Roles of TGF-β signalling pathway-related lncRNAs in cancer (Review)

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Abstract. Long non-coding RNAs (lncRNAs) are a class of RNAs that are >200 nucleotides in length that do not have the ability to be translated into protein but are associated with numerous diseases, including cancer. The involvement of lncRNAs in the signalling of certain signalling pathways can promote tumour progression; these pathways include the transforming growth factor (TGF)-β signalling pathway, which is related to tumour development. The expression of lncRNAs in various tumour tissues is specific, and their interaction with the TGF-β signalling pathway indicates that they may serve as new tumour markers and therapeutic targets. The present review summarized the role of TGF-β pathway-associated lncRNAs in regulating tumorigenesis in different types of cancer and their effects on the TGF-β signalling pathway.

Contents

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Abbreviations: lncRNA, long non-coding RNA; TGF-β, transforming growth factor β; EMT, epithelial-mesenchymal transition; TNF, tumour necrosis factor; TRAF, receptor-associated factor; ERK, extracellular signal-regulated kinase; CRC, colorectal cancer; HCC, hepatocellular carcinoma; GC, gastric cancer; NSCLC, non-small cell lung cancer

Key words: cancer, lncRNA, TGF-β signalling pathway

1. Introduction

Long non-coding RNAs (lncRNAs) are newly discovered RNAs that are >200 nucleotides in length and are involved in a variety of molecular regulatory processes, including transcriptional and posttranscriptional regulation, protein localisation and RNA interference (1-3). Although the full function of a number of lncRNAs is unknown, their role in cancer is becoming increasingly clear (4,5).

The transforming growth factor (TGF)-β signalling pathway consists of multiple signalling proteins that control a variety of cell functions, including proliferation, differentiation, apoptosis and survival (6). Its inactivation leads to a variety of pathological states, including malignancy, immune system disorder and inflammatory responses (7). However, the role of the TGF-β pathway in carcinogenesis is complex, and it exerts either tumour-suppressive or tumour-promoting effects depending on the cellular environment (8). The complex regulatory mechanisms of the TGF-β pathway in cancer are currently unknown.

There is growing evidence of the interaction between the TGF-β signalling pathway and lncRNAs in tumours and several members of the TGF-β signalling pathway have been identified as targets of lncRNAs (9-11). The present review summarizes knowledge of crosstalk between the TGF-β signalling pathway and lncRNAs in cancer.

2. Role of lncRNAs in cancer

LncRNAs that participate in chromatin remodelling, transcriptional control, posttranscriptional processing, protein modification and RNA degradation (12-14). After the discovery of the first lncRNAs in 1990 (15), lncRNAs have received increasing attention. Numerous lncRNAs participate in the pathogenesis of different diseases (16); these include lncRNA CDC6 in breast cancer (17), lncRNA OIN1 in ovarian cancer (18) and lncRNA RP11-567G11.1 in pancreatic cancer (19). Owing to the development of sequencing

technology, lncRNAs have been found to serve an important role in tumour cell proliferation, apoptosis, differentiation and invasion (11,20).

lncRNAs are considered to be an important component of cancer, but they play different roles in different types of cancer. For instance, lncRNA FGD5-AS1 accelerates cell proliferation in pancreatic cancer by regulating the microRNA (miRNA or miR)-520a-3p/KIAA1522 axis (21), high expression levels of lncRNA PCAT1 are associated with drug resistance in colorectal cancer (CRC) (22) and lncRNA LNMICC promotes cervical cancer lymph node metastasis by reprogramming fatty acid metabolism (23). High or low expression of lncRNAs in tumours contributes to disease via multiple molecular mechanisms and they have a variety of unique functions and characteristics. Guide lncRNAs bind enzymatically active protein complexes and direct them to target gene promoter regions or genome-specific loci (24). Scaffold lncRNAs build a central platform to which multiple protein complexes attach, thus guiding them to their designated locations (24). Decoy lncRNAs activate or silence downstream target genes by binding and interacting with transcription factors or repressors (25). In addition, lncRNAs are associated with a number of key signalling pathways. Regardless of the position of these lncRNAs in the signalling pathway, they serve different functions. For example, Wei *et al* (26) found that lncRNA MEG3 inhibits proliferation and metastasis of gastric cancer (GC) cells via the TP53 (a tumour suppressor gene) signalling pathway. High levels of lncRNA p21 in thoracic aortic aneurysms may be associated with regulating vascular smooth muscle cell proliferation and apoptosis by activating the TGF-β signalling pathway (27).

lncRNAs are known to be involved in cellular physiological and pathological processes (28). Therefore, lncRNAs are also relevant for diagnosis, treatment and prognosis evaluation (29).

3. TGF-β signalling pathway

The TGF-β superfamily has numerous members, including TGF-β isoforms, bone morphogenetic protein, growth differentiation factors, activators, inhibitors and nodulins (30,31). TGF has three receptor ligands, TGF-β1, 2, and 3, which have similar, but not identical, biological activities *in vitro* (32). The TGF-β signalling pathway consists of two distinct intracellular pathways: SMAD-dependent (known as the classical TGF-β pathway) and non-SMAD-dependent pathway (known as the non-classical TGF-β pathway; Fig. 1) (32). By contrast with other signalling pathways, the classical TGF-β pathway is widely evolved and distributed in a variety of organisms (from drosophila and nematodes to mice and humans). Activated TGF-β is altered by binding to TGF-β type II receptor (TGFβR-II), which affects its structure, then TGFβR-II phosphorylates TGFβR-I on specific serine and threonine residues (33). In the classical pathway, the activated receptor complex phosphorylates receptor-SMADs (R-SMADs; including SMAD2 and SMAD3), which are primarily responsible for the activation of downstream signalling pathways (34). The receptor-activated SMAD anchor recruits R-SMADs into the activated receptor complex. Finally, the activated receptor complex binds to SMAD4 (Co-SMAD4 or common mediator SMAD4) in a large complex and enters the nucleus, where it interacts with transcription factors and coactivators to regulate expression of target genes (34,35).

SMAD6 and SMAD7, also known as inhibitory SMADs (I-SMADs), serve an important role in the inhibition of the TGF-β signalling pathway through multiple mechanisms. Firstly, SMAD6/7 competes with R-SMADs for recruitment to type I receptors and prevents activation of R-SMADs by phosphorylation (36). SMAD7 induces ubiquitination and degradation of type I receptors by recruiting the E3 ligases SMURF1 and SMURF2 (37,38). SMAD7 recruits ubiquitin-conjugated E2 enzyme UbcH7 to stimulate SMURF1/2 activity in the R-SMAD7SM-URF1/2 complex (39). SMAD7 induces degradation and inactivation of TGFβR-I by recruiting two HECT-type E3 ligases (WWP1/Tiul1 and NEDD4-2) (40). This suggests that I-SMADs are involved in negative feedback regulation in the TGF-β/SMAD pathway. Although SMAD proteins are the basis of TGF-β regulation of various cellular signalling pathways, numerous signalling responses are stimulated by TGF-β, which is not regulated by SMADs (32). For example, in the non-classical pathway, the activated TGF-β receptor complex promotes or inhibits downstream cell biological processes through a number of other transduction factors, such as tumour necrosis factor (TNF), TNF receptor-associated factor 4 (TRAF4), TRAF6, p38 MAPK, Ras homology (Rho), phosphoinositide 3 kinase (PI3K)/AKT, extracellular signal-regulated kinase (ERK) and NF-κB, to promote or inhibit downstream cell biological processes (32).

TGF-β serves as both an oncogene and an oncogene promoter. In normal tissue, TGF-β promotes tissue stabilisation and suppresses inflammatory responses. In premalignant progression, TGF-β serves as an oncogene to promote apoptosis and cytostasis and inhibit tumorigenesis. However, in cancer cells, TGF-β serves as a pro-oncogene, promoting tumour growth and metastasis (41,42). TGF-β signalling promotes epithelial-mesenchymal transition (EMT) by increasing expression of mesenchymal markers, such as N-cadherin and vimentin, and decreasing expression of epithelial markers, such as E-cadherin (43,44). Since TGF-β acts extensively in cells, blocking TGF-β and its downstream signals is a therapeutic tool. Therefore, anti-TGF-β signalling therapy is an additional therapeutic tool along with the currently used CAR-T (45) and anti-PD-L1 (46) therapy.

4. TGF-β pathway-related lncRNAs and CRC

Aberrant lncRNAs in CRC are hypothesized to contribute to activation or inactivation of the TGF-β pathway to regulate tumour development. TGF-β pathway-associated CRC lncRNAs are discussed here, to explore the roles of lncRNAs in the progression of CRC.

CRC is the third leading cause of cancer-associated death worldwide and there are 1.85 million new cases and 850,000 CRC-associated deaths each year (47). The majority of CRC tumours arise from precursor lesions, such as adenoma transforming to adenocarcinoma (48). Therefore, it is key to identify useful biomarkers to diagnose CRC at the early stages of disease. Numerous studies have demonstrated the novel role and therapeutic potential of lncRNAs in CRC (49,50) (Fig. 2). lncRNA SNHG6 is upregulated in CRC and binds UPF1 to activate the downstream TGF-β/SMAD signalling

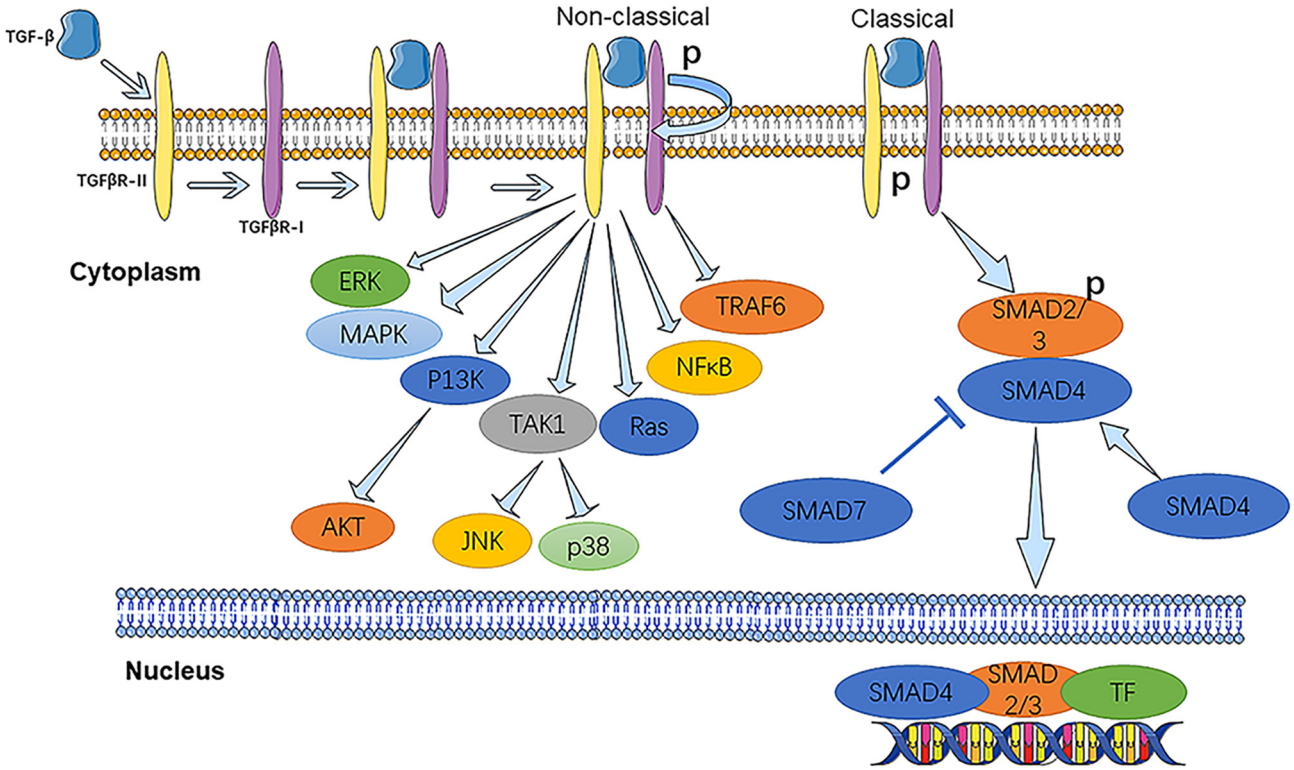

Figure 1. Classical and non-classical TGF-β signaling pathway. TGF-β ligands bind to TGFβR-II to modify its conformation and mediate its action. TGFβR-II phosphorylates TGFβR-I on specific serine and threonine residues. In the classical pathway, the activated receptor complex phosphorylates receptor-SMADs (SMAD2 or SMAD3), forms a heterogeneous complex with SMAD4 and translocates to the nucleus, where it interacts with transcription factors, coactivators or co-repressors to regulate expression of target genes. In the non-classical pathway, TGF-β activates MAPKs, NFκB, Ras, TRAF6, TAK1/p38/JNK and PI3Ks, leading to biological effects. ERK, extracellular signal-regulated kinase; TAK1, TGF-β-activated kinase 1; TF, transcription factor; TGFβR-I/II, transforming growth factor-β receptor type I/II; TNK1, tyrosine kinase non-receptor 1; TRAF6, TNF receptor-associated factor 4; p, phosphorylated.

pathway to promote proliferation, migration and invasion of CRC cells (51). Upregulation of lncRNA LOC646329 promotes CRC cell proliferation by competing for binding to miR-29b-1 (52). In addition, knockdown of lnc00858 reduces the proliferative capacity of CRC cells by inducing production of p53 and blocking the G0/G1 phase of CRC cells (53). lnc00858 upregulation is negatively correlated with miR-25-3p and SMAD7 is a downstream target of miR-25-3p (53). Similarly, miR-93-5p serves as an competing endogenous RNA (ceRNA) for lncRNA CTBP1-AS2 and activates the TGF-β/SMAD2/3 pathway to promote proliferation, invasion and resistance to apoptosis in colon cancer cells (54). Shen *et al* (11) demonstrated that TGF-β promotes CRC metastasis via the lncRNA TUG1/TWIST1/EMT signalling pathway. TGF-β induces metastasis, and knockdown of TUG1can inhibit metastasis (11). However, expression of TGF-β does not increase after TUG1knockdown, suggesting that TUG1is located downstream of TGF-β. TUG1 may serve as a drug target to inhibit CRC development by suppressing TGF-β pathway activation (11). Furthermore, Wu *et al* (49) found that lnc00941 promotes EMT by directly competing with β-transducin repeats-containing protein to bind to the MH2 structural domain on SMAD4, thereby preventing SMAD4 protein degradation and activating the TGF-β/SMAD2/3 signalling pathway. lncRNA CASC9 is upregulated in CRC, and high expression of CASC9 predicts a low prognosis and an association with TNM stage I (55). Luo *et al* (55) demonstrated that CASC9 enhances the function of the telomerase Reverse Transcriptase (TERT) complex in CRC cells by regulating expression of TGF-β2 mRNA and upregulating levels of TGF-β2 and TERT, leading to phosphorylation of SMAD3 and activation of the TGF-β signalling pathway, thereby enhancing its Tumorigenic ability.

Since colon cancer only shows symptoms in the advanced stages of disease, it is necessary to improve the early detection rate of CRC. An increasing number of studies have found that TGF-β/SMAD signalling pathway involvement with lncRNAs serves an important role in the development of colon cancer, which provides a new avenue for early diagnosis and treatment (49,51,55).

5. TGF-β pathway-related lncRNAs and hepatocellular carcinoma (HCC)

HCC ranks fourth in the world for cancer-associated death (56). HCC is a common cancer with a poor prognosis and high economic cost and disease burden; the 2019 Global Cancer Report released by the World Health Organization (WHO) (57) states that about 705 million people worldwide currently suffer from liver cancer, with about 700,000 new liver cancer patients each year (57). lncRNAs are involved in the physiological and pathological processes of HCC cells (28) (Fig. 2). Certain lncRNAs, such as lnc01278, SBF2-AS1, SNAI3-AS1 and NORAD, have been shown to promote proliferation, migration and invasion of HCC by participating in the TGF-β signalling pathway. Huang *et al* (58)

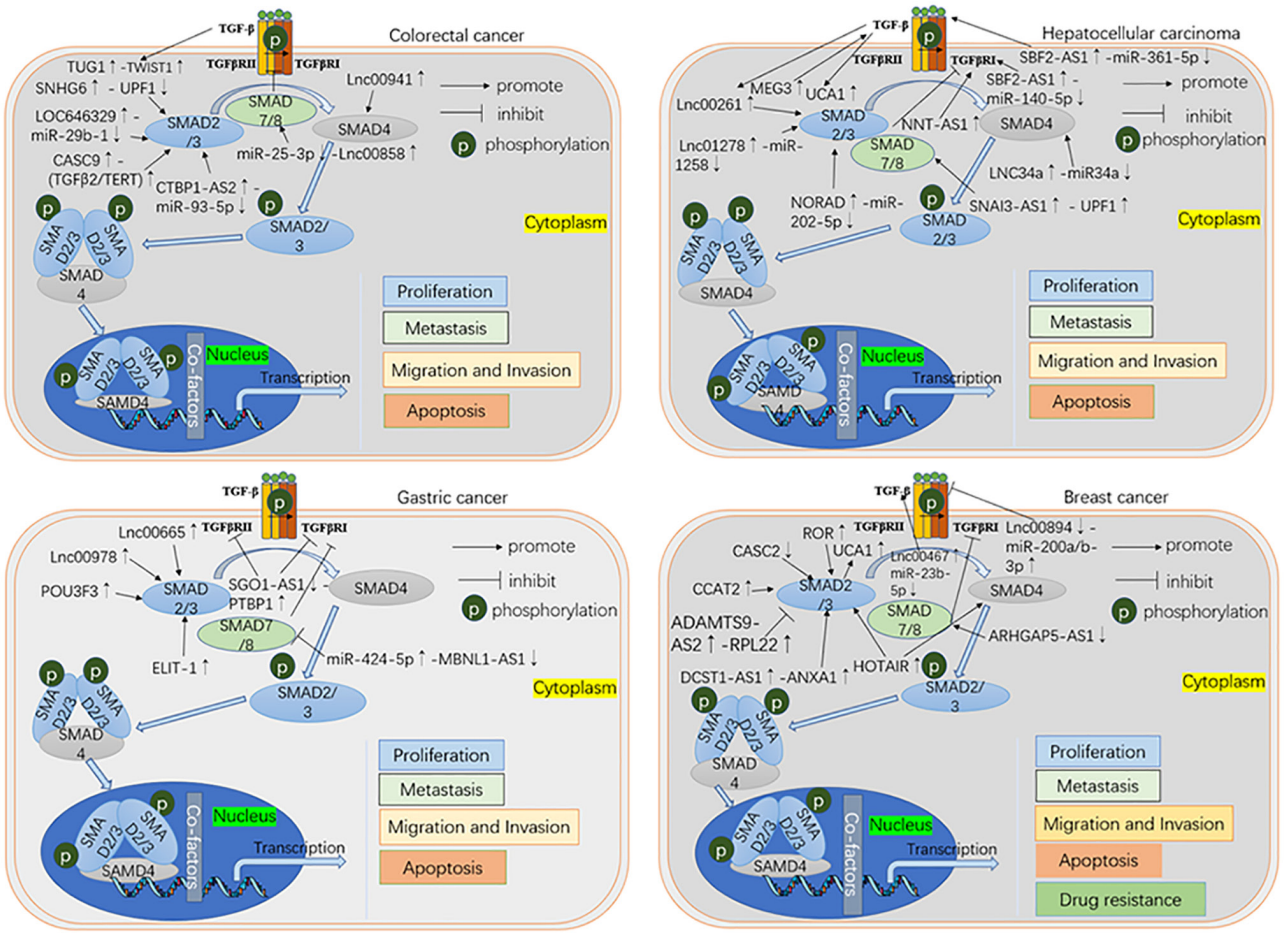

Figure 2. Molecular mechanisms of TGF-β signalling pathway involved in lncRNAs in hepatocellular carcinoma, colorectal, gastric and breast cancer. Oncogenic lncRNAs in hepatocellular carcinoma and colorectal, gastric and breast cancer activate the TGF-β signalling pathway primarily by degrading and activating the three major targets of the complex, SMAD2, SMAD3, and SMAD7, while certain lncRNAs may directly regulate TGF-β as well as TGFβR-II and TGFβR-II, thereby affecting tumorigenesis. lncRNA, long non-coding RNA; miR, microRNA; TGFβR-I/II, transforming growth factor-β receptor type I/II.

found that the lnc01278/miR-1258/SMAD2/3 axis promotes HCC metastasis. lnc01278 promotes the expression of the SMAD2/3 target gene by silencing expression of miR-1258. Similarly, downregulation of lncRNA SBF2-AS1 inhibits proliferation and migration of HCC by regulating the miR-361-5p/TGF-β1 signalling pathway (59). SBF2-AS1 promotes the expression of TGFβR-I via sponge adsorption of miR-140-5p and in turn promotes the migration and invasion of HCC cells (60). In addition, SNAI3-AS1 promotes proliferation and metastasis of HCC cells by regulating UPF1 and activating the TGF-β/SMAD pathway (61). Yang *et al* (62) found that lncRNA NORAD is upregulated in HCC tissue and that lncRNA NORAD may serve as a ceRNA to regulate miR-202-5p, which promotes HCC progression by targeting TGFβRs. TGF-β1 is a positive upstream regulator of UCA1, while UCA1 is a positive upstream regulator of HXK2, which forms the TGF-β1/UCA1/HXK2 axis to promote proliferation of HCC cells (63). In addition, Dong *et al* (64) found that downregulation of lncRNA MEG3 promotes HCC proliferation, migration and invasion through the upregulation of TGF-β1.

SMAD3 (an R-SMAD) and SMAD4 (a co-SMAD) are key proteins involved in the classical TGF-β signalling pathway. Chen *et al* (65) found that lnc00261 inhibits SMAD3 expression and phosphorylation and that SMAD3 may be involved in transcriptional regulation in TGF-β1 signalling. lnc00261 inhibits EMT in HCC cells by inactivating the TGFβ1/SMAD3 signalling pathway. In addition, lncRNAs also participate in the TGF-β pathway through epigenetic modifications. Zhang *et al* (66) found that lncRNA 34a recruits DNA methyltransferase 3α through prohibitin-2 to methylate promoters of miR-34a and histone deacetylase 1 to influence histone modification, thereby inhibiting miR-34a expression. miR-34a targets SMAD4 and downregulation the expression of downstream genes. In the immune system, activation of TGF-β signalling suppresses recruitment of tumour-infiltrating lymphocytes, leading to tumour immune escape. Wang *et al* (67) found that relatively high levels of lncRNA NNT-AS1 are associated with a decrease in the number of infiltrating $CD4^+$ lymphocytes and that knockdown of lncRNA NNT-AS1 decreases expression of TGF-β and TGFβR-I in HCC cells. In conclusion, lncRNA NNT-AS1 impairs $CD4^+$ T cell infiltration in HCC by activating the TGF-β signalling pathway through a novel mechanism.

Biomarkers useful for early HCC diagnosis are still lacking and available serum biomarkers show low sensitivity and specificity, such as α-fetoprotein and des-gamma-carboxy

prothrombin (68). TGF-β signalling pathway-associated lncRNAs are typically upregulated in HCC and may be a novel target for early screening.

6. TGF-β pathway-related lncRNAs and GC

GC is the fifth most deadly cancer in the world (69). Globally, 1 million new cases of stomach cancer are diagnosed each year (70). Oncogenic lncRNAs serve an important role in regulating TGF-β and are regulated in multiple ways (Fig. 2). lnc00665 promotes cell proliferation, invasion and metastasis by activating the TGF-β pathway in GC and silencing Lnc00665 inhibits EMT and decreases the expression levels of TGF-β1, SMAD2 and α-smooth muscle actin (SMA) (71). Similarly, knockdown of Lnc00978 inhibits activation of the TGF-β/SMAD2 signalling pathway and thus inhibits cell cycle progression, migration, invasion and proliferation and induces apoptosis in GC cells (72). The differentiation of regulatory T cells is associated with the TGF-β signaling pathway (73). Xiong *et al* (74) found that lncRNA POU3F3 activates the TGF-β signalling pathway by increasing phosphorylation of SMAD2/3, thus increasing the number of regulatory T cells in peripheral blood and leading to the proliferation of GC cells. Huang *et al* (75) found that SGO1-AS1 inhibits EMT and metastasis by competitively binding TGF-β1 and TGF-β2 with polypyrimidine tract binding protein, leading to a decrease in TGF-β. In addition, TGF-β inhibits SGO1-AS1 transcription by forming a negative feedback loop to induce ZEB1 production. This SGO1-AS1/TGF-β/ZEB1 axis may provide a novel means for cancer treatment. LncRNAs can also act as cofactors for SMAD. Sakai *et al* (76) identified the EMT-associated lncRNA ELIT1, which enhances SMAD promoter activity via TGF-β induction and recruiting SMAD3 to the promoter region of its target gene. In addition, lncRNA MBNL2-AS1 forms a ceRNA network with miR-424-5p and SMAD7, inactivating the TGF-β/EMT pathway and inhibiting GC cell proliferation, migration and invasion (77).

lncRNAs regulate gene expression at genomic, transcriptomic and posttranscriptional levels and are recognized as biomarkers and therapeutic targets for GC (Fig. 2) (77,78). The TGF-β signalling pathway is an important pathway that promotes development of GC and studying the effect of the interaction of this pathway with lncRNAs in the development of GC may provide an important target for early diagnosis (71).

7. TGF-β pathway-related lncRNAs and breast cancer

Globally, breast cancer is the most frequently diagnosed cancer in women and ranks second among causes of cancer-related deaths in women (79). Although breast cancer can be diagnosed early and there are numerous treatments available, it is typically lethal once it metastasises (80). Therefore, it is key to find clinically useful biomarkers present in the early stages of breast cancer. Certain lncRNAs have been shown to promote the development of breast cancer via the TGF-β signalling pathway (Fig. 2). For example, CASC2 (81) and CCAT2 (82) have been shown to be tumour therapeutic targets by participating in TGF-β/SMAD2 signalling and thus promoting proliferation and metastasis of breast cancer cells. lncRNA ROR knockdown inhibits SMAD2 and α-SMA expression and thus inactivates the TGF-β signalling pathway to inhibit tumour growth (83). ARHGAP5-AS1 induces a decrease in SMAD7 ubiquitination and degradation by interacting with SMAD7, leading to a decrease in SMAD7 binding to SMURF1 and SMURF2 (84). In addition, ARHGAP5-AS1 may inhibit the TGF-β signalling pathway by stabilising SMAD7. ADAMTS9-AS2 has been shown to target downstream ribosomal protein L22 to inhibit SMAD2 expression, thereby regulating the TGF-β signalling pathway, inhibiting cell cycle arrest in breast cancer cells *in vitro* and suppressing tumour growth *in vivo* (85). Loss of Merlin in breast cancer cells affects functional cellular metabolism. Mota *et al* (86) found that the cooperative activity of TGF-β transcriptional effectors results in upregulation of UCA1, which leads to a decrease in Merlin activity against STAT3. Similarly, Bo *et al* (87) predicted that lnc00467 may be involved in signalling pathways involved in peroxisomal lipid metabolism and immunity via miR-23b-5p targeting TGF-β2. LncRNAs can also be involved in drug resistance. Zhang *et al* (88) found that knockdown of lnc00894-002 downregulates miR-200a-3p and miR-200b-3p, upregulates TGF-β2 and ZEB1 and is involved in the development of tamoxifen resistance. LncRNA DCST1-AS1 enhances TGF-β/SAMD2 signalling in BT-549 cells by targeting ANXA1 and promoting EMT (89). Ren *et al* (90) discovered that SMAD2/3/4 binds to the promoter site of HOTAIR and is directly transcribed by HOTAIR, which provides a novel idea for treatment of breast cancer.

Based on the established role of TGF-β-associated lncRNAs in regulating cell proliferation, cell cycle, apoptosis and other aspects of cell physiology, future studies should evaluate the potential of these transcripts as therapeutic targets for breast cancer.

8. TGF-β pathway-related lncRNAs and lung cancer

Lung cancer remains the leading cause of cancer-associated deaths worldwide (91). One of the reasons for the high mortality rate of lung cancer is that it often progresses to an advanced stage before it is diagnosed (92). Therefore, it is key to determine the molecular mechanisms of lung tumours and find new molecular biomarkers for diagnosis and treatment. Wang *et al* (93) found that lncRNA ANCR inhibits non-small cell lung cancer (NSCLC) cell migration and invasion via downregulation of TGF-β1 expression. Similarly, Su *et al* (94) found that upregulation of lncRNA GASL1 may inhibit tumour growth in NSCLC via downregulation of TGF-β1. NKILA expression is regulated by the upstream TGF-β signalling pathway and interferes with the NF-κB/Snail signalling pathway to inhibit migration and invasion of NSCLC cells (95). Knockdown of SMASR in lung cancer promotes phosphorylation of SMAD2/3, thereby inducing EMT via the TGF-β signalling pathway and promoting migration and invasion of lung cancer cells (96). XIST serves as a sponge to directly adsorb miR-137 and negatively regulate its expression. miR-137 overexpression inhibits proliferation and EMT in A549 and H1299 cells (97). In addition, Notch-1 has been identified as a direct gene target of miR-137 (97). Similarly, lncRNA SOX2OT overexpression serves as a ceRNA to adsorb miR-104-5p, thereby regulating RAC1 expression and activating the

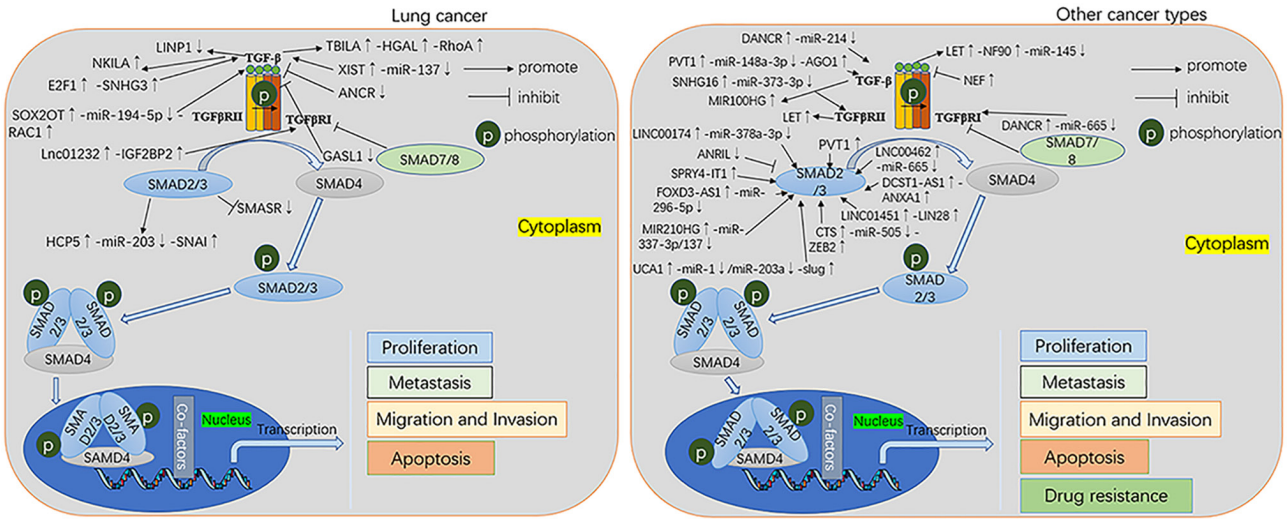

Figure 3. Molecular mechanisms of TGF-β signalling pathway involved in lncRNAs in lung and other cancer types. Oncogenic lncRNAs in lung cancer and other types of cancer activate the TGF-β signalling pathway primarily by degrading and activating the three major targets of the SMAD2, SMAD3 and SMAD7, while certain lncRNAs may directly regulate TGF-β as well as TGFβR-I and TGFβR-II, thereby affecting tumorigenesis. lncRNA, long non-coding RNA; miR, microRNA; TGF-β, transforming growth factor β; TGFβR-I/II, TGF-β receptor type I/II.

TGF-β/parathyroid hormone-associated protein/RANKL signalling pathway (98).

lncRNAs act as transcribed molecules. Shi *et al* (99) demonstrated that E2F1 activates SNHG3 and promotes NSCLC cell proliferation and migration via the TGF-β and IL-6/JAK2/STAT3 pathways. Similarly, Zhu *et al* (100) found that forkhead box P3 protein increases NSCLC cell stemness by activating Lnc01232 and thus regulating TGFβR-I, activating the TGF-β signalling pathway and recruiting IGF2BP2 to stabilise TGFβR-I. This may provide a theoretical basis for lncRNA-based treatment of NSCLC. Furthermore, upregulation of TBILA enhances RhoA activation by binding to the SMAD transcription factor complex, which promotes expression of human hair centre-associated lymphoma (101). Jiang *et al* (102) found that lncRNA HCP5 is induced by TGF-β and transcriptionally regulated by SMAD3 to promote lung adenocarcinoma tumour growth and metastasis. In addition, lncRNA LINP1 inhibits EMT in lung cancer cells by suppressing the TGF-β pathway (9).

In the aforementioned lung cancer studies, multiple differentially expressed lncRNAs have been identified, some of which activate the TGF-β pathway to drive tumorigenesis, while others inactivate the TGF-β pathway to inhibit tumour progression (Fig. 3). Further study of the role of lncRNAs in the TGF-β pathway may help develop molecular markers for early diagnosis of lung cancer.

9. TGF-β pathway-related lncRNAs and other cancer types

In thyroid cancer, lncRNA FOXD3-AS1 serves as a sponge to adsorb miR-296-5p and upregulate miR-296-5p expression, which inhibits the migration and invasion of thyroid cancer cells by inactivating the TGF-β1/SMAD signalling pathway (103). Zhao *et al* (104) found that ANRIL may decrease expression of cyclin-dependent kinase 4 by inhibiting the TGF-β/SMAD signalling pathway and promoting invasion and metastasis of thyroid cancer cells. Similarly, silencing SPRY4-IT1 inhibits TGF-β1 and phosphorylated SMAD2/3 levels, thereby inhibiting proliferation and migratory capacity of thyroid cancer cells; knockdown of SPRY4-IT1-mediated functions can be rescued by interference with TGF-β1 (105).

In cervical cancer, knockdown of lncRNA NEF decreases the expression of TGF-β1, which inhibits the migration and invasion of cervical cancer cells (106). In addition, miR-665 serves as a ceRNA for lncRNA DANCR and targets TGFβR-I through the ERK/SMAD pathway to suppress the malignant phenotype of cervical cancer cells, which may provide a novel therapeutic strategy for cervical cancer treatment (107). Similarly, lncRNA CTS enhances migration and invasive ability of cervical cancer cells as well as TGF-β1-induced EMT (108). The expression of lncRNA CTS has a negative correlation with miR-505 expression and ZEB2 may act as the target of miR-505 (108). lncRNA CTS promotes cervical cell migration and invasion via the miR-505/ZEB2/TGF-β/SMAD axis (108).

In lymphoma, knockdown of lncRNA ANRIL may inhibit proliferation and promote apoptosis of Burkitt's lymphoma cells by regulating the TGF-β1 signalling pathway (109).

In glioma, UAC1 promotes Slug expression and thus participates in TGF-β-induced EMT by targeting miR-1 and miR-203a (110). In addition, p53 inhibits expression of PVT1and thus inactivates the TGF-β/SMAD pathway, inhibiting the proliferation, migration and invasion of glioma cells, inducing cell apoptosis and inhibiting tumour growth (111).

In endometrial cancer, lncRNAs promote tumorigenesis and metastasis via the MIR210HG/miR-337-3p/137-HMGA2 axis, which activates the TGF-β/SMAD3 signalling pathway (112).

In prostate cancer, SNHG16 promotes proliferation and migration of prostate cancer cells by targeting the TGF-βRII/SMAD axis (113).

In pancreatic cancer, knockdown of PVT1 inhibits cell survival, adhesion, migration and invasion by suppressing TGF-β/SMAD2/3 signalling (114). These findings reveal that PVT1 may serve an oncogenic role in pancreatic cancer by

Table I. lncRNAs associated with the TGF-β signalling pathway in cancer.

First author, year	lncRNA	Cancer type	Expression pattern	Interaction with TGF-β signalling	Cancer phenotype	Molecular mechanism	(Refs.)
Wang *et al*, 2019	SNHG6	CRC	↑	Activation	Promotes proliferation, invasion and migration	lncRNA SNHG6↑, UPF1 (protein)↓, SMAD2/3↑	(51)
Javanmard *et al*, 2020	LOC646329	CRC	↑	Activation	Promotes proliferation	lncRNA LOC646329↑, miR-29b-1↓, SMAD2/3↑	(52)
Zhan *et al*, 2020	LNC00858	CRC	↑	Repression	Inhibits proliferation, promotes apoptosis	lnc00858↑, miR-25-3p↓, SMAD7↑	(53)
Li *et al*, 2021	CTBP1-AS2	CRC	↑	Activation	Promotes proliferation and invasion, inhibits apoptosis	LINCRNA CTBP1-AS2↑, miR-93-5p↓, TGF-β/SMAD2/3↑	(54)
Shen *et al*, 2020	TUG1	CRC	↑	Activation	Promotes metastasis	TGF-β↑, lncRNA TUG1↑, TWIST1↑	(11)
Wu *et al*, 2021	LNC00941	CRC	↑	Activation	Promotes EMT	lnc00941↑, SMAD4↑, TGF-β/SMAD2/3↑	(49)
Luo *et al*, 2019	CASC9	CRC	↑	Activation	Promotes proliferation, inhibits apoptosis	LINCRNA CASC9↑, TGF-β2/TERT↑, SMAD3↑	(55)
Huang *et al*, 2020	LINC01278	HCC	↑	Activation	Promotes proliferation, migration, and invasion	LINC01278↑, miR-1258↓, SMAD2/3↑	(58)
Wu *et al*, 2021; Li *et al*, 2018	SBF2-AS1	HCC	↑	Activation	Promotes proliferation, migration, and invasion	LINCRNA SBF2-AS1↓, miR-361-5p↑, TGF-β1↑, LINCRNA SBF2-AS1 ↑, miR-140-5p↓, TGFβR-I↑	(59,60)
Li *et al*, 2019	SNAI3-AS1	HCC	↑	Activation	Promotes proliferation, migration, and invasion	LINCRNA SNAI3-AS1↑, UPF1↑, SMAD7↑	(61)
Yang *et al*, 2019	NORAD	HCC	↑	Activation	Promotes proliferation, migration, and invasion	LINCRNA NORAD↑, miR-202-5p↓, SMAD2/3↑	(62)
Hu *et al*, 2018	UCA1	HCC	↑	Activation	Promotes proliferation	TGFβ↑, UCA1↑, HXK2↑	(63)
Dong *et al*, 2019	MEG3	HCC	↑	Suppression	Inhibits proliferation, migration, and invasion	MEG3↑, TGFβ1↓	(64)
Chen *et al*, 2022	LNC00261	HCC	↑	Suppression	Inhibits EMT and stem cell-like features	TGF-β1↑, LINC00261↓, SMAD3↓	(65)
Zhang *et al*, 2019	LNCRNA 34a	HCC	↑	Activation	Promotes proliferation	LNC34a↑, miR34a↓, SMAD4↑	(66)
Wang *et al*, 2020	NNT-AS1	HCC	↑	Activation	Promotes $CD4^+$ T cell infiltration	LINCRNA-NNT-AS1↑, TGF-β, TGFβR-I, SMAD5↑	(67)

Table I. Continued.

First author, year	lncRNA	Cancer type	Expression pattern	Interaction with TGF-β signalling	Cancer phenotype	Molecular mechanism	(Refs.)
Zhang *et al*, 2021	LNC00665	GC	↑	Activation	Promotes proliferation, invasion, and metastasis	LINC00665↑, TGF-β1, SMAD2, α-SMA↑	(71)
Fu *et al*, 2018	LNC00978	GC	↑	Activation	Promotes proliferation, invasion and metastasis, induces apoptosis	LINC00978↑, TGF-β/SMAD2↑	(72)
Xiong *et al*, 2015	POU3F3	GC	↑	Activation	Promotes proliferation	LINCRNA POU3F3↑, TGF□β/SMAD2/3↑	(74)
Huang *et al*, 2021	SGO1-AS1	GC	↑	Suppression	Inhibits EMT and metastasis	LINCRNA SGO1-AS1↓, PTBP1↑, TGFβR-I/II↓, ZEB1↑	(75)
Sakai *et al*, 2019	ELIT-1	GC	↑	Activation	Promotes EMT progression	LINCRNA ELIT-1↑, TGFβ/SMAD3↑	(76)
Su *et al*, 2022	MBNL1-AS1	GC	↓	Suppression	Inhibits proliferation, migration, and invasion	LINCRNA MBNL1-AS1↓, miR-424-5p↑, SMAD7↓	(77)
Zhang *et al*, 2019	CASC2	Breast	↑	Activation	Promotes proliferation and metastasis	LINCRNA CASC2↓, TGFβ/SMAD2↑	(81)
Wu *et al*, 2017	CCAT2	Breast	↑	Activation	Promotes proliferation and metastasis	LINCRNA CCAT2↑, TGFβ/SMAD2↑	(82)
Hou *et al*, 2018	ROR	Breast	↑	Activation	Promotes growth, migration, and invasion	LINCRNA ROR↑, TGFβ/SMAD2↑	(83)
Wang *et al*, 2021	ARHGAP5-AS1	Breast	↑	Suppression	Inhibits migration	LINCRNA ARHGAP5-AS1↑, SMAD7↑	(84)
Ni *et al*, 2021	ADAMTS9-AS2	Breast	↑	Suppression	Inhibits tumor growth, promotes apoptosis and cell cycle arrest	LINCRNA ADAMTS9-AS2↑, RPL22↑, SMAD2↓	(85)
Mota *et al*, 2018	UCA1	Breast	↑	Activation	Promotes aerobic glycolysis	MERLIN↓, SMAD2/3↑, UCA1↑	(86)
Bo *et al*, 2021	LNC00467	Breast	↑	Activation	Promotes proliferation and metastasis	LINC00467↑, miR-23b-5p↓, TGF-β2↑	(87)
Zhang *et al*, 2018	LNC00894-002	Breast	↑	Activation	Promotes the development of tamoxifen resistance	lnc00894-002↑, miR-200a/b-3p↑, TGF-β↓, ZEB1↑	(88)
Tang *et al*, 2020	DCST1-AS1	Breast	↑	Activation	Promotes EMT and chemoresistance	DCST1-AS1↑, ANXA1↑, TGF-β/SMAD2↑	(89)

Table I. Continued.

First author, year	lncRNA	Cancer type	Expression pattern	Interaction with TGF-β signalling	Cancer phenotype	Molecular mechanism	(Refs.)
Ren *et al*, 2018	HOTAIR	Breast	↑	Activation	Inhibits proliferation, migration, and invasion	HOTAIR↑, SMAD2/3/4↑	(90)
Wang *et al*, 2018	ANCR	Lung	↑	Suppression	Inhibits migration and invasion	LINCRNA ANCR↑, TGF-β1↓	(93)
Su *et al*, 2018	GASL1	Lung	↑	Suppression	Inhibits tumor growth	LINCRNA GASL1↑, TGF-β1↓	(94)
Lu *et al*, 2017	NKILA	Lung	↓	Suppression	Inhibits migration and invasion	TGF-β↑, LINCRNA NKILA↑, NF-κB↓	(95)
Xu *et al*, 2021	SMASR	Lung	↑	Suppression	Inhibits migration and invasion	TGF-β↑, SMAD2/3↑, SMASR↓, TGFBR-I↓	(96)
Wang *et al*, 2018	XIST	Lung	↑	Suppression	Inhibits proliferation and EMT	LINCRNA XIST↑, miR-137↓, TGF-β1↑	(97)
Ni *et al*, 2021	SOX2OT	Lung	↑	Activation	Promotes proliferation and metastasis	LINCRNA SOX2OT↑, miR-194-5p↓, RAC1↑, TGF-β↑	(98)
Shi *et al*, 2020	SNHG3	Lung	↑	Activation	Promotes proliferation and migration	E2F1↑, LINCRNA SNHG3↑, TGF-β↑	(99)
Zhu *et al*, 2022	LNC01232	Lung	↑	Activation	Promotes proliferation and migration	FOXP3↑, LINC0123↑, IGF2BP2↑, TGFβR-I (mRNA)↑	(100)
Lu *et al*, 2018	TBILA	Lung	↑	Activation	Enhances the pro-survival pathway	TGFβ↑, TBILA↑, HGAL↑, RhoA↑	(101)
Jiang *et al*, 2019	HCP5	Lung	↑	Activation	Promotes tumor growth and metastasis	TGF-β/SMAD3↑, LINCRNA HCP5↑, miR-203↓, SNAI↑	(102)
Zhang *et al*, 2018	LINP1	Lung	↓	Suppression	Inhibits proliferation, migration, and invasion	TGFβ1↓, LNCRNA LINP1↓	(9)
Chen *et al*, 2020	FOXD3-AS1	Thyroid	↑	Suppression	Inhibits proliferation and migration	lncRNA FOXD3-AS1↓, miR-296-5p↑, TGF-β1/SMADs↑	(103)
Zhao *et al*, 2016	ANRIL	Thyroid	↑	Suppression	Promoting invasion and metastasis	lncRNA ANRIL↓, TGF-β/SMADs↓, p15INK4B↓	(104)
Zhou *et al*, 2018	SPRY4-IT1	Thyroid	↑	Suppression	Inhibits proliferation and migration	lncRNA SPRY4-IT1↑, TGF-β/SMAD↑	(105)

Table I. Continued.

First author, year	lncRNA	Cancer type	Expression pattern	Interaction with TGF-β signalling	Cancer phenotype	Molecular mechanism	(Refs.)
Ju *et al*, 2019	NEF	Cervical	↑	Suppression	Inhibits migration and invasion	LNCRNA NEF↑, TGF-β1↓	(106)
Cao *et al*, 2019	DANCR	Cervical	↑	Suppression	Inhibits migration and invasion	LNCRNA DANCR↑, miR-665↓, TGFβR-I↑, ERK/SMAD↑	(107)
Feng *et al*, 2019	CTS	Cervical	↑	Activation	Promotes migration and invasion	LNCRNA CTS↑, miR-505↓, ZEB2↑, TGF-β/SMAD↑	(108)
Mao *et al*, 2021	ANRIL	Lymphoma	↑	Activation	Promotes proliferation, inhibits apoptosis	lncRNA ANRIL↓, TGF-β1↑	(109)
Li *et al*, 2018	UCA1	Glioma	↑	Activation	Promotes EMT and stemness	UCA1↑, miR-1↓, miR-203a↓, slug↑-TGF-β↑	(110)
Li *et al*, 2022	PVT1	Glioma	↑	Activation	Promotes proliferation, migration, invasion	P53↑, LINCRNA PVT1↓, TGF-β/SMAD↓	(111)
Ma *et al*, 2021	MIR210HG	Endometrial	↑	Activation	Promotes proliferation, migration, invasion, and EMT	LINCRNA MIR210HG↑, miR-337-3p/137↓, HMGA2↑, TGF-β/SMAD3↑	(112)
Weng *et al*, 2021	SNHG16	Prostate	↑	Activation	Promotes proliferation and migration	lncRNA SNHG16↑, miR-373-3p↓, TGFβR-II↑	(113)
Zhang *et al*, 2018	PVT1	Pancreatic	↑	Activation	Promotes survival, adhesion, migration and invasion	lncRNA PVT1↑, TGF-β/SMAD↑	(114)
Papoutsoglou *et al*, 2021	MIR100HG	Pancreatic	↑	Activation	Promotes EMT and stemness	TGFβ↑, MIR100HG↑	(115)
Zhou *et al*, 2018	LNC00462	Pancreatic	↑	Activation	Promotes proliferation and migration	lnc00462↑, miR-665↓, TGFβR-I/TGFβR-II↑, SMAD2/3↑	(116)
Wu *et al*, 2021	PVT1	Ovarian	↑	Activation	Promotes proliferation, inhibits apoptosis	LINCRNA PVT1↑, miR-148a-3p↓, AGO1↑, TGF-β↑	(117)
Huang *et al*, 2020	DANCR	Ovarian	↑	Activation	Promotes viability, migration, and invasion	LINCRNA DANCR↑, miR-214↓, TGF-β↑	(118)

Table I. Continued.

First author, year	lncRNA	Cancer type	Expression pattern	Interaction with TGF-β signalling	Cancer phenotype	Molecular mechanism	(Refs.)
Shi *et al*, 2021	LINC01451	Bladder	↑	Activation	Promotes proliferation, invasion, and metastasis	LINC01451↑, LIN28↑, TGF-β/SMAD↑	(119)
Zhuang *et al*, 2017	LET	Bladder	↑	Activation	Promotes chemoresistance	TGFβ1↑, LINCRNA-LET↑, NF90↑, miR-145↓	(120)
Zheng *et al*, 2021	LINC00174	Osteosarcoma	↑	Activation	Promotes proliferation, invasion, and metastasis	LINC00174↑, miR-378a-3p↓, SSH2↑, TGF-β/SMAD↑	(121)

↓, downregulation; ↑, upregulation; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition; GC, gastric cancer; HCC, heptocellular carcinoma; lncRNA, long non-coding RNA; miR, microRNA; TGF-β, transforming growth factor β; TGFβR-I/II, TGF-β receptor type I/II.

regulating EMT via the TGF-β/SMAD pathway (114). In addition, miR100HG controls the intensity of TGF-β signalling via the production of TGFβR-I in tumours (115). Overexpression of Lnc00462 increases expression levels of TGFβR-I and TGFβR-II, thereby activating the SMAD2/3 pathway in pancreatic cancer cells (116). miR-665 is also a target of lnc00462 (116). Taken together, these findings indicate that the lnc00462/miR-665/TGFβR-I/II regulatory network may underlie the mechanism of pancreatic carcinogenesis.

In ovarian cancer, lncRNA PVT1 promotes tumour growth and proliferation via the PVT1/miR-148a-3p/AGO1/TGF-β axis (117). In addition, DANCR is a sponge for miR-214, while KLF5 is a target of miR-214 (118). Silencing DANCR inhibits TGF-β-treated ovarian cancer cell viability, migration and invasion via the miR-214/KLF5 axis and induces apoptosis (118).

In bladder cancer, lnc01451 directly targets LIN28 to activate the TGF-β/SMAD signalling pathway (119). In terms of drug resistance, Zhuang *et al* (120) found that gemcitabine-induced aberrant TGF-β1 regulation of the LET/NF90/miR-145 axis promotes urothelial bladder cancer chemoresistance by enhancing cancer cell stemness.

In osteosarcoma (OS), high levels of lnc00174 form a ceRNA network with miR-378a-3p/SSH2 and activate the TGF-β/SMAD pathway to promote OS cell proliferation (121).

The discovery of a large number of TGF-β-associated lncRNAs, their extensive expression patterns in various types of cancer (thyroid and cervical cancer, lymphoma, glioma and endometrial, prostate, pancreatic, ovarian and bladder cancer) and the biological properties that promote tumour cell proliferation, migration and invasion provides a novel basis for the development of cancer diagnosis and therapy.

10. Conclusions and future perspectives

lncRNAs are differentially expressed in different tissue and cells and are highly heterogeneous. They regulate gene expression and intracellular homeostasis via multiple mechanisms, including tumour cell proliferation, survival, migration and genomic stability (122). The present review confirmed that lncRNAs play an important role in tumour development, similar to protein-coding genes, and are associated with multiple cellular signalling pathways. Although there are multiple signalling pathways in tumours by which lncRNAs may regulate cell proliferation, the TGF-β signalling pathway is widely distributed in tumours and serves a key role in the development of different types of cancer (123). lncRNA transcription can activate or inhibit the TGF-β signalling pathway by interacting with other molecules in the cell, including DNA, protein and RNA, to provide malignant transformation signals. Thus, lncRNAs affect the pathology of different cancer types (124,125). Table I lists lncRNAs associated with the TGF-β signalling pathway in cancer. In addition, these lncRNAs may have different methods of targeting the TGF-β signalling pathway since they have high tissue and cell specificity. These lncRNAs can also act in different cancer types through the TGF-β pathway. For example, lncRNA UCA1 promotes tumour cell proliferation and EMT in breast and liver cancer and glioma (63,110). lncRNA PVT1 promotes tumour cell proliferation in pancreatic and ovarian cancer and

glioma (111,117). Although the same lncRNAs are involved in the TGF-β pathway in different cancer types, they act in different ways, either directly targeting SMADs or forming a ceRNA network with miRNAs, which makes clinical targeting difficult (126). Overall, TGF-β pathway-associated lncRNAs are differentially regulated in different types of cancer and targeted therapy is a potential way to disrupt key signalling pathways in tumour cells, such as the Wnt, Notch and TGF-β pathways, without compromising their essential functions in normal tissue (49,126,127). The lncRNA network and TGF-β signalling pathway could reveal new cancer diagnosis and treatment approaches.

Since the TGF-β signalling pathway is related to tumour development and metastasis, interfering with this cascade via inhibitors may be a valuable strategy in tumour treatment approaches. For example, SD-208, an inhibitor of TGFβR-I, significantly downregulates expression of miR-135b, a key tumour molecule, in SW-48 colon cells and nude mice implanted with tumours *in situ* (128). Han *et al* (129) found that dexamethasone inhibits AKT and ERK phosphorylation in colon cancer cells, leading to a decrease in cy61 expression, which in turn blocks TGF-β1-induced migration. Similarly, Koelink *et al* (130) found that 5-aminosalicylic acid eliminates the TGF-β1 cascade in HCT116 CRC cells and therefore disrupts phosphorylation of downstream SMAD3. These inhibitors or drugs act on an important molecular target in the TGF-β pathway, which affects the entire pathway. lncRNAs only indirectly affect expression of certain related proteins in the TGF-β pathway and, to the best of our knowledge, little is known about the potential involvement of lncRNAs in direct regulation. For TGF-β-induced lncRNAs, inhibition of TGF-β expression may be a promising therapeutic approach. Identifying these potential lncRNAs will provide a more comprehensive understanding of regulation of the TGF-β pathway.

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Authors' contributions

ZH is responsible for writing the article. YL and ML revised the manuscript for important intellectual content and constructed figures. YZ and CW conceived the study. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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