Cytokine 170 (2023) 156351

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Role of long non-coding RNAs and TGF-β signaling in the regulation of breast cancer pathogenesis and therapeutic targets

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ARTICLE INFO

Keywords:
Breast cancer
LncRNAs
TGF-β signaling
Drug resistance
Therapeutic targets

ABSTRACT

The cytokine known as transforming growth factor (TGF) is essential for cell development, differentiation, and apoptosis in BC. TGF-β dysregulation can either promote or inhibit tumor development, and it is a key signaling pathway in BC spread. A recently identified family of ncRNAs known as lncRNAs has received a great deal of effort and is an important regulator of many cellular processes, including transcription of genes, chromatin remodeling, progression of the cell cycle, and posttranscriptional processing. Furthermore, both TGF-β signaling and lncRNAs serve as important early-stage biomarkers for BC diagnosis and prognosis and also play a significant role in BC drug resistance. According to recent studies, lncRNAs can regulate TGF-β by modulating its cofactors in BC. However, the particular functions of lncRNAs and the TGF-β pathway in controlling BC progression are not well understood yet. This review explores the lncRNAs' functional properties in BC as tumor suppressors or oncogenes in the regulation of genes, with a focus on dysregulated TGF-β signaling. Further, we emphasize the

Abbreviations: 4EBP1, Eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1; AKT, v-Akt Murine Thymoma Viral Oncogene Homolog; ANCR, Antidifferentiation noncoding RNA; ANXA1, Annexin A1; ARHGAP5-AS1, ARHGAP5 Antisense RNA 1; ARNILA, Androgen-receptor negatively induced lncRNA; BC, Breast cancer; CAMTA1, Calmodulin binding transcription activator 1; CASC2, Cancer Susceptibility Candidate 2; CCAT1, Colon cancer-associated transcript-1; CCAT2, Colon cancer-associated transcript-2; CDX1, Caudal Type Homeobox 1; c-Myc, Cellular myelocytomatosis oncogene; CTNNB1, Catenin Beta 1; DNA, Deoxyribonucleic acid; DOX, Doxorubicin; DSCAM-AS1, Down syndrome cell adhesion molecule antisense RNA 1; E2F1, E2F Transcription Factor 1; EMT, Epithelial-mesenchymal transition; EPIC1, Epigenetically Induced lncRNA 1; EZR-AS1, Ezrin antisense RNA 1; HOTAIR, HOX antisense intergenic RNA; ITGB2, Integrin subunit beta2; ITGB2-AS1, Integrin Subunit Beta 2 Antisense RNA 1; KLF5, KLF Transcription Factor 5; lncRNAs, Long non-coding RNAs; MAPK, Mitogen-activated protein kinase; MEG3, Maternally expressed gene 3; MIR100HG, miRNA -100 host gene; MMP2, Matrix metalloproteinase-2; MMP9, Matrix metalloproteinase-9; mRNA, Messenger RNA; mTORC1, Mammalian target of rapamycin complex 1; ncRNAs, Non-coding RNA; NF-B/IB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NF-Kb, Nuclear factor kappa B; NKILA, NF-KappaB Interacting LncRNA; NNT-AS1, Nicotinamide nucleotide transhydrogenase-antisense 1; NORAD, Non-Coding RNA Activated by DNA Damage; OS, Overall survival; PI3K, phosphatidylinositol 3-kinase; PTEN, Phosphatase and tensin homolog; PTENP1, Phosphatase and tensin homolog pseudogene 1; PTP1B, Protein tyrosine phosphatase 1B; PVT1, Plasmacytoma variant translocation 1; RFS, Relapse-free survival; RNA, Ribonucleic acid; RUNX2, Runt-related transcription factor 2; S6K, Ribosomal S6 kinase; Smad2, Mothers against decapentaplegic homolog 2; Smad3, Mothers against decapentaplegic homolog 3; Smad4, Mothers against decapentaplegic homolog 4; SMAD7, Mothers against decapentaplegic homolog 7; Smad8, Mothers against decapentaplegic homolog 8; SNHG6, Small Nucleolar RNA Host Gene 6; SOCS1, Suppressor Of Cytokine Signaling 1; Sox4, SRY-box transcription factor 4; SPRY4-IT1, SPRY4 intronic transcript 1; SYVN1, Synoviolin 1; TGFBR3, Transforming growth factor beta receptor type 3; TGFR1, Transforming growth factor receptor type 1; TGFR2, Transforming growth factor receptor type 2; TGF-β, Transforming growth factor-β; TGF-β1, Transforming Growth Factor Beta 1; TME, Tumor microenvironment; TNBC, Triple-negative breast cancer; TP53, Transformation-related protein 53; TPA, Tissue Plasminogen Activator; TRI, Transforming growth factor type I receptor; TRII, Transforming growth factor type II receptor; TβRIII, Transforming growth factor β type III receptor; UCA1, Urothelial carcinoma associated 1; WT1-AS, Wilms tumor 1 antisense RNA; XIST, X-inactive specific transcript; ZEB1, Zinc Finger E-Box Binding Homeobox 1; ZNF-217, Zinc finger protein 217; α-SMA, Smooth muscle alpha-actin.

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https://doi.org/10.1016/j.cyto.2023.156351
Received 11 August 2023; Received in revised form 22 August 2023; Accepted 25 August 2023
Available online 30 August 2023

functional roles of lncRNAs and TGF-β pathway in the progression of BC to discover new treatment strategies and better comprehend the fundamental cellular pathways.

1. Introduction

Breast cancer (BC) is the second most frequently diagnosed malignant disorder in females and has the highest incidence in the number of cancer deaths after lung cancer globally [1–3]. BC treatments, including surgery [4], chemotherapy [5], radiotherapy [6], endocrine therapy [7], and targeted therapy [8] have allowed for more accurate and customized care for patients with early-stage. Previous studies have shown several potential mechanisms by which ncRNAs, like lncRNAs, and TGF-β play a part in regulating the progression of BC.

Recently, a new subclass of ncRNA with more than 200 nucleotides, called lncRNAs [9], has the potential to control physiological processes, considering transcription and post-transcription in organisms and epigenetics [10]. Furthermore, the development of several disorders, particularly malignancies, has been linked to the abnormal expression of these transcripts [11–13]. Some of these have been discovered to be quite important in BC processes like drug resistance, sensitivity, and metastasis, while others may inhibit these processes [14,15]. LncRNAs, as active molecules, participate in various signaling pathways and cellular processes even though proteins are not produced from them [16]. Recent research showed that lncRNAs work as TGF-β signaling effectors in various forms of malignancies [17]. Although there is emerging evidence suggesting that TGF-β and lncRNAs participate in the development and progression of BC [18]. For instance, it has been proved that TGF-β stimulates the EMT of BC cells, which corresponds to a rise in invasiveness and metastasis [19]. Additionally, in BC, it has been discovered that lncRNAs are dysregulated and play a part in the growth and spread of tumor cells [20]. The lncRNA-ATB, which was promoted by TGF-β signaling in MCF7 BC cells and has been discovered as a sign of a bad prognosis in BC, was found to be controlled by the TGF-β signaling [21].

Furthermore, drug resistance in BC treatment is a major challenge, reducing the effectiveness of traditional treatments [22]. In BC, both lncRNAs and the TGF-β pathway have been correlated with therapeutic resistance progression [23]. Several cellular processes, including drug efflux, DNA damage repair, cell survival, and apoptosis, can modulate BC drug resistance via dysregulation of lncRNAs [24]. Likewise, through the promotion of immune evasion and EMT, abnormal TGF-β signaling can contribute to drug resistance [25].

Overall, our understanding of lncRNA and TGF-β roles in BC has grown significantly over the last two decades, but their precise mechanisms remain unknown. Hence, we offer a detailed explanation of the various aspects of the lncRNA and TGF-β that contribute to the progression of BC as well as discuss the lncRNAs' importance as therapeutic targets for cancer treatment.

2. The role of TGF-β signaling in breast cancer

The TGF-β signaling is a complex intracellular signaling network that is crucial for the development and spread of BC [26]. TGF-β is a structural element of the class of homologous signaling pathways, which have developed amino acid sequences that match approximately 25% of their sequence identities. There are numerous nonmammalian superfamily members as well as 26 recognized members of the mammalian TGF-β superfamily receptors. The TGF-β superfamily receptors are categorized into type I and type II receptors based on functional characteristics and amino acid sequence homology [27,28]. There are five recognized type II receptors and seven known type I receptors in mammals. Particularly inside the kinase domain, the type I receptors - show a higher degree of amino acid sequence homology to one another than do the type II receptors [29]. The 112-residue mature TGF-β is released once the growth factor's N-terminal latent peptide is cleaved during expression [30].

TGF-β as a cytokine with several functions, regulates several cellular processes [31], including cell growth [32], differentiation [33], apoptosis [34], and immune function [35]. Further, it can either induce or suppress cancer progression, based on the BC's stage and circumstance [36]. For instance, TGF-β signaling regulates the development of the mammary gland by regulating both epithelial cell proliferation and regression by preventing the cell cycle from progressing in epithelial cells (Fig. 1) [37]. Similarly, TGF-β specifically regulates the proliferation of epithelial cells, extracellular matrix, and apoptosis, which are essential for secretory activity and mammary development [38]. TGF-β signaling plays a critical role in regulating breast tumorigenesis. Nevertheless, mutations in the pathway's key components, including TβRII, TβRI, Smad2, Smad3, and Smad4, are uncommon in human BC [39]. For instance, in the majority of human BCs, lower type III transforming growth factor-receptor (TβRIII) expression is correlated with decreased heterozygosity at the TGFBR3 gene locus [40]. The recurrence-free survival rates were lower in BC patients with low TβRIII levels because TβRIII expression declined as the disease progressed [41]. When TβRIII expression was restored in BC cells, tumor invasiveness was shown to be significantly decreased in vitro, as well as a significant suppression of tumor invasion, angiogenesis, and metastasis in vivo [40]. TGF-β attaches to the TβRIII, which then releases TGF-β to the dimeric TβRII or directly to TβRII [42]. The TβRII is recruited by ligand binding, which also recruits the TβRI. The TβRI kinase activity is then triggered by TβRII, activating TβRI in the cytoplasmic domain. When TβRI phosphorylates a Smad receptor (Smad1/2/3 or Smad1/5, Smad8), the receptor's activation is triggered. When Smad receptors are phosphorylated, they bind to Smad4, forming a complex that builds up within the nucleus and controls the TGF-β responsive genes transcription in a cell- and context-specific manner [40,43,44].

In response to ligand binding, TGFR1 is phosphorylated by TGFR2 to form an active heterotetrameric receptor complex. R-Smads are phosphorylated by TGF-R1, which creates heteromeric complexes with the partner Smad (co-Smad; Smad4 in mammals). Additionally, these R-Smads-co-Smad complexes move toward the nucleus, where they collaborate with additional DNA-binding transcription factors to regulate the expression of their target genes [45].

In brief, metastasis, tumor expansion, and medication resistance are all influenced by the deregulation of the TGF-β signaling system in BC. It is crucial to comprehend the complex mechanisms of TGF-β signaling in BC to create targeted treatments that can alter this pathway and enhance patient outcomes (see Fig. 2 and Fig. 3).

3. LncRNAs and the mechanisms of BC tumorigenesis

Numerous lncRNAs are affected by cancer, and depending on the circumstances, they may act as oncogenes or tumor suppressors. Recent studies in cancer cell lines have highlighted the role of lncRNAs in BC carcinogenesis by regulating gene expression at various levels, including mRNA stability, transcription, and translation. In the sections that follow, by utilizing this dataset, we describe how lncRNAs contribute to BC carcinogenesis.

3.1. Oncogenic role of lncRNA in breast cancer tumorigenesis

Different kinds of cell lines were used to find out how lncRNA upregulation induces BC progression (Table 1). In BC, lncRNAs can function as oncogenes by modulating various signaling pathways and biological processes, including the proliferation of tumor cells [46,47],

invasion, migration, and metastasis [48]. For instance, the SNHG6 is raised in BC and encourages the development and spread of tumors by promoting the progression of the cell cycle and inhibiting apoptosis [49]. Similarly, the lncRNA ITGB2-AS1 has been found to regulate the expression of several other genes involved in cancer expansions, like genes associated with migration and invasion [50]. Likewise, UCA1 can serve as a miR-206 sponge, leading to the upregulation of PTP1B expression and BC progression [51]. Furthermore, together with p27, MIR100HG produced a triplex structure and aided cell proliferation in TNBC by controlling the p27 expression [52]. Additionally, by functioning as a "sponge" for miR-185-3p to induce LINC00511 production, LINC00511 has an oncogenic effect on the growth of BC. LINC00511 then targets the E2F1 protein, which interacts with the Nanog promoter area to start its transcription [53].

According to these studies, lncRNAs have been upregulated in BC cell lines. However, understanding the carcinogenic lncRNA roles in BC carcinogenesis might help us understand the molecular mechanisms driving BC development.

3.2. Tumor suppressor role of lncRNA in breast cancer tumorigenesis

LncRNAs are often upregulated in BC cell lines; however, they can also be downregulated in other cell lines of BC (Table 2). For instance, the lncRNA LINC00993 was downregulated in BC and serves as a tumor suppressor by promoting cell cycle arrest and apoptosis and suppressing tumor cell proliferation [70]. Similarly, in BC cells, downregulation of the lncRNA AC073284. 4 suppressed EMT [71]. LncRNAs can also regulate BC tumorigenesis by interaction with different substances, like proteins and other RNA species. For instance, the KB-1980E6.3 can promote BC cell self-renewal and preservation of stemness through interaction with the IGF2BP1 protein to rise stability of c-Myc mRNA [72]. Similarly, the lncRNA NNT-AS1 can affect BC progression through interaction with the ZEB1 protein [62]. Additionally, lncRNAs can function as ceRNAs, competing for miRNA binding with mRNAs and thereby controlling the target gene's expression [73,74]. Therefore, understanding the tumor suppressor roles of lncRNAs in BC brings more attention to the complex regulatory systems involved in the growth and spread of tumors (see Table 3 and Table 4).

4. TGF-β and lncRNA interactions in breast cancer

LncRNAs have become essential players in several cellular processes, such as the initiation, progression, invasion, and migration of cancer, especially BC. The interaction among TGF-β and lncRNAs in the setting of BC has been thoroughly studied. lncRNAs can serve as oncogenes or tumor suppressors by modulating the TGF-β signaling. The following are the most important oncogenic and tumor suppressor lncRNAs in the control of the TGF-β signaling in BC.

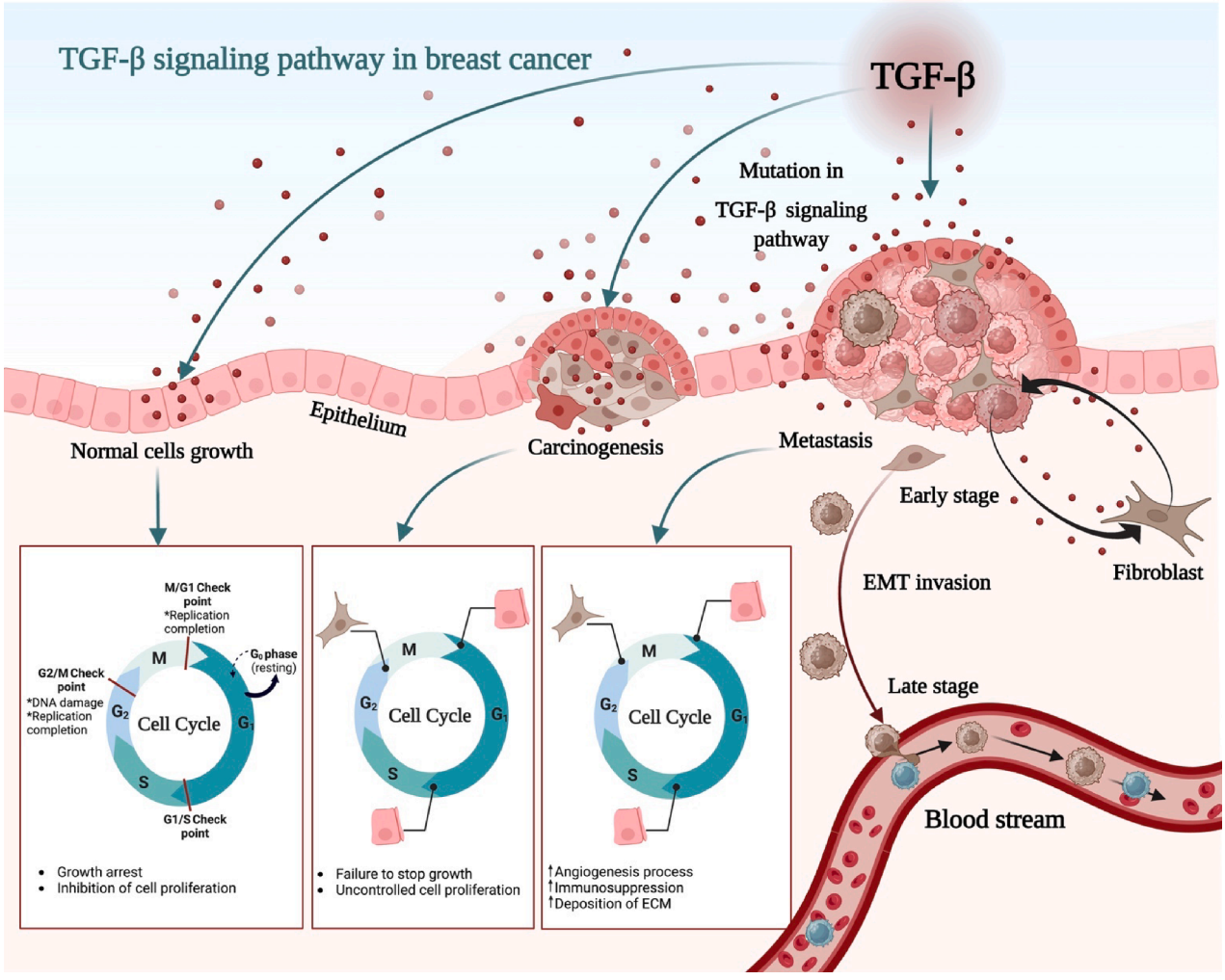

Fig. 1. The schematic diagram represents the TGF-β signaling and its functional role in the development of BC. TGF-β ligands inhibit normal cell growth and induce carcinogenesis by altering the cell cycle; as a result, they promote the growth and spread of tumor cells.

4.1. Oncogenic lncRNAs and TGF-β signaling in breast cancer

4.1.1. LncRNA CCAT2

LncRNA CCAT2, a novel transcript of lncRNA encompassing the rs6983267 SNP [81], was evident in BC [18]. In BC, CCAT2 silencing reduced cell expansions, invasion, and progression of the cell cycle both in vivo and in vitro, and it also prevented tumor growth [81]. Meanwhile, CCAT2 was downregulated, which prevented BC cells from proliferating, invading, and migrating [18]. Furthermore, previous research showed that CCAT2 triggers the TGF-β1 signaling, which encourages the development and spread of cancer [82], and their downregulation caused BC cells to cycle arrest in the G0/G1 phase and induced cell apoptosis. TGF-β, α-SMA, and Smad2 protein expression levels in BC cells were markedly reduced when CCAT2 was downregulated [18]. Thus, BC's interaction with the TGF-β signaling and the lncRNA CCAT2 reveals the highlighted regulatory mechanisms that play a role in the progression of BC.

4.1.2. Linc-ROR

In 2010, Loewer et al. reported the link-ROR as a 2.6 kb lncRNA [83], and several studies show the critical functions played by the linc-ROR in the progression and spread of various cancers [84]. In advanced BC, significantly high linc-ROR has been connected to cancer and drug resistance [85,86]. Numerous signaling pathways that are likely crucial for the initiation and development of cancer have been connected to the oncogenic action of linc-ROR [85]. Likewise, upregulation of the lincRNA ROR induces the proliferation of BC cells and invasion, as well as tumor growth, through controlling the TGF-β signaling pathway in vivo and in vitro [85]. Furthermore, Hou et al. show that linc-ROR expression levels influence several components in the TGF-β pathway, which may be crucial for the development of advanced BC [85]. To fully understand the molecular connections between the TGF-β pathway and the linc-ROR and explore the possibility of targeting this link in BC, more research is needed.

4.1.3. LncRNA NKILA

NF-κB-interacting lncRNA (lncRNA NKILA) has been discovered to be a BC-specific regulator of the TGF-β pathway [87]. In BC, the NKILA has a specific impact on EMT [88]. By suppressing the NF-κB pathway, the NKILA inhibits the TGF-β-induced EMT [88,89]. Liu et al. showed that the NKILA suppresses NF-κB signaling by attaching to the NF-κB/IκB complex and stabilizing it by covering the phosphorylation sites of IκB. However, low NKILA expression in high-grade cancers favors distant metastasis [90]. According to Wu et al, NKILA's expression is boosted by TGF-β, which stops NF-κB from being overactive. The expression of NKILA regulates the "on and off" switch of NF-κB activation through a negative feedback mechanism [88]. As a result, they prove that the NKILA controls TGF-β-promoted EMT in BC. Overall, NKILA is a well-studied lncRNA that is necessary for controlling TGF-β signaling. The genesis and progression of BC have been linked to the abnormal expression of this pathway.

4.1.4. LncRNA-HIT

HOXA antisense transcript induced by TGF-β (lncRNA HIT) is one of the top TGF-β up-regulated genes [91,92], and has a critical function in TGF-β-induced EMT [91], which was discovered recently and has been demonstrated to be crucial for cell development and the change from epithelial to mesenchymal tissue [91]. The highly metastatic c4 T1 cell

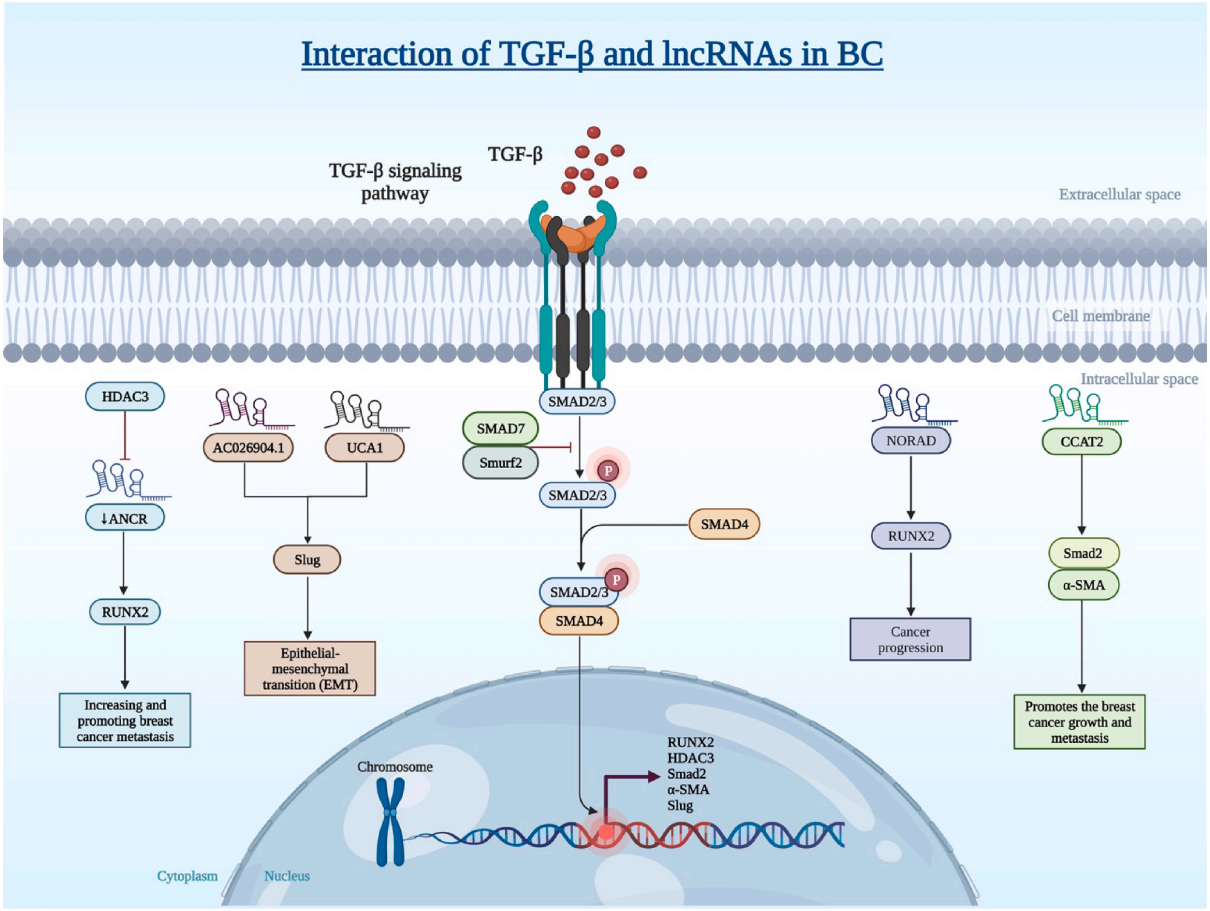

Fig. 2. The illustration shows the connection between TGF-β signaling pathways and lncRNAs in the progression of BC. LncRNAs can induce tumor development and spread in BC by targeting particular genes, including RUNX2, Slug, Smad2, and α-SAM.

line has greatly elevated HIT expression, while HIT deletion in 4 T1 cells reduced cell invasion and migration. Additionally, increased HIT expression was linked to patients' having more aggressive human breast cancer [91,93]. In addition, Richards et al. observed that the mRNA level and E-cadherin promoter activity were both severely decreased by lncRNA-HIT and that forced E-cadherin expression largely reversed lncRNA-HIT-induced EMT and metastasis. These results indicate that lncRNA-HIT, which controls E-cadherin through the trans method, has E-cadherin as one of its primary targets [91]. Furthermore, Cheng et al. have found that the lncRNA-HIT is a new BC-associated lncRNA that facilitates TGF-β forced EMT and migration [91].

4.1.5. LncRNA–NORAD

The lncRNA activated by DNA damage (lncRNA-NORAD) has been linked to several cellular processes, including BC [94]. In contrast to its knockdown, lncRNA-NORAD overexpression inhibited BC cell growth and metastasis [95]. In BC cells, inhibiting NORAD blocks the TGF-β signaling pathway. When NORAD was knocked down in the MDA-MB-231 and MCF-7 BC cells, the expression of TGFβ was downregulated, and downstream factors like Smad2 and RUNX2 were repressed. These findings strongly suggested that NORAD likely controlled the TGF-β signaling and contributed to the development of BC [96,97]. Additionally, the lncRNA-NORAD, which may be linked to RUNX2, is raised in BC cells and tissues and induces BC growth via the TGF-β signaling. Zhou et al. determined that the NORAD/TGF-/RUNX2 axis participates in the progression of BC tumors and that lncRNA-NORAD functions as an oncogenic lncRNA [97].

4.1.6. LncRNA-Smad7

The lncRNA-Smad7 plays an important part in controlling the TGF-β signaling in BC, which has anti-apoptotic functions [98]. In mouse BC cells, Arase et al. discovered lncRNA-Smad7 as a novel anti-apoptosis factor; however, they were unable to determine the regulatory mechanism of lncRNA-Smad7-induced apoptosis [98]. Similarly, in the mouse BC cell line JygMC (A), lncRNA-Smad7 appears to serve as a downstream anti-apoptotic agent of TGF-β without impacting the activation of Smad2 or the induction of EMT [99]. In brief, lncRNA-Smad7 is critical for the regulation of TGF-β signaling and the progression of BC.

4.1.7. LncRNA UCA1

Urothelial carcinoma-associated 1 (lncRNA UCA1] has an essential function in controlling many cellular processes in several cancers, including BC [100]. LncRNA UCA1, which is significantly expressed in several human malignancies, has been linked to the TNM stage, vascular invasion, depth of invasion, LNM, RFS, and OS [101,102]. Additionally, lncRNA UCA1 controls drug resistance, migration, invasion, apoptosis, and cell growth [103]. For instance, Wo et al. demonstrate the effect of TGF-β induced EMT on the regulation of the lncRNA UCA1. These results show that TGF-β induced EMT in BC may be mediated by the lncRNA UCA1, as TGF-β substantially increased vimentin protein levels while considerably reducing E-cadherin protein expression [23]. Further, Li et al. found that UCA1 and AC026904.1 cooperated to enhance Slug

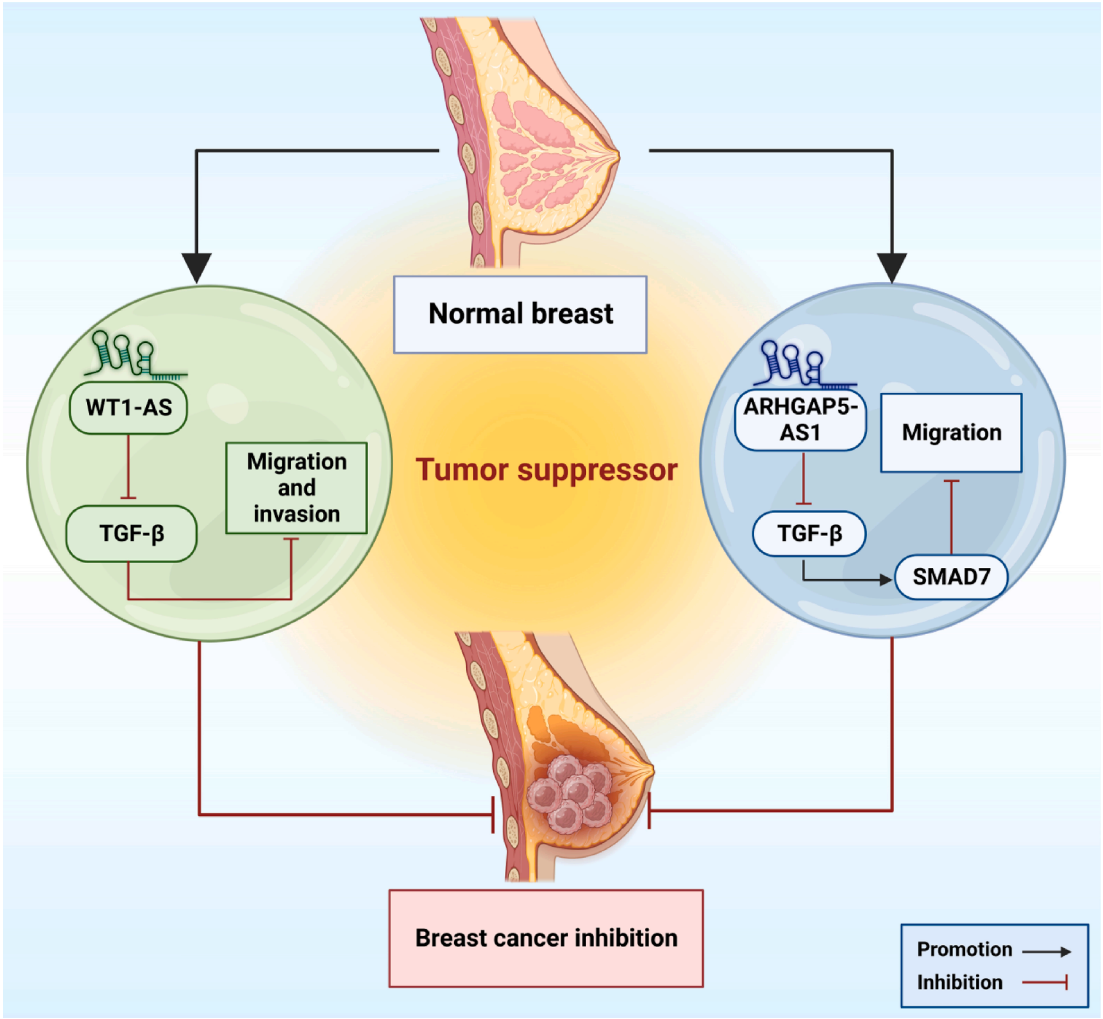

Fig. 3. An illustration shows the tumor suppressor role of lncRNAs and TGF-β signaling which inhibits the development and metastasis of BC.

during both transcriptional and post-transcriptional stages, promoting TGF-β-induced EMT in BC [104]. Additionally, according to multiple studies, the TGF-β/Slug/E-cadherin pathway is essential for EMT and tumor spread [105,106]. However, the crosstalk between TGF-β and lncRNA UCA1 is complex and multifaceted, and to fully comprehend the molecular processes behind their crosstalk in BC, more investigation is required.

4.1.8. LncRNA TPA

The lncRNA tissue plasminogen activator (lncRNA TPA) is another lncRNA that has an impact on the occurrence of EMT in human cancers, including BC, via the TGF-β signaling, which then encourages BC spread [107,108]. Fibronectin, vimentin, and TGF-β1 expression were dramatically upregulated, E-cadherin expression was considerably downregulated, and cell migration, invasion, and ability were all substantially enhanced by overexpressing the lncRNA TPA [107].

4.2. Tumor suppressor lncRNAs and TGF-β pathway in breast cancer

4.2.1. LncRNA-CASC2

The lncRNA cancer susceptibility candidate 2 (lncRNA CASC2) plays a critical role in the progression of BC [47]. It was located in a genomic region on chromosome 10q26 [110]. The inhibition of the TGF-β signaling by the CASC2 was reported to significantly reduce BC cell proliferation and spread [47]. By affecting the cell cycle, triggering cell apoptosis, and inhibiting cell metastasis, CASC2 overexpression could reduce BC cell proliferation. Additionally, the TGF-β signaling was deactivated by the high concentration of CASC2. As a result, CASC2 likely prevented BC from progressing by deactivating the TGF-β signaling [47,111].

4.2.2. WT1-AS

The lncRNA Wilms tumor 1 antisense RNA (WT1-AS) is particularly expressed in a variety of cancerous malignancies. In BC and colon cancer, WT1-AS expression is especially elevated [112]. WT1-AS dramatically decreased with increasing clinical stages and compared to non-tumor tissues was decreased in TNBC tissues [109]. TGF-β1 was overexpressed in TNBC tissues and exhibited an inverse relationship with WT1-AS. In BT-549 cells, TGF-β1 overexpression had no observable effects on WT1-AS, but TGF-β1 expression was negatively regulated by WT1-AS [109]. Overexpression of WT1-AS prevented TNBC cells from migrating and invading, and its upregulation was reduced by TGF-β1

Table 1
Oncogenic roles of various lncRNAs in BC tumorigenesis through regulation of target genes and signaling pathways (↑: upregulated, ↓: downregulated).

LncRNA	miRNAs	Compared to normal cell lines, levels in cancer cell lines	Cell lines	Interaction	Associated phenotypes with dysregulation of lncRNA	Ref
ARNILA	miR-204	Upregulated	MDA-MB-231, Hs578T	Sox4	↓ AR, ↑ ARNILA, ↓ miR-204, ↓ Sox4: ↑ EMT: ↑ invasion and metastasis	[50]
Lnc015192	miR-34a	Upregulated	4 T1, 891 cells	Adam12	↑ Lnc015192, ↓ miR-34a, ↑ Adam12: ↑ cell invasion and metastasis	[54]
EPIC1	–	Upregulated	MCF-7	AKT-mTORC1 signaling, 4EBP1, S6K	↑ EPIC1, ↑ AKT-mTORC1 signaling, 4EBP1, S6K: ↑ rapamycin resistance	[55]
DSCAM-AS1	–	Upregulated	MCF-7	–	↑ DSCAM-AS1: ↑ Control of 3′-end usage and alternative exon splicing	[56]
LncRNA-ITGB2-AS1	–	Upregulated	MCF-7, MDA-MB-231	ITGB2	↑ ITGB2-AS1, ↑ ITGB2: ↑ Migration and Invasion	[57]
MIR100HG	–	Upregulated	MDA-MB-231	p27	↑ MIR100HG, ↑ p27: ↑ proliferation, cell cycle arrest at G1/S	[52]
PVT1	–	Upregulated	BT549, ZR-7530, MCF7, T47D, MDA-MB-453, MCF10A, MDA-MB-468, MDA-MB-231	CTNNB1, KLF5/β-catenin signaling	↑ PVT1, ↑ KLF5/beta-catenin signaling: ↑ tumorigenesis	[58]
EZR-AS1	–	Upregulated	MCF-10A, MDA-MB-231, MCF7, SKBR-3, MDA-MB-468	Wnt/β-catenin pathway	↑ EZR-AS1, ↑ Wnt/β-catenin pathway: ↑ proliferation, migration, and invasion	[59]
Linc00617	–	Upregulated	T47D, MCF7, MCF10A, MDA-MB-468, BT474, MDA-MB-231	–	↑ Linc00617: ↑ mobility and Invasion	[60]
HI9	–	Upregulated	MCF-7, SK-BR-3	Wnt pathway	↑ HI9, ↑ Wnt pathway: ↑ EMT	[61]
NNT-AS1	miR-142-3p	Upregulated	MD-MB-468, MCF-10A, MD-MB-231, MCF-7	ZEB1	↑ NNT-AS1, ↓miR-142-3p, ↑ ZEB1: ↑ cell proliferation, spread, EMT	[62]
LNC00511	miR-185-3p	Upregulation	MCF-7, MDA-MB-468, ATCC, MDA-MB-453, MCF-10A, MDA-MB-231	E2F1/Nanog axis	↑ LNC00511, ↓miR-185-3p, ↓ E2F1: ↑ tumorigenesis	[53]
UCA1	miR-206	Upregulated	MCF-7, MDA-MB-231	PTP1B	↑ UCA1, ↓ miR-206, ↑ PTP1B: ↑ BC progression	[51]
CCAT2	–	Upregulated	MDA-MB-231, MCF-7	Wnt/β-catenin pathway	↑ CCAT2, ↑ Wnt/β-catenin pathway: ↑ tumor growth	[63]
CCAT1	miR-218	Upregulated	MDA-MB-231, MCF-10A, MDA-MB-436, MDA-MB-468	ZFX	↑ CCAT1, ↓ miR-218/ZFX signaling: ↑ cancer progression	[64]
CAMTA1	miR-20b	Upregulated	MDA-MB-231	MAPK, VEGF, JAK, ERK, STAT3, STAT1	↑ CAMTA1, ↓miR-20b, ↑VEGF, ↑ JAK/STAT3 and MAPK/ERK pathways: ↑ proliferation and mobility	[65]
HOTAIR	miR-206	Upregulated	MCF-7, T47D	Bcl-w Signaling	↑ HOTAIR, ↓ miR-206, ↑ Bcl-w signaling: ↑ Cell proliferation	[66]
RUSC1-AS-N	–	Upregulated	MDA-MB-231, SK-BR-3, T47D, MDA-MB-468, MCF7	Wnt/β-catenin signaling	↑ RUSC1-AS-N, ↑ Wnt/β-catenin signaling: ↑ cell proliferation and spread	[67]
SPRY4-IT1	miR-6882-3p	Upregulated	T47D, MCF-7	TCF7L2, Wnt/β-catenin signaling pathway	↑ LncRNA-SPRY4-IT1, ↓miR-6882-3p, ↑ TCF7L2, Wnt/β-catenin signaling pathway: ↑ Cell proliferation	[68]
	–	Upregulated	MCF-7, MD-MB-231, MD-MB-435S, MCF-10A,	ZNF703	↑ SPRY4-IT1, ↑ ZNF703: ↑ Cell proliferation	[69]

Table 2
Tumor suppressor functions of various lncRNAs in BC tumorigenesis through regulation of target genes and signaling pathways (↑: upregulated, ↓: downregulated).

LncRNA	miRNAs	Compared to normal cell lines, levels in cancer cell lines	Cell line	Interaction	Associated phenotypes with dysregulation of lncRNA	Ref
MEG3	miR-421	Downregulated	MCF-10A, MDA-MB-231, SKBR3, MCF-7	E-cadherin	↓ MEG3, ↓miR-421, ↑ E-cadherin: ↓ EMT	[75]
	miR-21	Downregulated	MCF-10A, MCF-7, T47D, MDA-MB-231, MDA-MB-453	PI3K/Akt signaling	↓ MEG3, ↑ miR-21, ↑ PI3K/Akt pathway: ↓ tumorigenesis	[76]
PTENP1	miR-19b	Upregulated	MDA-MB-231, MCF-7, MCF10A	PTEN, PI3K/Akt axis	↑ PTENP1, ↓miR-19b, ↑ PTEN: ↓ Cell proliferation, and spread	[77]
XIST	miR-155	Downregulated	MCF-10 A, MCF-7, MDA-MB-453, ZR-75–1, MDA-MB-468, HCC1937, MDA-MB-231	CDX1	↓ XIST, ↑ miR-155, ↑CDX1: ↓cell expansion, invasion, and migration	[78]
sONE	miR-15a, miR-34a, miR-16, let-7a	Downregulated	MDA-MB-231	c-Myc, TP53	↓sONE, ↑ miR-15a, let-7a, miR-16, miR-34a,↑ TP53, ↓c-Myc: ↓ tumor progression	[79]
LncRNA-CASC2	miR-96-5p	Downregulated	MCF10A, MDA-MB-231, MCF-7	SYVN1	↓ LncRNA-CASC2, ↓miR-96-5p, ↓ SYVN1: ↓ cell growth and metastasis	[80]

Table 3
Oncogenic lncRNA and TGF-β signaling expressions in human samples, animal models, and cell lines with targets and mechanisms of action in BC (↑: upregulated, ↓: downregulated).

LncRNA	Expression	Animal models	Clinical samples	Cell lines	Targets	Mechanism of action	Ref.
HIT	Upregulated	BALB/c mouse	–	NMuMG, 67NR	E-cadherin, Vimentin, TGF-β1	↑ HIT, ↓ E-cadherin, ↑ vimentin, TGF-β1: ↑ migration, Invasion, Metastasis, and Tumor Growth	[91]
CCAT2	Upregulated	–	[36] BC tissue with lymph node metastasis + [24] BC tissue without lymph node metastasis	MCF-7, HCC1937, MDA-MB_231, LCC9	α-SMA, Smad2, TGF-β	↑ CCAT2, ↑ TGF-β, Smad2, α-SMA: ↑ growth and metastasis	[18]
UCA1	Upregulated	–	15 paired BC tissue	MCF-7, MDA-MB-231, MDA-MB-468,	TGF-β, vimentin, E-cadherin	↑UCA1, ↓ E-cadherin ↑ vimentin, TGF-β1: ↑ doxorubicin resistance	[23]
NKILA	Downregulated	NOD/SCID mice	164 BCE tissue	MCF-7, BT474	E-cadherin, NF-κB, TGF-β	↓ NKILA, ↑ E-cadherin, ↓ NF-κB, TGF-β: ↓ EMT and metastasis	[88]
WT1-AS	Downregulated	–	62 TNBC tissue	BT-549	TGF-β1	↓ WT1-AS, ↓ TGF-β1: ↓ migration and invasion	[109]
LncRNA-NORAD	Upregulated	BALB/c mice	18 BC tissue	MDA-MB231, MCF-7, MCF10A	TGF-β, RUNX2	↑ NORAD, ↑ TGF-β signaling pathway: ↑ cancer progression	[97]
	Downregulated	–	46 BC tissue	MCF-10A, T-47D, SK-BR-3, HCC70, MCF-7	miRNA-155-5p, SOCS1	↓ LncRNA-NORAD, ↓MiR-155-5p, ↑ SOCS1: ↓ cell expansion and spread	[95]
LncRNA-Smad7	Downregulated		–	NMuMG, JygMC (A)	TGF-β	Inhibits apoptosis via unknown mechanism	[98]
LncRNA TPA	Upregulated	BALB/C nude mice	–	MCF-7TR SKBR-3	TGF-β1, E-cadherin, fibronectin, vimentin	↑ TPA, ↓ E-cadherin, ↑ vimentin, fibronectin, TGF-β1: ↑ invasion and metastasis	[107]

Table 4
Tumor suppressor lncRNAs and TGF-β signaling expressions in animal models and cell lines with targets and mechanisms of action in BC (↑: upregulated, ↓: downregulated).

LncRNA	Expression	Animal model	Cell line	Targets	Mechanism of action	Ref.
ANCR	Downregulated	BABL/c nude mice	MCF10A, MDA-MB-231, BT549, MCF7, T47D,	TGF-β, RUNX2	↓ ANCR, ↑ TGF-β signaling, ↓ RUNX2: ↑ EMT and metastasis	[114]
WT1-AS	Upregulated	–	BT-549	TGF-β	↑ WT1-AS, ↓ TGF- β: ↓ Metastasis	[109]
ARHGAP5-AS1	Downregulated	–	BT549, MDA-MB-231, SKBR3	SMAD7	↓ ARHGAP5-AS1, ↓TGF-β signaling, ↓ SMAD7: ↑ migration	[117]

overexpression, which displayed opposing activities [109].

4.2.3. LncRNA-ANCR

Anti-differentiation ncRNA (lncRNA-ANCR) is a lncRNA with 855-base-pair that is decreased during differentiation [113]. Growing data suggests that lncRNAs are crucial for EMT and tumor metastasis; it has been found that the ANCR participates in TGF-β1-induced EMT [114]. Similarly, the TGF-β signaling downregulates ANCR by increasing RUNX2 expression and fostering BC cell invasion and metastasis both in vivo and in vitro [114]. Li et al. demonstrated that in BC cells, knock-down of ANCR boosted RUNX2 expression, while ectopic production of ANCR was able to inhibit the expression of RUNX2 both at the mRNA and protein levels. These findings imply that ANCR can probably control RUNX2 transcriptional expression directly [115], and they verified that

in BC samples, high RUNX2 expression was associated negatively with low ANCR expression. According to these findings, ANCR is an anti-metastatic lncRNA and may be a valuable prognostic biomarker to identify individuals at an increased risk of BC progression [114]. HDAC3 is induced by TGF-β1 to increase, and once it adheres to ANCR's promoter region, it suppresses ANCR transcription. Additionally, when ANCR levels drop, RUNX2 expression rises, aiding in the spread of BC [114,116].

4.2.4. LncRNA ARHGAP5-AS1

LncRNA ARHGAP5 antisense RNA 1 (lncRNA ARHGAP5-AS1) expression is reduced in BC with advanced metastatic disease [117]. By preventing the growth of stress fibers in cells of BC, the lncRNA ARHGAP5-AS1 may prevent cell migration. In BC cell lines and tissues, ARHGAP5-AS1 is downregulated, which inhibits cell migration and the development of stress fibers in BC cells. In addition, it has been shown that SMAD7, a significant inhibitory Smad that adversely regulates the TGF-β pathway, crosstalks with ARHGAP5-AS1 and that ARHGAP5-AS1 affects SMAD7′s protein level [117]. However, more investigation is required to find new insights into the molecular mechanism supporting ARHGAP5-AS1 function in controlling TGF-β signaling in BC samples.

5. LncRNAs as a diagnostic biomarker in breast cancer

In various kinds of cancer, including BC, lncRNAs have been identified as significant regulators of tumor development and metastasis [118]. They regulate the expression of genes at several levels through modulating chromatin structure, miRNA sponging, and interacting with RNAs and proteins [119]. Different mechanisms, such as changes in lncRNA expression levels, genomic reorganizations, and epigenetic modifications, might lead to dysregulation of lncRNAs [120]. Further, several dysregulated lncRNAs have been demonstrated as potential biomarkers for the diagnosis and prognosis of BC [121] (Table 5). For instance, the lncRNA ANCR was shown to be a novel TGF-β downstream component in the metastasis of BC cells, suggesting that ANCR might develop into anti-metastasis and a predictive biomarker therapeutic target [114]. Similarly, Zhang et al. demonstrated that plasma H19 may serve as a possible biomarker for prognostic monitoring and early detection of BC. Plasma and BC tissues had significantly higher H19 levels when compared to healthy controls and were linked with LNM, ER expression, and PR expression [122]. Moreover, Ashmawy et al. revealed that both lncRNA-ATB and FAM83H-AS1 were considerably upregulated in the serum of BC patients when compared to healthy controls. They found that serum FAM83H-AS1 has the potential to be

Table 5
Functional roles of dysregulated lncRNAs in BC progression depend on studies in clinical samples their and association with clinicopathologic characteristics.

lncRNAs	Expression	Samples	Kaplan-Meier analysis	Target/ pathways	Association of dysregulation lncRNAs with clinicopathologic characteristics	Ref.
H19	Upregulated	– BC tissues = 24 pairs. – BC plasma = 20 pairs. – BC patients = 102. – Healthy controls = 96 subjects.	–		LNM, ER status, PR status.	[122]
FAM83H-AS1, LncRNA-ATB	Upregulated	– BC serum = 90. – Healthy controls = 30 subjects.	–	–	LNM, TNM stages, large tumor size.	[123]
LncRNA T376626	Upregulated	– -BC serum = 294. – Healthy controls = 78 subjects.	High levels of lncRNA T376626 correlated with poor prognosis.	LAMC2	Age, tumor size, histological type, PR, TNM stages, Her-2, ER, Ki-67, molecular type.	[124]
LINC00426	Upregulated	– -GDC Data Portal = 927 patients. – cohort = 3,052 patients.	A high level of l LINC00426 correlated with overall survival (OS).	–	Age, tumor size, LNM, TNM stages, ER, PR, Her-2, OS, metastasis status.	[125]
CYTOR	Upregulated	– BC tissues = 20 pairs. – BC plasma = 80.	–	–	ER, PR, Her-2, Ki-67.	[126]
LncRNA TINCR	Upregulated	– TNBC = 72 patients. – Non-TNBC =105 patients. – Benign case = 60 patients. – Healthy control = 86 subjects.	High levels of TINCR correlated with overall survival (OS).	–	LNM, Age, smoking, menopause, histological subtype, TNM stage, tumor size, tumor grade.	[127]
LncRNA XIST	Upregulated	– BC serum = 91.	High levels of lncRNA XIST correlated with poorer overall survival (OS).	–	Age, gender, tumor grade, KPS, Status (Recurrence), and (non-recurrence).	[128]
LncRNA MIAT	Upregulated	–	High levels of LncRNA MIAT correlated with overall survival (OS).	–	Age, BMI, menopause, TNM stage, LNM, tumor size, PR, Her-2, ER, Ki-67.	[129]
LncRNA ST7-AS1	Downregulated	– BC patients = 1,065.	Low levels of ST7-AS1 correlated with a bad prognosis.	–	Age, high grade, histological type, Her-2 status, menopause status.	[130]
LINC01614	Upregulated	– BC tissue = 929.	High levels of LINC01614 correlated with several genes, such as cell adhesion pathways, CDH1 signaling, and TGF-β1 response.	–	ER status, PR status, Her-2 status.	[131]
LncRNA Z38	Upregulated	– BC patients = 110.	High levels of lncRNA Z38 were a self-reported independent predictor of overall survival (OS).	–	TNM stage, LNM	[132]

used to monitor the development and staging of BC, and as a non-invasive diagnostic indicator for early-stage BC, serum lncRNA-ATB may be employed [123]. Furthermore, He et al. demonstrated that, through binding to LAMC2, lncRNA T376626 may function as a predictive and diagnostic biomarker based on TNBC serum and play a carcinogenic role in TNBC progression [124] (see Table 6).

In brief, these lncRNAs, along with other lncRNAs, have been demonstrated as potential biomarkers in BC. However, to prove lncRNAs' therapeutic relevance and create standardized biomarker detection and evaluation methods, more clarifications are needed.

6. Breast cancer drug resistance and lncRNAs/TGF-β pathway

Drug resistance has emerged as one of the main issues in BC as a result of its heterogeneity [133]. Despite some research improvements, drug resistance in BC continues to be a major factor in the disease's bad prognosis and relatively low survival rates [134]. According to recent studies, lncRNAs have key roles in several cellular and genomic processes that are connected to drug resistance and carcinogenesis [135]. Apoptosis, DNA repair, autophagy, drug efflux, cell cycle, EMT, epigenetic alteration, and TME are just a few of the important and diverse functions that lncRNAs play in BC chemoresistance [136].

TGF-β signaling and lncRNAs both play essential roles in various cellular processes, including drug resistance. For instance, Sheng-Jia et al. found that lncRNA-ATB may maximize the risk of trastuzumab resistance and the invasion-metastasis cascade in BC by inhibiting miR-200c competitively, controlling ZNF-217 and ZEB1 expressions, and ultimately triggering EMT [137]. Additionally, they found a connection between the greater amounts of lncRNA-ATB found in BC individuals and their resistance to trastuzumab. These results imply that lncRNA-ATB, a TGF-β signaling mediator, may make BC patients more susceptible to EMT and trastuzumab resistance [137] (Fig. 4a). Likewise, resistance to doxorubicin (DOX) continues to be a significant challenge to the adriamycin-based treatment of BC [138]. In BC cells and tissues, Wo et al. approve that the lncRNA UCA1 is a prospective target for enhancing chemotherapy for BC since it is increased in TGF-β treated BC cells and, through the EMT signaling pathway, supports TGF-β mediated DOX resistance [23] (Fig. 4b). Moreover, Tang et al. found that through ANXA1, DCST1-AS1 improves chemoresistance in TNBC cells and promotes TGF-β induced EMT, making it a potentially effective target for the treatment of metastatic BC [19] (Fig. 4c).

In brief, TGF-β signaling and lncRNAs both contribute to BC drug resistance. Different cellular functions involved in drug response can be impacted by dysregulated lncRNAs, while the TGF-β signaling can encourage drug resistance via the maintenance of CSCs, immune evasion, EMT, and pro-survival signaling. To enhance the efficacy of BC therapy, it can be helpful to comprehend the complex interactions between lncRNAs, TGF-β signaling, and drug resistance.

7. LncRNAs and TGF-β signaling as therapeutic targets in breast cancer

Breast cancer development, progression, and medication resistance have all been linked to abnormal expression and deregulation of particular lncRNAs [139]. In BC, the TGF-β signaling and lncRNAs have been identified as possible therapeutic targets [140]. The TGF-β signaling plays an essential role in several cellular processes [141]. This pathway's dysregulation has been linked to the spread and advancement of BC [142]. Additionally, lncRNAs have been identified as essential tumor growth regulators and as key players in a variety of chemoresistance processes, such as interfering with DNA damage repair, altering drug efflux, inducing apoptosis, and altering therapeutic targets [143].

Evidence suggests that lncRNAs and TGF-β signaling have been recognized as therapeutic targets in BC. For instance, NKILA overexpression dramatically inhibited tumor metastasis caused by TGF-β in vivo, which indicates that NKILA-induced negative feedback influences TGF-β-mediated activation of NF-κB, and this result shows that through inhibition of EMT, NKILA may be a helpful therapeutic substance in metastasis of BC [88]. Similarly, according to Wu et al., by modifying the TGF-β signaling, CCAT2 downregulation may reduce the proliferative and metastasis characteristics of BC cells and cause cell death [18].

Furthermore, TGF-β signaling components can be modulated and used as a treatment target in BC [144]. Therapeutic approaches may focus on specifically targeting and controlling TGF-β signaling pathway elements [145]. Potential therapeutics include small molecule inhibitors that precisely target TGF-β receptors or downstream effectors, including Smad proteins [146]. These small-molecule inhibitors can block abnormal TGF-β signaling and inhibit cancer cell proliferation and metastasis [147].

Clinical trials with small-molecule TβR kinase inhibitors targeting anti-TGF signaling in the treatment of cancer are ongoing. LY2157299 is a small molecule orally accessible inhibitor of TβRI (and, to a lesser extent, TβRII) that binds selectively to TβRI and inhibits the kinase activity of TβRI. In preclinical studies, LY2157299 demonstrated positive anti-tumor growth results in mice models [148]. It showed favorable preclinical results for anti-tumor growth in mouse tumor models. Furthermore, LY3200888 is a novel, highly selective, and highly potent ATP-competing TβRI-inhibitor that demonstrated anti-tumor activity in preclinical mouse models of TNBC [149]. There have been numerous preclinical trials evaluating the full spectrum of TβRI inhibitor drugs, but the primary SMI drug to be studied in the clinic has been galunisertib (Eli Lilly) or lY2157299 [150].

The FHD (first human dose) analysis was conducted as monotherapy for advanced-stage solid tumors in subjects with a novel T βRI kinase SMI (TEW-7197) called MedPacto [151,152]. It's been shown that TEW-7197 causes Smad4 to be broken down in the cells that make up the toxic T cells, which makes them more active and reduces the risk of breast cancer spreading to the lungs in mice [152]. Additionally, the other monoclonal antibodies have been identified and studied in clinical trials such as Metelimumab, Lerdelimumab, and Fresolimumab against TGF-

Table 6
Role of lncRNAs along with TGF-β signaling in BC drug resistance, depending on clinical sample study, cell line study, and animal study (↑: upregulated, ↓: downregulated).

Drug	LncRNAs	Clinical sample	Cell line	Animal study	Targets/ Signaling pathway	Mechanism of action	Ref.
Trastuzumab	LncRNA-ATB	BC case = 50	SKBR-3	–	miR-200c, ZEB1, ZNF-217/ TGF-β signaling	↑ lnc-ATB, ↓ miR-200c, ↑ ZEB1, ZNF-217: ↑ Trastuzumab resistance.	[137]
Doxorubicin	LncRNA-UCA1	BC case = 15	MDA-MB-231, MCF-7, MDA-MB-468	–	Vimentin, E-cadherin / TGF-β signaling pathway	↑ lncRNA UCA1, ↑ TGF-β signaling: ↑ Dox resistance	[23]
Doxorubicin, Paclitaxel	DCST1-AS1	–	MCF7, MDA-MB-231, T-47D, BT-549	–	ANXA1, SNAI1, E-cadherin, MMP9, MMP2, vimentin, TGF-β/Smad signaling	↑ DCST1-AS1, ↓ E-cadherin, ↑ TGF-β/Smad signaling: ↑ Doxorubicin and Paclitaxel resistance	[19]

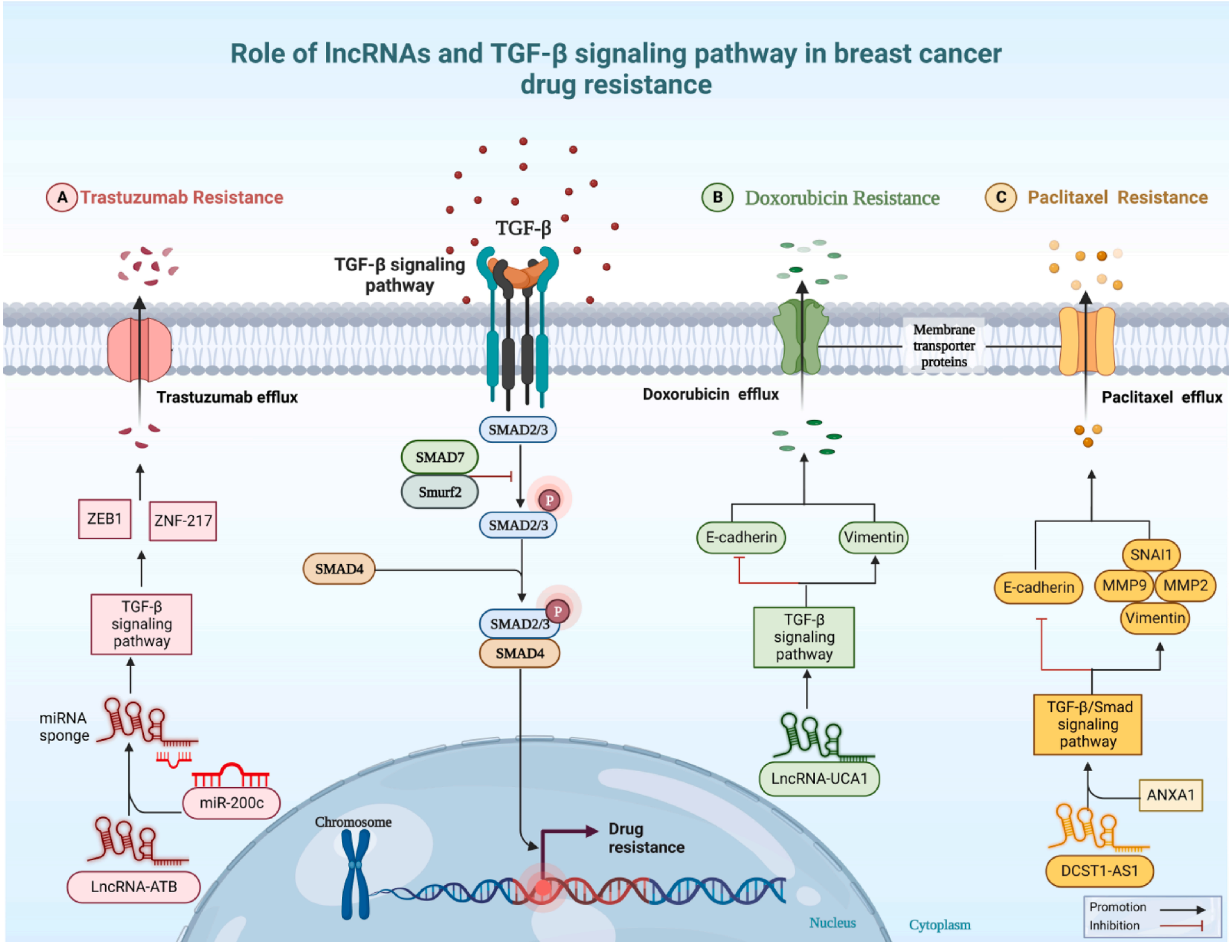

Fig. 4. The graphic emphasizes the significance that lncRNAs and the TGF-β signaling play in BC and treatment resistance by utilizing three different treatment approaches that lead to drug resistance.

β1 and TGF-β2 isoforms in breast cancer cells [153–155].

Even though there are treatment methods that target lncRNAs and TGF-β signaling seems promising, it's critical to remember that more research is necessary to fully understand the essential roles and modes of action of specific lncRNAs along with TGF-β signaling in the context of BC.

8. Conclusions

The crosstalk between lncRNAs and the TGF-β signaling offers enormous promise as a crucial regulatory mechanism in the progression of BC. Aberrant expression of lncRNAs and dysregulated TGF-β signaling pathway molecules induce BC progression. Recent studies highlighted the alteration of lncRNAs and TGF-β signaling in BC, therefore it affects cell proliferation, EMT, and metastasis. In cell line studies, animal models, and clinical samples of BC, lncRNAs and the TGF-β signaling pathway have been demonstrated to affect several cellular processes, including cell proliferation, metastasis, and EMT, and could be used as a potential diagnostic biomarker. Furthermore, they are dysregulated and lead to drug resistance in BC patients.

However, the opportunity exists for us to make substantial strides forward in our understanding of the pathophysiology of BC if we can gain a better comprehension of the complex interactions that take place between lncRNAs and the TGF-β signaling. The viability of these interactions in a clinical environment has not yet been assessed. Therefore, additional research is needed to expand new insights into this field.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgment

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation, and assistance throughout the period of study.

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