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Review:

Roles of miRNA and lncRNA in triple-negative breast cancer*

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Abstract: Triple-negative breast cancer (TNBC) is currently the most malignant subtype of breast cancer without effective targeted therapies, which makes its pathogenesis an important target for research. A growing number of studies have shown that non-coding RNA (ncRNA), including microRNA (miRNA) and long non-coding RNA (lncRNA), plays a significant role in tumorigenesis. This review summarizes the roles of miRNA and lncRNA in the progression, diagnosis, and neoadjuvant chemotherapy of TNBC. Aberrantly expressed miRNA and lncRNA are listed according to their roles. Further, it describes the multiple mechanisms that lncRNA shows for regulating gene expression in the nucleus and cytoplasm, and more importantly, describes lncRNA-regulated TNBC progression through complete combining with miRNA at the post-transcriptional level. Focusing on miRNA and lncRNA associated with TNBC can provide new insights for early diagnosis and treatment—they can be targeted in the future as a novel anticancer target of TNBC.

Key words: Biomarker; Long non-coding RNA (lncRNA); MicroRNA; Regulation mechanism; Triple-negative breast cancer (TNBC)

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1 Introduction

The Human Genome Project has shown that coding genes only account for 1.5% of the human genome, the remainder being non-protein-coding sequences (Harrow et al., 2012). Most of these DNA sequences are transcribed into non-protein-coding RNAs, which account for the majority of all RNA transcripts (Mattick, 2011; St. Laurent et al., 2015). There are multiple types of non-coding RNA (ncRNA), all of which can be roughly divided into long non-coding RNAs (lncRNAs) and short non-coding RNAs (sncRNAs) according to their length. The latter consist of small interfering RNAs (siRNAs), small nucleolar RNAs (snoRNAs), microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), etc. (Taft et al., 2010; Boon et al., 2016). Initially, ncRNA was viewed as "dark matter" or "transcriptional noise" (Evans et al., 2016). However, with the development of RNA sequencing technology, the recognition and research of the role of ncRNA is becoming more prominent. It is thought to participate in different levels of gene expression, including chromatin architecture, epigenetic memory, transcription, RNA splicing, translation, and others (Mattick and Makunin, 2006; Atkinson et al., 2012; Chadwick and Scott, 2013). Today, research increasingly suggests that miRNA and lncRNA are associated with different types of cancer, such as gastric cancer, colorectal cancer, cervical cancer, ovarian cancer, prostate cancer, bladder cancer, breast cancer (BC), and other types of cancer (Huarte, 2015; Zhang R et al., 2016; Delás and Hannon, 2017).

BC is one of the most prevalent malignancies affecting women worldwide. The latest data from the American Cancer Society show that there were estimated 42 260 deaths attributable to BC, and 271 270

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new cases of BC in 2019, which comprise around 30 percent of all cancer diagnoses in women (Siegel et al., 2019). According to individual features, BC is categorized into five tumor subtypes (Sørlie, 2004). These are: estrogen receptor (ER)-positive (+) tumors; progesterone receptor (PR)-positive (+) tumors; and ER and PR-negative (−) tumors, which are composed of the "basal-like" subtype, the "normal-like" subtype, and the human epidermal growth factor receptor 2 (HER2)-enriched subtype (Amorim et al., 2016; Verma et al., 2019). Triple-negative breast cancer (TNBC) is categorized under the basal-like subtype, which is characterized by the lack of expression of both ER and PR, together with the absence of HER2 (Karagoz et al., 2015). TNBC accounts for 15% of all BCs and is usually correlated with increased metastasis, which leads to high mortality as well as poor prognosis (Mayer et al., 2014; Wang PS et al., 2018). Furthermore, TNBC has a weak response to HER2 antagonists and hormone therapy (Collignon et al., 2016). It has become a major remedial challenge and there are no effective targeted agents (Li HY et al., 2017; Khaled and Bidet, 2019). Thus, early detection biomarkers and feasible targeted therapy are especially important for TNBC patients.

2 Role of lncRNA in TNBC

LncRNAs are non-coding transcripts that are usually longer than 200 nucleotides (Paraskevopoulou and Hatzigeorgiou, 2016). LncRNAs can be classified according to the relative location to the protein-coding gene as follows: intergenic lncRNA, intronic lncRNA, sense lncRNA, antisense lncRNA, and bidirectional lncRNA (Smith and Mattick, 2017). Functionally, lncRNAs are involved in gene expression, subcellular transport, protein degradation, and organelle biogenesis (Mattick et al., 2009; Taft et al., 2010). LncRNAs regulate gene expression in different ways, including through epigenetic regulation, transcriptional regulation, post-transcriptional regulation, and translational regulation (Sun et al., 2017). Recent studies have found that aberrant expression of lncRNAs, including *AFAP1-AS1* (actin filament-associated protein 1 antisense RNA 1), *MALAT1* (metastasis associated lung adenocarcinoma transcript 1), *NRON* (non-coding repressor of the nuclear factor of activated T cells), and *RMST* (rhabdomyosarcoma 2-associated transcript), significantly regulates TNBC cell proliferation, migration, metastasis, and tumorigenicity (Yang et al., 2016b; Zuo et al., 2017; Wang L et al., 2018; Niu et al., 2019). In this section, we summarize the roles of lncRNA in TNBC progression from two distinct levels.

2.1 LncRNA-regulated gene expression at the transcriptional level

Previous studies have demonstrated that lncRNAs have various working mechanisms, such as those that work through DNA, RNA, and proteins (Prensner and Chinnaiyan, 2011). Recently, lncRNAs were reported to bind to defined DNA sequences to regulate gene expression at the transcriptional level (Wang PS et al., 2018). Using a database from The Cancer Genome Atlas (TCGA), it was discovered that lncRNA *MIR100HG* was over-expressed in TNBC but not in other cancers. High expression of lncRNA *MIR100HG* in TNBC patients was associated with poor prognosis. Knockdown of MIR100HG expression significantly decreased TNBC cell proliferation and impaired tumor growth. Nuclear cytoplasmic separation and quantitative polymerase chain reaction (qPCR) experiments demonstrated that *MIR100HG* was located mainly in the nucleus. In addition, they found an obvious change in *CDKN1B*, a cell cycle-related gene, between the *MIR100HG* knockdown and control groups. *CDKN1B*, which encodes the p27 protein, regulates cell cycle progression and acts as a tumor suppressor (Yoon et al., 2012; Zhao et al., 2015). Furthermore, experiments show that *MIR100HG* binds to *p27* gene locus to form RNA–DNA triplex structures, which subsequently regulate the expression of p27 (Wang SW et al., 2018). Hence, lncRNA *MIR100HG* influences cell proliferation in TNBC at the transcriptional level.

Luo et al. (2018) found that lncRNA *LINC01638* over-expression dramatically promotes breast cell proliferation in vitro and is associated with poor outcomes in TNBC patients. Furthermore, *LINC01638* interacts with c-MYC to prevent its degradation; c-MYC transcriptionally enhances metadherin (MTDH) expression by activating the MTDH promoter. Given that MTDH contributes widely to therapeutic resistance, tumor growth and metastasis, Liang et al. (2015) found that MTDH promotes breast tumorigenicity by

regulating TWIST1, ultimately inducing epithelial–mesenchymal transition (EMT) in TNBC. In addition, c-MYC is reported to combine with other lncRNAs. For example, earlier research has shown that c-MYC transcriptionally promotes *SNHG12* (snoRNA host gene 12) expression through direct interaction with its promoter region. What is more, the expression of *SNHG12* is significantly increased in TNBC, which correlates with tumor size and lymph node metastasis. Enforced expression of *SNHG12* promotes TNBC cell proliferation and migration (Wang et al., 2017).

2.2 LncRNA-regulated gene expression at the post-transcriptional level

Increasing evidence also shows that lncRNAs may regulate gene expression at the post-transcriptional level (Costa, 2005). As important cytoplasmic regulators, miRNAs act as post-transcriptional regulators of their messenger RNA (mRNA) targets via mRNA degradation (Catalanotto et al., 2016). Research increasingly suggests that, in TNBC, high expression of lncRNA can competitively combine with miRNA, acting as a sponge to suppress miRNA functions and promote cancer progression. For example, Wang LH et al. (2019) observed that lncRNA *HCP5* (human histocompatibility leukocyte antigen (HLA) complex P5) was up-regulated in TNBC cell lines and specimens. Using bioinformatic methods, they found that microRNA-219a-5p (miR-219a-5p) not only combines with 3' untranslated region (3' UTR) of *BIRC3* (baculoviral inhibitor of apoptosis (IAP) repeat containing 3) mRNA to inhibit its expression, but also complementarily binds to *HCP5*. Further, experiments demonstrated that *HCP5* functions as a competing endogenous RNA (ceRNA) to impair miR-219a-5p-dependent *BIRC3* down-regulation, suggesting that lncRNA *HCP5*, associated with TNBC cell apoptosis and proliferation, plays an important role in carcinogenesis. Further, Li et al. (2020) found that over-expression of lncRNA *XIST* (X-inactive specific transcript) interacts with miR-454, which inhibits cell proliferation and EMT, and induces apoptosis in TNBC. *MALAT1* was found to likely serve as a ceRNA to sponge miR-129-5p in TNBC cells (Zuo et al., 2017). Some studies have shown that there is no one-to-one match from lncRNA to miRNA. Zheng et al. (2019) showed that *MALAT1* regulates the expression of *BLCAP* (bladder cancer-associated protein) mRNA by binding to miR-339-5p in BC cells.

LncRNA also regulates protein stabilization at the post-transcriptional level to promote TNBC progression. Shen et al. (2019) demonstrated that the promoter of *LINC00152* contains binding sites for the transcriptional factor yin yang 1 (YY1). High YY1 expression decreases *LINC00152* transcriptional activity. Furthermore, up-regulated *LINC00152* in TNBC does not influence *PTEN* (phosphatase and tensin homologue) mRNA expression but can repress *PTEN* stability via promotion of NEDD4-1 (neural precursor cell expressed, developmentally down-regulated-4-1)-mediated ubiquitination, which in TNBC, involves cancer proliferation and metastasis. Similarly, lncRNA *ZEB1-AS1* (zinc finger E-box-binding homeobox 1 antisense 1) maintains *ZEB1* mRNA stability by binding with ELAVL1 (embryonic lethal, abnormal vision like 1). However, *ZEB1* can regulate the expression of *ZEB1-AS1* by combining with its promoter. That feedback loop can facilitate TNBC progression (Luo et al., 2020). In addition, research showed that lncRNA *MALAT1* binds to the TDP-43 (transactive response (TAR) DNA-binding protein 43), which is a predominantly nuclear protein, to regulate alternative splicing, transcription, and RNA stability (Winton et al., 2008). In summary, lncRNA significantly regulates gene expression both in the nucleus and in cytoplasm (Fig. 1).

2.3 LncRNA in TNBC diagnosis

Cancer is the leading cause of death in the world. There is growing evidence that early diagnosis holds the key towards effective treatment outcome. Thus, multiple studies have concentrated on exploring biomarkers for cancer detection and progression. Plentiful lncRNAs are aberrantly expressed in TNBC patients, suggesting the high diagnostic value of lncRNAs at present. For example, Liu M et al. (2017) found that lncRNAs *ANRIL* (antisense non-coding RNA in the inhibitor of cyclin-dependent kinase 4 (INK4) locus), *HIF1A-AS2* (hypoxia inducible factor 1 α-antisense RNA 2), and *UCA1* (urothelial cancer associated 1) were over-expressed in plasma of BC patient, and could potentially distinguish between TNBC and non-TNBC. They constructed a regression equation named TNBC SigLnc-3 based on these three lncRNAs, whose area under the curve (AUC) value

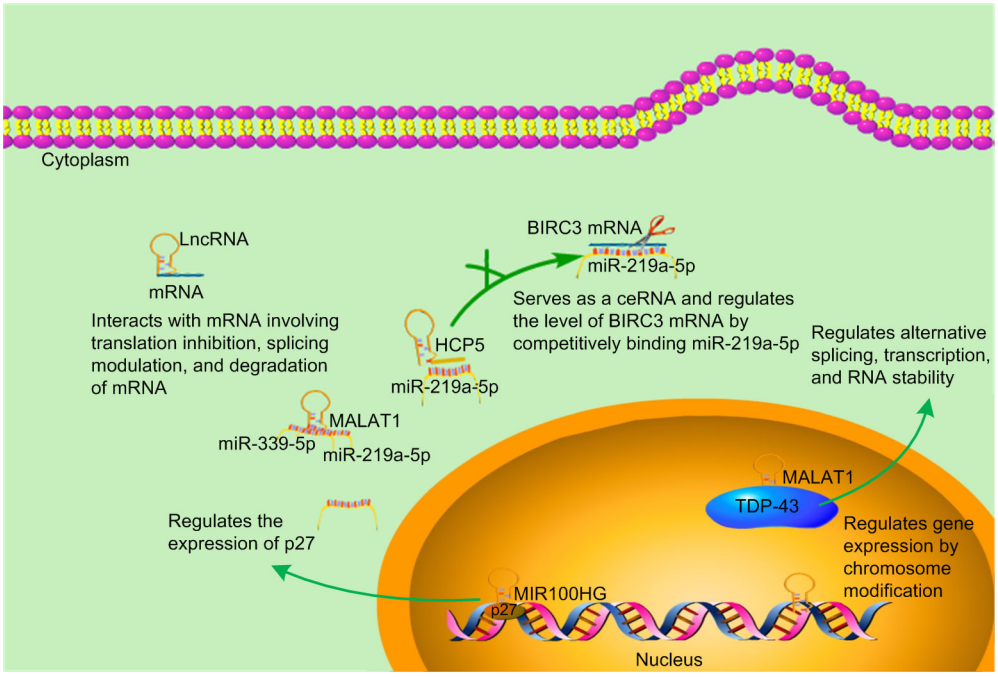

Fig. 1 LncRNA-regulated gene expression in both the nucleus and cytoplasm

LncRNA: long non-coding RNA; mRNA: messenger RNA; miR: microRNA; MALAT1: metastasis associated lung adenocarcinoma transcript 1; HCP5: human histocompatibility leukocyte antigen (HLA) complex P5; BIRC3: baculoviral inhibitor of apoptosis (IAP) repeat containing 3; TDP-43: transactive response (TAR) DNA-binding protein 43

was 0.934. It was superior to that of *ANRIL*, *HIF1A-AS2*, and *UCA1* alone. Compared with non-tumor tissues, Zhang KJ et al. (2016) found that *AFAP1-AS1* was clearly up-regulated in TNBC tissues. A series of cell experiments including methylthiazolyldiphenyl-tetrazolium bromide (MTT) assay showed that inhibiting the expression of AFAP1-AS1 could reduce cell migration and invasion in TNBC. Later, Zhang et al. (2018) provided mechanistic evidence that the expression of c-MYC and Wnt/β-catenin pathways is viral to promote tumorigenesis. Therefore, high expression of AFAP1-AS1 might have the potential as a novel biomarker of BC (Ma et al., 2019). Yang et al. (2019) found that lncRNA *POU3F3* (POU class 3 homeobox 3) was up-regulated more in tumor tissues than in adjacent healthy tissues of TNBC patients. LncRNA *POU3F3* over-expression promoted cell proliferation and inhibited cell apoptosis, and it may have diagnostic and prognostic values.

In contrast, lncRNAs *NRON*, *RMST*, and *PTCSC3* (papillary thyroid carcinoma susceptibility candidate 3) expression was down-regulated in TNBC. Previous studies demonstrated that lncRNA *NRON* maintained human immunodeficiency virus-1 (HIV-1) latency by inducing Tat (transactivator of transcription) protein degradation (Li J et al., 2016). Niu et al. (2019) found that lncRNA *NRON* inhibited cancer cell proliferation by down-regulating lncRNA *snaR* (small nuclear factor 90 (NF90)-associated RNA). As an alternatively spliced lncRNA gene, *RMST* was down-regulated in TNBC and low expression of RMST was associated with worse prognosis (Yang et al., 2016a). Wang N et al. (2019a) demonstrated that lncRNA *PTCSC3* inhibited TNBC cell proliferation by down-regulating lncRNA *H19*. Previous studies have shown that H19 was aberrantly up-regulated in BC tissues and cells and it promoted the proliferation and invasion (Zhang KJ et al., 2016; Li Z et al., 2017). Further analysis found that the lncRNA *H19* in 30 early-stage BC patients and 30 healthy controls revealed an AUC value of 0.81, with a sensitivity of 56.7% and specificity of 86.7% (Zhang KJ et al., 2016). These studies indicate that lncRNA severs as a novel diagnostic biomarker. However, large-scale clinical trials are needed to demonstrate that lncRNA can serve as a diagnostic biomarker for TNBC. Here, we divided lncRNAs in TNBC into two categories: oncogenic lncRNA and tumor suppressor lncRNA. Also, changes in lncRNA expression and its mechanism in TNBC are summarized in Tables 1 and 2.

Table 1 Ectopic expression of oncogenic lncRNAs in TNBC

LncRNA	Change	Biological function	Mechanism
RoR	Up	Promotes invasion, metastasis, and tumor growth in TNBC (Eades et al., 2015)	As a competitive endogenous RNA sponge, regulates lincRNA RoR/miR-145/ARF6 pathway
snaR	Up	Promotes proliferation, migration, and invasion in TNBC (MDA-MB-231) cells (Lee et al., 2016)	Unclear
MIAT	Up	Promotes proliferation, migration, invasion, and EMT in MDA-MB-231 cells (Luan et al., 2017)	As a competitive RNA sponge, regulates the expression of DUSP7 by combining miR-155-5p
HULC	Up	Promotes metastasis and malignancy of breast cancers (Wang N et al., 2019b)	As a competitive RNA sponge, regulates the expression of LYPD1 by combining miR-6754-5p
LINP1	Up	Enhances repair of DNA double-strand breaks; increases the sensitivity of tumor-cell response to radiotherapy (Zhang YY et al., 2016)	Serves as a scaffold linking Ku80 and DNA-PKcs, involved in EGFR signaling
ANRIL	Up	Promotes TNBC cell proliferation and tumor growth; promotes carcinogenesis; inhibits apoptosis (Xu et al., 2017)	Acts as a molecular "sponge" for miR-199a sponging; miR-199a targets ANRIL at 3' UTR
DANCR	Up	Promotes tumor growth, cell proliferation, and invasion in MDA-MB-231 cells; poor survival (Sha et al., 2017)	Associated with increased binding of EZH2 on the promoters of CD44 and ABCG2
LINK-A	Up	Promotes tumorigenesis in TNBC (Lin et al., 2016)	Active LINK-A-dependent signaling pathway
MALAT1	Up	Promotes cell proliferation, migration, and invasion in TNBC cells; poor survival (Zuo et al., 2017)	Target miR-129-5p
LUCAT1	Up	Accelerates cell proliferation, cell cycle progression, and metastasis; attenuates cell apoptosis (Mou and Wang, 2019)	Directly binds to miR-5702
HOTAIR	Up	Increases breast cancer cell invasion and migration; increases the rate of primary tumor growth (Gupta et al., 2010)	Reprograms chromatin state
MIR100HG	Up	Facilitates cell proliferation in TNBC; controls the cell cycle (Wang SW et al., 2018)	Participates in the formation of RNA–DNA triplex structures through *p27* locus
SNHG12	Up	Promotes TNBC cell proliferation and migration (Wang et al., 2017)	Regulates MMP13 expression
AFAP1-AS1	Up	Promotes cell proliferation, invasion, and tumor growth; inhibits cell apoptosis; poor prognosis (Zhang et al., 2018)	Activates Wnt/β-catenin pathway; increases the expression of c-MYC and EMT molecules
NEAT1	Up	Regulates apoptosis and cell cycle progression in TNBC cells (Shin et al., 2019)	Modulates chemoresistance and cancer stemness
Linc01638	Up	Promotes tumor proliferation and metastasis (Luo et al., 2018)	Activates MTDH-Twist1 signaling; prevents SPOP-mediated c-Myc degradation
Linc00339	Up	Promotes TNBC proliferation; inhibits cell cycle arrest; suppresses apoptosis (Wang XL et al., 2019)	Through miR-377-3p/HOXC6 signaling pathway
Linc00152	Up	Promotes tumor growth and cell invasion (Wu et al., 2018)	Inactivates the BRCA1/PTEN through DNA methyltransferases

LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; lincRNA: long intergenic ncRNA; RoR: regulator of reprogramming; ARF6: adenosine diphosphate (ADP)-ribosylation factor 6; DUSP7: dual specificity phosphatase 7; LYPD1: leukocyte antigen-6 (Ly6)/PLAUR domain-containing protein 1; DNA-PKcs: DNA-dependent protein kinase catalytic subunit; EGFR: epidermal growth factor receptor; ANRIL: antisense non-coding RNA in the inhibitor of cyclin-dependent kinase 4 (INK4) locus; UTR: untranslated region; EZH2: enhancer of zeste homolog 2; ABCG2: adenosine triphosphate (ATP)-binding cassette transporter G2; LINK-A: long intergenic non-coding RNA for kinase activation; EMT: epithelial–mesenchymal transition; MTDH: metadherin; SPOP: speckle-type POZ protein; HOXC6: homeobox C6; BRCA1: breast carcinoma susceptibility gene 1; PTEN: phosphatase and tensin homologue

3 Role of miRNA in TNBC

miRNAs are small ncRNAs that are generally 18 to 22 nucleotides in length. The vast majority of all human miRNAs are encoded in introns, exons, intro–exon junctions, or their own genes. The process of miRNA biogenesis is composed of several stages. First, miRNA is transcribed as primary miRNA

(pri-miRNA) via RNA polymerase II or III. Then it is cropped into a hairpin-shaped precursor miRNA (pre-miRNA), helped by Drosha and DGCR8. Next, pre-miRNA is exported to cytoplasm mediated by transporters and becomes mature miRNA (Shukla et al., 2011; Anfossi et al., 2018). Mature miRNA suppresses gene expression by guiding associated proteins to target sites in the 3' UTR of mRNAs (Gebert and MacRae, 2019). miRNAs could regulate various biological processes, such as proliferation, stress responses, cell adhesion, motility, inflammation, cell survival, senescence, and apoptosis, all of which are fundamental to tumorigenesis (Hata and Kashima, 2016). Increasing evidence suggests that the abnormal expression of miRNAs might be of clinical utility, especially in TNBC devoid of both predictive markers and potential therapeutic targets (Piasecka et al., 2018). To date, more than 3000 miRNAs associated with the occurrence and progress of tumors have been identified (miRbase database). Like lncRNAs, miRNAs can be divided into two categories: oncogenic miRNAs and suppressor miRNAs. Changes in miRNA expression and its role in TNBC are summarized in Tables 3 and 4.

3.1 miRNA involved in TNBC progression

3.1.1 EMT

In recent years, EMT, believed to be a major mechanism by which cancer cells become migratory and invasive, has received increasing attention (Tse and Kalluri, 2007). Research shows that miRNAs are involved in the process of EMT. Previous study identified miR-125b as down-regulated in TNBC cells, which is associated with poor prognosis and chemoresistance (Mathe et al., 2015). Functional in vitro studies have shown down-regulated expression of miR-125b in TNBC tissues as well as decreased cell

Table 2 Ectopic expression of antitumor lncRNAs in TNBC

LncRNA	Change	Biological function	Mechanism
GAS5	Down	Suppresses TNBC cell proliferation and invasion (Li SQ et al., 2018)	Competitively binds miR-196a-5p
NRON	Down	Suppresses cancer cell proliferation in TNBC (Niu et al., 2019)	Down-regulates lncRNA *snaR*
NEF	Down	Suppresses migration and invasion of TNBC cells (Song et al., 2019)	Negatively regulates the expression of miR-155
RMST	Down	Suppresses cell proliferation, invasion, and migration; enhances cell apoptosis in TNBC (Wang L et al., 2018)	Regulates the cell cycle and induces the block of the G0/G1 phase
DRHC	Down	Suppresses the proliferation of TNBC cell lines; correlates with tumor size (Yu et al., 2019)	Reduces expression of lncRNA *HOTAIR*
PTCSC3	Down	Suppresses TNBC cell proliferation (Wang H et al., 2019)	Reduces the expression of lncRNA *H19*
sONE	Down	Represses TNBC aggressiveness (Youness et al., 2019)	Induces the expression of miR-34a, miR-15a, miR-16, and let-7a
Aim	Down	Suppresses TNBC cell migration and invasion (Liu et al., 2017b)	Restrains Wnt/β-catenin/mTOR/PI3K signaling

LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; *snaR*: small nuclear factor 90 (NF90)-associated RNA; *HOTAIR*: Hox transcript antisense RNA; *sONE*: antisense mRNA transcript of endothelial nitric-oxide synthase (eNOS); mTOR: mammalian target of rapamycin; PI3K: phosphoinosmde-3-kinase

Table 3 Ectopic expression of oncogenic miRNAs in TNBC

miRNA	Change	Biological function	Mechanism
miR-21	Up	Promotes proliferation and invasion in TNBC cells (Fang et al., 2017)	Through targeting PTEN to regulate its expression
miR-25-3p	Up	Promotes TNBC cell proliferation in vitro and tumor growth in vivo (Chen H et al., 2018)	Activates the AKT and ERK-MAPK signaling pathways by inhibiting expression of BTG2
miR-93	Up	Promotes proliferation, invasion, and metastasis (Hu et al., 2015)	Unclear
miR-455-3p	Up	Enhances the abilities of cell proliferation, invasion, and migration in TNBC cell lines (Li ZS et al., 2017)	Targets tumor suppressor EI24 by binding to its 3' UTR

miRNA: microRNA; TNBC: triple-negative breast cancer; PTEN: phosphatase and tensin homologue; AKT: protein kinase B; ERK: extracellular signal-regulated kinase; MAPK: mitogen activated protein kinase; BTG2: B-cell translocation gene 2; UTR: untranslated region; EI24: etoposide-induced 2.4

Table 4 Ectopic expression of antitumor miRNAs in TNBC

miRNA	Change	Biologic function	Mechanism
miR-29c	Down	Inhibits proliferation and colony formation (Bhardwaj et al., 2017)	Through direct binding and regulation of TGIF2, CREB5, and AKT3
miR-30a-5p	Down	Suppresses the proliferation, migration, and invasion; modulates cell adhesion (Li WT et al., 2016)	Interrupts Erk/Ets-1 network by decreasing the expression of β3 integrin in TNBC
miR-34a	Down	inhibits proliferation and invasion; promotes sensitivity to dasatinib (Adams et al., 2016)	Targets the proto-oncogene c-SRC
miR-101	Down	Inhibits growth; induces apoptosis in vitro; suppresses tumorigenesis in vivo; increases paclitaxel sensitivity (Liu et al., 2015)	Through targeting MCL-1 to regulate its expression
miR-130a	Down	Suppresses migration and invasion in TNBC cells (Chen XW et al., 2018)	Directly targets *FOSL1* mRNA at its 3' UTR and increases ZO-1
miR-134	Down	Reduces cellular proliferation and enhances apoptosis induced by cisplatin (O'Brien et al., 2015)	Reduces STAT5B, Hsp90, and Bcl-2 levels
miR-200a/b/c	Down	Inhibits migration and proliferation in TNBC cells (Tsouko et al., 2015); inhibits EMT (Rhodes et al., 2015); induces cell apoptosis (Ren et al., 2014)	Regulates the oncogene EPHA2 by target its 3' UTR; regulates expression of genes associated with EMT including ZEB1/2, TWIST, and CDH1; targets XIAP and activates caspase-3
miR-203	Down	Inhibits cell proliferation and migration (Wang et al., 2012)	Targets the 3' UTR of BIRC5 and LASP
miR-206	Down	Decreases proliferation, migration, and invasion (Wang et al., 2014)	Induces G1-S cell cycle arrest and represses *CORO1C* mRNA and protein levels
miR-211	Down	Suppresses cell growth, cell cycle, migration, and invasion (Song and Zhao, 2015)	Targets the 3' UTR sequence of CDC25B
miR-223	Down	Increases the sensitivity of TRAIL-induced apoptosis in TNBC stem cells (Sun et al., 2016)	Targets anti-apoptotic protein HAX-1
miR-296-5p	Down	Suppresses cell growth, migration, and invasion; impairs paclitaxel-induced apoptosis (Onyeagucha et al., 2016)	Decreases the expression of BOK
miR-342-3p	Down	Decreases cell proliferation, viability, and migration (Romero-Cordoba et al., 2016)	Promotes lactate efflux changes by repressing MCT1 expression in the tumor cells
miR-361-5p	Down	Inhibits migration and invasion in TNBC cells (Han JJ et al., 2018)	Targets RQCD1 to inhibit the EGFR/PI3K/Akt signaling pathway
miR-378	Down	Suppresses migration and invasion in TNBC cells; alleviates the aggressive phenotype of TNBC cells (Browne et al., 2016)	Targets the 3' UTR of Runx1 and inhibits its expression
miR-384	Down	Inhibits the proliferation and migration of MDA-MB-231 cells in vitro and in vivo (Wang YX et al., 2018)	Negatively regulates the Wnt/β-catenin signaling pathway by targeting ACVR1
miR-490-3p	Down	Inhibits cell growth and invasion in TNBC cells; impairs tumorigenesis of TNBC cells in nude mice (Jia et al., 2016)	Regulates the expression of TNKS2 by binding to its 3' UTR; blocks β-catenin signaling
miR-603	Down	Inhibits cell proliferation, survival, invasion, and tumorigenesis (Bayraktar et al., 2017)	Targets the 3' UTR region of eEF2K
miR-613	Down	Inhibits cell migration and invasion of TNBC cells (Xiong et al., 2018)	Targets the Daam1/Rho A signaling pathway
miR-1296	Down	Suppresses cell proliferation of TNBC cell lines (Phan et al., 2016)	Regulates the expression of CCND1 by binding to its 3' UTR
miR-4306	Down	Suppresses cell proliferation, migration, and invasion; inhibits tumor growth, lung metastasis, angiogenesis, and lymph node metastasis (Zhao et al., 2019)	Targets SIX1/Cdc42/VEGFA to inactivate related signaling pathways

miRNA: microRNA; TNBC: triple-negative breast cancer; TGIF2: transforming growth factor-β (TGFB)-induced factor homeobox 2; CREB5: cyclic adenosine monophosphate (cAMP)-responsive element-binding protein 5; AKT3: v-akt murine thymoma viral oncogene homolog 3, protein kinase B γ; Erk: extracellular signal-regulated kinase; Ets-1: E26 transformation-specific sequence-1; MCL-1: myeloid cell leukemia 1; *FOSL1*: FOS-like antigen-1; UTR: untranslated region; ZO-1: tight junction protein; STAT5B: signal transducer and activator of transcription 5B gene; Hsp90: heat shock protein 90; Bcl-2: B-cell lymphoma 2; EMT: epithelial–mesenchymal transition; EPHA2: ephrin type-A receptor 2; ZEB1/2: zinc finger E-box-binding homeobox 1/2; CDH1: E-cadherin gene; XIAP: X-linked inhibitor of apoptosis protein; BIRC5: baculoviral IAP repeat-containing protein 5; LASP: Lim and SH3 domain protein; CORO1C: actin-binding protein coronin 1C; CDC25B: cell division cycle 25 phosphatases; TRAIL: tumor necrosis factor-related apoptosis inducing ligand; HAX-1: hematopoietic cell-specific protein-associated protein X 1; BOK: BCL2-related ovarian killer; MCT1: monocarboxylate transporter 1; RQCD1: required for cell differentiation 1 homolog; EGFR: epidermal growth factor receptor; PI3K: phosphoinositide 3-kinase; Runx1: Runt-related transcription factor 1; ACVR1: activin A receptor type 1; TNKS2: tankyrases 2; eEF2K: eukaryotic elongation factor 2 kinase; Daam1: disheveled-associated activator of morphogenesis-1; CCND1: cyclin D1; SIX1: Sine oculis homeobox 1; Cdc42: cell division control protein 42 homolog; VEGFA: vascular endothelial growth factor A

migration and invasion. Hong et al. (2016) found that mitogen-activated protein (MAP) kinase kinase 7 (MAP2K7) was a novel target of miR-125b and that its knockdown could inhibit EMT of TNBC cell (Hs578T). Data from TCGA show that miR-20a is up-regulated in human BC, especially in the triple-negative subtype. Liu et al. (2017a) demonstrated that miR-20a could promote tumor initiation and growth, showing the oncogenic function of miRNA during breast tumorigenesis. E-cadherin (CDH1) promotes the formation of adherens junctions and the establishment of the polarized cell monolayer, the loss of which is a fundamental event in EMT (Reshetnikova et al., 2007; Piasecka et al., 2018). The connection between miR-20a and EMT was reported by De et al. (2017), who found that in TNBC cells (MDA-MB-231) hsa-miR-20a could control downstream crucial markers such as CDH1, N-cadherin, and fibronectin, by regulating the expression of *Twist-1* mRNA. Furthermore, reporter assays established that miR-20a could abrogate transforming growth factor-β (TGF-β) by silencing the expression of TGF-β receptor 2 (TGFBR2), resulting in the inhibition of MET (De et al., 2017). miRNA-145 was reported to regulate tumor cell invasion in TNBC via targeting of adenosine diphosphate (ADP)-ribosylation factor 6 (ARF6). As a known regulator of cell invasion, ARF6 can change CDH1 localization and affect cell–cell adhesion (Eades and Zhou, 2014). Alongside some other miRNAs, such as miR-655, it has been approved for suppressing EMT by targeting Prrx1 (paired-related homeobox 1) in TNBC (Lv et al., 2016).

3.1.2 Migration, invasion, and metastasis

A series of studies have indicated that miRNAs are associated with cell migration, invasion, and metastasis in TNBC. For example, miR-21, functioning as an oncogene, was elevated in BC patients compared with healthy controls. Liu et al. (2019) found that miR-21 and lncRNA *AWPPH* (associated with poor prognosis of hepatocellular carcinoma) could up-regulate each other in TNBC cells. It was demonstrated that the over-expression of lncRNA *AWPPH* and miR-21 promotes cancer cell proliferation (Liu et al., 2019), and further, that miR-21 combined with the 3' UTR of LZTFL1 (leucine zipper transcription factor-like 1) and the miR-21/LZTFL1 axis promotes cell proliferation and metastasis (Wang H et al., 2019). Fang et al. (2017) showed that inhibition of miR-21 expression could decrease the proliferation, viability, and invasiveness of the TNBC cell line (MDA-MB-468) and enhance apoptosis (Fang et al., 2017). These results indicate that miR-21 may be a novel promising biomarker for TNBC diagnosis and prognosis. In addition, it was found that over-expression of miR-20a-5p could promote the migration and invasion of TNBC cells in vitro by significantly targeting RUNX3 as well as p21 (Bai et al., 2018). This suggests that miR-20a-5p has potential clinical applications.

Suppressor miRNAs play important roles in TNBC as well. miR-199a-5p was under-expressed in plasma of TNBC patients when compared with healthy controls; and cell proliferation could be reduced by transfecting miR-199a-5p mimic into breast cells (Shin et al., 2014). Chen et al. (2016) found the tumor-suppressive role of miR-199a-5p in TNBC via multiple experiments. Over-expression of miR-199a-5p inhibited cell proliferation, invasion, and migration ability, which attributed to EMT, by altering EMT-related gene expression, such as *CDH1* and *ZEB1* (Chen et al., 2016). miR-200b, one member of the miR-200 family, was significantly down-regulated in TNBC cells and tissues compared with other types of BC. Yang et al. (2017) demonstrated that miR-200b suppressed TNBC metastasis by targeting ARHGAP18 (Rho GTPase-activating protein 18) and enhancing Rho A activation.

3.2 miRNA in TNBC diagnosis

In recent years, the number of cancer patients has increased rapidly. Thus, early detection or screening methods are very important to enable tumor diagnosis. Multiple studies are focused on exploring biomarkers for BC detection and progression. Many miRNAs are aberrantly expressed in TNBC patients and tissues; for example, miR-20a, miR-25, miR-21, and miR-96 are up-expressed in BC patients (Fang et al., 2017; Chen H et al., 2018; Razaviyan et al., 2018; Kolesnikov et al., 2019), while other miRNAs are down-expressed in BC cells, such as miR-205 and miR-29c (Zhang et al., 2015; Bhardwaj et al., 2017). Razaviyan et al. (2018) found that miR-96 was up-expressed in MDA-MB-231 cell and TNBC clinical samples at the best cut-off point of 0.18. miR-96-5p has a receiver operating characteristic (ROC) AUC of 0.83, a sensitivity of 80%, and a specificity of 75% (Razaviyan

et al., 2018). Previous research has shown that miR-96 can reduce BC cell migration and invasion by decreasing the Palladin protein. Thus, it indicates a tumor-suppressive role of miR-96 and a potential anti-metastatic drug (Gilam et al., 2016). Zhang et al. (2015) found that miR-205 was under-expressed in 58 cases of BC patient sera compared with 93 controls with an AUC, sensitivity, and specificity of 0.87, 86.2%, and 82.8%, respectively. Their study determined that miR-205 has high clinical diagnostic value in the detection of BC. In addition, miR-20a was regarded as a biomarker for TNBC compared with luminal subtypes of BC; its AUC value was 0.949 via ROC analysis. The high expression of miR-20a in TNBC cells supports the characteristic of TNBC as the most aggressive subtype of BC (Kolesnikov et al., 2019).

4 Roles of miRNA and lncRNA in neoadjuvant chemotherapy

As a subtype of BC, TNBC has different characteristics than other subtypes of BC, such as a younger age incidence and being lymph node negative. It also has a high recurrence rate and invades easily (Lehmann et al., 2011; Zhao et al., 2017). However, due to the lack of estrogen, progesterone, or HER2 receptors, neither endocrine therapy nor conventional targeted therapy is the most effective treatment. At present, the primary treatments for TNBC patients include chemotherapy, surgery, and radiotherapy. Studies have shown that preoperative neoadjuvant chemotherapy in TNBC patients has a more prominent pathological complete response (PCR) rate compared with other subtypes of BC (Liedtke et al., 2008; Gülben et al., 2014; Biswas et al., 2017). Chemotherapy is an important treatment option for cancer, yet it also has drawbacks, such as drug resistance. It is because of drug resistance that tumor cells lose sensitivity to chemotherapy—one of main causes of chemotherapy failure. Recent studies have found that miRNA and lncRNA not only play important roles in the initiation and progression of human tumors but also are involved in drug resistance in malignant tumors (Deng et al., 2016; Fu et al., 2019).

LncRNA *UCA1*, located on the human chromosome 19p13.12-positive strand, is the most abundant subtype in various malignant tumors, such as bladder cancer and BC (Wang et al., 2006; Huang et al., 2014). Liu et al. (2016) showed that knockdown of lncRNA *UCA1* can increase the tamoxifen sensitivity of MCF-7 and T47D cells through inhibition of the Wnt/β-catenin pathway. Moreover, Wu and Luo (2016) found that lncRNA *UCA1* increases tamoxifen resistance in BC cells by inhibiting the mammalian target of rapamycin (mTOR) signaling pathway. Furthermore, miR-18a significantly modulates tamoxifen resistance by regulating cell cycle proteins. Li XN et al. (2016) found that the miR-18a inhibitor reduced the sensitivity of MCF-7 cells to tamoxifen, while miR-18a mimics sensitized BT474 cells to tamoxifen. Researchers have found that, acting as a molecular sponge for miR-222, over-expression of lncRNA *GAS5* (growth arrest-specific transcript 5) enhanced cell sensitivity to tamoxifen in MCF-7R cells, which suppresses phosphatase and tensin homologs (Gu et al., 2018). Expression levels of lncRNA *H19* have shown an obvious increase in most BC patients and have been reported to increase BC chemotherapeutic resistance. Han JG et al. (2018) investigated the expression level of lncRNA *H19* in paclitaxel-resistant and paclitaxel-sensitive cell lines. They found that the level of lncRNA *H19* expression was higher in paclitaxel-resistant cells. Moreover, knockdown of *H19* suppressed the Akt (protein kinase B) signaling pathway, which is associated with paclitaxel-resistance, to trigger apoptosis. Thus, they theorized that *H19* might restore drug resistance in paclitaxel-resistant TNBC by regulating the Akt signaling pathway. In recent years, researchers have found that knockdown of lncRNA *HOTAIR* (Hox transcript antisense RNA) could reduce drug-resistance via phosphoinosmde-3-kinase (PI3K)/Akt/mTOR signaling pathways (Li ZX et al., 2019).

With increasing attention paid to drug resistance, more lncRNAs are being reported to play vital roles in drug resistance in various cancers. In addition to the above lncRNAs, Chen et al. (2017) identified difficult lncRNAs associated with drug resistance in cancer, including *PVT1* (plasmacytoma variant translocation 1), *ANRIL*, *MRUL* (multidrug resistance (MDR)-related and upregulated lncRNA), and *CCAL* (colorectal cancer-associated lncRNA). At present, studies on cancer drug resistance related to lncRNAs and miRNAs are still in their infancy, and the role of ncRNA in chemotherapy resistance demands further investigation.

5 Clinical significance of miRNA and lncRNA in BC

BC is the third highest incident cancer worldwide and the second most common cause of death from cancer in women. The burden of BC is an important challenge for women's health throughout the world (Ferlay et al., 2010; Hiatt and Brody, 2018). Li N et al. (2019) described and studied the impact of geographical location, the social development index (SDI), age, and gender in BC events, death, and disability-adjusted life years (DALYs). Disease reduction has been observed in higher SDI regions and the gap between lower and higher SDI regions may become wider. Action is needed to address the BC burden to reduce disease in low SDI regions.

miRNAs and lncRNAs have great potential as effective biomarkers because of their high stability and efficient detection in body fluids (Kunej et al., 2014; Matamala et al., 2015). Numerous recent studies have shown that the expression levels of lncRNAs and miRNAs were associated with clinicopathological features. For example, Chen et al. (2012) found that high miR-155 expression showed significant correlation with higher tumor grade, advanced tumor stage, and lymph node metastasis, but no relation with age, tumor size, tumor histology, the status of ER, or PR and HER2 expression. Wang and Zhang (2012) found that the relative expression of miR-21 had no connection with gender, age, ER, PR, and KI-67 status. Using TCGA, researchers found that over-expressed miRNA-18a, miRNA-205, and miRNA-744 in breast tumor samples were all connected with better overall survival in ER/PR-positive and lymph node-negative diseases (Kim et al., 2017). High MALAT1 expression in BC tissue was significantly correlated with lymph metastasis, tumor size, and adverse 5-year disease-free survival (Miao et al., 2016; Li J et al., 2018). Tian et al. (2018) identified 48 lncRNAs correlated with clinicopathological features (including tumor size, lymph node metastasis, histological grade, tumor-node-metastasis (TNM) stage, and ER, PR, and HER-2 statuses of BC), and 32 lncRNAs involved in the survival of BC. They found that the increased levels of MALAT1 and TUSC7 (tumor suppressor candidate 7) expression were respectively connected with positive PR and positive HER-2 statuses. Moreover, high expression of CCAT2 (colon cancer-associated transcript 2), MALAT1, or NEAT1 (nuclear paraspeckle assembly transcript 1) had shorter overall survival (Tian et al., 2018). Certainly, the relationship between miRNAs or lncRNAs and clinical characteristics should be explored through further research with large sample sizes. The utilization of miRNAs and lncRNAs as biomarkers of BC has the potential to change present therapies.

6 Conclusions and prospect

In this study, we discussed the role of miRNA and lncRNA in TNBC progression and summarized lncRNAs and miRNAs which are abnormally expressed in TNBC. Previous studies have demonstrated that many miRNAs and some lncRNAs are involved in the occurrence and developmental progress of breast malignant tumors. This informs our reflections on the significance of the combination of lncRNAs and miRNAs in treating various cancers, including TNBC. It is well known that most miRNAs are able to function by binding to the 3' UTR of the mRNA to regulate target gene expression. However, new research has shown that miRNAs can also influence gene expression by attaching to the open reading frame (ORF) region of target genes. This raises important questions as to whether miRNAs and other ncRNAs regulate gene expression through other binding sites. As for cancer drug resistance, owing to the complexity of mechanisms caused by various factors, the research is still preliminary. More is required to identify unidentified lncRNAs related to BC and to elucidate corresponding function and molecular mechanisms. Furthermore, looking for highly specific and sensitive lncRNAs and miRNAs will provide new opportunities for the early diagnosis, clinical treatment, and prognosis monitoring of BC.

Contributors

Juan XU performed the preliminary framework of the article and wrote the manuscript. Kang-jing WU performed the analysis of data. Qiao-jun JIA and Xian-feng DING designed the article and edited the manuscript. All authors have read and approved the final manuscript and, therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Juan XU, Kang-jing WU, Qiao-jun JIA, and Xian-feng DING declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：miRNA 和 lncRNA 在三阴性乳腺癌中的作用

概　要：三阴性乳腺癌（TNBC）作为乳腺癌中最恶性的亚型，具有异质性高、增殖能力高、转移性强等特点，且缺乏有效的靶向治疗，因而其发病机制成为研究的重点。越来越多的研究表明，小 RNA（miRNA）和长链非编码 RNA（lncRNA）在内的非编码 RNA 在肿瘤的发生和发展中起着重要的作用。本文总结归纳了近些年来与 TNBC 相关的 miRNA 和 lncRNA，介绍了 lncRNA 调节基因表达的多种机制，概述了 miRNA 和 lncRNA 在 TNBC 进展、诊断以及新辅助化疗中的作用。本文探索 miRNA 和 lncRNA 与 TNBC 的关系，旨在为癌症的早期诊断和治疗提供新思路，使其成为治疗癌症的新靶点。

关键词：生物标志物；长链非编码 RNA（lncRNA）；小 RNA（miRNA）；调节机制；三阴性乳腺癌（TNBC）