The regulatory roles of IncRNAs in the process of breast cancer invasion and metastasis

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Breast cancer (BC) is the most common cancer and principal cause of death among females worldwide. Invasion and metastasis are major causes which influence the survival and prognosis of BC. Therefore, to understand the molecule mechanism underlying invasion and metastasis is paramount for developing strategies to improve survival and prognosis in BC patients. Recent studies have reported that long non-coding RNAs (lncRNAs) play critical roles in the regulation of BC invasion and metastasis through a variety of molecule mechanisms that endow cells with an aggressive phenotype. In this article, we focused on the function of IncRNAs on BC invasion and metastasis through participating in epithelial-to-mesenchymal transition, strengthening cancer stem cells generation, serving as competing endogenous IncRNAs, influencing multiple signaling pathways as well as regulating expressions of invasion-metastasis related factors, including cells adhesion molecules, extracellular matrix, and matrix metallo-proteinases. The published work described has provided a better understanding of the mechanisms underpinning the contribution of IncRNAs to BC invasion and metastasis, which may lay the foundation for the development of new strategies to prevent BC invasion and metastasis.

Introduction

Breast cancer (BC), as the most common malignant tumor among women, is one of the leading causes of cancer deaths worldwide. In 2017, approximately 252710 new cases of invasive BC and 40610 BC deaths are expected to occur among US women [1]. BC invasion and metastasis are the main causes of BC-related deaths. Bone, lung, brain, and liver are the primary target sites of BC metastasis [2]. BC metastasis is the spread of cancer cells to tissues and organs beyond where the tumor originated and the formation of new tumors which may eventually result in the death of most BC patients [3]. At least half of the cancer patients already present clinically detectable metastatic disease when the time of cancer diagnosis [4]. A higher number of cancer patients might also have micrometastases that is beyond conventional detection techniques. Thus, cancer metastasis is the most threatening event in cancer patients [5]. BC invasion and metastasis as intricate process means that cancer cells escape from the primary cancer and penetrate the blood circulation [6]. The process involves both the selection of traits that are advantageous to cancer cells and the concomitant recruitment of traits in the tumor stroma that accommodate invasion by metastatic cells [7,8]. The course of BC invasion and metastasis entails a series of molecules such as cells adhesion molecules (CAMs), extracellular matrix (ECMs), and matrix metallo-proteinases (MMPs). It
also involves the biological progresses including epithelial-to-mesenchymal transition (EMT) and cancer stem cells (CSCs) formation that cooperate on the formation of secondary tumors in distant organs [2,9]. Long non-coding RNAs (lncRNAs) are a novel class of RNA transcripts that are longer than 200 nucleotides (nt) in length without protein-coding capacity. The major functions of lncRNAs include: (1) participating in chromosome rearrangement and histone modification, (2) transcribing and interfering, (3) stabilizing mRNA, and (4) modifying alternative splicing sequence [10]. Recent studies have shown that lncRNAs exerted critically roles in multiple cancer biological processes, including carcinogenesis, apoptosis, differentiation, proliferation, invasion as well as metastasis [11]. Accumulating evidence has shown that ectopic expression of lncRNAs served as carcinogenic factors or tumor suppressors in BC invasion and metastasis [12,13]. In this review, we will sum up the precise mechanism of lncRNAs function on BC invasion and metastasis and reveal the clinical significance of dysregulated lncRNAs in BC metastasis. Knowledge obtained from this review could assist in the development of new strategies to treat or prevent the metastatic BC.

**LncRNAs participate in process of BC invasion and metastasis**

The process of BC invasion and metastasis is complex, which incorporates molecular factors, multiple cells, and stages. Some cancer cells detach from primary tumor through the repression of CAMs and the disruption of intercellular adhesion (detachment), followed by these cells invading through the ECMs and breaking down of ECMs (invasion), thus entering the circulation (intravasation). From this point, these cancer cells move away from the primary tumor and circulate in the blood circulation. Some cancer cells will adopt a process to leave the blood circulation (extravasation), in which cells adhere and penetrate the blood vessel again, eventually develop a secondary tumor at the other site [14,15] (Figure 1).

**CAMs**

CAMs include immunoglobulin superfamily, cadherins, integrins, and selectins which provide essential links between the extracellular environment and the intracellular signaling pathways. Thus, CAMs play key roles in cells behaviors such as differentiation, apoptosis, invasion, and even metastasis [16,17]. Among them, E-cadherin (E-cad) as the most well-studied member of the CAMs displays a crucial type of cell–cell adhesion to hold cancer cells tight together. An increasing number of studies have shown that down-regulation of E-cad by lncRNAs could decrease the strength of cancer cellular adhesion, resulting in the increase in cellular motility. This in turn may allow cells to cross the CAMs
and invade surrounding blood vessels in various cancers. For example, overexpression of IncRNA SPRY4-IT1 could increase in vitro motility of esophageal squamous cells carcinoma cells via decrease in E-cad [18]. In colon cancer, IncRNA activated by TGF-β (IncRNA-ATB) mediated E-cad repression may promote the progression of cancer and predicts poor prognosis [19]. In another study, IncRNA H19 levels were remarkably increased in bladder cancer tissues, and up-regulated H19 promoted bladder cancer cells migration by down-regulation of E-cad [20]. In BC, IncRNAs such as NEAT1, linc00617, OR3A4, and LINP1 were up-regulated in BC samples and significantly promoted the invasion and metastasis capacity in BC cells through decreasing the expression of E-cad [21-24].

**ECMs**

ECMs such as collagen, fibrinogen, laminin, fibronectin, and vitronectin provide structural and biochemical support to the surrounding cells. ECMS are essential for many cellular processes, including development, migration, and proliferation [25-28]. IncRNAs play key roles in the complex dynamics of cancer cells invasion and metastasis through the regulation of ECMS. The elevation of IncRNA HOTAIR mediated invasion and metastasis of BC. HOTAIR expression exhibited robust induction in laminin-rich ECMS through the canonical ECM signaling pathway, namely integrins and Src kinase [29]. In addition, IncRNA Malat1 knockdown could also increase adhesion and inhibit migration of BC cells through the up-regulation of Tenascin Xb (Tnxb), Tnxb as an ECM protein that has been shown to have anti-metastatic property [12].

**MMPs**

MMPs act important roles in tissue remodeling associated with various biology processes such as morphogenesis, angiogenesis, tissue repair, and metastasis. MMPs are also important components of cells invasion capable of degrading a range of ECMS proteins allowing cancer cells to migrate and invade [30-32]. Recent researches confirmed that IncRNAs regulate tumor invasion and metastasis partly because of their abilities to influence the expressions of MMPs. Such as, IncRNA SNHG12 was strongly up-regulated in Triple-negative BC (TNBC). Moreover, SNHG12 could promote BC cells migration by increasing expression of MMP13 [33]. In addition, HULC was another up-regulated IncRNA in TNBC tissues and cells lines. The increased HULC effectively promoted TNBC cells metastasis through regulating the expressions of MMP-2 and MMP-9 [34]. MMP-2 and MMP-9 could degrade basement-membrane collagen at the site of local invasion, thereby promoting cancer cells invasion and metastasis [35]. The expression of MMP-2 and MMP-9 could also be regulated by IncRNA ANCR. ANCR could act as a negative regulator of metastasis in BC cells through repressing MMP-9 and MMP-2 expression [36]. The expression level of IncRNA BANCOR in BC tissues was significantly increased. After BANCOR knockdown in BC MCF-7 cells, the cells invasion and metastasis capacity was significantly inhibited by decreasing expression of MMP-2 and MMP-9 [37]. Collectively, these findings revealed that IncRNAs such as NEAT1, linc00617, OR3A4, LINP1, HOTAIR, Malat1, SNHG12, HULC, ANCR, and BANCOR affected BC cells invasion and metastasis through regulating different molecules including CAMs, ECMS, and MMPs (Figure 1). Therefore, IncRNAs may serve as therapeutic targets for BC, particularly in patients with BC metastasis.

**LncRNAs participate in BC metastasis via affecting EMT**

EMT is a progression of cellular plasticity critical for BC cells migration and metastasis. It is characterized by the combined an increased expression of mesenchymal markers, such as vimentin, N-cadherin, fibronectin, and loss of epithelial cells junction proteins, including E-cad, claudins, α-catenin, ZO-1, and occludin [38-40]. Transforming growth factor-β (TGF-β) signaling pathway is a key regulator of various cancer biology, including cancer cells migration and invasion. TGF-β signaling pathway acts as an important regulator for EMT process through influencing the expressions of EMT-associated genes such as Zinc finger E-box-binding homeobox (ZEB), C/EBPα, RhoA, E-cad, vimentin, SNAIL, etc. [6]. Accumulating evidence shows that IncRNAs act crucial roles on EMT to influence BC metastasis. For instance, IncRNA ANCR could restrain the TGF-β1-induced EMT by inhibiting the phosphorylation of runt-related transcription factor 2 (RUNX2). On the contrary, TGF-β could decrease ANCR expression through decreasing the histone acetylation at ANCR promoter [41]. Moreover, ANCR could facilitate the ubiquitination and degradation of EZH2 (the Enhancer of Zeste Homolog 2), hence inhibit the invasion and metastasis of BC cells. The forced expression of EZH2 (an EMT inducer) increased the vimentin expression and decreased the E-cad expression [36]. IncRNA CCAT2 also plays an essential role in BC tumorigenesis, growth, and metastasis. The level of CCAT2 in BC tissues was significantly increased compared with adjacent normal tissues. The increased amount of CCAT2 promoted the proliferation, invasion, and migration by significantly reinforcing the expressions of TGF-β and Smad2.
LncRNAs such as ANCR, CCAT2, IncRNA-ATB, and HOXA-AS2 participate in BC invasion and metastasis through TGF-β-induced EMT. In addition, EMT-associated genes such as ZEB1/2, E-cad, N-cad, and vimentin were reported to be regulated by lncRNAs TP73-AS1, linc-ROR, MEG3, HOXA11-AS, NEAT1, linc00617, OR3A4, and LINP1.

Together, these results suggest that lncRNAs such as ANCR, CCAT2, IncRNA-ATB, and HOXA-AS2 participate in BC invasion and metastasis through TGF-β-induced EMT. In addition, EMT-associated genes such as ZEB1/2, E-cad, N-cad, and vimentin were reported to be regulated by lncRNAs TP73-AS1, linc-ROR, MEG3, HOXA11-AS, NEAT1, linc00617, OR3A4, and LINP1 (Figure 2). Thus, lncRNAs are involved in invasion and metastasis of BC cells by promoting EMT, providing potential therapeutic targets for BC.

LncRNAs influence BC metastasis by regulating CSCs generation

CSCs are a subpopulation of cancer cells with self-renewal capacity and high invasion and migration capacity as well as limitless proliferative potential [50,51]. Recent studies illustrate a direct link between lncRNAs and stemness of cancer cells. LncRNAs have emerged as important new players in the regulation of CSCs stemness acquisition and maintenance [52,53]. Recently, lncRNA linc00617 was reported to promote BC invasion and metastasis.
through increasing the percentage of the stem cells phenotype CD44(+)/CD24(−) subpopulation cells. Furthermore, the up-regulated lnc00617 promoted generation of stem-like cells and elevation of self-renewal ability in BC cells [22]. Also, the increased lncRNA linc-ROR was confirmed to affect the acquisition of CSC-like phenotype and the self-renewal capacity in BC cells. Linc-ROR promoted metastasis of BC cells by enhancing the ability to form multiple large-sized mammospheres [47]. What is more, lncRNA-Hh which was transcriptionally regulated by Twist could directly target GAS1 to stimulate the activation of hedgehog pathway. The activated hedgehog pathway increased the expression of GLI1, SOX2, and OCT4 to play a regulatory role in CSCs maintenance of BC cells [54]. In addition, lncRNA MALAT1 played a critical role in the acquisition of CSC-like phenotype of BC cells. Lysine-specific demethylase 5B protein (KDM5B) could enhance the maintenance of aggressive BC cells malignant phenotype via modulation of lncRNA MALAT1 activity [55].

Thus, these results suggest that lncRNAs including linc00617, linc-ROR, lncRNA-Hh, and MALAT1 play important roles in CSCs generation to increase invasion and migration capacity of BC cells. They may be explored as a prognostic and diagnostic molecule in BC patients with metastasis.

**LncRNAs serve as ceRNAs to influence BC metastasis**

Dysregulated miRNAs participate in multiple biological processes such as apoptosis, proliferation, invasion, and metastasis by repressing translation or induce degradation of their target miRNAs [56,57]. LncRNAs act crucial roles on BC metastasis partly via sponging to miRNAs or regulating the expression of miRNAs. For instance, NEAT1 could promote BC cells growth, migration, and invasion by inhibiting miR-448 and up-regulating ZEB1. NEAT1 could serve as a competing endogenous lncRNA (ceRNA) to modulate ZEB1 by sponging miR-448 in BC [58]. In addition, miR-218 was reported to be another direct target of NEAT1. NEAT1 promoted BC cells invasion by negatively regulating expression of miR-218 [59]. It was also found that down-regulation of NEAT1 could also inhibit EMT program of BC cells through miR-211/high mobility group AT-hook 2 (HMG2A) axis and there was a reciprocal repression between NEAT1 and miR-211 [60]. HMG2A has been reported to promote the action of transcriptional enhancers through binding to AT-rich regions in DNA and altering chromatin architecture. It is highly expressed in most cancers, including ovary, pancreas, lung, and BC, suggesting that HMG2A could promote tumor progression in BC [61,62]. HMG2A was identified as a target of miR-20a-5p, which significantly induced carcinogenesis of BC. MiR-20a-5p as a target of lncRNA HOTAIR had a negative correlation with HMG2A. HOTAIR affected BC cells growth, metastasis, and apoptosis via the miR-20a-5p/HMG2A axis in BC cells [63]. Moreover, the pro-metastatic role of lncRNA MALAT1 on BC migration and invasion was mediated by miR-129-5p. MiR-129-5p is a direct inhibitory target of MALAT1 and its expression has an inverse correlation with MALAT1 [64]. Another study showed that the ectopic lncRNA SNHG15 was correlated with TNM stage, lymph node metastasis, and survival in BC patients. Increased SNHG15 significantly reinforced the abilities of BC cells migration and invasion. SNHG15 could act as a competing endogenous RNA to sponge miR-211-3p [65]. In MCF-7 cells, repression of HOST2 was remarkably elevated in the expression of miRNA let-7b. Down-regulation of HOST2 could decrease BC cells motility, migration, and invasion by inhibiting let-7b in BC patients [66]. On the contrary, lncRNA XIST was significantly down-regulated in BC tissues and cells lines. Overexpression of XIST remarkably inhibited BC cells growth, migration, and invasion via sponging to miR-155 in BC. Moreover, caudal-type homeobox 1 (CDX1) was identified as a direct target of miR-155 and miR-155/CDX1 rescued the effects of XIST in BC cells [67]. BC migration and invasion could also be regulated by lncRNA SUMO1P3. Further study confirmed that SUMO1P3 functioned as an oncogenic lncRNA via binding to miR-320a, which had been identified as a tumor suppressor in many cancers [68]. LncRNA cancer susceptibility candidate 2 (CASC2) has been demonstrated to be a tumor suppressor in several types of cancer [69]. In the present study, the expression level of CASC2 was significantly decreased in BC tissues compared with adjacent normal tissues. The up-regulated CASC2 decreased the viability, migration, and invasion, and promoted apoptosis of BC cells through acted as a ceRNA for miR-96-5p, while miR-96-5p overexpression could increase BC cells viability, migration, and invasion by repressing the expression of its target gene, synoviolin (SYVN1) [70] (Table 1).

**LncRNAs regulate multiple signaling pathways in BC metastasis**

Changes in the multiple signaling pathways directing their regulation can lead to the pathological process of BC cells invasion and metastasis. For example, lncRNA LINP1 could promote BC cells metastasis and influence the expression of EMT-related markers. P53 overexpression inhibited BC cells migration partly by decreasing LINP1 expression. P53 is a regulator of LINP1 while increased LINP1 could in turn attenuate the anti-metastatic effects of p53 [24]. P53 signaling pathway has a key role in the negative regulation of tumor angiogenesis, migration, and cells motility [71,72].
Table 1 LncRNAs participate in BC metastasis by sponging to miRNA

<table>
<thead>
<tr>
<th>LncRNA</th>
<th>Expression</th>
<th>Sponing miRNA</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT1</td>
<td>Up</td>
<td>miR-448, miR-218, miR-211</td>
<td>NEAT1 facilitated cell growth and invasion via negatively regulating miR-218, as well as by regulating miR-211/HMG A2 axis and miR-448/2E B1 axis in BC.</td>
<td>[58-60]</td>
</tr>
<tr>
<td>HOTAIR</td>
<td>Up</td>
<td>miR-20a-5p</td>
<td>HOTAIR affected BC cell growth, metastasis, and apoptosis via the miR-20a-5p/HMG A2 axis.</td>
<td>[63]</td>
</tr>
<tr>
<td>MALAT1</td>
<td>Up</td>
<td>miR-129-5p</td>
<td>MALAT1 promoted triple-negative BC invasion via targeting miR-129-5p.</td>
<td>[64]</td>
</tr>
<tr>
<td>SNHG15</td>
<td>Up</td>
<td>miR-211-3p</td>
<td>SNHG15 promoted BC cell migration and invasion by sponging miR-211-3p.</td>
<td>[65]</td>
</tr>
<tr>
<td>HOST2</td>
<td>Up</td>
<td>let-7b</td>
<td>HOST2 decreased BC cell motility, migration, and invasion by inhibiting let-7b.</td>
<td>[66]</td>
</tr>
<tr>
<td>XIST</td>
<td>Down</td>
<td>miR-155</td>
<td>XIST inhibited BC cell growth, migration, and invasion via miR-155/CDX1 axis.</td>
<td>[67]</td>
</tr>
<tr>
<td>SUMO1P3</td>
<td>Up</td>
<td>miR-320a</td>
<td>SUMO1P3 facilitated BC progression by negatively regulating miR-320a.</td>
<td>[68]</td>
</tr>
<tr>
<td>CASC2</td>
<td>Down</td>
<td>miR-96-5p</td>
<td>CASC2 inhibited the growth and metastasis of BC through the miR-96-5p/SYVN1 axis.</td>
<td>[70]</td>
</tr>
</tbody>
</table>

Clinical significance of LncRNAs in BC metastasis

Accumulating evidence suggested that lncRNAs were abnormally expressed in various cancers and associated with cancer metastasis [84,85]. Dysregulated lncRNAs are also significantly related with multiple clinicopathological characteristics of BC, such as histological grade, ERBB2 expression, steroid-receptor expression, tumor size, TNM stage, and even lymph-node-metastasis (LNM) [12,86]. The expression of lncRNA H19 decreased significantly in adjacent normal tissues compared with BC tissues and plasma (P<0.05), and plasma levels of lncRNA H19 were significantly correlated with LNM (P=0.006) [87]. LncRNA TUG1 expression was significantly decreased in BC tissues compared with controls, and low TUG1 expression was significantly correlated with LNM (P=0.044) [88]. LncRNA FGF14 antisense RNA 2 (FGF14-AS2) was significantly restrained in BC tissues compared with adjacent normal tissues. Down-regulation of lncRNA FGF14-AS2 was correlated with more lymph node metastasis (P=0.000) [89]. BC patients with increased expressions of AC010729.1 and RP11-482H16.1 had a shorter metastasis-free survival (MFS) compared with patients with low expressions of AC010729.1 and RP11-482H16.1. Further analysis showed that AC010729.1 and RP11-482H16.1 could be useful prognostic markers to predict metastatic risk in BC patients [90]. LncRNA MALAT1 expressions were remarkably increased in 85.9% (67/78) of cancer tissues compared with adjacent normal tissues (P<0.01). Furthermore, the increased lncRNA MALAT1 in BC tissues was significantly associated with LNM (P=0.037) [91]. In matched metastatic and primary cancers, the expression of lncRNA HOTAIR increased in the metastatic carcinomas and its expression was a predictor of poor survival of BC patients [92]. Compared with BC tissues, lncRNA Z38 was down-regulated in normal breast tissues. High level of Z38 was significantly
**Table 2 Clinical significance of LncRNAs in BC metastasis**

<table>
<thead>
<tr>
<th>LncRNA</th>
<th>Expression</th>
<th>Clinical significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEG3</td>
<td>Down</td>
<td>Down-regulated MEG3 was significantly associated with TNM stage and LNM in BC patients.</td>
<td>[20]</td>
</tr>
<tr>
<td>OR3A4</td>
<td>Up</td>
<td>The expression level of OR3A4 was found to be associated with LNM, differentiation grade, HER-2/neu status, and TNM stage.</td>
<td>[23]</td>
</tr>
<tr>
<td>H19</td>
<td>Up</td>
<td>Plasma levels of lncRNA H19 were significantly correlated with LNM.</td>
<td>[87]</td>
</tr>
<tr>
<td>TUG1</td>
<td>Down</td>
<td>Low TUG1 expression was significantly correlated with LNM.</td>
<td>[88]</td>
</tr>
<tr>
<td>FGF14-AS2</td>
<td>Down</td>
<td>Down-regulation of lncRNA FGF14-AS2 was correlated with more lymph node metastasis.</td>
<td>[69]</td>
</tr>
<tr>
<td>AC010729.1</td>
<td></td>
<td>Increased expressions of AC010729.1 and RP11-482H16.1 had a shorter MFS compared with patients with low expressions of AC010729.1 and RP11-482H16.1.</td>
<td>[90]</td>
</tr>
<tr>
<td>RP11-482H16.1</td>
<td></td>
<td>Increased expressions of AC010729.1 and RP11-482H16.1 had a shorter MFS compared with patients with low expressions of AC010729.1 and RP11-482H16.1.</td>
<td>[90]</td>
</tr>
<tr>
<td>MALAT1</td>
<td>Up</td>
<td>Up-regulated MALAT1 was related to LNM.</td>
<td>[91]</td>
</tr>
<tr>
<td>HOTAIR</td>
<td>Up</td>
<td>HOTAIR increased in the metastatic carcinomas and its expression in BC was a predictor of poor survival.</td>
<td>[92]</td>
</tr>
<tr>
<td>Z38</td>
<td>Up</td>
<td>High level of Z38 was significantly related to advanced TNM stage and LNM.</td>
<td>[93]</td>
</tr>
<tr>
<td>LINC01296</td>
<td>Up</td>
<td>Increased LINC01296 was positive correlated with larger tumor size, positive LNM, and advanced TNM stage of patients with BC.</td>
<td>[94]</td>
</tr>
<tr>
<td>p10247</td>
<td>Up</td>
<td>The up-regulated expression of p10247 was significantly associated with progression of clinical stage and LNM.</td>
<td>[95]</td>
</tr>
</tbody>
</table>

The expression of MEG3 was significantly decreased in BC tissues compared with adjacent normal tissues. Down-regulated MEG3 was significantly associated with TNM stage and LNM in BC patients [20]. The expression of lncRNA OR3A4 was up-regulated in BC tissues compared with the adjacent normal tissues. The expression level of OR3A4 was found to be associated with LNM, differentiation grade, HER-2/neu status, and TNM stage [23]. LncRNA LINC01296 was aberrantly expressed in both BC tissue samples and cells. Increased LINC01296 was positive correlated with larger tumor size, positive LNM, and advanced TNM stage of patients with BC. Additionally, Cox regression analysis confirmed that LINC01296 could be an independent prognostic indicator for patients with BC [94]. LncRNA p10247 expression level in BC tissues was significantly up-regulated. More importantly, the overexpressed p10247 was associated with the development and progression of BC. The up-regulated expression of p10247 was significantly associated with progression of clinical stage \( P=0.045 \) and LNM \( P=0.039 \) [95] (Table 2).

**Prospects**

The emerging evidence demonstrated that lncRNAs played key roles in various biological processes of BC. However, only a few lncRNAs have been well characterized in BC invasion and metastasis. While surgery can successfully treat primary BC, invasion and metastasis have proven to be a largely insurmountable challenge [96-98]. One primary challenge in BC patients is that metastasis has already occurred prior to diagnosis. Thus, it is essential to find useful prognostic markers to predict metastatic risk in BC patients, which may allow BC patients to choose an individualized treatment. LncRNAs are stable expression in tissue and plasma which may provide markers for a noninvasive and rapid diagnosis for metastatic BC. However, it is well known that the molecular mechanisms of lncRNAs are complicated, including chromatin remodeling, cells cycle control, genetic imprinting, splicing regulation, translational regulation as well as mRNA decay. The detailed molecular mechanisms underlying the function of lncRNAs on BC invasion and metastasis are still unresolved mysteries. Thus, future researches are needed to reveal the underlying mechanisms of dysregulated lncRNAs influence BC metastasis. In the wake of developments in molecular biologic techniques, such as next-generation sequencing and microarray, perhaps the mystery of lncRNAs in BC invasion and metastasis will be unveiled soon. An improved understanding of the BC invasion and metastasis regulated by lncRNAs could assist the development of new strategies to treat or prevent metastatic BC.

**Conclusion**

In this review, we focused on the roles of lncRNAs as regulators during BC invasion and metastasis. Dysregulated lncRNAs participate in BC invasion and metastasis through participating in EMT transition, strengthening CSCs generation, serving as ceRNAs, influencing multiple signaling pathways as well as regulating expressions of CAMs, ECMs, and MMPs. We summarized the function and molecular mechanism of lncRNAs in BC invasion and metastasis as...
well as discussing the clinical significance of IncRNAs in BC staging and LNM. IncRNAs may act as pro-metastatic or anti-metastatic roles in BC. Through a clear understanding of the mechanism of IncRNAs in BC invasion and metastasis, IncRNAs could be promising therapeutic targets and novel molecular biomarkers for metastatic BC.

Funding
This research was supported by the National Key Research and Development Program of China [grant number 2016YFC0905900]; the “333” Talent Project of Jiangsu Province [grant number 4 (2016)]; the National Key Clinical Specialist Construction Programs of China [grant number 544 (2013)]; and Natural Science Foundation of Jiangsu Province [grant number BK20151579].

Competing interests
The authors declare that there are no competing interests associated with the manuscript.

Abbreviations
BC, breast cancer; CAM, cells adhesion molecule; CASC2, cancer susceptibility candidate 2; CDX1, caudal-type homeobox 1; ceRNA, competing endogenous lncRNA; CSC, cancer stem cell; E-cad, E-cadherin; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; EZH2, enhancer of Zeste Homolog 2; HMGA2, high mobility group AT-hook 2; lncRNA, long non-coding RNA; LNM, lymph-node-metastasis; MFS, metastasis-free survival; MMP, matrix metallo-proteinase; RUNX2, runt-related transcription factor 2; SYVN1, synovitin; TjR2, TGF-β receptor 2; TGF-β, transforming growth factor-β; Tnxb, Tenascin Xb; TR, trastuzumab-resistant; ZEB, Zinc finger E-box-binding homeobox.

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