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Prostate cancer cell heterogeneity and plasticity: Insights from studies of genetically-engineered mouse models

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Abstract

Although prostate adenocarcinoma lacks distinguishable histopathological subtypes, prostate cancer displays significant inter- and intratumor heterogeneity at the molecular level and with respect to disease prognosis and treatment response. In principle, understanding the basis for prostate cancer heterogeneity can help distinguish aggressive from indolent disease, and help overcome castration-resistance in advanced prostate cancer. In this review, we will discuss recent advances in understanding the cell types of origin, putative cancer stem cells, and tumor plasticity in prostate cancer, focusing on insights from studies of genetically engineered mouse models (GEMMs). We will also outline future directions for investigating tumor heterogeneity using mouse models of prostate cancer.

Keywords

cell of origin; cancer stem cell; lineage plasticity; castration-resistance; genetically engineered mouse model; tumor heterogeneity

1. Introduction

Unlike most other epithelial tumors, prostate cancer lacks distinguishable histopathological subtypes. Almost all prostate cancers are acinar adenocarcinomas, whereas histological variants such as ductal adenocarcinoma, basal cell carcinoma, and neuroendocrine prostate cancer are rare [1, 2]. Nonetheless, prostate adenocarcinoma displays significant inter- and intratumor heterogeneity at the genomic level [3–10], and can have significant differences in disease severity. Notably, patients with low- to intermediate-grade localized primary prostate cancer can have widely different outcomes, ranging from indolent to highly aggressive disease [11, 12].

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Competing interests
Nothing to declare

Since prostate cancer initially relies on ligand-mediated signaling through androgen receptor (AR) for tumor growth, androgen deprivation has been a mainstay of prostate cancer treatment [13, 14]. Although androgen deprivation therapy results in cancer regression, tumors frequently recur through restoration of AR signaling by a variety of molecular mechanisms, including de-regulation of the AR signaling pathway or activation of alternative signaling pathways, resulting in castration-resistant prostate cancer (CRPC) [14]. In recent years, CRPC has been effectively treated by second-generation anti-androgens such as abiraterone and enzalutamide [14, 15]. However, the extent and duration of response are variable, with many tumors developing lineage plasticity and AR-negative phenotypes, including aggressive neuroendocrine prostate cancers (NEPC) that progress to lethal disease [15]. Notably, genomic analyses have revealed that CRPC displays a high degree of inter- and intratumor heterogeneity [9, 10, 16–18]. Thus, a better understanding of the mechanisms that generate inter- and intratumor heterogeneity could help distinguish aggressive from indolent disease and inhibit emergence of castration-resistance.

The origins of inter- and intratumor cancer heterogeneity can potentially be explained by the “cell of origin” and “cancer stem cell” models, respectively. The cell of origin model proposes that differences in the normal cell type that undergoes oncogenic transformation give rise to distinct tumor subtypes that differ in histopathological or molecular properties as well as treatment response or disease outcome (Fig. 1A) [19–22]. However, the relevance of this model to prostate cancer has been unclear since it has been difficult to class prostate adenocarcinoma into distinct tumor subtypes at either the histopathological or molecular level [23]. Furthermore, until recently it has been unclear whether there is considerable cell type heterogeneity in the normal prostate epithelium.

The cancer stem cell model (Fig. 1B) posits that tumor cells are organized in a hierarchy of cancer stem cells and nontumorigenic cells to generate tumor heterogeneity, thereby accounting for progression and treatment response [22, 24–26]. While considerable evidence supporting the cancer stem cell model exists in hematological malignancies, this model is much more controversial in solid tumors such as prostate. Moreover, recent studies using lineage-tracing in GEMMs of various epithelial tumors have also shown that nontumorigenic cells can display lineage plasticity and acquire properties of stemness or transdifferentiate to other types of nontumorigenic cells in response to treatment or signals from the tumor microenvironment (Fig. 1C), further complicating analyses of putative cancer stem cells [24, 26, 27].

In the review, we will discuss recent advances in understanding prostate cancer heterogeneity and the emergence of castration resistance through the lens of the cell of origin and cancer stem cell models. In particular, we will focus on progress and insights from studies of GEMMs for prostate cancer, and outline directions for future research.

2. Epithelial heterogeneity and plasticity in the normal prostate

The prostate is a male sex accessory gland that produces and secretes fluids that contribute to the ejaculate, and thereby enhances male fertility. In men, the prostate is a walnut-sized tissue surrounding the urethra at the base of the bladder, containing a network of

branching ducts with a zonal architecture, corresponding to central, periurethral transition and peripheral zones [28, 29]. In contrast, the mouse prostate consists of multiple lobes that have distinct patterns of ductal branching and histological appearance [30, 31]. Despite these anatomical differences, recent single-cell RNA-sequencing analyses have indicated the conservation of cell populations between the mouse and human prostate [32, 33]. In particular, the mouse lateral lobe is most similar to the human peripheral zone, which harbors the majority of human prostate cancers [33, 34].

In both mouse and human, the prostate contains a pseudostratified epithelium that is composed of three primary cell types, corresponding to luminal cells, basal cells, and rare neuroendocrine cells [23, 35]. Lineage-tracing studies *in vivo* have shown that differentiated luminal and basal cells are largely maintained by unipotent progenitors during prostate homeostasis [36–38]. Similar conclusions have been provided by lineage reconstruction analyses using patterns of mitochondrial mutations and genome-wide spontaneous somatic mutations in human prostate [39–42]. Interestingly, a recent study has reported an expansion of luminal progenitor cells in the aging mouse and human prostate, raising the possibility that microenvironmental cues may modulate luminal differentiation during aging [43]. During organogenesis, however, both basal and luminal cells can display progenitor features. Bipotent basal progenitors can be detected from birth until approximately four weeks of age [44–46], whereas bipotent luminal progenitors are more transient and are only detectable in the first week postnatally [47]. Similarly, there is evidence for both bipotent basal and luminal progenitors contributing to androgen-mediated regeneration of the regressed prostate following castration [48–54].

Recent single-cell RNA-sequencing studies have demonstrated that luminal cells are heterogenous in both the mouse and human prostate [32, 33, 55–58]; there is also some reported evidence for heterogeneity in the basal population [53]. In the mouse, there is heterogeneity along the proximal-distal axis, with more distal luminal cells displaying the tall columnar secretory morphology typically associated with the luminal phenotype, and the proximal luminal cells displaying a more cuboidal non-secretory phenotype [32, 33, 57, 58] (Fig. 2). These distinct phenotypes are also associated with different progenitor potential in *ex vivo* assays, as the proximal luminal cells have increased organoid formation and grafting efficiency [32, 33, 57, 58]. Furthermore, these different luminal populations also appear to be conserved in the benign human prostate [32, 33].

In the adult mouse prostate, both basal and luminal cells can exhibit considerable plasticity in specific physiological contexts. Notably, basal-to-luminal differentiation can occur in contexts of tissue repair following epithelial damage or inflammation, as well as in *ex vivo* experimental assays involving their isolation from dissociated tissue (Fig. 3). Following cell death of luminal cells induced by deletion of E-cadherin, basal cells can differentiate into luminal cells to repair the prostate epithelium [59]. Similarly, in a mouse model of bacterial prostatitis, tissue damage also triggered basal-to-luminal differentiation [60]. Plasticity can also be observed in luminal cells, as distal luminal cells can acquire a more proximal progenitor-like state after castration, and can regenerate the distal luminal compartment after androgen re-administration [32]. Therefore, the potential plasticity of basal and luminal cells as well as their progenitor capabilities should be considered when investigating the

heterogeneity of prostate cancer, particularly with respect to the cell of origin and cancer stem cell models, as described below.

3. Cell types of origin for prostate cancer

The cell types of origin for prostate cancer have been investigated extensively using genetically-engineered mouse models [19, 23, 61–63]. Multiple studies have performed oncogenic transformation *ex vivo* followed by organoid culture and/or renal grafting, which have suggested that both basal and luminal cells can be cell types of origin for prostate cancer [64–70]. However, given the plasticity of basal cells in *ex vivo* assays, these results are potentially difficult to interpret with respect to *in vivo* contexts.

Thus, to identify cell types of origin *in vivo*, several groups have used Cre-mediated recombination together with Cre reporter alleles such as *R26R-YFP* or *mTmG* to mark and follow the fates of induced tumor cells in GEMMs (Table 1). For example, inducible GEMMs such as *CK5-CreER^{T2};Pten$^{flox/flox}$, CK14-CreER^{T2};Pten$^{flox/flox}$, CK8-CreER^{T2};Pten$^{flox/flox}$, PSA-CreER^{T2};Pten$^{flox/flox}$, Tmprss2-CreER^{T2};Pten$^{flox/flox}$*, and *Nkx3.1-CreER^{T2}; Pten$^{flox/flox}$* have been used to study the consequences of deletion of the *Pten* tumor suppressor in adult prostate basal cells or luminal cells [36–38, 71, 72]. Although inducible deletion of *Pten* in either basal or luminal cells resulted in high-grade PIN and adenocarcinoma, *Pten*-deleted basal cells undergo a basal-to-luminal differentiation to result in a luminal tumor phenotype [36, 38, 60, 65]. Bioinformatic analyses of expression profiles from these tumors showed that luminal-derived tumors were more aggressive than basal-derived tumors, and identified a molecular signature that could stratify human prostate tumors according to clinical outcome [36]. Related studies have shown that luminal progenitor cells in the regressed prostate, including castration-resistant Nkx3.1-expressing cells (CARNs) and castration-resistant Bmi1-expressing cells (CARBs), can also serve as cells of origin [49–51]. Finally, lineage-tracing analyses in a diverse range of GEMMs, including *Nkx3.1$^{+/-}$;Pten$^{+/-}$, Hi-Myc*, and *TRAMP* mice, as well as a hormonal carcinogenesis model, have indicated that luminal cells are favored as the cell of origin in each of these tumor models [73]. Consistent with these findings, recent bioinformatic analyses of human prostate tumors have been able to define distinct basal and luminal molecular subtypes that are associated with different clinical outcomes [74].

Notably, prostate inflammation promotes basal cell plasticity following deletion of *Pten* or *Nkx3.1*, resulting in increased basal to luminal differentiation (Fig. 3) [60, 75]. The plasticity of basal cells *ex vivo* is likely to account for the finding that basal cells can give rise to human prostate cancer after oncogenic transformation in culture followed by renal grafting methods [64–67]. Thus, although luminal cells are favored as the cell type of origin for prostate cancer, the plasticity of basal cells in response to tissue damage can potentially render them competent as cells of origin via basal-to-luminal differentiation. Events such as inflammation and tissue damage could therefore contribute to prostate cancer heterogeneity and correlate with distinct disease outcomes.

4. Identification of putative prostate cancer stem cells

The functional identification of cancer stem cells (CSCs) depends on their ability to self-renew and produce both tumorigenic and nontumorigenic tumor cell progeny through asymmetric cell divisions, thereby generating tumor heterogeneity [24–26]. Consequently, therapeutic targeting of CSCs could block prostate cancer progression and potentially overcome castration-resistance. Many studies have sought to identify prostate CSCs using established human cancer cell lines as well as xenografts, which have been summarized in several reviews [19, 22, 63, 76]. However, there have been more limited studies of CSCs in prostate GEMMs *in vivo* to date.

Interestingly, putative CSCs have been identified in prostate cancer GEMMs with either basal-like and luminal-like phenotypes [19] (Table 1). Notably, basal-like CSCs have been isolated as Sca-1^{+}CD49f^{high} cells from *Pb-Cre4; Pten*$^{flox/flox}$ mouse tumors, and were shown to have tumor-initiating properties in tissue reconstitution assays [77]. Subsequent work showed that a subset of Sca-1^{+}CD49f^{high} CSCs that have CD166 expression harbor increased tumor-initiating and other CSC properties [78], consistent with enrichment of basal-like CSCs.

In other studies, luminal-like CSCs have been isolated as Sca-1^{+}CD49f^{med} cells from *Pb-Cre4; Pten*$^{flox/flox}$, *Probasin-PRL (Pb-PRL)*, and *Hi-Myc* mouse models, and were shown to have highly proliferative and tumor-initiating properties [79]. Interesting, another population of luminal-like CSCs has been described as Epcam^{+}CD49$^{med/lo}$Prom1^{+} cells in the *Pb-Cre4; Trp53*$^{flox/flox}$; *Pten*$^{flox/flox}$ model [80]. These cells can generate tumor organoids in culture that display multi-lineage (luminal and basal) as well as luminal-only lineage differentiation, and form tumors with adenosquamous histology and adenocarcinoma, respectively, after transplantation into immunodeficient mice. These findings suggest the existence of two types of luminal CSCs that can be arranged in a hierarchical relationship, with multipotent CSCs giving rise to unipotent luminal-committed progenitors [80, 81].

5. Cellular plasticity in advanced prostate cancer

Many differentiated cell types can display some degree of plasticity by altering their fates in response to physiological stresses such as inflammation and tissue damage [82–85]. Plasticity is more prevalent in cancer, where the genetic and epigenetic constraints upon the differentiated state are weakened and stresses such as inflammation are accentuated. Notably, plasticity of cancer cells also contributes to tumor heterogeneity and provides mechanisms for tumor cells to evade immune surveillance and acquire metastatic potential [82, 85].

Following treatment with second-generation anti-androgens, recurrent CRPC can display a range of phenotypes with differing levels of expression for AR as well as neuroendocrine markers such as synaptophysin and chromogranin A [14, 15, 86, 87]. This heterogeneity of AR expression in CRPC is likely related to different responses to castration and enzalutamide treatment, as AR^{+} CRPC xenografts are enzalutamide-sensitive whereas $AR^{-/lo}$ CRPC xenografts are resistant [88]. Notably, CRPC can be classified into distinct

entities known as ARPC (AR-expressing prostate cancer) that lacks neuroendocrine marker expression, amphicrine (AMPC) that expresses both AR and neuroendocrine markers, DNPC (double-negative prostate cancer) that does not express either AR or neuroendocrine markers, and NEPC (neuroendocrine prostate cancer) that is AR-negative and expresses neuroendocrine markers [89–93]. While the relationships of AMPC, DNPC, and NEPC to each other are poorly understood at present, their frequent co-occurrence in proximity to ARPC suggests a close lineage relationship [15]. Furthermore, although *de novo* NEPC is rare in primary prostate cancer [1], neuroendocrine differentiation is much more common in CRPC [10, 15, 94–96], suggesting that AR down-regulation promotes neuroendocrine differentiation.

Several studies have explored the origin of neuroendocrine cells in prostate development and cancer. In studies of normal prostate organogenesis, lineage-tracing has been used to conclude that neuroendocrine cells arise from basal progenitors [44] as well as from caudal neural crest [97], but the basis for these apparently conflicting results has not yet been resolved. In addition, cell culture studies have shown that human prostate basal cells can be reprogrammed to neuroendocrine-like cancer cells by a common set of defined oncogenic drivers [98, 99]. In the case of NEPC, several GEMMs with neuroendocrine phenotypes have been described, including those with combined loss of the *Trp53*, *Rb1*, and/or *Pten* tumor suppressors, or together with activation of *N-myc*. For example, *Pten* deletion together with *N-Myc* overexpression or with deletion of *Rb1* and *Trp53* in the *Pb-Cre4;Pten*$^{flox/flox}$;*Rosa26*$^{LSL\text{-}MYCN}$ and *Pb-Cre4;Pten*$^{flox/flox}$;*Rb1*$^{flox/flox}$;*Trp53*$^{flox/flox}$ GEMMs induced prostate adenocarcinoma followed by emergence of NEPC [100–102] (Table 1). Notably, the NEPC phenotype in these and other GEMMs arises from prostate adenocarcinoma with a luminal phenotype, suggesting that tumor cell plasticity gives rise to neuroendocrine-like cells [51, 100–106]. Importantly, lineage-tracing studies in a GEMM of prostate cancer have directly demonstrated that neuroendocrine tumor cells arise by transdifferentiation from luminal adenocarcinoma cells [103] (Fig. 3).

6. Concluding remarks and future directions

The cell of origin and cancer stem cell models provide plausible explanations for the generation and maintenance of prostate cancer heterogeneity, but require much more investigation to establish their general validity. GEMMs for prostate cancer will remain central in future studies centered on these models.

With respect to the cell of origin model, the recent identification of different luminal populations by single-cell RNA-sequencing has raised the question of whether they represent distinct cell types of origin for prostate cancer. Notably, however, both distal as well as proximal luminal cells can give rise to prostate tumors following *Pten* deletion [36, 57], suggesting that further phenotypic and molecular analyses will be necessary to distinguish whether these tumors differ in aggressiveness as a consequence of their cell type of origin. Furthermore, new GEMMs for lineage-tracing of these luminal populations as well as cross-species analyses to validate their relevance for human prostate cancer will be essential to dissect the relevance of the cell of origin. Genetic barcoding approaches *in vivo*

[107, 108] may be particularly useful to identify stem/progenitor cells in prostate tumors, for example to investigate the cellular plasticity that gives rise to neuroendocrine differentiation.

Although putative cancer stem cells have been identified in GEMMs of prostate cancer, widely used candidate CSC markers have generated inconsistent results in differing experimental systems [19]. Importantly, definitive studies using direct lineage-tracing have not yet been performed to demonstrate that CSCs can generate both tumorigenic and non-tumorigenic cells, and that ablation of CSCs inhibit prostate cancer progression and improve treatment response. Such lineage-tracing approaches have been successfully used in other tumor types to define CSC populations [109–111]. At the technical level, such studies might benefit from improved GEMMs that utilize alternative recombination systems together with the Cre-loxP system, such as the Dre-rox system [112, 113]. In addition, the use of organoid approaches may permit lineage-tracing of CSCs in human prostate cancer [114]. Such future studies will undoubtedly provide rigorous tests of the CSC model for generating prostate cancer heterogeneity and guiding prostate cancer treatment.

Finally, cellular plasticity plays a central role in regulating prostate cancer progression and treatment response. For example, more differentiated tumor cells might display plasticity in de-differentiating into CSCs to compensate for the loss of pre-existing CSCs or to escape drug treatment [24, 115, 116]. In the case of CRPC, neuroendocrine differentiation represents a major mechanism of resistance to anti-androgen treatment. Understanding this form of lineage plasticity will likely require the generation of more sophisticated GEMMs that recapitulate specific molecular subtypes of CRPC, as well as the investigation of regulators of prostate cancer cell plasticity. Such advances will be essential for the development of new therapeutic approaches to overcome lineage plasticity and castration-resistance in prostate cancer.

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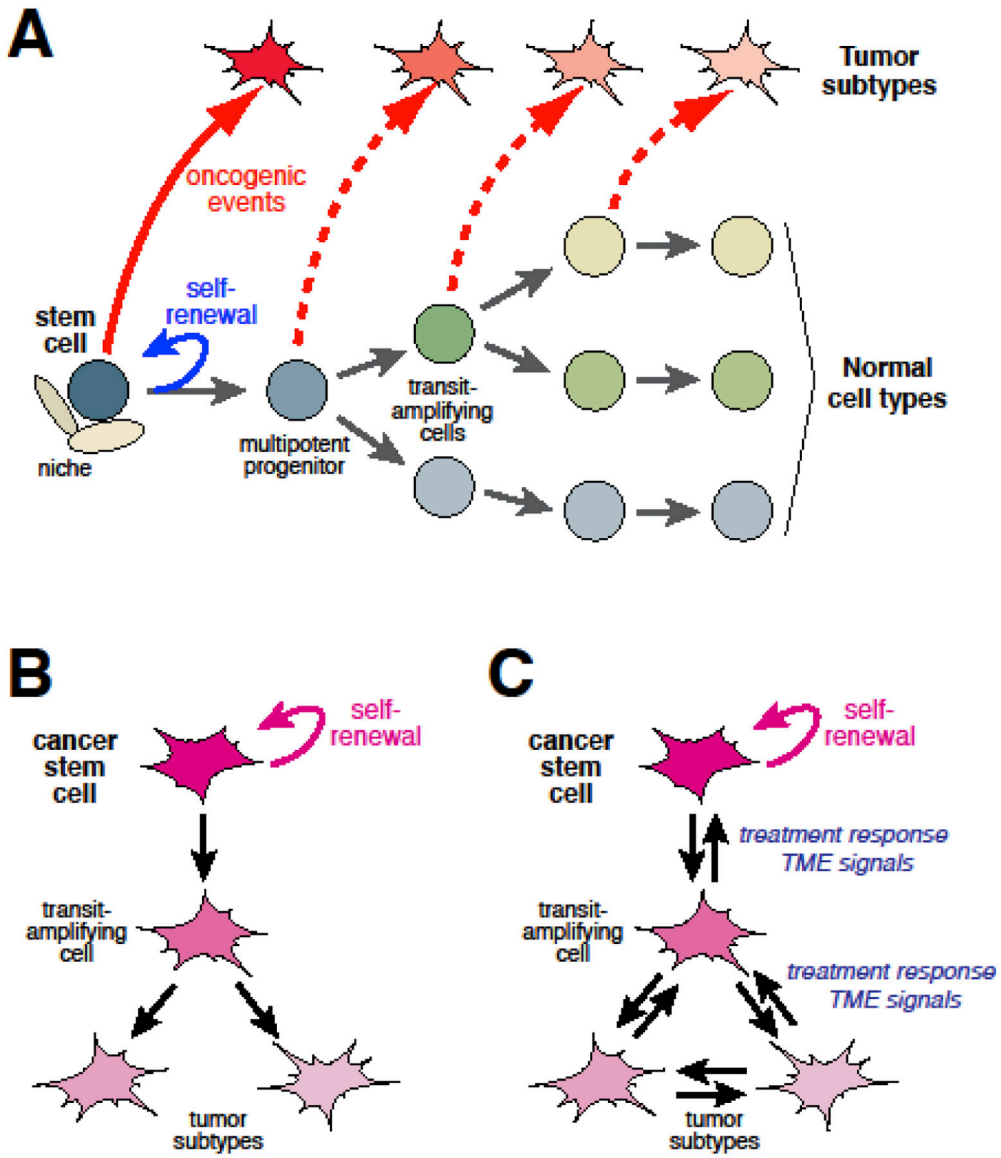

Fig. 1.

Models of cancer heterogeneity. (A) Cell of origin model. A schematic representation of the lineage hierarchy within an epithelial tissue, at the top of which resides a normal stem cell with properties of multipotency and self-renewal. Different tumor subtypes may arise from oncogenic transformation of the stem cell or non–stem cells within the lineage hierarchy (adapted from [117]. (B) Cancer stem cell model. Upon asymmetric division, a cancer stem cell can give rise to itself and a transit-amplifying cell, which in turn divides and undergoes differentiation to generate non-tumorigenic cancer cells. (C) Cellular plasticity in the cancer stem model. Differentiated non-tumorigenic cancer cells can convert to other tumor cell types via transdifferentiation or can be reprogrammed to cancer stem cells, potentially by modulation from intrinsic and/or extrinsic factors such as oncogenic insults and signals from the tumor microenvironment.

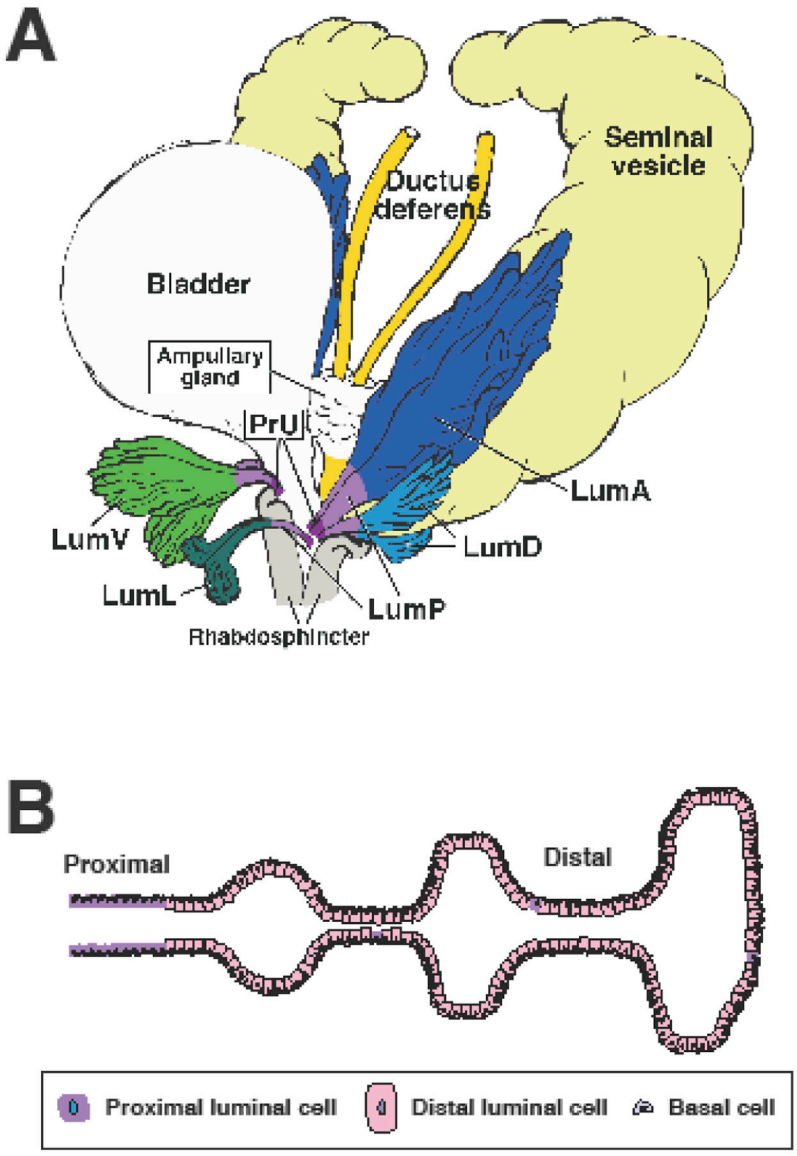

Fig. 2.

Epithelial heterogeneity in the adult mouse prostate. (A) Schematic depiction of prostate lobes indicating the distribution of luminal epithelial populations (adapted from [33]). (B) Proximal-distal heterogeneity of luminal epithelial cells. Note that cells with properties of proximal luminal cells occur sporadically in distal regions. Lum A: distal luminal cells in anterior lobe; Lum D: distal luminal cells in dorsal lobe; Lum L: distal luminal cells in lateral lobe; Lum V: distal luminal cells in ventral lobe; PrU: periurethral; LumP: proximal luminal cells.

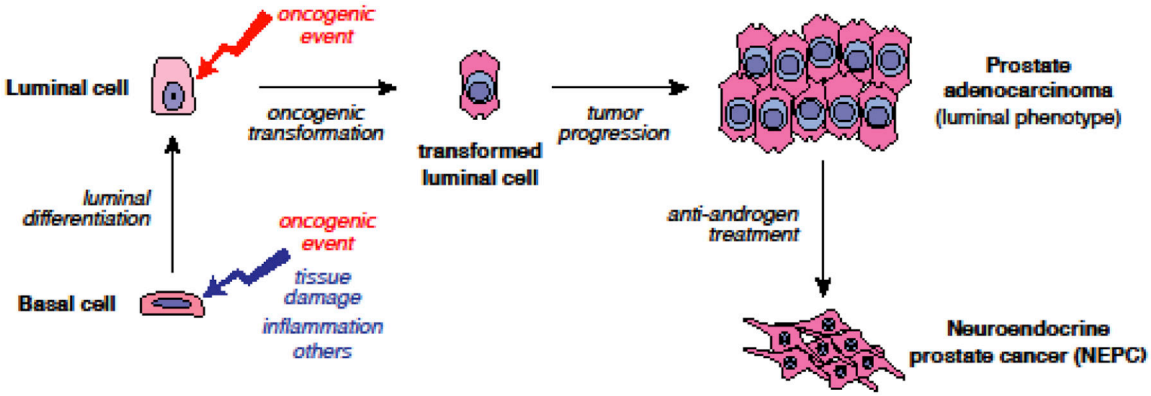

Fig. 3.

Cellular plasticity in prostate tumorigenesis. Following tissue damage, oncogenic insults, or inflammation and other factors, basal cells can undergo luminal differentiation. Transformed luminal cells can directly form prostate adenocarcinoma whereas basal cells need to undergo basal-to-luminal differentiation to generate luminal adenocarcinomas. During tumor progression and anti-androgen treatment, luminal adenocarcinoma cells can transdifferentiate to neuroendocrine-like cells. NEPC: neuroendocrine prostate cancer.

Table 1.

Representative GEMMs used in studies of prostate cancer heterogeneity and plasticity

Type	Name	Description	References
Basal cell origin and prostate cancer	*CK5-CreER^{T2};Pten$^{flox/flox}$*	Conditional deletion of *Pten* in keratin 5 expressing basal cells. Basal cell-derived prostate lesions exhibited PIN and luminal adenocarcinoma phenotype.	[36, 38]
	CK5-CreER^{T2}; Nkx3.1$^{+/-}$;Pten$^{+/-}$	Compound germline deletion of *Pten* and *Nkx3.1*. Keratin 5 expressing basal cells are lineage-marked and are not favored as cells of origin for prostate cancer.	[73]
	CK5-CreER^{T2}; Hi-Myc	c-Myc driven by ARR2PB promoter. Keratin 5 expressing basal cells are lineage-marked and are not favored as cells of origin for prostate cancer.	[73]
	CK5-CreER^{T2}; TRAMP	SV40 large tumor antigen (Tag) driven by a minimal rat probasin promoter (rPB). Keratin 5 expressing basal cells are lineage-marked and are not favored as cells of origin for prostate cancer.	[73]
	CK14-CreER^{T2};Pten$^{flox/flox}$	Conditional deletion of *Pten* in keratin 14 expressing basal cells. Basal cell-derived prostate lesions exhibited PIN and luminal adenocarcinoma phenotype.	[37]
Luminal cell origin and prostate cancer	*CK8-CreER^{T2};Pten$^{flox/flox}$*	Conditional deletion of *Pten* in keratin 8 expressing luminal cells. Induction of PIN and prostatic luminal adenocarcinoma.	[36–38]
	CK8-CreER^{T2};Nkx3.1$^{+/-}$;Pten$^{+/-}$	Compound germline deletion of *Pten* and *Nkx3.1*. Keratin 8 expressing luminal cells are lineage-marked and are favored as cells of origin for prostate cancer.	[73]
	CK8-CreER^{T2};Hi-Myc	c-Myc driven by ARR$_2$PB promoter. Keratin 8 expressing luminal cells are lineage-marked and are favored as cells of origin for prostate cancer.	[73]
	CK8 -CreER^{T2};TRAMP	SV40 large tumor antigen (Tag) driven by a minimal rat probasin promoter (rPB). Keratin 8 expressing luminal cells are lineage-marked and are favored as cells of origin for prostate cancer.	[73]
	PSA-CreER^{T2};Nkx3.1$^{+/-}$;Pten$^{+/-}$	Compound germline deletion of *Pten* and *Nkx3.1*. PSA expressing luminal cells are lineage-marked and are favored as cells of origin for prostate cancer.	[73]
	PSA-CreER^{T2};Hi-Myc	c-Myc driven by ARR$_2$PB promoter. PSA expressing luminal cells are lineage-marked and are favored as cells of origin for prostate cancer.	[73]
	PSA -CreER^{T2};TRAMP	SV40 large tumor antigen (Tag) driven by a minimal rat probasin promoter (rPB). PSA expressing luminal cells are lineage-marked and are favored as cells of origin for prostate cancer.	[73]
	PSA-CreER^{T2};Pten$^{flox/flox}$	Conditional deletion of *Pten* in PSA expressing luminal cells. Induction of PIN and prostatic luminal adenocarcinoma.	[71]
	Tmprss2-CreER^{T2};Pten$^{flox/flox}$	Conditional deletion of *Pten* in Tmprss2 expressing luminal cells. Induction of PIN and prostatic luminal adenocarcinoma.	[72]
	Nkx3.1-CreER^{T2};Pten$^{flox/flox}$	Conditional deletion of *Pten* in distal luminal cells under homeostasis or Nkx3.1-marked luminal progenitor cells after castration. Induction of prostatic luminal adenocarcinoma in both conditions.	[36, 49, 51]
	Bmi1-CreER^{T2};Pten$^{flox/flox}$	Conditional deletion of *Pten* in Bmi1-marked luminal progenitor cells after castration. Induction of prostatic luminal adenocarcinoma.	[50]
Cancer stem cell and prostate cancer	*Pb-Cre4; Pten $^{flox/flox}$*	Conditional deletion of *Pten* in the prostate driven by a minimal probasin promoter driving Cre recombinase. Basal- and luminal-like CSCs were isolated as Sca-1^{+}CD49f^{high} and Sca-1^{+}CD49f^{med} cells, respectively.	[77–79]

Type	Name	Description	References
	Probasin-PRL (Pb-PRL)	Prolactin transgene driven by the short probasin promoter. Luminal-like CSCs were isolated as Sca-1^{+}CD49f^{high} cells.	[79]
	Hi-Myc	c-Myc driven by ARR$_2$PB promoter. Luminal-like CSCs were isolated as Sca-1^{+}CD49f^{med} cells.	[79]
	Pb-Cre4; Trp53$^{flox/flox}$; Pten$^{flox/flox}$	Conditional deletion of *Pten* and *p53* in the prostate driven by a minimal probasin promoter driving Cre recombinase. Luminal-like CSCs were isolated as Epcam^{+}CD49$^{med/lo}$Prom1^{+} cells.	[80]
Cellular plasticity and prostate cancer	*Pb-Cre4;Pten$^{flox/flox}$;Rosa26$^{LSL-MYCN}$*	Conditional deletion of *Pten* and ectopic induction of *N-Myc* expression in the prostate driven by a minimal probasin promoter driving Cre recombinase. Development of poorly differentiated, invasive prostate cancer that is molecularly similar to human NEPC.	[101]
	Pb-Cre4;Pten$^{flox/flox}$;Rb1$^{flox/flox}$;Trp53$^{flox/flox}$	Conditional deletion of *Pten, Rb*, and *p53* in the prostate driven by a minimal probasin promoter driving Cre recombinase. Development of poorly differentiated, invasive prostate cancer that is molecularly similar to human NEPC.	[100, 102]
	Nkx3.1-CreER^{T2};Pten$^{flox/flox}$; Trp53$^{flox/flox}$	Conditional deletion of *Pten* and *p53* in distal luminal cells by Nkx3.1 promoter driving Cre recombinase. NEPC emerges from luminal adenocarcinoma in castrated mice with anti-androgen treatment.	[103]