PERSPECTIVE

Does the microenvironment influence the cell types of origin for prostate cancer?

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Despite several recent studies addressing the cells of origin for prostate cancer, there is still considerable discussion in the field regarding the most relevant target populations for transformation. Tissue regeneration studies have pointed to a basal cell origin for mouse and human prostate cancer. In contrast, genetically engineered mouse models demonstrate that cells within both the basal and luminal layers can initiate murine prostate cancer. Based on differences between these two approaches, we propose that further work should address the requirement for microenvironmental components such as immune or mesenchymal cells on epithelial cell types of origin for prostate cancer.

Experimental identification of the cell types of origin for prostate cancer

The cell of origin is the normal cell type that either acquires genetic damage or responds to changes in its environment, resulting in a multistep progression of tumorigenesis (Visvader 2011). Defining the cell types of origin and the signals promoting transformation toward a lethal phenotype will enhance our understanding of cancer initiation and likely lead to the development of new diagnostic tools or therapeutic targets to detect and treat lethal prostate cancer.

While prostate cancer is one of the most common causes of cancer and cancer-related deaths among males worldwide (Siegel et al. 2012), the majority of patients diagnosed with the disease have a relatively indolent form of prostate cancer that is unlikely to invade beyond the local tissue environment (Klotz 2013). However, a subset of prostate tumors exhibit aggressive properties, including rapid proliferation and metastatic spread to distant organ sites, including the lymph nodes, lung, bone, and brain (Logothetis and Lin 2005). Patients with localized disease can be treated by radical prostatectomy to remove diseased prostate tissue. When the tumor becomes metastatic, patients are often treated with anti-androgen hormonal

therapy, radiation, or both. Patients initially respond favorably to treatment, but tumors invariably return in a more aggressive castration-resistant state that is currently untreatable (Feldman and Feldman 2001; Hellerstedt and Pienta 2002; Zong and Goldstein 2013).

In order to model advanced disease, researchers have focused on identifying both the critical genetic alterations found in late stage tumors and the cells of origin in which these alterations occur to drive tumorigenesis. There has been a considerable effort during the past decade to acquire late stage prostate tumors for genome sequencing to discover the genetic alterations most commonly found in advanced disease (Berger et al. 2011; Barbieri et al. 2012; Grasso et al. 2012). In 2005, Chinnaiyan and colleagues (Tomlins et al. 2005) discovered a recurrent chromosomal translocation bringing the ETS transcription factor ERG (ETS-related gene) under regulation of the androgen-driven TMPRSS2 (transmembrane protease, Ser2) promoter occurring in up to 50% of prostate tumors (Mani et al. 2009). A large number of rearrangements have since been discovered in prostate cancer involving other ETS genes (Kumar-Sinha et al. 2008). In addition, prostate tumors are characterized by overexpression of Spink1 (Tomlins et al. 2008), activation of the RAS/RAF pathway (Mulholland et al. 2012; Wang et al. 2012), activation of the PI3K (phosphoinositide 3-kinase) pathway (Wang et al. 2003; Yoshimoto et al. 2006), loss of Rb (retinoblastoma protein) signaling (Taylor et al. 2010), and mutations in SPOP (speckle-type POZ protein) and FOXA1 (forkhead box protein A1) (Barbieri et al. 2012; Grasso et al. 2012). With the knowledge of the most common alterations that occur either alone or in combinations, several groups have addressed the cell types of origin for prostate cancer to determine which lineages acquire the genetic alterations that promote the initiation of aggressive disease.

A tissue recombination approach identifies basal cells as one cell type of origin for mouse and human prostate cancer

Two different technologies have been established to experimentally evaluate the target cells susceptible to transformation in the mouse and human prostate. The first

[Keywords: cell of origin; inflammation; prostate cancer]

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Article is online at <http://www.genesdev.org/cgi/doi/10.1101/gad.222380.113>.

method uses a tissue recombination approach originally developed by Cunha and Lung (1978) to examine epithelial and mesenchymal interactions in the developing prostate and later adapted to interrogate adult prostate epithelium. In this assay, dissociated prostate cells are fractionated into distinct epithelial subpopulations; engineered to express one, two, or three oncogenes by lentiviral delivery; and recombined with inductive urogenital sinus mesenchyme (UGSM) cells originally isolated from the midgestation mouse embryo (Xin et al. 2003, 2005; Zong et al. 2009). Upon transplantation under the renal capsule or subcutaneous space of immunodeficient mice, epithelial cells generate glands that represent varying stages of histological transformation depending on the oncogenes they express—from benign glands to prostatic intraepithelial neoplasia (PIN) lesions to full-blown adenocarcinoma (Zong et al. 2009). Certain oncogene combinations can promote an epithelial–mesenchymal transition (EMT) and metastasis (Xin et al. 2006; Cai et al. 2011). Murine prostate cells harboring genetic deletions of tumor suppressors such as *Rb* or *Pten* can be transplanted under the kidney capsule to evaluate the effects on transformation (Wang et al. 2000; Mulholland et al. 2009).

A major advantage of the tissue recombination model is the ability to perform parallel studies using rodent and human tissue. In addition, tissue grafts containing PIN or cancerous lesions generally develop in 2–3 mo, allowing for rapid assessment of a range of candidate genetic alterations identified by cancer genome sequencing. Any single oncogene or combination of genetic alterations can be assayed using the same epithelial cell preparation. In order to perform the tissue recombination, native tissue structures are disrupted, and new glands are regenerated in a distinct environment, either under the kidney capsule or in the subcutaneous space. Using the tissue recombination assay, Lawson et al. (2010) isolated basal and luminal cells from mouse prostate epithelium and found that a range of oncogenic influences could initiate prostate cancer efficiently from basal cells but not from luminal cells. Consistent with these findings, Mulholland et al. (2009) isolated tissue from young *Pten*-deficient prostate glands and found that only the CD49^{thi} basal fraction could initiate tumors upon transplantation under the renal capsule.

A human tissue recombination assay was developed to test the transformation capacity of naïve benign basal and luminal epithelial cells taken from freshly isolated clinical specimens (Goldstein et al. 2011). A combination of three oncogenes (AKT, ERG, and androgen receptor), each representing a commonly activated pathway in advanced disease, was sufficient to initiate human prostate cancer from the basal cell population following transplantation into the subcutaneous site (Goldstein et al. 2010). Further support for a basal cell origin in human prostate cancer was provided by Risbridger and colleagues (Taylor et al. 2012), demonstrating that basal-like cells could be transformed by hormonal stimuli (combined estrogen and testosterone) to initiate tumorigenesis in the renal capsule.

Genetically engineered mouse (GEM) models reveal target cells for murine prostate cancer within both the basal and luminal epithelium

In contrast to tissue recombination studies, GEM models offer an alternative approach that has been used by several laboratories to evaluate different lineages as candidate cells of origin for murine prostate cancer. Lineage-specific promoters activate the Cre recombinase to remove critical tumor suppressor genes or induce expression of oncogenes, typically from a young age in healthy mice equivalent to a teenage man (Lakso et al. 1992; Wang et al. 2009; Fuchs and Horsley 2011; Choi et al. 2012). The major advantage of this model is the ability to maintain native structures in the prostate epithelium, while the cost and timing required to maintain different strains make it more difficult to test a large set of individual genetic alterations and combinations in GEM models.

Three independent groups have recently investigated the effects of removing the tumor suppressor *Pten* in basal or luminal cells (Choi et al. 2012; Lu et al. 2013; Wang et al. 2013). Each group demonstrated that both lineages are capable of generating malignant lesions, although there is considerable disagreement over which lineage is capable of generating the most proliferative, aggressive disease depending on the strength of the promoter used and the background and genotype of the mouse. Xin and colleagues (Choi et al. 2012) found that basal cells were more resistant to transformation, which may be partially explained by recombination in only 17% of basal cells compared with recombination in up to 80% of luminal cells. Using a *Keratin 5* promoter-driven Cre that could delete *Pten* in up to 50% of basal cells, Chen and colleagues (Lu et al. 2013) reported that basal cell-derived tumors were more proliferative and invasive than lesions initiated by loss of *Pten* in luminal cells. Comparing deletion of *Pten* in *Nkx3-1*^{+/+} basal cells with heterozygous *Nkx3-1*^{Cre/+} luminal cells, Shen and colleagues (Wang et al. 2013) determined that luminal cell-derived tumors were more aggressive than basal cell-derived lesions. Since *Nkx3-1* is an important tumor suppressor regulating prostate transformation (Abate-Shen et al. 2003), perhaps a more balanced comparison would include *Pten* deletion in basal cells that also lack one allele of *Nkx3-1*.

The complexity of such results may be further complicated by lineage tracing studies performed by Blanpain and colleagues (Ousset et al. 2012) demonstrating a number of distinct progenitor cells within the developing mouse prostate, including unipotent and multipotent basal stem cells and unipotent luminal stem/progenitors. Given the range of results using experimental models, it is likely that any proliferative cell has the potential to be transformed, suggesting that progenitor-like cells within both the basal and luminal layer are the likely targets. It is also possible that sufficient oncogene activation in terminally differentiated cells could induce dedifferentiation and transformation, similar to recent results demonstrating that even mature neurons in the murine brain can initiate gliomas upon loss of tumor suppressors *NF1* and *p53* (Friedmann-Morvinski et al. 2012). While prostate

cancer may arise from the transformation of distinct target cells, the cell type of origin could influence biological properties of the resulting tumors, as has been demonstrated in a mouse model of T-cell acute lymphoblastic leukemia (Berquam-Vrieze et al. 2011).

Stromal-derived paracrine growth factors may preferentially transform basal cells in the tissue recombination assay

While the impact of cell-autonomous disease-promoting genetic alterations in prostate cancer has been well studied, the effects of paracrine- or endocrine-derived factors on prostate epithelium deserve discussion. Nonepithelial cell types, including mesenchymal, endothelial, and hematopoietic cells, are often grouped together under the umbrella of stromal components. For this discussion, we focus on the influence of mesenchymal or fibroblastic cells on epithelial transformation. Several studies have shown that dysregulation of mesenchymal/niche cell signaling and release of growth factors can act on nearby epithelial cells of origin to promote the initiation of prostate cancer. Alterations in stromal secretion of paracrine growth factors such as TGF- β (transforming growth factor β), Wnt ligands, and “andromedins” like FGF10 (fibroblast growth factor 10) can transform neighboring normal prostate epithelium (Memarzadeh et al. 2007; Franco et al. 2011; Zong et al. 2012). In addition, inclusion of mesenchymal cells, particularly through enhanced Wnt production in stromal cells induced by treatment, can promote stem-like properties in advanced prostate cancer cells (Liao et al. 2010a,b; Sun et al. 2012; Jachetti et al. 2013).

A major difference between the tissue recombination approach and GEM models is the requirement for embryonic mesenchyme as an inductive source to promote gland regeneration and tumorigenesis (Garber 2010). Given that basal cells are more readily transformed in the tissue recombination assay, they may preferentially respond to growth factors secreted by UGSM cells (Fig. 1). When specific stromal alterations have been examined for their capacity to transform isolated basal or luminal cells, basal cells have been demonstrated to preferentially respond to mesenchymal signals to initiate transformation (Lawson et al. 2010; Zong et al. 2012). These results may be explained in part by their expression of certain growth factor receptors and their native localization

against the basement membrane in close proximity to stromal cells.

Inflammation may play a critical role in luminal cell transformation

A second major difference between tissue recombination and GEM models is the presence or absence of a functional immune system. Given that studies demonstrating luminal cell-driven prostate cancer have been performed in immune-competent mice, inflammation may play a critical role in the proliferation and transformation of the luminal epithelium. In fact, inflammation has been predicted to serve as an important initiating event for the human disease. Inflammatory-related single-nucleotide polymorphisms (SNPs) are associated with prostate cancer risk (Kazma et al. 2012), suggesting that alterations in inflammatory signaling may increase susceptibility to disease. De Marzo et al. (1999, 2007a,b) have described a process, termed proliferative inflammatory atrophy (PIA), proposing that local inflammation can promote an atrophic phenotype in prostate glands, resulting in enhanced epithelial proliferation. The enhanced level of proliferation occurs most prominently within the luminal compartment, which normally has a terminally differentiated nonreplicative status (De Marzo et al. 1999, 2007a,b).

In areas of local inflammation around glands in the human prostate, luminal cells appear smaller in size and exhibit loss of cell cycle inhibitors, reduced expression of tumor suppressor proteins like p27, Nkx3-1, and Pten; reduction in androgen signaling; gain of anti-apoptotic proteins like BCL2; and an increased proliferative index (De Marzo et al. 1999, 2007a,b). Interestingly, a similar effect has been noted in the adult human pancreas, where inflammation is associated with an expansion of cells expressing progenitor markers (Ko et al. 2013). In the human prostate, an increase in luminal cell proliferation associated with inflammation—in addition to a boost of inflammatory-related cytokines in the local environment from infiltrating immune cells—likely enhances the susceptibility of epithelium to transformation (Fig. 1). Future studies will be necessary to determine whether inflammation can convert terminally differentiated luminal cells to proliferative progenitor-like cells or whether inflammation enriches for or expands a population of pre-existing intermediate-type cells within the luminal compartment (van Leenders et al. 2003).

Figure 1. Potential roles of mesenchymal and immune cell influences on the cells of origin for prostate cancer. (Left) Elevation in mesenchymal cell-derived paracrine growth factors, such as Wnt ligands or FGFs, preferentially transforms neighboring basal cells. (Right) Immune cell infiltration into the prostate results in increased luminal cell proliferation and may enhance their susceptibility to transformation.

Mouse models of prostate inflammation exhibit epithelial proliferation and increased susceptibility to prostate cancer

Mouse models have been able to replicate clinical observations associating immune infiltration with prostate epithelial proliferation (Mimeault and Batra 2013). In transgenic mouse prostates expressing the ovalbumin antigen in a *Pten* heterozygous background, the transfer of ovalbumin-specific CD8⁺ T cells (OT-1) leads to lymphocyte infiltration into the prostate, release of cytokines, and an increase in epithelial cell proliferation sustained for up to 3 mo following adoptive T-cell transfer (Haverkamp et al. 2011). Spontaneous prostatitis is found in mice lacking the autoimmune regulator gene *Aire*, which develop B- and T-cell responses to a prostate antigen (Anderson et al. 2002; Hou et al. 2009). Karin and colleagues (Ammirante et al. 2010) have shown that after castration, B cells can infiltrate into prostate tissues, release lymphotoxin- β , and have a growth-promoting effect through activation of epithelial IKK α and Stat3 signaling. Prostate-specific expression of a constitutively active form of IKK2 cooperates with *Pten* heterozygosity to promote inflammation, proliferation, and tumor progression (Birbach et al. 2011). Interestingly, the investigators note that even in control *Pten*^{+/-} mice lacking constitutively active IKK2, inflammation and occasional prostatitis were found with advanced age. Further interrogation of these models may reveal critical changes in luminal epithelium that lead to enhanced susceptibility to transformation.

Future considerations

Experimental GEM models of murine prostate cancer indicate that cells within both the basal and luminal cell layer can respond to loss of the tumor suppressor gene *Pten* by initiating prostate cancer (Wang et al. 2009; Choi et al. 2012; Lu et al. 2013; Wang et al. 2013). To date, cell of origin studies using human tissue have only described a role for basal cells in disease initiation showing their capacity to respond to both oncogene activation and chronic estrogen signaling (Goldstein et al. 2010; Taylor et al. 2012). While many luminal cells have a differentiated status, the luminal cells responding to inflammation are associated with a more proliferative status and, based on cell size and gene expression, possess more progenitor-like properties (De Marzo et al. 1999, 2007a,b). This inflammation-related acquisition of progenitor properties may increase the chances of luminal cell transformation.

While combined inactivation of two or more tumor suppressor genes in GEM models can lead to widespread prostate cancer (Ding et al. 2011), single-hit models such as *Pten* loss exhibit focal cancer development in which only a subset of target cells harboring a given genetic alteration will develop into full-blown cancer (Wang et al. 2006). Factors such as inflammation may contribute to local transformation by promoting epithelial cells to bypass senescence. For example, in the mouse esophagus and forestomach, epithelial overexpression of Sox2 can only promote progression to carcinoma when combined

with local inflammation, resulting in epithelial Stat3 activation (Liu et al. 2013). Although the extent of inflammation in GEM models of prostate cancer is not routinely reported, we might anticipate that local inflammation could induce or expand a dedifferentiated, progenitor-like luminal population. Given that androgen deprivation induces inflammation in the prostate, the castration-resistant Nkx3-1⁺ luminal (CARN) population (Wang et al. 2009) may contain inflammation-induced luminal stem/progenitor cells. To determine the precise role of inflammation in luminal cell transformation, cell type-specific deletion of *Pten* or other genetic alterations common to human prostate cancer should be evaluated in an immunodeficient genetic background. Alternatively, inflammation can be induced early on in basal- and luminal-driven prostate cancer models to determine whether cancer development is accelerated and whether the effects preferentially target one lineage. These future studies will be necessary to delineate the precise factors influencing the cells of origin for prostate cancer.

Acknowledgments

Studies from our laboratories were supported by a Prostate Cancer Foundation Challenge Award (to A.S.G. and O.N.W.), Creativity Award (to A.S.G. and O.N.W.), and Young Investigator Award (to A.S.G.); a National Cancer Institute U01 Tumor Microenvironment Grant (to A.S.G. and O.N.W.); the SU2C/AACR/PCF West Coast Dream Team on Prostate Cancer; and the California Institute for Regenerative Medicine (to A.S.G. and O.N.W.). O.N.W. is an Investigator of the Howard Hughes Medical Institute.

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Genes Dev. 2013, **27**:

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