An Insight about Long Non-Coding RNAs Possible Correlation with Breast Cancer

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Abstract

In women, breast cancer is the second leading cause of death worldwide. With an expected 22,700 new cases in 2020 and a projected 46,000 in 2050, breast cancer is the most frequent malignancy in Egyptian women and accounts for 38.8 percent of cancers. Breast cancer is responsible for the second-highest number of cancer-related deaths, after liver cancer. It is not yet known what precise mechanisms are responsible for the development of breast cancer. that breast cancer, like other malignant cancers, is regulated in part by long non-coding RNAs (lncRNAs). Breast cancer malignant behaviours such as cell proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), and apoptosis are all regulated by lncRNAs, and their roles in this process are briefly discussed in this review.

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Introduction:

Almost 31% of all cancers diagnosed in women are breast cancers, making it the most common form of cancer in women and the second leading cause of cancer death among women overall. (1,2)

Breast cancer accounts for 38.8 percent of all malignancies diagnosed in women in Egypt, with a number of about 22,700 new cases in 2020 and a projected number of approximately 46,000 in 2050. (3).The anticipated mortality rate from breast cancer is 11%, making it the second leading type of cancer-related death after liver cancer. (4)

According to estimates, there were 684,996 fatalities and 2,261,419 new breast cancers cases worldwide in 2020.[5] Histological subtypes of breast cancer include lobular, tubular, papillary, and ductal.[6]. Breast cancer is categorized according to its molecular heterogeneity as HER2-positive, luminal A, luminal B, or triple-negative (TNBC) [7,8]. Common treatments for breast cancers include tissue-targeted medicines, hormone therapy, chemotherapy, and drastic surgery.[9]. Half of initially treatable breast cancers become resistant to chemo through a variety of pathways, making treatment resistance a common concern in breast cancers cases. [10,11]

The ability to detect precancerous lesions and malignancies at earlier stages, when treatment choices have more efficacy, is a major benefit of screening techniques. [12, 13]. The term "liquid biopsy" refers to the collection and analysis of biofluid samples for cancer-related biomarkers such as circulating tumour cells (CTCs), exosomes, and circulating tumour DNA/RNA. [14, 15]. Tumors passively release CTCs into the bloodstream, where they may act as metastatic "seeds."[16–18]. Liquid biopsy, in contrast to traditional solid biopsy, is a minimally invasive and sensitive method that can be used for early cancer detection, patient stratification, prognosis, and disease monitoring. [19–23].

RNA transcripts longer than 200 nucleotides in length that cannot code for proteins are known as long non-coding RNAs (lncRNAs).[24]. High-throughput RNA sequencing and bioinformatics investigations have led to the discovery of hundreds of lncRNAs in recent years.[25]. In addition, many studies have shown that lncRNAs play important roles in a wide variety of biological processes, including cancer.[26]. Approximately 1059 lncRNAs with aberrant expression levels in breast cancer have been identified using the TCGA database.[27]

Numerous studies have shown that lncRNAs interact with DNA, RNA, proteins, or a combination of these at various stages of cancer development, making them a potential causal factor. Modulating regulatory pathways that foster cancer growth is an area of expertise for lncRNAs, although the ways in which they do so vary. The transcription, post-transcription, translation, and epigenetic modification stages of gene expression have all been shown to be significantly influenced by lncRNAs, according to an ever-growing body of research.[**28**]. In the epigenetic modification, lncRNAs are thought to have a restrictive effect on target genes via altering histones, rearranging chromatin, or methylating DNA. Well-studied lncRNAs including HOTAIR, linc-ROR, ANRIL, H19, and XIST are known to inhibit gene transcription by enlisting the help of chromatin-remodeling and histone-modifying proteins.[**29**]. To further complicate the molecular architecture of human malignancies, lncRNAs may function as oncogenes or tumor-suppressing agents.[**30**].

Table (1)LncRNAs participate in BC metastasis by sponging to miRNA .

LncRNA	Expression	Sponging miRNA	Function	Reference
NEAT1	Up	miR-448, miR-218, miR-211	NEAT1 facilitated cell growth and invasion via negatively regulating miR-218, as well as by regulating miR-211/HMGA2 axis and miR-448/ZEB1 axis in BC.	31-33
HOTAIR	Up	miR-20a-5p	HOTAIR affected BC cell growth, metastasis, and apoptosis via the miR-20a-5p/HMGA2 axis	34
MALAT1	Up	miR-129-5p	MALAT1 promoted triple-negative BC invasion via targeting miR-129-5p.	35
SNHG15	Up	miR-211-3p	SNHG15 promoted BC cell migration and invasion by sponging miR-211-3p	36
HOST2	Up	let-7b	HOST2 decreased BC cell motility, migration, and invasion by inhibiting let-7b.	37
XIST	Down	miR-155	XIST inhibited BC cell growth, migration, and invasion via miR-155/CDX1 axis.	38
SUMO1P3	UP	miR-320a	SUMO1P3 facilitated BC progression by negatively regulating miR-320a.	39
CASC2	Down	miR-96-5p	CASC2 inhibited the growth and metastasis of BC through the miR-96-5p/SYVN1 axis.	40

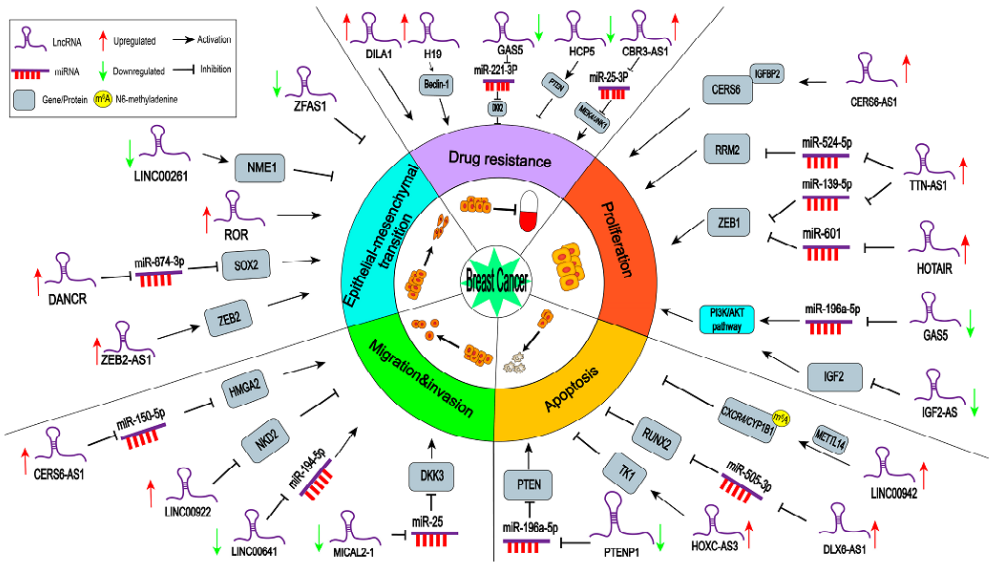

Figure1. The roles and molecular mechanisms of lncRNAs in breast cancer: (41)

Several lncRNAs have been implicated in breast cancer through their ability to regulate downstream target genes and signalling pathways that impact cell proliferation, apoptosis, cell migration, invasion, epithelial-mesenchymal transition (EMT), and drug resistance.

Abbreviations:

CERS6, ceramide synthase 6; CXCR4, chemokine receptor 4; CYP1B1, cytochrome P450 1B1; DKK2, dickkopf 2; DKK3, dickkopf 3; HMGA2, high-mobility group protein 2; IGFBP2, insulin-like growth factor binding protein-2; IGF2, insulin like growth factor 2; m6A, N6-methyladenine; METTL14, methyltransferase-like 14; NKD2, naked cuticle homolog 2; NME1, NME/NM23 nucleoside diphosphate kinase 1;PTEN, phosphatase and tensin homolog; RRM2, ribonucleotide reductase subunit 2; RUNX2, runt-related transcription factor2;SOX2, SRY-Box 2; TK1, thymidine kinase 1; ZEB1, zinc finger E-box binding homeobox 1; ZEB2, zinc finger E-box binding homeobox 2.

Roles of lncRNAs in Breast Cancer:

1-Long ncRNAs in Cell Proliferation:

Multiple signalling pathways contribute to the proliferation of cancer cells. (42). Multiple lncRNAs have been found to mediate cell proliferation in breast cancer by either stimulating or inhibiting distinct signalling pathways, according to recent studies. (Figure 2A).(43,44)

Akt (also called protein kinase B or PKB) signaling pathway:

Biological reactions such as apoptosis inhibition and cell growth promotion are mediated by the Akt signalling system (45).H19 is a 2.3-kb lncRNA that is considered an oncogene in many malignancies since it is encoded by the maternal allele(46,47). H19 antisense transcription results in the production of a novel lncRNA at the H19/IGF2 gene, designated 91H. In breast cancer, 91H lncRNA is crucial for maintaining the H19/IGF2(insulin growth factor 2) genomic imprinting by preventing histone and DNA methylation on the maternal allele at the H19/IGF2 locus (48). In breast cancer cells, E2F1(E2 promoter binding factor 1) activates H19, which therefore increases the G1-S transition (49).

By inhibiting c-Cb1 and -Cb1-b protein expression and by activating EGFR(Epidermal growth factor receptor) and c-Met (mesenchymal-epithelial transition factor), miR-675 from H19 promotes cell proliferation via Akt activation. (43).In a mouse model of breast cancer, Zhang(50) et al. demonstrated that overexpressing lncRNA MEG3(Maternally expressed gene 3) not only causes cell cycle arrest in G0/G1 phase, but also reduces tumour growth via Akt signalling. Downregulating MAPK (Mitogen-activated protein kinase) and AKT signalling pathways, Chen (51) et al. demonstrated that lncRNA PTENP1 suppresses breast cancer cell proliferation.

Mitogen-activated protein kinase signaling pathway:

The serine-threonine kinase mitogen-activated protein kinase plays a role in a variety of cellular processes, including proliferation, differentiation, migration, senescence, and apoptosis. (52). The long noncoding RNA CAMTA1(Calmodulin-Binding Transcription Activator 1) was shown to be significantly enriched in tumors of the liver.(53). By binding miR-20b and thereby inhibiting the production of vascular endothelial growth factor, an activator of (MAPK), CAMTA1 increases the proliferation of human breast cancer cells.(54). In four kinds of breast cancer, Wang et al. (55) found that lncRNAs mediate 12–44 pathway pairs that communicate with one another. Activation of MAPK and increased breast cancer cell proliferation were discovered to result from lncRNA LIFR-regulation AS1's of IL1R (interlukin 1 receptor) and TGFBR (transforming growth factor beta receptor) expression. Through the use of CRISPR/Cas9, Peng et al. (56) determined that linc-ROR (receptor tyrosine kinase-like orphan receptors) promotes estrogen-independent growth and activates the MAPK pathway in breast cancer cells.

Wnt signaling pathway:

There are two ways to activate the highly conserved Wnt signalling pathway: the canonical pathway and the noncanonical pathway. Initiation and development of breast cancer are profoundly influenced by the former (57,58) Critical components of the canonical pathway, such as MYC and β-catenin, are able to interact with long ncRNAs. It has been found that the expression of the new lncRNA CCAT2, which maps to 8q24, is highly elevated in breast cancer tissues and breast cancer cell lines. By increasing β-catenin expression, a critical downstream effector of Wnt signalling, CCAT2 encourages the growth of breast tumors (44).Activation of Wnt β-catenin signalling and tumour cell proliferation are both aided by the long noncoding RNA CRNDE, which is increased in breast cancer and acts as a molecular sponge for other miRNAs like miR-136.(59).

MYC signaling pathways:

In many cancers, an amplification of the MYC proto-oncogene leads to the activation of downstream genes that regulate cell cycle progression, cell proliferation, and angiogenesis (60).The epigenetic landscape of lncRNA genes was defined across a wide range of human malignancies, including breast cancer(55). By interacting with MYC and increasing its binding to many target genes, the researchers found that lncRNA EPIC1 promotes cell cycle progression and proliferation. There is a strong correlation between tumour growth and lymph node metastasis and the upregulation of the long noncoding RNA SNHG12 in triple-negative breast cancer. In addition, SNHG12 is a direct target gene of MYC, an essential member of MYC; suppressing SNHG12 expression reduces the proliferation of breast cancer cells (61).Different modes of signalling. The 289-kDa serine/threonine protein kinase mammalian target of rapamycin (mTOR) acts as a downstream effector of numerous frequently activated oncogenic pathways such as Akt and (MAPK) (62).This study (63) found that knocking down lncRNA-ASAH2B-2 reduced the proliferation of breast cancer cells by blocking mTOR signalling. Cancers that over prolife,

migrate, and invade are facilitated by the bcl-2 (B-cell lymphoma 2) family member bcl-w (64). In breast cancer(66) and other malignancies, the long noncoding RNA HOX transcript antisense RNA (HOTAIR), which is situated in the HOX gene locus(65), modifies miR-206-mediated bcl-w (antiapoptitic protein) signalling to facilitate cell proliferation (67,68).

2-Long ncRNAs in Cell Invasion and Metastasis

More than 90% of cancer deaths can be attributed to the invasion and metastasis processes, which are themselves a multi-step process. (69).Metastasis occurs when initial tumour cells travel via the circulatory system or lymphatics to distant secondary organs, where they grow (70). The following are some of the routes in which lncRNAs participate. (Figure 2B).

Signal Transducer and Activator of Transcription 3 signaling pathway:

Many cancers rely heavily on STAT3 activation for their dissemination to distant sites (71).FEZF1-AS1, a long noncoding RNA, increases colorectal cancer growth and metastasis by activating STAT3 through targeting pyruvate kinase 2 (PKM2) (72). Multiple cancers, including breast cancer, show increased levels of HOX transcript antisense RNA.(73).HOTAIR functions as a scaffold for PRC2 (Polycomb repressive complex 2) and lysine-specific demethylase 1 (LSD1) to regulate target gene expression by binding to PRC2 at its 5' end and to LSD1 at its 3' end (74).Both HOTAIR and EZH2 are overexpressed in metastases from breast cancer, and their expression is strongly associated in primary tumours and metastases (75).As a negative regulator of STAT3 and breast cancer cell EMT, miR-7 is indirectly suppressed by HOTAIR (76). To further facilitate STAT3 phosphorylation in response to oncostatin M and IL-6, lncRNA upregulates JAK2 (Janus Family Kinase-2) kinase activity. Lnc-BM encourages brain metastasis by breast cancer cells by increasing STAT3-dependent production of ICAM1(Intercellular Adhesion Molecule-1) and CCL2 (CC motif Chemokine Ligand 2). (77).

Nuclear factork-B signaling pathway:

A key component of the tumour microenvironment, nuclear factor-kB (NF-kB) connects inflammation and cancer. Some breast cancers feature persistent activation of nuclear factor kB (78).NKILA (nuclear transcription factor NF-κB interacting lncRNA), a tumour suppressor discovered by Liu et al. (79), binds to the NF-kB-IkB complex and inhibits NF-kB signalling, which is associated with breast cancer metastasis. Another study shows that TGF-b activates the lncRNA NKILA, which then blocks NF-kB signalling to prevent TGF-b (transforming growth factor b) induced EMT (epithelial–mesenchymal transition) in breast cancer. (80).

Transforming growth factor-b signaling pathway:

The TGF family includes the multifunctional cytokine transforming growth factor-2 Proliferation, differentiation, apoptosis, motility, invasion, extracellular matrix synthesis, angiogenesis, and

immune response are only some of the cellular processes that the TGF-b signaling pathway controls. (81).

TGF-b in breast cancer can arise from two different sources: It operates as an oncogene and promotes tumour proliferation and metastasis in later stages, but in early stages it slows epithelial cell cycle progression and induces apoptosis.(82).The 855-nucleotide long noncoding RNA (lncRNA) anti-differentiation noncoding RNA (ANCR) is repressed during differentiation.(83).In breast cancer, ANCR is a potential tumor suppressor and inhibits breast cancer cell migration and metastasis by decreasing RUNX2 expression in vitro and in vivo(84).HIT is a new lncRNA associated with breast cancer that was shown to increase TGF-b-induced migration, invasion, and epithelial-mesenchymal transition by Richards et al (85). By increasing the protein expression levels of TGF-b, Smad2, and smooth muscle actin—all of which are essential components of TGF-b signaling Wu et al (86) found that lncRNA CCAT2 also increases breast cancer growth and metastasis..

The Hippo signaling pathway:

Drosophila melanogaster was the first organism to reveal this mechanism, which controls cell growth, death, and spread. (87,88). Two important effectors of the Hippo signalling pathway are YAP and TAZ (Yes-associated protein (**YAP**) and transcriptional coactivator with a PDZ-binding motif (TAZ) (89).According to research by Li et al. (90), a lncRNA (MAYA) is a component of an RNA-protein complex that activates YAP and elicits osteoclast development and bone metastases via altering the HippoYAP pathway.

3-Long ncRNAs in Apoptosis:

The controlled cell death known as apoptosis is crucial for the healthy growth of tissues. Apoptosis dysregulation is associated with tumour development (91). Apoptosis is a process in which many lncRNAs take part. (Figure 2C).

Pathway of p53 Signaling:

Inhibition of cell cycle progression and differentiation, as well as apoptosis and growth arrest, are all regulated by the p53 tumor-suppressor protein. (92).Key players in the p53 pathway include long noncoding RNAs (93). The p53-responsive lncRNA GUARDIN was shown by Hu et al. (94) to be essential for the maintenance of breast cancer growth and its silencing to result in apoptosis in breast cancer cells. Inhibition of breast cancer proliferation and promotion of apoptosis via the AKT/GSK3b/b-catenin signalling cascade is mediated by the tumour suppressive lncRNA PICART1, which is activated by the p53 protein (95).

MALAT1, a long noncoding RNA (ncRNA) on chromosome 11q13.1, has been shown to inhibit apoptosis in breast cancer cells via controlling p53 acetylation through competition with SIRT1 and DBC1 (SIRT1: Sirtuin-1,DBC1: Deleted in breast cancer 1) (96).

The signalling caspases (cysteine aspartate specific proteases):

Caspases are a class of cysteine proteases that function in a coordinated cascade during apoptosis (97). Overexpression of LINC00628 causes cell cycle arrest in G0/G1 phase and increases cell death via modulating expression of caspase-3, Bax, and Bcl-2, as reported by Chen et al (98). Taurine upregulated gene 1 (TUG1) is a long noncoding RNA (lncRNA) with a role in the development of several malignancies. TUG1knockdown, as reported by Li et al. (99), results in increased apoptosis in breast cancer cells due to increased activity of caspases 3 and 9. Increased levels of lincRNA-APOC1P1-3 were found in breast cancer in Liao et al (100); this lncRNA was found to directly bind to tubulin, lowering a-tubulin acetylation, inactivating caspase3, and preventing apoptosis.

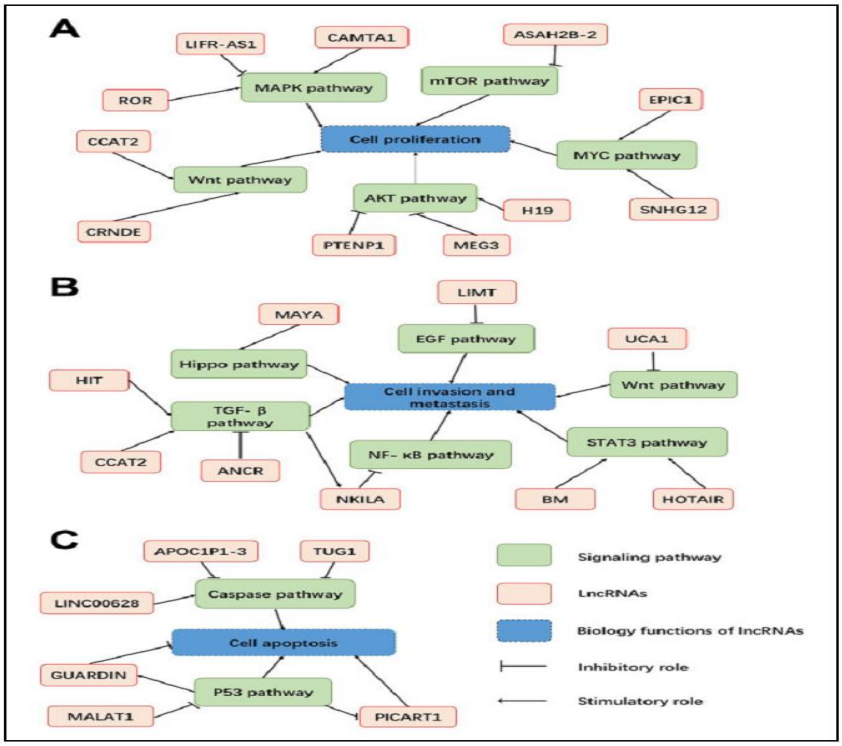

Figure 2.Regulatory long noncoding RNAs (lncRNAs) in the pathogenesis of breast cancer (101)

Abbreviations:

ANCR, anti-differentiation noncoding RNA; Caspases, cysteine aspartate specific proteases; EGF, epidermal growth factor; EMT,epithelial–mesenchymal transition; HOTAIR, HOX transcript antisense; lncRNAs, long non-coding RNAs; LSD1, lysine-specificdemethylase 1; MAPK, Mitogen-activated protein kinase; miRNAs, microRNAs; mRNA, messenger RNA; mTOR, mammalian target of rapamycin;; NFkB, nuclear factor-kB; PRC2, polycomb repressive complex 2; STAT3, signal transducer and activator of transcription 3; TGF-b, transforming growth factor-b; TUG1, taurineupregulated gene 1.

Conclusions

The role of ncRNAs in various physiological and pathological processes, including breast cancer, has become increasingly clear over the past decade. There has been a lot of recent interest in lncRNAs, the essential subtype of ncRNAs, and their role in breast cancer. In this review, we introduce information about the ways in which lncRNAs affect breast cancer and the functions they provide. These lncRNAs are involved in cell apoptosis, proliferation, and migration, all of which play a role in the development and spread of breast cancer when they are dysregulated.

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