Cancer Pathogenesis and Therapy 1 (2023) 195–204

Contents lists available at ScienceDirect

Cancer Pathogenesis and Therapy

journal homepage: www.journals.elsevier.com/cancer-pathogenesis-and-therapy

Review article

Emerging role of transforming growth factor-β-regulated long non-coding RNAs in prostate cancer pathogenesis

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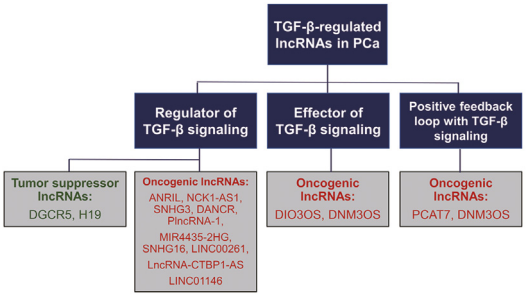
HIGHLIGHTS

- Long non-coding RNAs (lncRNAs) regulate prostate cancer (PCa) pathogenesis.
- LncRNAs act as effectors and regulators of the transforming growth factor-β (TGF-β) pathway in PCa.
- The TGF-β pathway is closely related to androgen receptor (AR) signaling.
- TGF-β-regulated lncRNAs are potential biomarkers and therapeutic targets for PCa.

GRAPHICAL ABSTRACT



Long non-coding RNA (LncRNAs) associated with the transforming growth factor-β (TGF-β) pathway regulate prostate cancer (PCa) pathogenesis. Many lncRNAs function as TGF-β signaling regulators. Some act as effectors and form a positive feedback loop with the TGF-β signaling pathway. LncRNAs involved in the TGF-β pathway can act as diagnostic and therapeutic targets for PCa.

ARTICLE INFO

Managing Editor: Peng Lyu

Keywords:
Prostate cancer
TGF-β
LncRNA
Castration-resistant prostate cancer
Androgen deprivation therapy
Androgen-independent prostate cancer
Prostate-specific antigen
Benign prostatic hyperplasia

ABSTRACT

Prostate cancer (PCa) is the most common malignancy in men. Despite aggressive therapy involving surgery and hormonal treatments, the recurrence and emergence of metastatic castration-resistant prostate cancer (CRPCa) remain a major challenge. Dysregulation of the transforming growth factor-β (TGF-β) signaling pathway is crucial to PCa development and progression. This also contributes to androgen receptor activation and the emergence of CRPC. In addition, TGF-β signaling regulates long non-coding RNA (lncRNA) expression in multiple cancers, including PCa. Here, we discuss the complex regulatory network of lncRNAs and TGF-β signaling in PCa and their potential applications in diagnosing, prognosis, and treating PCa. Further investigations on the role of lncRNAs in the TGF-β pathway will help to better understand PCa pathogenesis.

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https://doi.org/10.1016/j.cpt.2022.12.003
Received 23 October 2022; Received in revised form 1 December 2022; Accepted 20 December 2022

Introduction

Prostate cancer

Prostate cancer (PCa) is non-skin cancer primarily affecting men over the age of 60 years.[1] The Global Cancer Statistics 2020 (GLOBOCAN 2020) reported 1.4 million new PCa cases worldwide, representing approximately 7.3% of all cancers.[2] Prostate tumorigenesis is characterized by androgen receptor (AR) overexpression and an AR-mediated increase in proliferation, epithelial-to-mesenchymal transition (EMT), and metastasis.[1,3,4] AR belongs to the steroid hormone group of nuclear receptors and functions as a transcription factor that controls gene expression to promote differentiation in the normal prostate epithelium.[1,5] Androgen deprivation therapy (ADT) is the most common treatment for PCa.[3] However, ADT frequently changes AR expression or post-translational modifications, which results in therapeutic resistance leading to castration-resistant prostate cancer (CRPC) or androgen-independent prostate cancer (AIPC).[5–9] Alterations in the AR pathway, such as gain-of-function mutations in the AR and increased transcription and signaling, contribute to CRPC.[10] PCa that has progressed to the lymph nodes or bones is termed metastatic prostate cancer (mPCa). Serum prostate-specific antigen (PSA), clinical staging, and biopsy Gleason score are considered for risk stratification before PCa therapy.[11] Unfortunately, these indicators have 75–85% accuracy, as they do not consider the heterogeneous nature of the disease. Due to the inconsistencies in the current diagnostic methods and the shortcomings associated with therapy, novel biomarkers and therapeutic targets are needed for a better PCa prognosis. This is a rare review detailing the role of transforming growth factor-β (TGF-β)-regulated lncRNAs in PCa. Here, we discuss the function and mechanism of action of lncRNAs in the TGF-β pathway as oncogenes and tumor suppressors in regulating PCa. The potential use of TGF-β-regulated lncRNAs as diagnostic markers and therapeutic targets is also discussed.

Transforming growth factor-β signaling and prostate cancer

Among the various cytokines, transforming growth factor-β (TGF-β) plays a vital role in prostate gland development and PCa pathogenesis. TGF-β is a pleiotropic cytokine that regulates cell proliferation, differentiation, tissue homeostasis, motility and invasion, extracellular matrix production, angiogenesis, and immune response.[12,13] The detailed mechanisms underlying canonical small mothers against decapentaplegic (SMAD) and non-canonical pathways of TGF-β signaling have been extensively reviewed elsewhere.[14–16] During normal prostate development, TGF-β secreted by the stromal cells prevents proliferation and promotes apoptosis of the prostate gland's luminal epithelial cells after terminal differentiation, thus maintaining homeostasis.[17–19] Paracrine signaling between TGF-β and AR during prostate gland development is essential for normal prostate morphogenesis, and dysregulation of their interaction contributes to PCa progression.[17,18] Advanced prostate tumors and patients with advanced invasive tumors display elevated TGF-β1 levels, indicating the oncogenic role of the TGF-β1 ligand in PCa.[20] However, conditional knockout of the transforming growth factor-β receptor II (TGFβRII) in mice leads to prostatic neoplasia, implying the tumor suppressor role of TGFβRII in PCa.[20–22] Aberrant TGF-β signaling upon castration aids PCa cells in adapting to CRPC emergence by activating AR and β-catenin signaling pathways.[23] Moreover, the downregulation of TGFβRII and single nucleotide polymorphism in TGFβRII are risk factors for ADT resistance and CRPC onset.[24] Critical events of PCa progression include increased TGF-β expression in the epithelium and stroma, loss of TGF-β responsiveness in the epithelium, increased epithelial AR levels, and decreased stromal AR levels.[18] During carcinogenesis, the antiproliferative effect of TGF-β on the epithelial cells is lost, leading to uncontrolled epithelial cell proliferation.[19] In benign prostate epithelial cells, TGF-β inhibits proliferation and promotes apoptosis in a SMAD-dependent manner by repressing *c-Myc* and several cyclin-dependent kinases.[25,26] In advanced PCa, SMAD-dependent and independent TGF-β signaling are disrupted, enabling the tumor-promoting function of TGF-β.[27] The SMAD-mediated canonical TGF-β signaling and the non-canonical signaling in PCa promote (1) EMT by inducing the expression of genes, such as Snail, Slug, and Twist; (2) invasion by inducing matrix metalloproteinase 9 (MMP9); and (3) angiogenesis by upregulating vascular endothelial growth factor (VEGF).[28,29] TGF-β is also involved in resistance to therapy and evasion of immune surveillance.[25] The increased epithelial AR facilitate TGF-β production, promoting resistance to TGF-β-induced apoptosis and cancer progression.[30] Several TGF-β antibodies and inhibitors of the TGF-β pathway components are in the pre-clinical and clinical trials for PCa.[31–34]

Long non-coding RNAs and prostate cancer

The human genome is categorized into protein-coding genes (PCGs) and non-protein-coding regions. Less than 3% of the human genome codes for proteins, while the rest pervasively transcribe several non-coding transcripts.[35–39] Among the non-coding part of the genome, lncRNAs are the most abundant. They are loosely defined as transcripts longer than 200 bps with an inability to code for proteins.[35–38,40] LncRNAs regulate cellular processes like cell cycle, differentiation, metabolism, and diseases, including PCa.[41–46] LncRNAs do not code for proteins; however, they modulate gene expression in *cis* and *trans* through regulation of transcription, epigenetic modifications, protein/RNA stability, translation, and post-translational modifications by interacting with DNA, RNA, and proteins.[39,47] LncRNAs in the cytoplasm function primarily through the competing endogenous RNA (ceRNA) hypothesis by interacting with micro RNAs (miRNAs).[48] By sequestering the miRNAs, lncRNAs titrate and reduce miRNA availability to degrade their target.[48] Based on the coding genes, lncRNAs are classified into four categories: sense intronic lncRNAs, antisense lncRNAs, bidirectional lncRNAs, and intergenic lncRNAs.[49] LncRNAs regulate proliferation, metastasis, and drug resistance in several cancers, including PCa.[50–56] Moreover, lncRNAs are potential biomarkers for diagnosing and predicting the survival of patients with PCa.[57,58]

Transforming growth factor-β-regulated long non-coding RNAs in prostate cancer

Numerous lncRNAs dysregulated in cancer have been identified and characterized in PCa and are discussed elsewhere.[55,59–62] TGF-β signaling and lncRNAs regulate each other in multiple ways, contributing to PCa pathogenesis. For instance, TGF-β induces the expression of several oncogenic lncRNAs, enhancing the TGF-β pathway's tumor-promoting function.[63–65] LncRNAs can be effectors and regulators of the TGF-β pathway or form a positive feedback loop with the TGF-β pathway, regulating cancer progression.[66–76] TGF-β-regulated lncRNAs modulate invasion, metastasis, and EMT in several cancers, including PCa.[77–80] Interestingly, lncRNAs can also function as tumor suppressors, deregulating the TGF-β pathway and preventing PCa progression.[81,82] Here, we discuss the function and use of lncRNAs in the TGF-β pathway as potential biomarkers and therapeutic targets for PCa.

Transforming growth factor-β-regulated oncogenic long non-coding RNAs

Prostate cancer-associated transcript 7 (PCAT7)

Using The Cancer Genome Atlas (TCGA) data set, Lang et al. identified the lncRNA prostate cancer-associated transcript 7 (*PCAT7*) to be significantly associated with bone metastasis in PCa.[63] Human bone tumors from metastatic PCa also displayed *PCAT7* overexpression compared to adjacent normal tissues.[63] *PCAT7* levels are also higher in several PCa cell lines than in normal prostate epithelial cells (RWPE1). *PCAT7* upregulation was positively correlated with advanced pathological conditions, including Gleason score, tumor volume, lymph node metastasis, and bone metastasis status. It was also positively correlated with the poor overall and disease-free survival of PCa patients.[63] *PCAT7*

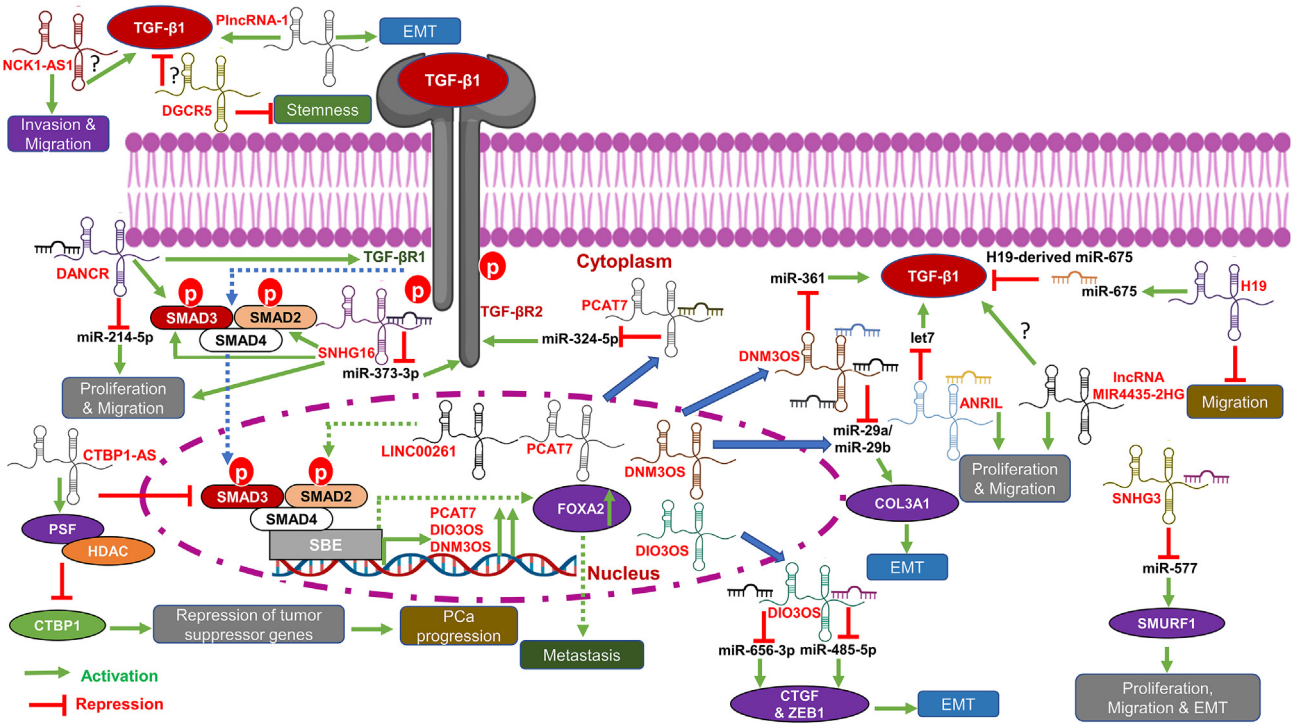

Figure 1. Regulation of prostate cancer progression by long non-coding RNAs via the transforming growth factor-β pathway. TGF-β induces the expression of lncRNAs *PCAT7*, *DIO3OS*, and *DNM3OS* in PCa cells; upon induction, *PCAT7* consequently activates TGF-β signaling and promotes PCa bone metastasis by acting as a ceRNA via sponging miR-324-5p to stabilize TGFβRII; *DNM3OS* upon induction by TGF-β counteracts the miR-29a/29b-mediated *COL3A1* suppression. It counteracts miR-361-mediated TGF-β1 suppression and promotes TGF-β1-mediated myofibroblast activation in PrSCs; *DIO3OS* is an effector of TGF-β signaling to mediate EMT and proliferation in BPH through sponging miR-656-3p and miR-485-5p and preventing degradation of CTGF and ZEB1; *LncRNAs–H19*, *DGCR5*, *NCK1-AS1*, *ANRIL*, *SNHG16*, *LINC00261*, *MIR4435-2HG*, *DANCR*, *PlncRNA-1*, *SNHG3*, and *CTBP1-AS* are not induced by TGF-β but regulate PCa progression by modulating TGF-β signaling; H19 acts as a tumor suppressor. It upregulates miR-675 and suppresses TGF-β1, thus preventing PCa cell migration; *DGCR5* exerts its tumor suppressor function in PCa by reducing TGF-β1 levels and by decreasing the stemness of PCa cells; *NCK1-AS1* upregulates TGF-β1 to promote TGF-β1-mediated PCa cell migration and invasion; *ANRIL* acts as a regulator of TGF-β signaling by sponging let7, thereby increasing the TGF-β1 and p-SMAD2 levels and decreasing p-SMAD7 levels, further activating TGF-β signaling and PCa cell proliferation and migration; *SNHG16* sponges miR-373-3p, prevents its binding to TGFβRII and promotes PCa cell proliferation and migration; *LINC00261* activates oncogene FOXA2 expression via chromatin recruitment of the SMAD2/3 complex in the FOXA2 promoter, thereby promoting PCa cell growth and metastasis. The red arrows indicate inhibitory function, and the green arrows indicate a stimulatory role. *MIR4435-2HG* promotes TGF-β1 levels and promotes PCa cell migration and invasion. *DANCR* sponges miR-214-5p to stabilize TGFβR1 and promote PCa cell proliferation and migration. PlncRNA-1 upregulates TGF-β1 expression and promotes PCa cell proliferation and invasion. SNHG3 sponges miR-577 and stabilizes *Smurf1* expression to promote PCa progression. *CTBP1-AS* is overexpressed in PCa tissues and CRPC. It binds to PSF protein and promotes AR-mediated repression of SMAD3 and p53, thereby promoting the cell cycle of PCa cells. *ANRIL:* Antisense RNA in the INK4 locus; *COL3A1*: Collagen type III alpha chain I; CTBP1-AS: LncRNA C-terminal binding protein-antisense; CTGF: Connective tissue growth factor; *DANCR*: Differentiation antagonizing non-protein-coding RNA; *DGCR5:* DiGeorge syndrome critical region gene 5; *DIO3OS*: DIO3 opposite strand upstream RNA; *DNM3OS:* Dynamin 3 opposite strand; EMT: Epithelial-to-mesenchymal transition; *FOXA2*: Forkhead box A2; lncRNAs: Long non-coding RNA; miR: microRNA; *MIR4435-2HG*: MIR4435-2 host genes; NCK1-AS1: Non-catalytic region of tyrosine kinase adaptor protein 1-antisense 1; PCa: Prostate cancer; *PCAT7*: Prostate cancer-associated transcript 7; PlncRNA-1: prostate cancer-upregulated long non-coding RNA 1; pSMAD2: Phospho-SMAD2; SMAD: Small mothers against decapentaplegic; Smurf1: SMAD ubiquitination regulatory factor 1; *SNHG3*: Small nucleolar RNA host gene 3; *SNHG16:* Small nucleolar RNA host gene 16; TGF-β: Transforming growth factor–β; TGFβR: Transforming growth factor-β receptor; TGFBI: Transforming growth factor β-induced protein; ZEB1: Zinc finger e-box binding homeobox 1. The red arrows indicate inhibitory function, and the green arrows indicate a stimulatory role.

promoter analysis using luciferase reporter assay, JASPAR database, and ChIP-seq data from the Encyclopedia of DNA Elements (ENCODE) identified DNA-binding cofactor SP1 as a critical activator of *PCAT7* expression downstream to TGF-β.[63] Luciferase reporter assays also revealed that the SMAD3/SMAD4 complex is involved in the transcriptional activation of *PCAT7*. SP1 also transcriptionally upregulates *PCAT7* independently of TGF-β/SMAD3 signaling. However, the TGF-β/SMAD3 pathway promotes the transcriptional regulatory efficiency of SP1 on *PCAT7*. *In vivo,* a nude mouse model displayed increased bone metastasis upon *PCAT7* overexpression and an adverse effect upon *PCAT7* depletion. Consistent with this, *PCAT7* promoted EMT, migration, and invasion *in vitro*.[63] Furthermore, TGF-β-induced mesenchymal transition in C4-2B cells was reversed by *PCAT7* knockdown. Mechanistically, *PCAT7* activates TGF-β signaling and promotes PCa bone metastasis by acting as a ceRNA via sponging miR-324-5p, and consequently, TGF-β induces *PCAT7* expression [Figure 1, Table 1]. This indicates the positive feed-forward loop between *PCAT7* and TGF-β signaling. Interestingly, *PCAT7* knockdown reduces p-SMAD3 levels, rescued by a miR-324-5p inhibitor. The study also revealed that TGFβRI is a direct target of miR-324-5p.[63] Moreover, a positive correlation of *PCAT7* with TGFβRI and p-SMAD3 and a negative correlation of *PCAT7* with miR-324-5p in metastatic PCa samples and TCGA datasets was identified. These results indicate the critical role of the SMAD3/SP1 complex-mediated constitutive active loop between TGF-β signaling and lncRNA *PCAT7* in PCa bone metastasis.[63]

Long non-coding RNA dynamin 3 opposite strand (DNM3OS)

Gene Expression Omnibus analysis of prostate stromal tissues microarray datasets by Wang et al. identified significantly upregulated lncRNAs.[64] Among these 17 lncRNAs, Dynamin 3 opposite strand (*DNM3OS*) was significantly upregulated in CD49a+ stromal cells. The expression of lncRNA *DNM3OS* was considerably upregulated by TGF-β treatment in the HPS-19I prostate stromal cell line with a concomitant upregulation of myofibroblasts.[64] Further, using microarray profiling of prostate cancer stromal cells (PrSCs) with and without TGF-β, Wang et al.

Table 1
Transforming growth factor-β-regulated oncogenic long non-coding RNA in prostate cancer.

LncRNA	Expression (Up ↑, Down ↓)	Type of regulation	Function	Mechanism of action in PCa	Type of model	Cell lines	Biomarker /Therapeutics	Reference
PCAT7	↑	Positive feedback loop	Promotes PCa bone metastasis	Induced by TGF-β, in turn, activates TGF-β signaling and promotes PCa bone metastasis by acting as a ceRNA via sponging miR-324-5p	Human; *in vitro; in vivo*-mouse	22RV1, LNCaP, DU145, VCaP, PC-3, C4-2B cell lines	−/+	63
DNM3OS	↑	Effector and a positive feedback loop of TGF-β signaling	Upregulated in CD49a+ stromal cells and promotes TGF-β1- mediated myofibroblast activation in PrSCs	Induced by TGF-β1. Counteracts the miR-29a/29b-mediated *COL3A1* suppression; counteracts miR-361-mediated TGF-β1 suppression, and promotes TGF-β1- mediated myofibroblast activation in PrSCs	Human; *in vitro*	PrSCs- primary culture from BPH tissues	−/−	64
ANRIL	↑	Regulator of TGF-β signaling	Activates TGF-β signaling, mediated proliferation, and migration of PCa cells	Acts as a regulator of TGF-β signaling by sponging let7, thereby increasing the TGF-β1 and p-SMAD2 levels and decreasing p-SMAD7 levels, further activating TGF-β signaling	Human; *in vitro*	LNCap, PC3, and DU145 PCa cell lines	−/−	65
NCK1-AS1	↑	Regulator of TGF-β signaling	Upregulated in PCa and promotes PCa cell migration and invasion	Upregulates TGF-β1 to promote TGF-β1 mediated PCa cell migration and invasion	Human*; in vitro*	DU145, 22Rvl, RC-92a, and PC-3M cell lines	+/−	66
SNHG3	↑	Regulator of TGF-β signaling	Overexpressed in PCa; promotes PCa proliferation, EMT, and migration	*SNHG3* directly binds to and sponges miR-577, thereby preventing depletion of *Smurf1* and promoting PCa cells proliferation, EMT, and migration	Human*; in vitro; in vivo*-mouse	PC3, DU145, 22RV1, LNCaP cell lines	+/−	67
SNHG3	↑	Regulator of TGF-β signaling	Overexpressed in patients with PCa and bone metastasis; promotes proliferation, migration, and invasion of PCa cells	*SNHG3* binds to and sponges miR-214-3p, preventing TGFβR1 depletion and promoting PCa progression	Human*; in vitro; in vivo*-mouse	PC3, and C4-2B cell lines	+/+	68
DANCR	↑	Regulator of TGF-β signaling	Upregulated in the serum of patients with PCa and promotes PCa proliferation and migration	*DANCR* competitively binds miR-214-5p and activates the TGF-β signal pathway to enhance PCa development	Human*; in vitro*	DU145, 22Rvl, RC-92a and PC-3M cell	+/−	69
PlncRNA-1	↑	Regulator of TGF-β signaling	Overexpressed in PCa cell lines and tissues; Promotes PCa cell proliferation and invasion	It upregulates TGF-β1 RNA levels. It promotes TGF-β-mediated PCa cell proliferation and invasion	*in vitro, in vivo*-mouse	LNCaP, C4-2, DU145, and PC3 PCa cell lines	−/−	64
MIR4435-2HG	↑	Regulator of TGF-β signaling	Upregulated in PCa and promotes PCa migration and invasion	Expression of MIR4435-2HG is positively correlated with TGF-β1 levels and upregulates TGF-β1 expression. It induces PCa cell migration and invasion via the TGF-β signaling pathway by interacting with additional downstream effectors of the TGF-β pathway, which is yet to be investigated	Human*; in vitro*	22Rv1	+/−	71
SNHG16	↑	Regulator of TGF-β signaling	Overexpressed in patients with PCa and promotes PCa cell proliferation and migration	Sponges miR-373-3p, preventing its binding to TGFβRII, and promotes PCa proliferation and migration	Human; *in vitro*	DU145	+/−	72
LINC00261	↑	Regulator of TGF-β signaling	Upregulated in NEPCs, PCa tissues	Activates FOXA2 expression via chromatin recruitment of the SMAD2/3 complex in the FOXA2 promoter, thereby promoting PCa cell growth and metastasis	Patient-derived xenograft models (PDXs)	PDX; H660 and PC-3 cell lines	+/+	73

(*continued on next page*)

Table 1 (*continued*)

LncRNA	Expression (Up ↑, Down ↓)	Type of regulation	Function	Mechanism of action in PCa	Type of model	Cell lines	Biomarker /Therapeutics	Reference
DIO3OS	↑	Effector of TGF-β signaling	Overexpressed in BPH; promotes TGF-β-mediated EMT and proliferation in BPH	Induced by TGF-β, it is an effector of TGF-β signaling to mediate EMT and proliferation in BPH through sponging miR-656-3p and miR-485-5p and preventing degradation of CTGF and ZEB1	Human; *in vitro*	BPH1, WPMY-1 cell lines	+/−	[68]
LncRNA CTBP1-AS	↑	Regulator of TGF-β signaling	Overexpressed in malignant PCa tissues and castration-resistant PCa cells	Binds to PSF protein and promotes AR-mediated repression of SMAD3 and p53, promoting the cell cycle of PCa cells	Human; *in vitro*; *in vivo*-mouse	LNCaP cells, VCaP cells, DU145 cells, RWPE cells	−/+	[75]
LINC01146	↑	Regulator of TGF-β signaling	Overexpressed in PCa tissues and cell lines – LnCaP, and PC-3	TGF-β-induced *LINC01146* binds to and promotes *F11R* expression, thereby inducing PCa progression	*in vitro*; *in vivo*-mouse	LnCaP and PC-3	−/+	[76]

Several lncRNAs are upregulated in PCa tissues and cell lines. The type of TGF-β pathway regulation by these oncogenic lncRNAs, mechanism of action, binding partners, and utility as biomarkers or therapeutic targets of PCa are listed in Table 1. ± denotes whether the lncRNA serves as a biomarker or therapeutic target.

identified the collagen type III alpha chain I (*COL3A1*) gene as a critical marker of myofibroblasts and an essential factor in TGF-β-mediated remodeling of the extracellular matrix (ECM).[64] The TGF-β-mediated increase in *COL3A1* levels was attenuated upon *DNM3OS* silencing. Luciferase reporter assays indicate that miR-29a and miR-29b bind to the 3' untranslated region (UTR) of *COL3A1* and *DNM3OS*, revealing that *DNM3OS* acts as a ceRNA for *COL3A1* and binds to miR-29a/29b to stabilize *COL3A1* expression. Consistent with this, the knockdown of *DNM3OS* followed by miR-29a/29b inhibition rescued *COL3A1* expression. Moreover, *DNM3OS* knockdown significantly reduced the expression of phospho-SMAD2 (p-SMAD2), TGF-β1, matrix metalloproteinase 1 (MMP1), and matrix metalloproteinase (MMP3), indicating that *DNM3OS* also modulates TGF-β signaling in PrSCs. Interestingly, Wang et al. demonstrated that miR-361 negatively regulated *DNM3OS* expression and TGF-β1 protein.[64] *DNM3OS* competed for miR-361 binding to inhibit miR-361-mediated TGF-β1 suppression. The expression levels of *DNM3OS*, *COL3A1*, and TGF-β1 were significantly upregulated. In contrast, miR-29a, miR-29b, and miR-361 expression levels were considerably downregulated in benign prostatic hyperplasia (BPH) tissues compared to those in normal prostate tissues. Moreover, *DNM3OS* expression was negatively correlated with miR-29a, miR-29b, and miR-361. These results suggest that TGF-β1 induces lncRNA *DNM3OS*, which promotes TGF-β-mediated myofibroblast activation in PrSCs. It acts as a TGF-β signaling effector by inhibiting the miR-29a/29b-mediated *COL3A1* suppression. It also exerts a positive feedback loop upon induction by TGF-β1 and sponges miR-361, which mediates TGF-β1 suppression [Figure 1, Table 1].[64]

Antisense RNA in the INK4 locus

Antisense RNA in the INK4 locus (*ANRIL*) is overexpressed in PCa tissues, and *ANRIL* knockdown reduces the proliferation and migration of LNCaP, PC3, and DU145 PCa cells.[65] *ANRIL* depletion significantly reduced TGF-β1 and p-SMAD2 expression, whereas the expression of p-SMAD7, an inhibitor of TGF-β signaling, was increased upon *ANRIL* knockdown. *ANRIL* depletion increased the expression of let7 miRNA, a tumor suppressor.[65] Furthermore, Zaho et al. uncovered that simultaneous depletion of *ANRIL* and let7 significantly increased TGF-β1 and p-SMAD2 levels and decreased p-SMAD7 levels in PCa cells. The proliferation and migration of PCa cells were reduced upon *ANRIL* knockdown, which was rescued upon let7 inhibition in *ANRIL*-depleted PCa cells.[65] These results indicate that *ANRIL* regulates TGF-β signaling by sponging let7, thereby increasing the TGF-β1 and p-SMAD2 levels and decreasing p-SMAD7 levels to modulate the proliferation and migration of PCa cells [Figure 1, Table 1].[65]

Non-catalytic region of tyrosine kinase adaptor protein 1-antisense 1

Non-catalytic region of tyrosine kinase adaptor protein 1 (*NCK1*) antisense RNA 1 is an oncogenic lncRNA. Guan et al. reported that lncRNA *NCK1*-antisense 1 (*NCK1-AS1*) was significantly higher in patients with PCa than in the plasma of patients with BPH and healthy male patients.[66] Increased *NCK1-AS1* expression distinguished patients with PCa from those with BPH and healthy male patients. Furthermore, there was a higher expression of *NCK1-AS1* in DU145 and 22Rvl PCa cell lines than in normal cells. The study also displayed a positive correlation between TGF-β1 and *NCK1-AS1* in the plasma of patients with PCa.[66] *NCK1-AS1* overexpression significantly increased TGF-β1 transcript and protein levels. However, TGF-β1 overexpression did not affect *NCK1-AS1* expression, indicating that *NCK1-AS1* upregulates TGF-β signaling in PCa [Figure 1, Table 1]. *NCK1-AS1* and TGF-β1 overexpression increased the invasion and migration of PCa cells, which was attenuated by treatment with a TGF-β inhibitor.[66] However, the exact mechanism by which *NCK1-AS1* promotes TGF-β1-mediated PCa cell migration and invasion is yet to be elucidated.

Small nucleolar RNA host gene 3 (SNHG3)

Li et al. reported that lncRNA small nucleolar RNA host gene 3 (*SNHG3*) is overexpressed in PCa cells compared to that in normal prostate epithelial cells.[67] Depleting *SNHG3* inhibits PCa cell

proliferation, migration, and EMT and promotes apoptosis in PCa cells. *In vivo* assays demonstrated increased tumorigenicity upon *SNHG3* overexpression. Additionally, *SNHG3* expression is positively correlated with SMAD ubiquitination regulatory factor 1 (*Smurf1*), which acts as an oncogene in PCa. *SNHG3* directly binds miR-577, thereby preventing the depletion of miR-577 target *Smurf1*.[67] Thus *SNHG3* promotes PCa progression by sponging miR-577 to increase *Smurf1* expression and is a potential therapeutic target of PCa [Figure 1, Table 1].[67]

Xi et al. observed that lncRNA *SNHG3* is overexpressed in PCa tissues.[68] Moreover, *SNHG3* is higher in patients with PCa experiencing bone metastasis samples than in those without bone metastasis.[68] Notably, elevated *SNHG3* directly correlates with a high Gleason score, advanced PCa stage, increased PSA, and poor prognosis, indicating that *SNHG3* can be a prognostic and diagnostic marker for PCa.[68] *SNHG3* depletion reduced the proliferation, migration, and invasion of PC3 and C4-2B PCa cells, suggesting a tumor-promoting function of *SNHG3*.[68] PCa mouse models reveal decreased bone metastasis upon silencing *SNHG3*. Depleting *SNHG3* increases the expression of miR-214-3p, and a reduction in PCa cell proliferation, migration, and invasion is partly rescued upon miR-214-3p overexpression.[68] *SNHG3* and transforming growth factor-β-receptor 1 (TGFβR1) are potential targets of miR-214-3p.[68] Furthermore, *SNHG3* knockdown significantly reduced the mRNA and protein levels of TGFβR1, which was rescued upon miR-214-3p overexpression. These results suggest that *SNHG3* promotes PCa progression by sponging miR-214-3p and stabilizing TGFβR1 [Figure 1, Table 1].[68]

Differentiation antagonizing non-protein-coding RNA (DANCR)

Differentiation antagonizing non-protein-coding RNA (*DANCR*) is highly carcinogenic and is a molecular sponge for miR-214-5p to promote TGF-β-mediated invasion in PCa.[69] *DANCR* expression is upregulated in PCa cell lines and serum of patients with PCa.[69] However, miR-214-5p was downregulated in the serum of patients with PCa, suggesting that *DANCR* regulates miR-214-5p expression.[69] Consistent with this, *DANCR* levels correlated with PSA, Gleason score, T stage, N stage, and M stage of PCa patients.[69] Overexpression of *DANCR* promotes PCa proliferation and migration with an increase in TGF-β, TGFβRI, and phosphor-SMAD3 (p-SMAD3) protein levels.[69] Similarly, miR-214-5p downregulation promotes PCa proliferation and migration by activating the TGF-β signaling pathway.[69] *DANCR* upregulation and miR-214-5p downregulation resulted in increased TGF-β, TGFβRI, and p-SMAD3 levels, indicating the activation of the TGF-β pathway [Table 1].[69] *DANCR* competitively binds miR-214-5p and activates the TGF-β signal pathway to enhance PCa development [Figure 1].[69]

Prostate cancer-upregulated long non-coding RNA 1

LncRNA prostate cancer-upregulated long non-coding RNA 1 (PlncRNA-1) is elevated in PCa tissues, LNCaP, C4-2, DU145, and PC3 cells.[70] It sponges miR-34c and miR-297, which target AR.[70] Interestingly, a significant positive correlation between PlncRNA-1 and TGF-β1 in PCa tissues was also observed. PlncRNA-1 positively regulates TGF-β1 expression during apoptosis.[70] Conversely, plncRNA1 downregulation promotes apoptosis and reduces TGF-β1 expression. PlncRNA-1 depletion results in loss of N-cadherin, Cyclin-D1 expression, and increased E-cadherin in LNCaP cells. In contrast, PlncRNA-1 overexpression in C4-2 cells increased TGF-β1, N-cadherin, and Cyclin-D1.[70] Furthermore, the invasiveness and cell cycle of C4-2 cells were blocked upon PlncRNA-1 overexpression, which was reversed upon treatment with a TGF-β1 inhibitor. Using the nude mice PCa model, Jin et al. revealed that prostate tumor growth was significantly more in the PlncRNA-1 overexpression group than in the control group and adding the LY2109761 inhibitor stopped tumor growth. These findings suggest that PlncRNA1 influences EMT in PCa via the TGF-β1 pathway [Figure 1, Table 1].[70]

MIR4435-2 host genes

Zhang et al. observed elevated plasma levels of lncRNA *MIR4435-2* host genes (*MIR4435-2HG*) and TGF-β1 in patients with PCa compared to those in healthy controls.[71] *MIR4435-2HG* overexpression upregulated TGF-β1 in 22Rv1 PCa cells and enhanced PCa cell migration and invasion [Table 1]. TGF-β1 treatment did not affect *MIR4435-2HG* expression. Treatment of PCa cells overexpressing *MIR4435-2HG* with TGF-β inhibitor SB431542 only partially reduced the effect of *MIR4435-2HG* on cancer cell migration and invasion.[71] These results suggest that *MIR4435-2HG* may interact with additional downstream effectors of the TGF-β pathway to regulate PCa cell migration and invasion [Figure 1].[71] However, elucidating the exact mechanism of action of *MIR4435-2HG* requires further investigation.[71]

Small nucleolar RNA host gene 16 (SNHG16)

LncRNA small nucleolar RNA host gene 16 (*SNHG16*) is overexpressed in patients with PCa and is linked with glucose transporter-1, which promotes glucose uptake and PCa cell proliferation.[72] LncRNA *SNHG16* knockdown reduced cell proliferation and increased apoptosis in PCa cells. In line with this, *SNHG16* overexpression promotes cell proliferation while preventing cell death. Furthermore, *SNHG16* suppression reduced cell invasion and migration in DU145 PCa cells. *SNHG16* overexpression increased c-MYC, TGFβRII, p-SMAD2, p-SMAD3, and E2F4 expression. These results suggest that *SNHG16* acted through the TGFRβII/SMAD signaling pathway to increase cell proliferation, migration, and invasion in PCa. Interestingly, miR-373-3p levels were considerably reduced in PCa tissues, and *SNHG16* interacted with miR-373-3p. TGFβRII knockdown decreased cell proliferation and induced apoptosis.[72] TGFβRII depletion also reduced cell invasion and migration. *SNHG16* functions as a ceRNA, modulating the miR-373-3p/TGFβRII axis-mediated PCa cell proliferation and migration [Figure 1, Table 1].[72]

LINC00261

Mather et al. performed transcriptomic profiling of patient-derived xenograft (PDX) with histological features of prostate adenocarcinoma and identified several lncRNAs upregulated upon neuroendocrine transdifferentiation.[73] Among these lncRNAs, *LINC00261* was selectively upregulated in metastatic neuroendocrine prostate cancer (NEPC] with a positive correlation with neuroendocrine markers.[73] *LINC00261* expression was higher in neuroendocrine H660 and PC-3 cells than in normal PCa and AR-positive PCa cells.[73] *LINC00261* is predominantly localized in the cytoplasm with a small fraction in the nucleus and performs a distinct function in the nucleus and cytoplasm.[73] A similar expression pattern and localization of the lncRNA was identified for its murine ortholog 9030622O22-Rik in murine OPT7714 NEPC cells.[73] Loss-of-function studies upon *LINC00261* knockdown revealed a reduction in proliferative and metastatic abilities of PC-3 cells with a subsequent downregulation of Chromobox 2 (CBX2) and Forkhead box A2 (FOXA2) genes.[73] *LINC00261* mediated PCa progression through the miR-8485-CBX2 axis in the cytoplasm. While in the nucleus, *LINC00261* functions as a transcriptional scaffold to induce SMAD-driven FOXA2 upregulation.[73] RNA immunoprecipitation revealed significant enrichment of *LINC00261* with FOXA2. *LINC00261* depletion followed by ChIP-seq in PCa cells revealed a marked decrease in the chromatin binding of the SMAD2/3 transcriptional complex at cis-regulatory elements of the FOXA2 gene and several bona fide TGF-β1/SMAD target genes [Figure 1].[73] These results suggest that nuclear upregulation of *LINC00261* activates FOXA2 expression via chromatin recruitment of the SMAD2/3 complex in NEPC cells, and FOXA2 consequently drives a gene program of anchorage-independent survival and growth at the metastatic site [Table 1].[73]

DIO3 opposite strand upstream RNA (DIO3OS)

LncRNA DIO3 opposite strand upstream RNA (*DIO3OS*) expression is significantly higher in tissues and stroma cells than in normal epithelial cells.[74] Treatment of BPH-1 and WPHY-1 cells with TGF-β significantly induced *DIO3OS* expression, and treatment with resveratrol reduced its expression.[74] Luciferase reporter and chromatin immune precipitation

(ChIP) assays revealed that the induction of lncRNA-*DIO3OS* by TGF-β is through the SMAD2/3 signaling. TGF-β mediated EMT and proliferation in BPH-1, and WPHY-1 cells were attenuated upon *DIO3OS* knockdown. Overexpression of *DIO3OS* facilitated the reversal of resveratrol-mediated attenuation of EMT and proliferation.[74] RNA pull-down and luciferase reporter assays suggest that miR-656-3p and miR-485-5p bind to *DIO3OS*.[74] In addition, EMT inhibition and proliferation upon *DIO3OS* knockdown were reversed upon treatment with miR-656-3p and miR-485-5p inhibitors in the presence of TGF-β. Connective tissue growth factor (CTGF) and zinc finger e-box binding homeobox 1 (ZEB1) were targets of miR-656-3p and miR-485-5p.[74] Overexpression of miR-656-3p and miR-485-5p reduced CTGF and ZEB1 protein levels. However, rescue experiments with *DIO3OS* knockdown and miRNA inhibitors restored their expression.[74] *DIO3OS* is an effector of TGF-β signaling to mediate EMT and proliferation of BPH cells by sponging miR-656-3p and miR-485-5p [Figure 1, Table 1].[74] However, the role of *DIO3OS* in the aggressive and advanced stage of PCa is yet to be investigated.

Long non-coding RNA C-terminal binding protein-antisense (CTBP1-AS)

Androgen-responsive lncRNA C-terminal binding protein-antisense (*CTBP1-AS*) is *cis* to AR corepressor *CTBP1*.[75] *CTBP1-AS* is upregulated, and *CTBP1* is downregulated in malignant PCa tissues compared to that in benign tissue samples.[75] High expression of *CTBP1-AS* is associated with poor survival in PCa patients and is positively correlated with high Gleason scores and AR levels. Luciferase reporter assay revealed that lncRNA *CTBP1-AS* positively regulates AR signaling. *CTBP1-AS* promotes tumor growth in hormone-dependent and castration-resistant conditions.[75] *CTBP1-AS* regulates PCa progression through AR-mediated mechanisms in *cis* and *trans*. *CTBP1-AS* downregulates the *CTBP1* gene in *cis* by binding to the polypyrimidine tract-binding protein (PTB)-associated splicing factor (PSF), activating AR. In *trans*, *CTBP1-AS* promotes the AR-mediated repression of SMAD3 and p53 through PSF [Figure 1, Table 1]. TGF-β mediated PCa cell apoptosis is prevented by AR signaling by inhibiting SMAD3.[83] SMAD3 regulation by *CTBP1-AS* can affect the TGF-β pathway. However, the direct impact of *CTBP1-AS* on TGF-β signaling needs to be further investigated.

LINC01146

Guo et al. observed significantly higher expression of *LINC01146* in PCa tissue and cell lines than in normal cells.[76] *LINC01146* expression was upregulated upon TGF-β treatment *in vitro* in LnCaP and PC-3 cells.[76] Increased expression of *LINC01146* was associated with a high Gleason score, pelvic lymph node metastasis, and tumor node metastasis. *LINC01146* promotes PCa cell migration and invasion but restricts apoptosis.[76] *LINC01146* knockdown reduces tumor size and weight in xenograft nude mouse models.[76] *LINC01146* promoted the expression of *F11R*, a TGF-β target gene. RNA pull-down assays demonstrated that *LINC01146* binds with the *F11R* protein.[76] Moreover, the reduction in PCa cell proliferation, migration, and invasion upon *F11R* depletion was reversed upon *LINC01146* overexpression.[76] Thus, TGF-β induced *LINC01146* binds to and promotes expression of *F11R* during PCa progression.[76]

Transforming growth factor-β-regulated tumor suppressor long non-coding RNAs

DiGeorge syndrome critical region gene 5 (DGCR5)

LncRNA DiGeorge syndrome critical region gene 5 (*DGCR5*) expression is downregulated in PCa tissues compared to that in adjacent healthy tissues of patients with PCa [Table 2].[81] Moreover, there is an inverse correlation between DGCR5 expression and TGF-β1 levels in human PCa tissue samples.[81] Kaplan–Meier survival analysis revealed that low *DGCR5* expression was correlated with poor overall survival of patients with PCa.[81] Overexpression of *DGCR5* significantly reduced TGF-β1 levels; however, TGF-β treatment did not affect *DGCR5* expression in PCa

Table 2
Transforming growth factor-β-regulated tumor suppressor long non-coding RNAs in prostate cancer.

LncRNA	Expression (Up ↑, Down ↓)	Type of regulation	Function	Mechanism of action in PCa	Type of model	Cell lines	Biomarker /Therapeutics	Reference
DGCR5	↓	Regulator of TGF-β signaling	Downregulated in PCa tissues; has a tumor suppressor function in PCa	Exerts its tumor suppressor function in PCa by reducing TGF-β1 levels and by decreasing the stemness of PCa cells	Human; *in vitro*	22Rv1, DU145 cell lines	+/−	[81]
H19	↓	Regulator of TGF-β signaling	Downregulated in metastatic PCa cells; represses PCa cell migration	H19 upregulates miR-675, which acts as a tumor suppressor by targeting TGF-βI and prevents PCa cell migration	Human; *in vitro*	P69 and PC3 cells	+/+	[82]

LncRNAs *DGCR5* and *H19* are downregulated in PCa tissues and cell lines. They prevent PCa progression by negatively regulating the TGF-β pathway. *DGCR5* serve as a biomarker of PCa, and *H19* is a potential biomarker and therapeutic target for PCa.LncRNAs: Long non-coding RNA; PCa: Prostate cancer; TGF-β: Transforming growth factor–β.

cells.[81] Further, overexpression of *DGCR5* reduced the stemness of PCa cells, as measured by the reduction in the number of CD133+ cells in 22Rv1 and DU145 cells.[81] *DGCR5* exerts a tumor suppressor function in PCa, by reducing TGF-β1 levels and the stemness of PCa cells [Figure 1].[81]

H19

LncRNA H19 and H19-derived microRNA-675 (miR-675) levels in the metastatic prostate cancer cell line M12 were significantly lower than those in the non-metastatic prostate epithelial cell line P69.[82] H19 overexpression increased miR-675 expression in P69 and PC3 PCa cells and repressed cancer cell migration. However, ectopic expression of H19 in metastatic M12 cells did not affect cell migration and could not increase miR-675 levels.[82] Ectopic expression of miR-675 suppressed PCa cell migration. Concomitantly, H19 and miR-675 expression levels in P69 cells are inversely correlated with the expression of transforming growth factor β-induced protein (TGFBI), an extracellular matrix protein that promotes cancer metastasis.[82] Dual-luciferase reporter assay confirmed the direct interaction of miR-675 and 3′ UTR of TGFBI. These findings suggest that the H19–miR-675 axis suppresses PCa metastasis by inhibiting TGFBI [Figure 1, Table 2].[82]

Discussion and conclusion

PCa diagnosis and therapy have not significantly improved over the past decade. LncRNAs have diverse functions in cancer cells. Aberrant TGF-β signaling in PCa alters lncRNA expression and *vice versa* to promote malignant phenotypes [Figure 1]. The close association of TGF-β in prostate gland development and its role in promoting PCa make it an attractive therapeutic target for PCa. Studies have reported using neutralizing antibodies, antisense oligonucleotides, and small-molecule inhibitors of the kinase activity of the TGF-β receptor complex to treat PCa.[19] However, given the multifaceted function of the TGF-β superfamily cytokines, complete inactivation of the signaling pathway using inhibitors might not be beneficial. LncRNAs regulated by the TGF-β pathway modulate multiple aspects of PCa pathogenesis and serve as potential diagnostic tools and attractive therapeutic targets [Table 1].

LncRNAs regulating the TGF-β pathway in PCa can be classified as (1) regulators of the TGF-β pathway, (2) effectors of the TGF-β pathway, and (3) lncRNAs that form a positive feedback loop with the TGF-β pathway. LncRNA expression is tissue-specific and is a diagnostic biomarker for PCa [Tables 1 and 2].

Most lncRNAs described here could be categorized as TGF-β signaling pathway regulators in PCa [Tables 1 and 2]. For instance, *ANRIL* TGF-β signaling by sponging let7 leads to higher TGF-β1 and p-SMAD2 and lower p-SMAD7 levels.[65] Some lncRNAs act as effectors of the TGF-β signaling pathway and regulate the expression of several target genes of the TGF-β pathway. For instance, lncRNA *DIO3OS* is induced by TGF-β and sponges miR-656-3p and miR-485-5p, preventing degradation of CTGF and ZEB1 from promoting TGF-β signaling.[74] Several lncRNAs induced by TGF-β signaling regulate the components of the TGF-β signaling pathway in PCa, affecting the magnitude of its response during tumor progression. LncRNAs, whose expression is regulated by the TGF-β pathway, potentiate the responses of the pathway and form a positive feed-forward loop with the TGF-β pathway. For instance, *PCAT7* is induced by TGF-β, which activates TGF-β signaling and promotes PCa bone metastasis by acting as a ceRNA.[63]

The TGF-β pathway is closely related to AR signaling and several other signaling pathways in prostate development and in promoting PCa progression. Takayama et al. reported that lncRNA *CTBP1-AS*, an antisense lncRNA to the *CTBP1* gene, enhances AR transcriptional activity and promotes hormone-dependent and castration-resistant PCa growth by repressing *CTBP1*, a corepressor of AR.[75] They also reported that *CTBP1-AS* represses p53 and SMAD3 expression.[75] In line with these findings and given the cross-talk of the TGF-β pathway with AR signaling, further investigation of TGF-β-regulated lncRNAs would benefit anti-TGF-β-based therapies for PCa.

Several miRNAs regulate PCa by inhibiting components of the TGF-β pathway.[84,85] LncRNAs functions as ceRNAs for miRNAs; therefore, it is crucial to understand the regulation of miRNAs modulating the TGF-β pathway by lncRNAs deregulated in PCa. Most studies on lncRNAs involved in TGF-β have been conducted on AR-positive cell lines, such as LNCaP, VcaP, and 22RV1 [Tables 1 and 2]. Given the importance of TGF-β signaling in the development and progression of AIPC,[23,26,75] more studies are required on the role of TGF-β-regulated lncRNAs in castration-resistant conditions.

TGF-β signaling promotes drug resistance and immune evasion by reducing the activity of cytotoxic and regulatory T cells.[25,26] LncRNAs promote drug resistance and evasion of immune surveillance in PCa.[52,86] The role of lncRNAs in TGF-β pathways regulating drug resistance and immune evasion needs to be investigated. Furthermore, the non-canonical TGF-β downstream targets, such as PI3K/Akt/mTOR pathways, promote PCa pathogenesis through TGF-β.[25] Some lncRNAs also regulate PCa progression through PI3K/Akt/mTOR pathways independent of TGF-β.[87,88] Further investigations on the role of lncRNAs in the TGF-β pathway regulating PI3K/Akt/mTOR signaling will help to better understand PCa pathogenesis.

In summary, TGF-β-regulated lncRNAs modulate multiple aspects of PCa pathogenesis. The anti-TGF-β-based therapies for PCa in combination with antisense oligos against the TGF-β-regulated lncRNAs warrant further investigation.

Funding

This research is supported by intramural funds from BITS Pilani, Hyderabad, India.

Author contributions

Vivek Sharma and Bakhya Shree conceived and designed the study. Bakhya Shree, Koyel Das, and Vivek Sharma designed, analyzed, and wrote the manuscript. Bakhya Shree and Vivek Sharma edited the final version of the manuscript. All the authors read and approved the final version of the manuscript.

Ethics statement

None.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflict of interest

None.

Acknowledgments

The authors dedicate this review article to Late Prof. Suman Kapur and thank Shashwat Sharad for his suggestions on an earlier version of this manuscript. BS acknowledges the Senior Research Fellowship from ICMR No. 2020-7940/GEN-BMS. We thank the reviewers for their constructive feedback on the manuscript.

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