IncRNA and breast cancer: Progress from identifying mechanisms to challenges and opportunities of clinical treatment

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Breast cancer is a malignant tumor that has a high mortality rate and mostly occurs in women. Although significant progress has been made in the implementation of personalized treatment strategies for molecular subtypes in breast cancer, the therapeutic response is often not satisfactory. Studies have reported that long non-coding RNAs (lncRNAs) are abnormally expressed in breast cancer and closely related to the occurrence and development of breast cancer. In addition, the high tissue and cell-type specificity makes lncRNAs particularly attractive as diagnostic biomarkers, prognostic factors, and specific therapeutic targets. Therefore, an in-depth understanding of the regulatory mechanisms of lncRNAs in breast cancer is essential for developing new treatment strategies. In this review, we systematically elucidate the general characteristics, potential mechanisms, and targeted therapy of lncRNAs and discuss the emerging functions of lncRNAs in breast cancer. Additionally, we also highlight the advantages and challenges of using lncRNAs as biomarkers for diagnosis or therapeutic targets for drug resistance in breast cancer and present future perspectives in clinical practice.

INTRODUCTION
Breast cancer (BC) is the first leading cause of cancer-related death worldwide and the most common malignancy in women. Although significant advances have been made in clinical management, the frequent occurrence of breast cancer has continued to increase mortality. Currently, based on the size, morphology, metastasis, and expression of estrogen receptor (ER), progesterone receptor (PR), Ki67, and human epidermal growth factor receptor-2 (HER2) of the tumor, the main therapeutic strategies of breast cancer are surgery, radiotherapy, endocrine therapy, and chemotherapy. The emergence of combination therapies of traditional therapy with targeted therapy, such as mammalian target of rapamycin (mTOR) inhibitors and cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors, combined with endocrine therapy, respectively, has greatly delayed tumor progression and prolonged patient survival. However, the effect of clinical treatment is far from satisfactory. Therefore, there is still an urgent need to explore the mechanisms that regulate the progression of breast cancer to develop new therapeutic targets.

Long non-coding RNAs (lncRNAs) are originally thought to be the noise of transcripts in the genome and have no biological function. Recently, the function of lncRNAs is beginning to attract widespread attention. Increasing studies have shown that lncRNAs are involved in various aspects of cellular physiological processes, such as proliferation, differentiation, migration, and apoptosis, by regulating gene transcription and post-transcriptional processing. In addition, lncRNAs are closely related to the occurrence, development, and prognosis of various cancers, such as breast, liver, colon, and lung cancer and even leukemia. According to lncRNA genomic position, subcellular localization, and function, they can be divided into six types (Figure 1). (1) Enhancer lncRNAs are derived from the promoter enhancer region, such as lncRNA-LEENE. (2) Intron lncRNAs are transcribed from the intron region of the gene. The gene-coding protein completely contained the intron lncRNA, which can stabilize the transcription or regulate the alternative splicing of the coding gene. (3) Antisense lncRNA: its transcription orientation is opposite to the transcription orientation of the adjacent protein-encoding gene, such as IncTALAM1 and PDCD4-AS1. (4) The sense IncRNA: its transcription orientation is the same as that of the adjacent protein-encoding gene, such as IncRNAAS5 and ecCEPBA. (5) Intergenic IncRNA, which can be transcribed between two protein-coding genes, is an autonomously transcribed
et al. have identified that LINC00908 encodes a differentially expressed polypeptide when the nascent RNA reanneals into the template DNA. Some antisense lncRNAs regulate sense mRNA transcription by forming R loops (Figure 2C). The local formation of the R loop can tether antisense lncRNAs to the nuclear genome, thereby inhibiting the metastasis-promoting signaling network caused by S100P. LncRNA PANDA is involved in the DNA-damage response. The combination of PANDA and nuclear transcription factor Y subunit A (NF-YA) may prevent NF-YA to transcriptionally activate apoptotic gene expression. Similar mechanisms have also been observed in lncRNA APTR and XIST (X-inactive-specific transcript). APTR inhibits the CDKN1A/p21 promoter to promote cell proliferation, whereas lncRNA XIST suppresses the transcriptional activity of SHARP by activating HDAC3.

The R loop is defined as a new type of DNA–RNA hybrid (a triple-stranded nucleic acid structure in which RNA hybridizes to triplex DNA) that is abundant on CpG islands, which can form an R loop when the nascent RNA reanneals into the template DNA. Some antisense lncRNAs regulate sense mRNA transcription by forming R loops (Figure 2C). The local formation of the R loop can tether lncRNA in cis and recruit transcription cofactors to the corresponding promoter region. Postepska-Igielska et al. discovered a regulatory lncRNA Khsps1 that activates the expression of the proto-oncogene sphingosine kinase 1 (SPHK1) through directly

**IncRNAs are involved in transcriptional regulation**

IncRNAs function as suppressors of transcription factors in the nucleus to keep it away from chromatin, thereby inhibiting gene transcription, such as lncRNA NORAD and PANDA (Figure 2B). NORAD binds and chelates S100P by using its multiple repeat sequences as a multivalent platform, thereby inhibiting the metastasis-promoting signaling network caused by S100P. In breast cancer cell lines, lncRNA PANDA is involved in the RNA damage response. The combination of PANDA and nuclear transcription factor Y subunit A (NF-YA) may prevent NF-YA to transcriptionally activate apoptotic gene expression. Similar mechanisms have also been observed in lncRNA APTR and XIST (X-inactive-specific transcript). APTR inhibits the CDKN1A/p21 promoter to promote cell proliferation, whereas lncRNA XIST suppresses the transcriptional activity of SHARP by activating HDAC3.

THE CELLULAR FUNCTIONS OF IncRNAs

IncRNAs are widespread in human organisms and are essential for the regulation of human gene expression, physiological and pathological processes. The function of IncRNAs is very complicated and has not been fully elucidated so far. According to the current research, there are five main ways that IncRNAs in cell physiological regulation, as shown in Figure 2. (1) IncRNAs encode polypeptides; (2) IncRNAs are involved in transcriptional regulation; (3) IncRNAs are involved in post-transcriptional regulation; (4) IncRNAs participate in epigenetic regulation; (5) IncRNAs function as a signal transducer.

IncRNA encodes a polypeptide

Although IncRNAs are non-protein transcripts by definition, recent studies have shown that part of the putative small open reading frame in IncRNAs is translated into a polypeptide (Figure 2A). Wang et al. have identified that LINC00908 encodes a differentially expressed polypeptide in triple-negative breast cancer (TNBC). They named this endogenously expressed polypeptide ASRPS. ASRPS directly binds to the signal transducer and activator of transcription 3 (STAT3) through a coiled-coil domain (CCD) and downregulates STAT3 phosphorylation level, which leads to a decrease in the expression of vascular endothelial growth factor (VEGF), thereby inhibiting tumor angiogenesis in breast cancer. The translation of micropeptide CIP2A-BP encoded by LINC00665 is affected by transforming growth factor (TGF)-β in breast cancer cell lines. CIP2A-BP directly binds to the oncogene CIP2A to replace the B56γ subunit of PP2A, thereby releasing PP2A activity to inhibit the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/nuclear factor κB (NF-κB) pathway, resulting in a decrease in the expression levels of MMP2, MMP9, and Snail. Another IncRNA EPR that responds to TGF-β induction also encodes a polypeptide to control cell proliferation. EPR affects both its transcription and mRNA decay-promoting factor through its interacts with SMAD3 and mRNA decay-promoting factor KHSRP, respectively, to regulate Cdkn1a gene expression. The downregulation of EPR caused by TGF-β reshapes the transcriptome and promotes cells to acquire epithelial characteristics to inhibit cell proliferation. These evidences suggest that IncRNA is another non-negligible factor besides the genome in the study of cancer treatment, whereas IncRNAs that encode a polypeptide may become a potential target for cancer treatment.

IncRNAs are divided into six types: (1) enhancer IncRNAs; (2) intron IncRNA; (3) antisense IncRNA; (4) sense IncRNA; (5) intergenic IncRNA; (6) bidirectional IncRNA.
interacting with the promoter. Tethering Khps1 to the high purine segment of the SPHK1 transcription start site (TSS) upstream results in the formation of an R loop, which anchors histone acetyltransferase p300/CRNC-binding protein (CBP) to the SPHK1 promoter. This recruitment increases local chromatin accessibility to establish a transcriptionally permissive chromatin structure and enhances E2F1-dependent transcriptional activation, thereby limiting apoptosis.\(^3^3\)

Arab et al.\(^3^4\) find that lncRNA TCF21 antisense RNA induces promoter demethylation (TARID) can form an R loop on the TCF21 promoter. The binding of GADD45A to the R loop triggers local DNA demethylation and TCF21 expression.\(^3^4\)

lncRNAs are involved in post-transcriptional regulation

At the post-transcriptional level, lncRNAs regulates mRNA splicing, mRNA stability, protein translation, and protein stability to control biological processes.  

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**Figure 2. The functions of lncRNAs**

(A) lncRNAs are translated into polypeptides to regulate gene expression, such as LINC00908 and LINC00665. (B) lncRNA NORAD binds to transcription factors in the nucleus to keep it away from chromatin to-inhibiting gene transcription, whereas lncRNA HOTAIR combines with transcription factors to promote gene transcription. (C) lncRNAs combine with the corresponding promoter region to form an R loop to increase transcription activity and DNA methylation, such as lncRNA Khps1 and TARID. (D) lncRNAs interfere with mRNA splicing and form different splicing forms, such as lncRNA LASTR, MALAT1, and SRSP. (E) lncRNA as a molecular decoy (NORAD) recruits proteins (1/2-sbsRNAs) or binds miRNA (lnc00899) to regulate mRNA stability. (F) lncRNAs interact with translation-related proteins to participate in the translation process of mRNA, such as lncRNA-p21, ROR, and AFAP1-AS1. (G) lncRNA NDRG1-OT1 and ANCR recruit different proteins to affect protein stability. (H) lncRNA BLAT1, BCLIN25, and H19 are involved in the DNA methylation process. In addition, lncRNA HOTAIR is closely related to histone modification. (I) Extracellular vesicle-packaged HIF-1α-stabilizing lncRNA from TAMs regulates aerobic glycolysis of breast cancer cells.
**IncRNA can interfere with mRNA splicing and form different splicing forms**

Massive high-throughput sequencing technology has identified thousands of IncRNAs, as well as a large number of different mRNA processing events that occur in higher organisms. IncRNAs directly encode polypeptide or regulate gene transcription. Recently, IncRNAs have been shown to play a crucial role in regulating the splicing efficiency (Figure 2D). For example, the RNA splicing factor SART3 is a lncRNA LASTR-interacting partner. LASTR improves splicing efficiency by controlling the combination of SART3 with U4 and U6 small nuclear ribonucleic proteins (snRNPs). LASTR depletion leads to increased association between SART3 and U4 snRNP, which reduces splicing efficiency. Similarly, IncRNA MALAT1 interacts with the serine/arginine (SR) splicing factor to regulate the distribution of SR to nuclear speckles, further changing the alternative splicing pattern of a set of pre-mRNA. Unlike IncRNA LASTR and MALAT1, IncRNA LOC90024, also known as SRSP, encodes a small 130-amino acid short peptide that interacts with splicing regulators, such as an SR-rich splicing factor 3 (SRSF3), to regulate mRNA splicing.

**IncRNAs can regulate mRNA stability**

IncRNAs can act as a molecular decoy involved in mRNA degradation (Figure 2D). In addition to affecting the mRNA splicing, IncRNA also participates in the process of mRNA degradation. IncRNA NORAD acts as a reservoir for PUMILO 1 and PUMILO 2 (also known as PUM1/2), which are proteins carrying a cognate sequence to limit their availability for target mRNA degradation. PUM1/2 binds to the 3'-UTR sequence of the PUMILO response element (PRE) at the 3'-UTR of the target mRNA and stimulates the adenylation and decapsulation of the mRNA, resulting in accelerated mRNA turnover and decreased translation. Knockout of the NORAD gene shows increased chromosomal instability. This possibly is attributable to the hyperactive PUM1/2 extensively downregulating the expression of PUMILO, which targets mRNA-encoding genome-stable proteins. Additionally, IncRNAs also recruit protein to stabilize mRNA (Figure 2E). IncRNAs containing Alu can trans-activate Staufen 1 (STAU1)-mediated mRNA decay (SMD). The SMD-targeted mRNA contains Alu elements in the 3'-UTR, which can base pair with the complementary Alu in IncRNA to form double-stranded RNA (dsRNA) recognized by STAU1 to inhibit SMD. These IncRNAs are named "half-STAU1-binding site RNAs (1/2-sbsRNAs)." Similarly, IncRNA PDCD4-AS1 forms RNA duplexes to stabilize the PDCD4 mRNA and controls the interaction between PDCD4 mRNA and RNA decay-promoting factors such as HuR. Furthermore, IncRNAs can compete with their shared DNA binding motif in the nucleus or act as suppressors to block microRNA (miRNA) binding sites to control the function of miRNAs. miRNAs induce the degradation of mRNA by complementary pairing with target mRNA, whereas IncRNAs act as an miRNA sponge to stabilize mRNA. For example, Inc00899 acts as a tumor suppressor by competitively binding to miRNA (miR)-425. miR-425 binds to the 3'-UTR of the DICER1 transcript and induces DICER1 mRNA degradation after transcription to promote breast tumor growth.

**IncRNAs modulate translation**

mRNA transport is closely related to protein translation and involved in many cell functions such as drug resistance in breast cancer. Studies have shown that IncRNA AFAP1-AS1 is more highly expressed in trastuzumab-resistant cells. Exogenous AFAP1-AS1 can induce trastuzumab resistance by binding to adenine and uracil-rich element binding factor 1 (AUF1) to promote ERBB2 translation without affecting mRNA levels. Although IncRNAs are not translated, ribosome profiling assays have identified several IncRNAs related to ribosome components (Figure 2F). For example, the interaction of IncRNA-p21 with HuR facilitates the recruitment of let-7/Ago2 to destroy the stability of lncRNA-p21. On the contrary, the decrease of HuR expression blocks the recruitment of let-7/Ago2 and thus promotes the accumulation of lncRNA-p21, and then lncRNA-p21 binds with JUNB and CTNNB1 mRNA through base pairing and then recruits the translation-repressor Rck129 to inhibit JUNB and CTNNB1 translation. lncRNA NORAD retinoid acid receptor related orphan receptor (ROR) inhibits the translation of p53 through direct interaction with hnRN P, which promotes the processing of precursor mRNA and transports the mRNA from the nucleus to the cytoplasm. Similarly, the interaction between intergenic non-coding RNA between ITGB1 and NRNP1 (LincIN) and NF90 regulates the expression of p21 at the translation level. However, the mechanism which linc IN mediates breast cancer metastasis through the NF90-p21 pathway is not clear. Besides, IncRNAs also can interfere with the translation initiation in eukaryotic cells. For example, the combination of IncRNA RP1 and the complex p-4E-BP1/elf4E can prevent the interaction of elf4E and elf4G and then reduce the translation efficiency of p27kip1 mRNA.

**IncRNAs regulate protein stability**

IncRNAs can recruit some proteins to affect their stability (Figure 2G). IncRNAs affect protein stability mainly by regulating protein ubiquitination degradation. Such as, studies in several breast cancer cell lines show that IncRNA NDRG1-OT1 is significantly upregulated and promotes the degradation of NDRG1 through ubiquitin-mediated proteolysis under hypoxic conditions. IncRNA ANCR can increase the phosphorylation level of EZH2 at Thr-345 and Thr-487 by potentiating the interaction of CDK1-EZH2, thereby promoting the ubiquitination and degradation of EZH2 to attenuate the invasion and metastasis ability of breast cancer. Similarly, lncRNA-p21 binds to hypoxia inducible factor-1α (HIF-1α) and Von Hippel–Lindau (VHL) and destroys the interaction between VHL and HIF-1α, thereby attenuating VHL-mediated HIF-1α ubiquitination and causing HIF-1α accumulation to promote glycolysis and tumor growth under hypoxia conditions.

**IncRNAs participate in epigenetic regulation**

Epigenetic regulation does not alter the DNA sequence to cause heritable changes in gene expression, including DNA methylation, histone modification, genome imprinting, and random chromosome inactivation.
Some important functions of IncRNAs are related to the epigenetic control of specific target genes (Figure 2H). For example, IncRNAs baseline breast cancer associated transcript 1 (BLAT1), BCLIN25, and H91 can regulate DNA methylation to participate in tumorigenesis. Han et al. find that BLAT1 expression is regulated at the epigenetic level by decreasing DNA methylation of CpG islands in the promoter. Patients with BLAT1-hypermethylated tumors have lower overall survival (OS). The increased BLAT1 expression with hypomethylation at CpG sites may contribute to the aggressive phenotype of breast cancer. BCLIN25 increases ERBB2 expression by enhancing CpG methylation of the miR-125b promoter, leading to downregulation of miR-125b and promoting the occurrence of breast cancer. Also, the IncRNA 91H of the H19/IGF2 locus is transcribed in the H19 antisense orientation. In breast cancer, 91H IncRNA prevents DNA methylation of the maternal allele at the H19/IGF2 locus, thereby increasing the aggressive phenotype of breast cancer cells. In addition, IncRNA also inhibits gene transcription by recruiting histone modification or chromatin remodeling proteins.

IncRNA HOX transcript antisense RNA (HOTAIR) plays a critical role in chromatin dynamics through the interaction with histone modifiers resulting in transcriptional gene silencing. HOTAIR is participated in the silencing of miR-205 by breaking the balance of histone modification between histone H3 at lysine 4 methylation (H3K4me3) and H3K27me3 on the miR-205 promoter to regulate cyclin J (CCNJ) expression.

**IncRNAs mediate intercellular signal communication**

Extracellular vesicles (EVs) have been considered as important mediators in intercellular communication, allowing for the exchange of horizontal information between tumor cells as well as the crosstalk between tumor and stromal cells. Increasing studies have shown that IncRNAs encapsulated in EVs can shuttle from inflammatory cells and reprogram tumor metabolism. In addition, EVs released from the primary tumor can circulate to distant organs, thereby forming a premetastatic niche (Figure 2I). For example, Dong et al. find that tumor-associated macrophage (TAM)-derived EVs containing HIF-1α-stabilizing IncRNA HISLA regulate the aerobic glycolysis of breast cancer cells. Lactate released from glycolytic tumor cells upregulates HISLA in macrophages, forming a feedforward loop between TAMs and tumor cells to enhance apoptosis resistance. Breast cancer cells also uptake exosomes containing IncRNA SNHG3 released from cancer-associated fibroblasts (CAF). IncRNA SNHG3 acts as a molecular sponge of miR-330-5p to control pyruvate kinase to reprogram the metabolic pathways of breast cancer cells. In addition, the release of HOAIR-containing exosomes from breast cancer cells is positively correlated with the status of receptor tyrosine kinase (RTK) ErbB2 (also known as HER2/Neu) in tumor tissues. The causal relationship between ErbB2 and HOAIR has been verified in isogenic breast cancer cell lines with and without ectopic ErbB2 expression.

**THE ROLE OF IncRNA IN BREAST CANCER MALIGNANT PROGRESS**

IncRNAs are involved in the regulation of normal mammalian gene expression or other biological processes and have significant effects on human diseases, such as neuropsychiatric diseases, atherosclerosis, and various cancers. Apparently, increasing evidences prove that abnormal expression of IncRNA regulates cell proliferation, invasion, migration, apoptosis, epithelial-mesenchymal transition (EMT), stemness, and drug resistance in various cancers especially in breast cancer. The following is a summary of the current understanding in the functional mechanisms of how IncRNAs control breast cancer progression. The function of IncRNAs in breast cancer was shown in Figure 3 and Table 1.

**IncRNAs modulate cancer cell proliferation**

Cell proliferation is critical to the progression of cancer and is usually mediated by the abnormal activation of intracellular growth signaling pathways. Emerging studies have shown that IncRNAs regulate cell proliferation by activating or inhibiting specific signaling pathways in breast cancer.

It has been reported that a variety of IncRNAs positively regulates the proliferation of breast cancer cells, such as IncRNA SPRY4 intron transcript 1 (SPRY4-IT1), DANC1, PVT1, CCAT1, and KCNQ1OT1 (Figure 3A). However, the mechanisms by which these IncRNAs promote the proliferation of breast cancer cells are different. For example, the expression level of SPRY4-IT1, a 708-bp IncRNA on chromosome 5, is positively related to the larger tumor size and advanced pathological stages in breast cancer patients. SPRY4-IT1 participates in tumor cell growth by regulating the expression of zinc finger 703 (ZNF703), which has been identified as a genetic driver of 8p12 amplification in luminal B breast tumors. However, the precise molecular mechanism of how SPRY4-IT1 controls ZNF703 expression needs further study. At present, it is clear that DANC1 and PVT1 activate the specific signal pathways by combining with “mediators.” DANC1 activates PIK3CA by binding to RXRA and enhancing its serine phosphorylation by glycogen synthase kinase-3β (GSK-3β), which subsequently enhances PI3K/AKT signaling to promote tumorigenesis. PVT1 binds to Kruppel-like factor 5 (KLF5) and increases its stability through BAP1, which upregulates the β-catenin signaling pathway, leading to enhanced TNBC tumorigenesis and growth. Besides, miRNA can also become a potential target of IncRNA and participate in cancer cell proliferation. For example, IncRNA CCAT1 is highly expressed in TNBC tissues and promotes the TNBC process. Bioinformatics analysis reveals that CCAT1 downregulates the expression of miR-218. Further study shows that ZFX is a putative downstream target of miR-218, and the overexpression of ZFX reversed the tumor-suppressive effect of miR-218 on the proliferation of TNBC cells. Another IncRNA, KCNQ1OT1, acts as a competitive sponge to regulate the miR-145/CCNE2 pathway, thereby promoting tumor growth in vivo.

On the contrary, several IncRNAs play a tumor-suppressor effect in breast cancer cell proliferation (Figure 3A). Ai et al. discovered that LINC01355 interacts with FOXO3 protein and stabilizes FOXO3, which leads to CCND1 transcriptional inhibition. However, overexpression of CCND1 or reduction of FOXO3 protein reverses LINC01355-mediated breast cancer growth inhibition.

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IncRNA SONE is a potential tumor-suppressor gene in TNBC cells. Downregulation of IncRNA SONE leads to a significant decrease in tumor protein p53 (TP53) levels and an increase in c-Myc expression, which alter the expression of downstream tumor-suppressor miR-34a, miR-15a, miR-16, and let-7a to promote breast cancer cell proliferation. A recent study has found that IncRNA MAGI2-AS3 is low expressed in breast cancer tissue and acts as a cis-acting regulatory element that downregulates the DNA methylation level in the promoter region of MAGI2. Overexpression of MAGI2-AS3 or MAGI2 in MCF-7 cells blocks the Wnt/β-catenin pathway and inhibits cell proliferation and migration. Moreover, the RNA-RNA interaction can also regulate breast cancer cell proliferation. IncRNA PTSC3 is downregulated in tumor tissues of TNBC patients. In contrast, IncRNA H19, an imprinted IncRNA only transcribed from the maternal genome, is upregulated and negatively correlated with PTSC3 in tumor tissue and plays an important role in breast cancer cell proliferation. Overexpression of PTSC3 leads to downregulation of the H19 level in TNBC cells, whereas upregulation of H19 has no effect on the expression of PTSC3. This result indicates that IncRNA PTSC3 inhibits the proliferation of TNBC cells by downregulating IncRNA H19.

**Figure 3. IncRNAs modulate the proliferation, metastasis, and apoptosis of breast cancer cells**

(A) IncRNA regulates cell proliferation by activating or inhibiting specific signaling pathways in breast cancer. (B) IncRNAs can regulate the expression of mesenchymal markers vimentin, fibronectin, N-cadherin, Twist1, ZEB1, and epithelial cell junction proteins E-cadherin, claudins, and α-catenin to affect tumor cell metastasis. IncRNA also regulates the stemness of CSCs to obtain metastatic ability. (C) IncRNA mainly affects tumor cell apoptosis through p53 and caspase signal transduction pathways. MALAT1 and PICART1 participate in the process of cell apoptosis by regulating the activity of p53, and APOC1P1-3 and LINC00628 promote cell apoptosis through the expression of caspase-3, Bax, and Bcl-2.
Table 1. Summarization of the cellular functions of IncRNAs in breast cancer (BC)

| IncRNA          | Expression in BC | Functions                                      | Pathway/target/mechanism                                                                 | Reference |
|-----------------|------------------|------------------------------------------------|-----------------------------------------------------------------------------------------|-----------|
| SPRY4-IT1       | upregulation     | proliferation, chemotherapy resistance, stemness | upregulating ZNF703 expression; competitively bind to microRNA (miR)-6882-3p with TCF7L2 | 70        |
| HOTAIR          | upregulation     | proliferation, survival, migration, invasion, chemotherapy resistance | regulating the p53/protein kinase B (AKT)/c-Jun N-terminal kinase (INK)/MMP signaling pathway; upregulating ERα expression to enhance ER signaling | 71,72     |
| TMPO-AS1        | upregulation     | proliferation, survival, migration, tamoxifen resistance | upregulating the expression of ESR1; regulated the ER signaling pathway | 72        |
| MALAT1          | upregulation     | oncogenic and tumor-suppressive roles           | targeting miR-485-3p to downregulate P-gp and Bcl-2 and upregulate Bax | 72        |
| DSCAM-AS1       | upregulation     | proliferation, migration, chemotherapy resistance | upregulating ribonucleotide reductase M2 (RRM2) and epidermal growth factor receptor pathway substrate 8 (EPS8) | 72        |
| BCAR4           | upregulation     | migration, invasion                            | regulating histone acetylation                                                        | 72        |
| BORG            | upregulation     | chemotherapy resistance, proliferation         | activating the NF-κB signaling pathway                                                | 72        |
| HCP5            | upregulation     | chemotherapy resistance                       | inhibiting PTEN expression                                                            | 74,75     |
| CASCAL 2        | upregulation     | chemotherapy resistance                       | activating and regulate cyclin-dependent kinase 19 (CDK19)                            | 75        |
| DANCR           | upregulation     | proliferation, migration, invasion            | regulating the expression of SOX2                                                    | 75        |
| LINC00922       | upregulation     | proliferation, survival, migration, invasion   | activating the Wnt signaling pathway; reduced the NDK2 expression                      | 76        |
| ST8SIA6-AS1     | upregulation     | proliferation, migration, invasion            | interacting with RNA-binding proteins                                                 | 77        |
| LINC00511       | upregulation     | proliferation, migration                       | regulating the expression of miR-150 and MMP13                                       | 77        |
| H19             | upregulation     | proliferation, migration, invasion            | regulating the miR-152/DNM1T1 axis                                                    | 71        |
| ROR             | upregulation     | promoting migration                            | regulating miR-145/ARF6 axis                                                          | 75        |
| LINC00461       | upregulation     | migration, invasion                            | upregulating expression of vimentin, E-cadherin, and zinc finger E-box binding homeobox 1 (ZEB1); regulated the miR-30a-5p/integrin β3 axis | 71        |
| NEAT 1          | upregulation     | proliferation, migration, invasion            | upregulating ZEB1 expression                                                         | 77        |
| Inc-SLC4A1-1    | upregulation     | migration, invasion                            | activating NF-κB signaling pathway to upregulate CXCL8 expression                     | 80        |
| RP1             | upregulation     | distant metastasis                             | regulating the Kruppel-like factor 5 (KLF5)/RP1/p27kip1 signaling pathway; interacting with complex p-4E-BP1/eIF4E | 79        |
| TINCR           | upregulation     | EMT, promoting proliferation, chemotherapy resistance | targeting miR-125b                                                                                 | 64        |
| LINP1           | upregulation     | chemotherapy resistance                       | decreasing ERα expression level                                                     | 77        |
| linc00518       | upregulation     | tumorigenesis and stemness                     | miR-185-3p/E2F1/Nanog axis                                                          | 81        |
| CRALA           | upregulation     | chemotherapy resistance                       | proliferation                                                                        | 82        |
| TMPO-AS1        | upregulation     | proliferation, survival, migration, and invasion | upregulating ESR1 mRNA stability                                              | 85        |
| CYTOR           | upregulation     | promoting the tamoxifen resistance and cell proliferation | inhibiting miR-125a-5p to increase the expression of SRF                        | 84        |
| MIR2052HG       | upregulation     | resistance to anastrozole                     | increasing the expression of LMTK3 to upregulate ERα expression                  | 85        |
| CCA1            | upregulation     | promoting proliferation and migration, stemness | regulating miR-218/ZFX axis; WNT/β-catenin                                            | 86        |
| TROJAN          | upregulation     | promoting proliferation                        | induced ZMYND8 degradation                                                          | 88        |
| LINC00339       | upregulation     | promoting proliferation and inhibited apoptosis | regulating miR-377-3p/HOXC6 axis                                                   | 88        |
| MIR100HG        | upregulation     | promoting proliferation and induced cell arrest in the G1 phase | negatively regulated p27 gene expression; targeting the miR-5590-3p/OTX1 axis | 89        |

(Continued on next page)
| IncRNA     | Expression in BC  | Functions                                      | Pathway/target/mechanism                                                                 | Reference |
|-----------|-------------------|------------------------------------------------|----------------------------------------------------------------------------------------|-----------|
| NRAD1     | upregulation      | promoting proliferation                         | positively regulated by ALDH1A3                                                        | 90        |
| DANCR     | upregulation      | promoting proliferation                         | by EZH2-dependent suppression of SOCS3 transcription                                    | 91        |
| NAMPT-AS  | upregulation      | promoting metastatic progression               | recruiting POU2F2 to activate NAMPT-regulated miR-348b-3p/NAMPT axis                    | 92        |
| lnc-ZNF469-3 | upregulation   | promoting migration                            | regulating miR-574-5p/ZEB1 axis                                                        | 93        |
| HULC      | upregulation      | promoting migration                             | upregulating MMP2 and MMP9; regulating LYPD1 expression by sponging miR-6754-5p         | 94        |
| SONE      | upregulation      | inhibiting proliferation and migration          | positively regulated TP53 and negatively regulated c-Myc                              | 95        |
| ARNILA    | upregulation      | invasion and metastasis                         | binding to miR-204                                                                      | 96        |
| Inc015192 | upregulation      | migration, invasion, and EMT                    | Inc015192-regulated Adam12 expression by functioning as a competing endogenous RNA (ceRNA) for miR-34a | 97        |
| EPIC1     | upregulation      | promoting proliferation                         | as an oncogenic lncRNA that interacts with MYC                                          | 98        |
| GACAT3    | upregulation      | promoting proliferation                         | regulating miR-497/CCND2 signaling                                                      | 99        |
| ITGB2-AS1 | upregulation      | migration and invasion                          | regulating NNT-AS1/miR-142-3p/ZEB1 axis                                                | 100       |
| NNT-AS1   | upregulation      | migration and invasion                          | by the regulation of ITGB1 levels                                                     | 101       |
| F10247    | upregulation      | metastasis                                      | modulating Wnt/β-catenin pathway                                                       | 102       |
| EZR-AS1   | upregulation      | tumor growth and metastasis                     | regulating miR-4766-5p/SIRT1 axis                                                      | 103       |
| PVT1      | upregulation      | proliferation and metastasis                    | serving as a competing endogenous RNA for miR-204-5p                                   | 104       |
| ATB       | upregulation      | promoting EMT                                   | upregulating the miR-200c/Twist1 axis                                                 | 105       |
| NEAT1     | upregulation      | metastasis                                      | inhibiting miR-146b-5p expression                                                      | 106       |
| AC026904.1| upregulation      | metastasis                                      | upregulating Slug expression at both transcriptional and post-transcriptional levels  | 107       |
| MEG3      | upregulation      | suppressed cell proliferation, migration and invasion, induces apoptosis | by miR-4513/PBLD axis                                                                | 108       |
| XIST      | upregulation      | brain metastasis and cell growth, chemoresistance | by sponging miR-200c-3p                                                               | 109       |
| PDCD4-AS1 | upregulation      | promoting cell proliferation                    | PDCD4-AS1 stabilizes PDCD4 RNA by forming RNA duplex and controls the interaction between PDCD4 RNA and RNA decay | 110       |
| UCA1      | downregulation    | tamoxifen resistance, proliferation             | activating Wnt/β-catenin; regulated PI3K/AKT signaling pathways                          | 111       |
| GAS5      | downregulation    | tumor-suppressive, downregulating tamoxifen resistance | upregulating the expression of miR-21                                                 | 112       |
| PTENP1    | downregulation    | chemotherapy resistance, proliferation          | upregulating PTEN expression                                                           | 113       |
| ILA       | downregulation    | metastasis                                      | inhibiting the breast EMT process                                                     | 114       |
| Inc00968  | downregulation    | ADR, Taxol, and vincristine resistance           | Wnt2/β-catenin/MRP1/BCRP/P-gp signaling                                               | 115       |
| LINC00472 | downregulation    | suppressing the phosphorylation of NF-κB        | possibly regulating several relapse or metastasis-related pathways, such as PI3K/AKT and Wnt signaling pathways | 116       |
| PTC5C3    | downregulation    | inhibiting proliferation                        | downregulating IncRNA H19                                                             | 117       |
| NEF       | downregulation    | inhibiting migration                            | negatively regulated miR-155                                                          | 118       |
| TUG1      | downregulation    | apoptosis, proliferation, and metastasis        | promoting cell cycle progression and regulating the expression of cyclin D1 and CDK4  | 119       |
| ANCR      | downregulation    | invasion and metastasis                         | ANCR interaction with EZH2 to promote its phosphorylation that facilitates EZH2 degradation. | 120       |
| MAGI2-AS3 | downregulation    | inhibiting cell proliferation and migration     | downregulating DNA methylation of MAGI2                                               | 121       |
| NKILA     | downregulation    | suppressing EMT                                 | NKILA-mediated negative feedback affects TGF-β-induced NF-κB activation               | 122       |
suppressor genes or oncogenes. Studies have shown that IncRNA can interfere with miRNAs to regulate tumor cell metastasis and invasion.\textsuperscript{129} For example, IncRNA NEAT1 can promote the migration and invasion of breast cancer cells. NEAT1 acts as a competing endogenous (ce)RNA sponge to regulate ZEB1 in breast cancer.\textsuperscript{130} miR-218 is reported to be another direct target of NEAT1. NEAT1 promotes breast cancer cell invasion by negatively regulating the expression of miR-218.\textsuperscript{131} Studies also find that the downregulation of NEAT1 inhibits the EMT program of breast cancer cells through the miR-211/high-mobility group AT-hook 2 (HMGA2) axis. In addition, there is a mutual inhibitory effect between NEAT1 and miR-211.\textsuperscript{132} IncRNA TUSC8 competes with miR-190b-5p to function as a ceRNA of myosin regulatory light chain interacting protein (MYLIP) and inhibits the expression of EMT-related markers, such as vimentin and ZEB1 to suppress breast cancer metastasis.\textsuperscript{133} Recent studies report that overexpression of IncRNA ROR induces EMT and promotes the migration and invasion of breast cancer cells. ROR acts as ceRNA to inhibit the activity of miR-205 to prevent degradation of miR-205 target genes ZEB1, vimentin, and N-cadherin, leading to lung metastasis of breast cancer, whereas knocking down the expression of ROR weakens breast cancer lung metastasis \textit{in vivo}.\textsuperscript{134} In addition, Fan et al.\textsuperscript{135} find that ROR can also prevent the recruitment of chromatin regulators G9a methyltransferase and abolish the histone H3K9 modification of the tescal-cin (TESC; also known as calcineurin B homologous protein 3 [CHP3]) promoter, leading to abnormal breast cancer metastasis.\textsuperscript{135} High expression of IncRNA ATB is associated with increased lymph node metastasis and advanced clinical stage, as well as shorter disease-free survival (DFS) and OS. In the TGF-\textbeta-induced EMT model, the expression of IncRNA ATB in breast cancer cells is upregulated and enhances tumor cell migration and invasion. Further research results show that IncRNA ATB acts as a sponge of the miR-200 family and restores Twist1 expression to promote breast cancer metastasis.\textsuperscript{136} In addition, ATB also binds to interleukin (IL)-11 mRNA, thereby increasing the stability of IL-11 and causing autocrine induction of IL-11 to activate STAT3 pathway to enhance breast cancer cell stemness and invasion.\textsuperscript{136}

In addition, IncRNA can also directly bind to proteins and promote tumor EMT to enhance invasion and migration capabilities. LINC01638 maintains the mesenchymal properties of TNBC cells. Knockdown of LINC01638 inhibits tumor proliferation and metastasis both \textit{in vivo} and \textit{in vitro}.\textsuperscript{137} Mechanistically, LINC01638 interacts with c-Myc to prevent SPOP-mediated c-Myc ubiquitination and degradation. The c-Myc transcriptionally activates metadherin (MTDH) expression to enhance the Twist1 level. Twist1 promotes TNBC invasion and metastasis by inducing cancer cell EMT.\textsuperscript{137} In breast cancer, HOTAIR as a scaffold carries two epigenetic protein complexes that promote cancer metastasis. The 5' domain of HOTAIR binds to polycomb inhibitory complex 2 (PRC2), whereas the 3' domain binds to the LSD1/CoREST/REST complex.\textsuperscript{138} Microarray analysis shows that the overexpression of HOTAIR-upregulated genes is related to stemness and EMT, such as STAT3, CD44, ZEB1, ALDH2, and vimentin.\textsuperscript{139} Breast cancer cells with high EMT ability are more likely to metastasize to distant organs including liver, brain, lung, and bones through blood, lymphatic vessels, and other channels. The metastasis of breast cancer causes the corresponding organ dysfunction and weakens the efficiency of chemotherapy to lead to higher mortality.\textsuperscript{135} Studies have shown that some small interfering RNAs (siRNAs) effectively inhibit breast cancer brain metastasis by depleting IncRNAs.\textsuperscript{140} IncRNA brain metastasis (BM)-increased JAK2 kinase activity promotes STAT3 phosphorylation to upregulate the expression of ICAM1 and CCL2, which mediated co-option of vascular and the recruitment of macrophages in the brain, respectively. The recruited macrophages produce oncostatin M and IL-6 to activate the Inc-BM/JAK2/STAT3 pathway and promote breast cancer brain metastasis, whereas depletion of Inc-BM with nanoparticle-encapsulated siRNAs effectively decreases JAK2 kinase activity to inhibit brain metastasis.\textsuperscript{140} Therefore, targeting IncRNAs to block breast cancer invasion and migration can provide new approaches for tumor therapy.

Cancer stem cells (CSCs) are a subpopulation of cancer cells, with self-renewal ability and limitless proliferation potential.\textsuperscript{141} CSCs are usually associated with EMT, which is crucial for cancer cell metastasis. Recent studies have shown that there is a direct link between EMT and the stemness of cancer cells.\textsuperscript{142} CSCs and EMT have many similarities in tumor recurrence, metastasis, and drug resistance.\textsuperscript{143} Both CSC stemness and EMT are regulated by various signal pathways such as Notch, Wnt/\textbeta-catenin, and TGF-\textbeta signaling pathway.\textsuperscript{144} In addition, the stemness genes in CSCs are regulated by EMT transcription factors such as TWIST, ZEB1, and SLUG. This implies that EMT may be the basis for stemness maintenance of CSC.\textsuperscript{145} IncRNAs have been identified and characterized as a new, important player in regulating the stemness acquisition and maintenance of CSCs.\textsuperscript{146} For example, Zhou et al.\textsuperscript{147} demonstrate that IncRNA-hedgehog (Hh) can directly target GAS1 to stimulate the activation of Hh signaling. The activated Hh can increase the expression of GLI1 and enhance the expression of CSC-related pluripotency genes, such as OCT4 and SOX2. IncRNA-Hh silencing in Twist-positive breast cancer cells attenuates activated Shh/GLI1 signaling and reduced CSC-related SOX2 and OCT4 levels, thereby reducing the mammosphere formation efficiency and tumorigenesis of transplanted tumors.\textsuperscript{142} In another example, a recent report finds that LINC00617 promotes breast cancer invasion and metastasis by increasing the percentage of a stem cell phenotype CD44(+)/CD24(-) subpopulation. LINC00617 upregulates the expression of SOX2 in breast cancer cells to act as an important regulator of EMT.\textsuperscript{147} The expression level of IncRNA XIST is negatively correlated with brain metastasis in breast cancer patients. The decreased expression of XIST stimulates EMT and activates c-Met through moesin (MSN)-mediated protein stabilization, thereby promoting the stemness of tumor cells. Knockout of XIST in mouse mammary glands accelerates the growth of primary tumors and brain metastasis.\textsuperscript{148} Together, these evidences indicate that IncRNA-Hh, LINC00617, and XIST play an important role in the regulation of CSCs and are closely related to the invasion and migration capabilities of breast cancer cells. They suggest that they could be used as
prognostic and diagnostic molecules in patients with breast cancer metastases.

**IncRNAs affect breast cancer cell apoptosis**

Apoptosis is a kind of autonomic physiological death of cells. The imbalance of pro-apoptotic and anti-apoptotic factors is related to the occurrence and development of many diseases, especially tumors. Increasing studies have confirmed that IncRNA can affect tumor cell apoptosis mainly through p53 and cysteine aspartate-specific proteases (caspases) signaling pathways (Figure 3C). p53 is a suppressor gene that can regulate the expression of various genes involved in apoptosis, growth arrest, and inhibition of cell cycle progression. The p53-induced tumor-suppressor IncRNA p53-inducible cancer-associated RNA transcript 1 (PICART1) inhibits breast cancer proliferation and promotes apoptosis through the AKT/GSK-3β/β-catenin signaling pathway. IncRNA MALAT1 is a widely expressed IncRNA, involving many aspects of cellular processes. Quantitative proteomics finds that MALAT1 interacts with DBC1 to regulate p53 acetylation to inhibit apoptosis. In addition, the induction of LINCO01125 by liver X receptor agonist LXR-623 activates phosphatase and tensin homolog (PTEN)/AKT/MDM2/p53 signaling pathway to mediate cell apoptosis. Caspas are a type of cysteine proteases that often trigger apoptosis in a cascade manner. Studies have found that IncRNAs are involved in the caspase-mediated apoptosis pathway. The low expression of LINCO0628 in breast cancer has a poor prognosis and a low OS rate. Overexpression of LINCO0628 inhibits the proliferation, invasion, and migration of breast cancer cells and arrests the cell cycle in the G0/G1 phase. LINCO0628 promotes cell apoptosis by regulating caspase-3, Bax, and Bcl-2 expression. IncRNA-APOCP1P3 is overexpressed in breast cancer, and hypomethylation in its promoter region is related to tumor size. In addition, APOCP1P3 can directly bind to tubulin to reduce the acetylation of α-tubulin, inactivate caspase-3, and thus inhibit cell apoptosis.

Inhibition of breast cancer cell apoptosis is also the reason for the unrestricted and excessive accumulation of tumor cells. Therefore, it is necessary to study the mechanism of cell apoptosis for cancer treatment. The intervention of IncRNA to control tumor cell apoptosis is expected to become an effective measure for the treatment of breast cancer.

**IncRNAs affect drug resistance in breast cancer cells**

Endocrine therapy, HER2-targeted therapy, chemotherapy, and immunotherapy are commonly used clinical treatment strategies for different breast cancers. However, drug resistance remains a clinical challenge in the treatment of breast cancer. The resistance mechanisms to different treatment strategies are similar, including increasing drug efflux, changing drug targets, activating bypass signaling pathways, inhibiting cell apoptosis, and maintaining cancer stemness. Besides, immunosuppression is also considered to be an important contributor in breast cancer immunotherapy resistance. A large number of studies have shown that abnormally expressed IncRNAs are related to the multidrug resistance of breast cancer.
breast cancer cells. Reduction of the ROR expression can attenuate the resistance of breast cancer cells to tamoxifen. ROR acts as a molecular sponge of miR-205 in breast cancer to increase the expression of ZEB1 and ZEB2, thereby promoting EMT and tamoxifen resistance. In another study, it is found that ROR can also promote estrogen dependence and tamoxifen resistance by activating the

Figure 4. lncRNA affects drug resistance in breast cancer cells
(A) lncRNAs participate in endocrine therapy resistance: lncRNA H19 increases endocrine therapy resistance by promoting autophagy and ERα expression. lncRNA TMPO-AS1 stabilizes the mRNA of ERα-encoding gene ESR1, leading to endocrine resistance. In addition, ROR promotes the degradation of ERK-specific phosphatase DUSP1, thereby enhancing ERK phosphorylation, activating ER signal transduction independent of estrogen, leading to intrinsic resistance to endocrine therapy. Furthermore, UCA1 confers tamoxifen resistance by regulating the EZH2/p21 axis. In contrast, GASS negatively regulates endocrine therapy resistance through PTEN/AKT/mTOR signaling. In addition, SNHG14 can inhibit trastuzumab-induced apoptosis by upregulating Bcl2. (B) lncRNAs participate in HER2-targeted therapy: lncRNA AFAP1-AS1 promotes the translation of HER2 by binding to AUF1 or is packaged into exosomes, acting on recipient cells to promote resistance to HER2-targeted therapy. AGAP2-AS1 increases H3K27 acetylation in the MyD88 promoter region and activates the NF-xB signaling pathway to resist HER2-targeted therapy. In addition, SNHG14 can inhibit trastuzumab-induced apoptosis by upregulating Bcl2. (C) lncRNAs in breast cancer chemoresistance: the activation of NF-xB mediated by lncRNA BORG can inhibit chemotherapy-induced DNA damage. lncRNA can affect the cell cycle by regulating the cyclin-related proteins in breast cancer to participate in chemotherapy resistance, for example, LINC00511, HIF1A-AS2, and AK124454. PTENP1 and LINC00968 regulate breast cancer chemotherapy resistance by activating PIK/AKT and WNT/catenin, respectively. (D) lncRNAs are involved in immunosuppression: LINK-A caused cAMP and PKA-mediated reduction of TRIM71 phosphorylation. The reduction of TRIM71 phosphorylation will enhance the degradation of PLC, leading to downregulation of antigenicity. lncRNA SNHG1 regulates the differentiation of Tregs by regulating the expression of IDO, thereby affecting the immune escape of breast cancer. lncRNA INCR1 regulates tumor interferon signaling. The main transcript of INCR1 binds to HNRNPH1 to block its inhibitory effect on neighboring genes PD-L1 and JAK2, thereby promoting the expression of PD-L1 and JAK2.

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Review
| lncRNA | Expression pattern | Pathway/target | Expression pattern drugs | Mechanisms | Reference |
|-------|-------------------|----------------|--------------------------|------------|-----------|
| H19   | upregulation      | ER, LIK and LOXA, H19-CUL4A-ABC1/MDR1 axis, H19/Let-7/LIN28 axis | tamoxifen, fulvestrant, paclitaxel, anthracycline, doxorubicin | activate the SAHH/DNMT3B axis to induce autophagy; promote ERα expression at the transcript and protein level; ceRNA: promoting the preservation of breast cancer stem cells | 136,137,138 |
| HOTAIR| upregulation      | ER             | tamoxifen, doxorubicin, trastuzumab | promote the expression of ERα and promote ERβ binding to chromatin; positively regulate the PI3K/AKT/mTOR signaling pathway | 159,160 |
| NEAT1 | upregulation      | ATP7A, ATP7B, cyclin E1, cyclin D1, caspase-3, miR-211/HMGGA2, miR-129/ZEB2 | cisplatin, paclitaxel, 5-FU | regulate cell apoptosis and cell cycle; promote cell growth | 161 |
| Inc712| upregulation      | Inc712/HSP90/Cdc37/CDK2 | palbociclib | reducing CDK2 activation and triggering cell proliferation | 162 |
| LINK-A| upregulation      | PIP3/GPCR/cAMP/PKA/TRIM71/PLC | immune checkpoint blockers | increased ESR1 transcription; reduced ER degradation by LMTK3; resistance to endocrine therapy | 163 |
| MIR2052HG| upregulation | EGR1, ER, ERz/PJ3/ACT | aromatase inhibitors | contributing to suppression of phosphatase and tensin homologs; ceRNA; contributes to cell proliferation | 164 |
| GAS5  | downregulation    | miR-222/PTEN, miR-378a-5p/SUFU, miR-21/mTOR/PTEN, miR-221-3p/DDK2/ Wnt/b-catenin | tamoxifen, paclitaxel, trastuzumab, Adriamycin | decreasing ERα expression level; regulate cell growth and apoptosis; EMT; diminishes the estrogen response | 165 |
| LINP1 | upregulation      | ER, caspase-8/9, caspase-9/Bax | doxorubicin, 5-FU, tamoxifen | regulating CDK2 activation and triggering cell proliferation | 166 |
| linc00518| upregulation     | miR-199a/MRP1 | Adriamycin, paclitaxel, vincristine | downregulate the expression of MRP1 | 167 |
| CRALA  | upregulation      | targeting CRALA | cisplatin, paclitaxel | promote cell growth | 168 |
| UCA1  | upregulation      | miR-18a/YAP1, miR-18a/HEF-1a, EZH2/p21, AKT/mTOR, Wnt/b-catenin signaling | trastuzumab, tamoxifen | promote cell apoptosis and arrest the cell cycle in G2/M phase | 169 |
| BC032585| downregulation   | MDR1            | paclitaxel, doxorubicin | regulate the expression of MDR1 | 170 |
| linc00968| downregulation  | Wnt2/b-catenin/MRP1/BCRP/P gp | Adriamycin, vincristine, Taxol, paclitaxel | inhibit Wnt2/b-catenin signaling pathway; reduce the ability of cell colony formation; and induce cell apoptosis | 171 |
| TINCR | upregulation      | miR-125b/ERBR2 | trastuzumab | regulating the expression level of HER2 | 172 |
| linc-ROR| upregulation     | DUSP7, MAPK/ERK, miR-194-3p/MECP2, miR-205-5p/ZEB1 | tamoxifen, mTOR inhibitor (rapamycin), paclitaxel, 5-FU | promoting estrogen-independent cell growth; EMT; autophagy; invasion; BC endocrine resistance | 173 |
| DCST1-AS1| upregulation    | ANXA1            | doxorubicin, paclitaxel | enhancing EMT and promotes TNBC chemoresistance to doxorubicin and paclitaxel | 174 |
| NKILA  | upregulation      | NF-kB            | immunotherapy | facilitating T cell vulnerability to AICD and decreasing CTL infiltration and apoptosis | 175 |
| TMPO-AS1| upregulation     | ER               | endocrine therapy | stabilizing ESR1 mRNA | 176 |
| DSCAM-AS1| upregulation    | hnRNPL, miR-137/EPS8 | tamoxifen | promoting cell proliferation and suppressing apoptosis | 177 |
| HOTAIRM1| upregulation     | EZH2             | tamoxifen | preventing H3K27 methylation (H3K27me3) of HOXA1 | 178 |
| CYTOR  | upregulation      | miR-125a-5p/SLF, Hippo, MAPK | tamoxifen | ceRNA; promoting cell survival | 179 |

(Continued on next page)
| IncRNA          | Expression patterns | Pathway/target          | Expression pattern drugs | Mechanisms                                                                 | Reference |
|-----------------|---------------------|-------------------------|--------------------------|-----------------------------------------------------------------------------|-----------|
| AFAP1-AS1       | upregulation        | AUF1/ERBB2              | trastuzumab              | enhancing HER2 translation and trastuzumab resistance                       | 46        |
| AGAP2-AS1       | upregulation        | hnRNP A2/B1, CBP/MyD88/H3K27/NF-xB | trastuzumab              | exosome-mediated dissemination; activating NF-kB signaling pathway          | 178       |
| SNHG14          | upregulation        | Bcl-2/Bax, PABPC1       | trastuzumab              | inhibiting apoptosis, exosome-mediated dissemination                        | 179       |
| AK023948        | upregulation        | DHX9/p85                | AKT inhibitors           | sustaining the stability of p85                                            | 180       |
| lncRNA-JADE     | upregulation        | BRCA1, Jade1            | Poly ADP-ribose polymerase (PARP) inhibitors | increasing transcription of DNA damage repair-related genes | 181       |
| GUARDIN         | upregulation        | BRCA1, TRF2             | PARP inhibitors          | maintaining genome integrity                                               | 182       |
| PHACTR2-AS1     | upregulation        | ribosome DNA genes      | PARP inhibitors          | triggering H3K9me3-mediated silencing of ribosome DNA genes                | 183       |
| FTH1P3          | upregulation        | miR-206/ABCB1           | paclitaxel               | ceRNA                                                                      | 184       |
| NONHSAT101069   | upregulation        | miR-129-5p/Twist1       | epirubicin               | ceRNA                                                                      | 185       |
| CASC2           | upregulation        | miR-18a-5p/CDK19        | paclitaxel               | ceRNA                                                                      | 186       |
| MAPT-AS1        | upregulation        | MAPT                    | paclitaxel               | increasing the stability of MAPT mRNA                                      | 187       |
| NONHSAT141924   | upregulation        | p-CREB/Bcl-2 apoptosis  | paclitaxel               | enhances BC resistance to paclitaxel                                       | 188       |
| ACO73284.4      | downregulation      | miR-18b-5p/Dock4        | paclitaxel               | ceRNA; attenuates paclitaxel resistance                                     | 189       |
| RP11.259N19.1   | upregulation        | PI3K/AKT, focal adhesions and WNT signaling | tamoxifen                | –                                                                         | 190       |
| KB.1460A1.5     | upregulation        | –                       | –                        | –                                                                          | 191       |
| PP14571         | upregulation        | –                       | –                        | –                                                                          | 192       |
| PINKLAS         | downregulation      | –                       | –                        | –                                                                          | 193       |
| KLF3-AS1        | downregulation      | –                       | –                        | –                                                                          | 194       |
| LINC00339       | downregulation      | –                       | –                        | –                                                                          | 195       |
| LINC00472       | downregulation      | –                       | –                        | –                                                                          | 196       |
| RP11.351I21.11  | downregulation      | –                       | –                        | –                                                                          | 197       |
| PKD1P6.NP1P1P1  | downregulation      | –                       | –                        | –                                                                          | 198       |
| PDCD4-AS1       | downregulation      | –                       | –                        | –                                                                          | 199       |
| KLF3-AS1        | downregulation      | –                       | –                        | –                                                                          | 200       |
| PP14571         | downregulation      | –                       | –                        | –                                                                          | 201       |
| RP11.69E11.4    | downregulation      | –                       | –                        | –                                                                          | 202       |
| CCAT2           | upregulation        | apoptosis/cell proliferation | tamoxifen                | apoptosis/cell proliferation; enhances the expression of OCT4, Nanog, and KLF4, as well as increases the ALDH+ CSC subpopulation in TNBC | 193       |
| ATB             | upregulation        | miR-200c/ZEB1, ZNF-217  | trastuzumab              | EMT                                                                        | 194       |
| HIF1A-AS2       | upregulation        | miR-130a-5p             | tamoxifen                | regulating PI3K/AKT/mTOR pathway                                           | 195       |
| AK124454        | upregulation        | miR-200c-3p             | doxorubicin              | metabolism and cell division                                               | 196       |
| NONHSAT057282   | upregulation        | miR-200c-3p             | doxorubicin              | metabolism and cell division                                               | 197       |
| NONHSAG023333   | upregulation        | miR-200c-3p             | doxorubicin              | metabolism and cell division                                               | 198       |
| DAMTS9-AS2      | upregulation        | miR-200c-3p             | doxorubicin              | regulating PI3K/AKT/mTOR pathway                                           | 199       |
| XIST            | upregulation        | miR-200c-3p             | doxorubicin              | metabolism and cell division                                               | 200       |
| Eleanors        | upregulation        | miR-200c-3p             | doxorubicin              | metabolism and cell division                                               | 201       |
mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinases (ERK) signaling pathway. Dual specificity phosphatase 7 (DUSP7) is an important inhibitor of the MAPK/ERK signaling pathway, and IncRNA ROR promotes the degradation of DUSP7 by activating ERK, leading to tamoxifen resistance. In contrast, IncRNAs can act as tumor suppressors to play an important role in decreasing tamoxifen resistance. For example, downregulation of IncRNA GAS5 is found in tamoxifen-resistant MCF-7R cells. GAS5 overexpression significantly enhances the cell sensitivity of MCF-7R to tamoxifen in vivo and in vitro. GAS5 acts as a molecular sponge of miR-222 to block inhibition of PTEN by miR-222, thus reducing the AKT/mTOR signaling pathway to increase the sensitivity of breast cancer cells to tamoxifen.

**IncRNAs and aromatase inhibitors.** Aromatase exists in breast tissue and mediates the conversion of testosterone and androstenedione to estradiol and estrone, respectively. Normal breast tissues have lower aromatase levels, whereas malignant tumor cells have higher aromatase expression.

Aromatase inhibitors, such as anastrozole and exemestane, inhibit the conversion of androstenedione to estrone in breast cancer patients, thereby significantly reducing plasma estrogen levels to inhibit the proliferation of ER-positive breast tumors. However, there are few studies on the relationship between IncRNAs and the function of aromatase inhibitors. Until now, only IncRNA MIR2052HG has been reported to be associated with breast cancer resistance to aromatase inhibitors. IncRNA MIR2052HG is a functional polymorphic gene and can increase ER expression to induce cell proliferation and colony formation in breast cancer cells. In breast cancer cells treated with anastrozole or exemestane, the expression of both MIR2052HG and ER is decreased. Other evidences also confirm the positive association between MIR2052HG and ER expression. Mechanistically, MIR2052HG interacts with EGR1 and promotes its recruitment to the LMTK3 promoter. LMTK3 maintains ERz levels by reducing protein kinase C (PKC) activity, which in turn leads to an increase in ESR1 transcription mediated by the AKT/FOXO3 pathway and a decrease in ERz degradation mediated by the PKC/mitogen-activated protein kinase kinase/ERK/ribosomal S6 protein kinase type 1 pathway to resist anastrozole or exemestane.

**IncRNAs participate in HER2-targeted therapy**

At present, trastuzumab and pertuzumab plus docetaxel have been used as the first-line treatment for HER2-positive breast cancer patients. As a key regulator of trastuzumab resistance in breast cancer, IncRNA asAFAP1-AS1 can bind to AUF1 and promote HER2 translation, which resulted in increased expression of HER2 and caused trastuzumab resistance. In addition, asAFAP1-AS1 in trastuzumab resistance can be packaged into exosomes and enhance the drug resistance of recipient cells. Mechanismly, IncRNA AGAP2-AS1 increases H3K27 acetylation (H3K27ac) in the MyD88 promoter region, leading to activation of the NF-κB signaling pathway and therapeutic resistance to trastuzumab. Another IncRNA SNHG14 has also been reported to regulate H3K27 acetylation in the PABPC1 gene promoter to induce PABPC1 expression, thereby activating the Nrf2 signaling pathway to resist trastuzumab. Additionally, IncRNA AGAP2-AS1 and SNHG14 promote the tolerance of breast cancer cells to trastuzumab through exosome-mediated diffusion. Moreover, IncRNAs also participate in drug resistance as a byproduct of physiological processes. A recent study reports that CBP-mediated H3K27 acetylation can activate IncRNA TINCR, leading to breast cancer resistance to trastuzumab. Mechanismly, TINCR acts as a sponge for miR-125b targeting HER2, thereby upregulating HER2 to weaken the anti-tumor effect of trastuzumab.

**IncRNAs in breast cancer chemoresistance**

Chemotherapy has been applied to almost all breast cancer subtypes and effectively prevents the postoperative recurrence and metastasis of breast cancer after surgery. Anthracycline, taxanes and platinum drugs are standard first-line chemotherapy drugs for breast cancer (Figure 4C).

**Anthracyclines.** Doxorubicin/Adriamycin (DOX/ADR), a member of the anthracycline family, is used as a first-line chemotherapeutic drug for cancers including breast cancer. DOX/ADR limit DNA replication, promote free radical generation, and inhibit topoisomerase II activity to cause DNA damage, binding, alklylation, and cross-linking, leading to cancer cells apoptosis. However, many patients show resistance to these drugs within a short recurrence time. It has been reported that several IncRNAs are involved in the resistance of breast cancer to DOX/ADR. For example, IncRNA BORG reduces DNA damage by activating the NF-κB signaling pathway, thereby enhancing DOX resistance in TNBCs. In breast cancer cells and improves DOX resistance by targeting staphylococcal nuclease domain-containing 1 (SND1).

Contrary to positive regulation of above IncRNAs in breast cancer resistance to anthracycline, some IncRNAs can reduce the drug resistance. IncRNA PTENP1 is downregulated in breast cancer cells and tissues. PTENP1 acts as an endogenous sponge of miR-20a to promote the expression of PTEN, thereby inhibiting the PI3K/AKT pathway. PTENP1 overexpression significantly reverses ADR resistance in breast cancer cells. The low expression of IncRNA MEG3 reduces apoptosis through the Bax/Bcl-2 axis to promote DOX resistance in breast cancer. LINC00968 can target and negatively regulate WNT2 through HEY1. Overexpression of LINC00968 or silencing of WNT2 inhibits the activation of the WNT2/β-catenin signaling pathway to reduce drug resistance.

**Epirubicin.** Epirubicin is a cell cycle non-specific drug that can directly intercalate between DNA nucleobase pairs to interfere with the mRNA transcription and inhibit the synthesis of DNA and RNA. In addition, epirubicin also has an inhibitory effect on topoisomerase II. Epirubicin is currently an important class of drugs, which has shown strong efficacy in anticancer chemotherapy and is mainly used for breast cancer. The novel IncRNA NONHSAT101069 is significantly overexpressed in breast cancer tissues and cell lines and epirubicin-resistant cell sublines. The
overexpression of NONHSAT101069 promotes epirubicin resistance, migration, invasion, and EMT of breast cancer cells in vitro and in vivo. Further studies on this mechanism find that NONHSAT101069 acts as a ceRNA to sponge miR-129-5p to regulate the expression of Twist1, thereby promoting the resistance of breast cancer cells to epirubicin.\(^\text{185}\)

**Taxanes.** Paclitaxel and docetaxel are two classical taxane agents with strong antitumor activity. These drugs can bind and stabilize microtubules to prevent depolymerization and block the process of mitosis.\(^\text{128}\) A new type of lncRNA, mitosis-related linc1 (MA-linc1), is involved in cell cycle regulation that facilitates the exit of the M phase. Silencing MA-linc1 can significantly enhance the apoptosis induced by paclitaxel in breast cancer cells.\(^\text{192}\) Jiang et al.\(^\text{192}\) show that IncRNA HIF1A-AS2 and AK124454 promote the proliferation and invasion of TNBC cells, as well as resistance to paclitaxel. By in vivo assay, it is found that both IncRNAs can interfere with the paclitaxel-induced G2-M-phase block, which may be achieved by changing the expression of metabolism- and cell division-related genes, respectively.\(^\text{192}\) In addition, IncRNA is also involved in breast cancer resistance to paclitaxel by regulating miRNA activation. For example, IncRNA CAS2 is upregulated in breast cancer cells and activates paclitaxel resistance in breast cancer by regulating the miR-18a-5p/CDK19 axis.\(^\text{220}\) IncRNA LINC00511 interacts directly with miR-29c and inhibits its expression, thereby increasing the expression of CDK6 and inhibiting paclitaxel-induced cytotoxicity.\(^\text{221}\) In paclitaxel-resistant MCF-7 breast cancer cells, IncRNA FTH1P3 is upregulated and enhances ABCB1 protein expression by acting as a sponge for miR-206, thereby enhancing paclitaxel resistance in breast cancer cells.\(^\text{166}\) In contrast, IncRNA EPB41LA4-AS2 is downregulated in docetaxel-resistant breast cancer cells, whereas low expression of EPB41LA4-AS2 upregulates ABCB1 and promotes docetaxel resistance in breast cancer cells.\(^\text{222}\)

**Cisplatin and 5-fluorouracil.** Cisplatin is a platinum drug commonly used in TNBC chemotherapy and significantly induce DNA damage in cancer cells.\(^\text{223}\) Multiple independent studies have shown that the lncRNA-miRNA-mRNA regulatory network plays an important role in modulating the cisplatin and 5-fluorouracil resistance in breast cancer. For instance, IncRNA NEAT1 confers resistance to paclitaxel, cisplatin, and 5-fluorouracil in breast cancer cells by the miR-129/ZEB2 and miR-211/HMGA2 pathways. This means that targeting NEAT1 has far-reaching significance for alleviating breast cancer chemotherapy resistance.\(^\text{161}\) Another example, IncRNA SNHG15, is upregulated in cisplatin-resistant MDA-MB-231 and MCF-7 cells, whereas knockdown of SNHG15 can increase cisplatin sensitivity in breast cancer cells by sponging miR-381.\(^\text{224}\) The novel IncRNA PRLB enhances 5-fluorouracil resistance by regulating the miR-4766-5p/SIRT1 axis in breast cancer.\(^\text{103}\) Besides an miRNA sponge, IncRNAs also directly inhibit protein activity to mediate cisplatin resistance. For example, in cisplatin-resistant MDA-MB-231 cells, HCP5 is found to be significantly upregulated. Moreover, overexpression of HCP5 promotes cisplatin resistance in MDA-MB-231 cells by inhibiting PTEN expression.\(^\text{225}\)

Small molecule inhibitor. CDK4/6 is a key protein that regulates the cell cycle and can trigger the transition of the cell cycle from G1 phase to S phase. In many malignant tumors, especially ER-positive breast cancer, the high expression of CDK4/6 promotes excessive proliferation of cancer cells, whereas CDK4/6 inhibitors can block the cell cycle in the S phase, thereby inhibiting tumor cell proliferation.\(^\text{226}\) CDK4/6 inhibitors, such as palbociclib, ribociclib, and abemaciclib, combined with anti-estrogens have shown significant progress-free survival (PFS) benefits, which may be due to the effect of breast cancer cells on cyclin D1 special dependence and estrogen-mediated activation of CDK2.\(^\text{227–229}\) Like all other treatment strategies, the emergence of CDK inhibitor resistance is an obstacle in clinical breast cancer treatment. Some studies imply the involvement of IncRNA in CDK inhibitor resistance. The newly identified IncRNA Inc712 can activate CDK2 by directly interacting with heat shock protein 90 (HSP90) to form a Inc712/HSP90/cell division cycle 37 (Cdc37) complex in breast cancer.\(^\text{230}\) These indicate that Inc712 is a promising biomarker for predicting drug response in breast cancer with its ability to enhance cancer cell resistance to CDK inhibitor palbociclib. Similarly, IncRNAs associated with other CDKs, including TUG1, CCAT2, and LINC01089, may also mediate resistance to CDK inhibitors.\(^\text{115,231,232}\)

Together, chemotherapy resistance imposes limits on the effectiveness of modern medicine in treating malignant tumors. However, the effect of IncRNA on chemotherapy resistance can provide new ideas for the treatment of breast cancer.

**IncRNAs are involved in the regulation of breast cancer immune response**

The imbalance of the immune response in the tumor microenvironment plays an important role in the occurrence and development of cancer.\(^\text{233}\) We have described in detail the regulation mechanisms of IncRNAs in tumor cell proliferation, apoptosis, metastasis, and drug resistance. Recent studies have shown that IncRNAs also have been shown to be involved in the regulation of the cancer immune response.\(^\text{234}\) Although IncRNAs do not directly encode innate or adaptive immune proteins in immune cells, they regulate the function of immune cells, such as inducing T cell differentiation and macrophage polarization and impacting the antigen presentation ability of dendritic cells (DCs).\(^\text{235}\) Cancer immunotherapy is an emerging treatment option that activates the human immune system and relies on autoimmunity to kill cancer cells and eliminate cancer cells. However, during immunotherapy, the loss of antigenicity, immune checkpoint evasion, and reactivation of oncogenic signals in malignant tumor cells and the increase of T lymphocyte activation-induced cell death (AICD) often lead to immunosuppression.\(^\text{236}\)

**IncRNAs and immune activation**

The relationship between IncRNAs and T lymphocytes has also been extensively studied. linc-MAF-4, a chromatin-related T helper (Th)1-specific lncRNA, has been shown to be negatively correlated with the expression of MAF, which is a Th2-related transcription factor. linc-MAF-4 inhibits MAF transcription by recruiting chromatin modifiers
LSD1 and EZH2. Downregulation of linc-MAF-4 induces T cell differentiation toward CD4+ Th cells by upregulating MAF.235 In addition, T cells can take up tumor-derived exosomes containing lncRNAs to differentiate toward regulatory T cells (Tregs). For example, tumor cells secrete exosomes rich in lncRNA RP11-323N12.5 to be taken up by T cells. LncRNA RP11-323N12.5 triggers the Hippo signaling pathway to further activate YAP1 in T cells, causing T cells to differentiate into Tregs.236 DCs, as the main antigen-presenting cells in the mammalian immune system, affect the innate and adaptive immune responses. Activation of DC is also regulated by lncRNA.239 For example, the lnc DC, a DC-specific lncRNA, is related to the differentiation of DC. lncDC can prevent the combination of STAT3 and SHP1 to promote the phosphorylation of STAT3, thereby guiding the differentiation of DC. Knockout of lnc DC impairs the DC differentiation in vitro and in vivo and reduces the ability of DCs to stimulate T cell activation.239 Phenotypic transition in TAMs is a major player in breast cancer malignancy and metastasis.240,241 lncRNA can directly or indirectly induce the polarizations of macrophages. Studies have shown that lncRNA XIST is upregulated in pro-inflammatory M1-type macrophages (M1). Knockdown of XIST in M1 can induce the transformation of M1 to anti-inflammatory M2 macrophage (M2) by inhibiting the expression of C/EBPa and KLF6 to promote tumor cell proliferation and migration.242 Unlike lncRNA XIST, another lncRNA expressed in breast cancer cells indirectly induces M2 polarization of macrophages through inducing tumor cells to secrete cytokines. For example, linc00514-overexpressed breast cancer cells increase the percentage of CD206 and CD163 (M2 markers)-positive macrophages. Mechanistically, linc00514 promotes phosphorylation of STAT3 to upregulate the expression of Jagged1. Subsequently, the Notch signaling pathway mediated by Jagged1 promotes breast cancer cells to secrete IL-4 and IL-6 to induce M2 polarization of macrophages.243

**lncRNAs and immnosuppression**

Recent studies have shown that lncRNA plays an important role in immunosuppression and may be used as a potential target for cancer immunotherapy (Figure 4D). Peptide loading complex (PLC) can enhance the presentation of antigen to the cell surface. However, TNBC develops resistance to drugs that block programmed cell death protein 1 (PD-1) by downregulating PLC.244 Interestingly, lncRNA LINK-A plays an important role in this process by promoting PLC degradation. LINK-A directly interacts with phosphatidylinositol-(3,4,5)-triphosphate and inhibitory G-protein coupled receptors (GPCRs) leading to a decrease in cyclic AMP (cAMP) levels and subsequent protein kinase A (PKA)-mediated phosphorylation of TRIM71. Phosphorylated TRIM71 enhances the degradation of PLC components, thereby reducing antigen presentation to the surface of breast cancer cells.160 For TNBC patients who are sensitive to pembrolizumab (anti-PD-1) treatment, the expression of LINK-A is relatively low, but it is accompanied by higher CD8+ T cell infiltration.45 Another study shows that NKILA interacts with NF-kB to inhibit NF-kB activity to enhance the sensitivity of T cells to AICD. Therefore, the apoptosis and subsequent reduced infiltration of cytotoxic T lymphocytes (CTLs) may contribute to immunotherapy resistance.174 These results indicate that CD8+ T cell infiltration is negatively correlated with LINK-A expression. Therefore, more efforts are urgently needed to show direct evidence of how lncRNA plays a role in immune cell infiltration to provide more immune targets.

Pei et al.246 have discussed the mechanism of lncRNA SNHG1 in breast cancer immune escape. They have found that lncRNA controls the differentiation of Tregs by regulating the expression of indoleamine 2,3-dioxygenase (IDO), thereby affecting the immune escape of breast cancer.246 Emerging studies have shed light on the mechanism by which lncRNA INCR1 regulates tumor interferon (IFN) signaling. The primary transcript of the INCR1 gene binds to HNRNPH1 to block its inhibitory effect on neighboring genes programmed death ligand 1 (PD-L1) and JAK2, thereby promoting PD-L1 and JAK2 expression. Silencing INCR1 will reduce the expression of PD-L1, JAK2, and several other IFN-γ-stimulated genes, thereby enhancing breast cancer cells sensitive to cytotoxic T cell-mediated killing to improve chimeric antigen receptor T (CAR-T) cell therapy.247 Similarly, lncRNA GATA3-AS1 is also closely related to the expression of PD-L1. GATA3-AS1 induces COP5 upregulation by isolating miR-676-5p as a positive regulator of COP5 mRNA. The activation of the miR-676-5p/COP5 axis induced by GATA3-AS1 promotes the deubiquitination of PD-L1 by upregulating CSN5, thereby causing immune escape.248

The mechanism of tumor immune escape is extremely complex. lncRNAs can be used as promising predictive biomarkers and therapeutic targets for breast cancer immunotherapy. Further research on lncRNA might provide new insights for tumor immunotherapy.

**lncRNAs AS BIOMARKERS AND THERAPEUTIC TARGETS FOR BREAST CANCER**

In recent years, the understanding of human RNA molecule compositions is gradually diversified and complicated with the advances in transcriptome profiling technology. lncRNAs play a vital role in the normal physiological development process; its aberrant expression is intrinsically linked to breast cancer.249 As we discussed in this review, lncRNAs are closely related to the proliferation, invasion, metastasis, and drug resistance of breast cancer. Importantly, there are many clinical data that show that some lncRNAs have obvious abnormal expression in the lesions and precancerous tissues of breast cancer patients. Therefore, lncRNAs can also be used as a biomarker for diagnosing tumors, judging patient prognosis, and predicting disease progression.25 In this part, we summarized the impact of some breast cancer-related lncRNA levels on the prognosis of breast cancer patients. Using lncRNAs as therapeutic targets will be a hot topic in breast cancer diagnosis, prognosis, and therapeutics.

**lncRNAs and clinical diagnosis**

Research on biomarkers for early diagnosis of breast cancer and molecular subtypes is extremely important for improving clinical efficacy. Abundant clinical data indicate that some lncRNAs have
obvious abnormal expression in the lesions and precancerous tissues. lncRNA ANRIL, HIF1A-AS2, and UCA1 are significantly upregulated in the plasma of TNBC patients than in non-TNBC, suggesting their promising use as TNBC-specific diagnostic biomarkers. In addition, an epigenome-wide association study (EWAS) shows that the hypermethylation of LINC00299 in the peripheral blood of TNBC patients can be used as a useful circulating biomarker for TNBC and has excellent diagnostic value. According to another recent study, the overexpression of HOTAIR is closely related to a luminal androgen receptor (LAR) subtype of TNBC, which is characterized by AR expression. In addition, circulating HOTAIR-derived fragments are detected in the serum of breast cancer patients and healthy individuals. This result shows that HOTAIR is a potential biomarker for breast tumors. Moreover, lncRNA CCTA1 upregulates TCF4 expression through competitively binding to miR-204/211 and promotes β-catenin translocation through interaction with miR-148a/152 and ANXA2. Conversely, TCF4 can also bind with the promoter of IncRNA CCAT1 to promote the transcription of IncRNA CCAT1, thereby forming a positive-feedback regulating circuit of CCAT1-TCF4-CCAT1 in breast cancer. Therefore, CCAT1 plays an important role in breast cancer progression and can be used as a new target for breast cancer diagnosis and treatment. These evidences indicate that lncRNAs as a biomarker for early diagnosis of breast cancer are expected to be applied in clinical practice.

**lncRNAs as prognosis biomarkers**

Despite significant progress having been made in the treatment of breast cancer, the prognosis of breast cancer remains poor due to frequent distal metastases and resistance to chemotherapy. Abnormal expression of some lncRNAs related to breast cancer metastasis and chemotherapy resistance, such as HOTAIR, HISLA, H19, and GAS5 in plasma and TINCR, LINP1, MALAT1, and LINC000473 in tissues, is associated with poor prognosis of breast cancer patients. As we reviewed above, HOTAIR can be used as a biological maker for early diagnosis of breast cancer and is closely related to breast cancer metastasis. Current studies have confirmed the correlation between the overexpression of HOTAIR in breast cancer tissues and the shortened survival of patients. The Kaplan-Meier survival curve shows that patients with high levels of circulating HOTAIR in plasma have worse DFS than patients with low circulating HOTAIR levels. Similarly, the high levels of HISLA, H19, and GAS5 in plasma are positively correlated with advanced lymph node metastasis and reduced OS. In addition, by analysis of preoperative and postoperative plasma samples, several studies show that the plasma levels of HISLA, H19, and GAS5 are significantly decreased in patients with positive lymph node metastasis. The reduced plasma levels of HISLA, H19, and GAS5 in breast cancer patients after operation have a better prognosis.

Meta-analysis of MALAT1 shows that the upregulation of MALAT1 expression in breast cancer tissues is positively correlated with lymph node metastasis and has a shorter 5-year DFS and OS. Further studies have shown that MALAT1 is also an important pro-inflammatory factor that regulates the inflammatory response induced by lipopolysaccharide in breast cancer endothelial cells. In breast cancer patients with postoperative fever, elevated MALAT1 expression can predict poor short-term recurrence-free survival (RFS). Clinical studies have shown that the increased expression of LINP1 is associated with advanced tumor, node, metastasis (TNM) stage; more lymph node metastasis; and poor pathological differentiation. In addition, the OS and DFS of patients with high LINP1 expression are shorter than those with low LINP expression. Similarly, the expression of TINCR and LINC000473 is also upregulated in breast cancer tissues and further increased during the progression and metastasis of cancer, which are associated with poor prognosis of breast cancer patients.

Due to the lack of effective targeted therapy and the high recurrence rate after chemotherapy, the prognosis of TNBC is the most unfavorable in all types of breast cancer. Recent research shows that some lncRNAs in TNBC patients can be used as novel prognostic biomarkers for TNBC patients, such as DANCR, NAMP-T-AS, ATB, MIR503HG, LINC01089, and PHACTR2-AS1. DANCR is considered to be closely related to breast cancer cell proliferation. Abnormal upregulation of DANCR expression is related to worse OS and TNM stages. In addition, the upregulation of NAMPT-AS and ATB expression is negatively correlated with OS and DFS in TNBC patients. Different from DANCR, ATB, and NAMPT-AS, MIR503HG is a tumor suppressor and can be used as a prognostic marker for TNBC. Compared with TNBC patients with high MIR503HG expression, low MIR503HG expression is an independent poor prognostic factor of OS in TNBC. Similarly, LINC01089 and PHACTR2-AS1 also have similar functions. Interestingly, the integrated mRNA-lncRNA signature based on the mRNA types of FCGR1A, RSAD2, and CHRD1 and the lncRNA types of HIF1A-AS2 and AK124454 can also be used as a reliable tool to predict the recurrence of tumors and the benefit of taxane chemotherapy in TNBC. These evidences suggest that the combination of lncRNAs with different expression levels or integrated mRNA-lncRNA signature will be a powerful biomarker for clinical prognosis. Altogether, the emerging evidences demonstrate that lncRNAs are useful prognostic markers to predict prognosis and metastatic risk in breast cancer patients.

**lncRNAs as therapeutic targets in breast cancer**

With the continuous discovery of lncRNA structural information and its function, increasing small molecule inhibitors against lncRNAs have been developed, and it has broad prospects for clinical diagnosis and treatment of tumors. The new anti-tumor drugs against lncRNAs have become a new trend in the development of anti-tumor drugs. At present, the research of new drugs targeting lncRNAs has made some progress. Some small molecule inhibitors, siRNAs, antisense oligonucleotides (ASOs), and CRISPR-Cas9 have been developed, and indirect modulators of lncRNAs are also new directions in drug development. For example, Singh et al. find that PIM serine/
threonine kinase can affect the expression level of H19 in cells by regulating the methylation of the H19 promoter. The overexpression of H19 can promote the further development of tumors. Therefore, the use of small molecule pan-PIM inhibitors in clinical trials indirectly regulates the level of H19 in tumor cells to exert anti-cancer effect.266 siRNA targeting breast cancer-related lncRNAs (such as HOTAIR) has been shown to inhibit the growth and invasion of breast cancer.267 Another study finds that depletion of lncRNA BM with nanoparticle-encapsulated siRNAs has been shown to be effective against breast cancer brain metastasis.140 ASO refers to a synthetic single-stranded oligonucleotide that is complementary to the target lncRNAs and can form a DNA/RNA heteroduplex that can be cleaved by RNase H.268 LINC02273 is stabilized by hnRNPL, which is increased in breast cancer metastatic lesions. The recruitment of hnRNPL-LINC02273 complex to the AGR2 promoter region increases local H3K4me3 and H3K27 acetylation expression, thereby upregulating AGR2 at the epigenetic level to promote breast cancer metastasis. ASO targeting LINC02273 blocks the production of the hnRNPL-LINC02273 complex to reduce AGR2 expression to inhibit breast cancer metastasis in vitro and in vivo.269 Additionally, ASO targeting NRD1 (also known as LINC00284) has been reported to reduce cell survival, tumor growth, and the number of cells with CSC characteristics in TNBC tumors.20

Increasing evidence shows that the CRISPR-Cas9 genome editing approach can be used to knock out lncRNAs.270 CRISPR-Cas9 technology can delete genomes at precise locations with a specific size and high fidelity. The expression of lncRNA NEAT1 positively regulates the expression of NAD(P)H: quinone oxidoreductase 1 (NQO1) in radiation-resistant MDA-MB-231 cells at the translation level. Inhibition of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant MDA-MB-231 cells at the translation level. Inhibition of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation of NEAT1 expression by CRISPR-Cas9 increases the sensitivity of radiation-resistant cells to radiation and reduces cell proliferation

Conclusions
LncRNAs play an important role in breast tumor development, diagnosis, and treatment, as well as predict a patient's prognosis. Currently, the function mechanisms of a few lncRNAs have been investigated clearly in preliminary research. However, the underlying function mechanisms of most of the lncRNAs in breast cancer remain undefined. It has been recognized that the regulation of lncRNA expression is more stringent, and the secondary structure of lncRNAs is more complex than that of mRNA. Similar to mRNA, a small part of lncRNAs also expresses polypeptide products. Therefore, the function mechanisms of lncRNAs are very complicated. This requires further wider and deeper studies. Since the number of lncRNA genes exceeds protein-coding genes, lncRNAs are more stable than mRNA, so they are more suitable as a diagnostic marker. Recently, more researchers are exploring the detection of lncRNAs in the circulatory system. Nevertheless, the current problem in clinical application of lncRNAs is the lack of effective and convenient detection methods. With the improvement of gene array and high-throughput RNA sequencing technologies, detection of lncRNAs is faster and more convenient. Although lncRNAs can be used as a therapeutic target for breast cancer, it is difficult to design small molecule drugs against lncRNAs, which limits the application of lncRNAs as a therapy target in cancer including breast cancer. All in all, lncRNAs open a new door for clinical diagnosis and treatment of breast cancer. However, there are still many difficulties that must be faced and overcome.

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AUTHOR CONTRIBUTIONS
Z.Z., H.J., and W.D. designed the study and drafted the manuscript. W.H., Y.J., and Q.T. collected the related references. Y.C. and Z.Z. revised the manuscript. All authors read and approved the final manuscript and agreed with the content of the manuscript.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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