Long non-coding RNAs as novel biomarkers for breast cancer invasion and metastasis (Review)

KAIJIONG ZHANG[1], ZHENGLIAN LUO[1], YI ZHANG[1], XIAOYU SONG[2],
LI ZHANG[2], LICHUN WU[2] and JINBO LIU[1]

[1]Department of Laboratory Medicine, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan 646000;
[2]Department of Laboratory Medicine, Sichuan Cancer Hospital, Chengdu, Sichuan 610041, P.R. China

Abstract. Breast cancer (BC) is now the most common malignancy worldwide, with high prevalence and lethality among women. Invasion and metastasis are the major reasons for breast cancer-associated mortality. However, the underlying mechanism of invasion and metastasis has not been entirely elucidated. Long non-coding RNAs (lncRNAs) are a large class of non-coding transcripts that are >200 bases in length and cannot encode proteins. Evidence has indicated that lncRNAs regulate gene expression at the levels of epigenetic modification, transcription and post-transcription. In addition, they are involved in diverse tumor biological processes, including cell proliferation, apoptosis, invasion, metastasis and angiogenesis. The present review focuses on the recent progress of lncRNAs in breast cancer invasion and metastasis, aiming to provide novel strategies for the clinical prevention, diagnosis and treatment of breast cancer.

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1. Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-associated mortality among women worldwide, with an estimated 1.7 million cases and 521,900 mortalities in 2012, which accounts for 25% of all cancer cases and 15% of all cancer-associated mortalities among females (1). With the development of society and the economy, the incidence of breast cancer is increasing rapidly, particularly in the less developed countries of the world (1). Although advances have been made in the treatment of breast cancer over the previous decades, the prognosis for patients remains poor due to the high rate of metastasis (1,2). Metastasis is the primary cause of relapse and mortality of patients with breast cancer (3-5). Once metastasis occurs, the 5-year survival rate is <25% (6). Therefore, there is an urgent requirement to identify novel molecular biomarkers of metastasis, which may be useful in the early diagnosis, prognosis assessment and prediction of response to therapy for breast cancer.

Metastasis is a multifactorial and multistep process, which is regulated by the abnormal expression of various genes, including snail family zinc finger (Snail1 and Snail2), zinc finger E-box binding homeobox (ZEB1 and ZEB2), twist basic helix-loop-helix transcription factor 1 (Twist1) and matrix metalloproteinases (MMPs) (7). In previous years, although numerous studies (7-9) have focused on the identification and characterization of the genes and gene products that drive a metastatic process, the precise molecular mechanism that governs the process has been largely unknown. The identification of non-coding RNAs (ncRNAs) has opened a novel avenue for studies on cancer metastasis. It has been reported that only ~2% of the human genome encodes protein-coding genes, and at least 70% of the human genome is actively transcribed, generating a vast range of ncRNAs (10,11). Although these ncRNAs were previously regarded as transcriptional 'noise', it has become clear that ncRNAs perform a crucial role in cellular development and tumor progression, including metastasis (12,13). Based on transcript size, ncRNAs are classified into two major groups. Transcripts shorter than 200 nucleotides (nts) are referred to as small ncRNAs, such as microRNAs (miRNAs/miRs) (14), which have been well established to extensively affect cancer invasion and metastasis (15,16). The other group is composed of long non-coding RNAs (lncRNAs), which are pervasively transcribed in the genome and exhibit emerging roles in tumorigenesis (17-20).

lncRNAs are a group of RNA molecules, which are >200 nts in length, lack functional open reading frames (ORFs) and cannot encode proteins; they regulate gene expression

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Correspondence to: Professor Jinbo Liu, Department of Laboratory Medicine, The Affiliated Hospital of Southwest Medical University, 25 Taiping Street, Luzhou, Sichuan 646000, P.R. China
E-mail: liujb7203@163.com

at the epigenetic, transcriptional and post-transcriptional levels (21,22). The majority of lncRNAs are located in the cytoplasm (23-25), and are transcribed by RNA polymerase II, spliced and polyadenylated (20,26). lncRNAs can be classified into five general categories according to their location relative to nearby protein-coding genes: Sense lncRNA, anti-sense lncRNA, bidirectional lncRNA, intronic lncRNA and intergenic lncRNA (27,28). Although thousands of lncRNAs have been identified to be involved in numerous physiological and pathological processes, including cellular metabolism, differentiation, proliferation and apoptosis (29-31), the precise mechanisms by which lncRNAs function remain poorly understood. An ever-growing amount of lncRNAs identified have essential roles in regulating oncogenic processes, such as metastasis, and their mechanisms require additional investigation to be fully understood.

2. Mechanisms of invasion and metastasis in breast cancer

Metastatic breast cancer frequently represents an incurable impasse and a poor prognosis for patients. Subsequent to receiving diagnosis, the mechanisms involved in metastasis are largely unknown (32). Metastasis is a complex succession of cell-biological events, collectively termed the invasion-metastasis cascade, which involves multiple factors and steps: Cancer cells break away from primary tumors, invade locally through surrounding extracellular matrix and stromal cell layers, intravasate into the circulation of blood or lymphatic vessels, survive within the vasculature, extravasate into distant tissues, and reinitiate proliferation and growth programs of tumors at metastatic sites (7). These complex cell-biological processes are coordinated by the expression of various genes and the regulation of signaling cascades, which confer the ability of incipient metastatic tumor cells to successfully generate high-grade, life-threatening malignancies (7,33).

Epithelial-mesenchymal transition (EMT) and its reverse process, mesenchymal-epithelial transition (MET), are essential for cancer metastasis and distal colonization (34,35). EMT is typically believed to be the first step of the invasion-metastasis cascade, and the significance of EMT for breast cancer invasion and metastasis has been shown in a large number of *in vitro* and *in vivo* studies (36-38). The most critical and well-studied EMT-associated molecule is the epithelial adhesion molecule, E-cadherin (39,40). In EMT, the expression of E-cadherin is decreased, while the expression of mesenchymal markers such as N-cadherin, vimentin or fibronectin is increased, and this switch promotes the capacity of cancer cell invasion and mobility (41,42). A decrease in E-cadherin expression is considered to be a fundamental event of EMT, and is prominently associated with breast cancer invasion and metastasis (43-45). The decrease in E-cadherin leads to inactivation of glycogen synthase kinase 3β through phosphorylation, thus stabilizing the released β-catenin, which results in the induction of wide-ranging transcriptional and functional changes, thereby promoting breast cancer cell metastatic dissemination (46). Notably, the expression of E-cadherin will be re-established in cells that come from metastatic tumor colonies (47). Once cancer cells disseminate to a secondary organ, the process of MET may occur, and the levels of E-cadherin will be increased in these cells compared with the

cells from the primary tumor (48). Furthermore, Snail1, Snail2, ZEB1, ZEB2 and Twist1 have all been shown to be important master factors of EMT (49,50). A typical example illustrated that Snail1 represses expression of epithelial genes by binding to E-box DNA sequences in the proximal promoter region of E-cadherin, which recruits the polycomb repressive complex 2 (PRC2), resulting in methylation and acetylation at histone H3 lysine (H3K)4, H3K9 and H3K27, and thereby silencing the expression of E-cadherin and initiating EMT-relevant processes to promote cancer metastasis (51-55).

Several signaling pathways have also been reported to be involved in EMT and metastasis, including the transforming growth factor (TGF)-β, Wnt/β-catenin, Hedgehog, phosphoinositide 3-kinase (PI3K)/AKT and nuclear factor (NF)-κB pathways (56-60). These pathways contribute to the activation of downstream transcriptional targets and ultimately initiate the program of cell adhesion, migration and metastasis. In addition to transcription factors of EMT, the invasion-metastasis cascade is also regulated by post-transcriptional regulatory networks, including lncRNAs and miRNAs (61,62). A previous study demonstrated that miRNAs exert their effects at multiple steps in the metastatic cascade by effecting cancer cell adherence, migration, invasion, motility and angiogenesis (63). However, the molecular mechanisms driving breast cancer invasion and metastasis have been scant, as lncRNAs have only recently been identified. The extent to which lncRNAs specifically facilitate metastasis remains unknown. This review focuses on individual lncRNAs involved in breast cancer metastasis, and investigates the mechanisms and functions of several known lncRNAs that have only recently been identified. This may provide valuable targets for potential clinical applications of breast cancer in early diagnosis and management.

3. Roles of invasion and metastasis-associated lncRNAs in breast cancer

HOX antisense intergenic RNA (HOTAIR). HOTAIR, a 2158-nt ncRNA located on chromosome 12q13.13, was identified in 2007 (64). HOTAIR expression is increased in primary and metastatic breast cancer, and its expression level in primary tumors is a powerful predictor of eventual metastasis and mortality (65). Overexpression of HOTAIR in breast cancer cells induced genome-wide retargeting of PRC2, leading to trimethylation of H3K27 (H3K27me3), gene expression, and increased cancer invasiveness and metastasis (65). Enhancer of zeste homolog 2 (EZH2), a subunit of PRC2, is highly expressed in breast cancer, and the levels of EZH2 have been found to be strongly associated with breast cancer invasion and metastasis (66). HOTAIR and EZH2 expression levels are highly associated; co-expression of HOTAIR and EZH2 are associated with a worse clinical outcome (67).

HOTAIR serves as a key regulator in controlling the multiple signaling mechanisms involved in EMT and stemness establishment; it promotes the repression of E-cadherin by PRC2, and silencing the expression of HOTAIR can prevent EMT induction and cancer stem cells arising (68). A subsequent study revealed that HOTAIR functions as a competing endogenous RNA to regulate EMT and the invasive program by competing for miR-7; the decrease in miR-7 promotes EMT of breast cancer stem cells by activating the signal transducer

and activator of transcription 3 (STAT3) pathway, and that inhibits the expression of HOTAIR, which may serve as a good strategy for treating highly invasive breast cancer (69). In metastatic breast cancer, HOTAIR also inhibits miR-568 to maintain the expression of nuclear factor of activated T cells 5, which promotes EMT and metastasis of breast cancer cells by transcriptionally activating calcium-binding protein S100A4 and vascular endothelial growth factor C (70).

HOTAIR is also significantly associated with estrogen receptor (ER) (71,72). The promoter of HOTAIR contains multiple functional estrogen response elements, and is transcriptionally induced by estradiol (E2) (73). ER and various ER coregulators, including histone methylases such as mixed-lineage leukemia (MLL)1 and MLL3, and CREB-binding protein/p300, bind to the promoter of HOTAIR in an E2-dependent manner (73,74). Knockdown of ER and MLLs can decrease E2-induced HOTAIR expression (73). HOTAIR overexpression may serve as an independent biomarker for the prediction of the risk of metastasis in patients with ER-positive breast cancer (72). Recently, Tao *et al* (75) demonstrated that estrogen promoted HOTAIR through G protein-coupled estrogen receptor 1-mediated miR-148a inhibition, and that estrogen-induced breast cancer cell migration was reversed by silencing HOTAIR in triple-negative breast cancer.

H19. H19 was the first lncRNA identified in 1991 (76); it is derived from a large imprinted locus on human chromosome 11p15.5, and performs a crucial role in genomic imprinting during growth and development (77). H19 is transcribed by RNA polymerase II, spliced and polyadenylated in the cytosol (78), and is largely or exclusively expressed from the maternal allele (79). Although H19 has been demonstrated to be involved in diverse biological processes of multiple numbers of tumors, there remains considerable debate about its roles. It has been reported that H19 serves as a tumor suppressor in Wilm's tumors, embryonic rhabdomyosarcoma and Beckwith-Wiedemann syndrome (80), while it functions as an oncogene in pancreatic (81), bladder (82), colorectal (83) and gastric (84) cancer. In breast cancer, H19 is proposed to function as an oncogene to potentiate the properties of tumorigenesis (85). H19 promotes breast cancer cell proliferation and invasion by hepatocyte growth factor and E2F transcription factor 1 (86,87). Matouk *et al* (88) indicated that H19 was highly expressed in all common metastatic sites regardless of tumor primary origin, and that its expression level was significantly associated with the metastatic potential of breast cancer cells. The overexpression of H19 abolished E-cadherin expression and increased N-cadherin and Slug expression through a mechanism that involves miR-675. Slug could also serve as a positive feedback loop to upregulate H19 expression and activate its promoter (88). In addition, TGF-β-induced EMT and H19/miR-675 expression level is associated with the PI3K/AKT pathway (89). Recently, Vennin *et al* (90) demonstrated that H19 could decrease ubiquitin ligase E3 family (c-Cbl and Cbl-b) expression through its miR-675 directly binding c-Cbl and Cbl-b, which increases the stability and the activation of epidermal growth factor receptor and c-Met, leading to sustained activation of their downstream AKT and ERK signaling pathways, thereby enhancing breast cancer cell proliferation, migration, tumor growth and metastasis.

Metastasis-associated lung adenocarcinoma transcript-1 (MALAT-1). MALAT-1, also termed nuclear-enriched abundant transcript 2, is a highly conserved lncRNA that is ~8,000 nts in length, which was identified in non-small cell lung cancer as a prognostic marker of distant metastasis (91). A number of studies have found that MALAT-1 is extensively dysregulated in several types of human malignant tumors, including lung cancer (91), pancreatic cancer (92), hepatocellular carcinoma (93), cervical cancer (94), colorectal cancer (95), bladder cancer (96) and breast cancer (97). MALAT-1 enhances the potential transcription of EMT and regulates tumor cell proliferation, migration, invasion and metastasis (98,99). MALAT-1 was markedly increased in breast cancer cells compared with in non-cancerous cell lines (97). High concentration E2 treatment causes transcriptional inhibition of MALAT-1 RNA, thus inhibiting the proliferation, migration and invasion of breast cancer cells (97). However, by contrast, Xu *et al* (100) revealed that MALAT-1 expression was decreased in breast cancer cell lines and tumor tissue. Lower expression of MALAT-1 was associated with axillary lymph node metastasis and clinical disease progression. knockdown of MALAT1 in breast cancer cell lines induced an EMT program by activating the PI3K/AKT pathway, thereby promoting breast cancer cell migration and invasion (100).

Long stress-induced non-coding transcript 5 (LSINCT5). LSINCT5 is a 2.6-kb transcript that is polyadenylated and transcribed on the negative strand. LSINCT5 is localized in the nucleus and potentially transcribed by RNA polymerase III (101). Studies by Silva *et al* (101,102) demonstrated that LSINCT5 is greatly overexpressed in breast cancer cell lines and tumor tissues, and its expression is associated with cellular proliferation. In addition, LSINCT5 is also involved in breast cancer invasion and metastasis. Knocking down the expression of LSINCT5 leads to decreased expression of CXC chemokine receptor 4 (CXCR4), a crucial breast cancer marker associated with invasion and metastasis (103). The decrease in CXCR4 will cause a decrease in MMP-9 expression and reversion of EMT, thereby enhancing apoptosis and reducing the incidence of tumor invasion and metastasis (103-105).

Long intergenic non-protein coding RNA-regulator of reprogramming (lincRNA-ROR). lincRNA-ROR is a large intergenic non-coding RNA ~2,600 nts in length that modulates reprogramming (106). lincRNA-ROR was first discovered in induced pluripotent stem cells (iPSCs), and it was reported to serve a vital role in promoting survival in iPSCs and embryonic stem cells, possibly by preventing the activation of cellular stress pathways, including the p53 response (106). lincRNA-ROR suppresses p53 translation through direct interaction with the heterogeneous nuclear ribonucleoprotein (hnRNP) I, and inhibits p53-mediated cell cycle arrest and apoptosis (107). lincRNA-ROR expression is controlled by a key cytoprotective transcription factor, nuclear factor-erythroid 2-related factor (NRF2), in mammary stem cells. NRF2 directly binds the ROR promoter at NRF2 response elements and subsequently inhibits lincRNA-ROR transcriptional activity (108). In addition to transcriptional silencing, knockdown of NRF2 leads to a significant decrease in EZH2 binding and in the repressive marker H3K27me3,

which is associated with increased lincRNA-ROR expression, resulting in mammary stem cell self-renewal (108).

lincRNA-ROR is also associated with miRNAs and may function as a competing endogenous RNA for specific miRNAs to interfere in their function. Wang *et al* (109) demonstrated that lincRNA-ROR is enriched in the cytoplasm and functions as a molecular sponge for miRNA-145 to upregulate its target genes, including octamer-binding transcription factor 4, sex-determining region Y-box (Sox)2, Kruppel-like factor 4 and Nanog expression. These genes are crucial for stem cell characteristics and the EMT program (110-112). Eades *et al* (113) identified that lincRNA-ROR is markedly upregulated in triple-negative breast cancer [ER(-), human epidermal growth factor receptor 2(-) and progesterone receptor(-)] and in metastatic disease, and competitive inhibition of miR-145 by lincRNA-ROR results in expression of small GTPase ADP-ribosylation factor 6 (ARF6). ARF6 has an essential role in breast cancer cell invasion (114). The overexpression of ARF6 regulates E-cadherin localization and affects cell-cell adhesion, and then performs an important role in the metastatic process (114-116). Additionally, lincRNA-ROR also competitively binds miRNA-205 to prevent the degradation of miRNA-205 target genes, such as ZEB1 and ZEB2 (116). lincRNA-ROR, as a critical positive regulator of EMT, potentiates breast cancer cell migration and invasion, and promotes the generation of stem cell properties (117). Silencing of lincRNA-ROR will repress breast cancer tumorigenesis and metastasis (116,117).

Translational regulatory lncRNA (treRNA). treRNA (originally termed ncRNA-a7) was identified through genome-wide computational analysis in 2010 and was revealed to function as an enhancer and regulate Snail transcription (118). treRNA consists of two exons and contains three putative ORFs, and its transcript is spliced and polyadenylated. treRNA employs different molecular mechanisms of gene regulation depending on its cellular location. In the nucleus, treRNA acts as an enhancer for neighboring genes such as Snail (118). In the cytoplasm (~75%), treRNA functions to downregulate the expression of E-cadherin by suppressing the translation of its mRNA. treRNA reduces the level of E-cadherin protein without affecting the level of its mRNA, but alters the polysome distribution of E-cadherin mRNA. In addition, treRNA promotes the formation of a novel ribonucleoprotein complex with RNA-binding proteins (such as hnRNP K, FMR autosomal homolog (FXR)1, FXR2, poly(U) binding splicing factor 60 and splicing factor 3b subunit 3). This treRNP complex interacts directly or indirectly with the 3'UTR of E-cadherin mRNA, and reduces the translation efficiency (119,120).

In breast cancer samples, treRNA is significantly upregulated in paired primary and lymph-node metastasis compared with healthy controls. Enforced expression of treRNA significantly promotes breast cancer cell migration and invasion *in vitro* and tumor lung metastases *in vivo*, whereas knockdown of treRNA markedly suppresses tumor cellular migration, invasion and metastasis (119). Furthermore, enhanced expression of treRNA could decrease the expression of E-cadherin, zonulaoccludens-1 and β-catenin, and increase the expression of fibronectin and vimentin, thus affecting the process of EMT, invasion and metastasis (119). Investigation

of the functions of treRNA and RNA-binding proteins may serve as potential diagnostic and prognostic markers, as well as providing therapeutic targets for breast cancer (119).

Brain cytoplasmic RNA 200 (BC200). BC200 is a 200-nt cytoplasmic non-coding RNA that is selectively expressed in the primate nervous system, where it is transcribed by RNA polymerase III (121-123). BC200 is not generally expressed in non-neural organs such as the colon, heart, kidney, liver, spleen or skeletal muscle (122). However, the neuron-specific expression is lost in various human tumors, including breast cancer (123). A previous study revealed that this non-coding RNA is more highly expressed in invasive compared with normal breast tissues or in benign tumors of breast cancer, and its expression in breast cancer cells may serve as a molecular indicator of invasive or potentially invasive malignancy (124). Furthermore, BC200 expression is strongly associated with tumor grade, and it may be used as a prognostic indicator to assess tumor progression (124,125). Therefore, the expression of BC200 may serve as a molecular marker in the diagnosis or prognosis of breast cancer (124,125).

lncRNA-activated by TGF-β (lncRNA-ATB). lncRNA-ATB was first identified in human hepatocellular carcinoma (HCC) cells following TGF-β treatment in 2014 (126). The lncRNA is poly(A)-negative, mainly localized in the cytoplasm and has three highly homologous loci on chromosomes 13, 14 and 22 (126,127). High expression of lncRNA-ATB is associated with tumor metastases and a poor prognosis (128,129). Evidence has indicated that lncRNA-ATB promotes HCC cell invasion by competitively binding the miR-200 family, upregulating ZEB1 and ZEB2 mRNA and protein levels, and then inducing EMT and invasion (126). By contrast, depletion of lncRNA-ATB is sufficient to abolish TGF-β-induced EMT, even though TGF-β is known to strongly induce a number of other EMT drivers, including Snail, Slug and Twist (127). In addition, lncRNA-ATB promotes organ colonization of disseminated tumor cells by binding interleukin-11 (IL-11) mRNA, increasing IL-11 mRNA stability, causing autocrine induction of IL-11 and triggering STAT3 signaling (126). IL-11 is a TGF-β target gene, the expression of which has been shown to promote bone metastasis of breast cancer (130). lncRNA-ATB has been found to upregulate and induce EMT not only in HCC, but also in colorectal (128) and breast (131) cancer. Shi *et al* (131) revealed that lncRNA-ATB is markedly upregulated in breast cancer cells and tissues. lncRNA-ATB may promote trastuzumab resistance and the invasion-metastasis cascade by competitively binding miR-200c and upregulating ZEB1 and zinc finger protein 217, thereby inducing EMT (131). Furthermore, the high level of lncRNA-ATB is associated with the trastuzumab resistance of patients with breast cancer (131). Therefore, lncRNA-ATB may serve as a promising biomarker and therapeutic target for breast cancer invasion and metastasis.

Breast cancer anti-estrogen resistance 4 (BCAR4). BCAR4 was identified by functional genetic screening in anti-estrogen resistance human breast cancer cells (132). It was reported to be associated with tumor aggressiveness and tamoxifen resistance (132,133). High BCAR4 mRNA levels may serve as

an independent predictive factor for poor survival following tamoxifen therapy in breast cancer (133). In addition, elevated BCAR4 expression is associated with ER, PR and ERBB2/3 signaling. Knockdown of ERBB2 or ERBB3 could inhibit cell proliferation (133,134). Recently, novel evidence demonstrated that BCAR4 presents close relevance with breast cancer metastasis and regulates a non-canonical Hedgehog/GLI2 transcriptional program (135,136). BCAR4 provides a driving force in the process of breast cancer progression and metastasis, which is markedly upregulated in breast cancer tissues and cells, and elevated expression of BCAR4 is associated with advanced lymph node metastasis stage and poor survival for patients with breast cancer (135). BCAR4 binds to the domain of unknown function of smad nuclear interacting protein 1 (SNIP1) and releases the inhibitory effect of SNIP1 on the histone acetyltransferase activity of p300, leading to the activation of p300 (135). The activated p300 enhances the acetylation of H3K18 on the promoters of GLI2 target transcription units, which releases the inhibitory roles of serine/threonine-protein phosphatase 1 regulatory subunit 10 (PPP1R10, also known as PNUTS) on protein phosphatase 1 enzymatic activity, which consequently modulates RNA Pol II Ser5 phosphorylation levels at GLI2 target gene promoter regions, thus activating the GLI-mediated transcriptional program and promoting cell migration and metastasis (135,137).

HOXA transcript induced by TGF-β (HIT). lncRNA-HIT is an uncharacterized lncRNA located in the HOXA gene cluster, which functions in the nucleus and is significantly induced by TGF-β (138). Richards *et al* (138) found that lncRNA-HIT performs an important role in TGF-β-induced EMT, migration and invasion. Depletion of lncRNA-HIT significantly increases E-cadherin and reduces vimentin in mouse mammary gland epithelial cells, and inhibits TGF-β induced migration, invasion and EMT. lncRNA-HIT is also significantly elevated in the highly metastatic mouse mammary tumor cell line (4T1) (138). Knockdown of lncRNA-HIT in this cell line results in significant reduction of cell migration, invasion, tumor growth and lung metastasis (138). Furthermore, lncRNA-HIT is conserved in humans and its expression is associated with more invasive breast cancer progression (138). The expression of lncRNA-HIT could be a potential therapeutic target of breast cancer.

NF-κB-interacting lncRNA (NKILA). NKILA, an NF-κB-induced lncRNA, is a 2570-nt intronless transcript that is encoded at chromosome 20q13. NKILA exerts its biological function in the cytoplasm, serves as a negative feedback regulator of NF-κB in resting and activated cells, and performs a pivotal inhibitory role in breast cancer progression and metastasis (139). NKILA binds to the NF-κB/inhibitor of NF-κB (IκB) complex, and inhibits IκB kinase-induced IκB phosphorylation, the NF-κB pathway and cancer-associated inflammation (139). In addition, NKILA is significantly reduced by miR-103/107-mediated degradation in high-metastatic breast cancer cells, and the decrease of NKILA results in abnormal NF-κB activation and thus contributes to cancer metastasis and poor patient outcome (139).

Neuroblastoma-associated transcript 1 (NBAT1). NBAT1 was identified in neuroblastoma as a tumor suppressing lncRNA, and it controls tumor progression by epigenetic silencing of target genes, including Sox9, oncostatin M receptor and versican (140). NBAT1 loss affects neuronal differentiation through activation of the neuronal-specific transcription factor neuron restrictive silencer factor/RE1-silencing transcription factor. Furthermore, loss of NBAT1 is associated with cellular proliferation and invasion (140). NBAT1 regulates tumor biological processes by interacting with PRC2 member EZH2, which suppresses its target gene that affects cell proliferation and migration (140,141). In breast cancer, loss of NBAT1 is also associated with tumor metastasis and poor clinical prognosis (142). Overexpression of NBAT1 could inhibit the migration and invasion of breast cancer cells through EZH2 (142). In addition, NBAT1 could suppress breast cancer metastasis by regulating dickkopf Wnt signaling pathway inhibitor 1 (DKK1) in a PRC2-dependent manner. DKK1 is an inhibitor of the Wnt signaling pathway, which inhibits the migration and invasion of breast cancer (143-145). Mechanically, overexpression of NBAT1 decreases the H3K27me3 level of the DKK1 promoter and activates the expression of DKK1, inhibiting breast cancer cell migration and invasion (146). Therefore, NBAT1 may serve as a breast cancer prognostic biomarker and as a potential therapeutic target to inhibit breast cancer metastasis.

Other lncRNAs. Other lncRNAs have also been found to be involved in breast cancer invasion and metastasis, including steroid receptor RNA activator (SRA), linc00617, LOC554202 and AK058003. SRA was reported to be overexpressed in breast cancer cells; knockdown of SRA in MDA-MB-231 cells reduced the invasiveness and expression of certain critical genes, including thrombospondin 1, caveolin 1, transmembrane protease serine (TMPRSS)2, TMPRSS3, MMP-1 and MMP-9 (147). linc00617 promotes breast cancer cell motility and invasion *in vitro* and potentiates breast cancer cell metastasis *in vivo* (148). Furthermore, linc00617 induces the generation of stem cells; it activates the transcription of stemness factor Sox2, which stimulates EMT transition and promotes breast cancer progression and metastasis (148). In addition, LOC554202 (149) and AK058003 (150) were also revealed to be upregulated in breast cancer cells and tissues, and the expression levels of these two lncRNAs were strongly associated with tumor size and advanced clinical stage. Knockdown of Loc554202 and AK058003 significantly inhibits breast cancer cell proliferation, invasion and metastasis (149,150).

4. Conclusions

Metastasis is the major cause of breast cancer-associated mortlaity, and the invasion-metastasis cascade of breast cancer is formed from a diverse range of biological processes. Therefore, it is essential to identify how to diagnose breast cancer at the early stage and develop anti-metastatic therapeutics. Emerging evidence is beginning to reveal the potential role of lncRNA in breast cancer pathogenesis, and it is now considered to perform an essential role in pro- and anti-metastatic processes (Table I). These novel findings provide fresh molecular insights into the invasion and metastasis of breast cancer and may suggest a novel strategy for breast cancer

Table I. Functions of lncRNAs in breast cancer invasion and metastasis.

lncRNA	Expression	Regulatory mechanisms of invasion and metastasis
HOTAIR	Upregulated	Trimethylation of histone H3K27 by recruiting PRC2
		Repression of E-cadherin by PRC2
		Competitively binds miR-7 and miR-568
		Transcriptionally induced by estradiol
		Induces EMT program and CSCs arising
H19	Upregulated	Induced by HGF and E2F1
		Increases EGFR and c-Met
		Decreases E-cadherin, increases N-cadherin and Slug
		Activates Akt and ERK signaling pathways
MALAT-1	Upregulated	Actives transcription
		Regulates expression of cell cycle genes
		Regulates EMT program
LSINCT5	Upregulated	Regulates CXCR4 expression
lincRNA-ROR	Upregulated	Suppresses p53 translation
		Transcriptionally inhibited by NRF2
		Competitively binds miRNA-145 and miRNA-205
		Promotes survival of iPSCs and ESCs
treRNA	Upregulated	Promotes formation of a ribonucleoprotein complex with
		hnRNP K, FXR1, FXR2, PUF60 and SF3B3
		Enhances Snail transcription
		Decreases expression of E-cadherin, zonulaoccludens-1 and β-catenin
		Increases fibronectin and vimentin expression
BC200	Upregulated	Sequesters PABP, preventing protein synthesis
lncRNA-ATB	Upregulated	Regulates trastuzumab resistance
		Competitively binds miR-200c, upregulating ZEB1 and ZNF-217
		Induces IL-11 expression
BCAR4	Upregulated	Induced by tamoxifen resistance
		Associated with ER, PR and ERBB2/3 signaling
		Activation of Hedgehog/GLI2
		Activation of p300
lncRNA-HIT	Upregulated	Induced by TGF-β
		Decreases E-cadherin and increases vimentin
		Regulator of TGF-β induced EMT
NKILA	Downregulated	Binds to NF-κB/IκB and represses NF-κB activation
		Regulated by miR-103/107
		Inhibits the NF-κB signaling pathway
		Inhibits cancer-associated inflammation
NBAT1	Downregulated	Interaction with PRC2 member EZH2
		Activation of DKK1 expression
		Inhibits the Wnt signaling pathway
SRA	Upregulated	Activation of GR, ERα, PR and SRAP
		Coactivates THBS1, CAV1, TMPRSS2, TMPRSS3, MMP-1 and MMP-9
linc00617	Upregulated	Activates the transcription of stemness factor Sox2
		Induces generation of stem cells
AK058003	Upregulated	Regulates γ-synuclein gene

lncRNA, long non-coding RNA; HOTAIR, HOX antisense intergenic RNA; H3K27, histone H3 lysine 27; miR, microRNA; PRC2, polycomb repressive complex 2; HGF, hepatocyte growth factor; E2F1, E2F transcription factor 1; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; MALAT-1, metastasis-associated lung adenocarcinoma transcript-1; EMT, epithelial-mesenchymal transition; CXCR4, chemokine (C-X-C motif) receptor 4; lincRNA-ROR, long intergenic non-protein coding RNA-regulator of reprogramming; NRF2, nuclear factor-erythroid 2-related factor; iPSC, induced pluripotent stem cell; ESC, endothelial progenitor cell; treRNA, translational regulatory lncRNA; hnRNP K, heterogeneous nuclear ribonucleoprotein K; FXR, FMR autosomal homolog; PUF60, poly(U) binding splicing factor 60; SF3B3, splicing factor 3b subunit 3; PABP, polyadenylate-binding protein; TGF-β, transforming growth factor-β; lncRNA-ATB, lncRNA-activated by TGF-β; ZEB1, zinc finger E-box binding homeobox 1; ZNF-217, zinc finger protein 217; IL-11, interleukin-11; ER, estrogen receptor; PR, progesterone receptor; ERBB2/3, erb-b2 receptor tyrosine kinase 2/3; BCAR4, breast cancer anti-estrogen resistance 4; HIT, HOXA transcript induced by TGF-β; NF-κB, nuclear factor-κB; NKILA, NF-κB interacting lncRNA; NBAT1, neuroblastoma-associated transcript 1; EZH2, enhancer of zeste homolog 2; DKK1, dickkopf Wnt signaling pathway inhibitor 1; GR, glucocorticoid receptor; SRAP, steroid receptor activator protein; THBS1, thrombospondin 1; CAV1, caveolin 1; TMPRSS2/3, transmembrane protease, serine 2/3; MMP-1/9, matrix metalloproteinase-1/9; Sox2, sex-determining region Y-box 2.

therapy. However, studies of lncRNAs remain in the early stages, and the underlying mechanism of lncRNAs in regulating the invasion and metastasis of breast cancer is not clear. Furthermore, the expression of lncRNAs in breast cancer lacks specificity and the biological functions of certain lncRNAs remain under considerable debate. Therefore, identification of highly specific and sensitive lncRNAs for the early monitoring of the invasion and metastasis of breast cancer remains an arduous task. An improved understanding of the network of genes and cellular pathways regulated by lncRNAs will aid in improving the understanding of breast cancer pathogenesis, and thus will open novel avenues for breast cancer diagnosis, prognosis and therapy.

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