Molecular Therapy
Nucleic Acids
Review

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

Huan Jin,[1,2,6] Wei Du,[3,6] Wentao Huang,[2,4] Jiajing Yan,[2,4] Qing Tang,[2,4] Yibing Chen,[1] and Zhengzhi Zou[2,4,5]

[1]Genetic and Prenatal Diagnosis Center, Department of Gynecology and Obstetrics, First Affiliated Hospital, Zhengzhou University, Zhengzhou 450052, China; [2]MOE Key Laboratory of Laser Life Science & Institute of Laser Life Science, College of Biophotonics, South China Normal University, Guangzhou 510631, China; [3]Department of Neurosurgery, First Affiliated Hospital, Zhengzhou University, Zhengzhou 450052, China; [4]Guangdong Provincial Key Laboratory of Laser Life Science, College of Biophotonics, South China Normal University, Guangzhou 510631, China; [5]Guangzhou Key Laboratory of Spectral Analysis and Functional Probes, College of Biophotonics, South China Normal University, Guangzhou 510631, China

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.[1,2] 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.[3,4] 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.[5,6] 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.[7] 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.[8,9] 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.[10–13] According to lncRNA genomic position, subcellular localization, and function, they can be divided into six types (Figure 1).[14] (1) Enhancer lncRNAs are derived from the promoter enhancer region, such as lncRNA-LEENE.[15] (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 lncTALAM1 and PDCD4-AS1.[16,17] (4) The sense lncRNA: its transcription orientation is the same as that of the adjacent protein-encoding gene, such as lncRNAGAS5 and ecCEPBA.[18,19] (5) Intergenic lncRNA, which can be transcribed between two protein-coding genes, is an autonomously transcribed

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[6]These authors contributed equally

Correspondence: Yibing Chen, MD, PhD, Genetic and Prenatal Diagnosis Center, Department of Gynecology and Obstetrics, First Affiliated Hospital, Zhengzhou University, 1 Jianshe Donglu, Zhengzhou, Henan 450052, China.
E-mail: chenyibing@zzu.edu.cn
Correspondence: Zhengzhi Zou, PhD, MD, MOE Key Laboratory of Laser Life Science and Institute of Laser Life Science, College of Biophotonics, South China Normal University, Guangzhou 510631, China.
E-mail: zouzhengzhi@m.scnu.edu.cn

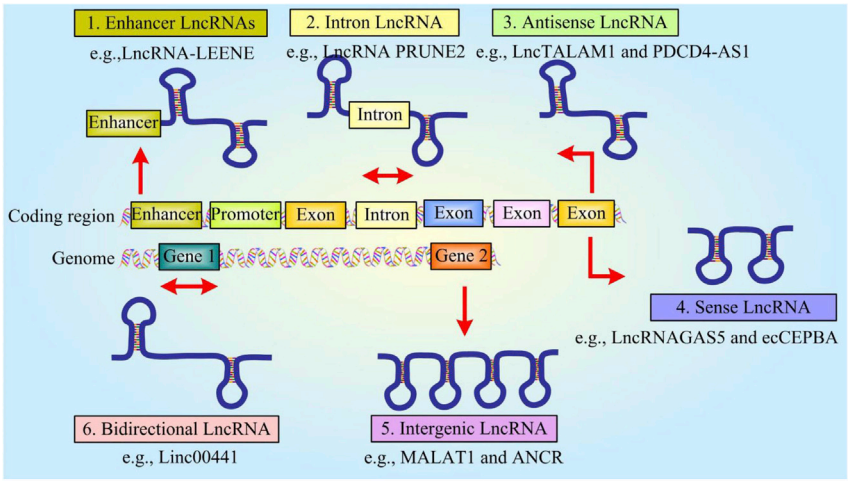

Figure 1. The classification of lncRNAs based on their genomic position, subcellular localization
lncRNAs are divided into six types: (1) enhancer lncRNAs; (2) intron lncRNA; (3) antisense lncRNA; (4) sense lncRNA; (5) intergenic lncRNA; (6) bidirectional lncRNA.

non-coding RNA that does not overlap with the annotated coding gene, such as MALAT1 and ANCR.[16,20] (6) Bidirectional lncRNA exists near the coding transcript of the opposite strand and can simultaneously transcribe from the same and opposite directions of adjacent protein-encoding genes, such as large intergenic noncoding RNA (linc)00441.[21]

Currently, emerging evidence suggests that lncRNAs play prominent roles in the tumorigenesis and development of breast cancer. However, the mechanisms in which lncRNAs affect tumor progression and drug resistance have not been fully described in breast cancer. In this review, we will focus on the function and regulatory mechanism of lncRNA in breast cancer. We also will explore the opportunities and challenges of targeting lncRNA for breast cancer treatment.

THE CELLULAR FUNCTIONS OF lncRNAs

lncRNAs are widespread in human organisms and are essential for the regulation of human gene expression, physiological and pathological processes.[22] The function of lncRNAs is very complicated and has not been fully elucidated so far. According to the current research, there are five main ways that lncRNAs in cell physiological regulation, as shown in Figure 2. (1) lncRNAs encode polypeptides; (2) lncRNAs are involved in transcriptional regulation; (3) lncRNAs are involved in post-transcriptional regulation; (4) lncRNAs participate in epigenetic regulation; (5) lncRNAs function as a signal transducer.

lncRNA encodes a polypeptide

Although lncRNAs are non-protein transcripts by definition, recent studies have shown that part of the putative small open reading frame in lncRNAs is translated into a polypeptide (Figure 2A).[23,24] Wang et al.[25] 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.[25] 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.[26] Another lncRNA EPR that responds to TGF-β induction also encodes a polypeptide to control cell proliferation. EPR affects both its transcription and mRNA decay through its interacts with SMAD3 and mRNA decay-promoting factor KHSRP, respectively, to regulate *Cdkn 1a* gene expression. The downregulation of EPR caused by TGF-β reshapes the transcriptome and promotes cells to acquire epithelial characteristics to inhibit cell proliferation.[27] These evidences suggest that lncRNA is another non-negligible factor besides the genome in the study of cancer treatment, whereas lncRNAs that encode a polypeptide may become a potential target for cancer treatment.

lncRNAs are involved in transcriptional regulation

lncRNAs 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).[23,28] 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.[23] 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.[28] 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,[29] whereas lncRNA XIST suppresses the transcriptional activity of SHARP by activating HDAC3.[30]

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.[31] 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.[32] Postepska-Igielska et al.[33] discovered a regulatory lncRNA Khps1 that activates the expression of the proto-oncogene sphingosine kinase 1 (SPHK1) through directly

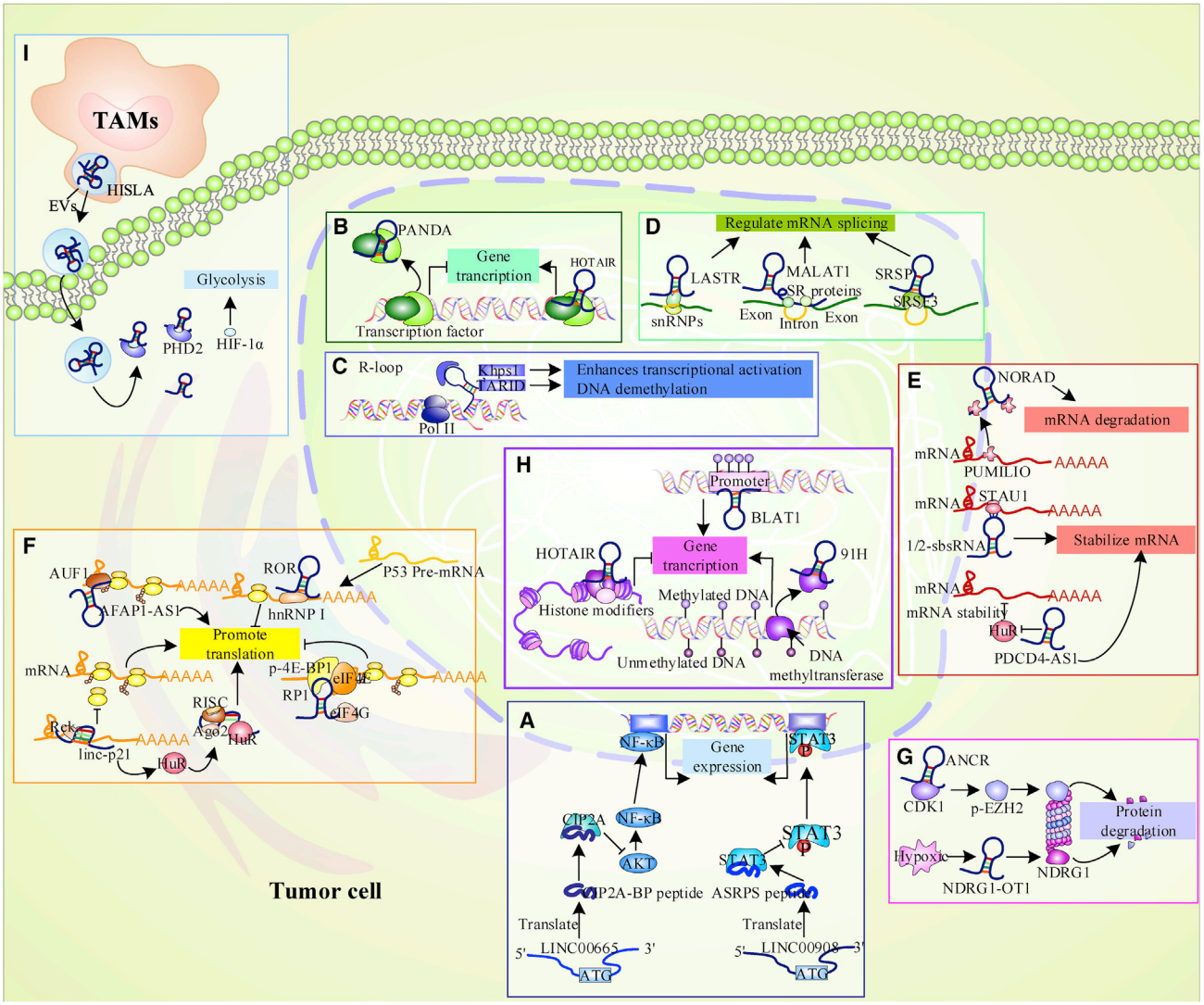

Figure 2. The functions of lncRNAs

(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 lincRNA-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.

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.[33] Arab et al.[34] 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.[34]

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.

lncRNA can interfere with mRNA splicing and form different splicing forms

Massive high-throughput sequencing technology has identified thousands of lncRNAs, as well as a large number of different mRNA processing events that occur in higher organisms. lncRNAs directly encode polypeptide or regulate gene transcription. Recently, lncRNAs 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.[35] Similarly, lncRNA 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.[36] Unlike lncRNA LASTR and MALAT1, lncRNA 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.[37]

lncRNAs can regulate mRNA stability

lncRNA can act as a molecular decoy involved in mRNA degradation (Figure 2D). In addition to affecting the mRNA splicing, lncRNA also participates in the process of mRNA degradation. lncRNA NORAD acts as a reservoir for PUMILIO 1 and PUMILIO 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 8-nt sequence of the PUMILIO 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.[38] Knockout of the NORAD gene shows increased chromosomal instability. This possibly is attributable to the hyperactive PUM1/2 extensively downregulating the expression of PUMILIO, which targets mRNA-encoding genome-stable proteins.[32,39] Additionally, lncRNAs also recruit protein to stabilize mRNA (Figure 2E). lncRNAs 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 lncRNA to form double-stranded RNA (dsRNA) recognized by STAU1 to inhibit SMD. These lncRNAs are named "half-STAU1-binding site RNAs (1/2-sbsRNAs)."[40] Similarly, lncRNA 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.[17] Furthermore, lncRNAs 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.[41–44] miRNAs induce the degradation of mRNA by complementary pairing with target mRNA, whereas lncRNAs act as an miRNA sponge to stabilize mRNA.[22] For example, lnc00899 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.[42] lnc00899 acts as a miR-425 sponge to relieve the inhibition of DICER1 by miR-425 to inhibit mRNA degradation.[45]

lncRNAs 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 lncRNA 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.[46] Although lncRNAs are not translated, ribosome profiling assays have identified several lncRNAs related to ribosome components (Figure 2F).[47] For example, the interaction of lincRNA-p21 with HuR facilitates the recruitment of let-7/Ago2 to destroy the stability of lincRNA-p21. On the contrary, the decrease of HuR expression blocks the recruitment of let-7/Ago2 and thus promotes the accumulation of lincRNA-p21, and then lincRNA-p21 binds with JUNB and CTNNB1 mRNA through base pairing and then recruits the translation-repressor Rck129 to inhibit JUNB and CTNNB1 translation.[48] lncRNA retinoid acid receptor related orphan receptor (ROR) inhibits the translation of p53 through direct interaction with hnRNP I, which promotes the processing of precursor mRNA and transports the mRNA from the nucleus to the cytoplasm.[49] Similarly, the interaction between intergenic noncoding RNA between ITGB1 andNRP1 (LincIN) and NF90 regulates the expression of p21 at the translation level.[50] However, the mechanism which linc IN mediates breast cancer metastasis through the NF90-p21 pathway is not clear. Besides, lncRNAs also can interfere with the translation initiation in eukaryotic cells. For example, the combination of lncRNA RP1 and the complex p-4E-BP1/eIF4E can prevent the interaction of eIF4E and eIF4G and then reduce the translation efficiency of p27kip1 mRNA.[51]

lncRNAs regulate protein stability

lncRNAs can recruit some proteins to affect their stability (Figure 2G). lncRNAs affect protein stability mainly by regulating protein ubiquitination degradation.[32,41] Such as, studies in several breast cancer cell lines show that lncRNA NDRG1-OT1 is significantly upregulated and promotes the degradation of NDRG1 through ubiquitin-mediated proteolysis under hypoxic conditions.[52] lncRNA 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.[53] Similarly, lincRNA-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.[54]

lncRNAs 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.[11,27]

Some important functions of lncRNAs are related to the epigenetic control of specific target genes (Figure 2H).[55] For example, lncRNAs basal-like breast cancer associated transcript 1 (BLAT1), BCLIN25, and H91 can regulate DNA methylation to participate in tumorigenesis.[9,27,56] Han et al.[57] find that BLAT1 expression is regulated at the epigenetic level by decreasing DNA methylation of CpG islands in the promoter. Patients with BLAT1-hypomethylated tumors have lower overall survival (OS). The increased BLAT1 expression with hypomethylation at CpG sites may contribute to the aggressive phenotype of breast cancer.[57] 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.[58] Also, the lncRNA 91H of the H19/IGF2 locus is transcribed in the H19 antisense orientation. In breast cancer, 91H lncRNA prevents DNA methylation of the maternal allele at the H19/IGF2 locus, thereby increasing the aggressive phenotype of breast cancer cells.[56] In addition, lncRNA also inhibits gene transcription by recruiting histone modification or chromatin remodeling proteins.[4] lncRNA HOX transcript antisense RNA (HOTAIR) plays a critical role in chromatin dynamics through the interaction with histone modifiers resulting in transcriptional gene silencing.[59] 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.[60]

lncRNAs 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.[61–63] Increasing studies have shown that lncRNAs 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).[62] For example, Dong et al.[64] find that tumor-associated macrophage (TAM)-derived EVs containing HIF-1α-stabilizing lncRNA 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.[64] Breast cancer cells also uptake exosomes containing lncRNA SNHG3 released from cancer-associated fibroblasts (CAFs). lncRNA SNHG3 acts as a molecular sponge of miR-330-5p to control pyruvate kinase to reprogram the metabolic pathways of breast cancer cells.[65] In addition, the release of HOTAIR-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 HOTAIR has been verified in isogenic breast cancer cell lines with and without ectopic ErbB2 expression.[66]

THE ROLE OF lncRNA IN BREAST CANCER MALIGNANT PROGRESS

lncRNAs 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.[67–69] Apparently, increasing evidences prove that abnormal expression of lncRNA 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 lncRNAs control breast cancer progression. The function of lncRNAs in breast cancer was shown in Figure 3 and Table 1.

lncRNAs 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 lncRNAs regulate cell proliferation by activating or inhibiting specific signaling pathways in breast cancer.[118]

It has been reported that a variety of lncRNAs positively regulates the proliferation of breast cancer cells, such as lncRNA SPRY4 intron transcript 1 (SPRY4-IT1), DANCR, PVT1, CCAT1, and KCNQ1OT1 (Figure 3A).[70,119–123] However, the mechanisms by which these lncRNAs promote the proliferation of breast cancer cells are different. For example, the expression level of SPRY4-IT1, a 708-bp lncRNA 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.[70] However, the precise molecular mechanism of how SPRY4-IT1 controls ZNF703 expression needs further study. At present, it is clear that DANCR and PVT1 activate the specific signal pathways by combining with "mediators."[119,122] DANCR 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.[119] 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.[122] Besides, miRNA can also become a potential target of lncRNA and participate in cancer cell proliferation. For example, lncRNA 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.[121] Another lncRNA, KCNQ1OT1, acts as a competitive sponge to regulate the miR-145/CCNE2 pathway, thereby promoting tumor growth *in vivo*.[123]

On the contrary, several lncRNAs play a tumor-suppressor effect in breast cancer cell proliferation (Figure 3A). Ai et al.[124] 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.[124]

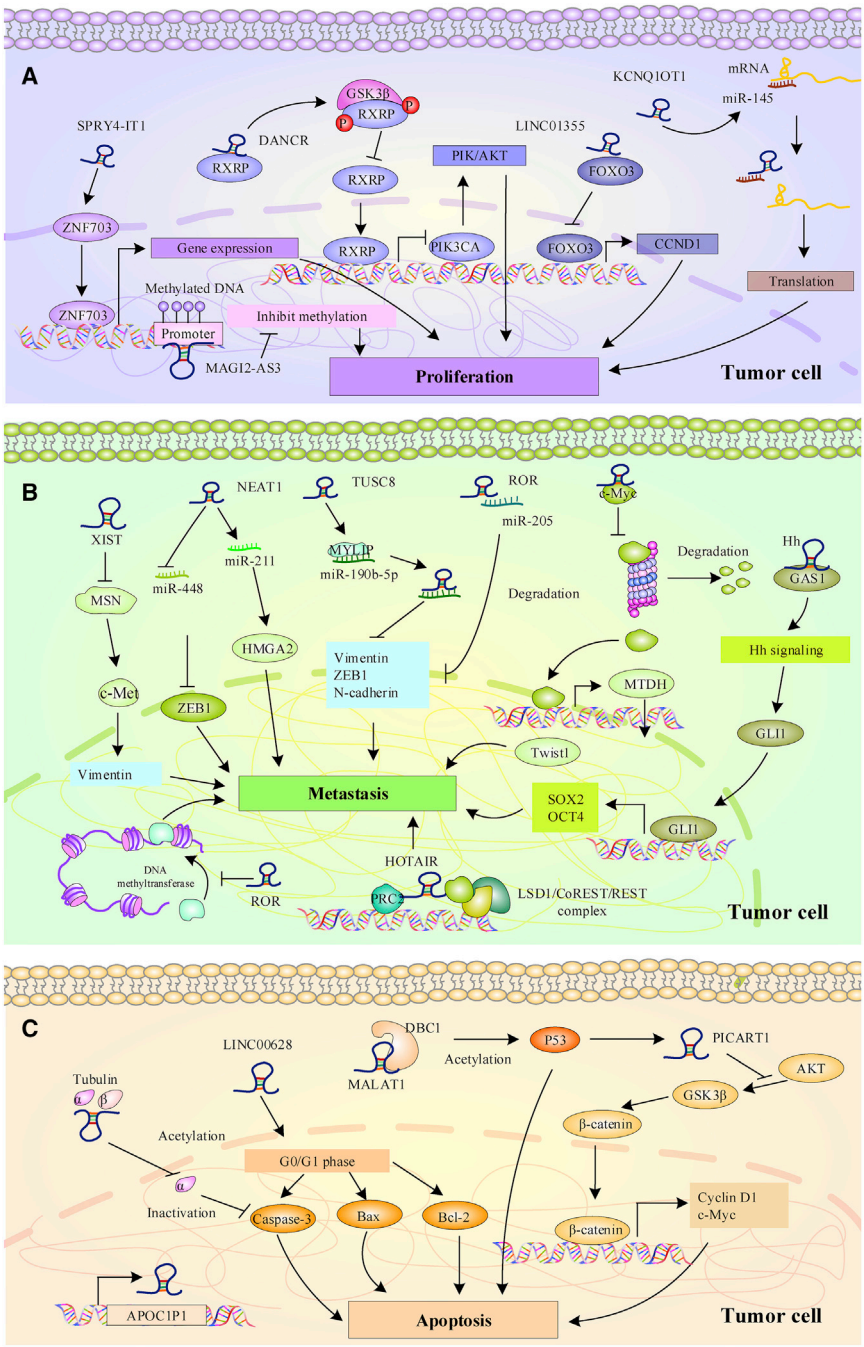

Figure 3. lncRNAs modulate the proliferation, metastasis, and apoptosis of breast cancer cells

(A) lncRNA regulates cell proliferation by activating or inhibiting specific signaling pathways in breast cancer. (B) lncRNAs 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. lncRNA also regulates the stemness of CSCs to obtain metastatic ability. (C) lncRNA 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.

lncRNA SONE is a potential tumor-suppressor gene in TNBC cells. Downregulation of lncRNA 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 lncRNA 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.[116] Moreover, the RNA-RNA interaction can also regulate breast cancer cell proliferation. lncRNA PTCSC3 is downregulated in tumor tissues of TNBC patients. In contrast, lncRNA H19, an imprinted lncRNA only transcribed from the maternal genome, is upregulated and negatively correlated with PTCSC3 in tumor tissue and plays an important role in breast cancer cell proliferation.[125,126] Overexpression of PTCSC3 leads to downregulation of the H19 level in TNBC cells, whereas upregulation of H19 has no effect on the expression of PTCSC3. This result indicates that lncRNA PTCSC3 inhibits the proliferation of TNBC cells by downregulating lncRNA H19.[113]

lncRNAs mediate breast cancer invasion and metastasis

Tumor invasion and metastasis are the most prominent biological characteristics and the main causes of death in breast cancer patients. The abnormal expression of lncRNA in breast cancer cells causes an aggressive phenotype such as invasion and metastasis through a variety of molecular mechanisms (Figure 3B).[41] EMT refers to the process by which epithelial cells transformed into mesenchymal cells under specific physiological and pathological conditions to gain invasiveness and migration capabilities.[127] EMT is characterized by increased expression of mesenchymal markers such as vimentin, fibronectin, N-cadherin, Twist1, and zinc-finger E-box binding homeobox 1 (ZEB1) and decreased expression of epithelial cells junction proteins, including E-cadherin, claudins, and α-catenin.[128] miRNAs are a type of widely distributed small non-coding protein RNAs that can function as tumor-

Table 1. Summarization of the cellular functions of lncRNAs in breast cancer (BC)

lncRNA	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 (JNK)/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	73
BORG	upregulation	chemotherapy resistance, proliferation	activating the NF-κB signaling pathway	74
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	76
LINC00922	upregulation	proliferation, survival, migration, invasion	activating the Wnt signaling pathway; reduced the NKD2 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	78
H19	upregulation	proliferation, migration, invasion	regulating the miR-152/DNMT1 axis	71
ROR	upregulation	promoting migration	regulating miR-145/ARF6 axis	79
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	71
lnc-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	72
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	83
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
CCAT1	upregulation	promoting proliferation and migration, stemness	regulating miR-218/ZFX axis, WNT/β-catenin	86
TROJAN	upregulation	promoting proliferation	induced ZMYND8 degradation	87
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*)

Table 1. *Continued*

lncRNA	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-548b-3p/NAMPT axis	92
linc-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
lnc015192	upregulation	migration, invasion, and EMT	lnc015192-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	55
GACAT3	upregulation	promoting proliferation	regulating miR-497/CCND2 signaling	98
ITGB2-AS1	upregulation	migration and invasion	upregulating integrin subunit beta 2 (ITGB2)	99
NNT-AS1	upregulation	migration and invasion	regulating NNT-AS1/miR-142-3p/ZEB1 axis	100
P10247	upregulation	metastasis	by the regulation of ITGB1 levels	101
EZR-AS1	upregulation	tumor growth and metastasis	modulating Wnt/β-catenin pathway	102
PRLB	upregulation	proliferation and metastasis	regulating miR-4766-5p/SIRT1 axis	103
PVT1	upregulation	promoting invasion and EMT	serving as a competing endogenous RNA for miR-204-5p	104
ATB	upregulation	promoting EMT	upregulating the miR-200c/Twist1 axe	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	17
UCA1	downregulation	tamoxifen resistance, proliferation	activating Wnt/β-catenin; regulated PI3K/AKT signaling pathways	72
GAS5	downregulation	tumor-suppressive, downregulating tamoxifen resistance	upregulating the expression of miR-21	110
PTENP1	downregulation	chemotherapy resistance, proliferation	upregulating PTEN expression	74
ILA	downregulation	metastasis	inhibiting the breast EMT process	71
linc00968	downregulation	ADR, Taxol, and vincristine resistance	Wnt2/β-catenin/MRP1/BCRP/P-gp signaling	111
LINC00472	downregulation	suppressing the phosphorylation of NF-κB	possibly regulating several relapse or metastasis-related pathways, such as PI3K/AKT and Wnt signaling pathways	112
PTCSC3	downregulation	inhibiting proliferation	downregulating lncRNA H19	113
NEF	downregulation	inhibiting migration	negatively regulated miR-155	114
TUG1	downregulation	apoptosis, proliferation, and metastasis	promoting cell cycle progression and regulating the expression of cyclin D1 and CDK4	115
ANCR	downregulation	invasion and metastasis	ANCR interaction with EZH2 to promote its phosphorylation that facilitates EZH2 degradation.	53
MAGI2-AS3	downregulation	inhibiting cell proliferation and migration	downregulating DNA methylation of MAGI2	116
NKILA	downregulation	suppressing EMT	NKILA-mediated negative feedback affects TGF-β-induced NF-κB activation	117

suppressor genes or oncogenes. Studies have shown that lncRNA can interfere with miRNAs to regulate tumor cell metastasis and invasion.[129] For example, lncRNA NEAT1 can promote the migration and invasion of breast cancer cells. NEAT1 acts as a competing endogenous (ce)RNA sponge miR-448 to regulate ZEB1 in breast cancer.[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.[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.[132] lncRNA 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.[133] Recent studies report that overexpression of lncRNA 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 *in vivo*.[134] In addition, Fan et al.[135] find that ROR can also prevent the recruitment of chromatin regulators G9A methyltransferase and abolish the histone H3K9 modification of the tescalcin (TESC; also known as calcineurin B homologous protein 3 [CHP3]) promoter, leading to abnormal breast cancer metastasis.[135] High expression of lncRNA 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-β-induced EMT model, the expression of lncRNA ATB in breast cancer cells is upregulated and enhances tumor cell migration and invasion. Further research results show that lncRNA ATB acts as a sponge of the miR-200 family and restores Twist1 expression to promote breast cancer metastasis.[105] 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.[136]

In addition, lncRNA 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 *in vivo* and *in vitro*.[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.[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.[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.[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.[139] Studies have shown that some small interfering RNAs (siRNAs) effectively inhibit breast cancer brain metastasis by depleting lncRNAs.[140] lncRNA 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 lnc-BM/JAK2/STAT3 pathway and promote breast cancer brain metastasis, whereas depletion of lnc-BM with nanoparticle-encapsulated siRNAs effectively decreases JAK2 kinase activity to inhibit brain metastasis.[140] Therefore, targeting lncRNAs 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.[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.[142] CSCs and EMT have many similarities in tumor recurrence, metastasis, and drug resistance.[143] Both CSC stemness and EMT are regulated by various signal pathways such as Notch, Wnt/β-catenin, and TGF-β signaling pathway.[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.[145] lncRNAs have been identified and characterized as a new, important player in regulating the stemness acquisition and maintenance of CSCs.[146] For example, Zhou et al.[142] demonstrate that lncRNA-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. lncRNA-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.[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.[147] The expression level of lncRNA 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.[148] Together, these evidences indicate that lncRNA-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.

lncRNAs 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.[149] Increasing studies have confirmed that lncRNA can affect tumor cell apoptosis mainly through p53 and cysteine aspartate-specific proteases (caspases) signaling pathways (Figure 3C).[150] 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 lncRNA p53-inducible cancer-associated RNA transcript 1 (PICART1) inhibits breast cancer proliferation and promotes apoptosis through the AKT/GSK-3β/β-catenin signaling pathway.[151] lncRNA MALAT1 is a widely expressed lncRNA, involving many aspects of cellular processes. Quantitative proteomics finds that MALAT1 interacts with DBC1 to regulate p53 acetylation to inhibit apoptosis.[152] In addition, the induction of LINC01125 by liver X receptor agonist LXR-623 activates phosphatase and tensin homolog (PTEN)/AKT/MDM2/p53 signaling pathway to mediate cell apoptosis.[153] Caspases are a type of cysteine proteases that often trigger apoptosis in a cascade manner. Studies have found that lncRNAs are involved in the caspase-mediated apoptosis pathway.[154] The low expression of LINC00628 in breast cancer has a poor prognosis and a low OS rate. Overexpression of LINC00628 inhibits the proliferation, invasion, and migration of breast cancer cells and arrests the cell cycle in the G0/G1 phase. LINC00628 promotes cell apoptosis by regulating caspase-3, Bax, and Bcl-2 expression.[155] lincRNA-APOC1P1-3 is overexpressed in breast cancer, and hypomethylation in its promoter region is related to tumor size. In addition, APOC1P1-3 can directly bind to tubulin to reduce the acetylation of α-tubulin, inactivate caspase-3, and thus inhibit cell apoptosis.[156]

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 lncRNA to control tumor cell apoptosis is expected to become an effective measure for the treatment of breast cancer.

lncRNAs 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.[126] 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.[126] A large number of studies have shown that abnormally expressed lncRNAs are related to the multidrug resistance of breast cancer.[137] Here, we described in detail the molecular mechanism of lncRNA-mediated breast cancer resistance to multiple drugs in Figure 4 and Table 2.

lncRNAs participate in endocrine therapy resistance

According to the expression of ER, PR, HER2, and Ki67, breast cancer has been classified into four subtypes, including luminal A, luminal B, HER2 positive, and TNBC.[195] Approximately 75% of breast cancer patients are diagnosed with a luminal subtype. This indicates that the ER signaling pathway driven by estrogen is the main oncogenic pathway in most breast cancer.[6] For these luminal subtype breast cancers, endocrine therapy, such as selective ER modulator (SERM), selective ER degraders (SERDs), and aromatase inhibitors, is highly effective by disrupting receptor binding or estrogen deprivation. However, the abnormal expression of lncRNAs often causes patients to develop resistance to endocrine therapy drugs (Figure 4A).[196]

lncRNAs and SERM and SERD. The first-line endocrine drug tamoxifen and other SERMs against ER antagonize the activity of estrogen, leading to transcriptional inhibition of ER target genes.[197] However, drug resistance reduces the efficacy of such treatments in up to 40% of breast cancer patients.[198] Autophagy is a cellular process that degrades misfolded proteins and dysfunctional organelles in cells through lysosomes or vacuoles.[157] Recent studies have shown that autophagy mediates breast cancer resistance to tamoxifen. Induction of autophagy by overexpression of Beclin1, a key mediator of autophagy, significantly reduces estrogen-induced signaling, thereby promoting the development of tamoxifen resistance in ER-positive breast cancer.[199] Wang et al.[157] find that lncRNA H19 is significantly upregulated in tamoxifen-resistant breast cancer cell lines and tumor tissues. Knocking out H19 can significantly inhibit the autophagy of MCF-7 tamoxifen-resistant cells. In contrast, overexpression of H19 promotes autophagy. Further study has shown that H19 downregulates the methylation in the Beclin1 promoter through the SAHH/DNMT3B axis to cause autophagy to resist tamoxifen.[157] H19 is also involved in breast cancer resistance to fulvestrant, which belong to SERD. H19 regulates ERα expression at the transcription and translation levels in LCC9 cells. Moreover, H19 attenuates fulvestrant-mediated downregulation of ERα protein to promote fulvestrant resistance.[200] lncRNA urothelial carcinoma associated protein 1 (UCA1) has been shown to be dysregulated in human breast cancer and promotes cancer progression. The expression level of UCA1 in tamoxifen-resistant breast cancer cells is significantly higher. UCA1 confers tamoxifen resistance by regulating the EZH2/p21 axis.[201] In addition, UCA1 expression is also detected in exosomes released from tamoxifen-resistant breast cancer cells. MCF-7 breast cancer cells pretreated with exosomes of tamoxifen-resistant LCC2 cells *in vitro* show increased resistance to tamoxifen, indicating that exosomes can carry the lncRNA UCA1 to spread tamoxifen resistance.[202] Furthermore, the PI3K/AKT/mTOR signaling pathway activated by UCA1 is also involved in breast cancer tamoxifen resistance.[203] In addition, lncRNA can act as a molecular sponge of miRNAs to promote drug resistance. For example, lncRNA ROR is involved in the occurrence, development, metastasis, and multidrug resistance of

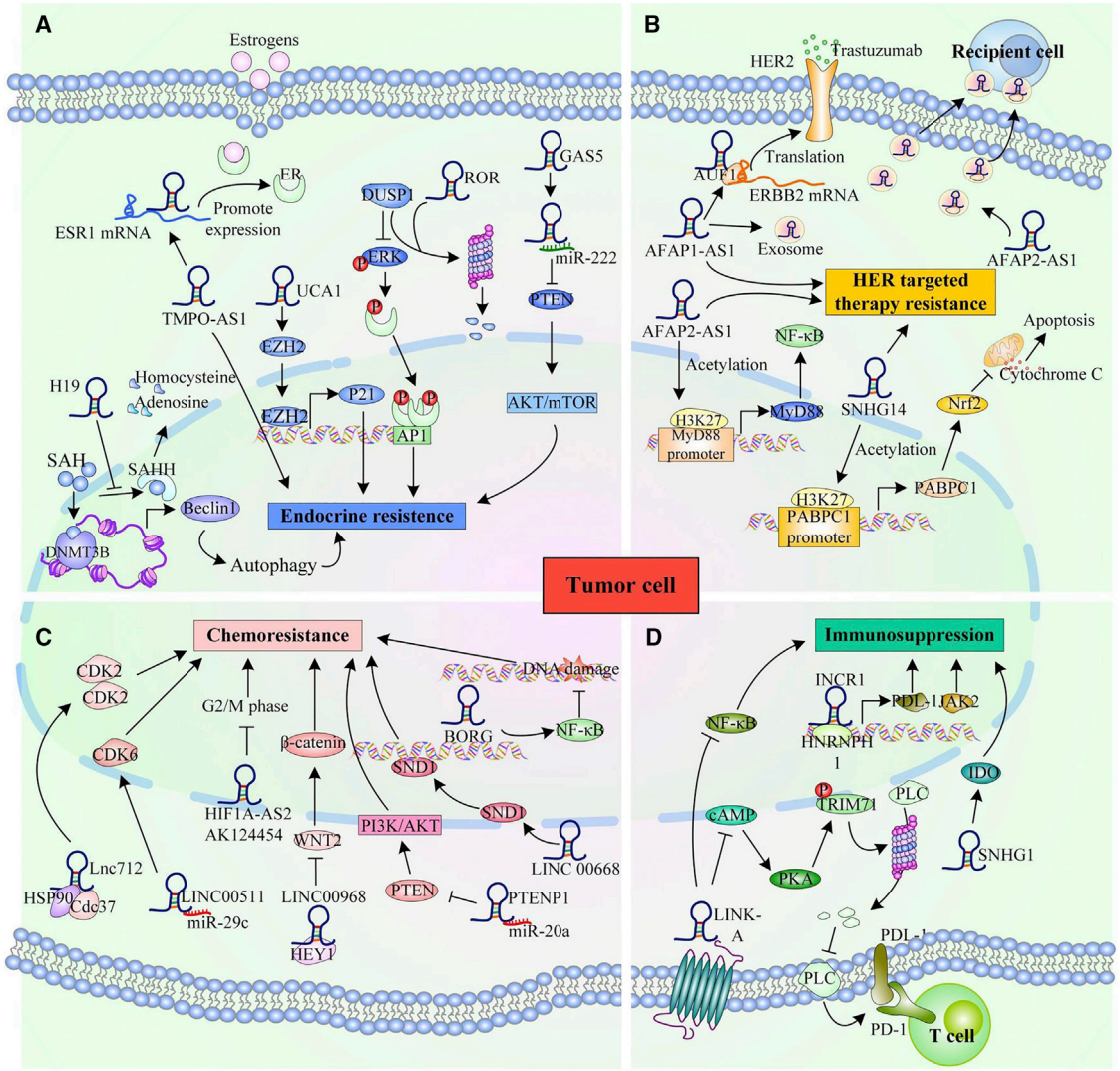

Figure 4. lncRNA affects drug resistance in breast cancer cells

(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, GAS5 negatively regulates endocrine therapy resistance through PTEN/AKT/mTOR signaling. (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-κB 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-κB mediated by lncRNA BORG can inhibit chemotherapy-induced DNA damage. lncRNA can affect the cell cycle by regulating the cycle-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.

breast cancer cells. Reduction of the ROR expression can attenuate the resistance of breast cancer cells to tamoxifen.[204] 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.[171] In another study, it is found that ROR can also promote estrogen dependence and tamoxifen resistance by activating the

Table 2. lncRNAs participate in the drug resistance of BC treatment

lncRNA	Expression patterns	Pathway/target	Expression pattern drugs	Mechanisms	Reference
H19	upregulation	ER, LIK and LOXA, H19-CUL4A-ABCB1/MDR1 axis, H19/Let-7/LIN28 axis	tamoxifen, fulverstrant, 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	126,157,158
HOTAIR	upregulation	ER	tamoxifen, doxorubicin, trastuzumab	promote the expression of ERα and promote ERα 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/HMGA2, miR-129/ZEB2	cisplatin, paclitaxel, 5-FU	regulate cell apoptosis and cell cycle; promote cell growth	161
lnc712	upregulation	lnc712/HSP90/Cdc37/CDK2	palbociclib	regulating CDK2 activation and triggering cell proliferation	162
LINK-A	upregulation	PIP3/GPCR/cAMP/PKA/TRIM71/PLC	immune checkpoint blockers	reducing antigenicity to avoid detection by antitumor; reduced antigen presentation on BC cell surface	163
MIR2052HG	upregulation	EGR1, ER, ERα/PI3K/AKT	aromatase inhibitors	increased ESR1 transcription; reduced ER degradation by LMTK3; resistance to endocrine therapy	164
GAS5	downregulation	miR-222/PTEN, miR-378a-5p/SUFU, miR-21/mTOR/PTEN, miR-221-3p/DDK2/Wnt/β-catenin	tamoxifen, paclitaxel, trastuzumab, Adriamycin	contributing to suppression of phosphatase and tensin homologs; ceRNA; contributes to cell proliferation	110,165
LINP1	upregulation	ER, caspase-8/9, caspase-9/Bax	doxorubicin, 5-FU, tamoxifen	decreasing ERα expression level; regulate cell growth and apoptosis; EMT; diminishes the estrogen response	166
linc00518	upregulation	miR-199a/MRP1	Adriamycin, paclitaxel, vincristine	downregulate the expression of MRP1	167
CRALA	upregulation	targeting CRALA	cisplatin, paclitaxel	promote cell growth	82
UCA1	upregulation	miR-18a/YAP1, miR-18a/HIF-1α, EZH2/p21, AKT/mTOR, Wnt/β-catenin signaling	trastuzumab, tamoxifen	promote cell apoptosis and arrest the cell cycle in G2/M phase	168,169
BC032585	downregulation	MDR1	paclitaxel, doxorubicin	regulate the expression of MDR1	170
linc00968	downregulation	Wnt2/β-catenin/MRP1/BCRP/P-gp	Adriamycin, vincristine, Taxol, paclitaxel	inhibit Wnt2/β-catenin signaling pathway; reduce the ability of cell colony formation; and induce cell apoptosis	111
TINCR	upregulation	miR-125b/ERBB2	trastuzumab	regulating the expression level of HER2	64
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	171,172
DCST1-AS1	upregulation	ANXA1	doxorubicin, paclitaxel	enhancing EMT and promotes TNBC chemoresistance to doxorubicin and paclitaxel	173
NKILA	upregulation	NF-κB	immunotherapy	facilitating T cell vulnerability to AICD and decreasing CTL infiltration and apoptosis	174
TMPO-AS1	upregulation	ER	endocrine therapy	stabilizing *ESR1* mRNA	175
DSCAM-AS1	upregulation	hnRNPL, miR-137/EPS8	tamoxifen	promoting cell proliferation and suppressing apoptosis	176
HOTAIRM1	upregulation	EZH2	tamoxifen	preventing H3K27 methylation (H3K27me3) of HOXA1	177
CYTOR	upregulation	miR-125a-5p/SRF, Hippo, MAPK	tamoxifen	ceRNA; promoting cell survival	84

(*Continued on next page*)

Table 2. *Continued*

lncRNA	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	hnRNPA2B1, CBP/MyD88/H3K27/NF-κB	trastuzumab	exosome-mediated dissemination; activating NF-κB 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	159
NONHSAT141924	upregulation	p-CREB/Bcl-2 apoptosis pathway	paclitaxel	enhances BC resistance to paclitaxel	187
AC073284.4	downregulation	miR-18b-5p/DOCK4	paclitaxel	ceRNA; attenuates paclitaxel resistance	188
RP11.259N19.1	upregulation	PI3K/AKT, focal adhesions and WNT signaling	tamoxifen	–	189
KB.1460A1.5	upregulation	–	–	–	189
PP14571	upregulation	–	–	–	189
PINK1.AS	downregulation	–	–	–	189
KLF3.AS1	downregulation	–	–	–	189
LINC00339	downregulation	–	–	–	189
LINC00472	downregulation	–	–	–	189
RP11.351I21.11	downregulation	–	–	–	189
PKD1P6.NPIPP1	downregulation	–	–	–	189
PDCD4.AS1	downregulation	–	–	–	189
KLF3.AS1	downregulation	–	–	–	189
PP14571	downregulation	–	–	–	189
RP11.69E11.4	downregulation	–	–	–	189
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	190
ATB	upregulation	miR-200c/ZEB1, ZNF-217	trastuzumab	EMT	191
HIF1A-AS2	upregulation		paclitaxel	metabolism and cell division	192
AK124454	upregulation		paclitaxel	metabolism and cell division	192
NONHSAT057282	upregulation	ELF1 and E2F1	anthracycline	metabolism and cell division	192
NONHSAG023333	upregulation	ELF1 and E2F1	anthracycline	metabolism and cell division	192
DAMTS9-AS2	downregulation	miR-130a-5p	tamoxifen	inhibiting miR-130a-5p activity to increase the expression of PTEN	193
XIST	upregulation	miR-200c-3p	doxorubicin	regulating PI3K/AKT/mTOR pathway	109
Eleanors	upregulation	upregulating ER expression	tamoxifen	increasing the expression of ESR1	194

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 lncRNA ROR promotes the degradation of DUSP7 by activating ERK, leading to tamoxifen resistance.[172] In contrast, lncRNAs can act as tumor suppressors to play an important role in decreasing tamoxifen resistance. For example, downregulation of lncRNA 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.[110]

lncRNAs 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.[205] 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.[206] However, there are few studies on the relationship between lncRNAs and the function of aromatase inhibitors. Until now, only lncRNA MIR2052HG has been reported to be associated with breast cancer resistance to aromatase inhibitors. lncRNA 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 MIR205HG and ER expression.[164] Mechanistically, MIR2052HG interacts with EGR1 and promotes its recruitment to the LMTK3 promoter. LMTK3 maintains ERα 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 ERα degradation mediated by the PKC/mitogen-activated protein kinase kinase/ERK/ribosomal S6 protein kinase type 1 pathway to resist anastrozole or exemestane.[85]

lncRNAs 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.[207] lncRNA as a key regulator of trastuzumab resistance in breast cancer has attracted increasing attention (Figure 4B).[64] For example, in trastuzumab-resistant breast cancer cells, lncRNA AFAP1-AS1 can bind to AUF1 and promote HER2 translation, which resulted in increased expression of HER2 and caused trastuzumab resistance. In addition, AFAP1-AS1 in trastuzumab resistance can be packaged into exosomes and enhance the drug resistance of recipient cells.[46] Mechanismly, lncRNA 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.[178] Another lncRNA 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.[179] Additionally, lncRNA AGAP2-AS1 and SNHG14 promote the tolerance of breast cancer cells to trastuzumab through exosome-mediated diffusion.[178,208] Moreover, lncRNAs also participate in drug resistance as a byproduct of physiological processes.[64] A recent study reports that CBP-mediated H3K27 acetylation can activate lncRNA 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.[64]

lncRNAs 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).[186]

Anthracycline. 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, alkylation, and cross-linking, leading to cancer cells apoptosis.[209,210] However, many patients show resistance to these drugs within a short recurrence time.[211] It has been reported that several lncRNAs are involved in the resistance of breast cancer to DOX/ADR. For example, lncRNA BORG reduces DNA damage by activating the NF-κB signaling pathway, thereby enhancing DOX resistance in TNBCs.[212] lncRNA LINC00668 is upregulated in breast cancer cells and improves DOX resistance by targeting staphylococcal nuclease domain-containing 1 (SND1).[213]

Contrary to positive regulation of above lncRNAs in breast cancer resistance to anthracycline, some lncRNAs can reduce the drug resistance. lncRNA 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.[214] The low expression of lncRNA MEG3 reduces apoptosis through the Bax/Bcl-2 axis to promote DOX resistance in breast cancer.[215] 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.[111]

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.[216] Epirubicin is currently an important class of drugs, which has shown strong efficacy in anticancer chemotherapy and is mainly used for breast cancer.[217] The novel lncRNA 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.[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.[218] 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.[219] Jiang et al.[192] show that lncRNA 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 lncRNAs 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.[192] In addition, lncRNA is also involved in breast cancer resistance to paclitaxel by regulating miRNA activation. For example, lncRNA CASC2 is upregulated in breast cancer cells and activates paclitaxel resistance in breast cancer by regulating the miR-18a-5p/CDK19 axis.[220] lncRNA LINC00511 interacts directly with miR-29c and inhibits its expression, thereby increasing the expression of CDK6 and inhibiting paclitaxel-induced cytotoxicity.[221] In paclitaxel-resistant MCF-7 breast cancer cells, lncRNA FTH1P3 is upregulated and enhances ABCB1 protein expression by acting as a sponge for miR-206, thereby enhancing paclitaxel resistance in breast cancer cells.[184] In contrast, lncRNA EPB41L4A-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.[222]

Cisplatin and 5-fluorouracil. Cisplatin is a platinum drug commonly used in TNBC chemotherapy and significantly induce DNA damage in cancer cells.[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, lncRNA 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.[161] Another example, lncRNA 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.[224] The novel lncRNA PRLB enhances 5-fluorouracil resistance by regulating the miR-4766-5p/SIRT1 axis in breast cancer.[103] Besides an miRNA sponge, lncRNAs 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.[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.[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 CDKs.[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 lncRNA in CDK inhibitor resistance. The newly identified lncRNA lnc712 can activate CDK2 by directly interacting with heat shock protein 90 (HSP90) to form a lnc712/HSP90/cell division cycle 37 (Cdc37) complex in breast cancer.[230] These indicate that lnc712 is a promising biomarker for predicting drug response in breast cancer with its ability to enhance cancer cell resistance to CDK inhibitor palbociclib. Similarly, lncRNAs associated with other CDKs, including TUG1, CCAT2, and LINC01089, may also mediate resistance to CDK inhibitors.[115,231,232]

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

lncRNAs 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.[233] We have described in detail the regulation mechanisms of lncRNAs in tumor cell proliferation, apoptosis, metastasis, and drug resistance. Recent studies have shown that lncRNAs also have been shown to be involved in the regulation of the cancer immune response.[234] Although lncRNAs 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).[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 cell. 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.[236]

lncRNAs and immune activation

The relationship between lncRNAs and T lymphocytes has also been extensively studied. linc-MAF-4, a chromatin-related T helper (Th)1-specific lincRNA, 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.[237] 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.[238] 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 polarization 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 secret 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 immunosuppression

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.[163] 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.[245] Another study shows that NKILA interacts with NF-κB to inhibit NF-κB 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 COPS5 upregulation by isolating miR-676-5p as a positive regulator of COPS5 mRNA. The activation of the miR-676-3p/COPS5 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.[22] 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 that in non-TNBC, suggesting their promising use as TNBC-specific diagnostic biomarkers.[250] 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.[251] 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.[252] 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.[253] 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 lncRNA CCAT1 to promote the transcription of lncRNA 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.[86] 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.[71]

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.[254] 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.[255] 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.[256–258] 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.[259] 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).[260] 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.[261] 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.[261]

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, NAMPT-AS, ATB, MIR503HG, LINC01089, and PHACTR2-AS1.[92,105,262–264] 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.[262] In addition, the upregulation of NAMPT-AS and ATB expression is negatively correlated with OS and DFS in TNBC patients.[92] 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.[263] Similarly, LINC01089 and PHACTR2-AS1 also have similar functions.[231,264] Interestingly, the integrated mRNA-lncRNA signature based on the mRNA types of FCGR1A, RSAD2, and CHRDL1 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.[192] 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.[265] For example, Singh et al.[266] 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 the 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 NRAD1 (also known as LINC00284) has been reported to reduce cell survival, tumor growth, and the number of cells with CSC characteristics in TNBC tumors.[90]

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 and the expression of tumor stem cell markers including BMI1, OCT4, and SOX2.[271] In addition, MEG3 knockout mediated by the CRISPR-Cas9 system significantly reduces the invasion ability of human triple-negative metastatic Hs578T cancer cells.[215] These evidences suggest that CRISPR-Cas9 genome editing can be used to precisely eliminate abnormally expressed lncRNAs in cancer cells, thereby providing a useful strategy to target oncogenes for the development of novel precision medicine therapies.

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 underdefined. 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., J.Y., 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.

REFERENCES

1. Harbeck, N., and Gnant, M. (2017). Breast cancer. Lancet *389*, 1134–1150.
2. Peng, L., Jiang, J., Tang, B., Nice, E.C., Zhang, Y.Y., and Xie, N. (2020). Managing therapeutic resistance in breast cancer: from the lncRNAs perspective. Theranostics *10*, 10360–10377.
3. Woolston, C. (2015). Breast cancer. Nature *527*, S101.
4. Cantile, M., Di Bonito, M., Cerrone, M., Collina, F., De Laurentiis, M., and Botti, G. (2020). Long Non-Coding RNA *HOTAIR* in Breast Cancer Therapy. Cancers (Basel) *12*, 1197.
5. Presti, D., and Quaquarini, E. (2019). The PI3K/AKT/mTOR and CDK4/6 Pathways in Endocrine Resistant HR+/HER2- Metastatic Breast Cancer: Biological Mechanisms and New Treatments. Cancers (Basel) *11*, 1242.
6. Augereau, P., Patsouris, A., Bourbouloux, E., Gourmelon, C., Abadie Lacourtoisie, S., Berton Rigaud, D., Soulié, P., Frenel, J.S., and Campone, M. (2017). Hormonoresistance in advanced breast cancer: a new revolution in endocrine therapy. Ther. Adv. Med. Oncol. *9*, 335–346.
7. Rion, N., and Rüegg, M.A. (2017). LncRNA-encoded peptides: More than translational noise? Cell Res. *27*, 604–605.
8. Kopp, F., and Mendell, J.T. (2018). Functional Classification and Experimental Dissection of Long Noncoding RNAs. Cell *172*, 393–407.
9. Pang, B., Wang, Q., Ning, S., Wu, J., Zhang, X., Chen, Y., and Xu, S. (2019). Landscape of tumor suppressor long noncoding RNAs in breast cancer. J. Exp. Clin. Cancer Res. *38*, 79.

10. Zeng, C., Yu, X., Lai, J., Yang, L., Chen, S., and Li, Y. (2015). Overexpression of the long non-coding RNA PVT1 is correlated with leukemic cell proliferation in acute promyelocytic leukemia. J. Hematol. Oncol. *8*, 126.

11. Huang, M.D., Chen, W.M., Qi, F.Z., Xia, R., Sun, M., Xu, T.P., Yin, L., Zhang, E.B., De, W., and Shu, Y.Q. (2015). Long non-coding RNA ANRIL is upregulated in hepatocellular carcinoma and regulates cell apoptosis by epigenetic silencing of KLF2. J. Hematol. Oncol. *8*, 50.

12. Dong, S., Qu, X., Li, W., Zhong, X., Li, P., Yang, S., Chen, X., Shao, M., and Zhang, L. (2015). The long non-coding RNA, GAS5, enhances gefitinib-induced cell death in innate EGFR tyrosine kinase inhibitor-resistant lung adenocarcinoma cells with wide-type EGFR via downregulation of the IGF-1R expression. J. Hematol. Oncol. *8*, 43.

13. Huang, X., Xiao, R., Pan, S., Yang, X., Yuan, W., Tu, Z., Xu, M., Zhu, Y., Yin, Q., Wu, Y., et al. (2017). Uncovering the roles of long non-coding RNAs in cancer stem cells. J. Hematol. Oncol. *10*, 62.

14. Iyer, M.K., Niknafs, Y.S., Malik, R., Singhal, U., Sahu, A., Hosono, Y., Barrette, T.R., Prensner, J.R., Evans, J.R., Zhao, S., et al. (2015). The landscape of long noncoding RNAs in the human transcriptome. Nat. Genet. *47*, 199–208.

15. Miao, Y., Ajami, N.E., Huang, T.S., Lin, F.M., Lou, C.H., Wang, Y.T., Li, S., Kang, J., Munkacsi, H., Maurya, M.R., et al. (2018). Enhancer-associated long non-coding RNA LEENE regulates endothelial nitric oxide synthase and endothelial function. Nat. Commun. *9*, 292.

16. Gomes, C.P., Nóbrega-Pereira, S., Domingues-Silva, B., Rebelo, K., Alves-Vale, C., Marinho, S.P., Carvalho, T., Dias, S., and Bernardes de Jesus, B. (2019). An antisense transcript mediates MALAT1 response in human breast cancer. BMC Cancer *19*, 771.

17. Jadaliha, M., Gholamalamdari, O., Tang, W., Zhang, Y., Petracovici, A., Hao, Q., Tariq, A., Kim, T.G., Holton, S.E., Singh, D.K., et al. (2018). A natural antisense lncRNA controls breast cancer progression by promoting tumor suppressor gene mRNA stability. PLoS Genet. *14*, e1007802.

18. Zhang, T., Hu, H., Yan, G., Wu, T., Liu, S., Chen, W., Ning, Y., and Lu, Z. (2019). Long Non-Coding RNA and Breast Cancer. Technol. Cancer Res. Treat. *18*, 1533033819843889.

19. Lai, F., and Shiekhattar, R. (2014). Where long noncoding RNAs meet DNA methylation. Cell Res. *24*, 263–264.

20. Kretz, M., Webster, D.E., Flockhart, R.J., Lee, C.S., Zehnder, A., Lopez-Pajares, V., Qu, K., Zheng, G.X., Chow, J., Kim, G.E., et al. (2012). Suppression of progenitor differentiation requires the long noncoding RNA ANCR. Genes Dev. *26*, 338–343.

21. Tang, J., Xie, Y., Xu, X., Yin, Y., Jiang, R., Deng, L., Tan, Z., Gangarapu, V., Tang, J., and Sun, B. (2017). Bidirectional transcription of Linc00441 and RB1 via H3K27 modification-dependent way promotes hepatocellular carcinoma. Cell Death Dis. *8*, e2675.

22. Mei, J., Hao, L., Wang, H., Xu, R., Liu, Y., Zhu, Y., and Liu, C. (2020). Systematic characterization of non-coding RNAs in triple-negative breast cancer. Cell Prolif. *53*, e12801.

23. Tan, B.S., Yang, M.C., Singh, S., Chou, Y.C., Chen, H.Y., Wang, M.Y., Wang, Y.C., and Chen, R.H. (2019). LncRNA NORAD is repressed by the YAP pathway and suppresses lung and breast cancer metastasis by sequestering S100P. Oncogene *38*, 5612–5626.

24. Hung, T., Wang, Y., Lin, M.F., Koegel, A.K., Kotake, Y., Grant, G.D., Horlings, H.M., Shah, N., Umbricht, C., Wang, P., et al. (2011). Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters. Nat. Genet. *43*, 621–629.

25. Wang, Y., Wu, S., Zhu, X., Zhang, L., Deng, J., Li, F., Guo, B., Zhang, S., Wu, R., Zhang, Z., et al. (2020). LncRNA-encoded polypeptide ASRPS inhibits triple-negative breast cancer angiogenesis. J. Exp. Med. *217*, jem.20190950.

26. Guo, B., Wu, S., Zhu, X., Zhang, L., Deng, J., Li, F., Wang, Y., Zhang, S., Wu, R., Lu, J., and Zhou, Y. (2020). Micropeptide CIP2A-BP encoded by LINC00665 inhibits triple-negative breast cancer progression. EMBO J. *39*, e102190.

27. Calanca, N., Paschoal, A.P., Munhoz, É.P., Galindo, L.T., Barbosa, B.M., Caldeira, J.R.F., Oliveira, R.A., Cavalli, L.R., Rogatto, S.R., and Rainho, C.A. (2019). The long non-coding RNA *ANRASSF1* in the regulation of alternative protein-coding transcripts *RASSF1A* and *RASSF1C* in human breast cancer cells: implications to epigenetic therapy. Epigenetics *14*, 741–750.

28. Puvvula, P.K., Desetty, R.D., Pineau, P., Marchio, A., Moon, A., Dejean, A., and Bischof, O. (2014). Long noncoding RNA PANDA and scaffold-attachment-factor SAFA control senescence entry and exit. Nat. Commun. *5*, 5323.

29. Negishi, M., Wongpalee, S.P., Sarkar, S., Park, J., Lee, K.Y., Shibata, Y., Reon, B.J., Abounader, R., Suzuki, Y., Sugano, S., and Dutta, A. (2014). A new lncRNA, APTR, associates with and represses the CDKN1A/p21 promoter by recruiting polycomb proteins. PLoS ONE *9*, e95216.

30. McHugh, C.A., Chen, C.K., Chow, A., Surka, C.F., Tran, C., McDonel, P., Pandya-Jones, A., Blanco, M., Burghard, C., Moradian, A., et al. (2015). The Xist lncRNA interacts directly with SHARP to silence transcription through HDAC3. Nature *521*, 232–236.

31. Chédin, F. (2016). Nascent Connections: R-Loops and Chromatin Patterning. Trends Genet. *32*, 828–838.

32. Yao, R.W., Wang, Y., and Chen, L.L. (2019). Cellular functions of long noncoding RNAs. Nat. Cell Biol. *21*, 542–551.

33. Postepska-Igielska, A., Giwojna, A., Gasri-Plotnitsky, L., Schmitt, N., Dold, A., Ginsberg, D., and Grummt, I. (2015). LncRNA Khps1 Regulates Expression of the Proto-oncogene SPHK1 via Triplex-Mediated Changes in Chromatin Structure. Mol. Cell *60*, 626–636.

34. Arab, K., Karaulanov, E., Musheev, M., Trnka, P., Schäfer, A., Grummt, I., and Niehrs, C. (2019). GADD45A binds R-loops and recruits TET1 to CpG island promoters. Nat. Genet. *51*, 217–223.

35. De Troyer, L., Zhao, P., Pastor, T., Baietti, M.F., Barra, J., Vendramin, R., Dok, R., Lechat, B., Najm, P., Van Haver, D., et al. (2020). Stress-induced lncRNA LASTR fosters cancer cell fitness by regulating the activity of the U4/U6 recycling factor SART3. Nucleic Acids Res. *48*, 2502–2517.

36. Bernard, D., Prasanth, K.V., Tripathi, V., Colasse, S., Nakamura, T., Xuan, Z., Zhang, M.Q., Sedel, F., Jourdren, L., Coulpier, F., et al. (2010). A long nuclear-retained non-coding RNA regulates synaptogenesis by modulating gene expression. EMBO J. *29*, 3082–3093.

37. Meng, N., Chen, M., Chen, D., Chen, X.-H., Wang, J.-Z., Zhu, S., He, Y.-T., Zhang, X.-L., Lu, R.-X., and Yan, G.-R. (2020). Small Protein Hidden in lncRNA LOC90024 Promotes "Cancerous" RNA Splicing and Tumorigenesis. Adv. Sci. (Weinh). *7*, 1903233.

38. Miller, M.A., and Olivas, W.M. (2011). Roles of Puf proteins in mRNA degradation and translation. Wiley Interdiscip. Rev. RNA *2*, 471–492.

39. Lee, S., Kopp, F., Chang, T.C., Sataluri, A., Chen, B., Sivakumar, S., Yu, H., Xie, Y., and Mendell, J.T. (2016). Noncoding RNA NORAD Regulates Genomic Stability by Sequestering PUMILIO Proteins. Cell *164*, 69–80.

40. Gong, C., and Maquat, L.E. (2011). lncRNAs transactivate STAU1-mediated mRNA decay by duplexing with 3′ UTRs via Alu elements. Nature *470*, 284–288.

41. Liu, L., Zhang, Y., and Lu, J. (2020). The roles of long noncoding RNAs in breast cancer metastasis. Cell Death Dis. *11*, 749.

42. Salmena, L., Poliseno, L., Tay, Y., Kats, L., and Pandolfi, P.P. (2011). A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell *146*, 353–358.

43. Rapicavoli, N.A., Qu, K., Zhang, J., Mikhail, M., Laberge, R.M., and Chang, H.Y. (2013). A mammalian pseudogene lncRNA at the interface of inflammation and anti-inflammatory therapeutics. eLife *2*, e00762.

44. Zhen, S., and Li, X. (2019). Application of CRISPR-Cas9 for Long Noncoding RNA Genes in Cancer Research. Hum. Gene Ther. *30*, 3–9.

45. Zhou, W., Gong, J., Chen, Y., Chen, J., Zhuang, Q., Cao, J., Mei, Z., and Hu, B. (2019). Long noncoding RNA LINC00899 suppresses breast cancer progression by inhibiting miR-425. Aging (Albany N.Y.) *11*, 10144–10153.

46. Han, M., Gu, Y., Lu, P., Li, J., Cao, H., Li, X., Qian, X., Yu, C., Yang, Y., Yang, X., et al. (2020). Exosome-mediated lncRNA AFAP1-AS1 promotes trastuzumab resistance through binding with AUF1 and activating ERBB2 translation. Mol. Cancer *19*, 26.

47. Ingolia, N.T., Lareau, L.F., and Weissman, J.S. (2011). Ribosome profiling of mouse embryonic stem cells reveals the complexity and dynamics of mammalian proteomes. Cell *147*, 789–802.

48. Yoon, J.H., Abdelmohsen, K., Srikantan, S., Yang, X., Martindale, J.L., De, S., Huarte, M., Zhan, M., Becker, K.G., and Gorospe, M. (2012). LincRNA-p21 suppresses target mRNA translation. Mol. Cell *47*, 648–655.

49. Zhang, A., Zhou, N., Huang, J., Liu, Q., Fukuda, K., Ma, D., Lu, Z., Bai, C., Watabe, K., and Mo, Y.Y. (2013). The human long non-coding RNA-RoR is a p53 repressor in response to DNA damage. Cell Res. *23*, 340–350.

50. Jiang, Z., Slater, C.M., Zhou, Y., Devarajan, K., Ruth, K.J., Li, Y., Cai, K.Q., Daly, M., and Chen, X. (2017). LincIN, a novel NF90-binding long non-coding RNA, is over-expressed in advanced breast tumors and involved in metastasis. Breast Cancer Res. *19*, 62.

51. Jia, X., Shi, L., Wang, X., Luo, L., Ling, L., Yin, J., Song, Y., Zhang, Z., Qiu, N., Liu, H., et al. (2019). KLF5 regulated lncRNA RP1 promotes the growth and metastasis of breast cancer via repressing p27kip1 translation. Cell Death Dis. *10*, 373.

52. Lin, H.C., Yeh, C.C., Chao, L.Y., Tsai, M.H., Chen, H.H., Chuang, E.Y., and Lai, L.C. (2017). The hypoxia-responsive lncRNA *NDRG-OT1* promotes NDRG1 degradation via ubiquitin-mediated proteolysis in breast cancer cells. Oncotarget *9*, 10470–10482.

53. Li, Z., Hou, P., Fan, D., Dong, M., Ma, M., Li, H., Yao, R., Li, Y., Wang, G., Geng, P., et al. (2017). The degradation of EZH2 mediated by lncRNA ANCR attenuated the invasion and metastasis of breast cancer. Cell Death Differ. *24*, 59–71.

54. Yang, F., Zhang, H., Mei, Y., and Wu, M. (2014). Reciprocal regulation of HIF-1α and lincRNA-p21 modulates the Warburg effect. Mol. Cell *53*, 88–100.

55. Wang, Z., Yang, B., Zhang, M., Guo, W., Wu, Z., Wang, Y., Jia, L., Li, S., Xie, W., and Yang, D.; Cancer Genome Atlas Research Network (2018). lncRNA Epigenetic Landscape Analysis Identifies EPIC1 as an Oncogenic lncRNA that Interacts with MYC and Promotes Cell-Cycle Progression in Cancer. Cancer Cell *33*, 706–720.e9.

56. Vennin, C., Spruyt, N., Robin, Y.M., Chassat, T., Le Bourhis, X., and Adriaenssens, E. (2017). The long non-coding RNA 91H increases aggressive phenotype of breast cancer cells and up-regulates H19/IGF2 expression through epigenetic modifications. Cancer Lett. *385*, 198–206.

57. Han, Y.J., Boatman, S.M., Zhang, J., Du, X.C., Yeh, A.C., Zheng, Y., Mueller, J., and Olopade, O.I. (2018). LncRNA BLAT1 is Upregulated in Basal-like Breast Cancer through Epigenetic Modifications. Sci. Rep. *8*, 15572.

58. Xu, S., Liu, H., Wan, L., Zhang, W., Wang, Q., Zhang, S., Shang, S., Zhang, Y., and Pang, D. (2019). The MS-lincRNA landscape reveals a novel lincRNA BCLIN25 that contributes to tumorigenesis by upregulating ERBB2 expression via epigenetic modification and RNA-RNA interactions in breast cancer. Cell Death Dis. *10*, 920.

59. Pawłowska, E., Szczepanska, J., and Blasiak, J. (2017). The Long Noncoding RNA HOTAIR in Breast Cancer: Does Autophagy Play a Role? Int. J. Mol. Sci. *18*, 2317.

60. Sun, X., Du, P., Yuan, W., Du, Z., Yu, M., Yu, X., and Hu, T. (2015). Long non-coding RNA HOTAIR regulates cyclin J via inhibition of microRNA-205 expression in bladder cancer. Cell Death Dis. *6*, e1907.

61. Pathania, A.S., and Challagundla, K.B. (2020). Exosomal Long Non-coding RNAs: Emerging Players in the Tumor Microenvironment. Mol. Ther. Nucleic Acids *23*, 1371–1383.

62. Costa-Silva, B., Aiello, N.M., Ocean, A.J., Singh, S., Zhang, H., Thakur, B.K., Becker, A., Hoshino, A., Mark, M.T., Molina, H., et al. (2015). Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. Nat. Cell Biol. *17*, 816–826.

63. Li, Z., Zhu, X., and Huang, S. (2020). Extracellular vesicle long non-coding RNAs and circular RNAs: Biology, functions and applications in cancer. Cancer Lett. *489*, 111–120.

64. Dong, H., Hu, J., Zou, K., Ye, M., Chen, Y., Wu, C., Chen, X., and Han, M. (2019). Activation of LncRNA TINCR by H3K27 acetylation promotes Trastuzumab resistance and epithelial-mesenchymal transition by targeting MicroRNA-125b in breast Cancer. Mol. Cancer *18*, 3.

65. Li, Y., Zhao, Z., Liu, W., and Li, X. (2020). SNHG3 Functions as miRNA Sponge to Promote Breast Cancer Cells Growth Through the Metabolic Reprogramming. Appl. Biochem. Biotechnol. *191*, 1084–1099.

66. Wang, Y.L., Liu, L.C., Hung, Y., Chen, C.J., Lin, Y.Z., Wu, W.R., and Wang, S.C. (2019). Long non-coding RNA HOTAIR in circulatory exosomes is correlated with ErbB2/HER2 positivity in breast cancer. Breast *46*, 64–69.

67. Guo, F.X., Wu, Q., Li, P., Zheng, L., Ye, S., Dai, X.Y., Kang, C.M., Lu, J.B., Xu, B.M., Xu, Y.J., et al. (2019). The role of the LncRNA-FA2H-2-MLKL pathway in atherosclerosis by regulation of autophagy flux and inflammation through mTOR-dependent signaling. Cell Death Differ. *26*, 1670–1687.

68. Wang, C.J., Zhu, C.C., Xu, J., Wang, M., Zhao, W.Y., Liu, Q., Zhao, G., and Zhang, Z.Z. (2019). The lncRNA UCA1 promotes proliferation, migration, immune escape and inhibits apoptosis in gastric cancer by sponging anti-tumor miRNAs. Mol. Cancer *18*, 115.

69. Hosseini, E., Bagheri-Hosseinabadi, Z., De Toma, I., Jafarisani, M., and Sadeghi, I. (2019). The importance of long non-coding RNAs in neuropsychiatric disorders. Mol. Aspects Med. *70*, 127–140.

70. Shi, Y., Li, J., Liu, Y., Ding, J., Fan, Y., Tian, Y., Wang, L., Lian, Y., Wang, K., and Shu, Y. (2015). The long noncoding RNA SPRY4-IT1 increases the proliferation of human breast cancer cells by upregulating ZNF703 expression. Mol. Cancer *14*, 51.

71. Huang, Q.Y., Liu, G.F., Qian, X.L., Tang, L.B., Huang, Q.Y., and Xiong, L.X. (2019). Long Non-Coding RNA: Dual Effects on Breast Cancer Metastasis and Clinical Applications. Cancers (Basel) *11*, 1802.

72. Takeiwa, T., Ikeda, K., Mitobe, Y., Horie-Inoue, K., and Inoue, S. (2020). Long Noncoding RNAs Involved in the Endocrine Therapy Resistance of Breast Cancer. Cancers (Basel) *12*, 1424.

73. Xing, Z., Lin, A., Li, C., Liang, K., Wang, S., Liu, Y., Park, P.K., Qin, L., Wei, Y., Hawke, D.H., et al. (2014). lncRNA directs cooperative epigenetic regulation downstream of chemokine signals. Cell *159*, 1110–1125.

74. Gooding, A.J., Zhang, B., Jahanbani, F.K., Gilmore, H.L., Chang, J.C., Valadkhan, S., and Schiemann, W.P. (2017). The lncRNA BORG Drives Breast Cancer Metastasis and Disease Recurrence. Sci. Rep. *7*, 12698.

75. Du, T., Shi, Y., Xu, S., Wan, X., Sun, H., and Liu, B. (2020). Long Non-Coding RNAs in Drug Resistance of Breast Cancer. OncoTargets Ther. *13*, 7075–7087.

76. Wang, Y., Dong, T., Wang, P., Li, S., Wu, G., Zhou, J., and Wang, Z. (2021). LINC00922 regulates epithelial-mesenchymal transition, invasive and migratory capacities in breast cancer through promoting NKD2 methylation. Cell. Signal. *77*, 109808.

77. Chen, Z., Huang, J., Feng, Y., Li, Z., and Jiang, Y. (2021). Profiling of specific long non-coding RNA signatures identifies ST8SIA6-AS1 AS a novel target for breast cancer. J. Gene Med. *23*, e3286.

78. Shi, G., Cheng, Y., Zhang, Y., Guo, R., Li, S., and Hong, X. (2021). Long non-coding RNA LINC00511/miR-150/MMP13 axis promotes breast cancer proliferation, migration and invasion. Biochim Biophys Acta Mol Basis Dis *1867*, 165957.

79. Zhou, Q., Guo, J., Huang, W., Yu, X., Xu, C., and Long, X. (2020). Linc-ROR promotes the progression of breast cancer and decreases the sensitivity to rapamycin through miR-194-3p targeting MECP2. Mol. Oncol. *14*, 2231–2250.

80. Yi, T., Zhou, X., Sang, K., Huang, X., Zhou, J., and Ge, L. (2019). Activation of lncRNA lnc-SLC4A1-1 induced by H3K27 acetylation promotes the development of breast cancer via activating CXCL8 and NF-kB pathway. Artif. Cells Nanomed. Biotechnol. *47*, 3765–3773.

81. Lu, G., Li, Y., Ma, Y., Lu, J., Chen, Y., Jiang, Q., Qin, Q., Zhao, L., Huang, Q., Luo, Z., et al. (2018). Long noncoding RNA LINC00511 contributes to breast cancer tumourigenesis and stemness by inducing the miR-185-3p/E2F1/Nanog axis. J. Exp. Clin. Cancer Res. *37*, 289.

82. Li, Y., Wang, B., Lai, H., Li, S., You, Q., Fang, Y., Li, Q., and Liu, Y. (2017). Long non-coding RNA CRALA is associated with poor response to chemotherapy in primary breast cancer. Thorac. Cancer *8*, 582–591.

83. Mitobe, Y., Ikeda, K., Sato, W., Kodama, Y., Naito, M., Gotoh, N., Miyata, K., Kataoka, K., Sasaki, H., Horie-Inoue, K., and Inoue, S. (2020). Proliferation-associated long noncoding RNA, TMPO-AS1, is a potential therapeutic target for triple-negative breast cancer. Cancer Sci. *111*, 2440–2450.

84. Liu, Y., Li, M., Yu, H., and Piao, H. (2020). lncRNA CYTOR promotes tamoxifen resistance in breast cancer cells via sponging miR-125a-5p. Int. J. Mol. Med. *45*, 497–509.

85. Cairns, J., Ingle, J.N., Kalari, K.R., Shepherd, L.E., Kubo, M., Goetz, M.P., Weinshilboum, R.M., and Wang, L. (2019). The lncRNA MIR2052HG regulates ERα levels and aromatase inhibitor resistance through LMTK3 by recruiting EGR1. Breast Cancer Res. *21*, 47.

86. Tang, T., Guo, C., Xia, T., Zhang, R., Zen, K., Pan, Y., and Jin, L. (2019). LncCCAT1 Promotes Breast Cancer Stem Cell Function through Activating WNT/β-catenin Signaling. Theranostics *9*, 7384–7402.

87. Jin, X., Ge, L.P., Li, D.Q., Shao, Z.M., Di, G.H., Xu, X.E., and Jiang, Y.Z. (2020). LncRNA TROJAN promotes proliferation and resistance to CDK4/6 inhibitor via CDK2 transcriptional activation in ER+ breast cancer. Mol. Cancer *19*, 87.

88. Wang, X., Chen, T., Zhang, Y., Zhang, N., Li, C., Li, Y., Liu, Y., Zhang, H., Zhao, W., Chen, B., et al. (2019). Long noncoding RNA Linc00339 promotes triple-negative breast cancer progression through miR-377-3p/HOXC6 signaling pathway. J. Cell. Physiol. *234*, 13303–13317.

89. Chen, F.Y., Zhou, Z.Y., Zhang, K.J., Pang, J., and Wang, S.M. (2020). Long non-coding RNA MIR100HG promotes the migration, invasion and proliferation of triple-negative breast cancer cells by targeting the miR-5590-3p/OTX1 axis. Cancer Cell Int. *20*, 508.

90. Vidovic, D., Huynh, T.T., Konda, P., Dean, C., Cruickshank, B.M., Sultan, M., Coyle, K.M., Gujar, S., and Marcato, P. (2020). ALDH1A3-regulated long non-coding RNA NRAD1 is a potential novel target for triple-negative breast tumors and cancer stem cells. Cell Death Differ. *27*, 363–378.

91. Zhang, K.J., Tan, X.L., and Guo, L. (2020). The long non-coding RNA DANCR regulates the inflammatory phenotype of breast cancer cells and promotes breast cancer progression via EZH2-dependent suppression of SOCS3 transcription. Mol. Oncol. *14*, 309–328.

92. Zhang, H., Zhang, N., Liu, Y., Su, P., Liang, Y., Li, Y., Wang, X., Chen, T., Song, X., Sang, Y., et al. (2019). Epigenetic Regulation of *NAMPT* by *NAMPT-AS* Drives Metastatic Progression in Triple-Negative Breast Cancer. Cancer Res. *79*, 3347–3359.

93. Wang, P.S., Chou, C.H., Lin, C.H., Yao, Y.C., Cheng, H.C., Li, H.Y., Chuang, Y.C., Yang, C.N., Ger, L.P., Chen, Y.C., et al. (2018). A novel long non-coding RNA linc-ZNF469-3 promotes lung metastasis through miR-574-5p-ZEB1 axis in triple negative breast cancer. Oncogene *37*, 4662–4678.

94. Wang, N., Zhong, C., Fu, M., Li, L., Wang, F., Lv, P., Zhu, M., Xiong, Y., Mi, H., and Gu, Y. (2019). Long Non-Coding RNA HULC Promotes the Development of Breast Cancer Through Regulating LYPD1 Expression by Sponging miR-6754-5p. OncoTargets Ther. *12*, 10671–10679.

95. Youness, R.A., Hafez, H.M., Khallaf, E., Assal, R.A., Abdel Motaal, A., and Gad, M.Z. (2019). The long noncoding RNA sONE represses triple-negative breast cancer aggressiveness through inducing the expression of miR-34a, miR-15a, miR-16, and let-7a. J. Cell. Physiol. *234*, 20286–20297.

96. Yang, F., Shen, Y., Zhang, W., Jin, J., Huang, D., Fang, H., Ji, W., Shi, Y., Tang, L., Chen, W., et al. (2018). An androgen receptor negatively induced long non-coding RNA ARNILA binding to miR-204 promotes the invasion and metastasis of triple-negative breast cancer. Cell Death Differ. *25*, 2209–2220.

97. Huang, X., Xie, X., Liu, P., Yang, L., Chen, B., Song, C., Tang, H., and Xie, X. (2018). Adam12 and lnc015192 act as ceRNAs in breast cancer by regulating miR-34a. Oncogene *37*, 6316–6326.

98. Zhong, H., Yang, J., Zhang, B., Wang, X., Pei, L., Zhang, L., Lin, Z., Wang, Y., and Wang, C. (2018). LncRNA GACAT3 predicts poor prognosis and promotes cell proliferation in breast cancer through regulation of miR-497/CCND2. Cancer Biomark. *22*, 787–797.

99. Liu, M., Gou, L., Xia, J., Wan, Q., Jiang, Y., Sun, S., Tang, M., He, T., and Zhang, Y. (2018). LncRNA ITGB2-AS1 Could Promote the Migration and Invasion of Breast Cancer Cells through Up-Regulating ITGB2. Int. J. Mol. Sci. *19*, 1866.

100. Li, Y., Lv, M., Song, Z., Lou, Z., Wang, R., and Zhuang, M. (2018). Long non-coding RNA NNT-AS1 affects progression of breast cancer through miR-142-3p/ZEB1 axis. Biomed. Pharmacother. *103*, 939–946.

101. Yang, Y.X., Wei, L., Zhang, Y.J., Hayano, T., Piñeiro Pereda, M.D.P., Nakaoka, H., Li, Q., Barragán Mallofret, I., Lu, Y.Z., Tamagnone, L., et al. (2018). Long non-coding RNA p10247, high expressed in breast cancer (lncRNA-BCHE), is correlated with metastasis. Clin. Exp. Metastasis *35*, 109–121.

102. Bai, Y., Zhou, X., Huang, L., Wan, Y., Li, X., and Wang, Y. (2018). Long noncoding RNA EZR-AS1 promotes tumor growth and metastasis by modulating Wnt/β-catenin pathway in breast cancer. Exp. Ther. Med. *16*, 2235–2242.

103. Liang, Y., Song, X., Li, Y., Sang, Y., Zhang, N., Zhang, H., Liu, Y., Duan, Y., Chen, B., Guo, R., et al. (2018). A novel long non-coding RNA-PRLB acts as a tumor promoter through regulating miR-4766-5p/SIRT1 axis in breast cancer. Cell Death Dis. *9*, 563.

104. Bian, Q. (2019). Circular RNA PVT1 promotes the invasion and epithelial-mesenchymal transition of breast cancer cells through serving as a competing endogenous RNA for miR-204-5p. OncoTargets Ther. *12*, 11817–11826.

105. Li, R.H., Chen, M., Liu, J., Shao, C.C., Guo, C.P., Wei, X.L., Li, Y.C., Huang, W.H., and Zhang, G.J. (2018). Long noncoding RNA ATB promotes the epithelial-mesenchymal transition by upregulating the miR-200c/Twist1 axe and predicts poor prognosis in breast cancer. Cell Death Dis. *9*, 1171.

106. Li, S., Hao, J., Hong, Y., Mai, J., and Huang, W. (2020). Long Non-Coding RNA NEAT1 Promotes the Proliferation, Migration, and Metastasis of Human Breast-Cancer Cells by Inhibiting miR-146b-5p Expression. Cancer Manag. Res. *12*, 6091–6101.

107. Li, G.Y., Wang, W., Sun, J.Y., Xin, B., Zhang, X., Wang, T., Zhang, Q.F., Yao, L.B., Han, H., Fan, D.M., et al. (2018). Long non-coding RNAs AC026904.1 and UCA1: a "one-two punch" for TGF-β-induced SNAI2 activation and epithelial-mesenchymal transition in breast cancer. Theranostics *8*, 2846–2861.

108. Zhu, M., Wang, F., Mi, H., Li, L., Wang, J., Han, M., and Gu, Y. (2020). Long non-coding RNA MEG3 suppresses cell proliferation, migration and invasion, induces apoptosis and paclitaxel-resistance via miR-4513/PBLD axis in breast cancer cells. Cell Cycle *19*, 3277–3288.

109. Zhang, M., Wang, F., Xiang, Z., Huang, T., and Zhou, W.B. (2020). LncRNA XIST promotes chemoresistance of breast cancer cells to doxorubicin by sponging miR-200c-3p to upregulate ANLN. Clin. Exp. Pharmacol. Physiol. *47*, 1464–1472.

110. Gu, J., Wang, Y., Wang, X., Zhou, D., Shao, C., Zhou, M., and He, Z. (2018). RETRACTED: Downregulation of lncRNA GAS5 confers tamoxifen resistance by activating miR-222 in breast cancer. Cancer Lett. *434*, 1–10.

111. Xiu, D.H., Liu, G.F., Yu, S.N., Li, L.Y., Zhao, G.Q., Liu, L., and Li, X.F. (2019). Long non-coding RNA LINC00968 attenuates drug resistance of breast cancer cells through inhibiting the Wnt2/β-catenin signaling pathway by regulating WNT2. J. Exp. Clin. Cancer Res. *38*, 94.

112. Zhang, J., Zhang, J., Zhang, D., Ni, W., Xiao, H., and Zhao, B. (2020). Down-regulation of LINC00472 promotes osteosarcoma tumorigenesis by reducing FOXO1 expressions via miR-300. Cancer Cell Int. *20*, 100.

113. Wang, N., Hou, M., Zhan, Y., and Sheng, X. (2019). LncRNA PTCSC3 inhibits triple-negative breast cancer cell proliferation by downregulating lncRNA H19. J. Cell. Biochem. *120*, 15083–15088.

114. Liu, Z., Zhang, S., Wang, T., Shao, H., Gao, J., Wang, Y., and Ge, Y. (2019). Neferine inhibits MDA-MB-231 cells growth and metastasis by regulating miR-374a/FGFR-2. Chem. Biol. Interact. *309*, 108716.

115. Fan, S., Yang, Z., Ke, Z., Huang, K., Liu, N., Fang, X., and Wang, K. (2017). Downregulation of the long non-coding RNA TUG1 is associated with cell proliferation, migration, and invasion in breast cancer. Biomed. Pharmacother. *95*, 1636–1643.

116. Xu, X., Yuan, X., Ni, J., Guo, J., Gao, Y., Yin, W., Li, F., Wei, L., and Zhang, J. (2021). MAGI2-AS3 inhibits breast cancer by downregulating DNA methylation of MAGI2. J. Cell. Physiol. *236*, 1116–1130.

117. Wu, W., Chen, F., Cui, X., Yang, L., Chen, J., Zhao, J., Huang, D., Liu, J., Yang, L., Zeng, J., et al. (2018). LncRNA NKILA suppresses TGF-β-induced epithelial-mesenchymal transition by blocking NF-κB signaling in breast cancer. Int. J. Cancer *143*, 2213–2224.

118. Sun, M., Gadad, S.S., Kim, D.S., and Kraus, W.L. (2015). Discovery, Annotation, and Functional Analysis of Long Noncoding RNAs Controlling Cell-Cycle Gene Expression and Proliferation in Breast Cancer Cells. Mol. Cell *59*, 698–711.

119. Tang, J., Zhong, G., Zhang, H., Yu, B., Wei, F., Luo, L., Kang, Y., Wu, J., Jiang, J., Li, Y., et al. (2018). LncRNA DANCR upregulates PI3K/AKT signaling through activating serine phosphorylation of RXRA. Cell Death Dis. *9*, 1167.

120. Xu, L., Chen, Y., Mayakonda, A., Koh, L., Chong, Y.K., Buckley, D.L., Sandanaraj, E., Lim, S.W., Lin, R.Y., Ke, X.Y., et al. (2018). Targetable BET proteins- and E2F1-dependent transcriptional program maintains the malignancy of glioblastoma. Proc. Natl. Acad. Sci. USA *115*, E5086–E5095.

121. Han, C., Li, X., Fan, Q., Liu, G., and Yin, J. (2019). CCAT1 promotes triple-negative breast cancer progression by suppressing miR-218/ZFX signaling. Aging (Albany N.Y.) *11*, 4858–4875.

122. Tang, J., Li, Y., Sang, Y., Yu, B., Lv, D., Zhang, W., and Feng, H. (2018). LncRNA PVT1 regulates triple-negative breast cancer through KLF5/beta-catenin signaling. Oncogene *37*, 4723–4734.

123. Feng, W., Wang, C., Liang, C., Yang, H., Chen, D., Yu, X., Zhao, W., Geng, D., Li, S., Chen, Z., and Sun, M. (2018). The Dysregulated Expression of KCNQ1OT1 and Its Interaction with Downstream Factors miR-145/CCNE2 in Breast Cancer Cells. Cell. Physiol. Biochem. *49*, 432–446.

124. Ai, B., Kong, X., Wang, X., Zhang, K., Yang, X., Zhai, J., Gao, R., Qi, Y., Wang, J., Wang, Z., and Fang, Y. (2019). LINC01355 suppresses breast cancer growth through FOXO3-mediated transcriptional repression of CCND1. Cell Death Dis. *10*, 502.

125. Raveh, E., Matouk, I.J., Gilon, M., and Hochberg, A. (2015). The H19 Long non-coding RNA in cancer initiation, progression and metastasis - a proposed unifying theory. Mol. Cancer *14*, 184.

126. Peng, F., Li, T.T., Wang, K.L., Xiao, G.Q., Wang, J.H., Zhao, H.D., Kang, Z.J., Fan, W.J., Zhu, L.L., Li, M., et al. (2017). H19/let-7/LIN28 reciprocal negative regulatory circuit promotes breast cancer stem cell maintenance. Cell Death Dis. *8*, e2569.

127. Zhou, S., He, Y., Yang, S., Hu, J., Zhang, Q., Chen, W., Xu, H., Zhang, H., Zhong, S., Zhao, J., and Tang, J. (2018). The regulatory roles of lncRNAs in the process of breast cancer invasion and metastasis. Biosci. Rep. *38*, BSR20180772.

128. O'Brien, S.J., Carter, J.V., Burton, J.F., Oxford, B.G., Schmidt, M.N., Hallion, J.C., and Galandiuk, S. (2018). The role of the miR-200 family in epithelial-mesenchymal transition in colorectal cancer: a systematic review. Int. J. Cancer *142*, 2501–2511.

129. Goodall, G.J., and Wickramasinghe, V.O. (2021). RNA in cancer. Nat. Rev. Cancer *21*, 22–36.

130. Jiang, X., Zhou, Y., Sun, A.J., and Xue, J.L. (2018). NEAT1 contributes to breast cancer progression through modulating miR-448 and ZEB1. J. Cell. Physiol. *233*, 8558–8566.

131. Zhao, D., Zhang, Y., Wang, N., and Yu, N. (2017). NEAT1 negatively regulates miR-218 expression and promotes breast cancer progression. Cancer Biomark. *20*, 247–254.

132. Li, X., Wang, S., Li, Z., Long, X., Guo, Z., Zhang, G., Zu, J., Chen, Y., and Wen, L. (2017). The lncRNA NEAT1 facilitates cell growth and invasion via the miR-211/HMGA2 axis in breast cancer. Int. J. Biol. Macromol. *105*, 346–353.

133. Zhao, L., Zhou, Y., Zhao, Y., Li, Q., Zhou, J., and Mao, Y. (2020). Long non-coding RNA TUSC8 inhibits breast cancer growth and metastasis via miR-190b-5p/MYLIP axis. Aging (Albany N.Y.) *12*, 2974–2991.

134. Hou, P., Zhao, Y., Li, Z., Yao, R., Ma, M., Gao, Y., Zhao, L., Zhang, Y., Huang, B., and Lu, J. (2014). LincRNA-ROR induces epithelial-to-mesenchymal transition and contributes to breast cancer tumorigenesis and metastasis. Cell Death Dis. *5*, e1287.

135. Fan, J., Xing, Y., Wen, X., Jia, R., Ni, H., He, J., Ding, X., Pan, H., Qian, G., Ge, S., et al. (2015). Long non-coding RNA ROR decoys gene-specific histone methylation to promote tumorigenesis. Genome Biol. *16*, 139.

136. Zhao, Z., Li, S., Song, E., and Liu, S. (2016). The roles of ncRNAs and histone-modifiers in regulating breast cancer stem cells. Protein Cell *7*, 89–99.

137. Luo, L., Tang, H., Ling, L., Li, N., Jia, X., Zhang, Z., Wang, X., Shi, L., Yin, J., Qiu, N., et al. (2018). LINC01638 lncRNA activates MTDH-Twist1 signaling by preventing SPOP-mediated c-Myc degradation in triple-negative breast cancer. Oncogene *37*, 6166–6179.

138. Tsai, M.C., Manor, O., Wan, Y., Mosammaparast, N., Wang, J.K., Lan, F., Shi, Y., Segal, E., and Chang, H.Y. (2010). Long noncoding RNA as modular scaffold of histone modification complexes. Science *329*, 689–693.

139. Pádua Alves, C., Fonseca, A.S., Muys, B.R., de Barros, E., Lima Bueno, R., Bürger, M.C., de Souza, J.E.S., Valente, V., Zago, M.A., and Silva, W.A., Jr. (2013). Brief report: The lincRNA Hotair is required for epithelial-to-mesenchymal transition and stemness maintenance of cancer cell lines. Stem Cells *31*, 2827–2832.

140. Wang, S., Liang, K., Hu, Q., Li, P., Song, J., Yang, Y., Yao, J., Mangala, L.S., Li, C., Yang, W., et al. (2017). JAK2-binding long noncoding RNA promotes breast cancer brain metastasis. J. Clin. Invest. *127*, 4498–4515.

141. Goto, H., Shimono, Y., Funakoshi, Y., Imamura, Y., Toyoda, M., Kiyota, N., Kono, S., Takao, S., Mukohara, T., and Minami, H. (2019). Adipose-derived stem cells enhance human breast cancer growth and cancer stem cell-like properties through adipsin. Oncogene *38*, 767–779.

142. Zhou, M., Hou, Y., Yang, G., Zhang, H., Tu, G., Du, Y.E., Wen, S., Xu, L., Tang, X., Tang, S., et al. (2016). LncRNA-Hh Strengthen Cancer Stem Cells Generation in Twist-Positive Breast Cancer via Activation of Hedgehog Signaling Pathway. Stem Cells *34*, 55–66.

143. Ishiwata, T. (2016). Cancer stem cells and epithelial-mesenchymal transition: Novel therapeutic targets for cancer. Pathol. Int. *66*, 601–608.

144. van der Horst, G., van den Hoogen, C., Buijs, J.T., Cheung, H., Bloys, H., Pelger, R.C., Lorenzon, G., Heckmann, B., Feyen, J., Pujuguet, P., et al. (2011). Targeting of α(v)-integrins in stem/progenitor cells and supportive microenvironment impairs bone metastasis in human prostate cancer. Neoplasia *13*, 516–525.

145. De, A., Beligala, D.H., Sharma, V.P., Burgos, C.A., Lee, A.M., and Geusz, M.E. (2020). Cancer stem cell generation during epithelial-mesenchymal transition is temporally gated by intrinsic circadian clocks. Clin. Exp. Metastasis *37*, 617–635.

146. McCabe, E.M., and Rasmussen, T.P. (2020). lncRNA involvement in cancer stem cell function and epithelial-mesenchymal transitions. Semin. Cancer Biol. S1044-579X(20)30272-8. https://doi.org/10.1016/j.semcancer.2020.12.012.

147. Li, H., Zhu, L., Xu, L., Qin, K., Liu, C., Yu, Y., Su, D., Wu, K., and Sheng, Y. (2017). Long noncoding RNA linc00617 exhibits oncogenic activity in breast cancer. Mol. Carcinog. *56*, 3–17.

148. Xing, F., Liu, Y., Wu, S.Y., Wu, K., Sharma, S., Mo, Y.Y., Feng, J., Sanders, S., Jin, G., Singh, R., et al. (2018). Loss of XIST in Breast Cancer Activates MSN-c-Met and Reprograms Microglia via Exosomal miRNA to Promote Brain Metastasis. Cancer Res. *78*, 4316–4330.

149. Bedoui, S., Herold, M.J., and Strasser, A. (2020). Emerging connectivity of programmed cell death pathways and its physiological implications. Nat. Rev. Mol. Cell Biol. *21*, 678–695.

150. Strasser, A., O'Connor, L., and Dixit, V.M. (2000). Apoptosis signaling. Annu. Rev. Biochem. *69*, 217–245.

151. Cao, Y., Lin, M., Bu, Y., Ling, H., He, Y., Huang, C., Shen, Y., Song, B., and Cao, D. (2017). p53-inducible long non-coding RNA PICART1 mediates cancer cell proliferation and migration. Int. J. Oncol. *50*, 1671–1682.

152. Chen, R., Liu, Y., Zhuang, H., Yang, B., Hei, K., Xiao, M., Hou, C., Gao, H., Zhang, X., Jia, C., et al. (2017). Quantitative proteomics reveals that long non-coding RNA MALAT1 interacts with DBC1 to regulate p53 acetylation. Nucleic Acids Res. *45*, 9947–9959.

153. Wan, W., Hou, Y., Wang, K., Cheng, Y., Pu, X., and Ye, X. (2019). The LXR-623-induced long non-coding RNA LINC01125 suppresses the proliferation of breast cancer cells via PTEN/AKT/p53 signaling pathway. Cell Death Dis. *10*, 248.

154. Kopeina, G.S., Prokhorova, E.A., Lavrik, I.N., and Zhivotovsky, B. (2018). Alterations in the nucleocytoplasmic transport in apoptosis: Caspases lead the way. Cell Prolif. *51*, e12467.

155. Chen, D.Q., Zheng, X.D., Cao, Y., He, X.D., Nian, W.Q., Zeng, X.H., and Liu, X.Y. (2017). Long non-coding RNA LINC00628 suppresses the growth and metastasis and promotes cell apoptosis in breast cancer. Eur. Rev. Med. Pharmacol. Sci. *21*, 275–283.

156. Liao, X.H., Wang, J.G., Li, L.Y., Zhou, D.M., Ren, K.H., Jin, Y.T., Lv, L., Yu, J.G., Yang, J.Y., Lu, Q., et al. (2016). Long intergenic non-coding RNA APOC1P1-3 inhibits apoptosis by decreasing α-tubulin acetylation in breast cancer. Cell Death Dis. *7*, e2236.

157. Wang, J., Xie, S., Yang, J., Xiong, H., Jia, Y., Zhou, Y., Chen, Y., Ying, X., Chen, C., Ye, C., et al. (2019). The long noncoding RNA H19 promotes tamoxifen resistance in breast cancer via autophagy. J. Hematol. Oncol. *12*, 81.

158. Wang, Y., Zhou, P., Li, P., Yang, F., and Gao, X.Q. (2020). Long non-coding RNA H19 regulates proliferation and doxorubicin resistance in MCF-7 cells by targeting PARP1. Bioengineered *11*, 536–546.

159. Xue, X., Yang, Y.A., Zhang, A., Fong, K.W., Kim, J., Song, B., Li, S., Zhao, J.C., and Yu, J. (2016). LncRNA HOTAIR enhances ER signaling and confers tamoxifen resistance in breast cancer. Oncogene *35*, 2746–2755.

160. Li, Z., Qian, J., Li, J., and Zhu, C. (2019). Knockdown of lncRNA-HOTAIR downregulates the drug-resistance of breast cancer cells to doxorubicin via the PI3K/AKT/mTOR signaling pathway. Exp. Ther. Med. *18*, 435–442.

161. Shin, V.Y., Chen, J., Cheuk, I.W., Siu, M.T., Ho, C.W., Wang, X., Jin, H., and Kwong, A. (2019). Long non-coding RNA NEAT1 confers oncogenic role in triple-negative breast cancer through modulating chemoresistance and cancer stemness. Cell Death Dis. *10*, 270.

162. Su, X., Malouf, G.G., Chen, Y., Zhang, J., Yao, H., Valero, V., Weinstein, J.N., Spano, J.P., Meric-Bernstam, F., Khayat, D., and Esteva, F.J. (2014). Comprehensive analysis of long non-coding RNAs in human breast cancer clinical subtypes. Oncotarget *5*, 9864–9876.

163. Hu, Q., Ye, Y., Chan, L.C., Li, Y., Liang, K., Lin, A., Egranov, S.D., Zhang, Y., Xia, W., Gong, J., et al. (2019). Oncogenic lncRNA downregulates cancer cell antigen presentation and intrinsic tumor suppression. Nat. Immunol. *20*, 835–851.

164. Ingle, J.N., Xie, F., Ellis, M.J., Goss, P.E., Shepherd, L.E., Chapman, J.W., Chen, B.E., Kubo, M., Furukawa, Y., Momozawa, Y., et al. (2016). Genetic Polymorphisms in the Long Noncoding RNA MIR2052HG Offer a Pharmacogenomic Basis for the Response of Breast Cancer Patients to Aromatase Inhibitor Therapy. Cancer Res. *76*, 7012–7023.

165. Chen, Z., Pan, T., Jiang, D., Jin, L., Geng, Y., Feng, X., Shen, A., and Zhang, L. (2020). The lncRNA-GAS5/miR-221-3p/DKK2 Axis Modulates ABCB1-Mediated Adriamycin Resistance of Breast Cancer via the Wnt/β-Catenin Signaling Pathway. Mol. Ther. Nucleic Acids *19*, 1434–1448.

166. Liang, Y., Li, Y., Song, X., Zhang, N., Sang, Y., Zhang, H., Liu, Y., Chen, B., Zhao, W., Wang, L., et al. (2018). Long noncoding RNA LINP1 acts as an oncogene and promotes chemoresistance in breast cancer. Cancer Biol. Ther. *19*, 120–131.

167. Chang, L., Hu, Z., Zhou, Z., and Zhang, H. (2018). Linc00518 Contributes to Multidrug Resistance Through Regulating the MiR-199a/MRP1 Axis in Breast Cancer. Cell. Physiol. Biochem. *48*, 16–28.

168. Li, X., Wu, Y., Liu, A., and Tang, X. (2016). Long non-coding RNA UCA1 enhances tamoxifen resistance in breast cancer cells through a miR-18a-HIF1α feedback regulatory loop. Tumour Biol. *37*, 14733–14743.

169. Liu, H., Wang, G., Yang, L., Qu, J., Yang, Z., and Zhou, X. (2016). Knockdown of Long Non-Coding RNA UCA1 Increases the Tamoxifen Sensitivity of Breast Cancer Cells through Inhibition of Wnt/β-Catenin Pathway. PLoS ONE *11*, e0168406.

170. Zeng, Y., Wang, G., Zhou, C.F., Zhang, H.B., Sun, H., Zhang, W., Zhou, H.H., Liu, R., and Zhu, Y.S. (2019). LncRNA Profile Study Reveals a Three-LncRNA Signature Associated With the Pathological Complete Response Following Neoadjuvant Chemotherapy in Breast Cancer. Front. Pharmacol. *10*, 574.

171. Zhang, H.Y., Liang, F., Zhang, J.W., Wang, F., Wang, L., and Kang, X.G. (2017). Effects of long noncoding RNA-ROR on tamoxifen resistance of breast cancer cells by regulating microRNA-205. Cancer Chemother. Pharmacol. *79*, 327–337.

172. Peng, W.X., Huang, J.G., Yang, L., Gong, A.H., and Mo, Y.Y. (2017). Linc-RoR promotes MAPK/ERK signaling and confers estrogen-independent growth of breast cancer. Mol. Cancer *16*, 161.

173. Tang, L., Chen, Y., Chen, H., Jiang, P., Yan, L., Mo, D., Tang, X., and Yan, F. (2020). *DCST1-AS1* Promotes TGF-β-Induced Epithelial-Mesenchymal Transition and Enhances Chemoresistance in Triple-Negative Breast Cancer Cells via ANXA1. Front. Oncol. *10*, 280.

174. Huang, D., Chen, J., Yang, L., Ouyang, Q., Li, J., Lao, L., Zhao, J., Liu, J., Lu, Y., Xing, Y., et al. (2018). NKILA lncRNA promotes tumor immune evasion by sensitizing T cells to activation-induced cell death. Nat. Immunol. *19*, 1112–1125.

175. Mitobe, Y., Ikeda, K., Suzuki, T., Takagi, K., Kawabata, H., Horie-Inoue, K., and Inoue, S. (2019). *ESR1*-Stabilizing Long Noncoding RNA *TMPO-AS1* Promotes Hormone-Refractory Breast Cancer Progression. Mol. Cell. Biol. *39*, e00261-19.

176. Niknafs, Y.S., Han, S., Ma, T., Speers, C., Zhang, C., Wilder-Romans, K., Iyer, M.K., Pitchiaya, S., Malik, R., Hosono, Y., et al. (2016). The lncRNA landscape of breast cancer reveals a role for DSCAM-AS1 in breast cancer progression. Nat. Commun. *7*, 12791.

177. Kim, C.Y., Oh, J.H., Lee, J.Y., and Kim, M.H. (2020). The LncRNA HOTAIRM1 Promotes Tamoxifen Resistance by Mediating HOXA1 Expression in ER+ Breast Cancer Cells. J. Cancer *11*, 3416–3423.

178. Zheng, Z., Chen, M., Xing, P., Yan, X., and Xie, B. (2019). Increased Expression of Exosomal AGAP2-AS1 (AGAP2 Antisense RNA 1) In Breast Cancer Cells Inhibits Trastuzumab-Induced Cell Cytotoxicity. Med. Sci. Monit. *25*, 2211–2220.

179. Dong, H., Wang, W., Mo, S., Liu, Q., Chen, X., Chen, R., Zhang, Y., Zou, K., Ye, M., He, X., et al. (2018). Long non-coding RNA SNHG14 induces trastuzumab resistance of breast cancer via regulating PABPC1 expression through H3K27 acetylation. J. Cell. Mol. Med. *22*, 4935–4947.

180. Koirala, P., Huang, J., Ho, T.T., Wu, F., Ding, X., and Mo, Y.Y. (2017). LncRNA AK023948 is a positive regulator of AKT. Nat. Commun. *8*, 14422.

181. Wan, G., Hu, X., Liu, Y., Han, C., Sood, A.K., Calin, G.A., Zhang, X., and Lu, X. (2013). A novel non-coding RNA lncRNA-JADE connects DNA damage signalling to histone H4 acetylation. EMBO J. *32*, 2833–2847.

182. Hu, W.L., Jin, L., Xu, A., Wang, Y.F., Thorne, R.F., Zhang, X.D., and Wu, M. (2018). GUARDIN is a p53-responsive long non-coding RNA that is essential for genomic stability. Nat. Cell Biol. *20*, 492–502.

183. Chu, W., Zhang, X., Qi, L., Fu, Y., Wang, P., Zhao, W., Du, J., Zhang, J., Zhan, J., Wang, Y., et al. (2020). The EZH2-PHACTR2-AS1-Ribosome Axis induces Genomic Instability and Promotes Growth and Metastasis in Breast Cancer. Cancer Res. *80*, 2737–2750.

184. Wang, R., Zhang, T., Yang, Z., Jiang, C., and Seng, J. (2018). Long non-coding RNA FTH1P3 activates paclitaxel resistance in breast cancer through miR-206/ABCB1. J. Cell. Mol. Med. *22*, 4068–4075.

185. Yao, N., Fu, Y., Chen, L., Liu, Z., He, J., Zhu, Y., Xia, T., and Wang, S. (2019). Long non-coding RNA NONHSAT101069 promotes epirubicin resistance, migration, and invasion of breast cancer cells through NONHSAT101069/miR-129-5p/Twist1 axis. Oncogene *38*, 7216–7233.

186. Sledge, G.W., Mamounas, E.P., Hortobagyi, G.N., Burstein, H.J., Goodwin, P.J., and Wolff, A.C. (2014). Past, present, and future challenges in breast cancer treatment. J. Clin. Oncol. *32*, 1979–1986.

187. Gu, M., Zheng, W., Zhang, M., Dong, X., Zhao, Y., Wang, S., Jiang, H., and Zheng, X. (2020). LncRNA NONHSAT141924 promotes paclitaxel chemotherapy resistance through p-CREB/Bcl-2 apoptosis signaling pathway in breast cancer. J. Cancer *11*, 3645–3654.

188. Wang, Y.Y., Yan, L., Yang, S., Xu, H.N., Chen, T.T., Dong, Z.Y., Chen, S.L., Wang, W.R., Yang, Q.L., and Chen, C.J. (2019). Long noncoding RNA AC073284.4 suppresses epithelial-mesenchymal transition by sponging miR-18b-5p in paclitaxel-resistant breast cancer cells. J. Cell. Physiol. *234*, 23202–23215.

189. Wang, K., Li, J., Xiong, Y.F., Zeng, Z., Zhang, X., and Li, H.Y. (2018). A Potential Prognostic Long Noncoding RNA Signature to Predict Recurrence among ER-positive Breast Cancer Patients Treated with Tamoxifen. Sci. Rep. *8*, 3179.

190. Xu, Z., Liu, C., Zhao, Q., Lü, J., Ding, X., Luo, A., He, J., Wang, G., Li, Y., Cai, Z., et al. (2020). Long non-coding RNA CCAT2 promotes oncogenesis in triple-negative breast cancer by regulating stemness of cancer cells. Pharmacol. Res. *152*, 104628.

191. Shi, S.J., Wang, L.J., Yu, B., Li, Y.H., Jin, Y., and Bai, X.Z. (2015). LncRNA-ATB promotes trastuzumab resistance and invasion-metastasis cascade in breast cancer. Oncotarget *6*, 11652–11663.

192. Jiang, Y.Z., Liu, Y.R., Xu, X.E., Jin, X., Hu, X., Yu, K.D., and Shao, Z.M. (2016). Transcriptome Analysis of Triple-Negative Breast Cancer Reveals an Integrated mRNA-lncRNA Signature with Predictive and Prognostic Value. Cancer Res. *76*, 2105–2114.

193. Shi, Y.F., Lu, H., and Wang, H.B. (2019). Downregulated lncRNA ADAMTS9-AS2 in breast cancer enhances tamoxifen resistance by activating microRNA-130a-5p. Eur. Rev. Med. Pharmacol. Sci. *23*, 1563–1573.

194. Tomita, S., Abdalla, M.O.A., Fujiwara, S., Matsumori, H., Maehara, K., Ohkawa, Y., Iwase, H., Saitoh, N., and Nakao, M. (2015). A cluster of noncoding RNAs activates the ESR1 locus during breast cancer adaptation. Nat. Commun. *6*, 6966.

195. Perou, C.M., Sørlie, T., Eisen, M.B., van de Rijn, M., Jeffrey, S.S., Rees, C.A., Pollack, J.R., Ross, D.T., Johnsen, H., Akslen, L.A., et al. (2000). Molecular portraits of human breast tumours. Nature *406*, 747–752.

196. Patel, H.K., and Bihani, T. (2018). Selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs) in cancer treatment. Pharmacol. Ther. *186*, 1–24.

197. Jordan, V. (2006). The science of selective estrogen receptor modulators: concept to clinical practice. Clin. Cancer Res. *12*, 5010–5013.

198. Sun, D.E., and Ye, S.Y. (2020). Emerging Roles of Long Noncoding RNA Regulator of Reprogramming in Cancer Treatment. Cancer Manag. Res. *12*, 6103–6112.

199. Lee, M.H., Koh, D., Na, H., Ka, N.L., Kim, S., Kim, H.J., Hong, S., Shin, Y.K., Seong, J.K., and Lee, M.O. (2018). MTA1 is a novel regulator of autophagy that induces tamoxifen resistance in breast cancer cells. Autophagy *14*, 812–824.

200. Basak, P., Chatterjee, S., Bhat, V., Su, A., Jin, H., Lee-Wing, V., Liu, Q., Hu, P., Murphy, L., and Raouf, A. (2018). Long Non-Coding RNA H19 Acts as an Estrogen Receptor Modulator that is Required for Endocrine Therapy Resistance in ER+ Breast Cancer Cells. Cell. Physiol. Biochem. *51*, 1518–1532.

201. Li, Z., Yu, D., Li, H., Lv, Y., and Li, S. (2019). Long non-coding RNA UCA1 confers tamoxifen resistance in breast cancer endocrinotherapy through regulation of the EZH2/p21 axis and the PI3K/AKT signaling pathway. Int. J. Oncol. *54*, 1033–1042.

202. Xu, C.G., Yang, M.F., Ren, Y.Q., Wu, C.H., and Wang, L.Q. (2016). Exosomes mediated transfer of lncRNA UCA1 results in increased tamoxifen resistance in breast cancer cells. Eur. Rev. Med. Pharmacol. Sci. *20*, 4362–4368.

203. Wu, C., and Luo, J. (2016). Long Non-Coding RNA (lncRNA) Urothelial Carcinoma-Associated 1 (UCA1) Enhances Tamoxifen Resistance in Breast Cancer Cells via Inhibiting mTOR Signaling Pathway. Med. Sci. Monit. *22*, 3860–3867.

204. Li, Y., Jiang, B., Zhu, H., Qu, X., Zhao, L., Tan, Y., Jiang, Y., Liao, M., and Wu, X. (2017). Inhibition of long non-coding RNA ROR reverses resistance to Tamoxifen by inducing autophagy in breast cancer. Tumour Biol. *39*, 1010428317705790.

205. Molehin, D., Filleur, S., and Pruitt, K. (2021). Regulation of aromatase expression: Potential therapeutic insight into breast cancer treatment. Mol. Cell. Endocrinol. *531*, 111321.

206. Cairns, J., Kalari, K.R., Ingle, J.N., Shepherd, L.E., Ellis, M.J., Goss, P.E., Barman, P., Carlson, E.E., Goodnature, B., Goetz, M.P., et al. (2021). Interaction Between SNP Genotype and Efficacy of Anastrozole and Exemestane in Early-Stage Breast Cancer. Clin. Pharmacol. Ther. https://doi.org/10.1002/cpt.2311.

207. Swain, S.M., Baselga, J., Kim, S.B., Ro, J., Semiglazov, V., Campone, M., Ciruelos, E., Ferrero, J.M., Schneeweiss, A., Heeson, S., et al.; CLEOPATRA Study Group (2015). Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N. Engl. J. Med. *372*, 724–734.

208. Dong, H., Wang, W., Chen, R., Zhang, Y., Zou, K., Ye, M., He, X., Zhang, F., and Han, J. (2018). Exosome-mediated transfer of lncRNA-SNHG14 promotes trastuzumab chemoresistance in breast cancer. Int. J. Oncol. *53*, 1013–1026.

209. Kalyanaraman, B. (2020). Teaching the basics of the mechanism of doxorubicin-induced cardiotoxicity: Have we been barking up the wrong tree? Redox Biol. *29*, 101394.

210. Minotti, G., Menna, P., Salvatorelli, E., Cairo, G., and Gianni, L. (2004). Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol. Rev. *56*, 185–229.

211. Jasra, S., and Anampa, J. (2018). Anthracycline Use for Early Stage Breast Cancer in the Modern Era: a Review. Curr. Treat. Options Oncol. *19*, 30.

212. Gooding, A.J., Zhang, B., Gunawardane, L., Beard, A., Valadkhan, S., and Schiemann, W.P. (2019). The lncRNA BORG facilitates the survival and chemoresistance of triple-negative breast cancers. Oncogene *38*, 2020–2041.

213. Qian, W., Zhu, Y., Wu, M., Guo, Q., Wu, Z., Lobie, P.E., and Zhu, T. (2020). Linc00668 Promotes Invasion and Stem Cell-Like Properties of Breast Cancer Cells by Interaction With SND1. Front. Oncol. *10*, 88.

214. Gao, X., Qin, T., Mao, J., Zhang, J., Fan, S., Lu, Y., Sun, Z., Zhang, Q., Song, B., and Li, L. (2019). PTENP1/miR-20a/PTEN axis contributes to breast cancer progression by regulating PTEN via PI3K/AKT pathway. J. Exp. Clin. Cancer Res. *38*, 256.

215. Deocesano-Pereira, C., Machado, R.A.C., De Jesus-Ferreira, H.C., Marchini, T., Pereira, T.F., Carreira, A.C.O., and Sogayar, M.C. (2019). Functional impact of the long non-coding RNA *MEG3* deletion by CRISPR/Cas9 in the human triple negative metastatic Hs578T cancer cell line. Oncol. Lett. *18*, 5941–5951.

216. Miyoshi, Y., Kurosumi, M., Kurebayashi, J., Matsuura, N., Takahashi, M., Tokunaga, E., Egawa, C., Masuda, N., Kim, S.J., Okishiro, M., et al.; Collaborative Study Group of Scientific Research of the Japanese Breast Cancer Society (2008). Topoisomerase IIalpha-positive and BRCA1-negative phenotype: association with favorable response to epirubicin-based regimens for human breast cancers. Cancer Lett. *264*, 44–53.

217. Zhang, Z., Yu, X., Wang, Z., Wu, P., and Huang, J. (2015). Anthracyclines potentiate anti-tumor immunity: A new opportunity for chemoimmunotherapy. Cancer Lett. *369*, 331–335.

218. Yared, J.A., and Tkaczuk, K.H. (2012). Update on taxane development: new analogs and new formulations. Drug Des. Devel. Ther. *6*, 371–384.

219. Bida, O., Gidoni, M., Ideses, D., Efroni, S., and Ginsberg, D. (2015). A novel mitosis-associated lncRNA, MA-linc1, is required for cell cycle progression and sensitizes cancer cells to Paclitaxel. Oncotarget *6*, 27880–27890.

220. Zheng, P., Dong, L., Zhang, B., Dai, J., Zhang, Y., Wang, Y., and Qin, S. (2019). Long noncoding RNA CASC2 promotes paclitaxel resistance in breast cancer through regulation of miR-18a-5p/CDK19. Histochem. Cell Biol. *152*, 281–291.

221. Zhang, H., Zhao, B., Wang, X., Zhang, F., and Yu, W. (2019). LINC00511 knockdown enhances paclitaxel cytotoxicity in breast cancer via regulating miR-29c/CDK6 axis. Life Sci. *228*, 135–144.

222. Huang, P., Li, F., Li, L., You, Y., Luo, S., Dong, Z., Gao, Q., Wu, S., Brünner, N., and Stenvang, J. (2018). lncRNA profile study reveals the mRNAs and lncRNAs associated with docetaxel resistance in breast cancer cells. Sci. Rep. *8*, 17970.

223. Florea, A.M., and Büsselberg, D. (2011). Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. Cancers (Basel) *3*, 1351–1371.

224. Mi, H., Wang, X., Wang, F., Li, L., Zhu, M., Wang, N., Xiong, Y., and Gu, Y. (2020). SNHG15 Contributes To Cisplatin Resistance In Breast Cancer Through Sponging miR-381. OncoTargets Ther. *13*, 657–666.

225. Wu, J., Chen, H., Ye, M., Wang, B., Zhang, Y., Sheng, J., Meng, T., and Chen, H. (2019). Long noncoding RNA HCP5 contributes to cisplatin resistance in human triple-negative breast cancer via regulation of PTEN expression. Biomed. Pharmacother. *115*, 108869.

226. Gil-Gil, M., Alba, E., Gavilá, J., de la Haba-Rodríguez, J., Ciruelos, E., Tolosa, P., Candini, D., and Llombart-Cussac, A. (2021). The role of CDK4/6 inhibitors in early breast cancer. Breast *58*, 160–169.

227. Sledge, G.W., Jr., Toi, M., Neven, P., Sohn, J., Inoue, K., Pivot, X., Burdaeva, O., Okera, M., Masuda, N., Kaufman, P.A., et al. (2017). MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J. Clin. Oncol. *35*, 2875–2884.

228. Finn, R.S., Martin, M., Rugo, H.S., Jones, S., Im, S.A., Gelmon, K., Harbeck, N., Lipatov, O.N., Walshe, J.M., Moulder, S., et al. (2016). Palbociclib and Letrozole in Advanced Breast Cancer. N. Engl. J. Med. *375*, 1925–1936.

229. O'Leary, B., Finn, R.S., and Turner, N.C. (2016). Treating cancer with selective CDK4/6 inhibitors. Nat. Rev. Clin. Oncol. *13*, 417–430.

230. Cui, Y., Lu, C., Zhang, Z., Mao, A., Feng, L., Fu, L., Gu, F., Ma, X., and He, D. (2020). A Long Non-coding RNA Lnc712 Regulates Breast Cancer Cell Proliferation. Int. J. Biol. Sci. *16*, 162–171.

231. Yuan, H., Qin, Y., Zeng, B., Feng, Y., Li, Y., Xiang, T., and Ren, G. (2019). Long non-coding RNA LINC01089 predicts clinical prognosis and inhibits cell proliferation and invasion through the Wnt/β-catenin signaling pathway in breast cancer. OncoTargets Ther. *12*, 4883–4895.

232. Deng, X., Zhao, Y., Wu, X., and Song, G. (2017). Upregulation of CCAT2 promotes cell proliferation by repressing the P15 in breast cancer. Biomed. Pharmacother. *91*, 1160–1166.

233. Yu, W.D., Wang, H., He, Q.F., Xu, Y., and Wang, X.C. (2018). Long noncoding RNAs in cancer-immunity cycle. J. Cell. Physiol. *233*, 6518–6523.

234. Wu, M., Fu, P., Qu, L., Liu, J., and Lin, A. (2020). Long Noncoding RNAs, New Critical Regulators in Cancer Immunity. Front. Oncol. *10*, 550987.

235. Zhang, Y., Liu, Q., and Liao, Q. (2020). Long noncoding RNA: a dazzling dancer in tumor immune microenvironment. J. Exp. Clin. Cancer Res. *39*, 231.

236. Kalbasi, A., and Ribas, A. (2020). Tumour-intrinsic resistance to immune checkpoint blockade. Nat. Rev. Immunol. *20*, 25–39.

237. Ranzani, V., Rossetti, G., Panzeri, I., Arrigoni, A., Bonnal, R.J., Curti, S., Gruarin, P., Provasi, E., Sugliano, E., Marconi, M., et al. (2015). The long intergenic noncoding RNA landscape of human lymphocytes highlights the regulation of T cell differentiation by linc-MAF-4. Nat. Immunol. *16*, 318–325.

238. Wang, J., Huang, F., Shi, Y., Zhang, Q., Xu, S., Yao, Y., and Jiang, R. (2021). RP11-323N12.5 promotes the malignancy and immunosuppression of human gastric cancer by increasing YAP1 transcription. Gastric Cancer *24*, 85–102.

239. Wang, P., Xue, Y., Han, Y., Lin, L., Wu, C., Xu, S., Jiang, Z., Xu, J., Liu, Q., and Cao, X. (2014). The STAT3-binding long noncoding RNA lnc-DC controls human dendritic cell differentiation. Science *344*, 310–313.

240. Chen, Y., Jin, H., Song, Y., Huang, T., Cao, J., Tang, Q., and Zou, Z. (2021). Targeting tumor-associated macrophages: A potential treatment for solid tumors. J. Cell. Physiol. *236*, 3445–3465.

241. Chen, Y., Song, Y., Du, W., Gong, L., Chang, H., and Zou, Z. (2019). Tumor-associated macrophages: an accomplice in solid tumor progression. J. Biomed. Sci. *26*, 78.

242. Zhao, Y., Yu, Z., Ma, R., Zhang, Y., Zhao, L., Yan, Y., Lv, X., Zhang, L., Su, P., Bi, J., et al. (2020). lncRNA-Xist/miR-101-3p/KLF6/C/EBPα axis promotes TAM polarization to regulate cancer cell proliferation and migration. Mol. Ther. Nucleic Acids *23*, 536–551.

243. Tao, S., Chen, Q., Lin, C., and Dong, H. (2020). Linc00514 promotes breast cancer metastasis and M2 polarization of tumor-associated macrophages via Jagged1-mediated notch signaling pathway. J. Exp. Clin. Cancer Res. *39*, 191.

244. Hulpke, S., and Tampé, R. (2013). The MHC I loading complex: a multitasking machinery in adaptive immunity. Trends Biochem. Sci. *38*, 412–420.

245. Li, H., Li, C.-W., Li, X., Ding, Q., Guo, L., Liu, S., Liu, C., Lai, C.-C., Hsu, J.-M., Dong, Q., et al. (2019). MET Inhibitors Promote Liver Tumor Evasion of the Immune Response by Stabilizing PDL1. Gastroenterology *156*, 1849–1861.e13.

246. Pei, X., Wang, X., and Li, H. (2018). LncRNA SNHG1 regulates the differentiation of Treg cells and affects the immune escape of breast cancer via regulating miR-448/IDO. Int. J. Biol. Macromol. *118* (Pt A), 24–30.

247. Mineo, M., Lyons, S.M., Zdioruk, M., von Spreckelsen, N., Ferrer-Luna, R., Ito, H., Alayo, Q.A., Kharel, P., Giantini Larsen, A., Fan, W.Y., et al. (2020). Tumor Interferon Signaling Is Regulated by a lncRNA INCR1 Transcribed from the PD-L1 Locus. Mol. Cell *78*, 1207–1223.e8.

248. Zhang, M., Wang, N., Song, P., Fu, Y., Ren, Y., Li, Z., and Wang, J. (2020). LncRNA GATA3-AS1 facilitates tumour progression and immune escape in triple-negative breast cancer through destabilization of GATA3 but stabilization of PD-L1. Cell Prolif. *53*, e12855.

249. Lorenzi, L., Avila Cobos, F., Decock, A., Everaert, C., Helsmoortel, H., Lefever, S., Verboom, K., Volders, P.J., Speleman, F., Vandesompele, J., and Mestdagh, P. (2019). Long noncoding RNA expression profiling in cancer: Challenges and opportunities. Genes Chromosomes Cancer *58*, 191–199.

250. Liu, M., Xing, L.Q., and Liu, Y.J. (2017). A three-long noncoding RNA signature as a diagnostic biomarker for differentiating between triple-negative and non-triple-negative breast cancers. Medicine (Baltimore) *96*, e6222.

251. Bermejo, J.L., Huang, G., Manoochehri, M., Mesa, K.G., Schick, M., Silos, R.G., Ko, Y.D., Brüning, T., Brauch, H., Lo, W.Y., et al. (2019). Long intergenic noncoding RNA 299 methylation in peripheral blood is a biomarker for triple-negative breast cancer. Epigenomics *11*, 81–93.

252. Milevskiy, M.J., Al-Ejeh, F., Saunus, J.M., Northwood, K.S., Bailey, P.J., Betts, J.A., McCart Reed, A.E., Nephew, K.P., Stone, A., Gee, J.M., et al. (2016). Long-range regulators of the lncRNA HOTAIR enhance its prognostic potential in breast cancer. Hum. Mol. Genet. *25*, 3269–3283.

253. Zhang, Z., Peng, Z., Olsen, D., deKay, J., Weaver, D.L., and Evans, M.F. (2014). Abstract 1498: Long non-coding RNA in situ hybridization signal patterns correlate with breast tumor pathology. Cancer Res. *74*, 1498.

254. Sun, M., Wu, D., Zhou, K., Li, H., Gong, X., Wei, Q., Du, M., Lei, P., Zha, J., Zhu, H., et al. (2019). An eight-lncRNA signature predicts survival of breast cancer patients: a comprehensive study based on weighted gene co-expression network analysis and competing endogenous RNA network. Breast Cancer Res. Treat. *175*, 59–75.

255. Lu, R., Zhang, J., Zhang, W., Huang, Y., Wang, N., Zhang, Q., and Qu, S. (2018). Circulating HOTAIR expression predicts the clinical response to neoadjuvant chemotherapy in patients with breast cancer. Cancer Biomark. *22*, 249–256.

256. Hu, H., Hu, J., Yang, Y., Zhou, W., and Ye, C. (2021). Assessment of circulating HISLA as a potential biomarker for breast cancer diagnosis and prognosis. Clin. Exp. Med. *21*, 29–34.

257. Alipoor, B., Parvar, S.N., Sabati, Z., Ghaedi, H., and Ghasemi, H. (2020). An updated review of the H19 lncRNA in human cancer: molecular mechanism and diagnostic and therapeutic importance. Mol. Biol. Rep. *47*, 6357–6374.

258. Han, L., Ma, P., Liu, S.M., and Zhou, X. (2016). Circulating long noncoding RNA GAS5 as a potential biomarker in breast cancer for assessing the surgical effects. Tumour Biol. *37*, 6847–6854.

259. Tian, T., Wang, M., Lin, S., Guo, Y., Dai, Z., Liu, K., Yang, P., Dai, C., Zhu, Y., Zheng, Y., et al. (2018). The Impact of lncRNA Dysregulation on Clinicopathology and Survival of Breast Cancer: A Systematic Review and Meta-analysis. Mol. Ther. Nucleic Acids *12*, 359–369.

260. Li, Z., Xu, L., Liu, Y., Fu, S., Tu, J., Hu, Y., and Xiong, Q. (2018). LncRNA MALAT1 promotes relapse of breast cancer patients with postoperative fever. Am. J. Transl. Res. *10*, 3186–3197.

261. Liu, X.M., Yang, B., and Han, J. (2018). Increased long noncoding RNA LINP1 expression and its prognostic significance in human breast cancer. Eur. Rev. Med. Pharmacol. Sci. *22*, 8749–8754.

262. Sha, S., Yuan, D., Liu, Y., Han, B., and Zhong, N. (2017). Targeting long non-coding RNA DANCR inhibits triple negative breast cancer progression. Biol. Open *6*, 1310–1316.

263. Fu, J., Dong, G., Shi, H., Zhang, J., Ning, Z., Bao, X., Liu, C., Hu, J., Liu, M., and Xiong, B. (2019). LncRNA MIR503HG inhibits cell migration and invasion via miR-103/OLFM4 axis in triple negative breast cancer. J. Cell. Mol. Med. *23*, 4738–4745.

264. Xu, S.P., Zhang, J.F., Sui, S.Y., Bai, N.X., Gao, S., Zhang, G.W., Shi, Q.Y., You, Z.L., Zhan, C., and Pang, D. (2015). Downregulation of the long noncoding RNA EGOT correlates with malignant status and poor prognosis in breast cancer. Tumour Biol. *36*, 9807–9812.

265. Malih, S., Saidijam, M., and Malih, N. (2016). A brief review on long noncoding RNAs: a new paradigm in breast cancer pathogenesis, diagnosis and therapy. Tumour Biol. *37*, 1479–1485.

266. Singh, N., Padi, S.K.R., Bearss, J.J., Pandey, R., Okumura, K., Beltran, H., Song, J.H., Kraft, A.S., and Olive, V. (2020). PIM protein kinases regulate the level of the long noncoding RNA H19 to control stem cell gene transcription and modulate tumor growth. Mol. Oncol. *14*, 974–990.

267. Li, M., Li, X., Zhuang, Y., Flemington, E.K., Lin, Z., and Shan, B. (2017). Induction of a novel isoform of the lncRNA HOTAIR in Claudin-low breast cancer cells attached to extracellular matrix. Mol. Oncol. *11*, 1698–1710.

268. Lee, J.S., and Mendell, J.T. (2020). Antisense-Mediated Transcript Knockdown Triggers Premature Transcription Termination. Mol. Cell *77*, 1044–1054.e3.

269. Xiu, B., Chi, Y., Liu, L., Chi, W., Zhang, Q., Chen, J., Guo, R., Si, J., Li, L., Xue, J., et al. (2019). LINC02273 drives breast cancer metastasis by epigenetically increasing AGR2 transcription. Mol. Cancer *18*, 187.

270. Zhu, S., Li, W., Liu, J., Chen, C.H., Liao, Q., Xu, P., Xu, H., Xiao, T., Cao, Z., Peng, J., et al. (2016). Genome-scale deletion screening of human long non-coding RNAs using a paired-guide RNA CRISPR-Cas9 library. Nat. Biotechnol. *34*, 1279–1286.

271. Lin, L.C., Lee, H.T., Chien, P.J., Huang, Y.H., Chang, M.Y., Lee, Y.C., and Chang, W.W. (2020). NAD(P)H:quinone oxidoreductase 1 determines radiosensitivity of triple negative breast cancer cells and is controlled by long non-coding RNA NEAT1. Int. J. Med. Sci. *17*, 2214–2224.