COMMENTARY

Transforming growth factor-β receptor III downregulation in prostate cancer: is inhibin B a tumor suppressor in prostate?

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Abstract

The transforming growth factor-β (TGF-β) pathway plays dual roles in cancer, inhibiting epithelial cell growth under normal physiologic conditions, but promoting invasion and metastasis once growth inhibitory responses are lost. Two recent papers show that TGF-β receptor III is the most common TGF-β pathway component downregulated in prostate cancer. Here, we discuss the implications of these findings and what it may mean about the biology of this disease.

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Text

One of the six hallmarks of cancer proposed by Hanahan & Weinberg (2000) is an acquired insensitivity to inhibitors of cell growth. Transforming growth factor-β (TGF-β) is probably the best-characterized antigrowth pathway. Acquired resistance to growth inhibition induced by TGF-β signaling is a characteristic of the early stages of many solid tumors (Elliott & Blobe 2005). The canonical TGF-β pathway involves the heterodimerization of TGF-β receptor I (TGFβRI) and TGFβRII, followed by phosphorylation and activation of TGFβRI by TGFβRII. A third receptor, TGFβRIII, is involved in TGF-β signaling, with a function that is not well defined and will be discussed further later. Once activated by TGFβRII, TGFβRII phosphorylates SMAD2 and SMAD3 (the receptor SMADs or R-SMADs) and these phosphorylated R-SMADs associate with the common SMAD, SMAD4. The phosphorylated R-SMAD/SMAD4 complex is retained in the nucleus, where it regulates the transcription of TGF-β responsive genes (Shi & Massague 2003).

Accordingly, resistance to TGF-β signaling is mediated by perturbations in various members of this pathway. The mechanisms of resistance in many solid tumors are well defined. For example, mutations in TGFβRII are frequently found in colon cancer (Grady et al. 1999) and SMAD4 deletions are found in pancreatic tumors (Hahn et al. 1996). In prostate cancer, loss of TGFβRI or TGFβRII expression is found in about 30% of cases (Kim et al. 1996, Guo et al. 1997), but the mechanism of TGF-β resistance in the majority of prostate cancers remained undefined. This prompted two recent studies of TGFβRIII in prostate cancer, both of which suggest that loss of TGFβRIII expression is the most commonly perturbed TGF-β pathway component in prostate cancer (Sharifi et al. 2007, Turley et al. 2007).

Sharifi et al. (2007) sought to address changes in the expression of TGF-β pathway components in prostate cancer. Using Oncomine, a freely available web-based database of DNA microarray studies of various malignancies (Rhodes et al. 2004), they found that TGFβRIII is the most commonly downregulated TGF-β component across seven DNA microarray studies of benign prostate versus localized prostate cancer. Then, TGFβRIII mRNA was also found to be downregulated in the majority of prostate cancer cell lines tested. To determine if TGFβRIII downregulation might play a role in development of prostate intraepithelial neoplasia (PIN), a precursor to invasive prostate cancer, the effect of TGFβRIII downregulation on markers of carcinogenesis was evaluated. These studies showed that TGFβRIII levels had significant effects on vimentin expression. shRNA knockdown of TGFβRIII in non-cancerous prostate epithelial cells leads to downregulation of vimentin mRNA and protein, indicating that TGFβRIII controls vimentin expression. This is significant because vimentin expression is decreased in the transition from benign prostate to local prostate cancer in the majority of DNA microarray studies in Oncomine, and previously published findings show that vimentin protein is expressed in benign prostate and
lost in prostate cancer and PIN (Nagle et al. 1991). Since vimentin expression is lost as early as PIN and is dependent on TGFβRIII for expression, it follows that TGFβRIII may be lost as early as PIN. This hypothesis was confirmed in another set of studies by Turley et al. (2007) who examined TGFβRIII protein by immunochemistry and showed decreased expression in clinical prostate cancer specimens. Loss of TGFβRIII at the mRNA level was confirmed using Oncomine. Furthermore, it was found that the protein is downregulated in the transition from benign prostate to high-grade PIN and that TGFβRIII loss occurs continuously throughout progression of prostate cancer.

These two studies also reveal the phenotypic and genetic consequences of TGFβRIII expression. Sharifi et al. (2007) showed that shRNA knockdown of TGFβRIII in an immortalized prostate epithelial cell line causes focus formation, increased cell surface expression of a prostate stem cell marker and downregulation of one of the most potent inhibitors of angiogenesis, SERPINF1 (also known as pigment epithelium derived growth factor; Doll et al. 2003). Turley et al. (2007) reexpressed TGFβRIII in a prostate cancer cell line that had lost expression, and showed decreased cell migration, invasiveness and tumorigenicity. Together, these studies strongly support a role for TGFβRIII as a tumor suppressor in prostate cancer.

Despite the findings of TGFβRIII downregulation and characterization of phenotypic changes that correlate with TGFβRIII expression, the exact function of TGFβRIII in the prostate remains unclear. TGFβRIII can affect prostate epithelial signaling through at least four mechanisms. First, TGFβRIII acts as a coreceptor and enhances TGF-β signaling by augmenting ligand binding to TGFβRII (Wang et al. 1991). This function would support the role of TGFβRIII loss as a means of resistance to the canonical TGF-β pathway early in prostate tumorigenesis. Second, involves the role of the soluble form of TGFβRIII. Soluble TGFβRIII is formed by proteolytic cleavage of the extracellular domain and can antagonize TGF-β function by TGF-β ligand sequestration (Lopez-Casillas et al. 1994). In this scenario, loss of TGFβRIII would lead to an increase in TGF-β signaling, and increased inhibitory responses in the absence of other pathway perturbations. Third, is the possibility that TGFβRIII may function in a noncanonical pathway. TGFβRIII can interact with Gα-interacting proteins and β-arrestins (Turley et al. 2007). This supports a signaling role that may be
independent of the SMADs. It is possible that this pathway is necessary for growth inhibitory responses or maintenance of normal tissue architecture.

A fourth and very interesting possibility, however, is that TGFβRIII downregulation plays an altogether different role in the prostate. In addition to acting as a coreceptor for TGF-β ligands, TGFβRIII is also a receptor for and tightly binds inhibins, which are TGF-β superfamily cytokines that have antagonistic actions to activins (Lewis et al. 2000). In most systems studied, activins have similar properties to TGF-β and signal through the same SMAD pathway (Massague et al. 2005). The antagonistic property of inhibin has to do with inhibin binding the type II activin receptor and TGFβRIII, forming a complex that interferes with activin binding the type II receptor, thereby inhibiting signal transduction. Although inhibins are mechanistically antagonistic to activin-mediated signal transduction, a signaling mechanism for inhibins that does not involve activin antagonism has not been ruled out. Whatever the function of inhibins may be downstream of TGFβRIII, this may have hormonal and physiological implications for prostate biology.

Inhibins have an important role in male reproduction and reproductive organs (O’Connor & De Kretser 2004). Inhibin B is secreted by the testes, found in circulating blood, and correlates with male fertility. The following model that we propose is of a role for TGFβRIII and inhibin B in prostate biology that is antagonistic and may be physiologically complementary to the role of androgens. Androgens produced by the testes stimulate the growth of prostate cancer cells and androgen deprivation reverses this growth stimulation (Sharifi et al. 2005). Androgens are also involved in stimulating the development of PIN and early prostate tumorigenesis (Tomlins et al. 2007). Inhibins may act as a negative regulator of prostate growth, in which case TGFβRIII downregulation in prostate cancer may represent resistance to testicular inhibin B (Fig. 1). Furthermore, male inhibin-α subunit knockout mice form tumors in both testes and adrenal glands (Matzuk et al. 1992, 1994), which may reflect loss of feedback inhibition on these organs. If gonadal inhibin is a prostate tumor suppressor, prostate cancer may be expected from inhibin knockout mice. However, these mice die of gonadal stromal tumors. To allow prolonged survival, inhibin knockout mice had to be gonadectomized and the consequent loss of this major source of androgens may explain why prostate tumors were not observed. It may also be physiologically relevant that both of the organs – testes and adrenals – that produce androgens and inhibins, form tumors when inhibin is knocked out in mouse. Together, these data combined with the observation of TGFβRIII downregulation in prostate cancer suggest that there may be a role for inhibin-mediated tumor suppression in prostate. Inhibins have had a controversial role in prostate cancer where its expression has been studied mainly in prostate tissue (Ball et al. 2004); it may be that the relevant perturbation in signaling had not been described prior to these two studies of TGFβRIII in the prostate. If TGFβRIII downregulation in prostate cancer signifies inhibin resistance, it may open a new window on hormonal physiology and an interplay between hormones and cancer.

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