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REVIEW ARTICLE

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Long non-coding RNAs and TGF-β signaling in cancer

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Abstract

Cancer is driven by genetic mutations in oncogenes and tumor suppressor genes and by cellular events that develop a misregulated molecular microenvironment in the growing tumor tissue. The tumor microenvironment is guided by the excessive action of specific cytokines including transforming growth factor-β (TGF-β), which normally controls embryonic development and the homeostasis of young or adult tissues. As a consequence of the genetic alterations generating a given tumor, TGF-β can preserve its homeostatic function and attempt to limit neoplastic expansion, whereas, once the tumor has progressed to an aggressive stage, TGF-β can synergize with various oncogenic stimuli to facilitate tumor invasiveness and metastasis. TGF-β signaling mechanisms via Smad proteins, various ubiquitin ligases, and protein kinases are relatively well understood. Such mechanisms regulate the expression of genes encoding proteins or non-coding RNAs. Among non-coding RNAs, much has been understood regarding the regulation and function of microRNAs, whereas the role of long non-coding RNAs is still emerging. This article emphasizes TGF-β signaling mechanisms leading to the regulation of non-coding genes, the function of such non-coding RNAs as regulators of TGF-β signaling, and the contribution of these mechanisms in specific hallmarks of cancer.

KEYWORDS

non-coding RNA, signal transduction, Smad, transcription, transforming growth factor-β

1 | INTRODUCTION

Cancer represents a large group of diseases that affects many organs. Cancers are characterized in their onset by genetic mutations in key genes that subsequently unleash a cohort of cell biological processes; the various pathological processes ultimately lead to the growth of malignant tissue in the form of tumors and even further, but infrequently, to disseminating cells into metastases in nearby or distant organs.[1,2] Secreted growth factors control the communication between cells and the organization of tissues. For these reasons, growth factor genes, upon mutagenic alteration, can act as initiators of the malignant process (oncogenes), but also as functional mediators of the malignant evolution through various stages.[1,3] Since its discovery, transforming growth factor β (TGF-β) has been linked functionally with and continues to provide new lessons on mechanisms that govern cancer development.[4-7]

2 | TGF-β SIGNALING IN CANCER

TGF-β is the prototype member of a large family of polypeptide growth factors that has exhibited evolutionary conservation in

Abbreviations: EMT, epithelial-mesenchymal transition; lncRNA, long non-coding RNA; TGF-β, transforming growth factor β.

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all animals since the emergence of multicellularity.[8] TGF-β signaling pathways participate in developmental morphogenetic programs and contribute to young or adult organismic homeostasis; the growth factors of this family regulate differentiation, proliferation, and motility.[5,8] TGF-β (encompassing 3 isoforms, TGF-β1/2/3) is secreted from many cells via a well controlled mechanism that delivers a latent, inactive form of the growth factor, together with other proteins, to the extracellular matrix.[8] Upon activation, TGF-β signals via its receptors, serine-threonine and weak tyrosine kinase enzymes, known as type II (TGFβRII) and type I (TGFβRI) receptors.[8] When TGF-β binds to TGFβRII, recruitment of TGFβRI is followed by trans-phosphorylation of serine and threonine residues in TGFβRI by TGFβRII kinase, conformational activation of TGFβRI, which subsequently phosphorylates Smad2 and Smad3, members of the Smad family of signal transducers and latent transcription factors.[8] The phosphorylated Smad2 and Smad3 interact with Smad4 to generate trimeric complexes that associate directly with DNA and many transcription factors that mediate the regulation of target gene expression.[5] A negative feedback mechanism is mediated by the inhibitory Smad7. TGF-β induces Smad7 expression, which inhibits signaling via direct interaction of Smad7 with TGFβRI, Smad complexes, and several ubiquitin ligases that ubiquitylate and degrade either the receptor, upon its internalization, or the active Smad complexes.[5] The TGF-β receptor complex also recruits ubiquitin ligases that then, via ubiquitylation, activate protein kinases that lead to downstream engagement of the mitogen-activated protein (MAP) kinases.[8] The same ubiquitylation-dependent mechanism also controls a cleavage and translocation of the cytoplasmic, protein kinase domain of TGFβRI, to the nucleus for further signaling in association with Smad and other transcriptional cofactors.[8] The coordinated activity of Smads, phosphorylation inputs generated by TGF-β-mediated MAP kinase activation and nuclear TGFβRI intracellular domain mediate the diverse biological actions of TGF-β.[5]

Similar to its actions in adult homeostasis, TGF-β signaling limits the development of hyperplastic, pre-malignant lesions in many organs.[4-7] Once tumorigenesis has progressed, TGF-β cooperates with diverse oncogenic pathways and facilitates the development of aggressive, less differentiated, and invasive tumors.[4-7] TGF-β also facilitates cancer metastasis.[4-7] Homeostatic signaling fighting against hyperplastic growth is exemplified by the ability of TGF-β to induce the expression of cyclin-dependent kinase inhibitors, including CDKN1A ($p21^{CIP1}$), CDKN1B ($p27^{KIP1}$), CDKN2B ($p15^{INK4B}$).[5,7] These cell cycle inhibitors stall the epithelial, endothelial, lymphocytic, and erythropoietic cell cycle in the early G1 phase.[5,7] In hepatocytes, prostate, and other epithelial cell types, TGF-β can also induce apoptosis via coordinated signaling actions: (i) Smad-mediated induction of pro-apoptotic genes (*Bim*, *DAPK*); (ii) activation of MAP kinases and cytochrome c release from mitochondria, leading to pro-caspase activation.[5-7] Furthermore, the TGF-β receptors and the Smad genes can be mutated in various tumors.[9] Genetic alterations cause either complete loss of responses or preferential loss of the cytostatic and pro-apoptotic responses to TGF-β by malignant cells.[5]

Once malignancy progresses, TGF-β secretion by cancer cells, cancer-associated fibroblasts, or in some cases even from immune cells, is abundantly observed.[4] In carcinomas, EMT is potently induced by TGF-β and contributes to the invasive and pro-metastatic phases of tumor development.[6,10] TGF-β inhibits the proliferation and differentiation of B and T lymphocytes, causing a local immune suppression that promotes expansive tumor growth and invasiveness.[4] TGF-β can indirectly stimulate neo-angiogenesis that feeds the growing malignancy and facilitates invasiveness and metastatic dissemination.[5,6] These multi-faceted effects of TGF-β have, in recent years, stimulated several clinical trials. As a combinatorial treatment, together with more classical chemo- or radio-therapy, TGF-β pathway inhibitors have shown ability to limit expansion of various tumors.[4,6]

3 | LONG NON-CODING RNAs

The majority of the biological activities of TGF-β can be explained by regulation of expression of a large cohort of mRNAs and their encoded proteins. In recent years, attention has been given to the functional roles of non-protein-coding RNAs. Among the various non-coding RNAs, much focus has been given to microRNAs (miRNAs); TGF-β signaling regulates miRNA gene expression and miRNA maturation from precursor transcripts, whereas various miRNAs can regulate TGF-β signaling in the context of cancer.[11-13] Here, we focus exclusively on long non-coding RNAs (lncRNAs), whose regulation by TGF-β signaling and functional participation in multiple responses to TGF-β form an emerging field.[6,12]

lncRNAs are structurally identical to mRNAs. They are transcribed by RNA polymerase II into 250 nt or longer RNAs; they have 5′ modified caps and poly-adenylated tails at their 3′-end, and localize in the nucleus, cytoplasm or both (Figure 1).[14-16] lncRNAs almost universally carry open reading frames, which are small, initiating with non-optimal start codons, embedded in the lncRNA sequence far away from the 5′-end and are often considered incapable of encoding polypeptides.[14-16] The non-coding capacity of lncRNAs is bioinformatically attested and only rarely experimentally tested. Examples of lncRNAs encoding for functional polypeptides exist. The putative lncRNA LOC100507537 encodes for the 34 amino acid-long peptide "dwarf open reading frame," which associates with and activates the sarcoplasmic reticulum calcium pump sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) in cardiomyocytes, thus regulating heart muscle contraction.[17] In the context of cancer, the homeobox B cluster antisense RNA 3 (HOXB-AS3) encodes a 53 amino acid-long polypeptide; the polypeptide binds to arginine-rich sequences in the hnRNP A1 splicing factor regulating alternative splicing of the pyruvate kinase M.[18] By inducing expression of pyruvate kinase isoform M2, the HOXB-AS3 polypeptide facilitates manifestation of the oncogenic Warburg effect in colorectal cancer.[18]

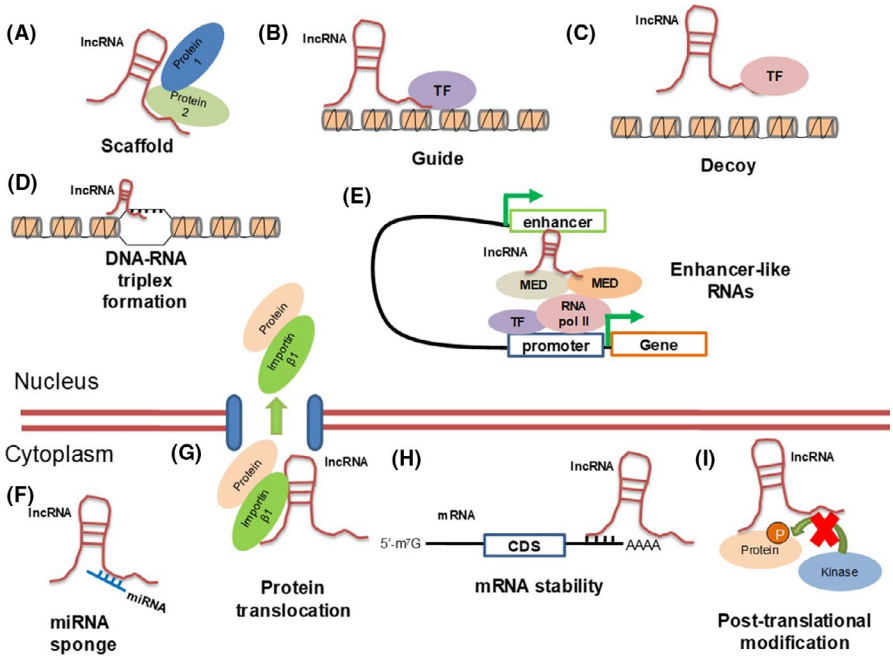

FIGURE 1 Molecular functions of lncRNAs. Nuclear lncRNAs act as scaffold (A), guide (B) or decoy (C) molecules. They also form triple helix formations by directly binding to DNA (D), and act as enhancer-like RNAs, promoting gene transcription (E). Cytoplasmic lncRNAs function as sponges for miRNAs (F), facilitate nucleocytoplasmic protein translocation (G), affect mRNA stability (H) and interfere with post–translational modifications of proteins (I). CDS: coding sequence, MED: component of the mediator complex, RNA pol II: RNA polymerase II, TF: transcription factor

lncRNAs are classified based on the position of their gene relative to protein-coding genes. Antisense lncRNAs are transcribed from the opposite DNA strand of a protein-coding gene and partially overlap with mRNAs.[19,20] Intronic lncRNAs are completely embedded in the intron of a protein-coding gene.[21] Divergent lncRNAs do not overlap with mRNAs but share promoter-enhancer sequences with a protein-coding gene and are transcribed in the opposite direction relative to the mRNA.[21] Enhancer RNAs (eRNAs) or ncRNA-activating, are encoded by genes that overlap characterized enhancer sequences and regulate expression of the genes that are controlled by the enhancer.[22,23] Finally, intergenic lncRNAs map as independent genes far away from protein-coding genes.[21]

Similar to mRNAs, the biological functions of lncRNAs permeate all essential cell biological processes, and their actions are often linked to cancer development. These functions range from the control of stemness and differentiation, including genomic imprinting and the mechanism of X chromosome inactivation, to immunity and programmed cell death.[14-16,24] Mechanistically (Figure 1), lncRNAs regulate gene expression by acting as scaffolds, guides, or decoys or by base-pairing with DNA, through formation of triple helices.[16] lncRNAs associate with nuclear proteins and affect nucleosome remodeling,[21] including histone modifications catalyzed by protein methyltransferases, such as the polycomb repressor complex 2 (PRC2).[16,25] lncRNAs can regulate mRNA splicing, stability, or translation.[21] A widely established function of lncRNAs, especially when they are located in the cytoplasm, is the "sponge" or competing endogenous (ce) RNA function; this indicates their ability to base-pair with miRNAs (Figure 1), and thus shield the action of the miRNAs toward target mRNAs.[26] Most of these molecular mechanisms of action have been demonstrated in the context of cancer cell biology.

4 | lncRNAs ACT AS EFFECTORS OF TGF-β SIGNALING

The list of lncRNAs, described as effectors of TGF-β signaling, is constantly growing (Figure 2). Table 1 summarizes TGF-β-regulated lncRNAs and their roles in different cancer types. Furthermore, lncRNAs acting as effectors of TGF-β signaling have been reported in a plethora of different cancer types. One of the first lncRNAs, demonstrated to be modulated by TGF-β, is the *lncRNA-activated by TGF-β* (*lncRNA-ATB*) in hepatocellular carcinoma (HCC).[27] TGF-β upregulates *lncRNA-ATB* in order to favor EMT and establish a pro-metastatic program. *lncRNA-ATB* acts as a sponge for the epithelial-specific *miR-200*.[27] *miR-200* was previously established as a negative regulator of the EMT transcription factors ZEB1/2 and, accordingly, *lncRNA-ATB* acts by enhancing ZEB1/2 expression. Moreover, *lncRNA-ATB* stabilizes *interleukin-11* mRNA, leading to increased cytokine signaling mediated by STAT3, which potentiates tumor colonization in secondary tissues to ensure efficient metastasis.[27] Similar to HCC, *lncRNA-ATB* is induced by TGF-β in MCF7 breast cancer cells and was established as a marker of poor prognosis in breast cancer; *lncRNA-ATB* promotes EMT by sponging *miR-200* and thus, upregulating Twist1 expression, the latter being another transcription factor of the EMT program.[28] In intrahepatic cholangiocarcinoma, the *TGF-β-induced long noncoding RNA* (*TLINC*) boosts a pro-migratory phenotype and positively regulates interleukin-8, reinforcing a pro-inflammatory tumor microenvironment.[29] In pancreatic ductal adenocarcinoma (PDAC), TGF-β induces the *mir-100-let-7a-2-mir-125b-1 cluster host gene* (*MIR100HG*), a lncRNA that gives rise to *mir-100*, *let-7a-2*, and *mir-125b-1* miRNAs. *miR-100* and *miR-125b* promote PDAC progression and EMT, by downregulating p53 and apoptotic pathways and upregulating the pro-survival phosphatidylinositol 3´-kinase/Akt signaling pathway.[30] In colorectal cancer, the *taurine*

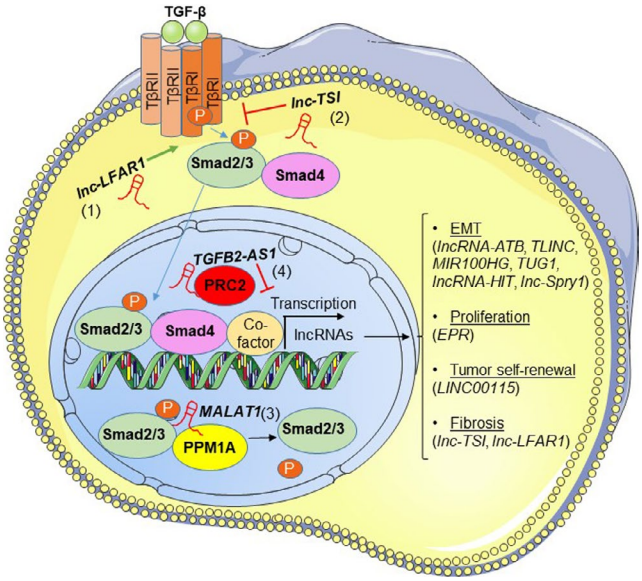

FIGURE 2 TGF-β signaling regulates lncRNA expression and mechanisms of TGF-β signaling control by lncRNAs. TGF-β signals through Smad2/3/4 proteins to regulate the expression of lncRNAs, acting as effector molecules that mediate the physiological responses of the signaling pathway (listed on the right hand-side). lncRNAs target TGF-β signaling at different stages of the pathway. At the level of Smad2/3 activation by TGFβRI, *lnc-LFAR1* (1) enhances the association of Smad2/3 with TGFβRI, leading to increased activation of the pathway. *lnc-TSI* (2) blocks the interaction of Smad3 with TGFβRI, attenuating the pathway. In the nucleus, *MALAT1* (3) shifts the Smad2/3 levels toward the non-phosphorylated state, by promoting the association of the phosphatase PPM1A to Smads and inhibiting TGF-β-mediated responses. *TGFB2-AS1* (4) epigenetically silences TGF-β-target genes by recruiting the PRC2 repressive complex to their promoters

up-regulated gene 1 (*TUG1*) lncRNA is a mediator of TGF-β-induced EMT in vitro and metastasis in vivo; *TUG1* is enhanced in response to TGF-β, in order to increase Twist1 expression, resulting in enhanced migration, invasion, and lung metastasis.[31]

Using a genome-wide screen for identifying TGF-β-regulated lncRNAs in NMuMG mouse mammary epithelial cells, the *homeobox A (HOXA) transcript induced by TGF-β* (*lncRNA-HIT*) was shown to enhance EMT, migration, and invasion, by specifically inhibiting E-cadherin expression.[32] TGF-β signaling can additionally negatively regulate repressors of the EMT process, in order to elicit its pro-tumorigenic role. For example, TGF-β inhibits a lncRNA located in close proximity to the *Spry1* gene, designated as *lnc-Spry1*, in NMuMG cells.[33] *lnc-Spry1* interacts with the splicing factor U2AF65 and suppresses EMT, by affecting the alternative splicing of fibroblast growth factor receptors.[33] In NMuMG cells, TGF-β initially upregulates and, upon sustained signaling, it downregulates the *epithelial cell program regulator* (*EPR*), an epithelial lncRNA that attenuates cell proliferation, by positively regulating the cell cycle inhibitor *Cdkn1a*, both transcriptionally and post-transcriptionally.[34] At the transcriptional level, *EPR* directly binds to the *Cdkn1a* promoter and interacts with Smad3 during early TGF-β signaling, thereby activating *Cdkn1a* transcription.[34] Upon sustained TGF-β signaling *Cdkn1a* levels return to basal, a response that coincides with the delayed EPR downregulation. At the post–transcriptional level, *EPR* associates with the RNA-binding protein KHSRP (KH-type splicing regulatory protein) and prevents its binding to *Cdkn1a* mRNA, thereby increasing *Cdkn1a* stability.[34]

TGF-β regulates lncRNA expression not only in carcinomas but also in tumors of diverse tissue origin. For example, *LINC00115* is overexpressed in glioblastoma and is upregulated by TGF-β in glioma stem-like cells, in order to facilitate their self-renewal.[35] *LINC00115* interferes with the binding of *miR-200* to its target mRNAs *ZEB1* and *ZNF596* (*zinc finger protein 596*), leading to increased expression of these proteins and potentiation of downstream pro-tumorigenic signals that elicit tumor growth.[35] Table 1 presents additional lncRNAs which are not discussed here in the interest of space.

5 | lncRNAs ACT AS REGULATORS OF TGF-β SIGNALING

In addition to being effectors of TGF-β signaling, lncRNAs modulate several components of the pathway, thereby affecting the magnitude of its response, during tumor progression (Figure 2). Several lncRNAs can regulate TGF-β signaling in a wide range of cancers (Table 2). In HCC cells, *metastasis-associated lung adenocarcinoma transcript 1* (*MALAT1*) alters the balance between phosphorylated (p-) and de-phosphorylated Smad2 and Smad3 levels.[36] *MALAT1* interacts with p-Smad2 and p-Smad3, through the protein known as SET domain containing 2 (SETD2), which serves as a scaffold that facilitates complex formation between the phosphatase PPM1A (protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1A) and p-Smad2/3. Thus, *MALAT1* promotes the termination of TGF-β signaling, by inducing the PPM1A-mediated de-phosphorylation of activated p-Smad2/3.[36] In colorectal cancer, the *cancer susceptibility candidate 9* (*CASC9*) is a lncRNA that predicts poor survival for patients.[37] The pro-tumorigenic function of *CASC9* is due to the increased stabilization of *TGFB2* levels, which lead to active TGF-β2 signaling and enhanced p-Smad3 levels.[37] The positive contribution of *CASC9* to TGF-β signaling depends on its binding to the protein cleavage and polyadenylation specific factor 3 (CPSF3), an mRNA-processing factor, which is capable of directly interacting with *TGFB2* mRNA.[37] *Liver fibrosis-associated lncRNA 1* (*lnc-LFAR1*) potentiates TGF-β signaling by enhancing *TGFB1*, *Smad2*, and *Smad4* mRNA levels in the intrahepatic cholangiocarcinoma cell line QBC939.[38] Moreover, *lnc-LFAR1* exerts pro-EMT functions, by enhancing vimentin and downregulating E-cadherin protein levels and reinforces migration and invasion of QBC939 cells.[38] In colorectal cancer, the *small nucleolar RNA host gene 6* (*SNHG6*) activates the TGF-β pathway by reducing UPF1 (UPF1 RNA helicase and ATPase), a regulator of Smad7, leading to reduced Smad7 expression and, therefore, increased p-Smad2/3 levels.[39] Thus, *SNHG6* promotes cell proliferation, migration, and

TABLE 1 TGF-β-regulated lncRNAs

LncRNA	Type of regulation	Function	Mechanism of action	Cancer type/ cell line	Ref.
TUG1	Up	Induces EMT in vitro; metastasis in vivo	Enhances Twist1	Colorectal cancer	31
LINC00273	Up	Promotes invasion and metastasis	Activates ZEB1 via sponging *mir200a-3p*	A549 adenocarcinoma cells	51
LINC00115	Up	Promotes cell self-renewal	Upregulates *ZEB1* and ZNF596, via sponging *miR-200*	Glioma stem-like cells	35
EPR	Up (early) Down (late)	Inhibits cell proliferation	Positively regulates *Cdkn1a*	NMuMG breast epithelial cells	34
MIR155HG	Up	Promotes EMT	Regulates the *miR-155-5p*/ SOX10 axis	Laryngeal squamous cell carcinoma	52
MACC1-AS1	Up	Fatty acid oxidation-dependent stemness and chemoresistance	De-represses stemness and FAO genes, via sponging *miR-145-5p*	Gastric cancer	53
HCP5	Up	Promotes EMT	Upregulates Snail and Slug by sponging *miR-203*	Lung adenocarcinoma	54
PTAF	Up	Promotes EMT and invasion	Enhances *SNAI2* by targeting *miR-25*	Ovarian cancer	55
MIR100HG	Up	Hosts pro-tumorigenic miRNAs	*miR-100* and *miR-125b* downregulate p53 and apoptotic pathways and activate the PI3K pathway	PDAC	30
TLINC	Up	Promotes cell migration and pro-inflammatory tumor microenvironment	Positively regulates pro-inflammatory cytokines	Intrahepatic cholangiocarcinoma	29
MEG8	Up	Induces EMT	Upregulates *SNAI1* and *SNAI2*, by epigenetically suppressing *miR-34a* and *miR-203*	A549, LC-2/ad, Panc1 cells	56
UCA1	Up	Promotes cell proliferation	Upregulates HXK2	HCC	57
	Up	Promotes EMT	Enhances *Slug* by targeting *miR-1* and *miR-203a*	Glioma	58
	Up	Promotes EMT	Unknown	Gastric cancer	59
NKILA	Up	Inhibits cell migration and invasion	Suppresses MMP14 by inhibiting the NF-κB pathway	Esophageal squamous cell carcinoma	60
	Up	Inhibits EMT	Blocks the NF-κB pathway	MCF7 breast cancer cells	61
LINP1	Down	Inhibits EMT	Enhances *CDH1* and represses mesenchymal genes (mechanism unknown)	Lung cancer	62
lncRNA-ATB	Up	Promotes EMT	Upregulates Twist1 by sponging *miR-200*	MCF7 breast cancer cells	28
	Up	Promotes EMT in vitro and metastasis in vivo	Enhances ZEB1/2, by sponging *miR-200* and stabilizes *IL-11* mRNA	HCC	27
lnc-MMP2-2	Up	Regulates cell migration and invasion	Promotes MMP2 expression	A549 lung adenocarcinoma exosomes	63
TBILA	Up	Promotes tumor progression in vitro and in vivo	Enhances RhoA and S100A7-JAB1 pathway activation	Non-small cell lung cancer	64
H19	Down	Increases tumorigenic potential in vivo	Unknown	Tumor-initiating hepatocytes	65
	Up	Enhances cell invasion in vitro and metastasis in vivo	Upregulates *Slug* and inhibits CDH1 via *miR-675*	Hep3B HCC cells	66
has2as	Up	Promotes EMT and cancer stemness	Induces *has2*, by facilitating Smad2/3 binding to its promoter	NMuMG breast epithelial cells	67
EPB41L4A-AS2	Down	Inhibits cell migration and invasion	Inhibits *TGFBR1* expression	Head and neck squamous cell carcinoma	68

(Continues)

TABLE 1 (Continued)

LncRNA	Type of regulation	Function	Mechanism of action	Cancer type/ cell line	Ref.
lnc-Spry1	Down	Suppresses EMT	Alternative splicing of FGFRs, via binding to U2AF65	NMuMG breast epithelial cells	33
MEG3	Up	Induces EMT	Represses *CDH1* and *miR-200* by facilitating recruitment of JARID2 and EZH2 on their promoters	A549, LC-2/ad cells	69
LINC01186	Down	Inhibits EMT	Suppresses mesenchymal markers and induces *CDH1*, (mechanism unknown)	A549 lung adenocarcinoma cells	70
lncRNA-LET	Down	Represses cancer cell stemness	Decreases NF90 stability leading to *miR-145* upregulation	Urinary bladder cancer	71
linc00673	Up	Induces EMT	Upregulates ZEB1, by sponging *miR-150-5p*	Non-small cell lung cancer	72
LINC01133	Down	Inhibits EMT and metastasis	Blocks SRSF6 function	Colorectal cancer	73
lncRNA-HIT	Up	Enhances EMT, migration, invasion	Represses *CDH1*	NMuMG breast epithelial cells	32
MALAT1	Up	Induces EMT	Represses *CDH1*, via binding to SUZ12	Bladder cancer	74
lncRNA-Smad7	Up	Inhibits apoptosis	Unknown	NMuMG, JygMC(A) breast cancer cells	75

invasion in vitro and colorectal tumor growth in vivo.[39] In HCC, the *nuclear enriched abundant transcript 1* (*NEAT1*) acts as a ceRNA for *miR-139-5p*, thereby protecting *TGFB1* mRNA from *miR-139-5p*-induced degradation.[40] Thus, *NEAT1* is an activator of TGF-β signaling and promotes HCC growth.[40] In ovarian carcinoma, the *LINK-A* is frequently overexpressed and positively correlated to the TGF-β1 protein levels.[41] Ectopic expression of *LINK-A* leads to enhanced TGF-β1 expression, as well as enhanced migratory and invasive behavior of ovarian cancer cells.[41] In lung adenocarcinoma cells, the *NORAD* (*non-coding RNA activated by DNA damage*) is predominantly cytoplasmic and promotes the association between Smad3 and importin-β1, thereby facilitating the TGF-β-induced nuclear translocation of Smad3.[42] *NORAD* positively regulates the activity of Smad-responsive luciferase reporter genes, as well as the expression of TGF-β-target and EMT-related genes, such as *SERPINE1*, *SNAI1*, and FN1. In addition, by activating the TGF-β pathway, *NORAD* promotes the migration of A549 lung adenocarcinoma cells, in response to TGF-β.[42] In invasive pituitary tumors, the oncogenic *lnc-SNHG1* upregulates *TGFBR2*, by preventing receptor degradation by the *miR-302/372/373/520* cluster, leading to enhanced Smad3 nuclear accumulation and increased migration and invasion, accompanied by a pro-EMT phenotype of pituitary tumor cells.[43] In breast cancer cells, *maternally expressed 3* (*MEG3*), in co-operation with the co-repressor complex PRC2, promotes epigenetic silencing of members of the TGF-β pathway, such as *TGFB2*, *TGFBR1*, and *Smad2*, via formation of RNA-DNA triple helical structures in GA-rich, distal regulatory elements of these genes.[44] These cases clearly illustrate that essentially every component of the TGF-β signaling pathway can be targeted for regulation by lncRNAs (Figure 2).

6 | lncRNAs FORM FEEDBACK LOOPS WITH TGF-β SIGNALING

Some of the lncRNAs whose expression is regulated by the TGF-β pathway, as described above, potentiate or diminish the responses of the pathway itself. We categorize these lncRNAs into 2 subclasses: first, lncRNAs that are transcriptionally upregulated by TGF-β, which then enhance TGF-β signaling output, forming positive feedback loops; second, TGF-β-induced lncRNAs, with inhibitory roles on TGF-β responses, thereby belonging to negative feedback loops. Examples of lncRNAs that form positive feedback loops with TGF-β are the lncRNAs *PCAT7*, *ELIT1*, *HOTAIR*, *lincRNA-p21*, *MALAT1* and *lncRNA-ATB* (Table 3). In prostate cancer, *PCAT7* (*prostate cancer-associated transcript-7*) is upregulated by TGF-β via the transcriptional complex of Smad3 with Sp1 and then positively regulates TGF-β signaling by sponging *miR-324-5p*, leading to enhanced *TGFBR1* expression, as *TGFBR1* is downregulated by *miR-324-5p*.[45] In endothelial progenitor cells, the TGF-β-induced *MALAT1* described earlier, is required for the induction of endothelial-to-mesenchymal transition, a process similar to the EMT that has been implicated in the dissemination of tumor cells to metastatic sites. Mechanistically, *MALAT1* binds to the tumor suppressor *miR-145* and sequesters it away from its target mRNAs *TGFBR2* and *Smad3*, resulting in increased TGF-β activation.[46] In hepatocytes, *lincRNA-p21* is involved in a positive feedback loop, whereby TGF-β induces its expression, in order to strengthen the magnitude of the pathway, by sponging *miR-30*, leading to increased *KLF11* levels, as *miR-30* downregulates *KLF11*; the transcription factor KLF11 represses *Smad7*, and thus enhances TGF-β signaling, which promotes liver fibrosis.[47] In keloid fibroblasts, the TGF-β-induced

TABLE 2 lncRNAs that modulate TGF-β signaling

lncRNA	Type of regulation	Mechanism of action	Cancer type/cell line	Ref.
MALAT1	Negative	Promotes de-phosphorylation of Smad2/3 by PPM1A	Hep3B, PLC/PRF/5, SK-Hep1 HCC cells	36
CASC9	Positive	Increased stabilization of *TGFB2* mRNA	Colorectal cancer	37
HAND2-AS1	Negative	Downregulates TGF-β1	Non-small cell lung cancer	76
lnc-LFAR1	Positive	Enhances *TGFB1*, *Smad2*, and *Smad4* mRNAs	Intrahepatic cholangiocarcinoma cells (QBC939)	38
AWPPH	Positive	Upregulates TGF-β1	Non-small cell lung cancer cells (H1581, H1993)	77
POU3F3	Positive	Upregulates TGF-β1	Nasopharyngeal carcinoma cells (HTB-43, C666-1)	78
SNHG6	Positive	Reduces *Smad7* expression	Colorectal cancer cells (RKO)	79
SBF2-AS1	Positive	Enhances *TGFBR1* through sponging *miR-140-5p*	HCC	80
NORAD	Positive	Facilitates Smad3 nuclear transport	A549 lung adenocarcinoma cells	42
LINK-A	Positive	Enhances TGF-β1 expression	Ovarian carcinoma	41
lnc-SNHG1	Positive	Upregulates *TGFBR2*, by sponging the *miR-302/372/373/520* cluster	Pituitary tumor cells (GH1, RC-4B/C)	43
NEAT1	Positive	Prevents *TGFB1* mRNA degradation by sponging *miR-139-5p*	HCC	40
UCA1	Positive	Positively regulates TGF-β	Multiple myeloma	81
LINC00978	Positive	Enhances TGF-β and p-Smad2 levels	Gastric cancer cells (MGC-803, SGC-7901)	82
SPRY4-IT1	Positive	Positively regulates TGF-β1 and p-Smad2/3 levels	Thyroid squamous cell carcinoma (SW579), papillary thyroid carcinoma (TPC-1) cells	83
EPB41L4AAS2	Negative	Suppresses *TGFBR1*	Head and neck squamous cell carcinoma	68
CCAT2	Positive	Positively regulates TGF-β and Smad2	Breast cancer	84
XIST	Positive	Upregulates TGF-β1 via targeting *miR-185*	Gastric cancer	85
TUG1	Positive	Promotes p-Smad2/3	PDAC	86
BX357664	Negative	Suppresses TGF-β1	Renal cell carcinoma	87
ANRIL	Negative	Inhibits TGF-β1	Thyroid cancer	88
	Negative	Inhibits TGF-β1	Esophageal squamous cell carcinoma	89
MEG3	Negative	Epigenetically silences *TGFB2*, *TGFBR1*, and *Smad2*, via RNA-DNA triplex formation	Breast cancer	44

TABLE 3 List of lncRNAs that form feedback loops with TGF-β signaling

lncRNA	Feedback loop	Mechanism of action	Cancer type/cell line	Ref.
PCAT7	Positive	Upregulation of TGFBR1 via sponging *miR-324-5p*	Prostate cancer	45
TGFB2-AS1	Negative	Epigenetic silencing of TGF-β-target gene promoters via PRC2	HaCaT keratinocytes, A549 lung adenocarcinoma cells	49
ELIT-1	Positive	Binds to Smad3 and facilitates its recruitment to promoters of EMT-related genes	Huh7 HCC, A549 lung adenocarcinoma cells	90
lnc-TSI	Negative	Blocking the interaction of Smad3 with TGFβRI	Renal tubular epithelial cells	50
lincRNA-p21	Positive	Interaction with *miR-30* leading to KLF11-mediated suppression of Smad7	AML12 hepatocytes	47
MALAT1	Positive	Upregulation of TGFBR2 and Smad3 via sponging *miR-145*	Endothelial progenitor cells	46
lncRNA-ATB	Positive	Increased secretion of TGFβ2 via sponging *miR-200c* and induction of ZNF217	Keloid fibroblasts	48

lncRNA-ATB described earlier, facilitates TGF-β-dependent responses, by acting as a ceRNA for *miR-200c*, leading to ZNF217 upregulation and increased secretion of TGFβ2.[48]

Conversely, *TGFB2-AS1* and *lnc-TSI* participate in negative feedback loops with TGF-β signaling (Table 3). TGF-β induces the expression of *TGFB2 antisense RNA 1* (*TGFB2-AS1*) in human immortalized

keratinocytes and lung adenocarcinoma cells. *TGFB2-AS1*, in turn inhibits Smad-mediated transcriptional responses, via interaction with the PRC2 complex, leading to epigenetic silencing of TGF-β target genes.[49] During renal fibrosis, the kidney-specific *TGF-β/Smad3-interacting long noncoding RNA* (*lnc-TSI*) is upregulated by TGF-β and forms a negative loop, by binding to the MH2 domain of Smad3, thereby blocking the association of Smad3 with TGFβRI and inhibiting receptor signaling.[50] This mechanism seems to not involve the function of Smad7, and results in lower TGF-β signaling and therefore diminished TGF-β-induced renal fibrogenesis.[50] Although some of these examples do not stem from studies of cancer biology, they are useful as they illustrate the importance of feedback control of the TGF-β signaling pathway, a mechanism whereby previously well established proteins are now demonstrated to cooperate with lncRNAs in order to elicit their full action.

7 | CONCLUDING REMARKS

The large spectrum of biological actions engaging the TGF-β signaling pathway during cancer development has necessitated the elucidation of many target genes of this pathway, and their functions. Whereas the first 35 y of TGF-β signaling research focused on protein-coding genes, the past 5 y have demonstrated the important function of lncRNAs. Most of the studied lncRNAs act either as regulators of chromatin modifications and transcriptional control or as sponges that limit the abundance of miRNAs. We anticipate the elucidation of completely new mechanisms of action of lncRNAs downstream of TGF-β in cancer. Equally interesting is the large number of lncRNAs that regulate specific steps of TGF-β signaling. Whereas TGF-β ligand expression is a frequent target for regulation by lncRNAs, examples of very intricate mechanisms, such as regulation of Smad phosphorylation or Smad translocation to the nucleus, have been described to engage lncRNAs. In cancer, differentially expressed oncogenic lncRNAs that modulate TGF-β signaling could serve as biomarkers to stratify patients that may benefit from anti-TGF-β-based therapies. Placing such lncRNAs together with protein-based mechanisms into the biology of specific tumors is a challenging task. Completion of this task promises a more coherent understanding of the mistakes made as cancer cells aim to survive and spread their biological potential in multiple organs of the afflicted patients.

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