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

1. Introduction
2. Role of lncRNA in breast cancer
3. Interplay of lncRNA and TRAIL in breast cancer
4. Conclusion

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 heterogeneous 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
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 IncRNA that promotes proliferation and metastasis in breast cancer (65). NEAT1 IncRNA 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 to be induced 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 MITT 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 cheimo-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 (lincRNA) 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 shHOXA11-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 lncRNAs with breast cancer development (77). The activity of caspases is a chief factor that is modulated by most lncRNAs in
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.

Table I. lncRNAs whose expression modulates caspase activity.

| Author, year | IncRNA | Affected caspase | IncRNA 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) |

IncRNAs, long non-coding RNAs.

Caspase 3 Inhibits activity (113)
Caspase 3, 9 Inhibits activity (99)
Caspase 3, 7, 8 Inhibits activity (107)
Caspase 3 Inhibits activity (65)
Caspase 9 Enhances proteolytic activation (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 onco- genetic 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 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).

POU3F3 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).

The extrinsic and intrinsic apoptotic pathways are both regulated by various lncRNAs (101). Death receptor triggering the activation of caspases. Several lncRNAs serve pivotal roles in the regulation of caspase activity (101). Hoxasi/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 GASS/AFAP-AS1 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 (APAF1), 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).

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 onco- genetic influence makes it prognostically significant in cases of breast cancer (111).

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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
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.

### 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) |
| 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.
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 IncRNA 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 reprogramming (linc-ROR) IncRNA 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 IncRNA linc-ROR, the expression of IncRNA 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 IncRNA Smad7 (139). The results from TUNEL staining and RT-qPCR have established that IncRNA 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 IncRNA 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 IncRNA 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. IncRNAs 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 IncRNA in tumor biology. Identifying IncRNA 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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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.

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