Long non-coding RNA regulation of TRAIL in breast cancer: A tangle of non-coding threads (Review)

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Abstract. Breast cancer is a complex disease posing a serious threat to the female population worldwide. A complex molecular landscape and tumor heterogeneity render breast cancer cells resistant to drugs and able to promote metastasis and invasiveness. Despite the recent advancements in diagnostics and drug discovery, finding an effective cure for breast cancer is still a major challenge. Positive and negative regulation of apoptosis has been a subject of extensive study over the years. Numerous studies have shed light on the mechanisms that impede the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) signaling cascade. Long non-coding RNAs (lncRNAs) have been implicated in the orchestration, development, proliferation, differentiation and metastasis of breast cancer. However, the roles of lncRNAs in fine-tuning apoptosis regulating machinery in breast cancer remain to be elucidated. The present review illuminates the roles of these molecules in the regulation of breast cancer and the interplay between lncRNA and TRAIL in breast cancer. The present review also attempts to reveal their role in the regulation of apoptosis in breast cancer appears a promising approach for the development of new diagnostic and therapeutic regimens.

Contents

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1. Introduction

In recent years, there has been an upsurge in cancer burden worldwide, and cancer has become the leading cause of death, following cardiovascular diseases, in both men and women globally (1). There are nearly 18 million cases of cancer registered worldwide; among them, 268,600 are breast cancer patients (2). Among the different cancer types, breast cancer is one of the major causes of death in the female population (3). Compelling evidence suggests that specific genetic, epigenetic and environmental factors play a critical role in the development of breast cancer. The prevalence of breast cancer is caused by many factors, including unhealthy lifestyle, excessive consumption of red meat, alcohol, smoking and genetics (4). Nowadays, high-throughput technologies, such as next-generation sequencing have begun to elucidate tumor

heterogeneity and has brought us closer towards devising new diagnostic and therapeutic strategies (5). Advanced experimental methodologies have started to categorize proteome into sub-classes of pro-apoptotic and anti-apoptotic proteins (5). This has led to characterization of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) sub-proteomes (5). Alterations in the TRAIL-mediated signaling pathway are associated with the proliferation of breast cancer (6). Translation and functional studies have clarified the underlying mechanisms and biomolecular signatures responsible for impeding cancer treatment (7,8) Thus, the search for better diagnostic and management of breast cancer is needed.

Positive and negative regulation of apoptosis has been a subject of extensive study over the past decades (9). There has been an increase in new regulators of apoptosis that have deepened our understanding of the process (10). A number of studies have investigated the mechanisms that impede the TRAIL signaling cascade (11-13). Knowledge of the association between different pro-survival and cell death pathways in cancer is vital for devising therapeutic strategies for cancer. TRAIL belongs to a small subset of pro-apoptotic protein ligands in the TNF superfamily, which also includes TNF and cluster of differentiation (CD)95L (FasL/APO-1L) (14). TRAIL has been investigated since 1997, when it was observed that TRAIL-mediated apoptosis was responsible for death in cancer cells, leaving normal cells intact (15). This was followed by a number of studies documenting the molecular characteristics of TRAIL-mediated apoptosis in various cancer types, such as breast (16), thyroid (17), colorectal (18), renal (19), bladder, prostate (20) and ovarian cancer (21). Parallel studies revealed that in cancer cells, TRAIL was underexpressed, leading to loss of TRAIL-induced apoptosis (22-24). TRAIL-induced apoptosis is triggered through the activation of death receptors (DRs), specifically DR4 and DR5 (25). This interaction in turn facilitates the attachment of the apoptosis antigen 1 (Fas)-associated death domain containing protein (FADD) (26). FADD attachment results in the recruitment of adapter proteins to the cytoplasmic domain of DR (26). Recruitment of adapter proteins facilitates the activation of pro-caspases 8 and 10, which then trigger the activation of caspase 3 (27). Activation of caspase 3 in turn leads to activation of either the extrinsic pathway (caspase 8-mediated) or the intrinsic pathway, which involves the release of cytochrome *c* (28). Cytochrome *c*-mediated activation of procaspase 9 to caspase 9 promotes activation of the intrinsic pathway, which involves the translocation of the BH3 interacting-domain death agonist to the mitochondria (29). This facilitates recruitment of Bax/Bak, which aid in the transportation of cytochrome *c* and second mitochondria-derived activator of caspases/Diablo homolog through the formation of the mitochondrial pore (30,31).

Long non-coding RNAs (lncRNAs) are RNA molecules in the range of 200-2,000 bp (32). lncRNAs have been found to play a crucial role in the development of various cancer types, including breast (33), thyroid (34), renal (35), colorectal (36), prostate (37) and ovarian cancer (38), and have been reported to interact with various molecules during transcription, chromosome remodeling, cellular trafficking and translation (39). In addition, lncRNAs serve regulatory roles during transcription, mRNA processing, maturation of mRNAs, modification of histone complexes and DNA methyltransferase modifications that occur during epigenetic regulation (Fig. 1) (40). Mutations in the signaling cascades responsible for growth arrest and apoptosis are predominant in most breast cancers. lncRNA-mediated regulation of apoptosis machinery in breast cancer remains to be elucidated. Nevertheless, various studies have reported the regulatory role of lncRNAs in apoptosis and growth arrest (41,42). Exploring the role of lncRNA in the regulation of the apoptosis and growth arrest in breast cancer appears a promising approach, which may aid in the development of lncRNA-based therapeutics, as well as being a biomarker for disease diagnosis.

2. Role of lncRNA in breast cancer

Bioinformatics studies and RNA sequencing have been used to delineate the role of lncRNA in breast cancer (43). Genetic heterogeneity of the individual tumor is a crucial factor that triggers activation of certain lncRNAs (44).

X inactive specific transcript (XIST) is an oncogenic lncRNA that plays a significant role in the progression of breast cancer. XIST RNA directs transcriptional changes by binding to poly comb repressive complex 2 (PRC2). Deregulated XIST promotes tumor progression (45). XIST activation has been reported to accelerate tumor growth of breast cancer gene 1-deficient ovarian cell lines (46). Accumulation of XIST promotes the expression of X-linked oncogenes, including the V-RAF murine sarcoma 3611 oncogene homolog 1 and member of ETS oncogene family, which triggers the growth of tumor cells (47). Several factors are prerequisite for triggering XIST. A recent study has reported that scaffold attachment factor A, also known as heterogenous ribonucleoprotein U, aids lncRNA attachment to the X chromosome. This promotes activation of SMART/histone deacetylase (HDAC)1-associated repressor protein, which recruits HDAC C3 and PRC2 components to formulate histone repressive complex (48). In addition, high-throughput sequencing has revealed that several XIST interactors serve a role in the activation of XIST. In a recent study, lower expression of XIST was reported in triple-negative breast cancer (TNBC). The restored expression of XIST reduces the epithelial-mesenchymal transition (EMT) property of cancer cells and cell proliferation, and induces apoptosis (49). XIST in TNBC functions by inhibiting microRNA (miR)-454 (49). XIST expression is also reported to be downregulated in estrogen receptor-negative (ER^-) and progesterone receptor-negative (PR^-) breast cancer (50). However, XIST is highly expressed in human epidermal growth factor receptor 2 (HER2)-positive breast cancer (51).

HOX antisense intergenic RNA (*HOTAIR*) is another lncRNA that has been reported to facilitate cancer progression (52). Despite its location at chromosome 12, *HOTAIR* has been reported to activate distant genes. Functional studies have shed light on the important role of *HOTAIR* in metastasis and invasion. Hepatocyte nuclear factor 4-α (HNF4-α), an initiator of epithelial differentiation, represses the transcription of *HOTAIR* (53). HNF4-α promotes the release of the chromatin loop on the *HOTAIR* regulatory element and a decrease in the expression levels of homeobox D cluster-targeted genes (54). PRC2 and lysine-specific demethylase 1 (LSD1) are the

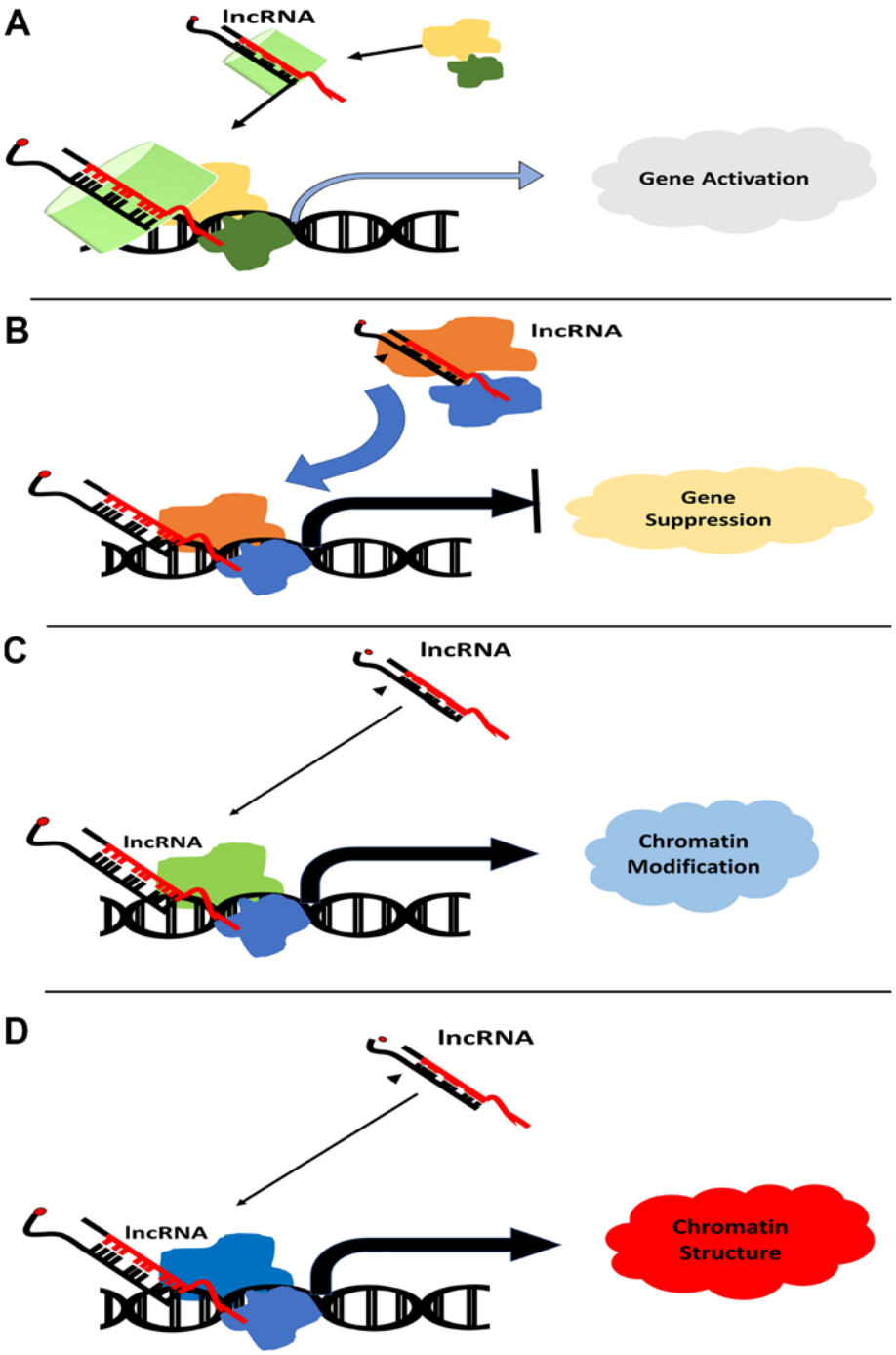

Figure 1. lncRNA-based modulation of gene expression via epigenetic modification. lncRNA can induce (A) gene activation or (B) suppression by inducing histone demethylation and histone methylation, respectively. Histone modification further allows recruitment of transcription factors or transcription repressor to the promoter region according to the fate of the gene. (C) and (D) lncRNAs also induce chromatin modification for silencing or promoting expression of gene. lncRNA, long non-coding RNA.

two regulators of chromatin dynamics that interact with *HOTAIR* (55). *HOTAIR* interacts with either LSD1 or PRC2 via various mechanisms; its interaction with PRC2 is through its 5' end, which enhances repression of PRC2 target loci (56). By contrast, *HOTAIR* interacts with LSD1 through its 3' end to regulate gene silencing (57). *HOTAIR* is highly overexpressed in various cancer types, such as hepatocellular carcinoma (58), lung (59) and breast cancer (60) and has been reported to serve a decisive role in tumor proliferation, invasion and metastasis (61). Thus, *HOTAIR* could be considered as a plasma based biomarker for breast cancer and various tumors. Furthermore, the consistent overexpression of *HOTAIR* is observed in ER^+/PR^+ breast cancer (62). Overexpression of *HOTAIR* increases invasiveness in metastatic breast cancer (63). This has led to the conclusion that *HOTAIR* is a valid biomarker for breast cancer (64).

NEAT1 is an oncogenic lncRNA that promotes proliferation and metastasis in breast cancer (65). *NEAT1* lncRNA is highly expressed in breast cancer tissues, and its expression correlates with tumor size and metastatic potential. *NEAT1*

interacts with the *FOXN3*, *SIN3* and *SIN3A* repressor complex. This has been brought to light by RNA immunoprecipitation and high-throughput sequencing. Together, this trio forms a nucleoprotein complex that facilitates EMT, invasion and metastasis in ER^+ cells via inhibition of GATA binding protein 3 (GATA3), a transcription factor (66). In addition, overexpression of *NEAT1* and FOXN3 decreases overall survival rate in breast cancer patients (66). Elevated *NEAT1* expression has also been reported in TNBC, and its inhibition via short hairpin (sh)*NEAT1* in TNBC cells leads to sensitization to chemotherapy and reduced cancer stemness (67). *NEAT1* overexpression is directly associated with enhanced tumor growth, proliferation and metastasis (68,69). Tests, including MTT and wound healing assays, on BC MDA-MB-468 and MCF-7 cell lines revealed that the suppression of *NEAT1* expression via small interfering (si)RNA, not only reduces cell proliferation and inhibits metastasis, but also prompts apoptosis via the activation of caspase 3 (65). The expression of *NEAT1* is modulated by miR-548ar. Overexpression of miR-548ar significantly reduced *NEAT1* expression levels in MCF-7 and MDA-MB-231 human breast cell lines and also facilitated the induction of cellular apoptosis (70). The role *NEAT1* plays in breast cancer proliferation, invasiveness and chemo-resistance makes it a potential diagnostic biomarker and a therapeutic target for this cancer (69).

BCAR4 is another lncRNA that has been demonstrated to confer tamoxifen resistance independently of ER1 expression (71). Ectopic expression of *BCAR4* in MCF7 and ZR-75-1 cell lines was able to increase proliferation in estrogen-free media (72). Furthermore, *BCAR4* overexpression was shown to promote growth and metastasis in primary breast tumor cells. In xenograft models, *BCAR4* is a potent proliferative agent; its expression is tissue-specific, thus making it a suitable target for treating anti-estrogen resistance in breast cancer (72). *BCAR4* promotes the expression of *GLI-2* via activation of the non-canonical hedgehog-Gli pathway (73). This activation, in turn, promotes metastasis, migration and invasiveness. *BCAR4* also promotes the activation of phosphatase 1 (PP1) via Smad nuclear interacting protein 1 (SNIP1), thus inhibiting p300-mediated histone acetylation (74). PP1 interaction with SNIP1 also promotes the dephosphorylation of pol II ser5, which promotes activation of *GLI2* target genes (75).

DSCAM-AS1 is another oncogenic lncRNA whose expression is regulated by ER (76). *DSCAM-AS1* has been reported as a downstream effector of ER and its upregulation has been observed in ER^+ and ER^- breast tumors (76). Strong estrogen induction in MCF7 and T47D cells can promote overexpression of DSCAM-AS1 (77). Knockdown of *DSCAM-AS1* results in growth arrest and decreased migration and invasiveness, suggesting that *DSCAM-AS1* functions downstream of ER (76). These findings shed light on the use of *DSCAM-AS1* as a potential biomarker for the detection of breast cancer.

Few studies have been performed to indicate breast cancer subtype-specific expression of lncRNAs (78); however, the underlying mechanism for the tumorigenicity in breast cancer remains to be elucidated.

lncRNA in metastatic breast cancer. The contribution of lncRNAs to the growth, proliferation and survival of different types of cancer has been studied (36,46,79-83) Several studies have emphasized the potential of lncRNAs in promoting metastasis in breast cancer cell lines and tissues (84,85). Dysregulation of lncRNA inhibiting proliferation and metastasis (*NLIPMT*) has been reported to enhance growth and metastasis in breast cancer tissue. Restoration of *NLIPMT* expression in the breast cancer MDA-MB-231 cell line inhibits cellular proliferation by suppressing glycogen synthase kinase 3β phosphorylation (86). Some lncRNAs are overexpressed in breast cancer cells, which facilitates tumor growth, spread and survival by targeting the transcription of proteins. Such lncRNAs are associated with cell growth suppression and apoptosis (87). High expression of lncRNA *FOXD3-AS1* in cancer tissues has a direct correlation with tumor size increase and distant metastasis (88). A high level of lncRNA *AWPPH* in patients' plasma is associated with enhanced cell growth in early stage TNBC (89). Overexpression of lncRNA *AWPPH* causes resistance to carboplatin treatment (89).

Dysregulation of some lncRNAs is also associated with the potential of breast tumor cells to metastasize to different organ sites (90). The majority of studies have reported an lncRNA role in the metastasis of breast cancer to the lungs (91,92). *LINC00478*-associated cytoplasmic RNA (lacRNA) is a cleaved version of lncRNA *LINC00478*. *LINC00478* is significantly downregulated in metastatic breast tumors and promotes active transcription of *MYC* proto-oncogene (*MYC*)-activated genes (93). lncRNA overexpression suppresses the metastatic and invasive potential of breast cancer cells by stabilizing prohibitin-2 (PHB2) protein. PHB2 then brings about transcriptional inhibition of *MYC* target genes (93). Furthermore, its overexpression inhibits lung metastasis in mouse models (93). lncRNA *HOXA11-AS* is also reported to be associated with breast cancer metastasis to the lungs; it modulates EMT by downregulating E-cadherin and vimentin expression. In mouse models treated with sh*HOXA11-AS*, the expression of *HOXA11-AS* is decreased in both primary and secondary tumors (94). lncRNA *ANCR* is downregulated in breast tumor cells and induces metastasis via active signal transduction through the TGF-β pathway (95). Upon introduction of *ANCR*-deficient MDA-MB-231-*ANCR* cells into BABL/c nude mice, these cells metastasize to the lungs (95).

The role of lncRNAs in promoting metastasis in breast cancer subtypes with different molecular signatures, such as luminal A, luminal B, HER2-type, normal-like and triple-negative, has yet to be properly studied. This indicates the need for further studies in the area to better understand the role of lncRNAs in breast cancer according to the different subtypes. This may be helpful in designing more effective therapeutics for this disease.

3. Interplay of lncRNA and TRAIL in breast cancer

lncRNAs have a dual role in cellular homeostasis. Depending on their interactive molecular landscape they can either favor survival of the cancer cells or apoptosis (84). TRAIL-mediated apoptosis is one such pathway and the alteration in the expression of its members shifts the balance of the cell in favor of survival (96,97). Recent advances in biomolecular studies have hinted towards the association of the interplay of TRAIL and lncRNA with breast cancer development (77). The activity of caspases is a chief factor that is modulated by most lncRNAs in

Table I. lncRNAs whose expression modulates caspase activity.

Author, year	lncRNA	Affected caspase	lncRNA role	(Refs.)
Yang *et al*, 2019	*POU3F3*	Caspase 9	Enhances proteolytic activation	(99)
Zhang *et al*, 2019	*NEAT1*	Caspase 3	Inhibits activity	(65)
Gooding *et al*, 2017	*BORG*	Caspase 3, 7, 8	Inhibits activity	(107)
Wang *et al*, 2018	*Z38*	Caspase 3, 9	Inhibits activity	(110)
Li *et al*, 2017	*TUG1*	Caspase 3, 9	Inhibits activity	(98)
Ma *et al*, 2019	*AFAP1-AS1*	Caspase 3	Inhibits activity	(113)

lncRNAs, long non-coding RNAs.

breast cancer to ensure the rapid multiplication and growth of cancerous cells (98). Table I contains a list of lncRNAs whose dysregulation in breast cancer disrupts the TRAIL-induced apoptosis pathway by modulating the activity of caspases. The modulatory role of lncRNA in the extrinsic pathway is illustrated in Fig. 2.

lncRNA-mediated regulation of the extrinsic apoptotic pathway in breast cancer. POU3F3 lncRNA modulates the TRAIL pathway by modulating caspase activation (99). Data have suggested a positive correlation between tumor proliferation in TNBC and *POU3F3* (99). *POU3F3* inhibits the proteolytic cleavage-mediated activation of caspase 9 (99). High *POU3F3* expression in tumor tissues and in the blood plasma of patients suggests its use as a diagnostic marker for TNBC (99).

In addition, *in vitro* knockdown of POU3F3 leads to enhanced cleavage of caspase 9, restoring the intrinsic apoptotic pathway, triggering growth arrest, and inhibiting tumor migration and invasiveness (100). A previous study showed that exogenous induction of procaspase 9 cleavage brings about attenuation in the oncogenic effects of overexpressed *POU3F3* and leads to cell apoptosis (99). These findings suggest that *POU3F3* as a potential therapeutic target for TNBC.

The extrinsic and intrinsic apoptotic pathways are both regulated by the various lncRNAs (101). Death receptor triggers the activation of caspases. Several lncRNAs serve pivotal roles in the regulation of caspase activity (101). *HOXAS1/2* is involved in inhibition of caspase 8 and 3 (102). *NEAT1* inhibits the activity of caspase 3 (65) and *TUG* promotes the activity of caspase 8. Signals from caspases are transferred to mitochondria and lead to apoptosis. lncRNAs such as *GAS5/AFAP1-AS* and *MAG12-AS3* promote the upregulation of *BCL-2* and *FAS* genes and facilitate apoptosis (103-105). lncRNA *PANDA* (p21-associated ncRNA DNA damage activated) downregulates the expression of proapoptotic proteins such as the Fas cell surface death receptor (FAS)/BCL-2 interacting killer (BIK) and apoptotic protease activating factor (APAF)1, thus inhibiting apoptosis and promoting cell growth in breast cancer cells (106).

BORG (BMP/OP Responsive Gene) is another highly expressed oncogenic lncRNA in breast cancer that affects caspases activity in order stop the apoptotic pathway of cells and promote aggressive tumor proliferation (107). High expression of *BORG* has been reported in TNBC and is also associated with chemoresistance and high cancer cell growth (108). The activity of caspase 3, 7 and 8 significantly reduces the expression of *BORG* in *BORG*-expressing cell lines (107).

Suppression subtractive hybridization in combination with reverse dot-blotting suggests the correlation between high expression of lncRNA *Z38* and tumorigenesis in breast cancer cells. Suppression of *Z38* expression via shRNA causes inhibition of *in vivo* tumorigenesis and a reduction in cell viability. In addition, the TUNEL assay performed after administration of *Z38* siRNA reveals induction of apoptosis in cancerous cells (109). This study indicated that the administration of *Z38* siRNA mechanistically activates the intrinsic apoptotic pathway. Knockdown of *Z38* negatively influences cell proliferative rate together with the induction of apoptosis in gastric cancer in a similar way in breast cancer (109). *Z38* acts through the activation of caspase 3 and 9 to initiate the apoptotic pathway (110). High expression of *Z38* and its oncogenic influence makes it prognostically significant in cases of breast cancer (111).

AFAP1-AS1 is also among the lncRNAs whose aberrant expression in breast cancer leads to the inactivity of various caspases. *AFAP-AS1* is mapped on chromosome 4 in humans and its transcription occurs in an anti-sense direction from the *AFAP1* gene (112). Reverse transcription-quantitative PCR (RT-qPCR) confirms that *AFAP1-AS1* overexpression is observed in breast cancer tissues and MCF-7, SK-BR3, MDA-MB-231 and MDA-MB-436 breast cancer cell lines. Caspase 3 activity assay, cell cycle analysis, and Bax and Bcl-2 expression analyses demonstrate that the rate of apoptosis is increased in *AFAP1-AS1* siRNA-transfected cell lines due to the restored activity of caspase 3 and increased Bcl-2 expression (113).

The malignant role of lncRNA *TUG1* is controversial. However, recent data has reported the association of *TUG1* high expression with malignancy and increased invasiveness in breast cancer (98). *TUG1* overexpression is observed in malignant breast cancer cell lines such as MDA-MB-231, MDA-MB-436, MCF7 and T47D. *TUG1* overexpression is reported at the highest levels in the breast cancer highly invasive MDA-MB-231 and MDA-MB-436 cell lines (98). *TUG1* promotes cell proliferation by inhibiting caspase 3 and caspase 9 activities. The knockdown of *TUG1* results in augmented activity of both caspases, which leads to a reduction in metastasis and increased apoptosis (98). Conversely, *TUG1*

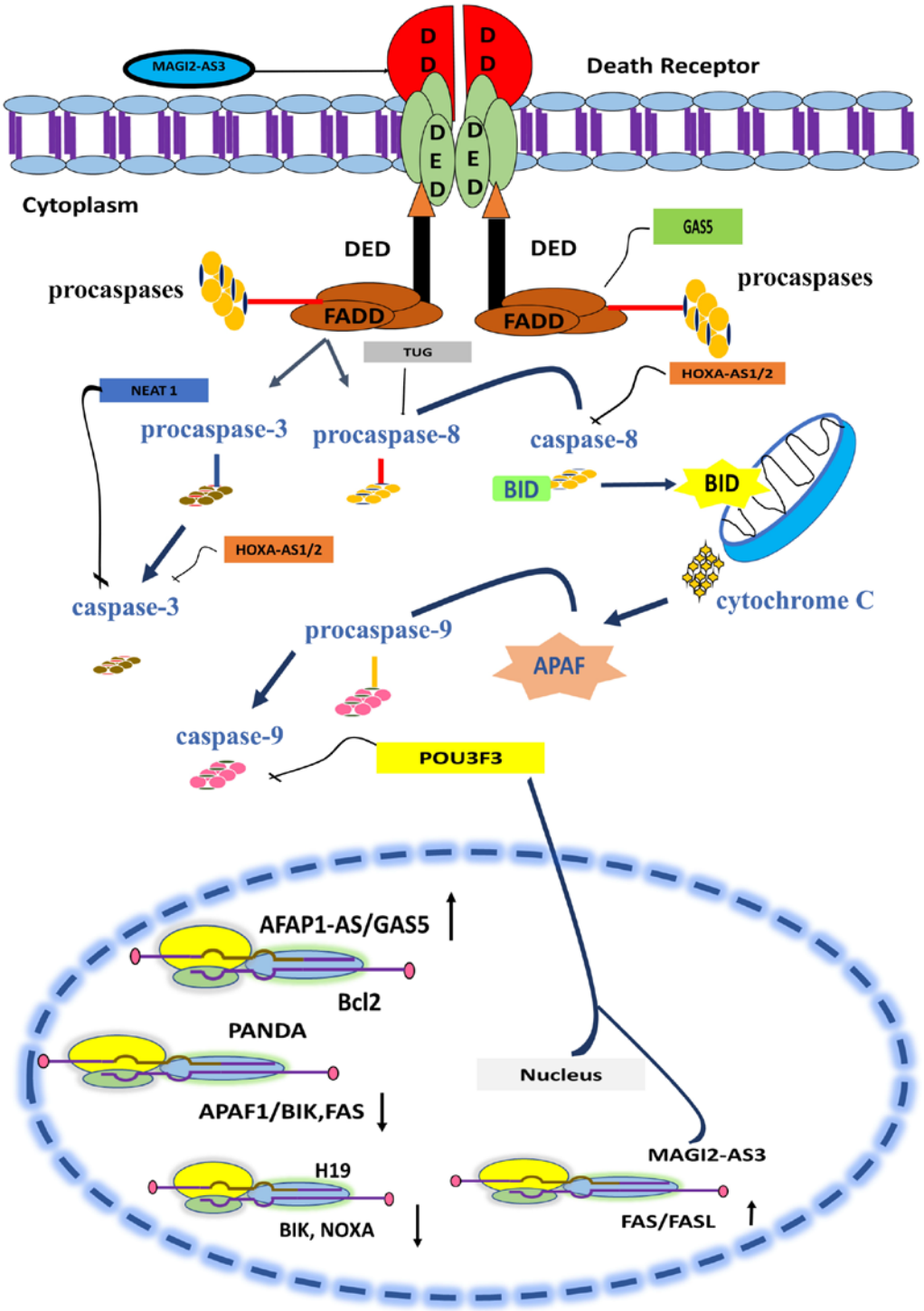

Figure 2. Schematic description of TRAIL signaling cascade and interaction of lncRNA. lncRNAs modulate the apoptotic pathway at different levels. A few lncRNAs promote apoptosis; for instance, MAGI2-AS3 enhances Fas ligand expression and APAF1-AS/GAS5 upregulates Bcl-2 expression. A few lncRNAs halt apoptosis and promote cell survival and growth; PANDA downregulates pro-apoptotic BIK protein, APAF-1 and Fas expression, and H19 downregulates BIK expression. NEAT-1 and HOXA-AS1/2 inhibit caspase 3 activity, while POU3F3 causes inhibition of caspase 9. HOXA-AS1/2 and TUG suppress activation of caspase 8. TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; lncRNA, long non-coding RNA; BIK, Bcl2 interacting killer; APAF, apoptotic protease-activating factor-1; Fas, apoptosis antigen 1.

expression induced in MDA-MB-231 and MCF7 by transfecting them with pCDNA-*TUG* suggests that the overexpression of *TUG1* has tumor-suppressive effect on cancer cells where it modulates cell growth by suppressing the expression of cyclin D1 and CDK4, and promotes cell apoptosis and retards cancer cell growth (114). The tumor-suppressive role of *TUG1* is also demonstrated in TNBC. A recent study has reported that lower expression of *TUG1* induces chemo-therapy resistance and promotes cell proliferation, but whether its high expression activates TRAIL-induced apoptosis is not demonstrated (115).

Cancer cells manage to grow and survive after hijacking TRAIL-mediated apoptosis (116). Tumor cells use Fas

Table II. TRAIL-specific lncRNAs involved in breast cancer and their targets.

Author, year	lncRNA	Expression	Target	Mechanism	(Refs.)
Si *et al*, 2016	*H19*	High	BIK	Blocking promoter region	(121)
Hung *et al*, 2011, Zhang *et al*, 2014	*PANDA*	High	APAF1, BIK, FAS	Interact with NF-YA	(127,128)
He *et al*, 2015	*GAS-5*	Low	BIK	Expression activation via epigenetic modification	(133)
Zhang *et al*, 2019	*CASC-2*	Low	Smad-2	Direct inhibition	(137)
Si *et al*, 2016	*HOXA-AS2*	High	TGFBR2	Expression facilitation via directly inhibiting miR-520c-3p	(121)

BIK, Bcl2 interacting killer; APAF, apoptotic protease-activating factor-1; CASC-2, cancer susceptibility 2; FAS, apoptosis antigen 1; GAS, growth arrest-specific 5; HOXA-AS2, HOXA cluster antisense 2 RNA; NF-YA, nuclear transcription factor Y; PANDA, p21-associated ncRNA DNA damage activated; TGFBR2, tumor growth factor β receptor 2.

receptor as a reserve route to initiate activation of caspase 8 via proteolytic cleavage and hence induce apoptosis (117,118). In breast cancer, the expression levels of Fas and FasL are also downregulated, eliminating all apoptotic threats for cancerous cells and making their proliferation possible (119). In breast cancer tissue, the expression of Fas and FasL is reported to be positively correlated with the expression of lncRNA *MAGI2-AS3* (105). Using transcript transfection and lentiviral approaches, Yang *et al* (120) reported that *MAGI2-AS3* expression facilitates the upregulation of Fas and FasL expression in MDA-MB-231 and MCF-7 cell lines. CCK-8 assay and flow cytometry further demonstrated that the lentivirus-induced expression of *MAGI2-AS3* reduces cell viability and promotes cell death via activation of the Fas/FasL-induced apoptotic pathway (120).

lncRNA-mediated regulation of the intrinsic apoptotic pathway in breast cancer. A few identified lncRNAs negatively modulate the TRAIL-induced apoptotic pathway by affecting the transcription of pro-apoptotic proteins whose expression is triggered by TRAIL signaling (Table II). Among them; overexpression of *H19* is reported in ERα$^+$ breast cancer cells, where it halts apoptotic signaling of the cell by suppressing transcription of *BIK* and *NOXA* genes (121). Due to its aberrant levels in ERα$^+$ breast cancer tissues and patients' plasma, it has the potential to be used as a diagnostic marker for this breast cancer type (122-124). lncRNA *H19*, with the help of epigenetic modification, brings about the silencing of the *BIK* gene; it blocks the promoter region of *BIK* by facilitating the recruitment of EZH2, which then induces trimethylation of histone H3 at lysine 27 (121). A recent development has revealed that the expression of lncRNA H19 is modulated by lncRNA *PTCSC3* in TNBC (77). The high H19 level in TNBC tumor tissues is inversely correlated with *PTCSC3* expression. Wang *et al* (121,122) transfected the BT-549 and HCC70 cell lines with *PTCSC3* vectors and reported that overexpression of *PTCSC3* attenuates the expression of lncRNA *H19* and consequently suppresses cancer cell proliferation. Considering the role of lncRNA *H19* in the rapid proliferation and chemo-resistance of breast cancer (125), treatment with *PTCSC3* could be a potential strategy to counter the oncogenic effects of *H19* in breast cancer.

lncRNA *PANDA* is also highly expressed in breast cancer (126). The expression of *PANDA* in primary breast cancer cells is induced in response to DNA damage to suppress apoptosis; its expression is reported in cells that do not contain p53 mutations, but *PANDA* elevated expression has no effect on p53 expression. Instead, it exerts its oncogenic influence in breast cancer cells by hindering the expression of pro-apoptotic proteins, including apoptotic protease-activating factor 1 (APAF1), BIK and FAS (126). Mechanistically, it first interacts with nuclear transcription factor NF-YA, restraining the expression of pro-apoptotic activators. Suppression of *PANDA* expression promotes apoptosis by upregulating the expression of *APAF-1*, *FAS* and *BIK* gene (127,128).

It has been demonstrated that the expression of lncRNA *GAS5* induces apoptosis in breast cancer cells (129). Low *GAS5* expression in breast cancer is associated with tumor progression and suppression of the apoptotic pathway (130). It has been found through use of lncRNA RT-PCR arrays that *GAS5* expression in breast cancer is modulated by the high expression of miR-21. The exon 4 of *GAS5* possesses a binding site for miR-21, and abolition of that site markedly reduces miR-21 affinity for *GAS5* and also attenuates suppression of apoptosis in MDA-MB-231 cells (131). In breast cancer, miR-21 negatively regulates expression of the pro-apoptotic protein Bcl-2 (132). It is reported that the ectopic expression of *GAS5* downregulates miR-21, which negatively affects the growth of tumor cells and enhances cellular death (131). More data on the tumor-suppressive capability of *GAS5* have been provided by Pickard and Williams (129). The study reported that *GAS5* contains *HREM* sequences through which it interacts with the DNA-binding domain of the glucocorticoid receptor, halting cellular growth and promoting apoptosis. The study further demonstrated that *HREM* oligonucleotides alone also have the capability to induce apoptosis in the absence of endogenous *GAS5* expression in resistant breast cancer cells. Unfortunately, the mechanism that is triggered for inducing apoptosis upon employment of *HREM* sequences is not known.

GAS5 also gives rise to the small RNA *pi-sno75*, which has direct correlation with enhanced TRAIL expression in breast cancer cells; it utilizes the tool of epigenetic modification to enhance the expression of TRAIL ligand. Mechanistically, *pi-sno75* binds with PIWIL1/4 protein. The pair then interact with WD repeat domain 5, which brings about recruitment of human complex of proteins associated with Set 1-like complexes comprising *MLL3* and *UTX* at the promoter region of TRAIL, which causes H3K4 methylation and H3K27 demethylation, hence facilitating activation of TRAIL transcription (133). This finding emphasizes the therapeutic significance of *GAS5* and *pi-sno75*, the exogenous administration of which could promote apoptosis and reduce cellular viability by initiating the TRAIL-induced apoptotic pathway in breast cancer cells.

A few more involvements of lncRNA in breast cancer have been demonstrated to modulate the TRAIL-mediated apoptotic pathway by regulating downstream factors of the TGF-β signaling pathway. It has been well established by various studies that TGF-β induces TRAIL expression, which is necessary for preventing cancerous cell growth (28,134) By contrast, the tumor-suppressive role of TGF-β reverses in advanced types of cancer, including in breast cancer, where it promotes cancer advancement and metastasis by downregulating the expression of TRAIL (135). Long intergenic non-protein coding RNA regulator of reprograming (linc-ROR) lncRNA plays a crucial role in the upregulation of TGF-β expression in advanced stages of cancer (136); it is highly expressed in tumor tissue and also in the highly invasive breast cancer MCF-7 and MDA-MB-231 cell lines. Knockdown of linc-ROR through siRNA in MCF-7 and MDA-MB-231 cells showed that linc-ROR silencing negatively regulates TGF-β and the expression of its downstream factors, which consequently attenuates aggressive tumor growth (136). Unlike lncRNA linc-ROR, the expression of lncRNA *CASC2* is downregulated, which facilitates TGF-β pathway activation in advanced breast cancer (137). Induced expression of *CASC2* in MCF-7 and LCC-9 cell lines via transfection with pcDNA-CASC2 results in *CASC2* overexpression in these cell lines. Furthermore, *CASC2* inhibits cell metastasis and promotes cell death by targeting smad-2 (a downstream factor of the TGF-β pathway) and triggering TRAIL apoptosis (137).

TGF-β needs to halt the apoptotic pathway in order to ensure tumor proliferation and metastasis (138). Through the application of northern blotting and qPCR, it has been determined in several mouse breast cancer cell lines, that to prompt suppression of the apoptotic pathway, TGF-β induces the expression of a ~3-kb long transcript of lncRNA *Smad7* (139). The results from TUNEL staining and RT-qPCR have established that lncRNA *Smad7* functions as a downstream anti-apoptotic factor of TGF-β signaling, the overexpression of which halts apoptosis by inhibiting Bim expression and upregulating anti-apoptotic protein differentiated embryonic chondrocyte-expressed gene 1 expression in invasive breast cancer cell lines (139,140).

In TNBC, the elevated expression of lncRNA *ANRIL* has also been reported (141). *ANRIL* uses the TGF-β signaling pathway for tumor exponential growth and suppression of the apoptotic pathway (142). CCK-8 assays in MDA-MB-231 and MDA-MB-468 cell lines have revealed that knocking down *ANRIL* enhances the rate of apoptosis and reduces cellular proliferation (141). RNA immunoprecipitation and luciferase reporter assays have further demonstrated that *ANRIL* exerts its oncogenic influence in TNBC cell lines by sponging tumor-suppressive miR-199a, which is reported to downregulate the expression of TGF-β in TNBC (141,143-146). These findings indicate the prognostic significance of *ANRIL*, whose knockdown in xenografted mice not only attenuates tumor proliferation, but also promotes cell apoptosis (94,141).

Elevated lncRNA *HOXA-AS2* expression in tissues and cell lines of breast cancer has direct regulatory control over TGF-β signaling via upregulation of the expression of transforming growth factor β receptor 2 (TGFBR2), which causes tumor proliferation and invasiveness (145). *HOXA-AS2* promotes TGFBR2 expression by negatively modulating expression of miR-520c-3p (146). The silencing of *HOXA-AS2* causes an elevation in miR-520c-3p levels, which in turn induces suppression of TGFBR2 expression (146) The silencing of *HOXA-AS2* in model mice by subcutaneously administrating siRNA-*HOXA-AS2*-transfected MCF-7 cells leads to a reciprocal increase in miR-520c-3p expression, which by targeting TGFBR2 induces tumor growth inhibition (146). Although this finding emphasizes that *HOXA-AS2* could be implemented as a therapeutic target for breast cancer, how miR-520c-3p inhibits TGF-β signaling and activates TRAIL-mediated apoptosis currently needs to be explored.

4. Conclusion

Breast cancer is a highly complex disease involving a number of types and genetics. Thus, an efficient and precise therapeutic regimen for breast cancer patients can only be achieved by rapid and comprehensive prognosis and diagnosis. lncRNAs have crucial implementations in different cancer types; they have established themselves as important regulators of transcription, as well as activators of various signaling cascades. These non-coding RNA molecules are tissue-specific and have the potential to serve as biomarkers for breast cancer. However, few studies have elucidated the involvement of these micromanagers in regulating apoptosis and even fewer have addressed their interplay with TRAIL-mediated apoptosis. Technological advances in bioinformatics, sequencing and mass spectrometry have, to some extent, delineated the role of lncRNA in tumor biology. Identifying lncRNA as non-invasive biomarkers that can be robustly detected in liquid biopsies could revolutionize the way breast cancer is detected. Unearthing the many functions of ncRNAs in cancer development delves into the genomic complexity of cancer and further highlights the extensive interplay between various genetic elements in the cells.

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Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

ZJ, KK and BS wrote the manuscript. MI, QR, TA, BS and SR revised the review. HS, JR and WC conceptualized the study and revised it critically. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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