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# The multiple functions and mechanisms of long non-coding RNAs in regulating breast cancer progression

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Breast cancer (BC) is a malignant tumor that has the highest morbidity and mortality rates in the female population, and its high tendency to metastasize is the main cause of poor clinical prognosis. Long non-coding RNAs (lncRNAs) have been extensively documented to exhibit aberrant expression in various cancers and influence tumor progression via multiple molecular pathways. These lncRNAs not only modulate numerous aspects of gene expression in cancer cells, such as transcription, translation, and post-translational modifications, but also play a crucial role in the reprogramming of energy metabolism by regulating metabolic regulators, which is particularly significant in advanced BC. This review examines the characteristics and mechanisms of lncRNAs in regulating BC cells, both intracellularly (e.g., cell cycle, autophagy) and extracellularly (e.g., tumor microenvironment). Furthermore, we explore the potential of specific lncRNAs and their regulatory factors as molecular markers and therapeutic targets. Lastly, we summarize the application of lncRNAs in the treatment of advanced BC, aiming to offer novel personalized therapeutic options for patients.

KEYWORDS

**lncRNAs, BC, cell cycle, the tumor microenvironment, autophagy, drug resistance**

## 1 Introduction

BC is the second most prevalent cancer globally, following lung cancer, and it is the most frequently diagnosed cancer among women, constituting one of the principal causes of cancer-related mortality (Bray et al., 2024). In recent years, significant strides have been made to improve BC treatment. Conventional therapeutic approaches encompass local resection, radical surgery, endocrine therapy, targeted therapy, chemoradiotherapy, and immunotherapy (Singh D. et al., 2022). Early diagnosis and personalized treatment strategies have substantially increased the lifespan of BC patients, with the 5-year survival rate for early-stage BC approaching 100%. Nevertheless, organ damage resulting from metastasis significantly impairs treatment efficacy. The development of metastatic lesions in BC often signifies the loss of the optimal treatment window, indicating a poor prognosis. While chemotherapy, hormone therapy, and radiotherapy can delay tumor progression and modestly extend patient survival (Steeg, 2006). Approximately one-third of BC patients experience distant organ metastases, reducing the 5-year survival rate to

29% (Torre et al., 2015; Giaquinto et al., 2022). Nearly all BC-related deaths are attributed to tumor metastasis, as advanced metastatic cancer remains incurable (Yofe et al., 2023).

The metastasis of BC is recognized as a multifaceted biological phenomenon, potentially necessitating a prolonged incubation period. The timing, location, and degree of malignancy of metastasis vary significantly among individuals, and numerous questions regarding the interplay between the primary tumor and metastatic lesions remain unresolved (Nguyen et al., 2009). The initial site of metastasis is typically the lymph nodes, which is strongly correlated with adverse prognosis. Metastasis can extend beyond the mammary parenchyma via lymphatic and vascular routes, affecting other organs such as the kidneys, bones, brain, liver, or lungs (Schito and Rey, 2017). BC metastasis is marked by its complexity, heterogeneity, and genomic instability, and recent research has demonstrated that lncRNAs play a crucial role in this process (Marino et al., 2013; Li et al., 2016).

The majority of mammalian noncoding genomes are transcribed in a cell-specific manner, generating noncoding RNAs exceeding 200 nucleotides in length. Research has demonstrated that the expression of most lncRNAs is highly specific, with their expression in the adult mouse brain being associated with particular tissues, cell types, and subcellular localization, exhibiting a more precise expression profile compared to mRNA (Mercer et al., 2008; Quinn and Chang, 2016). However, the functional specificity of lncRNAs remains a subject of debate. Recent studies indicate that lncRNAs can modulate gene transcription in the nucleus, influence mRNA stability and translation, and modify proteins in the cytoplasm. These activities impact various signaling pathways and play crucial roles in numerous cellular and biochemical processes (Yao et al., 2019; Cabili et al., 2011). Additionally, the intrinsic characteristics of cancer cells, such as proliferation capacity, metabolic activity, and apoptosis, are closely linked to lncRNAs (Statello et al., 2021). This evidence suggests that lncRNAs may influence the initiation, metastasis, and colonization of tumor cells at metastatic sites during the metastatic progression of BC. Furthermore, given the pronounced tissue-specific expression of lncRNAs, distinct lncRNA clusters may exert effects at different metastatic sites.

LncRNAs are aberrantly expressed during the progression of BC and exert regulatory functions through diverse mechanisms and factors. This review aims to elucidate the molecular mechanisms and current understanding of lncRNA-mediated multimodal regulation in BC progression (Amelio et al., 2021).

# 2 Generation, function, and classification of lncRNA

## 2.1 LncRNA generation

More than 80% of the human genome is transcribed to produce RNA or engage in chromatin-related activities, while less than 2% of protein-coding genes are transcribed to form mRNA. The majority of these transcripts are lncRNAs (Herman et al., 2022; ENCODE Project Consortium, 2012). LncRNAs are predominantly localized in the nucleus, although they are also present in the cytoplasm. They are transcribed by RNA polymerase II (RNAP II) from intergenic, exonic, and intronic regions of the chromatin, exhibiting lower expression levels compared to protein-coding genes, limited primary sequence conservation, and undergoing splicing, capping, and polyadenylation. Approximately 98% of lncRNAs undergo splicing and are flanked by typical splicing sites (GT/AG), sharing similar splicing signals with protein-coding genes (Derrien et al., 2012). The transcription and processing of lncRNAs are analogous to those of mRNAs, although recent studies have highlighted differences in these processes, which are closely associated with lncRNA expression and functional localization.

## 2.2 LncRNA functions

Through genomic and cellular analysis methods, lncRNAs have been demonstrated to possess multiple functions during the differentiation and proliferation of embryonic stem cells (Guttman et al., 2009). Existing studies have shown that lncRNAs participate in various cellular regulatory processes and play significant roles at different stages. Their influence on subcellular localization even determines functional characteristics (Geisler and Coller, 2013; Chen, 2016). Nuclear lncRNAs interact with chromatin modification complexes, RNA-binding proteins (RBPs), or trans-acting factors to regulate the expression of coding genes. In contrast, cytoplasmic lncRNAs primarily exert post-transcriptional regulatory functions, such as mRNA degradation and protein modification following translation (Chen et al., 2020; Batista and Chang, 2013). LncRNAs serve as molecular vectors to achieve these functions through diverse mechanisms. For instance, Xist has recently been identified as a molecular scaffold that binds to binding proteins to form ribonucleoprotein (RNP) complexes, which are implicated in developing autoimmune diseases (Dou et al., 2024). Acting as a "molecular sponge," LINC00680 adsorbs miR-423-5p to modulate the expression of PAK6 in esophageal squamous cell carcinoma (ESCC) (Xue et al., 2022). Additionally, lncRNA P53RRA can directly interact with the G3BP1 protein in the cytoplasm, regulating the transcription of metabolic genes, promoting ferroptosis, and inhibiting tumor progression (Mao et al., 2018). With the advancement and maturation of genetic technologies, other mechanisms by which lncRNAs influence cancer progression are gradually being elucidated, and new evidence of lncRNAs' involvement in human diseases continues to emerge (Ferrer and Dimitrova, 2024; Liu S. J. et al., 2021).

## 2.3 Classification of lncRNAs

Currently, research on lncRNAs remains incomplete. Various studies categorize lncRNA differently, classifying it into distinct categories shown in Figure 1 based on its transcription site transcription direction, and functional characteristics (Tsagakis et al., 2020).

1. Intergenic lncRNAs (lincRNAs) arise from the intergenic regions situated between protein-coding genes, without overlapping with any other genes. This category also

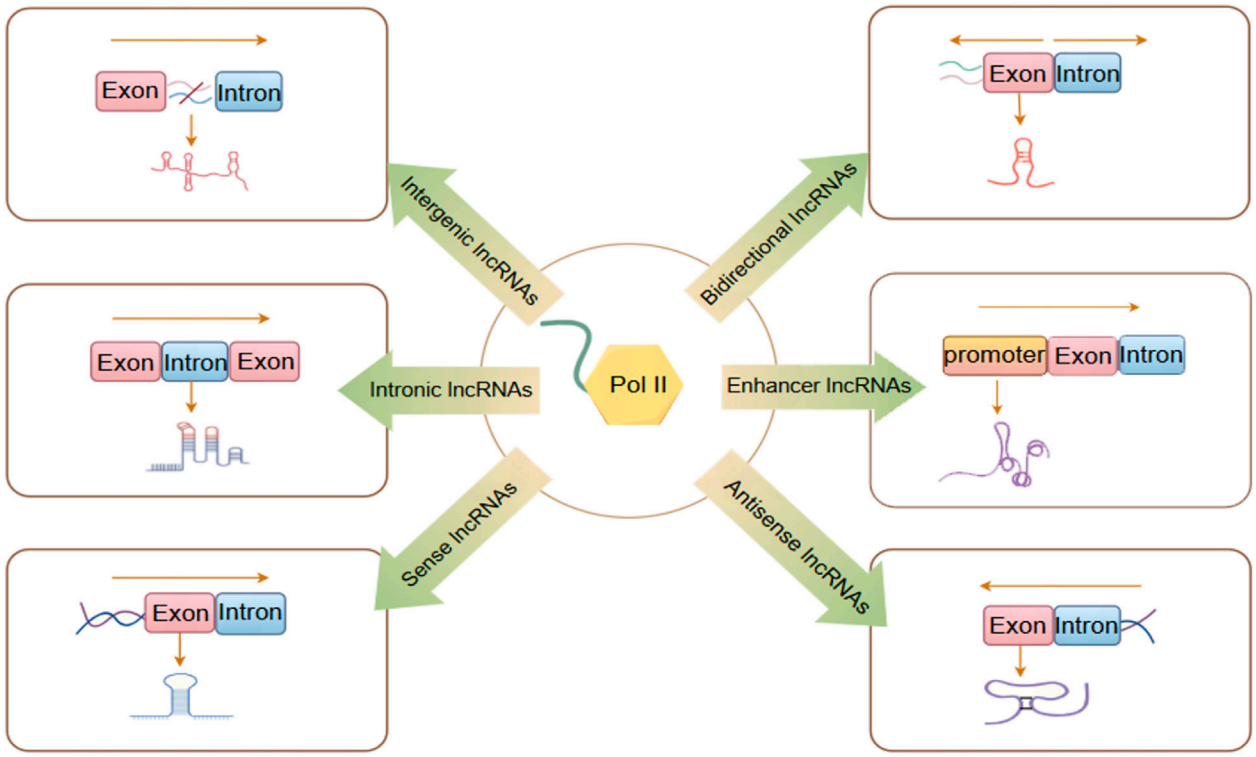


FIGURE 1
LncRNAs are classified into six different categories. By Figdraw.

encompasses very long intergenic lncRNAs (vlincRNAs), which are transcribed from extensive intergenic regions (ranging from 50 to 700 kilobases), exemplified by Nostrill and vlincRNA VAD (Sharmin et al., 2024; Lazorthes et al., 2015).

2. Intronic lncRNAs(lincRNAs) are generated by transcribing introns within protein-coding regions and typically undergo alternative splicing. This process can facilitate stable transcription and cis-regulation of coding genes, exemplified by ci-ankrd52 and ANRASSF1 (Li X. et al., 2021; Beckedorff et al., 2013).
3. Sense lncRNAs are generated within the exon regions of protein-coding genes. While some protein-coding exons overlap with mRNA and are retained, the majority lack functional open reading frames and are incapable of undergoing protein translation, exemplified by lncRNA GAS5 (Tu et al., 2023).
4. Antisense lncRNAs are transcribed in the reverse orientation relative to protein-coding or non-protein-coding genes, primarily by RNA polymerase III (RNAP III), exemplified by HIFAL and ZNF561-AS1 (Zheng et al., 2021; Si et al., 2021).
5. Bidirectional lncRNAs are transcribed in both directions from the vicinity of the transcription initiation site of protein-coding genes, typically within a distance of less than 1,000 base pairs. These lncRNAs may exhibit biological functions similar to those of their corresponding mRNA partners, as exemplified by LINC00882 (Peralta-Alvarez et al., 2024).
6. Enhancer or promoter lncRNAs are transcribed from enhancer or promoter regions. This category also encompasses transcripts derived from recently identified enhancer clusters, known as Super Enhancer lncRNAs (SE-lncRNAs), exemplified by Carmn and LINC01503 (He et al., 2023; Shen et al., 2020).

## 3 LncRNAs can inhibit or promote BC metastasis

LncRNAs comprise a large family with diverse types and functions (Figure 2). According to the current research, different lncRNAs, or even the same lncRNAs, may exhibit either synergistic or opposing effects in regulating BC metastasis due to variations in their regulatory mechanisms and modes of action (Guzel et al., 2020).

The expression levels of lncRNAs may increase or decrease during tumor metastasis, and the causal relationship between these changes and metastasis remains to be elucidated (Mondal and Meeran, 2020). Generally, lncRNAs that promote cancer metastasis tend to be upregulated in tumors, and silencing these lncRNAs typically suppresses tumor metastasis or induces apoptosis. For instance, lncRNA BRE2 is upregulated in metastatic BC, preventing the interaction between NICD1 and WWP2, thus enhancing the stability of NICD1, activating Notch signaling, and driving BC progression and lung metastasis (Zhang Z. et al., 2023). Conversely, lncRNAs that inhibit cancer metastasis are often downregulated in tumors, and the inactivation of these lncRNAs frequently increases the likelihood of metastasis. Upon cleavage by RNase, LINC00478 undergoes polyadenylation to

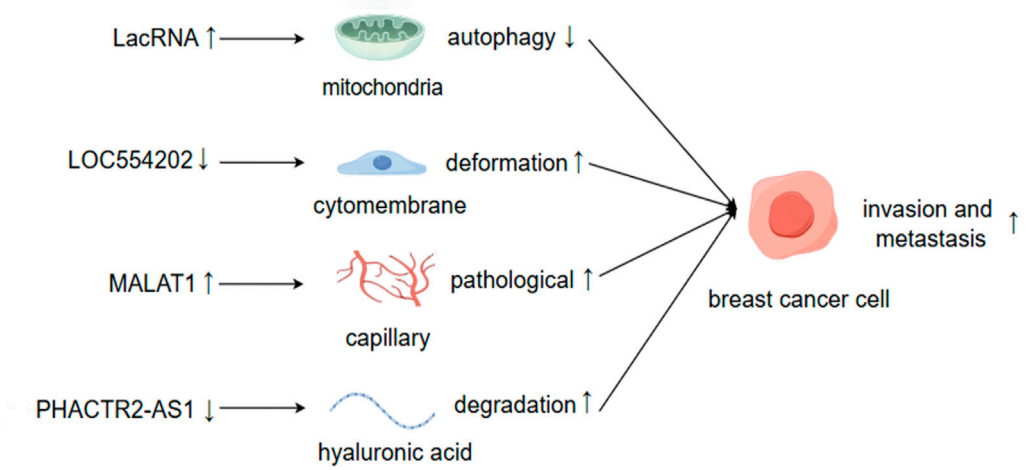


FIGURE 2
LncRNAs facilitate BC invasion and metastasis through the modulation of both intracellular and extracellular alterations. By Figdraw.

generate mature cytoplasmic RNA (LacRNA). The 61-140-nucleotide region at the 5′terminus of LacRNA can competitively bind to the PHB domain of PHB2, which interacts with the autophagy recognition protein LC3 on the surface of autophagosomes, thereby inhibiting the autophagic degradation of PHB2 protein in mitochondria. The complex formed by LacRNA and PHB2 directly binds to c-Myc and promotes its degradation, leading to the inhibition of the oncogene Myc and, consequently, the suppression of BC metastasis (Guo et al., 2023).

Existing studies employ various methodologies and technologies, utilizing multiple observation indicators. Consequently, the same lncRNA may exert similar or opposing roles in regulating diverse biological functions, such as cellular drug resistance, the tumor microenvironment, and the cell cycle of BC metastasis. The ultimate inhibitory or promoting effect likely hinges on the predominant factors (Augoff et al., 2012; Sossey-Alaoui et al., 2007). LOC554202 stands out as one of the initial lncRNAs identified for its regulatory role in BC metastasis (Kurisu et al., 2005). Katarzyna Augoff et al. demonstrated that LOC554202, acting as the host gene of miR-31, modulates its transcriptional level. This interaction confers LOC554202 with a significant role in BC metastasis. Promoter methylation associated with LOC554202 reduces the expression of both LOC554202 and miR-31 in triple-negative BC (TNBC) cell lines, thereby influencing the expression and activity of the downstream target molecule WAVE3 during the invasion-metastasis cascade. The expression level of WAVE3 is significantly correlated with BC progression. LOC554202 primarily regulates miR-31, affecting the formation of membrane fold types, thus controlling cell movement—a critical step in BC metastasis. Yongguo Shi et al. reported that the expression of LOC554202 in BC tissues correlates positively with tumor size and clinical stage, and it is overexpressed in two types of triple-negative BC cells (MDA-MB-231 and MDA-MB435S), which contrasts with Katarzyna's findings (Shi et al., 2014). The same lncRNA can exhibit markedly different functions across various tumor cells and tissues. For instance, lncRNA PHACTR2-AS1 (PAS1) promotes the proliferation and metastasis of hepatocellular carcinoma (HCC) and gastric cancer cells (Chen et al., 2019; Chen et al., 2018). However, the opposite effect was observed in BC organizations. EZH2-mediated methylation results in the loss of PHACTR2-AS1 expression, enhanced ribosome and protein synthesis, and increased genomic instability, ultimately contributing to the development of BC (Chu et al., 2020). PAS1 can also reduce the degradation of hyaluronic acid in the extracellular matrix and inhibit the growth and metastasis of BC by suppressing PH20 (Fu et al., 2022). MALAT1 is a highly expressed long non-coding RNA (lncRNA) in cancer tissue, primarily functioning as an oncogene (Goyal et al., 2021). A study of 20 randomly selected pairs of BC samples found that the expression of MALAT1 in tumor tissues was significantly higher than that in normal non-cancerous tissues. MALAT1 may regulate the activity of endothelial cells through the miR140-5p-JAG1/VEGFA pathway, thereby generating new pathological blood vessels and promoting BC invasion and metastasis (Huang et al., 2018; Liu J. et al., 2023). However, other studies have demonstrated that the downregulation of MALAT1 expression is associated with the proliferation and metastasis of BC, indicating its role as a tumor suppressor. Jongchan Kim et al. employed more rigorous research methods to show that MALAT1 inhibits BC metastasis in various models and can inhibit or even inactivate the transcriptional activity of the transcription factor TEAD (Kim et al., 2018). Gene silencing strategies employing short hairpin RNA (shRNA), small interfering RNA (siRNA), or antisense oligonucleotides (ASOs) without concurrent specific gene verification can complicate the interpretation of phenotypic outcomes following the knockdown of long non-coding RNA (lncRNA) expression. This ambiguity arises because the resultant phenotypes may not be distinctly attributable to the silencing of the targeted lncRNA but rather to the attenuation of other associated genomic elements. For instance, MALAT1 predominantly resides in the nucleus, implying that the application of these various silencing techniques could engender unintended genome-wide effects, particularly concerning nuclear lncRNAs (Abo-Saif et al., 2023). Consequently, the observed phenotypes may stem from the

interference with unintended genes rather than the intended targets, thus elucidating the phenomenon wherein identical lncRNAs yield divergent phenotypic consequences (Bassett et al., 2014; Lin et al., 2017). LncRNAs are potential targets for disease treatment and prognosis, and their regulation of BC metastasis is not direct. Clarifying their inhibitory or promoting effects, as well as the interactions between them, is of significant importance for the research and development of lncRNA-based molecular targeted drugs (Yip et al., 2021).

The mechanism by which lncRNAs regulate gene expression remains incompletely understood. A substantial body of research has demonstrated that lncRNAs can interact with various molecules, including DNA, transcription factors, mRNA, miRNA, and proteins (Chen Y. et al., 2021). However, there are relatively few reports on the regulatory relationships among lncRNAs. For instance, Fatemeh Khani Habibabadi et al. discovered a potential feedback loop between HOTAIR and MALAT1. Specifically, HOTAIR downregulates MALAT1 through the sequestration of miR-217. The reduced expression of MALAT1 facilitates its binding to miR-1, thereby promoting HOTAIR expression and forming a positive feedback loop (Khani-Habibabadi et al., 2022). Currently, there is limited research on the interactions between lncRNAs in the context of BC progression. Studies have shown that XIST and MALAT1 exhibit opposing expression patterns in cancer tissues and TNBC cells. In the regulation of BC progression, XIST can counteract the oncogenic effects of MALAT1, establishing a novel immunomodulatory network: the MALAT1/XIST/miR-182-5p/PD-L1 axis (Samir et al., 2021). These findings indicate that lncRNA-lncRNA interactions play a crucial role in cellular functions and gene expression. Identifying these interactions can contribute to a deeper understanding of the underlying mechanisms and the discovery of therapeutic targets (Qian et al., 2019; Singh S. et al., 2022). The structural flexibility of lncRNAs and the limitations of conventional assay techniques have hindered our comprehension of their structure and spatial roles. However, with the ongoing advancements in high-throughput sequencing and other cutting-edge technologies, the study of lncRNA-lncRNA interactions is poised to transform our understanding of their roles in cancer and open new avenues for investigating BC metastasis.

## 4 LncRNAs affect BC metastasis by regulating the cell cycle

The cell cycle mechanism is primarily regulated by cyclins and cyclin-dependent kinases (CDKs), which are responsible for driving cell growth and proliferation (Hafner et al., 2019; Malumbres and Barbacid, 2009). This regulatory mechanism is frequently impaired in cancer. CDK4/6 inhibitors (CDK4/6i) have been effectively utilized in the treatment of hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic or advanced BC patients, demonstrating the ability to delay cancer progression and enhance patient quality of life. However, these inhibitors also exhibit cytotoxic side effects and can lead to the development of cellular resistance over time (Hafner et al., 2019; Klein et al., 2018; Lynce et al., 2018; Turner et al., 2019). Research indicates that lncRNAs play a role in regulating cyclins, CDKs, and other cell cycle regulators shown in Figure 3. Consequently, cell cycle-specific lncRNA-targeted therapies are anticipated to emerge as potential alternative treatments in the future (Kitagawa et al., 2013).

LncRNAs influence cyclin expression by acting as competing endogenous RNAs (ceRNAs). Cyclin D1 is overexpressed in approximately 50% of BC cells and is associated with the risk of BC progression and metastasis (Fu et al., 2004; Yu et al., 2008). Cyclin D1 regulates various biological functions, including cell proliferation and migration, angiogenesis, maintenance of stem cell activity, and regulation of microRNA (miRNA) subsets, and serves as a key regulator of the G1-S transition (Yu et al., 2013). MIR497HG was initially identified as dysregulated in bladder cancer, and subsequent studies have shown that it primarily functions as a tumor suppressor in tumors (Zhuang et al., 2020; Eissa et al., 2019). Deletion of MIR497HG downregulates the expression of miR-195/497, increases cyclin D1 levels, and inhibits the PI3K-AKT signaling pathway. Downregulation of MIR497HG mediates the involvement of cyclin in the mechanism of tamoxifen resistance, thereby facilitating BC progression and metastasis (Tian et al., 2023). PRNCR1, another highly expressed lncRNA in BC tissues, may inhibit cell cycle progression by regulating the phosphorylation levels of CHK2 and AKT (Pang et al., 2019). Knockdown of PRNCR1 downregulates the expression of cyclin D2, induces G0/G1 phase arrest of the BC cell cycle, and inhibits BC progression through the miR-377/CCND2/MEK/MAPK axis (Ouyang et al., 2021).

LncRNA can directly interact with cyclin to influence its stability and activity. Cyclin E1, encoded by the CCNE1 gene, binds and activates CDK2, leading to the deactivation of Rb through phosphorylation and promoting the transition from the G1 phase to the S phase of the cell cycle (Chu et al., 2021; Hwang and Clurman, 2005; Zeng et al., 2023). Overexpression of cyclin E1 in BC is associated with poor prognosis and drug resistance (Caldon et al., 2012; Scaltriti et al., 2011). LncRNA EILA stabilizes cyclin E1 by directly affecting the phosphorylation site at the C-terminal of cyclin E1, preventing the binding of cyclin E1 to the ubiquitin ligase FBXW7, thus inhibiting ubiquitination-mediated proteasomal degradation. This stabilizing effect results in increased cyclin E1 expression and contributes to the development of BC resistance to CDK4/6 inhibitors (Cai et al., 2023). DILA1, a nucleolar lncRNA similar to MALAT1, contains a hairpin A structure that binds directly to the Thr286 phosphorylation site of cyclin D1, leading to a decrease in phosphorylated cyclin D1 (Thr286) and subsequent reduction in nucleoplasmic translocation and degradation of cyclin D1. By upregulating cyclin D1, DILA1 accelerates G1 phase progression, which is essential for inducing cell proliferation and tamoxifen resistance (Shi et al., 2020).

CDKs are essential regulators of the cell cycle, playing a pivotal role in cellular processes. Their activation depends on the binding of cyclins, which enables their kinase activity and includes both cell cycle-associated CDKs and those linked to transcription (Chou et al., 2020). These influential kinases integrate vital signal transduction pathways that promote tumor growth, positioning them as promising targets for novel molecular therapies. Furthermore, CDKs can interact with lncRNAs during tumor progression, underscoring their multifaceted involvement in cancer biology

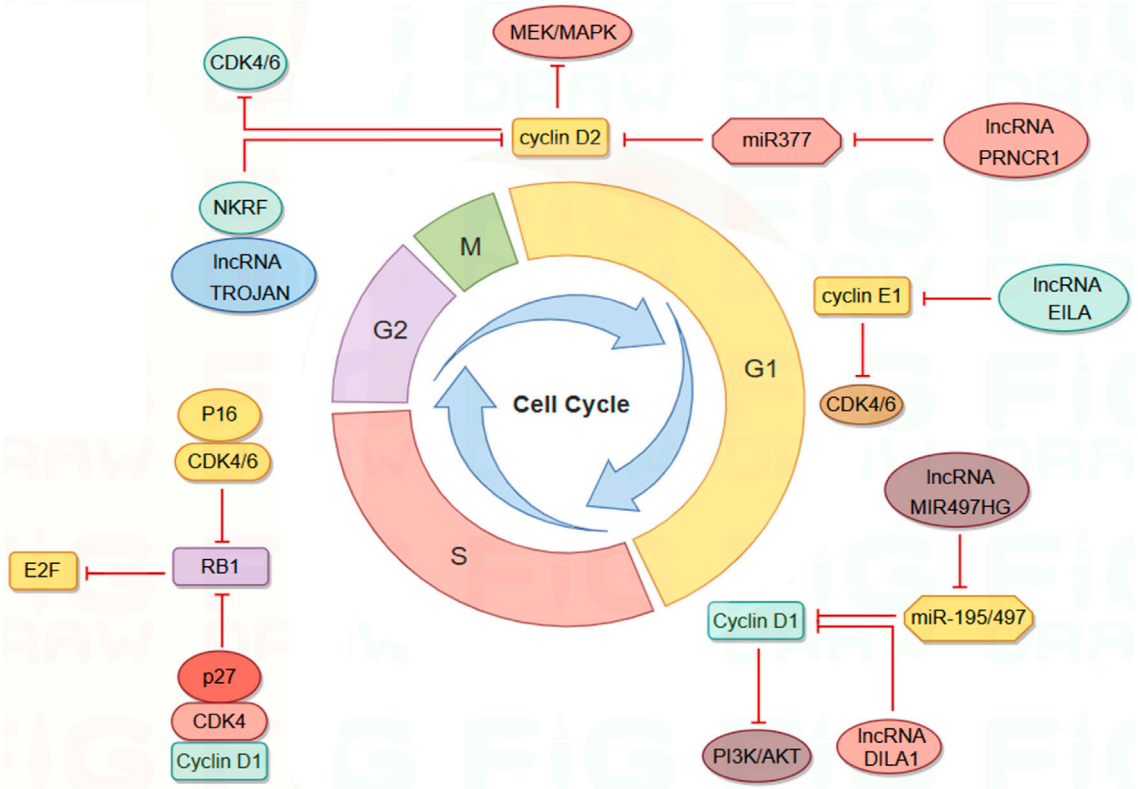


FIGURE 3
LncRNAs modulate the cell cycle of BC cells via interactions with Cyclin/CDK complexes. By Figdraw.

(Siddique et al., 2024). Given the structural and functional similarities between CDK4 and CDK6, which facilitate functional compensation, studying these enzymes together is crucial for enhancing our understanding of cancer treatment strategies (Pavletich, 1999). The INK family and the CIP/KIP family serve as kinase inhibitors controlling cell cycle transitions, primarily through the inhibition of CDK4/6 to modulate the cell cycle (Bury et al., 2021). P16, a ubiquitously expressed member of the INK family, forms complexes with CDK4 and CDK6, thereby reducing the formation of the CDK4/6-cyclin D complex and inhibiting the phosphorylation of retinoblastoma protein 1 (RB1). Reduced RB1 phosphorylation enhances its affinity for the E2F transcription factor family, increasing the inhibitory effect on E2F upon binding and suppressing transcription (Hiebert et al., 1992; Sellers et al., 1995). While CIP/KIP proteins are generally regarded as CDK inhibitors, research by Seth M. Rubin et al. indicates that p27, a member of the CIP/KIP family, functions as an allosteric activator. Tyrosine-phosphorylated p27 activates CDK4 and binds to the CDK4-cyclin D1 complex, inducing alterations in the ATP binding site and releasing kinase-activating fragments, leading to the inhibition of the cell cycle by phosphorylated RB (Guiley et al., 2019). To address resistance to CDK4/6 inhibitors, efforts are underway to identify various biomarkers to predict CDK4/6 sensitivity and to develop novel combination drug strategies (Pandey et al., 2019; Rugo et al., 2021). Given the diverse mechanisms by which lncRNAs regulate the cell cycle, the relationship between lncRNAs and CDK4/6 inhibitors appears very promising (Guiducci and Stojic, 2021). Research has shown that the expression of lncRNA TROJAN is significantly elevated in estrogen receptor-positive BC ($ER^+$BC) cells, correlating with reduced patient survival rates. Both *in vivo* and *in vitro* studies have demonstrated that the combination of Anti-TROJAN ASO with CDK4/6 inhibitors more effectively inhibits tumor growth compared to the use of either inhibitor alone, indicating a significant synergistic effect. Mechanistic investigations have revealed that TROJAN binds to NKRF (NF-κB inhibitor), indirectly activating transcription factors in the NF-κB signaling pathway, which is implicated in BC cell proliferation, metastasis, and endocrine therapy resistance (Devanaboyina et al., 2022). In the presence of CDK4/6 inhibitors, the TROJAN-NKRF complex upregulates the expression of CDK2, enabling BC cells to enter the S phase via an atypical pathway and continue the cell proliferation process. The regulatory mechanism of TROJAN-NKRF-CDK2 offers a plausible explanation for CDK4/6 inhibitor resistance and identifies a potential target for overcoming this resistance (Jin et al., 2020; Jin et al., 2019). Identifying cancers that depend on a single CDK for proliferation, enhancing the diversity and interchangeability of selective inhibitors are crucial for developing safe and effective drugs (Morrison et al., 2024). CDK7 functions as a CDK-activated kinase (CAK) responsible for activating the kinase activities of CDK1, CDK2, CDK4, and CDK6, thereby regulating downstream cell cycle processes. Additionally, CDK7 collaborates with cyclin H and MAT1 to form the core of transcription factor IIH (TFIIH), which activates

the C-terminal domain (CTD) of RNA polymerase II, facilitating transcription (Sava et al., 2020; Li et al., 2022). Given its pivotal roles in cell cycle regulation and transcription, CDK7 represents a promising target for cancer drug development. Furthermore, CDK7 mediates the activity of the ER α through phosphorylation at serine 118, and elevated blood estrogen levels are associated with an increased risk of BC. This suggests that CDK7 inhibitors (CDK7i) hold significant potential in BC therapy (Song et al., 2024; Chen et al., 2002). LIMD1-AS1 is a lncRNA associated with super-enhancers (SEs) and acts as an oncogene specifically overexpressed in glioma. It promotes the proliferation and invasiveness of glioma cells and exhibits a negative correlation with patient survival. CDK7 enhances the transcription of LIMD1-AS1 by phosphorylating the transcription coactivator MED1, which subsequently binds to HSPA5 and activates the interferon signaling pathway (Chen et al., 2023). Other studies have utilized esophageal squamous cell carcinoma (ESCC) as a model to successfully predict several SE-associated competing ce-lncRNAs using a computational method named GloceRNA. Additionally, these studies have demonstrated that the specific CDK7 inhibitor THZ1 downregulates SE-associated ce-lncRNAs by inhibiting transcription factors, such as reducing the expression of LINC00094 in ESCC cells (Wang et al., 2020). While there is substantial evidence supporting a reciprocal regulatory relationship between lncRNAs and CDK7 in various tumor types, a significant gap persists: no direct evidence has yet been established linking lncRNAs associated with BC metastasis to the regulation of CDK7.

Various lncRNAs influence the cell cycle by modulating the activity of CDKs through diverse mechanisms, and these regulatory effects may play a crucial role in the progression and metastasis of BC. The impact of lncRNAs on cyclin kinase activity is a key aspect of the complex pathogenesis of cancer, and further experimental data are required to elucidate the specific mechanisms of this interaction.

## 5 Significance of lncRNAs in tumor microenvironment

The tumor microenvironment (TME) encompasses a sophisticated network comprising cancer cells, non-cancerous cells (including stromal and immune cells), and the molecules secreted both before and following tumor development. This intricate system significantly influences tumor initiation, invasion, metastasis, inflammatory responses, proliferation maintenance, and immunosuppression (Xiao and Yu, 2021). As tumors expand, they release active factors and generate metabolites that modify the TME's composition (Figure 4), thereby further facilitating tumor progression (Economopoulou et al., 2020). The metastatic potential and prognosis of BC are intimately linked to alterations in the TME, underscoring the critical need to elucidate the compositional changes and regulatory mechanisms within this environment (Qian et al., 2011).

As key players among immune cells in the TME, tumor-associated macrophages (TAMs) exhibit dynamic changes in their polarization states, which can be influenced by various factors (Murray et al., 2014). Research has primarily identified two phenotypes of macrophages: M1 and M2. M1 macrophages display pro-inflammatory and anti-tumor activities, while M2 macrophages exhibit anti-inflammatory and pro-tumor behaviors. Despite the limitations of this classification, it remains valuable for understanding tumor immunity (Van den Bossche et al., 2017). Monocytes recruited from the peripheral circulation of the TME predominantly differentiate into M2 macrophages, which secrete angiogenic factors, cell proliferation factors, immunosuppressive factors, and stromal proteolytic enzymes, thereby supporting cancer cell growth and metastasis (Hagemann et al., 2005; Leek et al., 1996). Consistent with this, lncRNAs have been identified as regulators of TAMs polarization across various cancer types, often contributing to pro-tumor activities, often exerting pro-tumor effects. For instance, exosomes secreted by TAMs can transfer lncMMPA, leading to the formation of M2-type macrophages. The binding of highly expressed lncMMPA to miR-548s in hepatocellular carcinoma enhances aerobic glycolytic pathways and cell proliferation (Xu et al., 2022). Similarly, lncRNA-PACERR is overexpressed in TAMs derived from pancreatic ductal adenocarcinoma (PDAC) and binds to miR-671-3p *in vitro*, releasing KLF12 and activating the AKT/c-myc pathway, thus promoting M2 macrophage polarization (Liu et al., 2022). BC has a notably higher proportion of TAMs within the tumor, sometimes accounting for up to 50% of the tumor volume (Wagner et al., 2019). Although the number of TAMs varies significantly among individuals, they consistently contribute to BC progression, highlighting the critical role of macrophage phenotype in BC invasion and metastasis (Biswas et al., 2013; Xiao et al., 2022). LncRNA SNHG1 regulates macrophage phenotype via the STAT pathway, promoting BC metastasis and angiogenesis at the metastatic site (Zong et al., 2021). LncRNA NR_109 has emerged as a critical factor in macrophage polarization, competing with JTV-1 to bind to the C-terminal of FUBP1. This interaction inhibits the ubiquitin-mediated degradation of FUBP1, resulting in a significant increase in c-Myc expression and promoting a shift towards M2-like macrophage polarization (Zhang C. et al., 2023). Emerging evidence suggests that the transformation of TAMs from a pro-tumor to an anti-tumor phenotype could alter the TME and provide a platform for inhibiting tumor growth, proliferation, and metastasis, with lncRNAs being a potential breakthrough direction. The utilization of macrophage phagocytosis to enhance innate immunity has garnered increasing attention in cancer therapy (Chen S. et al., 2021). Recent studies have demonstrated that, in addition to regulating TAM polarization, lncRNAs can also inhibit macrophage phagocytosis and promote cancer cell immune escape. For instance, LINC00460 promotes the overexpression of CD47, which inhibits the recognition and phagocytosis of colorectal cancer (CRC) cells by macrophages, hindering cancer cell clearance (Luo et al., 2024). Similarly, in epithelial ovarian cancer (OC), lncRNA IL21-AS1 mediates the regulation of a novel antiphagocytic protein, CD24, through HIF-1α and/or miR-561-5p, rather than CD47 (Liu et al., 2024). In TNBC, a novel engineered nanoparticle (P-ACD24/CEL + P/shMFN1) synergistically elicits an anti-tumor immune response by blocking CD24, inducing tumor cell apoptosis, and reversing the M2-TAMs phenotype, thereby achieving the effect of combined immunotherapy (Zhao et al., 2023). These findings underscore the significance of enhancing macrophage phagocytosis in immunotherapy, where anti-phagocytosis proteins serve as critical regulators. CD24 and CD47 are frequently overexpressed in solid tumor samples from BC patients, with their expression levels varying across different BC subtypes. Specifically, CD24 expression in fibroadenomas is higher than in

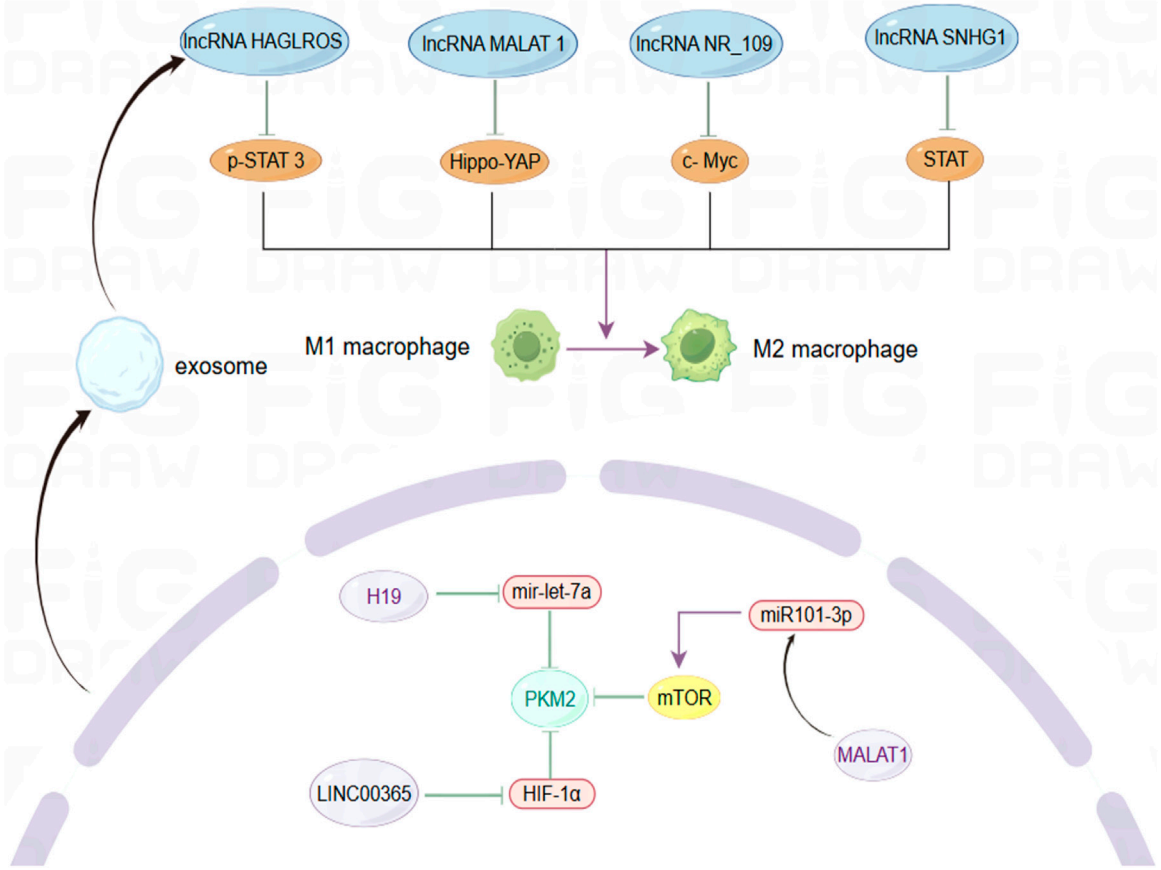


FIGURE 4
The role of lncRNAs in modulating macrophage phenotype and metabolic enzyme expression within the BC microenvironment. By Figdraw.

phyllodes tumors, while CD47 is predominantly expressed in drug-resistant HER2$^+$ BC cells (Ahmed et al., 2022; Zhang B. et al., 2024). Moreover, CD24 is implicated in the invasive and metastatic behavior of cancer cells, with its expression significantly elevated at distant metastatic sites compared to primary tumors (Shipitsin et al., 2007). Additionally, CD24 deletion in mouse models of BC xenotransplantation has been shown to inhibit primary tumor growth and, more importantly, may hinder the colonization and growth of cancer cells in distant organs such as the lungs by reducing the formation of microvessels and lymphatics (Chan et al., 2019). Despite this, targeted therapy against CD24 has yielded promising results. LncRNAs plays a crucial role in regulating the expression of these immune checkpoints through mechanisms such as acting as a "molecular sponge."

Pyruvate kinase M2 (PKM2) is a critical rate-limiting enzyme in glycolysis that plays a pivotal role in regulating cellular metabolism within the TME. Metabolic reprogramming is a hallmark of cancer cells, and PKM2 is essential for the metabolic phenotype associated with aerobic glycolysis (Hanahan and Weinberg, 2011; Christofk et al., 2008). In normal cells, the dimeric form of PKM2 exhibits low catalytic efficiency and is subject to intricate regulation as a protein kinase (Gui et al., 2013). Unlike mechanisms that manipulate genetic information, this lncRNA influences cancer cell proliferation by modulating the activity of metabolic enzymes, thereby enhancing our understanding of lncRNA function. The altered expression of PKM2 is a significant factor in various cancers, with emerging evidence underscoring the critical role of lncRNAs in regulating this enzyme (Zhu et al., 2021). For instance, lncRNA 495810 is essential in CRC, as it stabilizes PKM2 activity by preventing its degradation through ubiquitination (Cui et al., 2023). Furthermore, the transcription factor YY1 enhances the expression of lncRNA-ARAP1-AS2 and ARAP1, resulting in persistent activation of EGFR, PKM2 transformation, and the accumulation of HIF-1α. This interplay has significant implications, driving the abnormal glycolysis seen in diabetic nephropathy (DKD) and contributing to renal tissue fibrosis (Li et al., 2023). Conversely, lncRNA PWRN1 inhibits hepatocellular carcinoma (HCC) growth, invasion, and metastasis by forming a stable tetramer and increasing PKM2 activity, suppressing aerobic glycolysis and reducing lactate levels (Fei et al., 2024). Additionally, PKM2 is a key mediator in the polarization of macrophages through metabolic reprogramming pathways (Palsson-McDermott et al., 2015). Recent studies have demonstrated that annexin A5 (Anx A5) targets PKM2 to reduce its nuclear translocation, inhibit glycolysis, and shift metabolism towards tricarboxylic acid (TCA) cycle-dependent oxidative phosphorylation (OXPHOS), thus facilitating the transition of liver macrophages from the M1 to the M2 phenotype (Xu et al., 2020). PKM2 fulfills multiple roles in cancer, serving not only as a catalytic enzyme in metabolism, catalyzing the final step of glycolysis, but also as a protein kinase

and transcriptional regulator with oncogenic functions, thereby promoting gene transcription and tumor progression (Yang et al., 2011; Yang et al., 2014). By skillfully balancing both metabolic and non-metabolic roles, PKM2 effectively orchestrates the complex process of tumorigenesis. However, the intricacies of its dual role continue to prompt debate, underscoring its relevance in cancer research and potential therapeutic strategies. For instance, PKM2-deficient xenograft tumor models established *in vivo* did not exhibit restricted tumor growth, and similarly, PKM2 knockdown had no significant inhibitory effect on TNBC (Cortés-Cros et al., 2013; Israelsen et al., 2013). Research has demonstrated that the absence of PKM2 triggers a shift in the TNBC metabolic pathway from glycolysis to fatty acid beta-oxidation (FAO), which continues to supply energy for cancer cell activity (Zhang Y. et al., 2024). PKM2 is associated with advanced metastasis, tumor classification, and poor prognosis in BC. Fluctuations in estrogen and progesterone levels before and after menopause influence the expression of glycolysis-related genes, indicating a potential interplay between hormonal changes and PKM2 (Xiao et al., 2020; Ishfaq et al., 2022). MALAT1 regulates BC processes via the miR101-3p/mTOR/PKM2 pathway (Shao et al., 2021). LINC00365 may suppress the expression of key glycolytic enzymes by targeting HIF-1α (Liu B. et al., 2023). These studies have elucidated a novel mechanism of BC-associated lncRNA-mediated regulation of PKM2 activity. Before metastasis, BC secretes small molecules that act on normal cells at the metastatic site, reducing their energy consumption and facilitating metastasis by "sequestering" cancer cells in pre-metastatic niches (Fong et al., 2015). Following BC metastasis, cancer cells at the metastatic site exhibit altered metabolic processes to adapt to the distinct TME. BC cells with liver metastasis display aerobic glycolysis-dependent metabolic characteristics, whereas BC cells from bone or lung metastasis tend to rely on OXPHOS (Dupuy et al., 2015; Biondini et al., 2024). Some studies have also demonstrated that the upregulation of OXPHOS during BC invasion and migration is a transient phase, and aerobic glycolysis remains predominant after colonization. Energy metabolism is a critical and dynamic component throughout BC metastasis process (Liu YM. et al., 2023). It is essential to deepen our understanding of the mechanisms of energy consumption at various stages of progression and across different metastatic sites. Although PKM2 is a promising therapeutic target, its effectiveness as a standalone agent in targeted small molecule therapy is somewhat limited. The strategic combination of PKM2 inhibitors with other anticancer metabolic drugs holds great promise for effectively disrupting metabolic processes and, as a result, halting tumor growth. Additionally, the unique characteristics of lncRNAs and their regulatory influence on metabolic pathways provide exciting new avenues for targeted molecular therapies in BC.

## 6 LncRNAs modulate the drug resistance of BC cells through the regulation of autophagy

Autophagy is a highly conserved self-protective mechanism present in eukaryotic cells, playing an essential role in maintaining cellular health. It functions by degrading and recycling damaged organelles and residual proteins within the cytoplasm, thereby mitigating their detrimental effects on cellular function (Debnath et al., 2023). Remarkably, even in the presence of cancer, the integrity of the autophagy machinery remains largely intact at the DNA level, with a significantly lower frequency of mutations observed in autophagy-related protein (ATG) genes compared to normal tissues (Levine and Kroemer, 2019). It suggests that mutations in ATG genes are not a primary driver of disease progression. Nevertheless, aberrant autophagy has garnered significant attention in oncology, indicating that certain regulatory factors or pathway interaction elements may modulate the autophagy pathway, leading to either tumor suppression or tumor promotion.

Extensive research has shed light on the complex and often ambiguous role of autophagy in BC, demonstrating that its effects are influenced by key factors such as tumor stage, oncogenic genes, and changes in the microenvironment. Beclin 1, an autophagy-related gene that exerts a negative regulatory effect on BC, was the first to establish a specific connection between autophagy and BC (Liang et al., 1999). In the early stages of cancer, appropriate levels of autophagy can facilitate DNA repair and regulate cell division, thereby counteracting the stimulatory effects of oncogenes and preventing tumor progression. However, as the tumor advances to later stages, the products of autophagic degradation are exploited by cancer cells to support their energy metabolism and biosynthetic requirements, which promotes rapid tumor growth and proliferation, thus contributing to the pro-tumorigenic role of autophagy in cancer progression (Rybstein et al., 2018; Wang et al., 2023). Numerous studies have confirmed the involvement of lncRNAs in the development of drug resistance in BC, and their interaction with autophagy plays a crucial role in enhancing multidrug resistance and advanced metastasis. The expression levels of lncRNAs are closely associated with the emergence of clinical drug resistance in various treatment modalities, including endocrine therapy, chemotherapy, and targeted therapy. This concerning trend reveals the complex interplay of multiple signaling pathways, highlighting the urgent need to address lncRNA-driven mechanisms in the battle against drug-resistant BC. For instance, lncRNAs may enhance tumor resistance via autophagy mediated by the ERK/mTOR, AKT/mTOR, or TGF-β/Smad3 pathways (Li et al., 2019; Xing et al., 2024; Liu X. et al., 2023). Tamoxifen (TAM) is an efficacious medication for the treatment of BC across all clinical stages; however, the development of long-term drug resistance has constrained its therapeutic efficacy. The transcription factor EB (TFEB), lactate dehydrogenase A, and certain lysosome-associated protective proteins can induce endocrine resistance via the autophagy of BC cells. Conversely, vitamin D may potentiate the sensitivity of drug-resistant BC cells to TAM by inhibiting autophagy (Boretto et al., 2023; Das et al., 2019; Actis et al., 2021; Li Y. et al., 2021). LncRNA H19 has been identified as an oncogene in BC, exhibiting a strong correlation with ER expression. Additionally, H19 plays a role in the mechanisms of autophagy or drug resistance in various malignancies, including liver, colorectal, and BC. The H19/SAHH/DNMT3B axis facilitates TAM resistance in BC by modulating DNA methylation and activating autophagy (Basak et al., 2015; Wang et al., 2019). Paclitaxel (PTX) is a frontline chemotherapeutic agent for BC, primarily targeting mitotic processes. Nonetheless, the emergence

of drug resistance is inevitable following prolonged administration. In the context of BC chemotherapy resistance, autophagy is a survival strategy for cancer cells adapting to extended treatment regimens. Therefore, inhibiting autophagy can render chemoresistant cancer cells resensitized to chemotherapy agents (Abu et al., 2019). LncRNAs, acting as a regulator of autophagy, have emerged as a promising therapeutic target for overcoming chemotherapy resistance. Indeed, existing research has shown that targeting lncRNAs can inhibit autophagy-mediated activation, thereby enhancing the efficacy of chemotherapy in BC cells. Specifically, knocking down lncRNA DDIT4-AS1 alleviates the suppression of the DDIT4-mTOR signaling pathway, significantly inhibits autophagy, and restores the sensitivity of TNBC to paclitaxel (Jiang et al., 2023). Additionally, the downregulation of lncRNA OTUD6B-AS1, functioning as a competing ceRNA, modulates the expression of miR-26a-5p, inhibits autophagy, and improves paclitaxel-induced cytotoxicity (Li P. P. et al., 2021). Conversely, lncRNA EGOT, a clinical biomarker for assessing paclitaxel sensitivity, enhances paclitaxel sensitivity by upregulating ITPR1 expression and promoting autophagy (Xu et al., 2019). Trastuzumab represents the initial first-line targeted therapy for HER2-overexpressed metastatic BC; however, over 50% of patients receiving this treatment eventually develop resistance. Resistance to HER2-targeted therapies can arise through various mechanisms, including HER2 heterogeneity, tumor immune responses, activation of compensatory pathways, HER2 site mutations, or epitope deletions. Clinical studies have demonstrated that HER2 positivity in primary tumors is associated with a significantly increased risk of central nervous system (CNS) metastasis. Given the limited ability of trastuzumab to penetrate the blood-brain barrier, the CNS may serve as a potential sanctuary for cancer cells, potentially exacerbating drug resistance (Lin and Winer, 2007; Swain et al., 2023). Research has shown that lncRNA ZNF649-AS1 enhances ATG5 transcription by binding to PTBP1, promoting autophagy and contributing to trastuzumab resistance (Han et al., 2020). This novel perspective on the lncRNA-autophagy-cancer axis highlights a promising direction for identifying potential drug resistance mechanisms and enhancing the efficacy of cancer treatments, paving the way for more targeted therapeutic approaches.

## 7 Conclusion and future perspectives

This review comprehensively explores the characteristics and mechanisms by which lncRNAs facilitate the invasion and metastasis of BC. It provides an in-depth analysis of the regulatory interactions between lncRNAs and various factors, including cell cycle mechanisms, TME, and autophagy-related drug resistance shown in Table 1. Notably, the mechanisms by which certain lncRNAs mediate BC metastasis are not completely independent. For instance, lncRNAs not only exert influence over tumor cells through cyclins but also play a significant role in modulating the TME (Deng et al., 2018; Goel et al., 2017). Similarly, lncRNAs regulate BC drug resistance through multiple pathways, with their molecular basis being a complex regulatory network influenced by various processes and factors. Investigating the molecular foundation and mechanisms underlying these interactions will not only enhance our understanding of lncRNA-mediated BC metastasis but also highlight the potential of specific lncRNAs as prognostic biomarkers for BC progression and treatment (Miao et al., 2021).

As the understanding of lncRNAs in the regulation of BC progression continues to expand, our objective is to systematically synthesize the relevant mechanisms and characteristics underlying these regulatory processes. This synthesis aims to provide a foundational framework for the identification of novel anti-cancer targets and the development of innovative therapeutic strategies for advanced BC within the paradigm of precision medicine. A substantial body of preclinical and clinical research has persistently underscored the potential biological significance and therapeutic value of lncRNAs in the context of cancer treatment. Significant advancements have been achieved in the exploration of lncRNAs within the domain of human genetics; however, numerous scientific gaps and technical challenges persist. The redundancy and functional complexity associated with lncRNAs hinder the establishment of a unified standard for their classification and nomenclature. For instance, a single lncRNA may be designated by different names across various databases and literature (e.g., GAS5 is also referred to as SNHG2), thereby exacerbating the complexity of research outcomes and complicating data integration efforts. Furthermore, the functions of over 90% of lncRNAs remain poorly defined, and the identification of functional lncRNA transcription sites is impeded by several obstacles, including sequence conservation, expression heterogeneity, and technical constraints. Consequently, elucidating the functions of lncRNAs and systematically annotating their transcription sites is crucial for enhancing the understanding of gene regulation. Previous research has indicated that lncRNAs are differentially expressed in the context of cancer development, highlighting their regulatory functions. Nonetheless, their relevance to the occurrence of human diseases has been largely overlooked in clinical genomic analyses. A seminal study by Ganesh et al. has demonstrated for the first time that the deletion of lncRNA CHASERR gene can result in neurodevelopmental disorders. This finding underscores the association of lncRNAs with a broader spectrum of human diseases and raises important questions regarding whether the loss, mutation, or amplification of lncRNAs may contribute to the pathogenesis of cancer, necessitating further investigation (Allou et al., 2021; Ganesh et al., 2024). While certain lncRNAs, such as H19, exhibit potential utility in the diagnosis of BC, it is important to note that their sensitivity and specificity remain inferior to those of traditional protein biomarkers. Additionally, the stability of lncRNAs in the bloodstream is adversely affected by the activity of RNA-degrading enzymes, which poses a challenge to their clinical application (Badowski et al., 2022).

Regarding the therapeutic application of lncRNAs associated with BC metastasis, despite the relative maturity of small siRNAs and antisense oligonucleotides, challenges remain in terms of delivery, stability, and immunogenicity. Excitingly, advancements in RNA therapy technology have enabled researchers to design and synthesize high-affinity artificial lncRNAs (alncRNAs) by utilizing RNA aptamers and lncRNA HOTAIR to specifically target and degrade key oncogenic proteins.

TABLE 1 Summary of recent updates regarding the actions and regulatory targets of various lncRNAs in BC progression.

| Pathway of action for lncRNAs -on | LncRNA | Dysregulation | Target | References |
|---|---|---|---|---|
| Cell cycle | MIR497HG | ↓ | ↓ miR-195/497, | Tian et al. (2023) |
| | | | ↓ PI3K-AKT | |
| | PRNCR1 | ↑ | ↓ miR-377. | Ouyang et al. (2021) |
| | | | ↑ MEK/MAPK pathway | |
| | EILA | ↑ | ↑ cyclin E1, | Cai et al. (2023) |
| | | | ↓ CDK4/6i | |
| | DILA1 | ↑ | ↑ cyclin D1 | Shi et al. (2020) |
| | TROJAN | ↑ | ↓ NKRF, | Devanaboyina et al. (2022) |
| | | | ↑ NF-κB pathway | |
| | SLC16A1-AS1 | ↓ | ↑ miR-182, | Jiang et al. (2022) |
| | | | ↑ PDCD4 | |
| | SNHG5 | ↑ | ↓ miR-299, | Huang et al. (2022) |
| | | | ↑ BACH1 | |
| | LINC02613 | ↓ | ↑ Wnt pathway | Cui et al. (2022) |
| TME | SNHG1 | ↑ | ↑ STAT pathway | Zong et al. (2021) |
| | NR_109 | ↑ | ↑ c-Myc | Zhang et al. (2023b) |
| | HAGLROS | ↑ | ↓ miR-135b-3p, | Meng et al. (2024) |
| | | | ↑ p-STAT3 | |
| | MALAT1 | ↑ | ↑ Hippo/YAP pathway | Wang et al. (2024) |
| | PCAT6 | ↑ | ↑ VEGFR/AKT/mTOR pathway | Dong et al. (2020) |
| | IRENA | ↑ | ↑ NF-κB | Liu et al. (2021b) |
| | Linc00514 | ↑ | ↑ Notch pathway | Tao et al. (2020) |
| | Xist | ↑ | ↓ miR-101, | Zhao et al. (2021) |
| | | | ↑ C/EBPα and KLF6 | |
| | lincRNA-p21 | ↑ | ↓ NF-κB pathway, | Zhou et al. (2020) |
| | | | ↓ STAT3 pathway | |
| Autophagy | H19 | ↑ | ↑ SAHH, | Wang et al. (2019) |
| | | | ↑ DNMT3B | |
| | DDIT4-AS1 | ↑ | ↓ mTOR pathway | Jiang et al. (2023) |
| | EGOT | ↓ | ↓ ITPR1 | Xu et al. (2019) |
| | ZNF649-AS1 | ↑ | ↑ PTBP1, | Han et al. (2020) |
| | | | ↑ ATG5 | |

While several challenges persist, the emergence of lncRNA-targeted therapeutic strategies signifies a noteworthy advancement, offering potential pathways for more effective interventions in BC metastasis (Cao et al., 2024). Simultaneously, nanotechnology-based drug delivery systems have demonstrated advantages in combination therapy for the treatment of BC. Notably, nanoparticles conjugated with siRNA and chemotherapeutic agents exhibit substantial antitumor effects in both *in vivo*, *in vitro*, and organoid studies (Jiang et al., 2023). Furthermore, the field of small molecule therapy, which targets lncRNAs, has emerged as a promising area of research. This domain seeks to disrupt the interactions between lncRNAs and small molecules, thereby modulating the functional roles of lncRNAs in oncogenesis and therapeutic resistance (Alkan et al., 2024). Considering the tissue and organ-specific nature of lncRNAs, they hold significant potential as diagnostic and

prognostic biomarkers, as well as therapeutic targets for evaluating clinical outcomes and guiding targeted therapies. Advances in sequencing, probing, and immunoprecipitation techniques have facilitated a more comprehensive understanding of lncRNAs, and their role in the progression and metastasis of BC is poised to yield imminent breakthroughs.

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