Prostate Cancer: Beta Control Your Hormones

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Differentiation status influences the prognosis for localized prostate cancer. In this issue of *Cancer Cell*, Mak and coworkers describe a signaling pathway involving estrogen receptor β (ERβ) that governs whether prostate carcinoma cells maintain an epithelial phenotype or undergo epithelial-mesenchymal transition, suggesting that ERβ would have prognostic or therapeutic value.

Prostate cancer is the most common cancer in men and the second leading cause of cancer death in men. Charles Huggins received the Nobel Prize in 1966 for the demonstration that prostate cancers respond to the administration of estrogen or withdrawal of androgens. Unfortunately, inhibition of androgen function, with or without cytotoxic chemotherapy, is palliative, but not curative. It remains the mainstay of treatment for metastatic prostate cancer, however, because no new, validated, molecular targets have emerged for this disease in the past 50 years.

Early-stage prostate cancer, in contrast to disseminated disease, is often cured by surgery or radiation. This knowledge has motivated aggressive screening programs centered on measuring circulating prostate specific antigen (PSA). Although this strategy has undoubtedly saved lives, it has also assuredly led to the diagnosis of indolent prostate cancers that would never have become clinically manifest. Indeed, the prevalence of occult prostate cancers in autopsy series reaches as high as 80% in men 80 years and older. This potential overdiagnosis is important because both surgery and radiation can cause significant morbidities.

Traditional methods of predicting outcomes after local therapy for prostate cancer have focused on clinical and pathologic features, including the clinical stage of disease, pretreatment PSA (a measure of tumor burden), and state of tumor differentiation (Gleason score). As a result of PSA screening, however, most prostate cancers are both small and organ-confined at diagnosis. This negates the use of stage or volume as discriminatory parameters to predict aggressiveness and the subsequent development of metastases. Importantly, this leaves Gleason score as arguably the most important prognostic parameter in prostate cancer. Gleason grade is a measure of the degree of differentiation of prostate tumor cells; the sum of the primary (predominant) Gleason pattern and the secondary pattern is the Gleason score (scaled 5–10). Patients with a Gleason score ≤ 6 almost invariably have a benign, nonaggressive, clinical course, while patients with a Gleason score >8 are at high risk of recurrence and death. Unfortunately, the vast majority of newly diagnosed prostate cancers have a Gleason Score of 7, and it is not yet possible to reliably predict their outcome. This is a significant problem because approximately 30% of this subgroup will eventually relapse (Andriole et al., 2009; Schroder et al., 2009).

Estrogens, via the interaction with their receptors, regulate the growth and development of both the mammary gland and the male reproductive system. The molecular effects of estrogens on prostate epithelium are still largely unknown even though their antitumor properties have been known since the time of Huggins. Whereas estrogen receptor α (ERα) and ERβ share some structural and functional properties, individual characteristics allow them to have distinct biological functions. While the DNA-binding domains of ERα and ERβ are highly conserved, their amino termini, important for transactivation, are not. Although both receptors bind the natural ligand 17β estradiol with about equal affinity, phytoestrogens, 3β-Adiol, and some selective estrogen receptor modulators bind preferentially to either ERα or ERβ (Dutertre and Smith, 2000). Cellular localization also differs: while ERα is expressed only in stromal cell nuclei, ERβ is expressed in basal cells of normal prostatic acini, as well as in stromal cells. In addition, tumor cells only express ERβ.

In this issue of *Cancer Cell*, Mak et al. report that ERβ, when activated by its specific ligand 3β-Adiol, maintains an epithelial phenotype and represses mesenchymal characteristics in prostate cancer cells (Mak et al., 2010). The authors show that ERβ promotes the destabilization of HIF-1α and downregulates the canonical HIF target *VEGF*. Loss of ERβ therefore increases VEGF production, which engages the VEGF receptor neuropilin 1. This, in turn, leads to AKT activation, GSK3β inactivation, and ultimately, the nuclear localization of SNAIL, which promotes an epithelial to mesenchymal transition (EMT) characterized by the loss of E-cadherin and increased expression of vimentin (Figure 1A). Importantly, the authors show that high Gleason grade (poorly differentiated) prostate carcinomas exhibit decreased ERβ protein levels and increased levels of HIF1α, VEGF, and nuclear SNAIL, relative to low-grade lesions. ERβ mRNA levels were previously found to be decreased in hormone refractory prostate cancers, supporting the contention that loss of ERβ correlates with disease progression (Latil et al., 2001). On the other hand, another recent study reported that high ERβ protein levels associated with a *worse* prognosis in prostate cancer patients (Nanni et al., 2009). Clearly it will be important to understand whether these discrepancies are due to technical differences between the studies.

Hypoxia and HIF activation have been linked to the induction of EMT in other

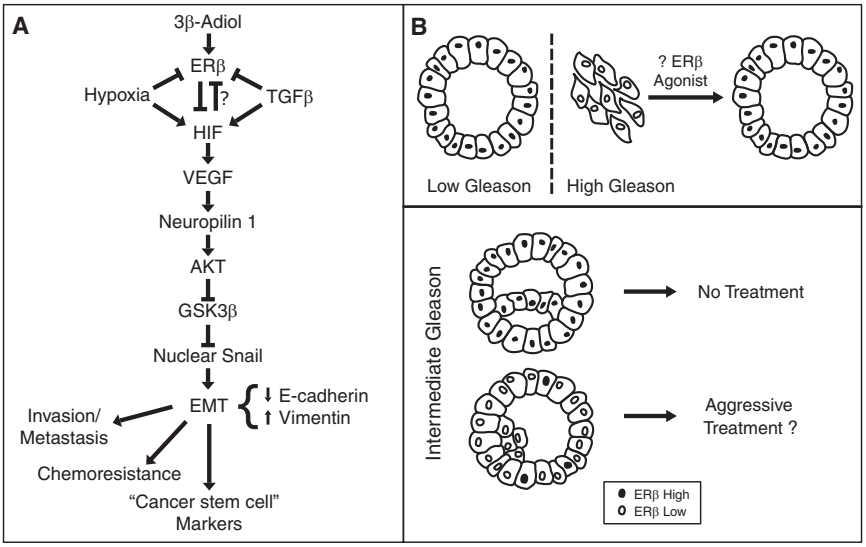

Figure 1. Regulation of EMT by ERβ

(A) Schematic linking ERβ activation by its ligand, 3β-Adiol, to inhibition of HIF and suppression of an EMT. (B) ERβ is associated with differences in prostate cancer biology. Low-grade lesions typically have high levels of ERβ, while high-grade lesions have low levels of ERβ. Treatment with an ERβ agonist might, however, promote differentiation of high-grade lesions. ERβ status might also, in time, be shown to predict outcomes for patients with intermediate-grade lesions and, hence, the need for additional therapy.

contexts. For example, loss of the VHL tumor suppressor protein leads to constitutive HIF activation, which induces renal epithelial cells to undergo EMT as a result of increased expression of transcriptional repressors such as SIP1 and SNAIL (Evans et al., 2007). EMT is believed to increase tumor cell invasiveness and, hence, metastasis, as well as chemotherapeutic resistance. Moreover, cells induced to undergo EMT in vitro upregulate cell surface markers that are used to identify "cancer stem cells" (Mani et al., 2008). The ability of HIF to induce EMT might account for the frequent association of intratumoral hypoxia and increased HIF levels with a poor prognosis in diverse cancers, including prostate cancer (Nanni et al., 2009). A caveat, however, is that aggressive tumors are more likely to outgrow their blood supplies, which leads to hypoxia and HIF stabilization. Hence, it can be difficult to tease out cause and effect from such descriptive clinical studies.

Although it is tempting to invoke EMT as a basis for aggressive cancer cell behavior in vivo, this area remains controversial. There is no convincing evidence for conversion of epithelial cells into mesenchymal cell lineages in human tumors. In fact, the appearance of vimentin staining in human tumors is taken as prima facie evidence that they are not of epithelial origin. Furthermore, the biological repertoire of carcinoma cells is sufficient to account for biologic behavior, such as development of metastases, without invoking changes in cell lineage (Tarin et al., 2005). Finally and importantly, most tumors do not dedifferentiate as they metastasize but retain the original morphology and differentiation state found in the primary tumor (Kramer et al., 1981). Nonetheless, EMT in vitro might be mirrored by more subtle state changes in vivo that influence tumor cell behavior. Moreover, such changes might be highly plastic, responsive to microenvironmental changes such as hypoxia.

The study by Mak et al. raises the possibility that measurement of ERβ and EMT markers will help to subclassify patients with intermediate Gleason scores into groups with a high or low risk of progression and, hence, guide therapeutic decision making (Figure 1B). Second, it suggests that drugs that modulate ERβ, or its downstream effectors such as HIF, VEGF, neuropilin-1, and AKT, could favorably alter the natural history of this disease. It also raises a number of questions. For example, how do hypoxia and TGFβ lead to loss of ERβ? One possibility, based on the knowledge that hypoxia and TGFβ induce HIF, is that HIF and ERβ are mutually inhibitory (Figure 1A). A second question relates to how, mechanistically, ERβ destabilizes HIF. Conceivably, ERβ regulates one or more of the prolyl hydroxylases that mark HIF for destruction. In this regard, ERα transcriptionally activates the PHD1 prolyl hydroxylase, which has recently been linked to the control of breast cancer proliferation (Zhang et al., 2009). Finally, might some of the salutary effects of high-dose estrogen in prostate cancer be mediated by ERβ? Answers to questions such as these might eventually add a new chapter to the story begun by Huggins.

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