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Cell types of origin for prostate cancer

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Analyses of cell types of origin for prostate cancer should result in new insights into mechanisms of tumor initiation, and may lead to improved prognosis and selection of appropriate therapies. Here, we review studies using a range of methodologies to investigate the cell of origin for mouse and human prostate cancer. Notably, analyses using tissue recombination assays support basal epithelial cells as a cell of origin, whereas *in vivo* lineage-tracing studies in genetically-engineered mice implicate luminal cells. We describe how these results can be potentially reconciled by a conceptual distinction between cells of origin and cells of mutation, and outline how new experimental approaches can address the potential relationship between cell types of origin and disease outcome.

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The cell of origin is defined as the cell type within a normal tissue that undergoes oncogenic transformation to initiate tumor formation [1–3]. In particular, the cell of origin model proposes that different cell types of origin give rise to tumors of distinct subtypes, which have specific histopathological and/or molecular features that correlate with treatment response and patient outcome. If so, identification of cell types of origin might be highly relevant for disease prognosis and might guide effective therapy.

In the case of prostate cancer, the cell of origin model is of particular interest since patients who present with low to intermediate grade primary tumors can have widely different outcomes, either having indolent prostate cancer that can be monitored without therapeutic intervention, or highly aggressive disease that requires treatment. Nonetheless, it has been remarkably difficult to categorize histopathological or molecular subtypes of prostate cancer that differ in patient outcomes [4,5]. Thus, if the cell of origin model applies to prostate cancer, studies of the cell of origin may be highly advantageous by leading to the identification of biomarkers that may have prognostic significance, or may reduce overtreatment and guide appropriate therapy [6,7].

The prostate epithelium consists of two major epithelial cell types, corresponding to the luminal tall columnar epithelial cells that produce secretory proteins, and to the adjacent basal cells, together with rare neuroendocrine cells [4,8]. Notably, these three epithelial cell types are believed to originate from multipotent basal progenitors during prostate organogenesis [9–12]. During cancer progression, however, the precursor state known as prostatic intraepithelial neoplasia (PIN) has reduced basal cell numbers, while prostate adenocarcinoma has a luminal phenotype and is deficient in basal cells [4]. Thus, the luminal phenotype of prostate adenocarcinoma implies either that luminal cells correspond to a cell of origin or that a basal cell of origin results in transformed cells that acquire luminal characteristics. (The origin of small cell neuroendocrine tumors as well as other rare prostate cancer variants will not be discussed here.)

Experimental approaches used to investigate the cell of origin for prostate cancer include: (a) descriptive studies of early tumor formation to identify likely cells of origin; (b) tissue recombination assays in which explanted epithelial cells are subjected to oncogenic events and placed in grafts together with embryonic urogenital sinus mesenchyme to promote graft growth; (c) analyses of tumor initiation in three-dimensional organoid culture; and (d) lineage-tracing using cell type-specific inducible promoters in genetically-engineered mouse (GEM) models. These methods can also be combined and further modified to explore related issues, such as the role of the tissue microenvironment on the cell of origin.

Here, we review the current status of the cell of origin model for prostate cancer, and discuss studies using mouse as well as human models. We also present an interpretation that can potentially reconcile several of the apparently discordant findings in the published literature.

Descriptive studies of the cell of origin

Descriptive approaches to examine the cell of origin have been employed in both GEM models as well in studies of human prostate cancer. In particular, studies of GEM models have examined cellular proliferation in PIN lesions as a clue to identify likely cells of origin. Thus, analyses of early hyperplastic lesions of prostate-specific antigen (PSA)-*Cre*; *Pten*$^{flox/flox}$ mice implicated luminal cells as the likely origin of these lesions [13]. However, other analyses have focused on GEM mice in which *Pten* is deleted using the *PB-Cre4* transgene, which uses an artificial promoter based on that for the secretory protein Probasin [14], but drives Cre-mediated recombination in both luminal and basal cells [15]. These studies concluded that basal cells were likely to serve as the cell of origin in *PB-Cre4*; *Pten*$^{flox/flox}$ mice [15].

In studies of human prostate cancer, cytological analyses of PIN lesions have suggested that mutational events that are believed to occur early in prostate tumor initiation and progression occur in luminal cells, including telomere elongation and c-Myc upregulation [16,17]. Further evidence supporting a luminal origin of human prostate tumors is provided by the *TMPRSS2-ERG* chromosomal rearrangement, which is an early event that occurs in approximately 50% of prostate tumors [18–20]. The occurrence of this rearrangement is driven by induced chromosomal proximity through AR binding, and thus is likely to occur in luminal cells, which express AR at high levels [21–23]. In contrast, retrospective clonal analyses of cells with mitochondrial DNA mutations in normal human prostate epithelium as well as PIN lesions support a basal localization of stem cell activity [24,25], as well as a basal cell of origin [25]. Although informative, all of these approaches are correlative, and need to be complemented by functional studies.

Cell of origin analyses in tissue recombination assays

A key functional approach to investigate the cell of origin for prostate cancer takes advantage of a tissue recombination methodology initially developed to study epithelial–mesenchymal interactions, with subsequent modifications [26,27]. In this assay, prostate tissue is enzymatically dissociated, followed by flow sorting to isolate the desired epithelial population. The resulting epithelial cells are then combined with urogenital mesenchyme cells in a collagen gel, and transplanted into immunodeficient recipients, usually as a renal graft. Multiple laboratories have used variations of this tissue recombination approach to investigate the stem/progenitor potential of prostate epithelial cell types [28–33,34••,35•]. In particular, this assay has been used to show that mouse prostate basal cells can generate all three prostate epithelial cell types [32,34••].

Several studies have used tissue recombination assays to evaluate whether oncogenic insults in explanted luminal or basal epithelial cells can induce prostate cancer. In the mouse prostate, tissue recombination analyses showed that lentiviral-mediated overexpression of Erg or activated Akt in Lin^{-}Sca-1^{+}CD49^{hi} basal cells resulted in PIN lesions, while co-activation of Akt and androgen receptor (AR) signaling gave rise to adenocarcinoma [36]. For the human prostate, naïve benign basal and luminal epithelial cells have been isolated from clinical specimens, and used for lentiviral-mediated overexpression and tissue recombination assays [37]. These studies showed that co-expression of activated AKT and ERG in human basal cells resulted in PIN lesions in grafts, whereas co-expression of AKT, ERG, and AR generated adenocarcinoma [37]. In addition, expression of MYC and activated AKT in human basal cells resulted in grafts containing tumors with adenocarcinoma as well as squamous phenotypes [38•]. A basal cell of origin has also been supported in experimental paradigms that do not involve oncogene expression, by combining cells expressing basal markers isolated from the human benign BPH-1 cell line with cancer-associated fibroblasts, or with urogenital mesenchyme followed by treatment with testosterone and 17β-estradiol in a hormonal carcinogenesis paradigm [39]. In each case, oncogenic transformation of basal cells in tissue recombination assays led to tumors with luminal phenotypes [36,37,38•], suggesting that luminal differentiation from basal cells occurs at an early step of tumor initiation. Notably, both mouse and human studies found that only prostate basal cells could initiate tumorigenesis, whereas no tumors formed from grafted luminal cells.

However, there are important limitations of the tissue recombination approach that are relevant for interpretation of published findings. First, this methodology utilizes transplantation of dissociated cells into immunodeficient mice, and therefore tumor development proceeds in the absence of a functional immune system as well as an intact tissue microenvironment. Secondly, normal prostate basal cells can display significant plasticity by acquiring facultative progenitor properties and giving rise to luminal progeny after their explant and recombination with embryonic urogenital mesenchyme [30,32,34••,36], which is known to have reprogramming properties [40]. Finally, prostate luminal cells are highly susceptible to cell death due to anoikis, which is induced by lack of appropriate contact with the extracellular matrix or neighboring cells [41], and thus their survival is likely to be strongly compromised during the tissue recombination procedure.

Cell of origin analyses in organoid models

To date, it has been unclear whether the failure to observe transformation of prostate luminal cells in tissue recombination assays might be due to their inability to survive after tissue dissociation. To overcome this limitation, recent work has led to the development of explant culture systems that can support the survival and growth