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More than an accessory: implications of type III transforming growth factor- β receptor loss in prostate cancer

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Abstract

The type III transforming growth factor- β receptor (TGF β R3, betaglycan), a tumour suppressor, is the most frequently lost TGF β pathway component. This event appears to be very important in the transition of the TGF β pathway from having tumour-suppressor activity in early prostate tumour development, to having tumour-promoting activity in metastatic disease. Moreover, loss of the TGF β R3 can also affect the cellular response towards testosterone, inhibin/activin, and dysregulate growth-factor pathways that mediate growth and angiogenesis. In this review we discuss how TGF β R3 normally functions as an accessory protein in the TGF β pathway how its loss is related to tumour progression, and the treatment implications of TGF β R3 loss in individuals with prostate cancer.

Keywords

betaglycan; TGF β III receptor; prostate cancer; testosterone

INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer and is the second leading cause of cancer-related death in men in the USA[1]. Many men will develop recurrent metastatic disease after initial surgery and radiotherapy, and depending on the stage of the disease, early androgen-dependent metastatic prostate cancer is typically treated with androgen-deprivation therapy (ADT). Men with early androgen-dependent, metastatic

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CONFLICT OF INTEREST

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disease are administered GnRH agonists that result in inhibition of FSH and LH production, and ultimately inhibition of testosterone production by the testes. Eventually most men with androgen-dependent prostate cancer will progress to androgen-independent prostate cancer (AIPC) that carries a poor prognosis and short life-expectancy [2].

The type III TGF β receptor (TGF β R3, betaglycan) has recently surfaced as a tumour suppressor within the prostate, and its loss in prostate cancer promotes tumour progression [3,4]. TGF β R3 might also be involved in the overall regulation of testosterone production by the testes [5]. Given its classical role as an accessory protein, i.e TGF β R3 has no signalling domain, but rather facilitates the ligand binding of TGF β R1/2 [6], the significance of TGF β R3 in the development and progression of cancer might have been overlooked. However, recent findings have elucidated the vital role of TGF β R3 within the TGF β pathway, and within other pathways [3,7] that regulate both prostate cell homeostasis and tumour progression. Although the precise role of TGF β R3 signaling in cancer development and progression remains unclear, TGF β R3 appears to have a greater role in this process than previously suspected, and is more than just an accessory protein. The purpose of this review is to describe a potential role for TGF β R3 in prostate homeostasis to explore how TGF β R3 loss in prostate cells might affect prostate tumour progression, and finally to describe how TGF β R3 loss could affect the clinical treatment of prostate cancer.

THE TGF β R3 SIGNALLING PATHWAY

TGF β R3 is a transmembrane protein that classically functions in the TGF β pathway by binding a reservoir of TGF β ligand at the cell surface, and transferring that ligand to the type II receptor (TGF β R2; Fig. 1 [8]). Signalling via TGF β -2 is completely dependent on transfer of the TGF β ligand from TGF β R3, as TGF β R2 has a low affinity for TGF β 2, the ligand-binding receptor that initiates the TGF β signalling cascade [3,7]. On stimulation from ligand transfer, TGF β R2 binds and phosphorylates the type I receptor (TGF β R1), which in turn phosphorylates either the Smad2 or Smad3 transcription factor. Phosphorylation of Smad2/3 promotes binding to Smad4. The whole complex is then translocated into the nucleus where it regulates the transcription of myriad genes related to growth inhibition, production of the extracellular matrix, and apoptosis among others [9]. It was previously thought that the cytoplasmic domain of TGF β R3 served little or no function, but Blobe *et al.* [6] showed that deletion of the cytoplasmic domain retards the ability of TGF β R3 to propagate signalling through TGF β 2 and that the TGF β R2/1 receptor complex cannot dissociate from TGF β R3 without its cytoplasmic domain. Another proposed mechanism of TGF β R3-mediated tumour suppression is through a soluble form of the receptor (sTGF β R3), produced by proteolytic cleavage of the extracellular domain. Extracellular TGF β binding through sTGF β R3 hinders binding of the ligand to TGF β R2 and attenuate signalling [4]. Finally although TGF β R3 is not required for the transfer of TGF β 1 [6], sTGF β R3 binds to extracellular TGF β 1, thereby also inhibiting signalling through this cytokine [10].

In addition to its participation in classical TGF β signalling, TGF β R3 also binds basic fibroblast growth factor (bFGF) via its heparin sulphate chains, and might be involved in an interaction between TGF β and bFGF signalling pathways, or presentation of the bFGF

ligand to its receptor [11]. As will be discussed in subsequent sections, TGF β R3 also binds inhibins produced by the testes, thus opposing tumour growth promotion via activins, and playing a role in the overall regulation of the prostate towards testosterone secretion pathways via the hypothalamic-pituitary-testes axis [4]. Recently, *in vitro* studies have shown that TGF β R3 also inhibits breast, ovarian, and prostate cancer cell migration [3,7].

IMPLICATIONS OF TGF β R3 ON FSH SECRETION AND TESTOSTERONE REGULATION

Gonadal androgen production is regulated by signals from the hypothalamus and pituitary gland (Fig. 2). GnRH is released from the hypothalamus, causing the secretion of LH and FSH from the pituitary gland. LH signalling in the Leydig cells of the testes stimulates testosterone synthesis, while FSH is instrumental in the production of LH receptors in the Sertoli cells [2]. In Sertoli cells, FSH also increases the production of androgen-binding protein, thereby promoting spermatogenesis and stimulating inhibin production, providing a negative feedback loop that opposes FSH secretion by the pituitary [2,5]. In this way FSH and LH constitute a self-regulating pathway that regulates overall androgen secretion by the testes.

Testosterone secretion is further regulated by activins and inhibins, that are also members of the TGF β family and each antagonises the action of the other. Activins work synergistically with GnRH in the pituitary by increasing the number of GnRH receptors at the surface of pituitary cells and up-regulating the transcription of the FSH monomer and the secretion of mature FSH [12]. Inhibins are co-secreted from the testes with testosterone upon LH stimulus and act in a negative-feedback loop to attenuate the release of FSH from the pituitary gland [5].

The activin signalling pathway is similar to the aforementioned TGF β pathway. Activin binds to the type II activin receptor, which complexes with and phosphorylates the type I activin receptor. Transcriptional regulation of activin responsive genes is mediated through the same Smad proteins involved in TGF β signalling [13]. Activins are necessary but not sufficient for prostate cancer cell growth, promote adhesion, cell viability [14] and cell migration through bone matrices and bone metastasis in men with prostate cancer [15]. The only known function of inhibin is to antagonize activin signalling [16].

TGF β R3 mediates inhibin antagonism of activin signalling by forming a complex between TGF β R3 and the type II activin receptor, which prevents the binding of activin ligand. HEK-293T cells treated with a fixed concentration of activin and varying concentrations of inhibin showed elevated activin promoter-controlled luciferase activity when transfected with TGF β R3 shRNA or treated with TGF β R3 IgG. Conversely, cells transfected with control shRNA or IgG had a concentration-dependent decrease in luciferase activity in response to inhibin treatment [5]. As will be explored in later sections TGF β R3 expression is lost during prostate cancer progression [3,17]. Thus while prostate cancer has typically been thought of as a disease driven by androgen secretion, and is treated with ADT in the context of early metastatic disease [18], TGF β R3 appears to regulate a separate pathway that is also driven by the hypothalamus-pituitary-testes axis. Therefore, the loss of TGF β R3

might have implications for prostate cancer progression to an androgen-independent state, and it might affect the treatment of prostate cancer with ADT.

IMPLICATIONS OF THE LOSS OF TGF β R3 ON METASTATIC PROSTATE CANCER PROGRESSION

TGF β signalling has tumour-suppressor activity that has implications for early tumour development but it also has tumour-promoting activity in metastatic disease [6,9]. TGF β R3 is the most frequently lost component of the TGF β pathway in prostate cancer [17], and the loss of TGF β R3 coincides with more aggressive and metastatic disease, indicating that TGF β R3 might be a tumour suppressor in prostate cancer [3,17]. Although the mechanism behind prostate tumour promotion in the absence of TGF β R3 is currently unclear, its loss appears to affect several cellular functions important in tumour progression. Firstly, the loss of TGF β R3 would be expected to promote increases in vascularity, tumour grade, and metastasis brought on by up-regulation of TGF β 1 signaling in prostate cancer [10]. Indeed, TGF β 1 up-regulation is observed in more advanced disease [19]. Second, loss of TGF β R3 might also be involved in dysregulating bFGF, thereby promoting its growth and angiogenic potential [11]. Finally, recent evidence suggests that the loss of TGF β R3 might be involved in tumour growth promotion through activin signalling, given that TGF β R3 normally suppresses activins by binding inhibins within the prostate itself [4]. Moreover, androgen receptor (AR) gene expression is also up-regulated by activin (via SMAD2 and SMAD3) in patients with bone metastases and activin signalling promotes AR expression through Smad binding sites on the AR promoter [15].

TGF β R3 had previously been shown to slow the migration of prostate cancer cells [3]. However, if TGF β R3 mediates inhibin antagonism of activin signalling in prostate cells and if activin signaling increases AR gene expression, then the loss of TGF β R3 might also signify progression to AIPC [20, 21]. Perhaps prostate tumour cells evade tumour suppression from inhibins by down-regulating the expression of TGF β R3 [4]. Therefore, while further studies are warranted to clarify the mechanism behind TGF β R3 loss, it appears that this event promotes tumour growth, metastasis, angiogenesis, and might provide a means to evade androgen regulation within prostate cells.

IMPLICATIONS OF TGF β R3 LOSS ON PROSTATE CANCER TREATMENT

Early studies evaluating the prognostic potential of TGF β R3 loss have validated that it is associated with the transition from benign to malignant disease [3,17]. Other evidence suggests that its loss is associated with increases in tumour grade, evasion of endogenous growth suppression through inhibins, AR expression, angiogenesis, migration, and metastasis [4,10,11,15,19–21]. However, larger studies in patients with prostate cancer are required to clinically validate TGF β R3 loss as a biomarker for prostate cancer progression that might require more aggressive treatment with anti-angiogenesis agents (e.g. bevacizumab, sorafenib, dasatinib, thalidomide, etc.), or agents targeting the AR (e.g. bicalutimide). Introduction of sTGF β R3 might also provide a means to inhibit prostate cancer growth by binding and sequestering TGF β ligands in the metastatic setting. Preclinical studies on mouse xenograft tumours treated with sTGF β R3 administered by

ether an osmotic pump or bolus i.p. injections yielded promising results. Tumours treated with sTGF β R3 were up to 3.7 times smaller than those treated with a placebo, regardless of the formulation. Tumours were significantly less vascularized, had significantly more intratumoral apoptosis, expressed significantly less matrix metalloprotease-9, which is up-regulated by TGF β 1 and implicated in angiogenesis. sTGF β R3 was also well tolerated in all mice at both low and high doses [10].

The most important application of TGF β R3-based therapy in prostate cancer might be that TGF β R3 is central to prostate tumour progression in a low-testosterone environment during ADT. Inhibin secretion is actually decreased by surgical castration [12], and might also be decreased by chemical castration (i.e. ADT) as a result of reduced testosterone and FSH secretion, thereby promoting activin signalling pathways. If the tumour lacks TGF β R3 expression, it could be expected that ADT would actually promote tumour progression through activin-related signalling. Moreover, TGF β R3 loss might be involved in AR reactivation during ADT as a result of increased activin signalling [15], resulting in a tumour phenotype that is able to use AR signalling even in a low-androgen environment. However, these hypotheses have yet to be explored in the context of ADT.

CONCLUSIONS

TGF β R3 is a major regulator of inhibition of prostate tumour growth, regulating not only the TGF β pathway, but also other pathways involved in tumour growth, angiogenesis and metastasis. The loss of TGF β R3 in prostate cancer could be a means of evading gonadal and paracrine inhibin signalling, and even be an important step to the transition from androgen-dependent to androgen-independent disease. Although more research is required to fully exploit the therapeutic potential of TGF β R3 in prostate cancer, initial studies suggest that it might be an important target in the treatment of early metastatic prostate cancer.

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Abbreviations:

ADT	androgen-deprivation therapy
AR	androgen receptor
AIPC	androgen-independent prostate cancer
(s)TGFβ	(soluble) TGF β receptor
bFGF	basic fibroblast growth factor

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FIG 1.

The role of TGFβ R3 in normal cell homeostasis, TGFβ R3 binds TGFβ, and transfers the ligand to the TGFβ R2 receptor followed by TGFβ R1 binding and phosphorylation. This results in phosphorylation of Smads and subsequent transcription. sTGFβ R3 also binds TGFβ ligand, preventing signalling through the TGFβ R2 receptor, and binds bFGF through proteoglycan chains on the cytoplasmic domain.

FIG. 2.
The role of TGFβ R3 in activin/inhibin signaling pathways in normal prostate homeostasis. TGFβ R3 binds inhibin and prevents activin binding of activin receptor IIA (ACIRIIA) and ACIRIIB. Factors in green promote prostate growth pathways, pathways in red suppress prostate tumour formation and progression, while pathways in orange promote spermatogenesis.