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# Comparative lineage tracing reveals cellular preferences for prostate cancer initiation

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The interplay of different cell types of origin and distinct oncogenic mutations may determine the tumor subtype. We have recently found that although both basal and luminal epithelial cells can initiate prostate tumorigenesis, the latter are more likely to undergo transformation in response to a range of oncogenic events.

The cell of origin for cancer is defined as a normal tissue cell that is targeted by oncogenic events and is transformed to give rise to a tumor. Over the past few years, there has been increasing evidence to support a model in which cancer subtypes with distinct histopathological features or patient outcomes may originate from different cell types of origin within a given tissue.<sup>1</sup> Therefore, because of the significant implications of understanding the cell of origin for facilitating patient stratification and personalized treatment, identification of the cells of origin for cancer has received considerable interest.

In the normal untransformed prostate, basal cells and luminal cells represent the two major epithelial cell types. However, human prostate adenocarcinomas all display luminal features, and in fact are diagnosed on the basis of the absence of basal cells. Nonetheless, it has been quite controversial whether basal or luminal cells, or both, represent the cells of origin for prostate cancer. For example, previous studies have isolated human prostate basal or luminal cells followed by their transduction with oncogenes and found that only the basal population could support tumor formation in renal grafts in immunodeficient mice, suggesting basal cells as the cell of origin.<sup>2,3</sup>

A major caveat of the renal grafting approach is that cancer initiation and progression does not occur in the context of a native tissue environment. To overcome this limitation, we and others have utilized genetic lineage tracing and conditional deletion of the *Pten* tumor suppressor gene specifically in basal or luminal cells of the mouse prostate, and showed that both basal and luminal cells could serve as cell types of origin for prostate cancer *in vivo*.<sup>4-6</sup> Interestingly, tumors originating from basal cells displayed luminal phenotypes since transformed basal cells rapidly differentiated into luminal cells, which then propagated the luminal features of prostate cancer. However, despite their similar end-stage histopathology, luminal-derived mouse tumors progressed more rapidly than basal-derived tumors and had a distinct molecular profile that correlates with more aggressive phenotypes in human patients.<sup>4</sup>

These findings led us to investigate whether luminal cells might be more susceptible to oncogenic transformation *in vivo*. Furthermore, we were interested in determining whether different oncogenic drivers might affect the ability of a given cell type to serve as a cell of origin. Therefore, to test which cell type(s) is favored as the cell of origin for prostate cancer in response to distinct oncogenic drivers, we

performed comparative lineage tracing of basal or luminal cells in a diverse range of genetically engineered mouse models of prostate cancer.<sup>7</sup>

Unlike previous cell-of-origin studies in which oncogenic drivers were introduced specifically into cell types of interest, we took the converse approach of expressing the oncogenic drivers throughout the prostate epithelium, followed by determination of whether the basal or luminal cells had generated tumor lesions. For this purpose, we used mouse models in which tumor formation was driven by *Myc* overexpression (*Hi-Myc* mice), inactivation of the *Nkx3-1* and *Pten* tumor suppressors, inactivation of the *Trp53* and *Rb1* pathways by SV40 T antigen (*TRAMP* mice), and elevated levels of androgen and estrogen hormones, all of which can drive human prostate tumorigenesis.<sup>8</sup> To determine the cell type of origin in each mouse model, we lineage marked basal or luminal cells in histologically normal prostate prior to tumor formation and then investigated whether marked cell clusters were present in the tumors that subsequently arose. Notably, we found that luminal cells were consistently the observed cell of origin in all of the models tested.

Our results strongly support the notion that luminal cells are more prone to

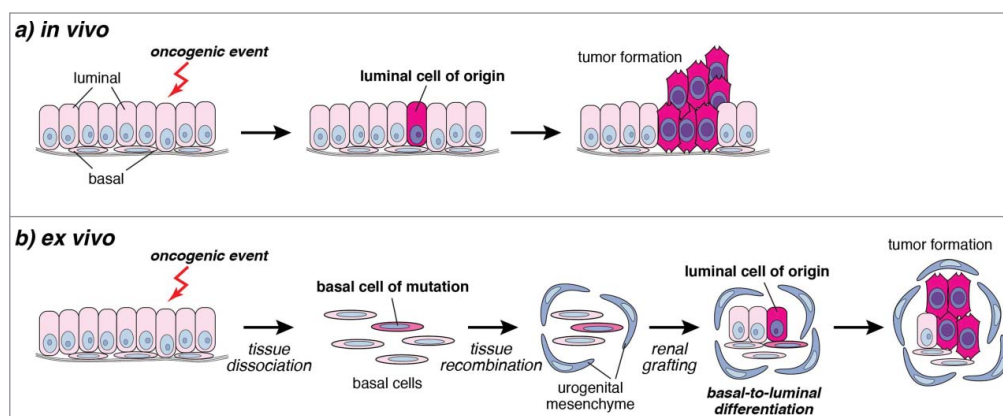
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**Figure 1.** Cellular sources of prostate cancer. (A) Oncogenic events *in vivo* result in transformation of a luminal cell of origin and subsequent tumor formation. (B) When basal cells are dissociated *ex vivo* and placed in a tissue recombinant with urogenital mesenchyme followed by renal grafting, cells that carry oncogenic events (cells of mutation) undergo basal-to-luminal differentiation to form luminal cells. These luminal cells can act as cells of origin, being transformed to initiate tumor formation.

oncogenic transformation than basal cells and are the favored cell type of origin in the endogenous prostate tissue environment. One potential caveat is that the genetically engineered models used for our study express oncogenic events throughout the prostate epithelium, rather than in a smaller subset of cells. However, since the oncogenic stimuli indiscriminately affected both basal and luminal cells, we could directly compare their susceptibility to oncogenic transformation in a controlled manner. Furthermore, the hormonal carcinogenesis model does not rely on any genetically engineered oncogenic event, and provides unequivocal evidence for luminal cells as the preferred cell of origin. Although our conclusions differ from those of Witte and colleagues,<sup>2</sup> the experimental data from these studies are consistent. In particular, when we isolated the basal cells from our mouse models and performed renal grafts in immunodeficient nude mice, the grafted cells readily generated prostate tissue with tumor phenotypes. Therefore, both normal and transformed basal cells demonstrate significant plasticity when removed from their endogenous tissue environment.<sup>4,7</sup>

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One model to explain our findings utilizes the concept of “cell of mutation” that was first proposed in studies of the cell of origin for glioma.<sup>9</sup> In this view, basal cells carrying oncogenic events display plasticity by acquiring progenitor properties in renal grafts and behave as cells of mutation, generating progeny luminal cells that are authentic cells of origin. A recent report showing that prostate cancer can be derived from basal cells in renal grafts and then propagated by luminal cells<sup>10</sup> is consistent with this model. In particular, since the renal graft assay involves generation of prostate tissue from a small number of dissociated cells, a process analogous to prostate organogenesis, this assay may not accurately indicate true cell types of origin, which only reside in the adult prostate (Fig. 1).

It should be noted that our finding that luminal cells are favored as cells of origin in the mouse models examined does not exclude the possibility that basal cells are cells of origin for different models or for distinct tumor subtypes. Previous lineage tracing studies have shown that adult basal cells have the capability to initiate cancer *in situ*<sup>4-6</sup> and may be responsible for a less

malignant subtype of human prostate cancers.<sup>4</sup> This raises the question of why we did not observe any tumors with a basal cell of origin. One possibility is that such tumors might be observed in experimental contexts using different oncogenic drivers. Alternatively, another possibility is that transformed luminal cells can out-compete transformed basal cells and their growth into tumors in a non-cell-autonomous manner.

In conclusion, our work complements prior lineage tracing studies, and together with previous work provides a clearer understanding of the cell types of origin for prostate cancer.

While both luminal cells and basal cells can in principle serve as cells of origin for prostate cancer, luminal cells are more susceptible to oncogenic transformation. Future research aimed at correlating cells of origin with subtypes of human prostate cancers may lead to the identification of novel molecular biomarkers as well as therapeutic targets.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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