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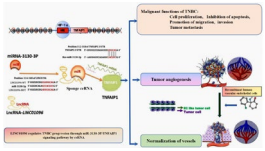
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REVIEW ARTICLE

Title: LncRNA regulates the progression of Triple-negative breast cancer

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Abstract: Managing triple negative breast cancer (TNBC) is difficult because of its unfavorable outlook, diversity, increased invasiveness, tendency to recur and spread, and absence of targeted treatment options. Recent research has found that numerous long non-coding RNAs (lncRNAs) are essential in TNBC. We examined the existing research on the impact of lncRNAs in the development, resistance to treatment, and outlook for TBNC individuals. LncRNAs act as sponges, regulating the expression of genes, miRNAs, and transcription factors related to the pathogenesis and progression of TNBC. LncRNA affects the progression of TNBC by participating in cancer stemness, EMT, regulating cell proliferation and apoptosis, participating in cell invasion and metastasis, and participating in angiogenesis regulation. In addition, lncRNAs can be used to assist in the diagnosis and prognosis evaluation of TNBC patients. Large scale research is needed on the lncRNAs to fully understand and utilize their potential as biomarkers or therapeutic targets.

Keywords: Triple-negative breast cancer; lncRNA; Prognosis; Stemness; EMT; Angiogenesis

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1. Introduction

Triple negative breast cancer (TNBC) is considered to be a heterogeneous and complex subtype of breast cancer, with strong aggressive biological behavior, high recurrence rate, high risk of distant metastasis, and poor prognosis. So far, there is still the main focus of public health attention. Managing TNBC in a clinical setting is difficult because of its diverse nature, aggressive biological characteristics, and absence of targeted treatments, leading to limited effectiveness of endocrine and targeted therapies. The combination of surgery, radiation therapy, and cytotoxic chemotherapy is the preferred method for treating TNBC patients. In addition, resistance to traditional therapies may be caused by several treatment cycles or intrinsic factors composed of cancer. Hence, individuals are eagerly anticipating gaining a deeper insight into the patterns and mechanisms of tumor development in TNBC cells, as well as discovering reliable biomarkers for diagnosing and predicting outcomes for TNBC patients.

Long non-coding RNAs (lncRNAs) are a subclass of ncRNAs, consisting of over 200 nucleotides. The number of LncRNAs greatly exceeds the number of protein coding genes in the human genome. Reports indicate that lncRNAs are crucial in the complex process of TNBC tumor formation and the development of TNBC. The importance of lncRNAs in signaling specific cellular states, detecting cellular pathologies like cancer, and guiding treatment decisions for cancer patients is now widely acknowledged. LncRNA controls the aggressive actions of TNBC cells through multiple intricate pathways, such as competitive endogenous RNA (ceRNA) where lncRNA competes with target genes to attach to miRNA, which is the primary mechanism for many of the previously mentioned lncRNAs.

Our prior studies have shown that lncRNA LINC01096 has the ability to interact with miR-3130-3p [1], leading to the derepression of TNFAIP1 by miR-3130-3p, thereby enhancing the growth, infiltration, and movement of TNBC cells (Fig 1). LINC01096 is abnormally expressed in TNBC, and LINC01096 can serve as a potential sponge

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ceRNA to adsorb miR-3130-3p. The miR-3130-3p has the ability to attach to the 3'UTR of TNFAIP1 mRNA, leading to the regulation of TNFAIP1 transcription by miR-3130-3p. LINC01096 is highly expressed, while miR-3130-3p is lowly expressed. LINC01096 and miR-3130-3p are associated with malignant biological behaviors such as TNBC cell proliferation, invasion, apoptosis inhibition, tumor angiogenesis and metastasis. miR-3130-3p is down regulated and negatively regulated by LINC01096. In turn, overexpression of miR-3130-3p can inhibit the growth of TNBC cancer cells and tumor angiogenesis[2]. miR-3130-3p is expected to become a new target for breast cancer. Identification of miR-3130-3p target interaction network has theoretical and clinical significance. Following phosphorylation, it moves from the cytoplasm to the nucleus where it is involved in critical processes including hypoxia response, angiogenesis, DNA replication, and damage repair. It has the characteristics of molecular changes and abnormal signaling pathways. It has the characteristics of molecular changes and abnormal signaling pathways.

In recent years, research on lncRNAs in cancer has significantly grown, making it a prominent subject in the field of RNA biology[3]. Because of the tissue specific expression and up-regulated expression of lncRNA in cancer, lncRNA represents an attractive target and biomarker for breast cancer prognosis, therapeutic response, disease recurrence, and differentiation between tumor and non tumor tissues. In addition, different subtype specific lncRNAs can assist in diagnosis and subsequent treatment pathways, helping patients stratify[4].

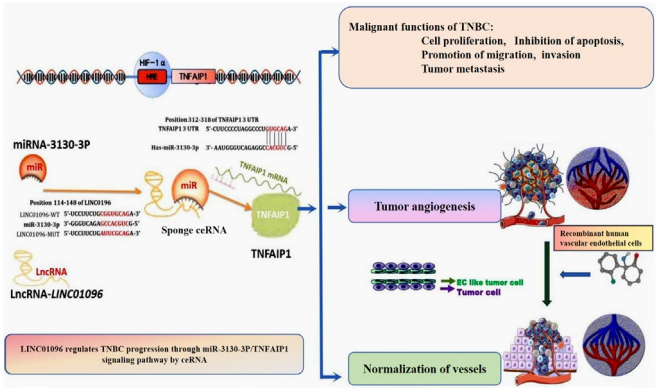


Fig. (1). LncRNA regulates the progression of TNBC. LINC01096 regulates progression through miR-3130-3P/TNFAIP1 signaling pathway by sponge ceRNA by participating in cancer stemness, EMT, regulating cell proliferation and apoptosis, invasion and metastasis, and participating in angiogenesis regulation including tumor angiogenesis and vascular normalization in tumor microenvironment hypoxia.

2. LncRNAs involved in cancer stemness of TNBC

TNBC contains a high concentration of mesenchymal stem/stromal cells (MSCs), fibroblast progenitor cells that are essential for the development and advancement of TNBC[5]. A higher percentage of tumor initiating MSCs may lead to increased cancer invasiveness, chemotherapy resistance, and worse outcomes. This could be especially accurate for TNBC cases with a significant amount of bone marrow mesenchymal stem cells and a negative outlook[6]. Recently, there has been increasing recognition of the significant impact lncRNAs have on the advancement of TNBC, with certain ones showing particular connections to MSCs in breast cancer. Identification of certain long non-coding RNAs associated with the onset, advancement, and spread of TNBC. LncRNAs play a role in regulating various biological processes of TNBC, including cancer-related activities like cell growth, cell death, cell movement, cell invasion, and the development of triple-negative breast cancer. In CSCs, it has been reported that several lncRNAs such as ROR, H19, HOTAIR, ARSR, UCA1 play an important role by sponge like adsorption of various microRNAs through ceRNA[7–9]. MSCs significantly stimulate the expression of LINC01133 in neighboring TNBC cells, enhancing the traits and proliferation of cells resembling cancer stem cells. Research demonstrated that lncRNA DANCR enhances the activation of TNBC cancer stem cell indicators by preventing EZH2 from binding to CD44 and ABCG2 promoters. Reports indicate that LINC01638 prevents the degradation of c-Myc by SPOP and triggers MTDH/Twist1 signaling through its interaction with c-Myc, thus preserving the mesenchymal characteristics of TNBC cells, such as heightened EMT signaling and cancer stemness[10]. Furthermore, various other long non-coding RNAs, including LUCAT1, lncRNA-Hh, NEAT1, LINC-ZNF469-3, NRAD1, FGF13-AS1, and ES1-NEAT1, are implicated in the control of TNBC stemness by enhancing signaling pathways and regulating key factors in stem cell biology (such as Wnt/β-catenin, Hedgehog, myc, SOX2, OCT4, KLF4, and NANOG), ultimately promoting the stem-like properties of TNBC cells and facilitating tumor progression, invasion, and metastasis[6,11–13].

3. LncRNAs involved in TNBC EMT

Research has shown that extracellular matrix (ECM) is a major component of the microenvironment, playing a crucial action in regulating tumor cell growth, promoting tumor proliferation, infiltration, metastasis, and influencing treatment sensitivity. Long non-coding RNAs are involved in controlling the immune system through their impact on the tumor microenvironment, epithelial-mesenchymal transition(EMT), dendritic cells, and myeloid progenitor cells. These have been identified as predictive biomarkers for various cancers and are closely related to immune cell infiltration, making them potential therapeutic targets for TNBC[14]. EMT plays a role in the development of cancer and gives cancer cells the ability to spread by increasing cell movement, invasion, and resistance to cell death signals. AFAP1-AS1 exhibits

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carcinogenic activity in TNBC. AFAP1-AS1 is capable of triggering the Wnt/β-catenin pathway, enhancing tumor formation and cell invasion through upregulate c-myc and EMT in TNBC[15]. AFAP1-AS1 is situated in the cytoplasm, while AFAP1-AS2 enhances the progression of TNBC cells by regulating SP1 in TNBC. Moreover, the muted AFAP1-AS1 suppresses the activity of genes in the mTOR pathway, including EIF4B[16], MAPKAP1, SEH1L, SGK1, and their target NEDD4L, while enhancing the expression of SKP2 genes. The upstream interaction between AFAP1-AS2 and SP1, as well as downstream regulation of mTOR signaling, participate in the development of TNBC [17]. Migration and invasion of TNBC cells are enhanced by lncRNA PAPAS through the suppression of miR-34a. According to reports, lncRNA sONE can also inhibit eNOS induced NO production, regulate protein levels of c-Myc and TP53, and ultimately alter a group of tumor suppressor miRNAs express level [18]. Furthermore, sONE has been demonstrated to block TNBC cell movement and infiltration caused by H2S by triggering the sONE/NOS3/NO signaling pathway[19]. As members of the ZEB transcription factor family, ZEB1 and ZEB2 are crucial for EMT process[20]. Reports indicate that lncRNA LINC-ZNF469-3 boosts invasion capability and stem cell characteristics by activating the miR-574-5p/ZEB1 pathway in TNBC, leading to the advancement of lung metastasis. LncRNA ZEB2-AS1 has been shown to activate epithelial-mesenchymal transition through the PI3K/Akt/GSK3 β/ZEB2 signaling pathway to promote metastasis[21]. A different lncRNA, PVT1, has been found to enhance epithelial-mesenchymal transition and cell movement through the control of p21 and KLF5/β-catenin signaling in TNBC[22–24]. With research on tumors and TME, immunotherapy and targeted therapy have become current research hotspots and future development directions[25]. Through the study of TNBC and TME, therapeutic strategies that rely on the body's immune system function to specifically kill tumor cells or inhibit tumor growth can be provided for TNBC.

4. LncRNAs regulate cell proliferation and apoptosis

The foundation of tumor growth lies in genetic mutations that cause cells to multiply uncontrollably and prevent cell death[26]. Extensive research has also been conducted on lncRNAs involve TNBC cells proliferate and apoptosis. The primary focus of research is on the ceRNA mechanism and network formation, which involves sequestering miRNA and releasing its protein-coding counterpart from post-translational regulation. This mechanism is primarily investigated as the key molecular process underlying the biological functions of lncRNA[27]. Reports indicate that lncRNA GAS5 enhances TNBC cell death and hinders growth through the regulation of miR-378a-5p/SUFU and miR-196a-5p signaling pathways[28–30]. In TNBC, HOST2 enhances cell proliferation and migration through STAT3 by sequestering let-7b as a competitive endogenous RNA[31]. LINC00096 enhances cellular growth by binding to miR-383-5p and controlling the levels of RBM3 in TNBC[32]. LINC00339/miR-377-3p/HOXC6 signaling pathway promotes TNBC proliferation and inhibits cell apoptosis [33]. The lncRNA FAM83H-AS1 enhances the advancement of TNBC by controlling the miR-136-5p/metadherin pathway[34]. Furthermore, Multiple lncRNAs participate in regulation the growth and cell death of TNBC cells, such as HCP5[35], LncRNA NRON[36,37], LUCAT1[38], HAND2-AS1[39–41], POU3F3[42]. Further research is needed to determine the functional significance of these lncRNAs in TNBC cell proliferation and apoptosis, making them potential candidates for future research. Cyclin dependent kinases (CDKs) control the advancement of the cell cycle, being triggered by cyclin attachment and blocked by CDK inhibitors[43,44]. TNBC is largely resistant to CDK4/6 inhibitors due to the expression of CDK2/cyclin E, while free CDK2 inhibitors exhibit normal tissue toxicity, limiting their therapeutic application in TNBC[44]. P27 inhibits CDK by binding to both the cyclin E/CDK2 complex and the cyclin D/CDK4, 6 complex, playing a role in cell cycle regulation[45]. Reports indicate that LncRNA MIR100HG prevents G1 phase cell arrest by interacting with p27 to create RNA-DNA triple helix structures. Within TNBC, it has been demonstrated that LUCAT can speed up the cell cycle by controlling miR-5702[39]. Moreover, LncRNA RMST induces G0/G1 phase blockade in TNBC[46,47]. Additional mechanistic research is required to explore how lncRNAs influence the advancement of the cell cycle in TNBC cells.

5. LncRNAs regulate cell invasion and metastasis

Metastasis, a complex process involving gene regulation, signaling pathways, and cell interactions, is the primary reason for cancer-related fatalities. The significance of lncRNAs in tumor invasion and metastasis is becoming more widely acknowledged. Increased levels of GAS5 have been demonstrated to interfere with the cancer-promoting impacts caused by miR-196a-5p abnormal expression, such as cell invasion and stimulation of the signaling pathway of FOXO1/PI3K/Akt. The Trojan virus has the ability to attach to the transfer inhibitory factor ZMYND8, leading to an increase in its degradation via the ubiquitin proteasome pathway[48]. The ncRNA ST8SIA6-AS1 enhances the triple-negative breast cancer cells growth and spread by interacting with miR-145-5p/CDCA3 to block the p53/p21 signaling pathway[49,50]. By suppressing miR-218/ZFX signaling, lncRNA CCAT1 is able to enhance the movement and infiltration of TNBC cells[51]. The lncRNA MIR503HG suppresses the movement and penetration of cells in TNBC by affecting the miR-103/OLFM4 pathway[52]. Furthermore, elevated levels of seven long non-coding RNAs (MALAT1, LUCAT1, HULC, ADPGK-AS1, LINC00096, ZEB2-AS1 HIF1A-AS2) were associated with metastasis, whereas increased expression of MIR503HG showed a reduced incidence of distant metastasis[37]. The elevated levels of

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LINK-A in TNBC cells facilitate the breakdown of PLC and endogenous tumor suppressor genes Rb and p53, resulting in the diminished antigenicity of the tumor, allowing it to evade immune surveillance and enhance tumor cell migration[53]. LncRNA NAMPT-AS regulates NAMPT expression through epigenetics, regulates autophagy and promotes metastasis. In TNBC, NAMPT-AS has the ability to bring in POU2F2 to trigger the transcription of NAMPT, or function as a competing endogenous RNA to prevent the breakdown of NAMPT by miR-548b-3p[54]. Additional lncRNAs, such as LINC01096, HIF1A-AS2, AIRN, MALAT1, and HULC, play a role in the progression of TNBC through invasion and metastasis[2,46]. Overall, the research suggests that long non-coding RNAs are crucial in controlling invasion and spread of TNBC cells.

6. LncRNAs involved in angiogenesis

TNBC patients exhibit increased angiogenesis compared to other types of breast cancer patients, with angiogenesis playing a crucial role in breast cancer growth and spread. Microvessel density (MVD) serves as a predictive factor for familial cancer, with vascular endothelial growth factor being the primary angiogenic factor of great significance in TNBC[55]. Recent studies suggest that lncRNAs may be associated with angiogenesis in TNBC. The XBP1SBM peptide produced by lncRNA stimulates the growth of blood vessels and spread of TNBC via the XBP1s pathway. Deprivation of glutamine led to increased transcription of XBP1s, which elevated the levels of XBP1SBM, consequently trapping XBP1s in the nucleus to boost VEGF expression[56]. XBP1SBM also enhanced glutamine levels in TNBC, ultimately supporting angiogenesis and metastasis[44]. The lncRNA ASRPS is capable of binding to STAT3 directly, preventing STAT3 phosphorylation, which results in decreased VEGF expression and angiogenesis[57]. In addition, extracellular vesicle SNHG12 promotes HUVEC angiogenesis through PBRM1 and MMP10, and SNHG12 enhances cancer malignancy by promoting HUVEC angiogenesis through the PBRM1-MP10 axis[57]. Vasculogenic mimicry (VM) is a unique vascular network found in malignant tumors that is not made up of endothelial cells. This network supplies oxygen and nutrients to tumor cells, aiding in the advancement of the tumor. The expression of long non-coding RNA TP73-AS1 is increased in TNBC tissues that are positive for vasculogenic mimicry, contributing to the development of TNBC vasculogenic mimicry through activation of the miR-490-3p/TWIST1 pathway[58]. Thus, focusing on the development of TNBC VM could aid in cancer treatment, offering a novel potential indicator of prognosis and target for therapy in TNBC[56].

7. LncRNAs as a markers for the diagnosis of TNBC

In order to investigate the role of lncrna in the diagnosis of tnbc patients, many researchers have established study groups for tnbc, with non tnbc patients and healthy individuals as control groups, to study the differences in lncrna expression levels in tissue specimens, plasma, and exosomes between different groups. It has now been discovered that there are differential expressions of various lncrnas in tnbc compared to non tnbc patients or healthy controls. For example, linc01096 is overexpressed expression in tnbc, significantly higher than in normal breast tissue and adjacent tissues, suggesting that linc01096 could be useful as a marker for the diagnosis of tnbc[32]. Recently several studies also demonstrated that there is increasing evidence shown lncrnas have diagnostic potential for clinical tnbc patients. The expression levels of lncrnas x inactive-specific transcript (xist) and nuclear paraspeckle assembly transcript 1 (neat1) were significantly higher in the tnbc group than in the benign breast lesion and healthy patients group[59], which could be used to distinguish tnbc from other breast cancer types. Fan identified three lncrnas including ac091043.1, ap000924.1 and foxcut maybe have strong diagnostic value for tnbc diagnosis by comprehensive analysis of lncrna expression profiles and clinical data of 1097 breast cancer samples from tcga database[60]. The research results show that lncrna anril, hif1a-as2, and uca1 have diagnostic value for tnbc, and the combined diagnostic performance of the three is 0.934 in the area under the curve (auc), which is better than the diagnostic effect of using them alone [61,62]

8. LncRNA in prognostic evaluation of TNBC

TNBC is the most serious subtype with high invasion, and distant metastasis, and different prognosis[62]. Early comprehension of the disease prognosis can lead to improved treatment for patients and better prognostic outcomes. Current prognostic indicators are inadequate for accurately forecasting the survival rate of TNBC. Variations exist in the lncRNA expression in TNBC, with growing evidence indicating the prognostic value of lncRNA for TNBC patients, encompassing OS, DFS, and metastasis. Various long non-coding RNAs such as AC091043.1, AP000924.1, FGF10-AS1, AL354793.1, AC010343.3, and FOXCUT have been linked to the clinical outlook of patients with triple-negative breast cancer[63]. Select LINC00989 to construct a prognostic feature linRNA combination with clinical markers CEA and CA125[64]. A meta-analysis revealed a strong association between the levels of 9 long non-coding RNAs (lncRNAs) - HIF1A-AS2, SNHG12, MALAT1, HOTAIR, LUCAT1, LINC00096, HULC, LINC000173, and ZEB2-AS1 - and the presence of lymph node metastasis[65].

8. Conclusion and future vision

Many lncRNAs are abnormally expressed in TNBC and participate in proliferation, apoptosis, EMT, progression,

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invasion, and metastasis, affecting prognosis, which serve as potential therapeutic targets for TNBC. Functional lncRNAs and their regulatory factors have the potential to develop novel lncRNA therapy methods targeting lncRNAs, which have clinical significance. Nevertheless, multiple factors and obstacles must be taken into account. There is still a lack of knowledge regarding the various types and pathways of lncRNA in TNBC, and further research is necessary to uncover their potential as biomarkers or targets for therapy. Large scale studies on the translation of lncRNAs are needed to fully understand and utilize their potential in TNBC treatment. Moreover, it is crucial to conduct additional analysis on these compounds in order to uncover their possible significance as therapeutic targets, as well as diagnostic and prognostic indicators for TNBC treatment in clinical settings.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Ethics Committee of the Fourth Affiliated Hospital, Zhejiang University School of Medicine, China (protocol code K2022011 and date of approval January 12, 2022), and also Approval of Ethics Review by the Medical Ethics Committee of Rizhao People's Hospital (2021- Ethical Review-KY-42, and date of approval November 20, 2022).

HUMAN AND ANIMAL RIGHTS

Research Involving Humans

Not applicable.

Research Involving Animals

Not applicable.

Research Involving Plants

Not applicable.

CONSENT FOR PUBLICATION

Not applicable..

AVAILABILITY OF DATA AND MATERIALS

Not applicable..

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Not applicable

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