A plethora of progenitors in the post-natal prostate

Andrew S. Goldstein & Owen N. Witte

The prostate gland is of great interest due to the prevalence of prostate cancer worldwide. Understanding its cellular hierarchy might provide insights into both the cells of origin for cancer and the tumour cells that maintain the disease and resist treatment. Several distinct approaches have been taken to define primitive stem-like cells in the mouse prostate including tissue regeneration on transplantation, castration followed by androgen-mediated regeneration and genetic lineage tracing. These studies have led to the identification

of basal stem cells, luminal stem cells and unipotent basal and luminal progenitor cells [1–4]. In a recently published issue of *Nature Cell Biology*, Blanpain and colleagues showed the use of several promoters to amass the largest lineage tracing effort so far in the mouse prostate, adding complexity to the epithelial hierarchy in the mouse prostate [5].

Multipotent basal stem cell existence

It has been debated whether all epithelial cell types in the prostate, including the

rare neuroendocrine cells, originate from a common progenitor. In 2008, we demonstrated that basal stem cells expressing high levels of CD49f, Sca-1 and Trop2 isolated from a β -actin-DsRed transgenic mouse could regenerate glands containing basal, luminal and neuroendocrine cells, which all contained the label of the initial purified donor cell on transplantation into immune-deficient mice [6]. By following the progeny of labelled basal cells using the keratin 5 (K5) and keratin 14 (K14) promoters, Blanpain and co-workers have demonstrated that basal cells give rise to basal, luminal and neuroendocrine cells [5]. Although emerging data from epithelial tissues including the mammary gland, skin and sweat glands suggest that transplantation assays and lineage tracing do not yield identical results [7,8], here two approaches were used to confirm the presence of multipotent basal stem cells that give rise to all three lineages. The *in vivo* data support a model in which multipotent basal stem cells are located at the top of the epithelial hierarchy in the mouse prostate (Fig 1).

Basal compartment heterogeneity

Whilst lineage-tracing studies reveal the presence of basal stem cells, clonality experiments suggest that the basal layer is functionally heterogeneous. By labelling and following the fate of single basal cells separated from each other by approximately ten cells, Blanpain and colleagues have demonstrated that a subset of these cells preferentially give rise to similarly labelled basal cells. A fraction of individually labelled basal cells generate labelled luminal cells, whilst other labelled basal cells generate clones containing labelled basal and luminal cells. Interestingly, tracing with K5 and K14 promoters generates

Fig 1 | Genetic labelling of epithelial cells in the post-natal mouse prostate allows lineage tracing to determine the progeny of basal or luminal cells. These results suggest that the prostate epithelial hierarchy contains multipotent basal stem cells and several intermediate progenitor cells.

different results, with a higher frequency of labelled luminal cells one month after labelling K14⁺ cells than after labelling K5⁺ cells. These results suggest that K14⁺ basal cells are more primitive, and that K14⁺ basal cells are preferentially committed to the basal lineage. It is unclear if there are truly distinct basal-committed, luminal-committed or bipotent basal progenitors. Further markers are necessary to distinguish these subsets and functionally compare their developmental potential, by using lineage-tracing or transplantation-based approaches. Such heterogeneity and lineage bias within a population was demonstrated in the haematopoietic stem cell compartment, with subsets that are predisposed to differentiation towards a myeloid or lymphoid fate [9].

Progenitor cells in cancer

It is interesting to determine whether these different progenitors can serve as cells of origin for prostate cancer. As the predominant histological subtype of prostate cancer acinar-type adenocarcinoma has a luminal phenotype, any cell type capable of generating a luminal phenotype under normal conditions is a candidate for generating luminal tumours during transformation. Both basal and luminal cells have been previously demonstrated to differentiate into luminal cells and initiate murine prostate cancer [1,3,4]. The study from the Blanpain lab suggests that several progenitors are capable of differentiation into luminal cells. Long-term lineage

tracing would determine the cell types that survive long enough to acquire sufficient genetic hits to initiate cancer. It is also important to determine whether there are cancer analogues for these progenitors that could potentially serve as tumour-propagating cells, or as populations contributing to long-term tumour maintenance and castration resistance. Determining the levels of androgen receptor and the response to castration for each normal population might be informative.

Relevance to human prostate

The traditional methods used for genetic lineage tracing in the mouse prostate have not been reported in human prostate tissue. As an alternative strategy, we have isolated highly enriched epithelial subsets from freshly isolated human prostate tissue, subjected them to lentiviral transduction and performed *in vivo* tissue regeneration. We have shown that basal cells marked with a red fluorescent protein regenerate benign human prostate glands containing labelled basal and luminal epithelium [10]. In response to oncogenic stimulation, basal stem cells initiate prostate cancer with the expression of fluorescent proteins and oncogenes in luminal tumour cells that were originally introduced into basal cells [10]. Our findings demonstrate that basal cells in the human prostate are multipotent and can initiate prostate cancer. It is probable that other progenitor cells exist in the human prostate and might contribute to human prostate cancer initiation

and progression, which will require future identification and functional testing.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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