells. Either of these differentiation pathways can converge with the opposing lineage (indicated by dotted lines).

These observations led the biologists to put forth a hypothesis that accuses the normal prostate stem cells to give birth to prostate cancer stem cells. Prostate stem cells which normally differentiate into CD24+ TA cells, turn into cancer stem cells upon acquiring and accumulating mutations in various oncogenes and tumor-suppressor genes.² On the other side of the coin, lineage tracing and lineage specific gene targeting experiments have indicated that both basal and luminal compartments of prostatic epithelia are equipotent of developing prostate cancer, though the disease initiated from the basal cells had prolonged latency and required basal-luminal transdifferentiation.²⁶ Being AR-negative prostate basal stem cells are insensitive to androgen.^{2,3} Hence, these cells are being considered as the ‘culprits’ and possible therapeutic targets for androgen-insensitive high-grade prostate cancer. A recent study has found that the local prolactin and its downstream target Stat5 cause tumorigenic alterations in basal stem-like cell population in the prostate, arousing a new hope for cancer treatment.²⁷ In summary, prostatic epithelial cells seem to have an overwhelming plasticity. So, identifying one specific cell population as the cradle of prostate cancer and targeting them is apparently difficult.

Conclusion

The roles of prostate epithelial stem cells and their interactions with other cells & surrounding niche in acinar development, branching morphogenesis and cancer development, progression & relapse need to be dissected with utter sincerity. These will not just help us to better understand the prostate and other prostate-like tubuloalveolar glands whose development and growth are hormone-induced, but also lead to the advent of a more reliable targeted therapy against cancer.

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Conflict of interests

Authors declare that there is no conflict of interests.

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