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PINing Down the Origin of Prostate Cancer

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Abstract

The epithelium that lines the surface of prostate glands contains several cell types, including luminal secretory cells and basal cells of unclear function. Despite the fact that prostate tumors contain cells with a luminal phenotype and lack basal cells, a recent report indicates that the cell of origin for human prostate cancer is a basal cell and not a luminal cell. In contrast, another study indicates the reverse. It is possible that both basal and luminal stem/progenitor cells may independently give rise to prostate cancer; a comparison of the molecular signatures of the target cells of transformation with those of prostate tumors may aid in predicting the phenotypes of tumors with aggressive characteristics.

INTRODUCTION

Evidence suggests that malignant transformation originates in a subset of primitive cells and that most cells in an organ do not generate tumors (1, 2). Determining which cell type(s) give rise to a given form of cancer (the cell of origin) will permit us to design more individualized approaches for treating different types of cancer. Advancement in the identification of the cell of origin in prostate cancer has been limited by the lack of good models with which to study human prostate cancers and by morphological and biochemical differences between human and rodent prostates that limit the utility of rodent models. The prostate consists of a glandular portion and a fibromuscular portion. In both humans and rodents, the glands are lined with an epithelium that is made up of a continuous layer of columnar luminal secretory cells, basal cells of undefined function, and scattered neuroendocrine cells (Fig. 1A). Cells within the luminal and basal compartments may be heterogeneous in function; stem cells may be included in both of these compartments. Human prostate carcinoma is marked by an expansion of cells that morphologically and biochemically resemble luminal cells and by an absence of basal cells. Two recent papers identified cells with stem cell properties as the cell of origin of prostate cancer. However, the stem cells identified are in different cell compartments.

A BASAL CELL ORIGIN FOR PROSTATE CANCER

In a recent paper in *Science* (3), Goldstein *et al.* describe a model system in which questions about the cell of origin and oncogenic pathways of human prostate cancers can be addressed. Using two cell surface antigens, Trop2 (TACSTD2) and CD49f (integrin $\alpha 6$), Goldstein *et al.* (3) separated luminal (Trop2⁺/CD49f⁻) from basal (Trop2⁺/CD49f⁺) cells in digests of benign human prostate tissue. When each of these populations, along with urogenital sinus

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mesenchyme cells that promote the proliferation of primitive prostate cells, was injected subcutaneously into immunodeficient (NOD-SCID-IL2R $\gamma^{-/-}$) mice, the basal cell population gave rise to prostate-like structures containing both basal and luminal cells, whereas the luminal population did not grow, confirming observations from mouse prostate (4) that the basal layer contains prostatic epithelial stem cells. Goldstein *et al.* (3) then used lentiviral vectors to transform these cells with genes encoding activated Akt and ERG, which are commonly associated with human prostate cancers. When transplanted into the mouse, the transformed basal cells formed tissues that resembled prostatic intraepithelial neoplasia (PIN) (that is, microscopic groups of atypical epithelial cells that represent a premalignant state), containing both basal and luminal cells, whereas transformed luminal cells did not grow. Finally, addition of the androgen receptor gene, which is often up-regulated in prostate cancer, to the genes expressing activated Akt and ERG in the basal cells gave rise to frank adenocarcinomas with an expanded luminal cell population and an absence of basal cells, whereas expression of these same genes in luminal cells did not generate any prostatic tissue. The authors conclude that basal stem cells are the target of transformation in the generation of prostate tumors.

This experiment provides the first definitive experimental data that show selective transformation of subsets of human prostate cells by oncogenes known to be commonly expressed in human tumors. It also makes the landmark observation that transformation of a basal stem cell population can result in prostate tumors with a luminal phenotype. Furthermore, until now, investigations into the etiology of human prostate tumors have been limited by a lack of good models. The model described here will provide a useful assay to further characterize human prostate stem cells and to examine the role of additional oncogenes in tumor formation.

A LUMINAL CELL ORIGIN FOR PROSTATE CANCER

At first glance, these findings seem to be in conflict with those in a recent paper from Wang *et al.* (5) that concludes that a luminal epithelial stem cell is the target of transformation in prostate cancer. This conclusion relies on lineage-tracing studies in the mouse prostate. Wang *et al.* (5) found that expression of a prostate-specific homeobox gene, *Nkx3-1*, marked rare luminal epithelial cells but was never observed in basal cells in prostates after castration-induced involution. When mice are castrated to abolish the production of testicular androgens, the prostate involutes, resulting in a reduction in size due to apoptosis of most luminal cells and of a small fraction of basal cells. When androgens are readministered, the prostate regenerates. When castration-resistant *Nkx3-1*-expressing cells (CARNs) marked with yellow fluorescent protein (YFP) were followed, it was found that these cells expanded over ninefold during regeneration of the prostate after androgen replenishment and gave rise to luminal, basal, and neuroendocrine cells. Reimplantation of single YFP-marked CARNs, along with urogenital sinus mesenchyme, under the renal capsule (a fibrous layer surrounding the kidney) of immunodeficient (nude) mice generated prostatic ducts containing both basal and luminal cells that were completely YFP-positive. Specifically deleting the tumor suppressor gene *PTEN* (which regulates the Akt signaling pathway and is often inactivated in human prostate cancer) in CARN cells led to the rapid development of tumors with a luminal phenotype and an absence of basal cells upon prostate regeneration. These results suggested that CARNs are prostate stem/progenitor cells and targets of transformation.

COMMON GROUND

There is nothing inherently contradictory in the results described by Wang *et al.* (5) and Goldstein *et al.* (3), because it is possible that both basal and luminal stem/progenitor cells

may independently serve as cells of origin for prostate cancer. Indeed, it is also possible that oncogenic stimuli may differ in their effectiveness in transforming distinct cell populations. The tumors that arise from different target cells may also vary in their biological behavior and genetic profiles.

There are also indications that normal prostate stem cells may reside in both the basal and the luminal compartments. Thus, if stem cells are preferentially targeted during malignant transformation, both compartments may contain cells of origin for prostate cancer. Most of the scientific evidence indicates that prostate stem cells reside in the basal layer and give rise to the secretory luminal cells via transit-amplifying cells, which are intermediate in phenotype between stem cells and terminally differentiated cells (6). There is definitive evidence that (i) secretory cells of the adult murine prostate derive from cells that express p63, a transcription factor that is expressed by all basal cells in the prostate (7), and (ii) p63-expressing basal cells are required for prostate development (8). In addition, prostate basal cells (human and murine) have greater proliferative activity in vitro and in vivo than luminal cells (3, 4, 9, 10). The molecular signature of prostate stem cells also identifies a basal-like phenotype, as they express cytokeratins 5/14, p63, and integrin $\alpha 6$ (11). There is also evidence, however, that the luminal compartment may contain stem/progenitor cells and that these give rise to basal cells. Experiments involving labeling cells with the synthetic nucleoside bromodeoxyuridine to detect those that are proliferating indicate that slow-cycling stem cells are concentrated in the proximal region of prostatic ducts adjacent to the urethra and that both basal and luminal compartments contain slow-cycling cells (12). Cells from this region have substantial growth potential in vivo and in vitro and can be serially passaged in vivo at least four times (13). It is not known whether CARNs are concentrated in the proximal region, but if so, CARNs may comprise some of the slow-cycling proximal luminal cell population. These data indicate that both the basal and luminal compartments may independently contain stem/progenitor cell populations that maintain prostate homeostasis, regenerate prostatic tissue after androgen deprivation and replenishment, and serve as cells of origin for prostate cancer.

It is possible that basal cells serve as the primary reservoir of stem cells that divide infrequently and are largely quiescent. Normal prostatic homeostasis and the more rapid, initial phase of prostate regeneration after androgen ablation and replenishment may largely depend on a small population of young transit-amplifying luminal cells, with considerable proliferative potential (Fig. 1, B and C). Indeed, in an intact androgen-replete animal, the luminal compartment contains significantly more cycling cells than the basal compartment, indicating that luminal cells are quite capable of maintaining tissue homeostasis in intact animals (12). In this instance, the prostate may resemble the skin epithelium, which has two separate stem cell compartments: the slow-cycling cells in the hair follicle bulge and the more proliferative cells in the basal layer of the interfollicular epidermis. Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis, which relies on the interfollicular stem cell compartment for its normal turnover (14). These two stem cell compartments can also be distinguished by their differential sensitivity to the loss of transforming growth factor- β signaling (15). Thus, a luminal CARN population may serve a function analogous to that of the interfollicular epidermal stem cells, with quiescent basal cells dividing only infrequently to maintain tissue homeostasis and regeneration. The basal cell population would therefore house a reserve stem cell population like the epidermal bulge stem cells, whereas the luminal compartment contains a small subset of cells that are designed to respond more rapidly and serve as the primary population that is responsible for initial regeneration and daily turnover (Fig. 1, B and C). Both populations may serve as cells of origin for prostate cancer. The specific target cell and the molecular nature of the oncogenic event may determine the biological properties of the resulting tumor (Fig. 1D). Interestingly, activation of the Hedgehog signaling pathway in hair follicle bulge cells did

not result in basal cell carcinomas, whereas activation of this pathway in the interfollicular epidermal population did, indicating that these two populations of stem cells respond differentially to oncogenic stimuli (16).

The findings of Goldstein *et al.* (3) were based on human basal and luminal cells isolated from benign prostate tissue. If CARNs were present in the luminal population, one would expect that the luminal population would also have prostate-regenerating capacity. It is possible that the human prostate does not contain CARNs or contains them at a frequency too low to detect in these assays. It is also possible that CARNs do not survive the isolation procedures used by Goldstein *et al.* (3) or may be susceptible to apoptosis once isolated. Because of these limitations, it is still not clear whether the human prostate luminal compartment contains stem cells.

FUTURE STUDIES

Wang *et al.* (5) show that a rare luminal stem/progenitor cell is the target of transformation but do not exclude the possibility that basal cells or other luminal cells might also be targets. Goldstein *et al.* (3) demonstrate that the basal compartment of the human prostate contains stem/progenitor cells as well as targets of transformation but have not positively identified these as the same cell. Because it is now possible to test isolated human prostate cell compartments using the assays described by Goldstein *et al.* (3), it would be useful to further fractionate these populations to more narrowly identify prostate stem cell characteristics and to verify that these cells are indeed the targets of transformation.

If prostate cancers originate in different cell types, they may give rise to tumors with different biological outcomes requiring distinct therapeutic responses. The outcome of patients with human hepatocellular carcinoma can be predicted based on the similarity of the tumor gene expression profile to that of a fetal rat hepatoblast gene expression profile (17). Similarly, molecular signatures of human and murine prostate stem cell compartments may aid in predicting the characteristics and aggressiveness of human prostate tumors. This capacity may result in our ability to provide appropriate therapeutic regimens to those individuals most likely to benefit.

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Fig. 1. Stem cells in normal prostate homeostasis, regeneration, and tumor formation

(A) General organization of cells in the prostate epithelium. (B) Luminal cells maintain the functional integrity of the prostate during normal homeostasis. (C) Androgen withdrawal results in an involuted prostate with the loss of significantly more luminal than basal cells. After androgen replenishment, luminal stem/progenitor cells are the first to divide. Further expansion of the epithelial population requires the contribution of a reserve basal stem/progenitor subset. (D) Transformation of a luminal stem/progenitor cell results in the formation of adenocarcinoma with a luminal phenotype. Basal stem/progenitor cell transformation leads to PIN lesions containing both basal and luminal cells that progress to adenocarcinomas containing only luminal cells.