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Review Article

Long Non-Coding RNAs (lncRNA) Are Key Factors in the Complex Puzzle of Breast Cancer Immunopathogenesis: A Review Study

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Abstract

Long non-coding RNAs (LnC RNAs) exert a substantial influence on breast cancer by exerting both positive and negative control over signaling pathways. LncRNAs are transcribed similarly to mRNA, however they do not undergo the process of translation to become proteins. Initially, these RNAs were classified as "Junk RNAs" since they were thought to lack any practical use. Comprehensive research has demonstrated that they play a vital role in the progression of various diseases, including malignancies, allergies, autoimmune and autoinflammatory disorders, infectious diseases, cardiovascular disease, and atherosclerosis. Despite multiple efforts, breast cancer continues to be a substantial concern and is one of the most prevalent forms of malignancy, especially among women. Recently, researchers have been dedicated to acquiring a deeper understanding of how complex signaling pathways are controlled by Lnc-RNAs in breast cancer. In the setting of breast cancer, Lnc-RNAs have a contradictory effect. The objective of this study is to Review and categorize previous studies An investigation was conducted to examine the impact of long non-coding RNAs on breast cancer. This will improve the capacity to identify topics of research that require further investigation in future studies.

Keywords: Breast; Cancer; Immunology; Long-Non-Coding; RNA; Signaling Pathway.

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Introduction

Ensuring the safety and security of the breasts is paramount. Both male and female genital anatomy have structures known as breasts, which serve multiple functions, including the production of breast milk. The apocrine glands are situated in the pectoral region of the body and their primary function is the secretion of breast milk. The breasts, which are a component of the genital anatomy in both males and females, serve various roles, including breastfeeding. The apocrine glands are situated in the pectoral region of the body and are

responsible for the secretion of breast milk. **Figure 1** depicts the anatomical structure of the glandular organ known as the breast. It consists of 15 to 20 lobes, each containing lobules responsible for milk secretion. Ducts transport the milk from the lobules to the nipples. The nipples contain nerves and ducts. The amount of fatty tissue present influences the size of the breast. The breast also includes lymph nodes, which are part of the immune system, as well as muscles, fibrous skin, blood vessels, nerves, and areolae. The areolae

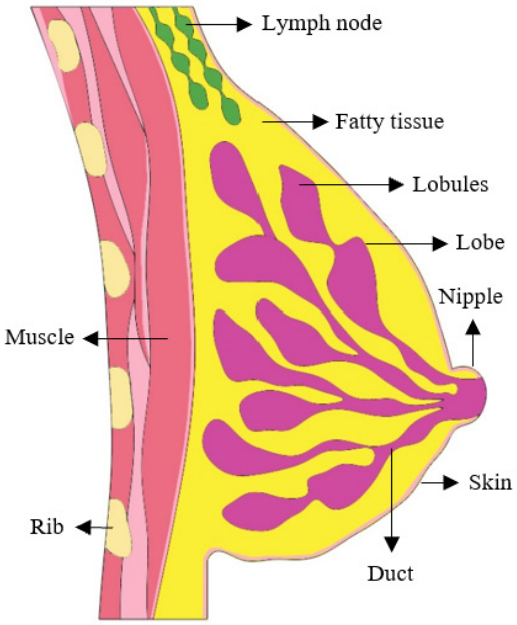

Figure 1. Breast structure

secrete lubricating oil to protect the nipples (1). The female breast function is regulated by three hormones: prolactin, estrogen, and progesterone. The pituitary gland releases prolactin, which promotes the growth of the mammary glands and controls the production of progesterone hormones. Progesterone increases the size and number of lobules. The duct serves as a secondary branch that is stimulated by estrogen to enhance the transportation of milk (2).

Cancer typically arises from the unregulated proliferation of cells. Several factors can increase the likelihood of developing breast cancer, including older age, a family history of the disease, previous occurrences of non-cancerous tumors, being overweight, and alcohol consumption (3). There are two distinct categories of breast cancer: non-invasive, which does not spread beyond its initial location in the breast, and invasive. The classification of invasive cancer differs based on the specific region of the breast that is impacted: Invasive ductal carcinoma and aggressive lobular carcinoma are two types of aggressive breast cancers. The initial form manifests within the ducts and subsequently disseminates to other regions of the breast or to other areas of the body, a process known as metastasis. Usually, the latter originates in the lobules of the chest and then metastasizes to other areas of the body or chest (4). Hence, there exists a diverse range of therapeutic modalities for breast cancer, encompassing surgical intervention, chemotherapy, and radiotherapy. In addition to this, gene therapy is also a viable alternative. Following a mutation, the protein's normal conformation is reinstated to prevent or treat illnesses such as cancer. Due to changes in the DNA sequence, proteins can be either deleted or generated with errors (5). Researchers are evaluating long non-coding RNAs (lncRNAs) for their potential use in gene therapy. It is crucial to emphasize that only a minority of RNAs can encode proteins. RNAs that are unable to encode proteins and have a length exceeding 200 nucleotides are referred to as lncRNAs. These lncRNAs do not possess an open reading frame, which is a sequence of codons that includes a start and an end codon for protein synthesis (6). LncRNAs coordinate the arrangement of RNA and proteins at the transcriptional level through unique processes. RNA polymerase 2 transcribes them in a manner that is comparable to mRNA. Multiple papers have provided evidence that LncRNA-RNAs have a role in the development of breast tumors (7, 8). Moreover, Long non-coding RNAs (LncRNAs) have a pivotal function in regulating gene expression and can have an impact on the initiation and advancement of cancer (9). The objective of this study is to examine existing studies on non-coding RNAs that demonstrate efficacy in combating breast cancer. Consequently, we will sequentially present lncRNAs and signaling pathways that are pertinent to this type of cancer, and analyze their interconnections.

Signaling Pathway and lncRNAs

Every subsection commences with an elaborate depiction of the signaling pathway, followed by an introduction to the LncRNAs that are linked to it. Moreover, **Figure 2** depicts these correlations in a visual format.

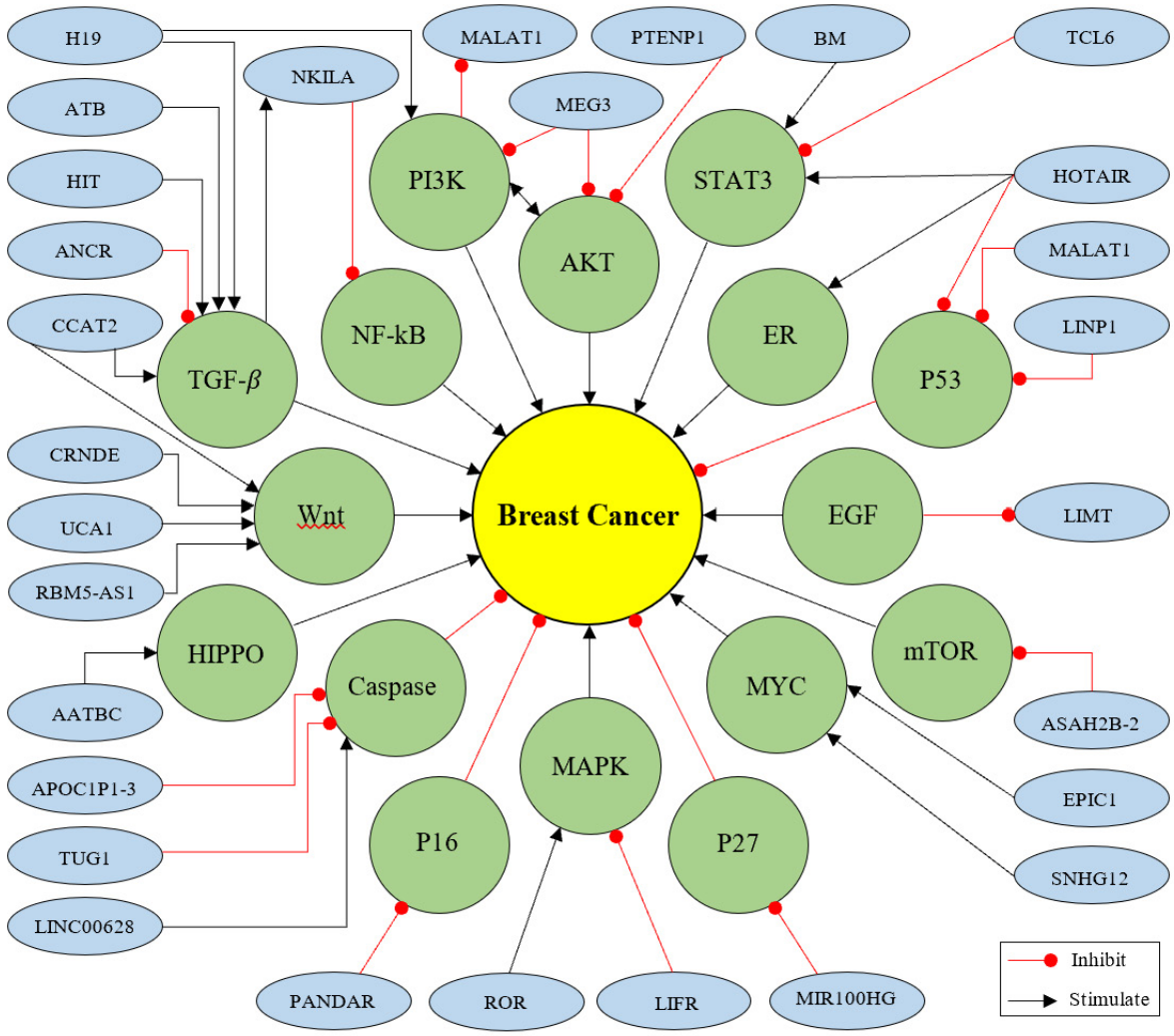

Figure 2. A schematic of the relationship between pathways and LncRNA-RNAs in breast cancer.

m-TOR signaling pathway and related lncRNAs

The mTOR pathway, comprising many proteins, effectively prevents resistance to endocrine therapy in breast cancer. The growth of breast cancer cells is facilitated by the action of this pathway. In addition to its efficacy in protein creation, metabolism, and autophagy, The mTOR pathway is also crucial in tumor formation (10). During experiments, everolimus effectively inhibits the activity of p70S6 and 4E-BP1, which are essential elements of this pathway. Although this medicine triggers the expression of LncRNA-ASAH2B-2 and thus activates the mTOR pathway, its therapeutic potential is not significant, and its clinical impact is moderate, as documented by Li et al (11). The oncogene LNCRNA-ASAH2B-2 is situated in close proximity to the 10q11.23 region of the chromosome. The downregulation of these long non-coding RNAs (lncRNAs) results in the repression of the mechanistic target of rapamycin (mTOR) signaling pathway, hence impeding the proliferation of breast cancer cells. SiRNA is capable of efficiently suppressing the expression of LncRNA-ASAH2-2. SiRNA transfection into two hundred thousand cancer cells resulted in the inhibition of LncRNA-ASAH2B-2 expression. The number of these cells was determined using qRT-PCR and western blot techniques. This approach unveiled a reduction in the density of cells.

TGF-β signaling pathway and related lncRNAs

TGF-β is a potent stimulator of epithelial-mesenchymal transitions (EMTs). Moreover, it is postulated that this pathway contributes to the dissemination of malignancies to distant anatomical sites. Several studies have shown that cancer cells stimulate the activation of TGF-β and generate its receptor (12). Furthermore, the

activation of the Smad-cascade by TGF-β leads to the growth of tumors associated to epithelial-mesenchymal transition (EMT) (13). A Smad protein is a constituent of the TGF-β protein family responsible for controlling cell signaling and gene expression. According to Li et al. (14), they found that a specific type of noncoding RNA called LncRNA-ANCR acts as a tumor suppressor. LncRNA-ANCR is composed of 855 nucleotides. This Long non-coding RNA (LncRNA) hinders the process of cellular differentiation. LncRNA-ANCR suppresses the TGF-β pathway by repressing the expression of the RUNX2 gene, which is a transcription factor. Moreover, epithelial-mesenchymal transition (EMT) is inhibited by this lncRNA. Furthermore, it has offered a groundbreaking remedy for the identification and management of breast cancer. Experimental findings demonstrate that the expression of ANCR is reduced in MCF7 cells when exposed to TGF-β. Overexpressing ANCR suppresses the activity of Smad2/3, a critical component of the TGF pathway. In addition, this tumor inhibitor diminishes the capacity of cells to infiltrate and traverse the TGF-β pathway. As stated by Wu et al (15), The lncRNA-TCL6, sometimes referred to as long non-coding RNA colon cancer-associated transcript-2, has a significant impact on tumor growth by influencing the TGF-β pathway. The gene exhibits elevated expression in breast cancer tissue relative to adjacent non-cancerous tissue. Suppression of LncRNA-CCAT2 results in a reduction in cancer cell proliferation, invasion, and migration. Furthermore, the levels of LncRNA-CCAT2 are increased in three distinct types of breast cancer cells, specifically MCF7, LCC9, and MDA-MB-231, exhibiting a roughly four-fold rise in comparison to normal breast tissue cells. Cancer growth and metastasis can be hindered by infecting cancer cells with siCCAT2, leading to the disruption of CCAT2 expression. Introducing siCCAT2 into cancer cells enhances apoptosis by approximately threefold and induces entry into the G1 and G0 phases of the cell division cycle, hence impeding cell division. Recent research (16-18) has demonstrated that LncRNA-H19 exhibits significant expression levels in breast cancer and contributes to the facilitation of the TGF-β-induced EMT signaling pathway.

The expression of LncRNA-H19 is upregulated in cancer tissue compared to healthy tissue, facilitating the differentiation between healthy and cancerous tissues. Utilizing lncRNA can aid in the timely identification of breast cancer, a leading contributor to mortality. H19 and HER2 have a connection that enhances the growth of cancer cells. The researchers Richards et al. (19) examined the impact of LncRNA-Hit on breast cancer. This study demonstrates that the upregulation of this Long non-coding RNA (LncRNA) amplifies the signaling pathway of Epithelial-Mesenchymal Transition (EMT) triggered by TGF-β. Knocking down LncRNA-HIT in 4T1 cells leads to a decrease in migration, invasion, tumor development, and metastasis. Shi et al.(20) conducted a study which established that LncRNA-ATB (Long noncoding RNA activated by transforming growth factor) exerted an influence on the advancement of breast cancer. Overexpressing this LncRNA in TR SKBR-3 cells resulted in increased cancer cell proliferation, migration, and invasion. In addition, the existence of ATB causes the cancer cells to become resistant to trastuzumab, an anti-cancer drug.

Wnt signaling pathway and related lncRNAs

The Wnt signaling pathway regulates various biological activities, such as cell growth and differentiation. Breast cancer can be acquired by this pathway. This route consists of multiple intermediaries, including the antheral-catenin protein present in both the nucleus and cytoplasm. Wnt enhances the activity of EMT. The user's text is (21) . Xiao et al.(22) found that the urothelial carcinoma-associated 1 (LncRNA-UCA1) enhances the proliferation and infiltration of breast cancer via activating the Wnt pathway. Research indicates that one of these isoforms has a crucial role in the onset and progression of breast cancer. This lncRNA promotes the growth of tumors and inhibits the programmed cell death (apoptosis) of cancer cells by decreasing the activity of P27 and other proteins that prevent tumor formation. Furthermore, the decrease in UCA1 expression results in a decrease in the ability of cancer cells to invade. The suppression of this LncRNA effectively reduces the mesenchymal characteristics of cells during Epithelial-Mesenchymal Transition (EMT). The outcome is a reduction in mesenchymal cell markers and an elevation in epithe-

lial cell markers. This study aims to decrease the growth, spread, and movement of cancer cells. The UCA1 gene is silenced to deactivate the Wnt pathway through the inhibition of the beta-catenin protein. The study conducted by Huan et al. (23) investigates the potential use of the colorectal neoplasia differentially expressed gene (LncRNA-CRNDE) in the treatment of breast cancer. CRNDE is characterized as an oncogene that stimulates the development of tumors by activating the Wnt pathway in collaboration with the beta-catenin protein. LncRNA-CRNDE was initially discovered on the 16th chromosome's long arm in colorectal cancer. Patients diagnosed with breast cancer who have CRNDE gene expression exhibit a bleak outlook, since its existence signifies the advancement of the disease. This lncRNA is essential for tumor growth and acts as a stimulant for their proliferation. The expression of CRNDE was observed to be 80-fold greater in breast cancer cells following the introduction of the pcDNA3.1 vector containing this gene. In addition to TGF-β, which was previously noted, Cai et al. investigated the impact of LncRNA-CCAT2 on other signaling pathways (24). The study suggests that an elevated level of CCAT2 is associated with various types of cancer, including breast cancer, lung cancer, esophageal squamous cell carcinoma, and gastric cancer. This is achieved by controlling the Wnt signaling pathway. Therefore, this long non-coding RNA (lncRNA) promotes the growth of cancer cells and their metastasis to other organs, while simultaneously reducing the efficacy of chemotherapy. The lncRNA is predominantly situated within the cellular nucleus, specifically on chromosome 8q24.21. Hypoxia-induced accumulation of RBM5-AS1 (RBM5 antisense RNA 1) triggers the activation of the Wnt/β-catenin pathway, hence promoting the proliferation, migration, and invasion of breast cancer cells. Li et al. acquired the findings (25).

HIPPO signaling pathway and related lncRNAs

The HIPPO signaling pathway promotes the metastasis, invasion, and migration of breast cancer cells. The YAP1 protein carries out this task. In addition to CTGF, YAP1 plays a crucial function in the transcriptional control of other genes. As a result of inhibiting YAP1, cancerous cells are less likely to invade and migrate (26). The expression of the apoptosis-associated transcript in bladder cancer (LncRNA-AATBC) is markedly elevated in breast cancer, leading to the activation of the Hippo pathway. The YBX1 protein interaction triggers the activation of the Hippo pathway, resulting in the infiltration and movement of breast cancer cells. By suppressing the target gene with siRNA, AATBC expression is reduced, resulting in Diminished migration and infiltration of malignant cell. The prognosis for cancers that exhibit elevated levels of LncRNA expression is bleak, and they are typically at an advanced stage of development. The microarray data indicates that the level of gene expression is 11 in healthy tissue and 153 in malignant tissue. Furthermore, AATBC controls the expression of EMT and metastatic markers, as documented by Wang et al. (27).

JAK/STAT signaling pathway and related LncRNAs

The Janus kinase signal transducer and transcription activator pathway (JAK/STAT) requires three essential components. (1) A transmembrane receptor facilitates the passage through the cell membrane; (2) A Janus kinase or JAK attaches to the receptor; (3) A signal transducer and transcription activator or STAT conveys molecular signals to the nucleus and DNA (28). Upon activation, the JAK2 gene facilitates the transport of growth factors and cytokines to the nucleus, hence promoting cell growth, differentiation, and migration. The JAK2 gene is responsible for encoding a protein that promotes cellular growth and division. This protein mediates the transmission of chemical signals from the extracellular environment to the nucleus via the JAK/STAT signaling pathway. It consists of receptor tyrosine kinase (RTK), JAK, and STAT3. The tyrosine kinase receptor, functioning as a trans-membrane receptor, consists of two distinct components: alpha and beta. Upon binding of the cytokine to its receptor, Janus kinase, which is located on the intracellular region of the receptor, through a process called phosphorylation, the receptor receives a phosphate group. This process results in the recruitment of STAT messenger and transcription activator proteins, which are then phosphorylated and form a dimeric complex. Dimers

enter the nucleus and attach to DNA, leading to the activation of gene transcription. A protein kinase is an enzyme that enhances the levels of phosphorus (29). Zhang et al. (30) conducted a study revealing that T-cell leukemia/lymphoma 6 (TCL6) is connected to the JAK/STAT pathway. A lncRNA called TNG1 or TNG2 is found on chromosome 14q32. The research has shown that TCL6 has the potential to suppress tumor growth. Furthermore, the correlation between TCL6 and immune infiltration suggests that it could serve as a molecular marker for predicting breast cancer prognosis. Wang et al. (31) conducted a study that discovered a correlation between long non-coding RNA for brain metastasis (LncRNA-BM) and the JAK/STAT system. This particular form of noncoding RNA promotes the dissemination of cancer cells to distant locations inside the body in persons diagnosed with breast cancer. Brain metastases in clinical mouse models exhibited a positive correlation with higher expression of BM. The HOTAIR gene is situated on chromosome 12, positioned between the HOXC12 and HOXC11 genes. A publication by Zhang et al. has been released. The findings from references (32-34) indicate that this LncRNA has the ability to stimulate the JAK/STAT pathway by suppressing miR-7, which is a tumor suppressor.

Caspase signaling pathway and related LncRNAs

Caspase proteins and protease enzymes regulate cell apoptosis. The expression of Caspase 3 is dysregulated during the process of carcinogenesis. During intrinsic apoptosis, the activation of pro-Caspase 3 is initiated by Caspase 8, leading to the generation of Caspase 3. Furthermore, cytochrome c has the capability to be discharged from mitochondria due to an external apoptotic trigger. It is hypothesized that the cytochrome that is released activates Caspase 9, hence triggering the activation of Caspase 3. Specifically, Caspase 3 induces cellular apoptosis via impacting the nucleus. Caspase 3 breaks down and triggers the activation of Caspase 6, 7, and 9 in the process of apoptosis. Apoptosis is regulated by this consecutive process (35). LINC00628 is a LncRNA. It prevents breast cancer cell growth and promotes programmed cell death. LINC00628 upregulates Caspase 3 and downregulates Bcl2. Chen et al.(36) have documented that this results in the initiation of mitochondrial apoptosis. According to the study conducted by Li et al.(37), Taurine up-regulated gene 1 (TUG1) is a long non-coding RNA (LncRNA) that is situated in the 22q12.2 region of the chromosome. The expression of TUG1 is increased in breast cancer tissues and invasive cell lines, and it is correlated with clinical variables such as tumor size and metastasis. Reducing TUG1 dramatically decreases the proliferation, migration, and invasion of breast cancer cell lines (MDA-MB-231 and MDA-MB-436). The rate of cell apoptosis increased as a result of heightened Caspase 3 and 9 activities under SiTUG1 therapy. TUG1 plays a pivotal function in the progression of breast cancer and can be used as a biomarker for the detection and treatment of breast cancer. The LncRNA-APOC1P1-3, a pseudogene of the Apo-lipoprotein C-I, is abundantly produced in breast cancer and is situated at the chromosomal location 19q13.2. The APOC1P1 promoter region exhibits hypo methylation, leading to the activation of transcription and subsequent rise in APOC1P1-3 production. The LncRNA reduces the acetylation of tubulin, hinders the activity of caspase 3, and hampers apoptosis by attaching to tubulin (38).

EGF signaling pathway and related LncRNAs

Breast cancer is linked to EGF signaling. Growth factor EGF has 53 amino acids. This cytokine helps many cells grow and metabolically. This growth factor promotes epidermal growth. The majority of breast cancer cells and tissue have HER1 receptors. When activated, this keratinocyte generates epidermal growth factor, which promotes breast cancer cell development (39). LncRNA-LIMT exerts an inhibitory effect on metastasis in breast cancer. On the other hand, the EGF signaling pathway (as demonstrated by Sas-Chen et al.) (40). hinders its progress. When EGF binds to its receptor, it triggers the creation of an active EGFR, which in turn causes the phosphorylation of the receptor's intracellular region. The activation of the RAS (rat sarcoma virus) initiates the ERK (extracellular-signal-regulated kinase) pathway. The ERK protein enhances cancer cell survival and migration by suppressing the transcription of the LncRNA-LIMT gene in the nucleus.

NF-kB signaling pathway and related LncRNAs

Typically, the nuclear factor-KB (NF-kB) forms a complex with the inhibitory protein IkB (inhibitor of NF-kB) in the cytosol when it is inactive. Upon the activation of IkB kinase and subsequent phosphorylation of IkB, IkB separates from NF-kB and undergoes degradation by the proteasome. After activation, activated NF-kB is found on a particular sequence called the response element within the nucleus. Besides DNA polymerases and coactivators, the DNA/NF-kB complex engages in DNA transcription with the assistance of other proteins (41). NKILA, also known as NF-KappaB Interacting LncRNA-RNA, is a specific subtype of LncRNA that engages in interactions with NF-kB. According to Liu et al. (42), NKILA can form a stable ternary complex with NF-kB/IkB. This combination prevents IkB

Table 1. The function of LncRNAs and signaling pathways involved in breast cancer.

No.	Lnc-RNAs	Function	Signaling pathway	Breast Cancer	Reference
1	ASAH2B-2	Inhibits	m-TOR	↓	(11)
2	ANCR	Inhibits	TGF-β	↓	(14)
3	CCAT2	Stimulates	TGF-β	↑	(15)
4	H19	Stimulates	TGF-β	↑	(16-18)
5	HIT	Stimulates	TGF-β	↑	(19)
6	ATB	Stimulates	TGF-β	↑	(20)
7	UCA1	Stimulates	Wnt	↑	(22)
8	CRNDE	Stimulates	Wnt	↑	(23)
9	CCAT2	Stimulates	Wnt	↑	(24)
10	RBM5-AS1	Stimulates	Wnt	↑	(25)
11	AATBC	Stimulates	HIPPO	↑	(27)
12	TCL6	Inhibits	JAK/STAT	↓	(30)
13	BM	Stimulates	JAK/STAT	↑	(31)
14	HOTAIR	Stimulates	JAK/STAT	↑	(32-34)
15	LINC00628	Stimulates	Caspase	↓	(36)
16	TUG1	Inhibits	Caspase	↑	(37)
17	APOC1P1-3	Inhibits	Caspase	↑	(38)
19	NKILA	Inhibits	NF-kB	↓	(42)
20	HOTAIR	Inhibits	P53	↑	(44)
21	LINP1	Inhibits	P53	↑	(45)
22	MALAT1	Inhibits	P53	↑	(46)
23	MEG3	Inhibits	PI3K/AKT	↓	(47)
24	MALAT1	Inhibited	PI3K/AKT	↓	(49)
25	PTENP1	Inhibits	PI3K/AKT	↓	(50)
26	H19	Stimulates	PI3K/AKT	↑	(18)
27	ROR	Stimulates	MAPK	↑	(52)
28	LIFR	Inhibits	MAPK	↓	(53)
29	EPIC1	Stimulates	MYC	↑	(55, 56)
30	SNHG12	Stimulates	MYC	↑	(57, 58)
31	HOTAIR	Stimulates	ER	↑	(59)
32	MIR100HG	Inhibits	P27	↑	(60)
33	PANDAR	Inhibits	P16	↑	(61)

dissociation by inhibiting phosphorylation. Thus, the combination inhibits NF-kB signaling and inflammation-related cancers. NF-kB is restricted to the ternary complex. Thus, NKILA expression is connected to breast cancer metastasis and poor patient outcomes.

P53 signaling pathway and related Ln-cRNA-RNAs

The *P53* gene has been recognized as a tumor suppressor in breast tumors by inhibiting the proliferation and mitosis of cancer cells. According to reports, mutations in the gene encoding this protein are linked to unfavorable prognoses in cancer patients (43). According to Yu et al (44), the LncRNA can promote the spread of breast cancer by suppressing the P53 protein Liang et al. (45) have reported that LINP1, a LncRNA involved in the non-homologous end-joining pathway, is associated with breast cancer. The gene is situated on chromosome 10. Suppression of LINP1 expression results in a higher count of cells in the G1 phase and a lower count in the S phase of breast cancer. Thus, Overexpression of LINP1 impedes apoptosis in breast cancer cells. Thus, it has a pivotal function in the rapid increase of cancer cells. Western blotting revealed that depletion of LINP1 resulted in decreased expression of cell cycle regulator genes cyclinD1, cyclinD3, and CDK4. Cytometry investigates the involvement of LINP1 in the process of apoptosis. LINP1 increased damaged cell apoptosis. MDA-MB-231 cells increased apoptosis from 14.82 to 18.86%, whereas MDA-MB-468 cells increased it from 20.64 to 36.1%.

An inquiry into the function of P53 in controlling the expression of LINP1 was conducted using the PROMO software. Overexpression of LINP1 can partially inhibit the action of P53, but overexpression of P53 can have the opposite effect, preventing cancer cells from migrating and becoming more invasive. LncRNA-RNA is the abbreviation for Long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1. The user has provided the term "MALAT1". When non-small cell lung cancer (NSCLC) is in its early stages, it was identified as a potential biomarker for metastatic disease. It has been found that MALAT1, along with DBC1 (a gene expression regulator), controls P53 activity by Chen et al (46). As a result of the combination of MALAT1 and DBC1, MALAT1 inhibits the interaction between DBC1 and SIRT1 and increases the deacetylation activity of SIRT1 (a cholesterol sensor). As a result of MALAT1, SIRT1 is prevented from being acetylated, which is necessary for the activity of P53. Increased MALAT1 activity reduces the acetylation of P53.

PI3K/AKT signaling pathway and related Ln-cRNAs

Phosphatidylinositol 3-kinases (PI3Ks) have a crucial function in the growth, proliferation, and differentiation of cells in breast cancer. Enzymes and AKT, also known as Protein Kinase B, are interconnected. These enzymes participate in the process of phosphorylation (47). MEG3, an imprinted gene, is a long non-coding RNA (Ln-cRNA) that functions to suppress tumor growth. Zhang et al. (48) found that the overexpression of MEG3 disrupts the processes of cell division, invasion, and angiogenesis in breast cancer cells. This LncRNA suppresses the phosphorylation of the PI3K/AKT signaling pathway. A western blot assay is employed to examine the function of MEG3.

MALAT1 regulates the activity of P53, as previously mentioned Xu et al. established that the PI3K/AKT pathway induces a reduction in the expression of this long non-coding RNA (Ln-cRNAs), resulting in enhanced invasiveness and migration of breast cancer cells (49). Chen et al. (50) discovered a correlation between the phosphatase and tensin homolog pseudo-gene (Ln-cRNA-PTENP1) and the AKT pathway. The Ln-cRNA is situated on chromosome 10. PTENP1 likely plays a crucial role in suppressing the formation of breast cancer tumors by negatively regulating the AKT pathway. There is a notable disparity in the rates of growth and migration observed across the groups that possess this Ln-cRNA. The presence of the indicated LncRNAs leads to a decrease in the p38 protein, which is a crucial element of this pathway. The final Ln-cRNAs in the sequence is H19, which is an oncogene that exhibits increased expression levels in breast cancer. There is data indicating that this LncRNAs enhances the EMT and activates the PI3K/AKT signaling pathways in response to TGF-β. The PI3K/AKT pathway functions to suppress cell death (18).

MAPK signaling pathway and related LncRNA-RNAs

The Mitogen-activated protein kinase (MAPK) pathway facilitates the transmission of information from the external environment to the nucleus, where certain genes control cellular growth and division. This route has both carcinogenic and anti-cancer properties, which vary depending on the specific tissue where it is expressed. Three signaling pathways are involved in the transmission of this specific pathway: ERKs, JNKs, and P38/SAPKs are types of protein kinases that are involved in signaling pathways outside of cells. ERKs are extracellular signal-regulated kinases, JNKs are Jun amino-terminal kinases, and P38/SAPKs are stress-activated protein kinases (51). Peng and his coworkers The user's text is (52). Linc-RoR, a type of RNA that does not code for proteins and is located in the non-coding regions between genes, has been demonstrated to be necessary for effective collaboration with the MAPK/ERK pathway. The expression of this LncRNAs is upregulated independently of estrogen, leading to an elevation in tamoxifen resistance. A separate study conducted by Wang et al. (53) examined the impact of leukemia inhibitory factor receptor (LncRNA-LIFR) on breast cancer. The cytokine LIF, which is released into the extracellular space, plays a pivotal function in various biological processes. These activities include the initiation of blood cancer cells, the attachment of embryos to the uterus, the ability of stem cells to repair themselves, the aggressive expansion of cells, the development of the nervous system, and the advancement of cancer. Therefore, they proved that individuals diagnosed with luminal B-type breast cancer and displaying a significant level of LIFR expression have a higher probability of survival. Increased production of this long non-coding RNA suppresses the MAPK signaling pathway.

MYC signaling pathway and related LncRNA-RNAs

The MYC signaling system controls gene transcription, which, in conjunction with certain LncRNAs, promotes the development of breast cancer (54). The study conducted by Wang et al. (55) reported that the presence of an epigenetically induced MYC interacting long non-coding RNA 1 (EPIC1) enhances the development of tumors through the activation of the MYC signaling pathway. This LncRNA is situated on chromosome 22q13.31(56). SNHG12, often referred to as Small Nucleolar RNA Host Gene 12, is a part of the LncRNA-RNA gene family situated on chromosome 1. Several studies have shown that this LncRNA can promote the development of cancer by enabling the activation of the MYC pathway (57, 58).

Other signaling pathways

LncRNA-HOTAIR up-regulation amplifies the estrogen receptor (ER) signaling pathway, leading to increased proliferation, survival, migration, invasion, and resistance to chemotherapy (59). MIR100HG is a lengthy RNA molecule that enhances cell growth by impeding the activity of the P27 protein. There is empirical data indicating that this protein operates as a tumor suppressor (60) . Additionally, there exists a protein called P16 that inhibits the transformation of cells into malignant cells. Therefore, the nuclear LncRNA called LncRNA-PANDAR collaborates with protein complexes like PRC1 to decrease the production of P16, leading to the proliferation of cancer cells (61). **Table 1** provides a concise summary of the information that has been presented thus far.

Conclusion

Recent studies have shown that LnC RNAs have a dual function in the progression of breast cancer. LncRNAs have a crucial impact on breast cancer by exerting both positive and negative control over signaling pathways. Consequently, the impact of their interactions with signaling pathways, such as LncRNA-MALAT1's associations with the P53 and PI3K pathways, dictates whether they impede or facilitate tumor proliferation. Signaling pathways can exert an influence on long non-coding RNAs. The EGF signaling pathway promotes the migration of cancer cells by suppressing LncRNA-LIMT. The review study revealed that a multitude of LncRNAs have the potential to serve as biomarkers for breast cancer. Hence, the potential therapeutic applications of LncRNAs and their signaling pathways can be harnessed following a comprehensive assessment of their efficacy. These tactics are expected to be more efficacious than the conventional ones. Nevertheless, further investigation is required as

the research in this domain is still in its nascent phase. Developing a deeper understanding of the exact role of Lnc RNAs in breast cancer will increase their effectiveness as diagnostic and therapeutic biomarkers in the future. In addition, Long non-coding RNAs (Lnc RNAs) are being proposed as potential candidates for therapeutic intervention in this specific illness.

Ethics approval

This study was reviewed and approved by Abadan University of Medical Sciences with the approval number: IR.ABADANUMS.REC.1402.048, dated 11 July 2023.

Consent for publication

All co-authors have read and agreed with the content of the manuscript.

conflict of interests

The authors declare that they have no conflict of interest.

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Authors' contributions

A-SB and MR-MS designed the study and edited the manuscript. M-L, MS-S, and F-SM contributed in comprehensive research and writing the original-draft. E-KS, and R-S participated in manuscript editing and design the figures. All authors read and approved the final manuscript.

Availability of data and materials

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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