Long Non-Coding RNA and Breast Cancer

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Abstract
Breast cancer, one of the most common diseases among women, is regarded as a heterogeneous and complicated disease that remains a major public health concern. Recently, owing to the development of next-generation sequencing technologies, long non-coding RNAs have received extensive attention. Numerous studies reveal that long non-coding RNAs are playing important roles in tumor development. Although the biological function and molecular mechanisms of long non-coding RNAs remain enigmatic, recent researchers have demonstrated that an array of long non-coding RNAs express abnormally in cancers, including breast cancer. Herein, we summarized the latest literature about long non-coding RNAs in breast cancer, with a particular focus on the multiple molecular roles of regulatory long non-coding RNAs that regulate cell proliferation, invasion, metastasis, and apoptosis.

Keywords
long non-coding RNA, breast cancer, molecular mechanisms, cell proliferation, invasion, metastasis, apoptosis

Abbreviations
ANCRA, anti-differentiation noncoding RNA; Caspases, cysteine aspartate specific proteases; EGF, epidermal growth factor; EMT, epithelial–mesenchymal transition; HOTAIR, HOX transcript antisense; IncRNAs, long non-coding RNAs; LSD1, lysine-specific demethylase 1; MAPK, Mitogen-activated protein kinase; miRNAs, microRNAs; mRNA, messenger RNA; mTOR, mammalian target of rapamycin; ncRNAs, non-coding RNAs; NFκB, nuclear factor-κB; ORF, open reading frame; PRC2, polycomb repressive complex 2; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-β; TUG1, taurine-upregulated gene 1.

Introduction
The American Cancer Society estimated that, in 2018, there were 1,735,350 new cancer cases and 609,640 cancer deaths in the United States.1 Breast cancer is the most prevalent cancer diagnosed in women in the United States and worldwide, and it is the second leading cause of cancer death among women after lung cancer.2 Although great advances have been made in early detection and therapeutics of breast cancer over the last 20 years, breast cancer remains a major public health problem.

The advances in next-generation sequencing technologies reveal that at least 75% of the human genome are actively transcribed into RNAs, although less than 2% of these transcripts are translated into proteins.3 Based on their length, non-coding RNAs (ncRNAs) are divided into two major groups: short ncRNAs and long ncRNAs (lncRNAs). Short ncRNAs are generally less than 200 nucleotides, which include small-
interfering RNAs, piwi-related RNAs, transfer RNAs, and microRNAs (miRNAs). The lncRNAs are greater than 200 nucleotides and sometimes as long as 100 kb. Over the past 20 years, short ncRNAs, especially miRNAs, have been extensively studied. The biological function of many miRNAs has been elucidated; however, our knowledge about the functional role of lncRNAs is rather limited, as these lncRNAs were often considered to be products of evolutionary waste or transcription noises. In this work, we will review the biological role of lncRNAs in human cancer, particularly in breast cancer.

Definition and Classification of lncRNAs

Long ncRNAs are endogenous RNA molecules with a length that ranges from 200 nt to 100 kb that lack open reading frames (ORFs). Based on their gene loci, characteristics, and relationship with their neighbor genes, the lncRNAs can be divided into 6 categories: (1) intergenic lncRNAs, also known as large intervening ncRNAs, or lincRNAs, which are defined as autonomously transcribed ncRNAs that do not overlap annotated coding genes, such as lncRNA MALAT1, LINK-A, IncRNA ALIEN, IncRAM, and IncRNA UCC; (2) intronic lncRNAs, which are produced internally by an intron without any epitope of an ORF that overlaps at either end, such as lncRNA SPRY4-IT1 and lncRNA MEG8-IT1; (3) bidirectional lncRNAs, which start from the divergence direction of the promoter or enhancer region, typically within hundreds of base pairs; these lncRNA are also termed as enhancer-related RNA, like lncRNA LEENE and lncRNA HCCL5; (4) overlapping sense lncRNAs, which are transcribed in the same direction as an ORF and overlap with the ORF for at least one exon, such as lncRNA GAS5; (5) antisense lncRNAs, also known as natural antisense transcript, are transcribed from the antisense strand of an ORF, such as lncRNA GATA6-AS, IncRNA ASBEL, IncRNA UCHL1, and lncRNA ANRIL; (6) lncRNAs that are hosted by an miRNA gene or an miRNA cluster, such as lncRNA LOC554202 and lncRNA MIR100HG.

Mechanism of lncRNAs in Cancer Biology

Long ncRNAs, lacking an ORF, participate in biological processes at 3 different levels: transcriptional level, posttranscriptional level, and epigenetic level (Figure 1). At transcriptional
level, (1) lncRNAs act as a signal or decoy to promote or suppress gene expression (Figure 1A and B)\(^3\); (2) lncRNAs function as scaffold molecules to regulate gene expression via assembling chromatin-modifying complexes at special loci (Figure 1C)\(^3\); (3) lncRNAs act as a miRNA sponge (also called competitive endogenous RNA) to reverse miRNA suppression of its target genes (Figure 1D).\(^3\) Similarly, lncRNAs may also function as competing endogenous RNAs (ceRNAs) to sponge miRNAs in malignant breast tumors. Feng\(^3\) et al demonstrated that lncRNA KCNQ1OT1 enhances tumor growth as a sponge of miR-145 to regulate the expression of CCNE2. At posttranscriptional level, lncRNAs regulate the translation of messenger RNAs (mRNAs) and control their stability via forming double-stranded RNA with mRNAs\(^3\) or regulate protein stability by binding\(^3\) (Figure 1E). In hepatocellular carcinoma, lncRNA-ATB upregulated ZEB1 and ZEB2 by competitively binding the miR-200 family and then induced epithelial–mesenchymal transition (EMT) and invasion. In addition, lncRNA-ATB promoted organ colonization of disseminated tumor cells by binding interleukin 11 mRNA and stimulated signal transducer and activator of transcription 3 (STAT3) signaling. In triple-negative breast cancer, lncRNA PVT1 binds with the KLF5 protein and increases its stability.\(^3\) lncRNA H19 is reported to function as the precursor harboring an miRNA (miR-675; Figure 1F).\(^3\) At epigenetic level, (1) lncRNAs regulate DNA methylation in the promoter region of a downstream gene to silence it (Figure 1G)\(^3\); (2) lncRNAs alter methylation, acetylation, or ubiquitination of histones by coacting with histone modification factors (Figure 1H)\(^3\); (3) lncRNAs directly bind to chromatin modification complexes to reconstruct a chromatin or alter its conformation for regulating the target gene transcription (Figure 1I).\(^3\)

### Functions of lncRNAs in Breast Cancer

Long ncRNAs play a pivotal role in various cancer types including breast cancer. Abnormal expression of lncRNAs contribute significantly to cancer initiation and progression in breast cancer. These lncRNAs include lncRNA MALAT1,\(^2\) lncRNA DANCR,\(^3\) lncRNA PDCD4-AS1,\(^4\) and so on. The functions of lncRNAs in breast cancer are summarized in Table 1.

### Long ncRNAs in Cell Proliferation

Cancer cell proliferation is induced by multiple signaling pathways.\(^6\) Recent research shows that multiple lncRNAs mediate cell proliferation through activating or restraining specific signaling pathways in breast cancer (Figure 2A).\(^7\)

**Akt signaling pathway.** The Akt signaling pathway is involved in various biological responses, such as inhibition of apoptosis and stimulation of cell proliferation.\(^7\) H19, a 2.3-kb lncRNA,
is encoded by the maternal allele and is considered as an onco-
genome in many cancers. A new lncRNA at the H19/IGF2 locus is transcribed in H19 antisense orientation and named 91H. In breast cancer, 91H lncRNA prevents histone and DNA methylation on the maternal allele at the H19/IGF2 locus and thereby is responsible for maintaining the H19/IGF2 genomic imprinting. H19 is activated by E2F1 and promotes the G1-S transition in breast cancer cells. The H19-derived miR-675 downregulates c-Cbl and Cbl-b proteins and activates EGFR and c-Met to promote cell proliferation through Akt activation. Zhang et al. found that overexpression of lncRNA MEG3 not only causes cell cycle arrest in G0/G1 phase but also suppresses tumor growth in a mouse model of breast cancer through Akt signaling. Chen et al. showed that lncRNA PTENP1 inhibits the proliferation of breast cancer cells through downregulating mitogen-activated protein kinase (MAPK) and AKT signaling pathways.

**Mitogen-activated protein kinase signaling pathway.** Mitogen-activated protein kinase, a part of the serine-threonine kinase family, is widely associated with cell proliferation, differentiation, migration, senescence, and apoptosis. Long ncRNA CAMTA1 was first reported to be upregulated in liver cancer cells. In breast cancer, CAMTA1 promotes proliferation of human breast cancer cells via binding miR-20b, which suppresses the expression of vascular endothelial growth factor, an activator of MAPK. Wang et al. identified 12 to 44 cross-talking pathway pairs mediated by lncRNAs in 4 breast cancer subtypes. They found that lncRNA LIFR-AS1 is a tumor suppressor regulating the expression of IL1R and TGFBR, which in turn activate MAPK and augment breast cancer cell proliferation. Peng et al. employed CRISPR/Cas9 to knockout lincROR in MCF-7 cells and found that linc-ROR promotes estrogen-independent growth and activates the MAPK pathway in breast cancer cells.

**Wnt signaling pathway.** The Wnt signaling pathway is a highly conserved and can be activated via the canonical or noncanonical route. The former plays a vital role in breast cancer initiation and progression. Long ncRNAs interact with critical molecules in the canonical pathway, including MYC and β-catenin. LncRNA CCAT2, a novel lncRNA mapping to 8q24, is significantly upregulated in both breast cancer tissues and breast cancer cell lines. CCAT2 promotes breast tumor growth by upregulating β-catenin, a key downstream effector of Wnt signaling. Long ncRNA CRNDE is upregulated in breast cancer and acts as a molecular sponge for different miRNAs such as miR-136 to activate Wnt β-catenin signaling and promote tumor cell proliferation.

**MYC signaling pathways.** The proto-oncogene MYC is amplified in many types of cancer, and MYC activates various downstream genes involved in cell cycle, cell growth, and angiogenesis. Wang et al. characterized the epigenetic landscape of lncRNA genes across a large number of human tumors including breast cancer. They observed that lncRNA EPIC1 promotes cell cycle progression and proliferation by interacting with MYC and enhances its binding to several target genes. Long ncRNA SNHG12 is upregulated in triple-negative breast cancer and is significantly correlated with tumor size and lymph node metastasis. Moreover, SNHG12 is a direct target gene of MYC, an important member of MYC; silencing SNHG12 expression inhibits breast cancer cells proliferation.

**Other signaling pathways.** Mammalian Target of Rapamycin (mTOR), a 289-kDa serine/threonine protein kinase, is a downstream effector of many frequently activated oncogenic pathways, including Akt and MAPK. Li et al. identified that silencing lncRNA-ASAH2B-2 inhibits breast cancer cell growth via inhibiting mTOR signaling. Bcl-2 family member bcl-w promotes cell proliferation, migration, and invasion in cancers. Long ncRNA HOX transcript antisense RNA (HOTAIR), located in the HOX gene locus, modulates miR-206-mediated bcl-w signaling to facilitate cell proliferation in breast cancer and other cancers.
**Long ncRNAs in Cell Invasion and Metastasis**

Cancer invasion and metastasis are a multistep process that is responsible for more than 90% of cancer death. Metastasis is a process in which the primary tumor cells disseminate to bloodstream or lymphocytic routes, reach distant secondary organs, and then proliferate. Here, we list the following pathways in which lncRNAs are involved (Figure 2B).

**Signal Transducer and Activator of Transcription 3 signaling pathway.** The activation of STAT3 plays a vital role in the metastasis of many cancers. Long ncRNA-FEZF1-AS1 promotes colorectal cancer proliferation and metastasis by targeting pyruvate kinase 2 (PKM2) to activate STAT3. HOX transcript antisense RNA is upregulated in multiple cancers, especially breast cancer. The 5‘end of HOXT is activated by the polycomb repressive complex 2 (PRC2), whereas its 3‘end binds lysine-specific demethylase 1 (LSD1) and acts as a scaffold for PRC2 and LSD1 to regulate target gene expression. Expression of HOXT and EZH2 is highly correlated in breast cancer tissues, and both lncRNAs are enriched in metastatic lesions compared to the paired primary breast tumors. miR-7, which is inhibited indirectly by HOXT, is a negative regulator of STAT3 and breast cancer cell EMT. Besides, lncRNA increases JAK2 kinase activity to promote brain translation. In breast cancer cells, Lnc-BM promotes STAT3-mediated oncostatin M- and IL-6-triggered STAT3 phosphorylation.

**Nuclear factor κB signaling pathway.** Nuclear factor-κB (NF-κB) is a critical link between inflammation and cancer that underlies the tumor microenvironment. Nuclear factor κB is constitutively activated in some breast cancers. Liu et al identified an NF-κB interacting lncRNA NKILA, as a tumor suppressor; NKILA is associated with breast cancer metastasis through binding to NF-κB-κB complex and repressing NF-κB signaling. In another report, lncRNA NKILA is activated by transforming growth factor β (TGF-β) and suppresses TGF-β-induced EMT via blocking NF-κB signaling in breast cancer.

**Transforming growth factor-β signaling pathway.** Transforming growth factor-β is a multifunctional cytokine belonging to the TGF superfamily. The TGF-β signaling pathway is instrumental in regulating cellular activities such as proliferation, differentiation, apoptosis, motility, invasion, extracellular matrix production, angiogenesis, and immune response. There are 2 facets of TGF-β in breast cancer: In early stages, it inhibits epithelial cell cycle progression and promotes apoptosis; however, in late stages, it acts as an oncogene and promotes tumor progression and metastasis. Anti-differentiation noncoding RNA (ANCR), an 855-nucleotide lncRNA, is downregulated during differentiation. In breast cancer, ANCR is a potential tumor suppressor and inhibits breast cancer cell migration and metastasis by decreasing RUNX2 expression in vitro and in vivo. Cheng et al demonstrated that lncRNA H1T, a novel breast cancer-associated lncRNA, promotes TGF-β-induced migration, invasion, and EMT. Wang et al observed that lncRNA CCAT2 also promotes breast cancer growth and metastasis by upregulating the protein expression levels of TGF-β, Smad2, and α smooth muscle actin, all key components of TGF-β signaling.

**Other signaling pathways.** The Hippo signaling pathway is first discovered in *Drosophila melanogaster* and is a highly conserved pathway regulating cell proliferation, apoptosis, and metastasis. YAP and TAZ are 2 key downstream effectors of the Hippo signaling pathway. Yang et al identified an ROR1-HER3-lncRNA signaling axis modulating the Hippo-YAP pathway to regulate bone metastasis; this lncRNA (MAYA) is part of an RNA–protein complex that activates YAP and elicits osteoclast differentiation and bone metastasis. The epidermal growth factor (EGF) is a small 53 amino acid residue protein involved in normal cell growth, oncogenesis, and metastasis. Yard et al found that knockdown of EGF-regulated lncRNA LIMIT enhances cellular migration and invasion in vitro as well as metastasis in breast cancer.

**Long ncRNAs in Apoptosis**

Apoptosis is programmed cell death that is essential to normal tissue development. Dysregulation of apoptosis promotes tumorigenesis. Many lncRNAs participate in cellular apoptosis (Figure 2C).

**p53 signaling pathway.** p53 is a tumor-suppressor protein that regulates the expression of a wide variety of genes involved in apoptosis, growth arrest, and inhibition of cell cycle progression and differentiation. Long ncRNAs are key components of the p53 pathway. Wu et al demonstrated that the p53-responsive lncRNA GUARDIN sustains breast cancer growth and GUARDIN silencing triggers apoptosis in breast cancer cells. p53-induced tumor suppressive lncRNA PICART1 inhibits breast cancer proliferation and promotes apoptosis through the AKT/GSK3β/β-catenin signaling cascade. Long ncRNA MALAT1, located on chromosome 11q13.1, has been reported to regulate the acetylation of p53 by competing with SIRT1 and DBC1 for p53 binding, resulting in reduced cell apoptosis in breast cancer cells.

**Caspase signaling pathway.** Cysteine aspartate specific proteases (Caspases) are a family of cysteine proteases that act in concert in a cascade during apoptosis. Liu et al found that lncRNA LINCO0628 is significantly downregulated in breast cancer and that overexpression of LINCO0628 causes cell cycle arrested in G0/G1 phase and promotes cell apoptosis by regulating the expression of caspase-3, Bax, and Bcl-2. Taurine-upregulated gene 1 (TUG1) is an lncRNA involved in the progression of several cancers. Li et al found that TUG1
knockdown increases breast cancer cell apoptosis via increases in the activities of caspase 3 and caspase 9. Zhou et al\textsuperscript{127} discovered that the lincRNA-APOC1P1-3 is overexpressed in breast cancer, and this lincRNA directly binds to tubulin to decrease \(z\)-tubulin acetylation, inactivate caspase,3, and inhibit apoptosis.

Prospects and Challenges
Initially regarded as transcriptional noises, it is now widely accepted that lncRNAs, like miRNAs, function as important regulators of gene expression and tumorigenesis. The lncRNAs are potential targets for the diagnosis, prognosis, and treatment of human cancers. As we discussed in the review, aberrant lncRNA expression is associated with breast cancer. Unlike protein-coding mRNAs and miRNAs, our understanding of lncRNAs is still in the preliminary stage. There are many gaps in our knowledge of lncRNAs. First, only a small fraction of lncRNAs have been experimentally studied. Whether abnormal lncRNA expression is a cause or consequence of tumorigenesis remains elusive. Second, with an increasing number of lncRNAs detected, their biological functions and mechanisms of action in cancer require further exploration. Third, many lncRNAs are present in the circulation. Several studies have demonstrated that circulating lncRNAs are potential biomarkers in multitype cancers, including cholangiocarcinoma,\textsuperscript{128} non-small-cell lung cancer,\textsuperscript{129} hepatocellular carcinoma,\textsuperscript{130,131} gastric cancer,\textsuperscript{132} and so on. However, studies on circulating lncRNAs in cancer are still in early stage. For circulating lncRNAs to be deployed as diagnostic, prognostic, or treatment biomarkers, extensive research is needed.

In conclusion, the discovery of lncRNAs has opened a new door in cancer research. The lncRNAs could become a significant player in cancer diagnosis, prognosis, and therapeutic development, benefiting patients with breast cancer and beyond.

Authors’ Note
Tianzhu Zhang, Cold Spring Harb Perspect Biol Hui Hu, and Ge Yan contributed equally to this work. Our study did not require an ethical board approval because it did not contain human or animal trials.

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