COMMENTARY

Inflammation promotes prostate differentiation

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Inflammation has been linked to a number of diseases including prostate cancer, but the mechanisms by which inflammatory signaling promotes tumorigenesis remain largely unknown (1). In PNAS, Kwon et al. (2) demonstrate that bacterial-induced inflammation in the mouse prostate is associated with both proliferation and basal-to-luminal differentiation, the limiting step in the transformation of basal cells. This differentiation process accelerates tumorigenesis starting in basal cells, supporting a unique role for inflammation in cancer initiation.

The prostate epithelium consists of a layer of basal cells, resting against the basement membrane in close proximity to nonepithelial cells, and a layer of luminal/secretory cells facing the fluid-filled lumen (3). In the developing mouse prostate, basal cells serve as the stem cells of the organ, generating all epithelial lineages (4). In the adult prostate, basal and luminal cells are largely maintained by distinct lineage-restricted progenitors (5). When basal cells are taken out of their niche and transplanted under the kidney capsule or skin of immune-deficient mice in combination with supportive urogenital sinus mesenchyme (UGSM) cells in a tissue-recombination assay, they readily generate both basal and luminal cells (6). However, lineage tracing in the native prostate microenvironment indicates that basal cells in the adult mouse prostate rarely differentiate into luminal cells (7). Kwon et al. (2) use a model of bacterial infection of the prostate to show that inflammation promotes basal-to-luminal differentiation. These findings suggest that the inflammatory environment may induce factors present during both early development and the tissue-recombination approach to induce basal cell differentiation. Given that embryonic mesenchyme plays an important role in tissue regeneration and differentiation (8), prostate inflammation may accelerate cancer development at least in part by promoting an embryonic state in the adult stroma. Further studies will be necessary to elucidate the common or analogous factors required to drive basal-to-luminal differentiation.

Numerous groups have investigated the cellular origins of prostate cancer in the mouse, and surprisingly, the results support progenitor cells in both the basal and luminal layers as targets for transformation following loss of the tumor suppressor phosphatase and tensin homolog (Pten) (5, 7, 9). Results regarding whether basal cell or luminal cell transformation is more potent vary greatly depending on the strain of mice, the strength of promoters, and the frequency of Pten deletion. Choi et al. (5) reported that basal cell transformation is limited by the rate of differentiation into luminal cells. In this study, Kwon et al. (2) find that inflammation-induced basal-to-luminal differentiation accelerates prostate cancer starting in basal cells (Fig. 1*A*).

In the human prostate, basal cells have been shown to behave as stem cells in the tissue-recombination assay, generating both basal and luminal cells in vivo (10, 11). Transformation of human prostate basal cells leads to tumors with a luminal cell phenotype, indicating that basal-to-luminal differentiation is also an important step in human prostate tumorigenesis starting in basal cells (10, 12, 13). In a recent issue of PNAS, Stoyanova et al. (14) found that tumor-propagating cells bearing a luminal cell phenotype could maintain cancer starting in basal cells (Fig. 1*B*). These findings indicate that the cells of origin that initiate cancer can be phenotypically distinct from the stem-like cells that maintain advanced disease. It will be interesting to determine whether luminal cells in the mouse prostate resulting from basal-to-luminal differentiation also develop into tumor-propagating cells that maintain mouse prostate cancers.

Inflammation has been predicted as an initiating event in prostate cancer, and the process of proliferative inflammatory atrophy has been well described by De Marzo et al. (15). An inflammatory environment may be

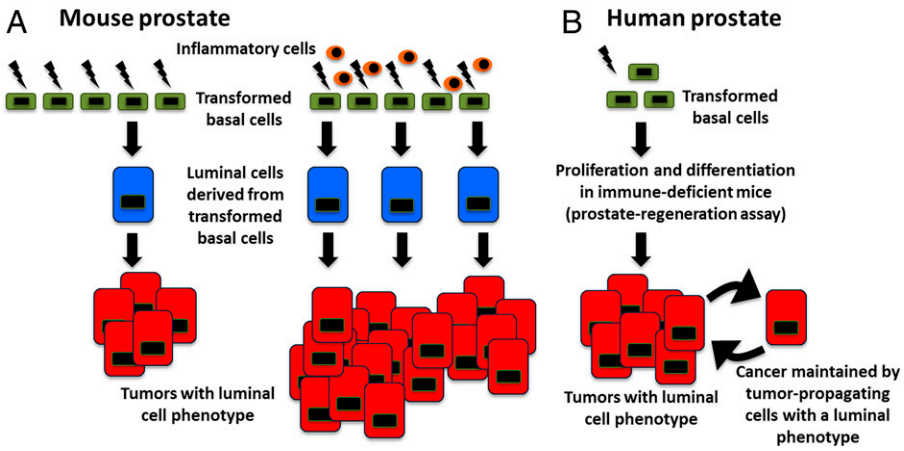

Fig. 1. Models of prostate cancer initiated in mouse and human basal cells. (*A*) Prostate cancer driven by loss of Pten in mouse basal cells is limited by a low rate of basal-to-luminal differentiation. Bacterial-induced inflammation promotes basal-to-luminal differentiation and accelerates prostate cancer initiation in Pten-null basal cells. (*B*) Oncogenic transformation of human prostate basal cells in the prostate-regeneration assay results in luminal tumors. Recent findings indicate that tumors originally initiated in basal cells can be maintained by tumor-propagating cells with a luminal phenotype.

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induced by a number of factors, including poor diet, alterations in hormone signaling, viral infection, and bacterial infection (16). Several models have been developed to investigate the consequences of inflammation in the mouse prostate, including the transfer of antigen-specific T cells to transgenic mice with an antigen-expressing prostate (17), genetic deletion of the immune regulatory gene *Aire* (18), and bacterial infection (19). Because the model of bacterial-induced inflammation used by Kwon et al. (2) is not necessarily representative of the majority of inflammation in the prostates of aged men, it will be important to evaluate distinct methods that cause inflammation to determine whether they all promote both proliferation and basal-to-luminal differentiation. In the mouse foregut, inflammation-mediated epithelial Stat3 activation is a required step in squamous cancer formation driven by Sox2 overexpression (20). These findings suggest that inflammation is an important mediator of tumorigenesis in diverse epithelial tissues. Comparing similar effects on epithelium of distinct tissue origins may help to define the critical inflammatory factors promoting epithelial transformation. Results from these studies may lead to new diagnostic tools to predict cancer susceptibility or to new therapies to prevent disease progression.

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