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Review

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Roles of lncRNA in the diagnosis and prognosis of triple-negative breast cancer

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Abstract: Breast cancer is a malignant tumor that seriously endangers women's lives. The prognosis of breast cancer patients differs among molecular types. Compared with other subtypes, triple-negative breast cancer (TNBC) has been a research hotspot in recent years because of its high degree of malignancy, strong invasiveness, rapid progression, easy of recurrence, distant metastasis, poor prognosis, and high mortality. Many studies have found that long non-coding RNA (lncRNA) plays an important role in the occurrence, proliferation, migration, recurrence, chemotherapy resistance, and other characteristics of TNBC. Some lncRNAs are expected to become biomarkers in the diagnosis and prognosis of TNBC, and even new targets for its treatment. Based on a PubMed literature search, this review summarizes the progress in research on lncRNAs in TNBC and discusses their roles in TNBC diagnosis, prognosis, and chemotherapy with the hope of providing help for future research.

Key words: Triple-negative breast cancer (TNBC); Long non-coding RNA (lncRNA); Diagnosis; Prognosis; Chemotherapy resistance

1 Introduction

The latest data for 2020 released by the World Health Organization (WHO)'s International Agency for Research on Cancer (IARC) show that breast cancer has officially replaced lung cancer as the cancer with the highest morbidity rate worldwide. Breast cancer is a serious health risk for women as it affects one in eight newly diagnosed cancer patients. In addition, as women age, the incidence and mortality rate of breast cancer increase (Chen et al., 2017; Zaheer et al., 2019). Breast cancer is now the most prevalent cancer among women in China (Cao et al., 2021).

Breast cancer can usually be classified according to the expression levels of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her-2/neu), and Ki-67 (Prat et al., 2015; Santamaría et al., 2019). Breast cancer lacking ER, PR, and Her-2 is a highly invasive clinical subtype called triple-negative breast cancer (TNBC) (Carey et al., 2010; Borri and Granaglia, 2021). TNBC accounts for 10%–25% of breast cancers and tends to have a higher incidence among young people than other cancers (Shen et al., 2015; Kumar and Aggarwal, 2016). At present, the main treatment strategies for TNBC are chemotherapy, surgery, and radiotherapy (Abramson et al., 2015). Although relevant studies have confirmed that TNBC patients can achieve a high pathological complete response after chemotherapy, the lack of therapeutic targets for Her-2 and hormone receptors combined with the high heterogeneity of this tumor type makes TNBC more aggressive, with earlier recurrence and distant metastases (Manjunath and Choudhary, 2021).

To treat TNBC patients more accurately and efficiently, previous studies analyzed the gene expression profile of tumor samples from 587 TNBC patients and found that TNBC can be divided into six subtypes: basal-like subtype 1 (BL1), BL2, mesenchymal (M), mesenchymal stem cell-like (MSL), immunomodulatory

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(IM), and luminal androgen receptor (LAR) subtypes (Lehmann et al., 2011; Vtorushin et al., 2022). Furthermore, Zhao et al. (2020) developed a set of Fudan typing standards for TNBC, which divided TNBC into a basal-like immunosuppressive subtype (BLIS), IM, LAR, and mesenchymal-like subtype (MES). In the meantime, investigators invented a set of immunohistochemistry (IHC)-based classifiers, providing a simpler and more economical typing method that can benefit more TNBC patients. A more precise classification of the disease would allow patients to benefit more from individualized treatment.

Protein-coding genes account for about 2% of the human genome sequence, and the rest are non-coding sequences (Djebali et al., 2012). Non-coding sequences were originally considered "dark matter" or "garbage." However, increasing evidence shows that non-coding RNA (ncRNA) plays an important role in the process of metabolism and development, and can participate in the regulation of gene expression, including transcriptional, post-transcriptional, translational, and epigenetic regulation (Kumar et al., 2013). Moreover, it plays a key role in the regulation of cancer's biological characteristics. Long non-coding RNA (lncRNA) is a ncRNA that consists of at least 200 nucleotides (nt) but lacks the function of encoding protein (Liu et al., 2017). An abnormal expression level of lncRNA is related to various malignant biological processes, including tumorigenesis, proliferation, angiogenesis, epithelial-mesenchymal transition (EMT), and distant metastasis (Fu PF et al., 2019). In recent years, many studies have found significant differences in the expression level of lncRNA in the tumors and blood of TNBC patients compared to normal controls (Xu et al., 2020; Qu et al., 2022). Therefore, it is inferred that lncRNA can be used as a diagnostic or prognostic marker for TNBC patients. In this paper, we summarize recent lncRNA research related to the diagnosis and prognosis of TNBC, and analyze the prospects and feasibility for its application in this field.

2 LncRNAs with diagnostic and prognostic functions

2.1 LncRNAs with diagnostic functions for TNBC

Early diagnosis of TNBC is the key to effective treatment. At present, the diagnosis of TNBC relies mainly on the IHC results of the patient's tumor tissue, and sometimes requires additional testing with fluorescence in situ hybridization (FISH) for those with Her-2 low expression, which is time-consuming and costly. However, with the rapid development of gene sequencing technology, the detection of ncRNA has become easier and more economical. Many studies have found abnormal expression of lncRNA in TNBC tissues, suggesting that lncRNA could be useful as a marker for the diagnosis of TNBC. For example, Swellam et al. (2021) examined the expression of lncRNAs X inactive-specific transcript (*XIST*) and nuclear paraspeckle assembly transcript 1 (*NEAT1*) in serum samples from breast cancer patients, benign breast lesion patients, and healthy volunteers by quantitative real-time polymerase chain reaction (qRT-PCR). They found that the expression levels of *XIST* and *NEAT1* were significantly higher in the breast cancer group than in the other two groups. The expression levels were higher in TNBC, which could be used to distinguish TNBC from other breast cancer types. In addition, Liu et al. (2017) performed microarray analysis of plasma from 25 TNBC patients and 35 non-TNBC (NTNBC) patients and found that the expression levels of the lncRNAs antisense ncRNA in the INK4 locus (*ANRIL*), hypoxia-inducible factor 1α-antisense RNA-2 (*HIF1A-AS2*), and urothelial carcinoma-associated 1 (*UCA1*) were significantly higher in the plasma of TNBC patients than in that of the NTNBC group. The result was verified in tumor tissues, suggesting that these three genes can be used to distinguish TNBC from NTNBC. The researchers further developed a TNBC SigLnc-3 regression equation based on the above three genes, which showed excellent diagnostic performance in a validation set with an area under the curve (AUC) of 0.934, which was superior to the diagnostic effects of *ANRIL*, *HIF1A-AS2*, and *UCA1* alone. However, not all lncRNAs are overexpressed in TNBC tissues. For instance, lncRNA ZNFX1 antisense RNA 1 (*ZFAS1*) is significantly underexpressed in the blood of TNBC patients, at about 1/3 of the blood level of a normal group, and the decreased expression can be used to diagnose TNBC (Sharma et al., 2021) (Table 1).

2.2 LncRNAs to predict the prognosis of TNBC

TNBC is the worst pathological type of breast cancer with higher invasiveness, recurrence, and distant

Table 1 LncRNAs related to the diagnosis of TNBC

LncRNA	Change	Source	Number of patients	Population study	Method	Reference
XIST, *NEAT1*	Up	Serum	178	TNBC and HC	qRT-PCR	Swellam et al., 2021
ANRIL, *HIF1A-AS2*, *UCA1*	Up	Plasma, tumor	60	TNBC and NTNBC	MA and PCR	Liu et al., 2017
ZFAS1	Down	Blood	80	TNBC and HC	qRT-PCR	Sharma et al., 2021

LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; *XIST*: X inactive-specific transcript; *NEAT1*: nuclear paraspeckle assembly transcript 1; *ANRIL*: antisense non-coding RNA in the INK4 locus; *HIF1A-AS2*: hypoxia-inducible factor 1α-antisense RNA-2; *UCA1*: urothelial carcinoma-associated 1; *ZFAS1*: ZNFX1 antisense RNA 1; HC: healthy control; NTNBC: non-TNBC; PCR: polymerase chain reaction; qRT-PCR: quantitative real-time PCR; MA: microarray analysis.

metastasis rates. It can be divided into different subtypes with different prognoses. If the prognosis of the disease can be understood at an early stage, patients can be treated better and their prognosis can be improved.

He et al. (2023) analyzed the relationship between the expression of lncRNA *T376626* in the serum of 282 breast cancer patients and the overall survival (OS) rate by the Kaplan-Meier (K-M) method. They found that in breast cancer and TNBC patients, a higher level of *T376626* was positively correlated with a higher stage of pathological differentiation, more aggressive molecular subtypes, and poorer prognosis. Moreover, by comparing the levels of serum extracellular vesicle lncRNA *XIST* between TNBC patients (n=91) and a healthy control group (n=50), they found that the expression level was significantly higher in the TNBC group than in the control group, and was significantly increased in TNBC recurrent patients. After tumor resection, the serum *XIST* content decreased. Results from the survival analysis showed that the higher the serum *XIST* content, the worse the patient's prognosis, indicating that *XIST* can be used as a prognostic indicator for TNBC patients (Lan et al., 2021). The blood contains tumor markers that may be produced by the death of tumor cells or by autocrine production of tumor cells. It is less invasive and more convenient to diagnose patients through blood biopsy.

In addition to blood, the level of gene expression can be measured in tumor tissue to reflect a patient's prognosis. For example, by analyzing 1085 TNBC tumor samples and 291 matched normal control samples from The Cancer Genome Atlas (TCGA) database, Sharma et al. (2021) found that the OS of breast cancer patients with a low expression of lncRNA *ZFAS1* was lower than that of a high expression group, and the expression of *ZFAS1* was positively correlated with the prognosis. Similarly, Kaushik et al. (2021) found 353 lncRNAs significantly different between shorter and longer OS groups by searching the The Atlas of Non-coding RNA in Cancer (TANRIC) database (OS was cut off at three years). Furthermore, using recursive feature elimination analysis, they found that lncRNAs long intergenic ncRNA for kinase activation (*LINK-A*) *LINC01139* and breast cancer antiestrogen resistance 4 (*BCAR4*) had high values in predicting a patient's prognosis. Moreover, Zhang KM et al. (2018) analyzed the relationship between the expression of actin filament-associated protein 1-antisense RNA 1 (*AFAP1-AS1*) and prognosis in 238 TNBC patients. The results showed that patients with high expression of *AFAP1-AS1* (n=132) had poorer disease-free survival (DFS) and OS compared to the low expression group (n=106). Their further analysis found that *AFAP1-AS1* can activate the Wnt/β-catenin pathway, increasing the expression of *C-myc* and EMT-related molecules to promote tumor cell proliferation and invasion and inhibit cell apoptosis, leading to poor prognosis. *LINK-A* was also found to be associated with TNBC in several studies. For example, Lin et al. (2016) showed that the expression of *LINK-A* under normoxic conditions can promote the reprogramming of breast cancer glycolysis and tumorigenesis by activating hypoxia-inducible factor-1α (*HIF-1α*) signaling. TNBC patients with high *LINK-A* expression had lower recurrence-free survival (RFS) than a low expression group (n=123). HIF-1α can accumulate under normoxic conditions, promoting angiogenesis and cancer progression (Kuschel et al., 2012). It has also been shown that HIF is involved in the progression, recurrence, and metabolic reprogramming of TNBC (Semenza, 2003; Wong et al., 2011). LncRNA differentiation antagonizing non-protein coding RNA (*DANCR*) can promote the proliferation and invasion of TNBC cells by reducing the expression level of the microRNA-216a-5p (*miR-216a-5p*) gene. Tao et al. (2019) divided 57 TNBC patients into a high *DANCR* expression group (n=25) and a low *DANCR* expression group (n=32), and the results of analysis showed that the OS of the low expression group was significantly higher than that of the high expression group.

Compared to normal tissues, lncRNAs *LINC01270*, *LINC00449*, and highly upregulated in metastatic TNBC (*HUMT*) were also all highly expressed in TNBC tumor tissues, and the expression levels were positively correlated with prognostic levels (Zheng SQ et al., 2020; Ping et al., 2021) (Table 2).

3 LncRNAs that promote the progression of TNBC

In recent years, numerous studies have pointed out that lncRNA is involved in the formation and progression of breast cancer, especially TNBC, which is more heterogeneous. The progression of TNBC is closely related to the biological processes of tumor cell proliferation, invasion, migration, and blood vessel formation. By detecting lncRNA in patients' tumor tissues or blood, we can judge the malignancy of tumors at an early stage, make relevant interventions, and improve prognoses.

3.1 LncRNAs that promote proliferation and invasion of TNBC cells

LncRNA lung cancer-associated transcript 1 (*LUCAT1*) plays an important role in the development of TNBC, and its expression level is positively correlated with the prognosis level of TNBC patients. Mou and Wang (2019) first discovered that *LUCAT1* can bind to *miR-5702* and promote the proliferation and migration of TNBC cells. Furthermore, they found that silencing its expression could inhibit the proliferation of TNBC cells and promote apoptosis. LncRNA WEE2-antisense RNA 1 (*WEE2-AS1*) also plays an instrumental role in the progression of TNBC. An investigation of the mechanism of action of *WEE2-AS1* in TNBC by Wang et al. (2020) found that the proliferation and invasion abilities of TNBC cells were inhibited after silencing the highly expressed *WEE2-AS1*. Moreover, through functional assays, they found that *WEE2-AS1* can combine with *miR-32-5p* and deregulate the repression of transducer of ERBB2.1 (*TOB1*) by *miR-32-5p*, leading to upregulation of *TOB1* expression and promotion of the proliferation, invasion, and migration of TNBC cells. LncRNA *LINC00173* plays a critical role in chemotherapy resistance among small cell lung cancers. In recent years, relevant studies have shown that *LINC00173* is also involved in the occurrence and development of TNBC cells. In in vitro studies, Fan et al. (2020) found that TNBC cells with high expression of the *LINC00173* gene had stronger proliferation and invasion abilities, which may be mediated by inhibiting the expression

Table 2 LncRNAs related to the prognosis of TNBC

LncRNA	Change	Mechanism	Outcome	Number of patients	Population study	Method	Reference
T376626	Up	Bind to LAMC2	Poor OS	282	BC/TNBC	K-M	He et al., 2023
XIST	Up	Unknown	Poor OS	141	TNBC/NC	K-M/Cox	Lan et al., 2021
ZFAS1	Down	Inhibit *p21* and *p27*, and promote EMT	Poor OS	1376	TNBC/NC	TCGA/K-M	Sharma et al., 2021
LINK-A, *BCAR4*	Up	HIF-1α pathway activation	Poor RFS	353/123	TNBC	TANRIC/ Gehan-Breslow test	Lin et al., 2016; Kaushik et al., 2021
AFAP1-AS1	Up	Activate Wnt/β-catenin pathway, increase the expression of *C-myc* and EMT-related molecules	Poor OS and DFS	238	TNBC	K-M	Zhang KM et al., 2018
DANCR	Up	Inhibit *miR-216a-5p* expression	Poor OS	57	TNBC	K-M	Tao et al., 2019
LINC01270, *LINC00449*	Up	Promote cell invasion and migration	Poor OS and DFS	200	TNBC	Cox	Ping et al., 2021
HUMT	Up	Hypomethylation of promoter region	Higher TN stage, poor OS and DFS	228	TNBC	K-M/log-rank test	Zheng SQ et al., 2020

LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; *XIST*: X inactive-specific transcript; *ZFAS1*: ZNFX1 antisense RNA 1; *LINK-A*: long intergenic non-coding RNA for kinase activation; *BCAR4*: breast cancer anti-estrogen resistance 4; *AFAP1-AS1*: actin filament-associated protein 1-antisense RNA 1; *DANCR*: differentiation antagonizing non-protein coding RNA; *HUMT*: highly upregulated in metastatic TNBC; LAMC2: laminin gamma 2; EMT: epithelial-mesenchymal transition; HIF-1α: hypoxia-inducible factor-1α; miR: microRNA; OS: overall survival; RFS: recurrence-free survival; DFS: disease-free survival; TN: tumor node; BC: breast cancer; NC: normal control; K-M: Kaplan-Meier; TCGA: The Cancer Genome Atlas; TANRIC: The Atlas of Non-coding RNA in Cancer.

of *miR-490-3p*. Animal experiments showed similar results, with silencing the *LINC00173* gene significantly reducing tumor weight (Fan et al., 2020).

Compared to their expression in other types of breast cancer, the lncRNAs *DANCR*, zinc finger E-box binding homeobox 2-antisense RNA 1 (*ZEB2-AS1*), human ovarian cancer-specific transcript 2 (*HOST2*), miR-100 host gene (*MIR100HG*), metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*), and POU class 3 homeobox 3 (*POU3F3*) are highly expressed in TNBC tissues and cell lines (Tang JM et al., 2018; Wang SW et al., 2018; Yang et al., 2019; Zhang GX et al., 2019; Zhang YD et al., 2019). The phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway plays a very critical role in the proliferation of TNBC cells (Hatem et al., 2016). Cellular experiments have shown that the *DANCR*–retinoid X receptor protein α (RXRA)–PI3K/AKT signaling axis is involved in TNBC proliferation and invasion. *DANCR* promotes proliferation and tumorigenesis in TNBC through activating ser49/78 phosphorylation of RXRA, thereby promoting phosphatidylinositol-4,5-biophosphate 3-kinase catalytic subunit α (PIK3CA) expression and subsequently enhancing PI3K/AKT signaling, causing TNBC tumorigenesis (Tang JM et al., 2018; Zhang GX et al., 2019). Likewise, lncRNA *ZEB2-AS1* is located mainly near *ZEB2* in the nucleus and can positively regulate *ZEB2* expression and activate EMT via the PI3K/AKT/glycogen synthase kinase 3 β (*GSK3β*)/*ZEB2* signaling pathway to further promote cell proliferation and migration (Zhang GX et al., 2019). *MALAT1* is an lncRNA about 8000 nt long, which is widely expressed and highly conserved in mammalian cells. By examining 43 TNBC tissues and paired adjacent non-tumor tissues, it was found that *MALAT1* was highly expressed in TNBC tissues, and that highly expressed *MALAT1* could promote proliferation, invasion, and cell cycling of TNBC cells, and that this effect might be mediated by *MALAT1*/*miR-129-5p* axis (Zuo et al., 2017) (Table 3, Fig. 1).

Table 3 LncRNAs that promote the proliferation and invasion of TNBC cells

LncRNA	Change	Mechanism	Outcome	Cells	Method	Reference
LUCAT1	Up	Bind to *miR-5702*	Progression	MCF-10A, TNBC cell lines (231, BT549, 453, and 468)	qRT-PCR, CCK-8, Transwell assay, WB, etc.	Mou and Wang, 2019
WEE2-AS1	Up	*WEE2-AS1*/*miR-32-5p*/*TOB1* axis	Progression	MCF-10A, TNBC cell lines (231, 436, and 468)	qRT-PCR, colony formation, Transwell assay, EdU, etc.	Wang et al., 2020
LINC00173	Up	Suppress *miR-490-3p*	Progression	TNBC cell lines (231, 468, and BT549)	qRT-PCR, colony formation, Transwell assay, cell proliferation assay	Fan et al., 2020
DANCR	Up	*DANCR*–RXRA–PI3K/AKT	Progression	TNBC cell lines (BT549, MCF-7, T47D, 231, 453, and 468)	RT-qPCR, ChIP-qPCR, luciferase promoter assay, RIP, colony formation, etc.	Tang JM et al., 2018
ZEB2-AS1	Up	PI3K/AKT/*GSK3β*/*ZEB2*	Progression	MCF-10A, TNBC cell lines (T47D, MCF-7, 435, and 231)	Wound healing, CCK-8, Transwell assay, qRT-PCR, etc.	Zhang GX et al., 2019
MALAT1	Up	Bind to *miR-129-5p*	Progression	MCF-10A, TNBC cell lines (231, 453, MCF-7, BT549, and BT474)	qRT-PCR, CCK-8, flow cytometry analysis, scratch assay, Transwell assay, etc.	Zuo et al., 2017
HOST2	Up	*Let-7b*/*CDK6* axis	Progression	MCF-10A, TNBC cell lines (231 and 468)	RT-qPCR, WB, flow cytometry with PI staining, CCK-8, etc.	Zhang YD et al., 2019
MIR100HG	Up	Inhibit p27 protein	Progression	TNBC cell lines (231 and BT549)	RT-qPCR, MTS assay, flow cytometry, BrdU, etc.	Wang SW et al., 2018
POU3F3	Up	Downregulate Caspase-9	Progression	TNBC cell lines (231 and BT20)	RT-qPCR, CCK-8, cell apoptosis assay, WB, etc.	Yang et al., 2019

LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; *LUCAT1*: lung cancer-associated transcript 1; *WEE2-AS1*: WEE2-antisense RNA 1; *DANCR*: differentiation antagonizing non-protein coding RNA; *ZEB2-AS1*: zinc finger E-box binding homeobox 2-antisense RNA 1; *MALAT1*: metastasis-associated lung adenocarcinoma transcript 1; *HOST2*: human ovarian cancer-specific transcript 2; *MIR100HG*: miR-100 host gene; *POU3F3*: POU class 3 homeobox 3; miR: microRNA; *TOB1*: transducer of ERBB2.1; RXRA: retinoid X receptor protein α; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; *GSK3β*: glycogen synthase kinase 3 β; *CDK6*: cyclin-dependent kinase 6; 231: MDA-MB-231; 453: MDA-MB-453; 468: MDA-MB-468; 436: MDA-MB-436; 435: MDA-MB-435; qRT-PCR, qPCR: quantitative real-time polymerase chain reaction; RT-qPCR: reverse transcription-qPCR; CCK-8: cell counting kit-8; WB: western blotting; EdU: 5-ethynyl-20-deoxyuridine; ChIP: chromatin immunoprecipitation; RIP: RNA immunoprecipitation; MTS: mitochondrial-targeting sequence; PI: propidium iodide; BrdU: bromodeoxyuridine.

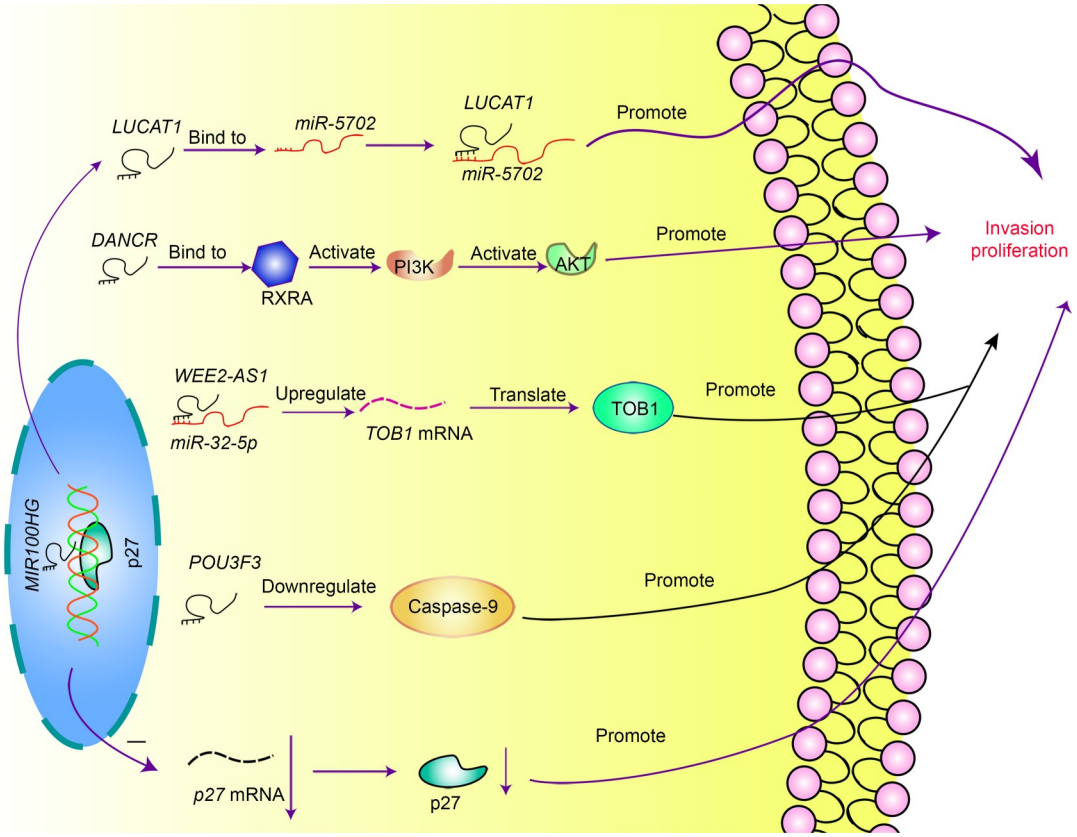

Fig. 1 Diagram of the mechanisms by which lncRNAs promote proliferation and invasion of TNBC cells. LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; *LUCAT1*: lung cancer-associated transcript 1; miR: microRNA; *DANCR*: differentiation antagonizing non-protein coding RNA; RXRA: retinoid X receptor protein α; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; *WEE2-AS1*: WEE2-antisense RNA 1; TOB1: transducer of ERBB2.1; mRNA: messenger RNA; *POU3F3*: POU class 3 homeobox 3.

In summary, the above lncRNAs are highly expressed in TNBC tissues or plasma and can promote tumor cell proliferation and invasion through different mechanisms. Silencing lncRNAs or their downstream key molecules can inhibit the proliferation and speed of invasion of TNBC cells, and even cause cell death due to the lack of relevant growth factors. Thus, this technology is expected to be applied in the clinic for the benefit of TNBC patients.

3.2 LncRNAs that promote TNBC cell metastasis

Metastasis refers to the process of malignant tumor cells leaving the primary site and arriving at tissues that are not contiguous with the primary site through various transport pathways, to continue to grow and form secondary tumors with the same pathological properties as the primary tumor. Metastasis is a multi-step and multi-factorial process linked to gene regulation, signaling pathways, and cellular junctions. LncRNA, as an important component of non-coding RNA, has been found to play an important role in cancer metastasis.

The immune system is able to exert anti-tumor effects by recognizing antigens on the surface of tumor cells. However, some studies have shown that tumor cells are able to evade the immune system through certain mechanisms preventing the body from producing effective anti-tumor effects and allowing cancer cells to continue to spread. For example, Hu et al. (2019) found that high expression of *LINK-A* in TNBC cells promoted the degradation of peptide-loading complex (PLC) and the intrinsic tumor suppressor genes Retinoblastoma (*Rb*) and *p53*, causing the tumor to lose its antigenicity and hence evade the body's immune examination and facilitate the migration of tumor cells. The main distant metastatic sites of TNBC are the lung, brain, liver, and bone (Foulkes et al., 2010). Wang PS et al. (2018) found via Transwell

assay that the metastatic ability of TNBC cells with high expression of linc-zinc finger 469-3 (*linc-ZNF469-3*) was 4.1-fold higher than that of a control group ($P<0.05$). After injecting this gene into mice, they found that the mice showed more and larger metastatic tumors in the lungs compared with the control group, suggesting that *linc-ZNF469-3* could function as a potential metastatic marker in TNBC patients. This biological function may act through the *linc-ZNF469-3*/*miR-574-5p*/*ZEB1* axis. Lin et al. (2018) found that the lncRNA *HIF1A-AS2* can promote colorectal cancer cell (CRC) proliferation, invasion, and EMT formation via the *miR-129-5p*/DNA (cytosine-5)-methyltransferase 3A (*DNMT3A*) axis. Wang YF et al. (2019) found that the expression of *HIF1A-AS2* was significantly elevated in TNBC cell lines compared with normal mammary epithelial cell lines. Besides, silencing the expression of *HIF1A-AS2* significantly inhibited the migration and invasion of TNBC cells. In addition, basic data showed that high expression of *HIF1A-AS2* was associated with lymph node metastasis, distant metastasis, and poor histological grading in TNBC patients. Similarly, the expression of the highly up-regulated in liver cancer (*HULC*) gene is also associated with the migration of TNBC cells and can exert biological functions by regulating the activity of the matrix metalloproteinase-2 (*MMP-2*)/*MMP-9* gene, which has the potential ability to determine whether TNBC patients have metastasis at an early stage (Shi et al., 2016) (Table 4, Fig. 2).

Distant metastasis is the leading cause of death and the most serious complication for cancer patients. Currently, patients with distant metastases are largely losing their chance for surgical treatment, and median survival is measured in months. The above studies found that by silencing metastasis-related lncRNAs, the migration ability of TNBC cells could be weakened, reducing the risk of distant metastasis and prolonging the survival of patients.

4 LncRNAs that inhibit the progression of TNBC

We found that lncRNA mainly plays a promotional role in tumor formation and development, and only a small number of lncRNAs play a role in inhibiting tumor formation and attenuating cell proliferation, invasion, and migration. These lncRNAs show low expression in TNBC tissues or cells.

For example, Sharma et al. (2021) found that lncRNA *ZFAS1* was differentially expressed in the plasma of TNBC patients versus normal individuals and could be used as a diagnostic marker for TNBC. After further analysis, they found that silencing the *ZFAS1* gene enhanced the EMT capacity of TNBC cells by inhibiting the expression of the cyclin-dependent kinase (CDK) inhibitors *p21* (CDKN1A) and *p27* (CDKN1B). This promoted the proliferation and migration of TNBC cells, leading to poorer prognoses (Sharma et al., 2021). In addition, lncRNA can exert biological effects by interacting with downstream microRNAs (miRNAs). For instance, lncRNA miR-503 host gene (*MIR503HG*) is able to inhibit cell migration and invasion via the *miR-103*/olfactomedin 4 (*OLFM4*) axis in TNBC cells, and low expression of

Table 4 LncRNAs that promote TNBC cell metastasis

LncRNA	Change	Mechanism	Effect	Cells	Method	Reference
LINK-A	Up	Enhance *PLC*, *Rb*, and *p53* degradation	Metastasis	MCF-10A, TNBC cell lines (231, 468, BT549, and HCC1187)	Flow cytometry, mass spectrometry, etc.	Hu et al., 2019
Linc-ZNF469-3	Up	*Linc-ZNF469-3*/*miR-574-5p*/*ZEB1* axis	Metastasis	TNBC cell lines (231, 361, 157, MCF-7, BT483, AU565, SKBR3, BT549, etc.)	qRT-PCR, RNA-seq, Transwell assay, soft-agar assay, sphere formation assay, etc.	Wang PS et al., 2018
HIF1A-AS2	Up	Unknown	Metastasis	MCF-10A, DU4475, HCC1806, and 468	qRT-PCR, Transwell assay	Wang YF et al., 2019
HULC	Up	Upregulate *MMP-2* and *MMP-9*	Metastasis	MCF-10A, TNBC cell lines (231, 468, BT549, and BT483)	qRT-PCR, standard MTT assay, Transwell assay, and WB	Shi et al., 2016

LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; *LINK-A*: long intergenic non-coding RNA for kinase activation; *ZNF469-3*: zinc finger 469-3; *HIF1A-AS2*: hypoxia-inducible factor 1α-antisense RNA 2; *HULC*: highly up-regulated in liver cancer; PLC: peptide-loading complex; *Rb*: retinoblastoma; miR: microRNA; ZEB1: zinc finger E-box binding homeobox 1; *MMP*: matrix metalloproteinase; 231: MDA-MB-231; 468: MDA-MB-468; 361: MDA-MB-361; 157: MDA-MB-157; HCC: hepatocellular carcinoma; qRT-PCR: quantitative real-time polymerase chain reaction; RNA-seq: RNA sequencing; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; WB: western blotting.

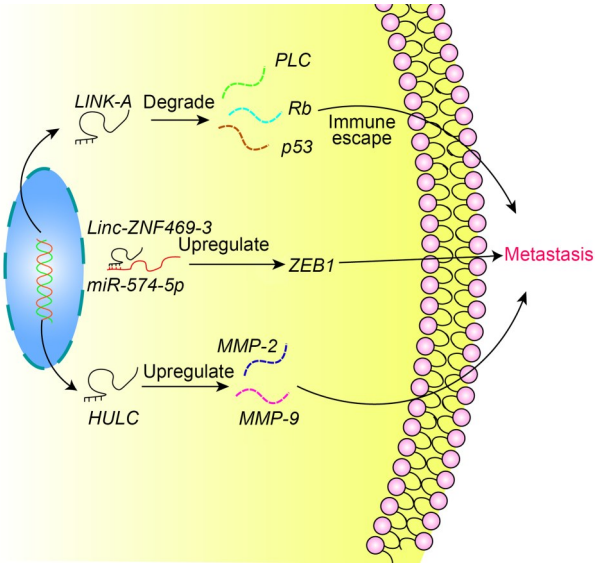

Fig. 2 Diagram of the mechanisms by which lncRNAs promote TNBC cell metastasis. LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; *LINK-A*: long intergenic non-coding RNA for kinase activation; *PLC*: peptide-loading complex; *Rb*: retinoblastoma; *ZNF469-3*: zinc finger 469-3; miR: microRNA; *ZEB1*: zinc finger E-box binding homeobox 1; *HULC*: highly up-regulated in liver cancer; *MMP*: matrix metalloproteinase.

MIR503HG is associated with clinically advanced stage, lymph node metastasis, and distant metastasis (Fu J et al., 2019).

Moreover, overexpression of lncRNA acetylserotonin *O*-methyltransferase-like-antisense RNA 1 (*ASMTL-AS1*) can reduce the colony formation, activity, and invasion ability of TNBC cells by more than 2.5 times. RNA pull-down and luciferase reporter gene analysis showed that *miR-1228-3p* directly combined with *ASMTL-AS1*, and *ASMTL-AS1* increased the expression of SRY-box transcription factor 17 (*SOX17*) by absorbing and inhibiting *miR-1228-3p*. Subsequently, the upregulated *SOX17* trans-suppressed β-catenin expression, resulting in the inactivation of carcinogenic Wnt/β-catenin signaling, thereby restraining TNBC cell growth and dissemination. Similar results have been observed in mouse tumorigenesis experiments (Sun J et al., 2021). Furthermore, lncRNA tumor suppressor candidate 7 (*TUSC7*) has been characterized as a tumor suppressor in osteosarcoma and colorectal cancers, but whether it also acts as an oncogenic suppressor in TNBC is unclear. Zheng et al. (2021) retrospectively found that low expression of *TUSC7* was an independent prognostic factor for poor OS in TNBC patients. Moreover, they found that *TUSC7* may silence the mitogen-activated protein kinase (MAPK), PI3K/AKT, and nuclear factor-κB (NF-κB) signaling pathways by binding to *miR-1224-3p*, inhibiting TNBC cell growth and metastasis in vitro and in vivo. LncRNA cardiac mesoderm enhancer-associated ncRNA (*CARMN*) is a host gene for *miR-143-3p*, and is able to downregulate the expression of the DNA replication initiation factor minichromosome maintenance complex component 5 (*MCM5*) by producing *miR-143-3p*, leading to the repression of DNA replication (Sheng et al., 2021). Transwell experiments by Song et al. (2019) showed that overexpression of lncRNA neighboring enhancer of FOXA2 (*NEF*) can inhibit the migration and invasion of TNBC cells, while cell counting kit-8 (CCK-8) experiment results showed that *NEF* has no significant effect on the proliferation of TNBC cells. The above biological behavior may be caused by the negative regulation of *miR-155* by *NEF*. The mechanism of action of lncRNA can involve interactions in addition to those with miRNA. For instance, lncRNA *H19* is significantly upregulated in TNBC tissue, and *H19* has the ability to promote TNBC cell proliferation. Wang N et al. (2019) found that low expression of lncRNA papillary thyroid carcinoma susceptibility candidate 3 (*PTCSC3*) can promote the proliferation of TNBC cells by increasing the expression of the *H19* gene, but has no significant effect on the migration or invasion of cancer cells. Long non-coding Kelch domain containing 7B (*LncKLHDC7B*) and lncRNA rhabdomyosarcoma 2-associated transcript (*RMST*) are weakly expressed in TNBC cells or tissues, and the lower the expression, the worse the invasiveness of cells and patient prognosis. However, the specific mechanism of action is still unclear and further exploration is needed (Wang L et al., 2018; Beltrán-Anaya et al., 2019). LncRNAs *TCONS_l2_00002973* and *RMST* are lowly expressed in TNBC tissues. With low expression, the prognosis of patients is worse, but the exact mechanism of action is still unclear and further investigation is needed (Table 5).

In summary, all of the above lncRNAs can play a role in inhibiting TNBC cell formation and progression. Some of them play important oncogenic roles not only in TNBC, but also in other cancers. Because a lower expression of lncRNAs in TNBC tissues is associated with a worse prognosis for patients, we could use upregulation of genes to inhibit cancer development and improve patient prognosis.

Table 5 LncRNAs that inhibit the progression of TNBC

LncRNA	Change	Mechanism	Effect	Cells	Method	Reference
ZFAS1	Down	Inhibit *p21* and *p27*, and promote EMT	Progression	231	qRT-PCR, MTT assay, colony-forming assay, etc.	Sharma et al., 2021
MIR503HG	Down	*miR-103*/*OLFM4* axis	Progression	MCF-10A, 231, and BT549	RT-PCR, luciferase reporter assay, Transwell assay, and WB	Fu J et al., 2019
ASMTL-AS1	Down	*miR-1228-3p*/*SOX17*/β-catenin	Progression	231 and 468	qRT-PCR, colony formation, CCK-8, Transwell assay, etc.	Sun J et al., 2021
TUSC7	Down	Regulate the MAPK, PI3K/AKT, and NF-κB signaling pathways	Progression	468	RT-qPCR, CCK-8, etc.	Zheng et al., 2021
CARMN	Down	Downregulate *miR-143-3p* and upregulate *MCM5*	Progression	MCF-10A, 231, and 468	RT-qPCR, CCK-8, colony formation, cell cycle, apoptosis assay, etc.	Sheng et al., 2021
NEF	Down	Upregulate *miR-155*	Progression	BT20 and 231	RT-qPCR, CCK-8, Transwell assay, etc.	Song et al., 2019
PTCSC3	Down	Upregulate of lncRNA *H19*	Progression	BT549 and HCC70	RT-qPCR, CCK-8, etc.	Wang N et al., 2019
LncKLHDC7B	Down	Unknown	Progression	MCF-10A, TNBC cell lines (BT20, 468, and 231), Hs578T, MCF-7, HCC1187	RT-qPCR, CCK-8, Transwell assay, and apoptosis assay	Beltrán-Anaya et al., 2019
RMST	Down	Unknown	Progression	MCF-10A, MCF-7, AU565, TNBC cell lines (BT20 and BT549)	qRT-PCR, CCK-8, colony formation, TUNEL assay, Transwell assay, etc.	Wang L et al., 2018

LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; miR: microRNA; *ZFAS1*: ZNFX1 antisense RNA 1; *MIR503HG*: miR-503 host gene; *ASMTL-AS1*: acetylserotonin *O*-methyltransferase-like (ASMTL)-antisense RNA 1; *TUSC7*: tumor suppressor candidate 7; *CARMN*: cardiac mesoderm enhancer-associated non-coding RNA; *NEF*: neighboring enhancer of FOXA2; *PTCSC3*: papillary thyroid carcinoma susceptibility candidate 3; *LncKLHDC7B*: long non-coding Kelch domain containing 7B; *RMST*: rhabdomyosarcoma 2-associated transcript; EMT: epithelial-mesenchymal transition; OLFM4: olfactomedin 4; SOX17: SRY-box transcription factor 17; MAPK: mitogen-activated protein kinase; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; NF-κB: nuclear factor-κB; *MCM5*: minichromosome maintenance complex component 5; 231: MDA-MB-231; 468: MDA-MB-468; qRT-PCR: quantitative real-time polymerase chain reaction (PCR); RT-PCR: reverse transcription-PCR; RT-qPCR: reverse transcription-quantitative PCR; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; WB: western blotting; CCK-8: cell counting kit-8; TUNEL: terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling.

5 Relationship between lncRNAs and chemotherapy resistance

Chemotherapy is one of the main treatments for TNBC patients. Unfortunately, chemotherapy resistance is very common in TNBC patients and is a major cause of treatment failure (Nedeljković and Damjanović, 2019; Yu et al., 2022).

Genomic instability (GIN) is crucial to modulating tumor drug resistance. *miR-26a-5p* is an upstream parameter that regulates GIN. When *miR-26a-5p* expression is increased, TNBC cells are more sensitive to paclitaxel, whereas silencing the expression of *miR-26a-5p* promotes autophagy and the emergence of drug resistance in cells. Furthermore, Li et al. (2021) identified the upstream regulator lncRNA ovarian tumor domain-containing 6B-antisense RNA 1 (*OTUD6B-AS1*) of *miR-26a-5p* through bioinformatics analysis and explored an *OTUD6B-AS1*/*miR-26a-5p*/metadherin (*MTDH*) signal axis regulating TNBC cell resistance through cytological, molecular, and zoological experiments.

The expression level of lncRNA *H19* was significantly increased in paclitaxel-resistant TNBC cells compared with paclitaxel-sensitive cells. *H19* can not only promote the proliferation of TNBC cells, but also inhibit apoptosis and promote paclitaxel resistance in TNBC cells by activating the AKT signaling pathway

(Han et al., 2018). Jiang et al. (2016) found that the half maximal inhibitory concentration (IC_{50}) of paclitaxel after silencing the expression of *HIF1A-AS2* and *AK124454* in TNBC cells was more than double that of a negative control group, indicating that the two genes can lead to paclitaxel resistance in TNBC cells. They also established a resistance prediction model based on these two genes, which can help TNBC patients develop personalized treatment plans. Cancer stem cells are located in the cancer cell mass, which is the "culprit" of cancer recurrence and metastasis. Shin et al. (2019) tested the serum of 192 normal people and 179 patients with breast cancer by reverse transcription-quantitative PCR (RT-qPCR) and found that the expression of *NEAT1* differed significantly. Its expression in the serum of TNBC patients was higher than that of patients with other cancer subtypes. Furthermore, in vitro and in vivo experiments have confirmed that knocking out *NEAT1* can make TNBC cells sensitive to chemotherapy, indicating its involvement in chemotherapy resistance. In contrast, the lncRNAs *TUSC7*, taurine upregulated gene 1 (*TUG1*), and growth stasis-specific transcript 5 (*GAS5*) increase chemosensitivity, which can enhance the apoptosis effect of chemotherapy drugs on TNBC cells. The above genes are lowly expressed in TNBC drug-resistant cells, and upregulation of specific lncRNA expression can reverse chemotherapy resistance (Tang TL et al., 2018; Zheng SP et al., 2020; Zheng BH et al., 2021) (Table 6, Fig. 3).

Studies on the relationship between lncRNA and drug resistance are increasing, and the outcomes of these studies show that lncRNAs play an important role (Singh et al., 2023). Some lncRNAs appear resistant to paclitaxel, while others are resistant to cisplatin. We hypothesize that lncRNAs could be used in the clinic to treat TNBC-resistant patients based on their ability to reverse drug resistance by regulating lncRNA expression in cellular experiments, but the idea is still in its infancy and further research is needed.

6 Summary of lncRNA regulatory mechanisms

LncRNA regulates the malignant behavior of TNBC cells through various complex mechanisms,

Table 6 LncRNAs associated with TNBC chemotherapy resistance

LncRNA	Change	Mechanism	Outcome	Cells	Method	Reference
OTUD6B-AS1	Up	*OTUD6B-AS1*/*miR-26a-5p*/*MTDH* axis	PTX resistance	231 and HCC1937	qRT-PCR, CCK-8, calcein AM/PI-staining assay, Transwell assay, etc.	Li et al., 2021
H19	Up	AKT signal pathway	PTX resistance	Hs578Bst, MCF-10A, TNBC cell lines (453, 157, and 231)	qRT-PCR, MTT assay, Annexin V/PI, WB, etc.	Han et al., 2018
HIF1A-AS2, *AK124454*	Up	Unknown	PTX resistance	231, BT549, Hs578T, and 293T	qRT-PCR, CCK-8, Transwell assay, and microarray data	Jiang et al., 2016
NEAT1	Up	Increase tumor stem cells	CIS and PTX resistance	231	qRT-PCR, MTT assay, Annexin V/PI, ALDH assay, etc.	Shin et al., 2019
TUSC7	Down	Bind with *miR-1224-3p*	PTX and carboplatin resistance	468	RT-qPCR, CCK-8, etc.	Zheng et al., 2021
TUG1	Down	*TUG1*/*miR-197*/*NLK* axis	CIS resistance	MCF-10A, 231, and BT549	qRT-PCR, CCK-8, dual luciferase reporter assay, etc.	Tang TL et al., 2018
GAS5	Down	*GAS5*/*miR-378a-5p*/*SUFU* axis	CIS and PTX resistance	231 and BT549	RT-qPCR, dual luciferase reporter gene, Annexin V/PI, etc.	Zheng SP et al., 2020

LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; *OTUD6B-AS1*: ovarian tumor domain-containing 6B-antisense RNA 1; *HIF1A-AS2*: hypoxia-inducible factor 1α-antisense RNA 2; *NEAT1*: nuclear paraspeckle assembly transcript 1; *TUSC7*: tumor suppressor candidate 7; *TUG1*: taurine upregulated gene 1; *GAS5*: growth stasis-specific transcript 5; miR: microRNA; MTDH: metadherin; AKT: protein kinase B; NLK: nemo-like kinase; SUFU: suppressor of fused homolog; PTX: paclitaxel; CIS: cisplatin; 231: MDA-MB-231; 453: MDA-MB-453; 157: MDA-MB-157; 468: MDA-MB-468; qRT-PCR: quantitative real-time polymerase chain reaction (PCR); RT-qPCR: reverse transcription-quantitative PCR; CCK-8: cell counting kit-8; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; PI: propidium iodide; WB: western blotting; ALDH: aldehyde dehydrogenase.

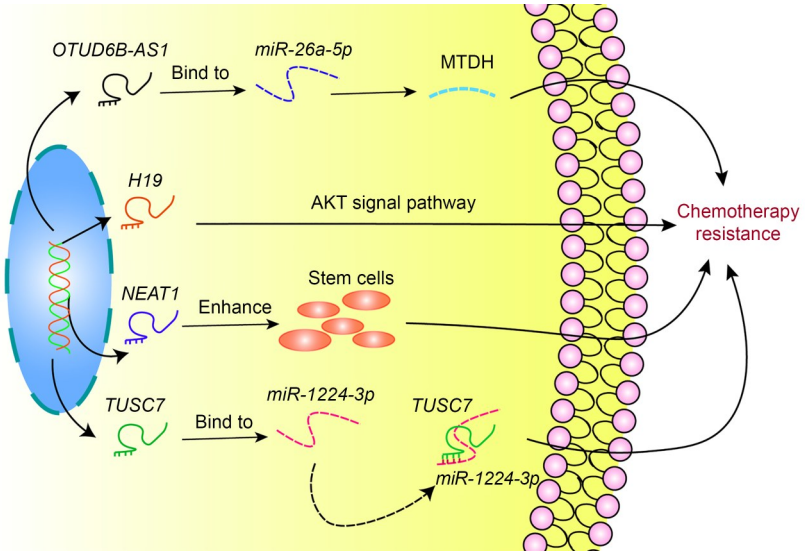

Fig. 3 Diagram of the mechanisms of action of lncRNAs associated with TNBC chemotherapy resistance. LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; *OTUD6B-AS1*: ovarian tumor domain-containing 6B-antisense RNA 1; miR: microRNA; MTDH: metadherin; AKT: protein kinase B; *NEAT1*: nuclear paraspeckle assembly transcript 1; *TUSC7*: tumor suppressor candidate 7.

including the following four main categories. Firstly, lncRNA can bind to proteins to regulate cell behavior. For example, lncRNA *T376626* can bind to laminin γ2 (LAMC2) protein to regulate TNBC proliferation, migration, and invasion (He et al., 2023). Secondly, lncRNA can regulate the transcription or translation of downstream genes. For example, signal transducer and activator of transcription 3 (*STAT3*) is a gene that can promote the occurrence of breast cancer and accelerate the proliferation, metastasis, and chemotherapy resistance of tumor cells, while *ZFAS1* can promote the occurrence and development of TNBC by increasing the expression of the STAT3 protein (Sharma et al., 2021). Similarly, lncRNA *PTCSC3* can reduce the expression of the lncRNA *H19* gene and inhibit the proliferation of TNBC cells (Wang N et al., 2019). Thirdly, lncRNA can also serve as a molecular blocker that binds to related molecules downstream and exerts biological effects by regulating related signaling pathways. For example, *DANCR* can bind to the *RXRA* gene, thereby activating the PI3K/AKT signaling pathway and promoting the proliferation and invasion of TNBC cells (Tang JM et al., 2018). Finally, competing endogenous RNA (ceRNA) is a mechanism by which lncRNA can competitively bind miRNA with target genes (Liu et al., 2014) and is the mechanism of action of most of the above lncRNAs. They can act as ceRNA to combine with miRNAs to regulate the expression of target genes in TNBC cells and exert biological effects. For example, lncRNA *WEE2-AS1* can bind to *miR-32-5p*, release the inhibition of *TOB1* by *miR-32-5p*, and promote the proliferation, invasion, and migration of TNBC cells (Wang et al., 2020). Besides, lncRNA *ASMTL-AS1* can bind *miR-1228-3p* competitively with *SOX17*, thereby regulating the expression of the target gene *SOX17* and inhibiting the growth and proliferation of TNBC cells (Sun J et al., 2021). Also, lncRNAs *ZNF469-3*, *LncMIR503HG*, *WEE2-AS1*, *CARMN*, and *OTUD6B-AS1* all play roles in TNBC invasion, proliferation, migration, and chemoresistance through ceRNA mechanisms (Wang PS et al., 2018; Fu J et al., 2019; Wang R et al., 2020; Li et al., 2021; Sheng et al., 2021). Nevertheless, some studies have shown that ceRNA profiles in breast cancer tissues differ from those of matched normal tissues. For example, several ceRNAs are active in cancer but not in normal cells, and vice versa (Paci et al., 2014). The use of the mechanism for the treatment of TNBC patients remains to be further explored (Fig. 4).

7 Universal effects of lncRNAs

The lncRNAs exemplified above play an important role not only in the development of TNBC but also in other types of breast cancer, and even other

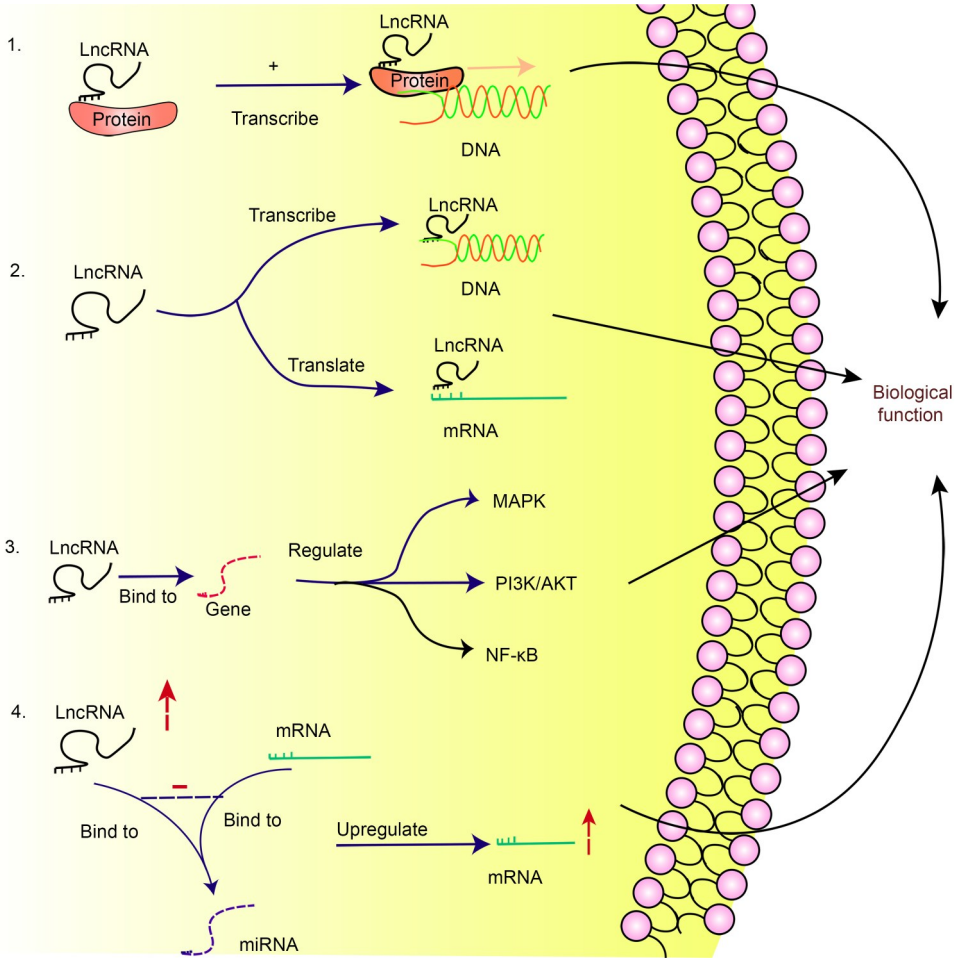

Fig. 4 Diagram of the pattern of lncRNA regulatory mechanisms in TNBC cells. 1: LncRNA binds to proteins; 2: LncRNA regulates downstream gene transcription or translation; 3: LncRNA regulates downstream-related signaling pathways; 4: The ceRNA mechanism of lncRNA and mRNA co-competing to bind miRNA. LncRNA: long non-coding RNA; TNBC: triple-negative breast cancer; mRNA: messenger RNA; MAPK: mitogen-activated protein kinase; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; NF-κB: nuclear factor-κB; miRNA: microRNA; ceRNA: competing endogenous RNA.

types of cancer. For example, Swellam et al. (2021) found that *NEAT1* is highly expressed in TNBC tissue or serum, and this can be used as a marker for the diagnosis of TNBC. However, Knutsen et al. (2022) found that NEAT1 is highly expressed not only in TNBC subtypes, but also in Her-2 positive and luminal B breast cancer subtypes. In addition, signal pathways such as PI3K/AKT and MAPK are found in most cellular metabolic processes, and lncRNAs that can affect these signaling pathways can regulate the occurrence and development of various cancers. For example, *DANCR* can regulate the proliferation and invasion of TNBC cells by influencing the PI3K/AKT signaling pathway, which also plays a crucial role in regulating cell proliferation and invasion in prostate cancer cells (Tang JM et al., 2018; Sun WD et al., 2021). The diagnostic lncRNAs *ZFAS1*, *XIST*, and *NEAT1* have also been reported in recent years to be highly expressed in pancreatic, cervical, and colon cancers, with the potential to promote the development of cancer cells (Zhang M et al., 2018; Zhu et al., 2018; Feng et al., 2019; Yang et al., 2020; Ghafouri-Fard et al., 2021; Lu et al., 2021; Rao et al., 2021; Shao et al., 2021). Therefore, finding a gene with TNBC specificity is not easy, and combining it with the patient's medical history or imaging examination may increase the accuracy of auxiliary judgment. Secondly, accuracy could also be increased by combining multiple genes, such as lncRNAs *TUSC7* and *NF-κB*. This pathway has a role only in TNBC cells, and

combining these two variables could provide more accurate information relevant to TNBC.

8 Immunotherapy of lncRNAs

Immunotherapy is a new treatment method. The normal immune system of the body can distinguish between its own cells and foreign cells through immune checkpoints, thereby preventing immune damage to its own healthy cells. Tumor cells can use immune checkpoints to evade killing (Jiang, 2014). Programmed cell death-1 (PD-1) is an immune checkpoint protein expressed on T lymphocytes that binds to programmed cell death-ligand 1 (PD-L1) on the surface of tumor cells, leading to T lymphocyte apoptosis, and plays an important role in tumor immune escape. Regulating the expression of PD-1/PD-L1 has become a current research hotspot (Wan et al., 2022). The KEYNOTE-522 trial has moved the PD-1 inhibitor Pabolizumab from advanced treatment of TNBC to early treatment and has achieved a good therapeutic effect (Mittendorf et al., 2020). The *XIST* mentioned above not only has a role in diagnosing TNBC and predicting its prognosis, but also is involved in the tumor immune escape mechanism (Samir et al., 2021). *XIST* can promote the occurrence and development of TNBC cells by affecting PD-L1. Moreover, *LINK-A* did not only lead to the progression of TNBC through *HIF-1α*. Hu et al. (2019) analyzed the potential relationship between *LINK-A* and the immune microenvironment through TCGA and found that human breast cancer tissue with high expression of *LINK-A* showed low $CD8^+CD3^+$ lymphocyte infiltration. They also measured the infiltration of $CD8^+$ T cells in TNBC patients after pembrolizumab (anti-PD-1) treatment and found that $CD8^+$ T cell infiltration was negatively correlated with *LINK-A* expression. The above results indicate that *LINK-A* plays an important role in the immune regulatory mechanism of TNBC (Hu et al., 2019). LncRNA regulates the occurrence and development of TNBC via the immune mechanism and can serve as a new target for TNBC immunotherapy.

At present, immunotherapy with lncRNA is still in its early stages and more, larger, multicenter studies are required.

9 Discussion

Treatment options for TNBC are limited due to the lack of effective therapeutic targets. Epigenetics refers to heritable changes in gene function that occur without sequence changes in DNA. These mechanisms include covalent modification of DNA and protein, chromatin remodeling, and regulation of ncRNA. They control biological phenotypes through regulating gene expression. Epigenetic modification abnormalities exist in a variety of cancers. Therefore, it is very important to explore the following issues related to the occurrence and development of TNBC: (1) Whether the epigenetic decorator pattern changes the expression of some genes; (2) Which dimension of epigenetics has changed; (3) How changes in gene expression and protein function cause changes in the pathological level of TNBC. Only by answering these questions can we understand the pathogenesis of TNBC more thoroughly and propose more targeted prevention, diagnosis, and treatment plans.

As an important dimension in epigenetics, lncRNA is an obvious object of study in basic TNBC research (Herman et al., 2022). There are two main ways by which lncRNA regulates the level of epigenetic modification. On the one hand, lncRNA can directly affect the methylation of DNA and RNA. For example, *miR-26b* is a tumor suppressor gene in breast cancer. Long et al. (2020) showed that TatD DNase domain-containing 1 (*TATDN1*) has a positive regulatory effect on the methylation of the *miR-26b* gene through methylation-specific PCR, and promotes the proliferation and invasion of TNBC cells by reducing the expression of *miR-26b*. Similarly, the methylation of *MALAT1* can promote high expression of B-cell CLL/lymphoma 11A (*BCL11A*) DNA methyltransferase 1 (*DNMT1*) by inhibiting the *miR-137*/*BCL11A* pathway, thereby inhibiting tumor development (Hu et al., 2023). On the other hand, lncRNA can affect protein modification to exert biological effects. For example, *DANCR* binds with RXRA and increases its serine 49/78 phosphorylation via GSK3β, resulting in activation of PIK3CA transcription, and subsequently enhances PI3K/AKT signaling and TNBC tumorigenesis (Tang JM et al., 2018).

Liquid biopsy refers to the examination of a patient's body fluid. By detecting the marker information released by tumor cells into the body fluid, we

can obtain comprehensive information regarding oncogene or protein expression in the patient's body. This has the advantages of convenient material selection, minimal trauma, and high accuracy, and can yield results consistent with histology. For example, Liu et al. (2017) performed RT-qPCR detection of lncRNAs *ANRIL*, *HIF1A-AS2*, and *UCA1* in the plasma and tumor tissues of enrolled patients, and found that the expression levels of these three genes in TNBC serum and tumor tissues were higher than those in NTNBC. Manoochehri et al. (2023) obtained similar results from examination of TNBC and normal breast tissue, peripheral blood of TNBC cases and controls, and TNBC cells. The above results indicate that the results of liquid biopsy are consistent with the histological results.

In this study, we found that some lncRNAs have value both in the diagnosis of TNBC and in assessing prognosis. For example, the detection of *NEAT1* in serum enables early diagnosis of TNBC patients, and the prognosis of patients can be measured by the level of expression of this gene. Similarly, *ZFAS1* can be used not only as a diagnostic marker for TNBC patients, but also to predict the proliferative capacity of tumor cells and patient prognosis by the level of expression. LncRNA is involved in various aspects of the physiological mechanisms of TNBC cells and plays a wide-ranging role. Therapeutic regimens targeting lncRNA may offer a ray of hope for TNBC patients, but reproducible biological targets are still extremely scarce in TNBC and more studies with larger sample sizes and stronger evidence are warranted. In addition, ceRNA is the mechanism of action of most lncRNAs and the network is interconnected and complicated. How to find the key nodes against ceRNA oncogenic mechanisms is very important, otherwise treatment may lead to failure and even secondary tumor occurrence. Thus, caution is needed (Giza et al., 2014; Kotterman and Schaffer, 2014; Nitzan et al., 2014). LncRNA is also involved in regulating various metabolic pathways in cells. In the future, we can explore whether lncRNA in TNBC regulates specific metabolic pathways from the perspective of metabolomics analysis, thereby finding new target biomarker sites (Zhu et al., 2022). In addition, lncRNA often interacts with miRNA to jointly regulate important physiological and pathological processes in the development of TNBC, so we speculate that the two could be combined to determine the prognosis of patients (Liu AN et al., 2019; Youness et al., 2019). With the deepening understanding of TNBC, it has been found that there are also many different subtypes of TNBC. In the future, it may be possible to pinpoint which specific lncRNA plays oncogenic roles in specific TNBC subtypes so that more precise individualized treatments can be developed. We can also measure the cancer risk of patients by combining the expression of lncRNA with their clinical characteristics, and develop a medical algorithm that relies on risk sharing to make the prediction results more reliable.

10 Conclusions

In this review, we discussed and summarized the roles of lncRNAs in the diagnosis, prognosis, and drug resistance of TNBC, and found that they play an important role in the development of TNBC. We can determine the condition of TNBC by detecting the expression levels of related lncRNAs in the patient's serum, and even combine this with downstream miRNAs or proteins to improve accuracy. In addition, these genes have the potential to become new therapeutic targets for TNBC.

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Author contributions

Qiuhui YANG: writing – original draft, conceptualization, and formal analysis. Yeqin FU: investigation and writing – review & editing. Jiaxuan WANG: software and visualization. Hongjian YANG: conceptualization, supervision, and writing – review & editing. Xiping ZHANG: conceptualization, funding acquisition, supervision, and writing – review & editing. 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

Qiuhui YANG, Yeqin FU, Jiaxuan WANG, Hongjian YANG, and Xiping ZHANG 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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