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*Review Article*

# Alterations in TGFβ signaling during prostate cancer progression

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**Abstract:** During prostate cancer progression, TGF-β acts as both a tumor suppressor and tumor promoter. TGF-β inhibits cell proliferation in normal and early-stage prostate cancer cells, but during later stages of the disease the cancer cells develop resistance to inhibitory effects on cell proliferation. In these cells, TGF-β promotes cancer progression due to its effects on epithelial to mesenchymal transition (EMT), cell migration and invasion, and immune suppression. The intracellular mechanisms involved in the development of resistance to TGF-β effects on cell proliferation are largely unknown. In this review, we summarized the roles of several intracellular proteins including PTEN, Id1 and JunD, which may play a role in this transition. The role of Ski/SnoN proteins in inhibition of Smad2/3 signaling is highlighted.

**Keywords:** TGF-β signaling, prostate cancer, cell proliferation, Ski/SnoN, JunD, Id1

## Introduction

The transforming growth factor beta (TGF-β) superfamily is a large family of growth factors named after the first member TGF-β1 and are similar in structure [1]. TGF-β superfamily ligands and receptors are widely expressed in invertebrate and vertebrate species and they play roles in dorso-ventral patterning, mesoderm induction and patterning, limb bud formation, bone and cartilage formation, and neuron differentiation [1]. Furthermore, TGF-β superfamily is essential in the development of a variety of tissues and organs [1, 2]. The transforming growth factor-β (TGF-β) superfamily also regulates processes at the tissue and organism level such as development, wound healing, fibrosis, and angiogenesis [3, 4]. At the cellular level, TGF-β superfamily signaling is involved in regulating intracellular processes involved in cell proliferation, differentiation, motility, adhesion, and apoptosis [3, 4]. The TGF-β superfamily of ligands includes Bone morphogenetic proteins (BMPs), Growth and differentiation factors (GDFs), Anti-Müllerian hormone (AMH), Activin, Nodal and TGF-βs [5]. For this review, we will discuss the complex network of TGF-β signaling pathway intersecting with several signaling molecules and their involvement in prostate cancer development and progression.

The TGF-β family consists of three isoforms, TGF-β1, TGF-β2 and TGF-β3 which exhibit 70-80% homology in most organisms [6, 7]. All three isoforms bind to the same membrane receptors and exhibit similar biological functions in cell based in vitro assays; however, differences in the potency of individual isoforms in these assays have been reported [8-11]. In addition, studies from knockout mice have shown that the three isoforms exhibit specific non-redundant biological functions in vivo [12-15]. TGF-β signaling is one of the most studied pathways in molecular biology and has several growth and development roles in nonmalignant and malignant cells [1, 16]. TGF-β signals through membrane serine/threonine kinase receptors, TGFβRI and TGFβRII. TGF-β binds to specific TGF-βRII which then recruits and phosphorylates TGFβRI leading to the activation of TGF-βRI [17]. Next, activated TGF-βRI recruits and phosphorylates SMAD2 and SMAD3 proteins. Activated Smad2/Smad3 form complexes with the cytosolic SMAD4 and these complexes are translocated to the nucleus to regulate target gene expression [17]. Conversely,

inhibitory SMADs, SMAD6/7, negatively regulate SMAD2/3 activity and nuclear translocation [18]. Activation of TGF-β leads to increased expression of SMAD7 which binds to TGFβRI to inhibit SMAD2/3 phosphorylation. In addition, SMAD7 induces proteasomal degradation of TGFβRI, TGFβRII and other SMAD proteins leading to attenuation of TGFβ signaling [19].

## TGFβ in prostate cancer

Functional development of epithelial tissues depends on cell proliferation followed by functional differentiation. Transforming growth factor-β (TGF-β) family plays critical roles in embryonic development and differentiation of glandular epithelial tissues including mammary, prostate, salivary and sebaceous glands [20-22]. During prostate development, paracrine signaling between epithelial and mesenchymal cells, involving TGF-β family members and androgen receptor (AR), instructs prostate morphogenesis [23]. In the adults, prostate epithelial component is comprised of a bilayer of two major cell types, luminal and basal cells. The luminal cells exhibit columnar morphology and represent the exocrine component of the epithelium, express androgen receptor (AR) and secrete prostate specific antigen (PSA). The basal cells are flattened cells which are located above the basal membrane and express low or undetectable AR [24]. Once terminally differentiated, luminal epithelial cells do not undergo cell proliferation. TGF-β plays a significant role in inhibition of cell proliferation and maintenance of differentiated function and morphology in in these cells [25-27]. TGF-β secreted by stromal cells inhibits proliferation and induces apoptosis of epithelial cells to maintain homeostasis [28, 29]. Loss of TGFβ effects on inhibition of cell proliferation results in increased cell division and de-differentiation of columnar epithelial cells leading to several lesions including carcinogenesis [30-32]. Prostate cancer is the second most diagnosed type of cancer found in men in the United States [33]. The American Cancer Society predicts that 1 in every 9 men will be diagnosed with prostate cancer during their lifetimes. According to American Cancer Society, 191,930 men will be diagnosed, and 33,330 men will die of prostate cancer in US in 2021.

TGF-β plays a dual role in prostate cancer; it acts as a major anti-proliferative factor in the initial stages of prostate cancer, while in the advanced stages of prostate cancer it acquires pro-oncogenic and pro-metastatic properties [25-27]. TGF-β secreted by stromal cells in the normal prostate exerts significant inhibitory effects on the proliferation of epithelial cells [28, 29]. Prostate tumor cells develop resistance to growth inhibitory effects of TGF-β [34] which leads to uncontrolled cell proliferation and plays a critical role in carcinogenesis [35-37]. It has been shown that loss of TGF-β type II receptor expression correlates with increasing tumor aggressiveness in prostate cancer [38]. However, the loss of TGFβ receptors and/or other components of TGF-β signaling may only be partly responsible for the resistance of tumor cells to growth inhibitory effects of TGF-β. A significant fraction of prostate cancers become TGFβ-resistant without mutation, deletion, or down-regulation of TGF-β receptors or Smad proteins or other downstream signaling molecules. The cellular and molecular mechanisms involved in development of resistance to TGF-β effects on cell proliferation in the presence of otherwise normal TGF-β signaling are not well known. Concomitant with the switch of TGF-β from growth inhibitory to growth-promoting signal, expression of TGF-β ligands and receptors is known to be altered in prostate cancer relative to normal prostate cells and is further altered in more aggressive androgen-refractory prostate cancer cells [38, 39]. Indeed, inhibition of TGF-β receptors led to decreased proliferation in murine model of HGPIN, suggesting that TGF-β act as tumor promoter instead of tumor suppressor already in these cells [40]. The study of TGF-β signaling pathway has been considered as a potential therapeutic target to treat prostate cancer and TGF-β receptor inhibitors have been evaluated in preclinical *in vivo* models and in the clinical setting in prostate cancer patients [18]. However, because of the dual role of TGF-β as both tumor suppressor and tumor promoter during different stages of disease, inhibition of its signaling could be challenging in eliciting a therapeutic effect [18].

## TGFβ signaling in cell proliferation

TGF-β is a pleiotropic cytokine whose signaling outcome is known to depend on the combination of available contributing factors and active pathways in each target tissue acting through both Smad dependent and independent mech-

anisms. It has also been well established that extensive interactions exist between TGF-β signaling pathway and other major signaling pathways including Wnt, Notch, Hedgehog, JNK, MAPK and AKT/PI3K [41-45]. TGFβ also regulates non-SMAD signaling pathways, such as, RhoA, MAPK, m-TOR, RAS, PI3K/AKT, c-Src, protein phosphatase 2A/p70s6K [6, 46] as well as the actin cytoskeleton effector cofilin [47, 48]. TGF-β signaling also intersects with several transcription factors, such as GL1, SOX4, Tieg3/Klf11, Id and AP-1 proteins [11, 49-52]. TGF-β inhibits proliferation and induces apoptosis in normal prostate epithelial cells and in the early stages of prostate cancer cells. When activated SMAD cascade leads to $G_1$ cell cycle arrest as a consequence of up-regulation of cyclin-dependent kinase inhibitors [17, 18] and down-regulation of Id1 [53] and c-Myc [54, 55] in target cells [56].

In advanced prostate cancer, the cancer cells become resistant to inhibitory effects of TGF-β on cell cycle arrest and cell proliferation presumably as a consequence of disruption of functional distribution of action between SMAD-dependent and Smad-independent signaling. As a result, TGF-β switches from a tumor suppressor to a tumor promoter allowing prostate cancer progression to metastasis [48]. Therefore, it is critical to determine the role of Smad-independent signaling pathways and other transcriptional regulators in development of resistance to inhibitory TGF-β on cell proliferation in prostate cancer cells. As described below, studies from our laboratory and others have shown that Id, AP-1 transcriptional regulators, Ski/SnoN, and PTEN proteins may play a significant role in the development of resistance to TGF-β effects on cell proliferation in prostate and other epithelial cancers.

### Role of Id-1 in TGFβ effects on cell proliferation

Id-1 (inhibitor of differentiation or DNA binding) protein belong to the helix-loop-helix (HLH) transcription factor family [57]. This family of proteins (Id-1, Id2, Id3, and Id4) lack a DNA binding domain, and thus function as dominant negative inhibitors of basic HLH (bHLH) transcriptional factors. They make dimers with other bHLH transcription factors, thereby inhibiting their effects on a wide variety of cellular functions [57]. Id proteins are critical in both developmental processes and cell cycle regulation that ultimately balances cell growth and cell differentiation [58-60]. These proteins tightly regulate the expression of cell cycle regulators, and its expression is usually positively regulated in undifferentiated, highly proliferative, embryonic or cancer cells [61, 62]. While all members of the Id family are expressed in many tissues and organs, they are differentially regulated, and they show distinctive expression patterns during the specific differentiation processes during normal development. For example, distributions of Id-1, -2, and -3 proteins show similar expression patterns in developing neuroblasts, while 1d-4 shows a unique pattern of distribution in migrating neurons [63-65]. Numerous studies have demonstrated specific roles of Id proteins in several contexts. Of all the Id family of proteins, Id-1 has been shown to be highly linked to cell proliferation and survival, cellular senescence, and tumorigenesis [60-62] while Id-4 has been shown to inhibit cell proliferation and act as a tumor suppressor [66]. Several studies have shown that Id-1 promotes cell proliferation and cell cycle progression through inactivation of tumor suppressors or cell cycle inhibitors including p16, p21, and p21 and activation of growth promoting pathways in mammalian cells [58, 67, 68]. Among several signaling mechanisms, TGF-β signaling pathway has been indicated as responsible for the action of Id-1 in promoting cell survival, differentiation, triggering epithelial-mesenchymal transition (EMT) in premalignant prostate epithelial progenitors, thus ultimately leading to tumorigenesis [69, 70]. We and others have confirmed an association between Id-1 and TGF-β signaling. Previous studies indicate TGF-β1 as an upstream effector of Id-1 expression in normal prostate epithelial cells, whereby its downregulation induced by TGF-β1 is mediated by Smad3 signaling in breast and colorectal cancer cells, by binding directly to the Id1 promoter [70, 71]. While TGF-β functions as a tumor suppressor in normal epithelial cell, thereby maintaining the context of the cells; during early cancer development, TGF-β switches its mechanisms thereby promoting cellular proliferation, and ultimately cancer progression [5, 11, 72, 73]. We previously demonstrated the inhibitory effects of TGF-β stimulus on normal prostate epithelial cell proliferation and early-stage

prostate cancer cell lines, whereas later stage prostate cancer cells developed resistance to TGF-β stimuli [5]. Results from our further studies indicate a robust correlation between Id-1 down-regulation and TGF-β-induced inhibition of cell proliferation [5]. In these studies, we demonstrated that treatment with TGF-β decreased Id-1 protein levels in normal prostate and prostate cancer cells representing early-stage of development while TGF-β significantly increased Id1 and Id3 expression and induced migratory capabilities in more aggressive forms of prostate cancer cells [5]. These results demonstrated that a loss of downregulation of Id1 by TGF-β leads to development of resistance to inhibitory effects of TGF-β on cell proliferation. Stimulatory role of Id1 in prostate cancer cells was confirmed by significant reduction in cell proliferation in both DU145 and PC3 cells after knockdown of endogenous Id1 protein [5]. Several studies have demonstrated the function of Id-1 and have confirmed that increased Id-1 expression is associated with cell proliferation, immortalization, invasion, and aggressive malignant phenotype in several human cell lines [69, 74, 75]. Its overexpression has been found in many types of human cancers, most of them of the epithelia origin; thus its expression levels has been indicated as a marker for malignant progression in over 20 types of human cancers suggesting its role as an oncogene [69, 74, 75]. For example, a study on the expression of Id-1 in human prostate cancer demonstrated that 100% of prostate cancer specimens were found to express Id-1 at significant levels, while only 20% cases of benign prostate hyperplasia and 0% of normal prostate specimens were positive for 1d-1 expression [76]. Similar results have been reported in many other cancer types as well [77, 78].

### Role of PTEN in TGFβ effects on cell proliferation

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) is a well-known tumor suppressor gene, frequently mutated in variety human cancers [79-81]. An in-depth collection of studies by several groups have demonstrated that PTEN regulates cell growth, apoptosis, and cell proliferation [79, 80]. PTEN acts as a tumor suppressor gene through its inhibition of phosphatidylinosito-3-kinase (PI3K)/AKT signaling pathway thus inhibiting cellular growth and survival [81-84]. PTEN activity is lost by mutations, deletions, or promoter methylation silencing at high frequency in many primary and metastatic human cancers [81, 83]. PTEN function can be compromised by genetic mutations, which can result in either a heterozygous loss usually detected in up to 60% of localized PCa or a homozygous loss normally linked to metastasis and androgen-independent progression [80, 85, 86]. The loss of function of the PTEN tumor suppressor, resulting in dysregulated activation of the PI3K/AKT signaling network, is recognized as one of the most common driving events in human cancers including prostate cancer development [80, 82, 87]. In fact, up to 70% of men with prostate cancer are estimated to have lost a copy of the PTEN gene at the time of diagnosis [88]. Activating mutations of the PI3-kinase pathway and loss of PTEN are extremely common in advanced cancer tumor progression [89], and has been previously shown that PTEN mutations in prostate cancers have led to higher basal levels of phosphorylated AKT ($pAKT^{Ser473}$) and increased survival of cells [87, 89, 90]. Numerous groups have employed studies to examine the role of PTEN's activity in prostate cancer progression with signaling molecules/pathways, including TGF-β signaling mechanisms. The loss of PTEN expression in human cancer had been indicated to contribute to TGF-β's role as a tumor enhancer with specific effects on cellular motility and invasion [91]. Previous studies demonstrated that specifically TGF-β3 isoform increased the invasiveness of endometrial carcinoma cells via a PI3-kinase-dependent pathway, which were distinct from TGF-β1 [11]. Similarly, our previous studies indicated TGF-β3 with more potent effects on inducing migratory and invasive behaviors in metastatic PCa cells compared to TGF-β1 effects [11]. Furthermore, these effects on migration and invasion in these cells are dependent on both TGF-βRI (TGF-β Receptor I) and Smad-3 and are mediated via the PI3-kinase pathway [11, 72, 92-94]. We also investigated the effects of TGF-β on PTEN expression in prostate cancer cells to determine whether PTEN play a role in TGF-β-induced effects on proliferation, migration, and activation of PI3-kinase/AKT pathway. Our recent studies have shown that TGF-β increases the stability of PTEN protein in normal and early stage prostate cancer cells which plays a role in its inhibitory effects on cell proliferation

while the lack of PTEN in metastatic prostate cancer cells resulted in enhanced TGF-β effects on cell migration [92]. These extensive studies have provided strong evidence for a role of PTEN in changing roles of TGF-β during different stages of prostate cancer.

### Role of JunD in TGFβ effects on cell proliferation

Previous reports have shown that additional intracellular proteins influence TGF-β effects on cellular proliferation including a number of transcription factors [95-97] including AP-1 (activating protein-1) proteins [7, 98]. The AP-1 family is composed of dimer combinations primarily formed between the Jun (JunB, c-Jun, and JunD) and Fos (FosB, c-Fos, Fra1, and Fra2) protein family [4, 99]. Members of AP-1 transcription (TF) family regulate cellular proliferation, survival, apoptosis inflammation, differentiation, locomotion and are often implicated as oncogenic cancer drivers [99-101]. In prostate cancer, AP-1 proteins are associated with disease recurrence and more aggressive clinical outcomes [102-105]. Among these proteins, there is a growing body of evidence that Jun proteins, specifically JunD, plays a major role in the control of cell proliferation and cell death by regulating the expression of cell cycle regulators [106-108]. In our previous studies, selective knockdown by siRNA or knockout of JunD by CRISPR/Cas9 in prostate cancer cells resulted in significant inhibition of cell proliferation while knockdown of cJun and JunB had very little, if any, effect on cell proliferation [99]. We also demonstrated that the essential role of JunD in PCa cell proliferation is dependent on its regulation of several genes required for the progression of the cell cycle including Id1 and c-MYC [54, 99]. Other studies have also shown that inhibition of JunD resulted in prostate tumor cell death and ultimately inhibition of tumor development [109].

Interestingly, our studies also uncovered that TGF-β effects on cell proliferation in prostate epithelial cells are dependent on down-regulation of JunD in these cells [99]. While TGF-β have no effect on JunD mRNA levels, it caused a significant decrease in JunD protein levels in cell lines derived from normal epithelial cells (RWPE-1, PZ-HPV7) and DU145 cells. This reduction in JunD levels correlated with inhibitory effects of TGF-β on cell proliferation [99]. On the other hand, TGFβ failed to cause reduction in JunD protein levels in PC3 cells which correlated with lack of its inhibitory effects on cell proliferation. Furthermore, we demonstrated that TGF-β leads to specific proteasomal degradation of JunD protein and this reduction in JunD protein levels is a pre-requisite for inhibitory effects of TGF-β on cell proliferation [99].

### Role of Ski/SnoN proteins during cancer progression

Activation of TGF-β receptors via ligand binding leads to the phosphorylation of Smad proteins, specifically Smad2/3, which then interact with Smad4, translocate into the nucleus, and ultimately regulate the expression of target genes [11, 72, 73, 110, 111]. Smad signaling is subject to multi-levels positive and negative regulation that target both the receptors and the intracellular mediators [112]. Among the negative regulators of Smad2/3 function, Sloan-Kettering Institute (Ski) protein family members suppress TGF-β signaling [73, 112]. Ski and Ski-related novel protein N (SnoN) are important negative regulator of TGF-β signaling through their ability to interact with and repress Smad proteins by binding to the N-terminus of R-Smads and SMAD4, thereby blocking the complex formation and transcriptional activity, ultimately suppressing TGF-β signaling [112-115]. In a negative feedback manner TGF-β, induces Ski and SnoN proteins to regulate or normalize its signaling and then downregulates these proteins by degradation via the ubiquitin-protease pathway which allow TGF-β effects on cellular mechanisms to be tightly regulated [115-117]. Ski and (SnoN) are proto-oncogenes and are expressed in all tissues at low levels [73, 112] and regulate growth and differentiation of several cell types. Overexpression of Ski and SnoN inhibits TGF-β-induced growth arrest and induces oncogenic transformation [112, 114, 118]. Moreover, the upregulation of Ski and/or SnoN expression is associated with tumor development and has been detected in several cancers including breast cancer, melanoma, pancreatic cancer, colorectal cancer, and prostate cancer [119-125]. This is due to these cells becoming resistant to TGF-β despite its presence. For example, increased expression of Ski proteins have been observed in human pancreatic can-

cer and is correlated with poor survival [118] and inhibition of Ski proteins in pancreatic tumor cells enhances TGF-β-signaling and promote TGF-β1-mediated p21 expression and growth inhibition [118].

Our previous studies showed expression of higher Ski protein levels in prostate cancer cells, while these levels were low in cell lines derived from normal cells [110]. We also showed that Ski proteins are higher in metastatic prostate cancer cells lines and correlated with high levels in prostate cancer patient tissues [110]. Furthermore, its down-regulation enhanced TGF-β signaling in prostate cancer cells and is required for TGFβ1-dependent phosphorylation of Smad3 and TGF-β effects on cell proliferation [110]. In addition, we also demonstrated that Ski proteins that are normally low in expression in normal prostate cell lines are increased when cultured in the presence of MG132, a proteasomal inhibitor, indicating that TGF-β-induced degradation of Ski is mediated by the proteasome pathway in prostate cancer cells and this degradation is required for increased Smad2 and Smad3 phosphorylation in response to TGF-β [110].

## Conclusions

TGF-β signaling pathway serves as a regulator of cell proliferation, differentiation, survival, apoptosis, and several other cellular processes. These biological effects in the target cells depend upon the cellular context and a complex interaction between both smad-dependent and smad-independent signaling pathways. In normal prostate epithelial cells, TGF-β inhibits cell proliferation and is required for maintenance of differentiated phenotype. During prostate cancer progression, cancer cells develop resistance to the inhibitory effects of TGF-β on cell proliferation as an early event in carcinogenesis. These cells usually maintain essential components of TGF-β signaling which are later employed for its tumor promoting activities. The intracellular mechanisms involved in the development of resistance to inhibitory effects of TGF-β on cell proliferation remain largely unknown. Recent studies from our laboratory and others have shown that several intracellular proteins including Ski/SnoN, PTEN, Id1, c-Myc and JunD play critical roles in TGF-β induced inhibition of cell proliferation. Our studies have shown that JunD plays an essential role in cell proliferation by upregulating the expression of several genes involved in cell cycle progression including 1d1 and c-Myc. TGF-β induces proteasomal degradation of JunD protein as a major mechanism in its inhibitory effects on cell proliferation and TGF-β fails to induce degradation of JunD in cells which have become resistant to its growth inhibitory effects. While these studies provide tremendous insights in cellular mechanisms involved in prostate cancer development, additional studies are required to discover therapeutics that may mitigate prostate cancer in its early stages of development.

## Disclosure of conflict of interest

None.

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