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Review Article

Regulatory Interplay of Long Non-Coding RNAs in Breast Cancer Progression

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Abstract
Globally, breast cancer is a severe and diverse disease with a high morbidity and death rate. Recent studies have highlighted the critical role of long non-coding RNAs (lncRNAs) play in the initiation and spread of breast cancer. lncRNAs are crucial regulators of gene expression and are implicated in various cellular processes, including tumorigenesis. The dysregulation of lncRNAs has been linked to aberrant cell proliferation in breast cancer. By modulating gene expression at transcriptional and post-transcriptional levels, lncRNAs can promote or suppress cell proliferation, influencing tumor growth and progression. lncRNAs can control the invasion and migration of breast cancer cells, thereby promoting the spread of metastatic cancer to other organs, through interactions with miRNAs and other molecular pathways. Understanding the intricate mechanisms by which lncRNAs contribute to these processes is essential for developing targeted therapies and improving patient outcomes. The crosstalk between lncRNAs and other intracellular proteins is important for understanding their functional roles in breast cancer progression. Protein interactions influence the stability, activity, and localization of lncRNAs, which in turn influences how these RNAs affect cellular processes. This review investigates the complex interactions of lncRNAs with miRNAs and proteins in breast cancer, with a focus on their roles in metastasis, proliferation, and other stages of the disease's progression. Moreover, with the ability to target specific genes, identifying novel biomarkers, therapeutic targets and potential in overcoming drug resistance lncRNAs represent an exciting area in RNA-based therapies and have the potential to transform breast cancer treatment.

Keywords: lncRNAs, Breast Cancer, miRNA, Cancer Pathways, Cancer Progression and Regulation
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Introduction

Breast Cancer and lncRNAs

Breast cancer is the primary cause of cancer-related illnesses and deaths among women worldwide. A favorable prognosis for every type of cancer depends critically on early detection and efficient treatment. Smaller tumors are associated with a much higher chance of survival and a much lower risk of cancer death for patients receiving a diagnosis.[1] One major factor that is significantly linked to an increased risk of breast cancer is the family history of the disease. Between 13 and 19% of breast cancer patients report having a first-degree relative with the disease.[2] Approximately 2,296,840 new cases of breast cancer were diagnosed among women worldwide in 2022, making it the most commonly diagnosed cancer globally.[3] The landscape of breast cancer in India presents a challenging scenario, with significant incidence and mortality rates impacting women across the country. Breast cancer stands as the most prevalent cancer among Indian females, with an age-adjusted rate as high as 25.8 per 100,000 women and a mortality rate of 12.7 per 100,000 women. Notably, there has been a statistically significant increase in age-adjusted rates over time in various regions, indicating a concerning trend in breast cancer prevalence.[4] Instead of a disease where a small number of genes, proteins,and/or signaling pathways simply, independently, and autonomously contribute to the progression of the disease, BC is a heterogeneous and complex disease in which each patient has unique morphological and molecular features. Further evidence of the high degree of heterogeneity in this illness comes from studies that show patients with the same type of breast cancer can respond differently to treatment.[5] Most breast cancer cells have features of epithelial cells and express HER-2 (a member of the epidermal growth factor receptor family) and/or estrogen receptors. Most breast cancer cells participate in the insulin-like growth factor (IGF) signaling pathway, regardless of the cell type. All cell proliferation inducers utilize both

transcriptional and non-transcriptional mechanisms to start the cascade of cyclin-dependent kinases that leads to the irreversible progression to the G1/S phase transition.[6] A variety of RNA types like long non-coding RNAs (lncRNAs), messenger RNAs (mRNAs), micro RNAs (miRNAs), Piwi-interacting RNAs (piRNAs), and extracellular RNAs have been explored and show promise as cancer diagnostic and prognostic biomarkers. Among them lncRNAs are more promising as a reliable diagnostic tool for breast cancer as they show greater tissue specificity compared to protein-coding mRNAs.[7] Long noncoding RNAs (lncRNAs) are sequences of 200 nucleotides or more that are transcribed from a large portion of the mammalian genome. While hypothesized to have a variety of biological roles, many lncRNAs remain largely functionally uncharacterized due to unique challenges associated with their investigation.[8] LncRNAs share structural similarities with mRNAs and are both cell-specific and evolutionarily conserved, serving as important transcriptional regulators. While most lncRNAs are found in the nucleus or cytoplasm of cells and do not code for proteins, they play a crucial role in regulating gene expression at various levels through their interactions with other RNA molecules.[9] LncRNAs that are transcribed can be classified based on three stages of transcription: pre-transcriptional, transcriptional, and post-transcriptional. Each of these stages plays a significant role in regulating physiological functions.[10] Although there is an increasing amount of evidence highlighting the functional significance of lncRNAs, many of them are still not well understood. The classification and annotation of lncRNAs present considerable challenges due to their rapid evolution and low conservation among different species. Current research efforts are focused on clarifying their mechanisms of action and exploring potential therapeutic applications in various diseases.[11] Numerous studies have shown that lncRNAs remain stable in blood, serum, and plasma, allowing them to be noninvasively extracted and measured from liquid biopsies.[12,13] lncRNAs have shown promise in detecting cancer at early, potentially curable stages, unlike many protein biomarkers that are often elevated only in late-stage disease[12] Recent comprehensive genomic investigations have uncovered a wide range of lncRNAs that control gene expression at the epigenetic, transcriptional, and post-transcriptional levels and are implicated in multiple diseases, including the progression of tumors. lncRNAs which are larger than 200 nucleotides in size and despite not being able to code for proteins, they perform multiple cellular functions.[14]

The intricate regulatory networks involving the interaction of lncRNAs with lncRNAs (Figure 1), lncRNAs with miRNAs, and lncRNAs with their target proteins underscore the complexity of breast cancer biology. Further research into these molecular interactions will enhance our understanding of breast cancer pathogenesis and progression Moreover, understanding the role of the tumor micro environment in modulating lncRNA, miRNA and regulatory proteins expression and function will be crucial for developing more effective therapeutic strategies. Integrating these molecular insights with clinical data will pave the way for the development of innovative diagnostic tools and targeted therapies, ultimately improving clinical outcomes for breast cancer patients.

To comprehensively review the role of long non-coding RNAs (lncRNAs) in breast cancer, the following methodology was followed:

1. Keyword Selection: Relevant keywords were identified to guide the search process. The primary keywords used were "lncRNA", "miRNA", "protein", and "breast cancer".
2. Data Collection: Articles were sourced from various academic databases and reputable online platforms which include Google Scholar and Pubmed. The search was conducted using combinations of the selected keywords to ensure a broad and relevant collection of literature.
3. Inclusion Criteria: Studies were included based on their relevance to the role of lncRNAs in breast cancer, particularly those that discussed interactions with miRNAs and proteins.
4. Analysis: The gathered articles were systematically reviewed to extract significant findings and insights regarding the mechanisms by which lncRNAs influence breast cancer progression and treatment.

The different developmental stages of breast cancer such as proliferation, migration, invasion and metastasis are significantly influenced by the interplay of lncRNAs with lncRNAs (Table 1), lncRNAs with other intracellular proteins (Table 2) and lncRNAs with miRNAs (Table 3) as discussed in further sections.

Proliferation

Variations in the rates of cell proliferation are implicated in the growth and progression of tumors. Together with tumor size, grade, nodal status, and steroid receptor status, proliferative assessment can be used as a prognostic indicator in early breast cancer.[62,63] Proliferation rates can give important details about the prognosis and degree of aggressiveness of specific cancers.[64]

Certain lncRNAs, such as LSINCT5, Zfas1, AWPPH, GAS5, MALAT1, H-19, DLG1-AS1, and lncCAMTA1, interact with miRNA to stimulate cell proliferation. Located on the negative strand and possibly transcribed by RNA polymerase III, LSINCT5 is a 2.6 Kb polyadenylated long stress-induced non-coding transcript that is localized in the nucleus. LSINCT5 is overexpressed in tumor tissues and cell lines from breast and ovarian cancer in comparison to its normal counterpart. Cellular proliferation is reduced in cancer-derived cell lines when LSINCT5 expression is knocked down. The knockdown of LSINCT5 was found to

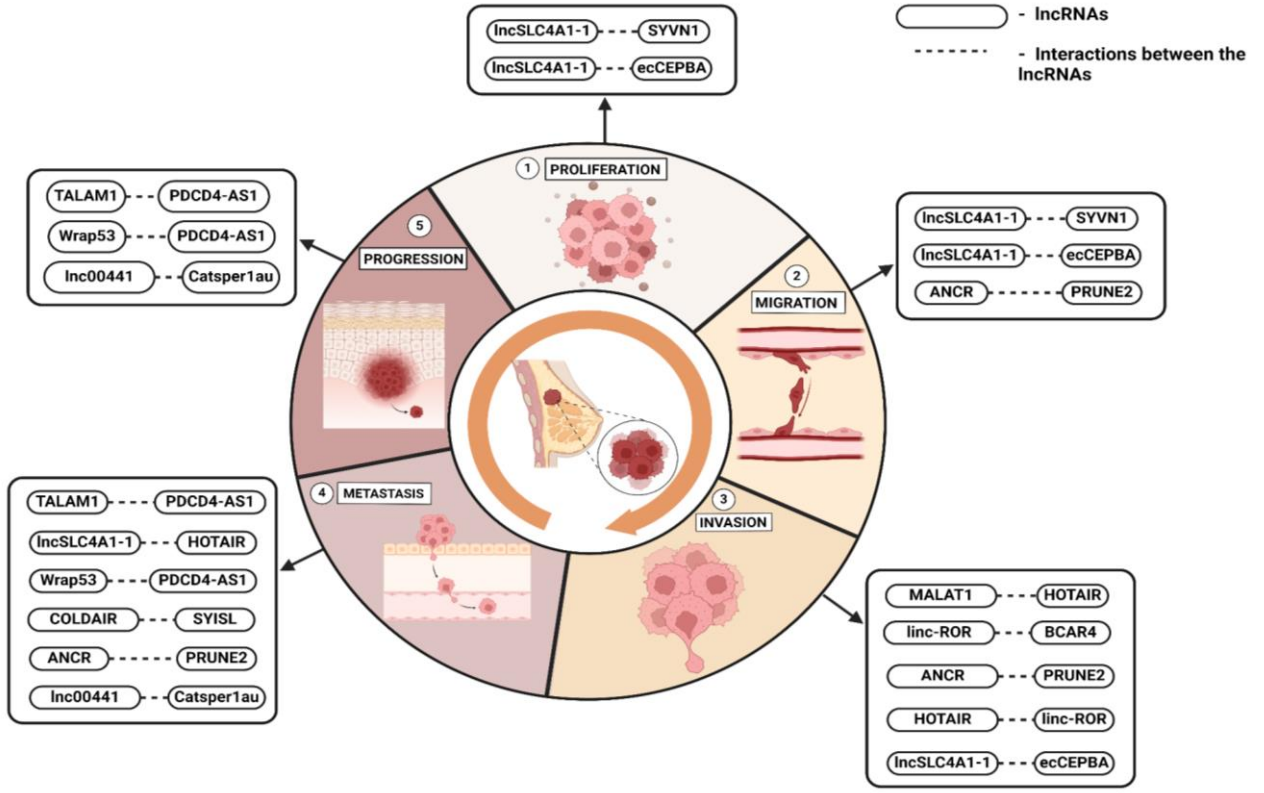

Figure 1. lncRNA-lncRNA Interaction and their Contribution to Breast Cancer Progression.

Table 1. Interaction between the lncRNA and lncRNA and its Effect on Breast Cancer

lncRNA 1*	lncRNA 2*	Effect on Breast Cancer	References
MALAT1	HOTAIR	Promotes invasion and metastasis of breast cancer cells	15
Linc-ROR	BCAR4	Abnormally upregulated in breast cancer cells, enhancing invasion capabilities	16
TALAM1	PDCD4-AS1	Potential role in breast cancer progression and metastasis	16
Linc00441	Catsper1au	Associated with breast cancer progression and metastasis	16
Lnc-SLC4A1-1	SYVN1	Dysregulation contributes to breast cancer cell proliferation and migration	15
ANCR	PRUNE2	Linked to migration, invasion, and metastasis of breast cancer	17
COLDAIR	SYISL	Involved in regulating breast cancer metastasis	17
Wrap53	PDCD4-AS1	Potential role in breast cancer progression and metastasis	17
ecCEPBA	Lnc-SLC4A1-1	Overlaps with introns and exons of different protein-coding genes	18
HOTAIR	linc-ROR	Abnormally upregulated in breast cancer cells, enhancing invasion capabilities	18
HOTAIR	ANRIL	Breast cancer progression, invasion, and metastasis	19
MALAT	TUG-1	Cancer cell proliferation and survival	20
lncRNA XIST	NEAT1	Proliferation, migration, and invasion	21
PVT1	HOTAIR	Metastasis	22

lncRNA 1* & lncRNA2* indicate the two lncRNAs that are interacting with each other

have an impact on several genes. It is interesting to note that the protein-coding gene PSPC1 and the lncRNA NEAT-1 both had substantial downregulations.[65] On the other hand, the silencing of lncRNA AWPPH had the opposite effect, lncRNA AWPPH overexpression enhanced cancer cell viability and promoted cancer cell proliferation when exposed to carboplatin. Furthermore, the effects of lncRNA AWPPH siRNA silencing on the behaviors of cancer cells were mitigated by miRNA-21 overexpression. In triple-negative breast cancer (TNBC) cells, overexpression of lncRNA AWPPH was associated with upregulated miRNA-21, and overexpression of miRNA-21 was also associated with significantly upregulated lncRNA AWPPH expression.[66] GAS5, an important lncRNA in breast cancer, interacts with various proteins (e.g., E2F1, EZH2, and YAP), DNA (e.g., the insulin receptor promoter), and various microRNAs (miRNAs). GAS5 binds to miR-21, miR-222, miR-221-3p, miR-196a-5p, and miR-378a-5p in breast cancer. Certain suppressor protein mRNAs, including PTEN, PDCD4, DKK2, FOXO1, and SUFU, are upregulated in response to

Table 2. Interaction between the lncRNA-Protein and its Effect on Breast Cancer

Protein	lncRNA	Type of Interaction	Role in Breast Cancer	References
RASSF7	RP11-70C1.3	Interaction	Potential role in luminal A breast cancer subtype	23
RBM20	GAS5	Binding	Dual role as tumor suppressor and oncogene in different cancer types	23
PCDH20	XIST	Competitive Binding	Dual role as tumor suppressor and oncogene in different cancer types	23
Y-Box Protein-1 (YBX1)	HOTAIR	Binding	Regulating diverse processes linked to cancer development	24
RUNX3	HOTAIR	Binding	facilitating its ubiquitin-dependent degradation, and enhances estrogen receptor (ER) signaling while conferring tamoxifen resistance in breast cancer cells	25
KLF5	PVT1	By blocking protein degeneration and ubiquitination through direct binding	enhance its binding to the BAP1 de-ubiquitinase, increasing its stability and contributing to cancer progression in TNBC	26
DCTPP1	DSCAM-AS1	Protect DCTPP1 mRNA from degradation mediated by miRNAs	promoting breast cancer development by increasing DCTPP1 expression	27
DCTPP1	LGALS8-AS1	competing endogenous RNA (ceRNA) network	lncRNA LGALS8-AS1 upregulates DCTPP1 to promote breast cancer progression through sponging miR-125b-5p, maintaining the overexpression of DCTPP1 in breast cancer cells	28
KLC3	RP1	Overexpression	This interaction involves KLF5 recruiting p300 and binding to lncRNA RP1 to enhance the activity of the RP1 promoter, leading to increased RP1 expression. Subsequently, RP1 interacts with the complex p-4E-BP1/eIF4E to attenuate p27kip1 translation, promoting breast cancer metastasis	29

Table 3. Interaction between the lncRNA and miRNA and its Effect on Breast Cancer

lncRNAs	miRNAs	Type of Interaction	Role in Breast Cancer	References
RP11-70C1.3	miR-6736-3p	CeRNA Network	Chemotherapy Resistance	30
AWPPH	miRNA-21	Mutual Regulation	Promoting Cancer Cell Proliferation and Chemosensitivity	30
GAS5	miR-196a-5p	Competitively Binds	Suppresses TNBC Cell Proliferation and Invasion	30
	miR-21	Sponging	promotes metastasis and proliferation	31
	miR-193a-3p	Overlapping	Impacts cell proliferation and invasion in breast cancer cells	15
NEF	miR-155	Negatively Regulates	Suppresses Migration and Invasion of TNBC Cells	30
RMST	miR-204	Downregulates	MiR-204 is sequestered by RMST, leading to the induction of epithelial-mesenchymal transition (EMT) and metastatic spread. When RMST is over-expressed, it can inhibit cancer invasion, migration, and metastasis by regulating miR-204	32
MALAT1	miR-124	Regulation	suppression of breast cancer progression	33
	miR-570e3p	Regulation	increased proliferation, metastasis, and doxorubicin resistance in breast cancer cells	34
	miR-3064-5p	Regulation	promotes breast cancer cell aggressiveness by enhancing proliferation, migration, and altering cell cycle distribution	35
	miR-485-3p	Downregulation	oncogenic and tumor-suppressive roles	36
	miR-45	Sponging	migration and invasion	37
	miR-145	Sponging	angiogenesis for tumor growth	38
ARF6	MiR-145	Loss of MiR-145	Promotes Cell Invasion in TNBC	39
H-19	miR-675	Upregulation	downregulates C-Cb1 and Cb1-b proteins that activate EGFR and C-Met causing cell proliferation	40
	miR-152	Upregulation	proliferation, migration, invasion	40
AC009283.1	miR-561	Regulation	Impact on gene expression in breast cancer cell lines	41
RP11-70C1.3	miR-6736-3p	competing endogenous RNA (ceRNA)	Potential role in breast cancer drug resistance	42
DLG1-AS1	miR-203	Downregulates	Promotes Cancer Cell Proliferation in Triple Negative Breast Cancer	43
	miR-145	Upregulation	promoting migration	43
HOTAIR	miR-34a	Sponging	EMT, proliferation	44
	miR-206	Sponging	progression of breast cancer by aiding in the growth of cancer cells.	45
LINC00511	miR-150	Upregulation	proliferation, migration	46
linc00518	miR-185-3p	Upregulation	tumorigenesis and stemness	47
CYTOR	miR-125a-5p	Inhibiting miRNA to increase the expression of SRF	promoting the tamoxifen resistance and cell proliferation	48
CCAT1	miR-218	Upregulation	promoting proliferation and migration, stemness	49
LINC00339	miR-377-3p	Upregulation	promoting proliferation and inhibiting apoptosis	50
linc-ZNF469-3	miR-574-5p	Upregulation	promoting migration	51
HULC	miR-6754-5p	Upregulating MMP2 and MMP9; regulating LYPD1 expression by sponging	promoting migration	52
	miR-125a-5p	Upregulating MCL-1 expression	inhibiting apoptosis	53
GACAT3	miR-497	Upregulation	promoting proliferation	54
NNT-AS1	miR-142-3p	Upregulation	migration and invasion	55

PRLB	miR-4766-5p	Upregulation	proliferation and metastasis	56
ATB	miR-200c	Upregulation	promoting EMT	57
NEAT1	miR-146b-5p	inhibiting miRNA expression	metastasis	58
MEG3	miR-4513	Upregulation	suppressed cell proliferation, migration and invasion, induces apoptosis	59
XIST	miR-200c-3p	Sponging	brain metastasis and cell growth, chemoresistance	60
LncRNA-LEENE	miR-96-5p	Enhancer	Implicated in breast cancer cell proliferation, migration, and invasion	61

GAS5, which promotes the growth of tumor cells. Through a variety of mechanisms, such as cell death receptors and mitochondrial signaling pathways, GAS5 can induce the death of normal cells in breast cancer. Additionally, GAS5 plays a major role in controlling Wnt/β-catenin, NF-κB signaling, and PI3K/AKT/mTOR, three important signal pathways involved in breast cancer. Through various mechanisms, including epigenetics, GAS5 can enhance susceptibility to various medications and prognoses.[67]

The lncRNA, MALAT1 regulates miR-3064-5p and miR-570e3p, two miRNAs that increase the aggressiveness of breast cancer cells by promoting migration, proliferation, and changes in the distribution of cell cycles.[68] To encourage proliferation, other lncRNAs interact with one another, including Lnc-SLC4A1-1, HOTAIR, TUG-1, and lncRNA XIST. Through the control of genes involved in proliferation, invasion, and metastasis, the lncRNA HOTAIR forms a complex with ANRIL, improving its stability and accelerating the progression of breast cancer.[69] The lncRNA TUG1 interacts with MALAT 1 to regulate the expression of tumor suppressor genes such as PTEN and p53, contributing to breast cancer cell proliferation and survival.[70]

Migration

Significant cytoskeleton remodeling that facilitates effective cell migration and invasion is what propels breast cancer metastasis.[71] Several different mechanisms, such as amoeboid cell migration, mesenchymal cell migration, and collective cell migration, can be used by cancer cells to spread and migrate. Certain unique and distinctive characteristics in the actin cytoskeleton, matrix adhesion, protease activity, and cell-cell junctions are displayed by these various movement strategies. As a tumor grows, cells navigate through the complex microenvironments and modify their migration tactics through reversible mesenchymal-amoeboid and individual-collective transitions.[72]

Among the lncRNAs that interact with miRNAs and encourage cell migration are RMST, MALAT1, H19, ROR, HOTAIR, ARNILA, LINC00511, CCAT1, and linc-ZNF469-3. MiR-204 is sequestered by RMST, a long noncoding RNA that is downregulated in breast cancer patients, which causes the epithelial-mesenchymal transition (EMT) and subsequent metastatic spread. Through the regulation of miR-204, overexpression of RMST can prevent cancer invasion, migration, and metastasis.[73] After interacting with miR-204/211, miR-148a/152, and Annexin A2 (ANXA2), LncCCAT1 can either promote the translocation of β-catenin to the nucleus, where it activates TCF4, or it can upregulate T-cell factor 4 (TCF4), which in turn activates wingless/integrated (Wnt) signaling. Additionally, TCF4 can bind to the LncCCAT1 promoter to increase LncCCAT1 transcription. This creates a positive feedback regulatory circuit in breast cancer stem cells that consists of LncCCAT1-TCF4-LncCCAT1.[74] Through its interaction with miR-601, HOTAIR inhibition in breast cancer reduced cell migration and invasion.[75] RACGAP1P targeted miR-345-5p, which allowed breast cancer cells to migrate and invade more easily.[76] Lnc-SLC4A1-1, ANCR, lncRNA XIST, MALAT1, ANRIL, HOTAIR, GAS5, H19, and HULC are a few examples of other lncRNAs that interact with one another to facilitate the migration of breast cancer cells and, consequently, to accelerate the progression of breast cancer disease. A few lncRNAs' mechanisms are briefly described below.

Through its ability to sequester miR-214, MALAT1 can cause an increase in ANRIL, which in turn stimulates the migration and invasion of breast cancer cells by regulating the expression of EZH2.[77] The miR-675/HULC axis is modulated when H19 competitively binds to miR-675, releasing the inhibitory effect of miR-675 on HULC.[78] HOTAIR contributes to migration through several interactions and mechanisms. Through competitive binding to miR-206, HOTAIR can alleviate its inhibitory effect on GAS5 and enhance the migration of breast cancer cells by modulating the miR-206/GAS5 axis.[79] HOTAIR alleviates miR-204's inhibitory effect on PVT1 by binding to it competitively. By controlling the miR-204/PVT1 axis, this interaction improves the migration of breast cancer cells.[80]

Additionally, HOTAIR may bind to miR-206 competitively, reducing the inhibitory effect it has on ANRIL. Through modulating the miR-206/ANRIL axis, this interaction promotes the migration and invasion of breast cancer cells. Certain lncRNAs regulate and modulate a few pathways involved in the migration of breast cancer cells in addition to interacting with proteins. These are a few of them explained below. To bring PRC2 to target gene promoters, ANRIL interacts with SUZ12, a member of the polycomb repressive complex 2 (PRC2), while HOTAIR interacts with the histone methyltransferase EZH2. Together, these interactions create complexes that epigenetically silence metastasis suppressor genes, repressing the expression of the target gene.[81,82] Pre-mRNA alternative splicing is regulated by MALAT1's

interaction with the splicing factor SF2/ASF (Splicing Factor 2/Alternative Splicing Factor) and UCA1's interaction with the RNA-binding protein hnRNP I. Genes involved in cell adhesion and cytoskeletal organization have their splicing patterns altered by the former interaction, whereas genes involved in cell motility and metastasis have their splicing patterns altered by the latter.[83,84]

Invasion

Breast cancer advances through invasion when carcinoma cells pierce the basement membrane (BM), a layer of nanoporous matrix that physically separates the main tumor from the stroma. Single cells can penetrate nanoporous three-dimensional matrices by force-mediated pore widening caused by invadopodial protrusions or protease-mediated degradation. However, as breast cancer advances, multiple cells invade through the physiological basement membrane collectively due to cell volume expansion and local contractility.[85]

The lncRNAs NNT-AS1, PVT1, MEG3, HOTAIR, ROR, ARF6, MALAT1, etc. are involved in cell invasion through their interactions with miRNAs. The mechanisms underlying some interactions are explained. The majority of the functions of the long non-coding RNA NNT-AS1, which is also transcribed in the same direction as nicotinamide nucleotide transhydrogenase (NNT), are still unknown. It has been verified that NNT-AS1 is a tumor promoter in colorectal cancer and cervical cancer. NNT-AS1 acts as a sponge for miR-142-3p in the particular interaction between NNT-AS1 and miR-142-3p in breast cancer cells. This indicates that miR-142-3p is bound by NNT-AS1, which inhibits it from binding to its target mRNAs. This leads to an upregulation of target mRNAs that miR-142-3p normally suppresses, which increases the invasion and metastasis of breast cancer cells. The specific downstream targets of miR-142-3p and how they facilitate invasion may differ based on the cellular environment and the breast cancer subtype.[86]

PVT1 is an additional lncRNA that receives miRNA sponging. Located at the human 8q24 chromosomal locus, PVT1 is a long non-coding RNA (lncRNA). It is linked to the growth, invasion, and metastasis of tumors and is upregulated in several cancers, including breast cancer. MicroRNA miR-204-5p has been found to function as a tumor suppressor in many cancers, including breast cancer. By attaching itself to target mRNAs '3' untranslated region (UTR) and causing translational repression or mRNA degradation, it controls the expression of specific genes. PVT1 acts as a sponge for miR-204-5p in the interaction between PVT1 and miR-204-5p in breast cancer cells. PVT1 relieves the suppressive effects of miR-204-5p on these target genes by binding to miR-204-5p and sequestering it from its target mRNAs. Increased invasion and EMT in breast cancer cells are caused in part by this dysregulation of the miR-204-5p target genes. EMT is a critical stage in the metastasis of cancer in which epithelial cells lose their properties and take on a mesenchymal phenotype, which allows them to migrate and invade neighboring tissues.[87]

The lncRNA HOTAIR enhances the invasive characteristics of cancer cells and facilitates the epithelial-mesenchymal transition (EMT) by acting as a ceRNA, sequestering miR-34a, and derepressing Snail.[88] Together, other lncRNAs like GAS5, RMST, and others cause invasion and migration, which were covered in-depth in the preceding sections. Among the lnc-lnc interactions involved in the invasion are MALAT1, HOTAIR, Linc-ROR, BCAR4, ANCR, PRUNE2, lncRNA XIST, and NEAT1. By stabilizing ANRIL and regulating genes involved in invasion and metastasis, the lncRNA HOTAIR forms a complex that advances the development of breast cancer.[81] By modifying chromatin organization and gene expression in breast cancer cells, the lncRNA XIST interacts with NEAT1 to affect cell invasion, migration, and proliferation.[89]

Certain lncRNAs aid in cell invasion through protein interactions that advance the course of disease. A few of these interactions are covered in the section below. ARF6 hybridizes with miR-145. One small GTPase protein, ARF6, is involved in cell migration, cytoskeleton remodeling, and membrane trafficking. Through encouraging cell invasion and EMT, it has been linked to the metastasis of cancer. MicroRNA miR-145 suppresses tumors in a variety of cancers, including breast cancer. It regulates gene expression by binding to the 3' untranslated region (UTR) of target mRNAs, leading to their degradation or translational repression. The interaction between ARF6 and miR-145 in breast cancer cells involves miR-145 directly targeting the mRNA of ARF6. MiR-145 binds to the 3' UTR of ARF6 mRNA to suppress its expression, which in turn prevents ARF6-mediated signaling pathways that are involved in EMT and cell invasion. MiR-145's dysregulation of ARF6 inhibits breast cancer cell invasion and epithelial-mesenchymal transition, which in turn prevents cancer metastasis.[90]

The lncRNA known as MALAT1, or Metastasis Associated Lung Adenocarcinoma Transcript 1, interacts with the chromatin remodeling complex to facilitate alternative splicing of pre-mRNAs, thereby enhancing tumor invasion and metastasis. This controls the expression of genes linked to the metastasis of breast cancer.[84] Research has shown that some lncRNAs, like HOTAIR, change chromatin states that depend on PRC2 and other protein complexes to promote the growth of cancer. These interactions aid in the invasion and dissemination of breast cancer cells to distant areas.[91]

Metastasis

Metastasis is the term used to describe the movement of cancer cells from the site of their original formation to another area of the body. When cancer cells metastasize,

they separate from the main tumor and move through the blood or lymphatic system to develop a new tumor in a different organ or tissue within the body. The primary tumor and the newly discovered, metastatic tumor belong to the same cancer type. For instance, cancer cells in the lung that metastasize from breast cancer are not lung cancer cells; rather, they are breast cancer cells. Metastasis requires tumor cell dissemination to different organs from the primary tumor. To accomplish directed cell migration, the protrusion, chemotaxis, invasion, and contractility activities of tumor cells must be molecularly coordinated. This is a complex phenomenon of cell motility known as dissemination.[92]

lncRNAs such as PRLB, NEAT1, CAMTA1, MALAT1, ROR, and others interact with miRNA to aid in metastasis. Certain lncRNAs can influence angiogenesis, a critical step in the growth and metastasis of tumors, through their interaction with miRNAs.[93] The lncRNA MALAT1 contributes to angiogenesis in breast cancer by binding to miR-145, upregulating VEGF-A expression, and encouraging the development of new blood vessels to support tumor growth.[94] By specifically targeting miR-155, overexpression of the long noncoding RNA X-inactive specific transcript (XIST) inhibits the proliferation, migration, and invasion of breast cancer cells. In breast cancer cells, XIST can alter the 3′-UTR of caudal-type homeobox 1 (CDX1), a direct target of miR-155. As a result, breast cancer metastasis is significantly influenced by the XIST/miR-155/CDX1 axis. [95] In patients with primary breast cancer, XIST is negatively correlated with brain metastasis but not with bone metastasis. By activating c-Met, the knockdown of XIST accelerates metastasis to the brain and increases the growth and stemness of primary tumors. In addition, XIST silencing increases the release of exosomal microRNA-503, which triggers microglia's M1–M2 polarization, immune-suppressive cytokines, and T-cell proliferation inhibition. Consequently, XIST affects signaling pathways and the tumor micro enviro nment that are involved in brain metastasis in breast cancer.[96]

The expression of miR-96-5p is downregulated, and synoviolin (SYVN1) is upregulated when lncRNA cancer susceptibility candidate 2 (CASC2) is upregulated. This leads to the inhibition of metastasis and the induction of apoptosis in breast cancer cells. Overexpression of miR-96-5p increases the ability of MDA-MB-231 cells to proliferate; this effect is offset by overexpression of SYVN1. On the other hand, lncRNA CASC2 may act as a ceRNA for miR-96-5p and control the expression of tumor suppressor SYVN1, one of miR-96-5p's direct targets. Thus, a key factor in the metastasis of breast cancer cells is dysregulation of the CASC2/miR-96-5p/SYVN1 axis.[97] On the other hand, lncRNA SNHG14 is implicated in the metastasis of breast cancer cells and is highly expressed in breast cancer tissues compared to adjacent ones.

Breast cancer metastasis is facilitated by upregulated lncRNAs such as HOTAIR, linc-ROR, and BCAR4.[98] Through controlling the expression of EMT-associated transcription factors, the lncRNA PVT1 interacts with HOTAIR to facilitate the epithelial-mesenchymal transition (EMT) and metastasis in breast cancer cells.[99]

LncRNAs interact with proteins in breast cancer to regulate many biological processes that are vital to the disease's initiation and progression. Several of these include CRNDE, MALAT1, LINC01116, and HOTAIR. Breast cancer-related oncogenic lncRNAs have an impact on cell survival and proliferation.

Oncogenic lncRNAs associated with breast cancer affect the survival and proliferation of cells. These lncRNAs are linked to cell cycle regulation. These lncRNAs promote tumor growth and metastasis by controlling the cell cycle.[91] The lncRNA CRNDE encodes the nuclear peptide CRNDEP, which is involved in cell turnover and overexpressed in tissues with high rates of proliferation.[91] Through its interaction with the STAT3 (Signal Transducer and Activator of Transcription 3) protein, lncRNA LINC01116 modulates the immune response in breast cancer. This helps with metastasis by promoting immune evasion by tumor cells and controlling the expression of immune checkpoint molecules such as PD-L1 (Programmed Death-Ligand 1).[100] It has been discovered that some lncRNAs, like HOTAIR, change chromatin states that help cancer spread by depending on protein complexes like PRC2. These interactions aid in the invasion and dissemination of breast cancer cells to distant areas.[91]

Mechanisms of Interaction of lncRNA with other Cellular Molecules

The competency of the cancer cell to advance through different stages of cancer is due to the significant change in the regulation of oncogenic pathways, epigenetic and chromatin remodeling, regulation of metastasis processes, modulation of tumor suppressor network, cell cycle regulation, cellular signaling pathway and immune response modulation. These changes are brought by the cancer cells through various mechanisms of interactions of lncRNAs as illustrated is Figure 2. The primary mechanism of interaction of lncRNAs with other cellular molecules are discussed below.

Direct base Pairing

Through complementary base pairing, lncRNAs can interact with one another in this mechanism and form RNA-RNA duplexes. Two or more lncRNAs may interact through this interaction, which may impact their localization, stability, or function.

Chromatin Modification

lncRNAs can bind transcription factors, chromatin-modifying enzymes, or ribonucleoprotein complexes to gene promoters,

thereby inducing transcription and affecting the expression of genes.

Regulation of Gene Expression (activation or suppression)

lncRNAs regulate gene expression via multiple mechanisms, including transcription, alternative splicing, regulation of protein activity, modification of protein localization, chromatin modification, and post-transcriptional processing.

Interaction with Proteins

By interacting with proteins, lncRNAs control gene expression that is connected to the start and spread of cancer. In breast cancer, lncRNAs interact with proteins to control several biological processes essential to the onset and spread of the disease. These relationships are important regulators of gene expression, cellular processes, and cancer phenotypes.

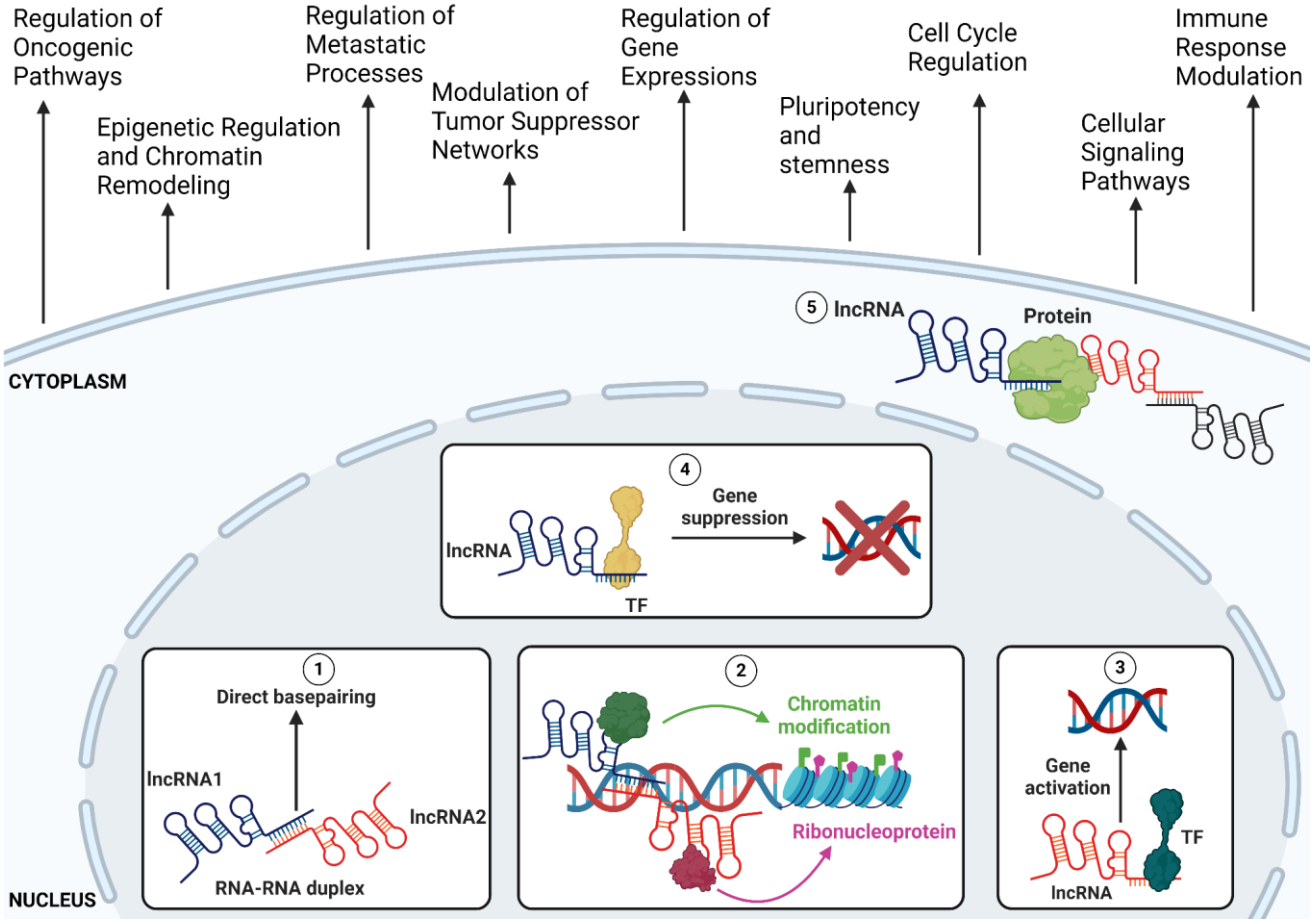

Figure 2. Mechanisms of Interaction of lncRNAs with other cellular molecules such as intracellular proteins, transcription factors (TF) and other lncRNAs in driving Breast Cancer Progression: **(1)** Direct base pairing; **(2)** Chromatin Modification; **(3)** Gene Activation; **(4)** Gene Suppression; **(5)** Interaction with protein.

Pathways Associated with Breast Cancer and Interference of lncRNA

lncRNAs affect several crucial signaling pathways linked to the emergence of breast cancer. Gaining insight into the importance of these interactions within pathways helps explain the molecular mechanisms underlying tumorigenesis key pathways that are regulated by the lncRNAs and their importance in breast cancer is illustrated in Figure 3.

Wnt/β-Catenin Pathway

The Wnt pathway is vital for regulating cell proliferation, differentiation, and stem cell maintenance. A common characteristic of breast cancer is the dysregulation of this pathway. Canonical Wnt signaling is mostly responsible for the proliferation of breast cancer cells and the maintenance of their "stemness." It is a β-Catenin-dependent pathway that is involved in lymphoid enhancer factor (LEF) and T cell factor (TCF). There is growing evidence that the two well-established β-Catenin-independent noncanonical Wnt pathways, Wnt–PCP and Wnt–Ca2+ signaling, are accountable for the metastasis of breast cancer cells.[101] Wnt proteins are involved in the metastasis of breast cancer by activating multiple signaling pathways. When Wnt is not present, β-catenin breaks away from an APC, axin, and GSK3β multienzyme

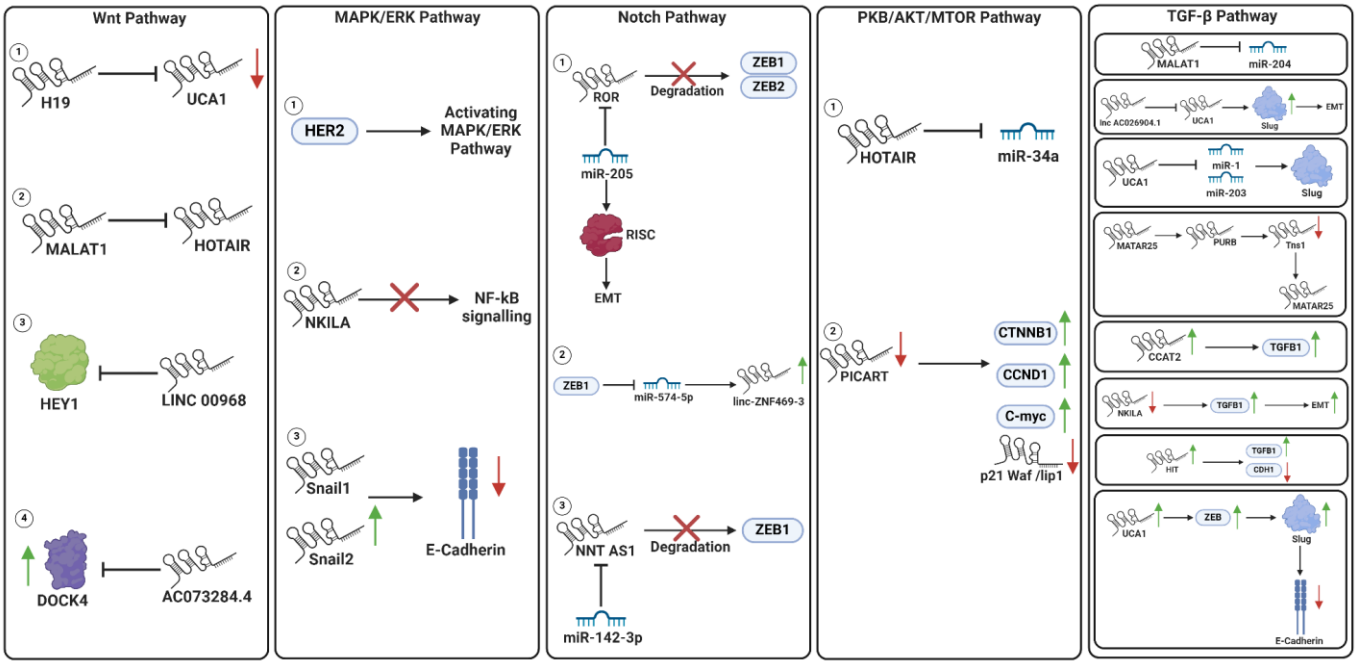

Figure 3. lncRNA Interaction and their Contribution to Different Breast Cancer Association Pathway.

complex. GSK3β phosphorylates β-catenin's N-terminal, Snail, and Slug, which results in β-catenin's degradation via the ubiquitin-proteasome degradation pathway. However, when Wnt is present, GSK3 activity is suppressed, which stabilizes β-catenin's nuclear localization. The induction of EMT is caused by the stable β-catenin aggregating inside the nucleus of tumor cells.[102] Downregulation of lncRNA H19 stimulates the translocation of β-catenin from nuclear to cytoplasm in tamoxifen-resistant breast cancer cells and upregulates the expression of E-cadherin and vimentin in breast cancer cells. Sequestering miRNAs that would otherwise target elements of the Wnt pathway, lncRNAs like HOTAIR and MALAT1 function as competing endogenous RNA (ceRNA). This interaction has the potential to cause aberrant Wnt signaling activation, which can encourage unchecked cell growth and aid in the development and spread of breast cancer.[103] Like H19, downregulating lncRNA UCA1 increases the sensitivity of breast cancer cells to tamoxifen by blocking the Wnt/β-catenin pathway, while overexpressing UCA1 causes EMT in breast cancer cells by triggering the Wnt/β-catenin signaling pathway.[104,105] One other lncRNA, AC073284.4, may upregulate the dedicator of cytokinesis protein 4 (DOCK4) in paclitaxel-resistant breast cancer cells, thereby sponging up miR-18b-5p to decrease invasion, metastasis, and EMT. lncRNA AC073284.4 represses EMT and migration in breast cancer cells by regulating the miR-18b- 5p/DOCK4 axis. [106]

Wnt2, a primary Wnt ligand implicated in vascularization, and the lncRNA LINC00968 control the Wnt2-mediated Wnt2/β-catenin signaling pathway in breast cancer by means of the transcriptional repressor HEY1. In breast cancer cells, overexpression of LINC00968 inhibits migration and invasion by blocking the activation of the Wnt2/β-catenin signaling pathway and EMT. On the other hand, by suppressing Wnt1 and β-catenin, the novel lncRNA RUSC1-AS-N inhibits cell proliferation and metastasis in breast cancer cells. Nevertheless, by counteracting the effects of RUSC1-AS-N knockdown, Wnt agonist 1, an activator of the Wnt signaling pathway, can enhance cell proliferation and metastasis.[107]

Notch Signaling Pathway

The Notch pathway is essential for maintaining stem cells, determining cell fate, and maintaining tissue homeostasis. Anomalous Notch signaling activation is linked to the development of breast cancer. The Notch pathway describes the interaction between two neighboring cells, one of which is carrying a ligand and the other a receptor that has been engineered to bind to the ligand.[108] By modifying the activity of miRNAs and thereby influencing the Notch pathway, long noncoding RNAs (lncRNAs) such as UCA1 and H19 have been linked to breast cancer. When this pathway is dysregulated, it can cause abnormal cell processes like increased proliferation and decreased apoptosis, which can further contribute to the pathophysiology of breast cancer.[109]

Snail 1 expression is stimulated by the Notch signaling pathway under hypoxic conditions. Hypoxia is an angiogenesis phase that lasts until the EMT process reaches the micrometastases stage. Hypoxia factor-1 (HIF-1) is released under hypoxic conditions, stabilizing Snail 1. Both a stable β-subunit and an unstable α-subunit are present in

HIF-1. HIF-1α stabilizes and translocates into the nucleus in hypoxic conditions, where it induces epigenetic modulation (EMT) by upregulating transcription activators or repressors associated with EMT, modulating EMT-associated inflammatory cytokines, signaling pathways, and epigenetic modulators.[110] Breast cancer EMT is accelerated when HIF-1α-mediated canonical hypoxia signaling is stimulated, resulting in the upregulation of TWIST, SNAIL, ZEB1, and E12/E47.[111] Increased lncRNA linc-ROR expression also stops ZEB1 and ZEB2 from degrading by sponging miR-205 during the EMT process by forming an RNA-induced silencing complex (RISC). The lncRNA NNT-AS1 controls ZEB1 expression similarly to Linc-ROR. Nicotinamide nucleotide transhydrogenase (NNT) is the enzyme that NNT-AS1 transcribes in the opposite direction, and the two do not intersect. NNT-AS1 functions as a ceRNA by sponging to miR-142-3p, and it has an inverse correlation with the latter. As an alternative, ZEB1 is positively regulated by NNT-AS1 and is another target point of miR-142-3p. By lowering ZEB1 expression through targeting miR-142-3p, downregulation of NNT-AS1 prevents breast cancer cells from proliferating, migrating, or forming EMTs.[86] On the other hand, lung-metastatic LM2-4175 TNBC cells overexpress the lncRNA linc-ZNF469-3, which enhances invasion capacity and stemness properties in vitro as well as lung metastasis *in vivo*. Increased expression of ZEB1 and sponging of miR-574-5p caused by over expression of linc-ZNF469-3 has been linked to tumor recurrence in TNBC patients.[112]

Transforming Growth Factor-beta (TGF-β) Signaling Pathway

Immune responses, cell growth, and differentiation are all regulated by TGF-β signaling. This pathway's dysregulation is linked to the spread and metastasis of breast cancer. Transforming growth factor-β (TGFβ) signaling controls the development of tumors through tumor-stroma interaction or tumor cell-autonomous mechanisms. Depending on the cellular environment, TGFβ signaling can either promote or suppress tumor growth. The intrinsic intricacy of TGFβ signaling poses challenging yet potentially fruitful tasks in the development of therapeutic approaches targeting malignant tumors.[113] The epithelial-mesenchymal transition (EMT) and enhanced metastatic potential in breast cancer cells are influenced by TGF-β signaling, which is influenced by lncRNA-miRNA interactions like the ceRNA network involving MALAT1 and miR-204. Their function in metastatic processes is highlighted by the way lncRNA-miRNA interactions modulate TGF-β signaling.[114]

Located at tight junctions, TGF-β receptors directly interact with Par6 and Occludin, two significant regulators of epithelial cells.[115,116] Apical-basal polarity and tight junctions are lost when the TGF-β type II receptor phosphorylates Par6.[116] The TGF-β signaling pathway also controls the expression of E-cadherin by activating Smads, which in turn suppresses the expression of Snail, Slug, SIP1, and Goosecoid.[117,118] Together, the long non-coding RNAs AC026904.1 and Urothelial carcinoma associated 1 (UCA1) upregulate Slug's transcriptional and post-transcriptional levels, playing crucial roles in both canonical and non-canonical TGF-β-induced epithelial-mesenchymal transitions. UCA1 and AC026904.1 have poor outcomes for patients with breast cancer and are highly expressed in metastatic breast cancer. In breast cancer cells, upregulation of UCA1 dramatically increases ZEB1 and Slug expression while downregulating E-cadherin expression and causing tumor metastasis. By preventing the expression of miR-1 and miR-203, UCA1, which serves as ceRNA, has been demonstrated to induce Slug expression in breast cancer. Similarly, AC026904.1 might function as an eRNA to trigger Slug expression in breast cancer.[119]

Another significant transcription factor implicated in the metastasis of breast cancer is Smad. After being phos phorylated by type II serine-threonine kinase receptors (TβRII), type I serine-threonine kinase receptors (TβRI) bind to TβRII and TβRI, respectively, to stimulate Smads. Cells consequently start to lose their adherence and attachment to nearby cells. To control breast cancer migration and invasion, MaTAR25, a nuclear enriched and chromatin-associated long noncoding RNA, interacts with purine-rich element binding protein B (PURB) and forms an association with Txensin 1 (Tns1), a significant downstream target. By downregulating Tns1, silencing of lncRNA MaTAR25 reduces focal adhesions, and microvilli, and reorganizes the actin cytoskeleton. Thus, a key factor in the metastasis of breast cancer is the MaTAR25/PURB/Tns1 DNA complex.[120] Likewise, there is a strong expression of colon cancer-associated transcript 2 (CCAT2) in breast cancer metastases.[121,122] By controlling the TGF-β signaling pathway, latent TGFβ-binding proteins (LTBPs) prevent metastasis; increased expression of CCAT2 promotes breast cancer cell invasion, migration, and proliferation.[123] LTBP3, a protein that controls the release of TGFβ, the invasion of primary tumors, and the spread of those tumors.[124,125] The fibrillar extracellular matrix network is formed in part by LTBP3.[126] This protein's activity is influenced by the primary tumor's microenvironment. Patients with ER-/PR-/PR-breast cancer have worse outcomes and increased metastatic dissemination when LTBP3 is overexpressed.[127]

PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR signaling pathway. When ligands (hormones, growth factors, and insulin) bind to RTKs as well as GPCRs (chemokines), PI3K is activated. This protein kinase will catalyze the phosphorylation of PIP2 to PIP3 once it is activated. AKT is recruited to the plasma

membrane, where it is phosphorylated twice: once at the threonine residue level, PDK1 catalyzes the reaction, and again, mTORC2 catalyzes the second. After being phos phorylated, AKT will phosphorylate other molecules, including the mTOR complex, which is ultimately linked to the production of new proteins and the proliferation of cells. Other phosphorylated substrates linked to cell survival and proliferation, like Fox01 and GSK-3, will be inhibited. The primary negative regulator of this signaling pathway that is involved in the dephosphorylation of PIP3 is PTEN.[128] By acting as a sponge for miR-34a, lncRNA HOTAIR promotes the activation of the PI3K/AKT pathway and advances breast cancer.[129]

MAPK/ERK- NF-κB Pathway

The initiation and progression of breast cancer are associated with the Mitogen-Activated Protein Kinase (MAPK) pathway, which regulates multiple cellular functions such as proliferation, differentiation, migration, and apoptosis. It has been repeatedly demonstrated that breast cancer is characterized by aberrant activation of the MAPK pathway, which encourages uncontrolled cell proliferation and tumor growth. Dysregulation of key players in this pathway, such as Ras, Raf, MEK, and ERK, can result from growth factor receptor activation, hormone signaling, genetic changes, and interconnected signaling pathways. This dysregulation contributes to the oncogenic transformation and resistance to therapy in breast cancer.[130]

Overexpression of human epidermal growth factor receptor 2 (HER2) activates the MAPK/ERK pathway. HER2-positive breast cancers have increased signaling through the MAPK/ERK pathway, which promotes the tumor's growth and dissemination.[131] One important factor in the development and progression of breast cancer is the NF-κB pathway, which controls a number of cellular functions such as invasion, metastasis, proliferation, survival, and inflammation. The transcription factor NF-κB is inactive in the cytoplasm and is bound to its inhibitor, IκB. The IKK complex phosphorylates IκB, causing it to degrade and release NF-κB, in response to various stimuli such as growth factors, cytokines, or stress signals. The released NF-κB moves into the nucleus, where it controls the expression of target genes linked to various aspects of cancer.[132] NKILA inhibits NF-κB signaling and promotes breast cancer metastasis by binding to the NF-κB/IκB complex, stabilizing it and hiding the phosphorylation sites of IκB.[18]

A class of transcription factors known as nuclear factor-κB (NF-κB) is involved in differentiation, survival, proliferation, immunity, and inflammation.[133] Like the TGF-β pathway, the Ras-MAPK and NFκB pathways target Snail to modify the EMT.[134] Through NFκB pathways, Snail1 contributes to the reduction of E-cadherin expression.[135] Similar to this, by triggering the Ras-MAPK pathway, Snail2 overexpression also reduces the expression of E-cadherin.[136] Through the MAPK-independent pathway, HGF stimulates the expression of Snail. Additionally, it plays a role in the binding of EGR-1 to the Snail1 promoter, which triggers the start of EMT.[137]

Insulin growth factor receptors aid NFκB in promoting epithelial-mesenchymal transition (EMT) in breast cancer. In mammary epithelial cells, IGF1R activation results in EMT, which is followed by a decrease in E-cadherin expression and an increase in N-cadherin, vimentin, and fibronectin expression. LncRNAs regulate the intricate web of signaling pathways to control EMT. A consequence of underlying inflammation in the tumor microenvironment is irregular NF-κB expression, which can encourage cancer invasion and metastasis in breast cancer cells. Through NF-κB signaling, inflammatory cytokines upregulate interacting LncRNA (NKILA). NKILA has an inverse correlation with NF-κB signaling. NKILA binds to NF-κB/IκB, and directly masks phosphorylation motifs of IκB, thereby hindering the IKK-induced IκB phosphorylation and NF-κB stimulation. Therefore, the downregulation of NKILA enhances NF-κB activity, which promotes the invasiveness of breast epithelial cells and leads to metastasis and a poor prognosis in breast cancer patients.[138]

Hedgehog Signaling Pathway

Comprising both canonical and non-canonical elements, the Hedgehog (Hh) pathway is a sophisticated signaling pathway**.** When ligands like Sonic Hedgehog bind to and inhibit the transmembrane receptor PTCH1, relieving its repression of SMO, the canonical pathway is activated. As a result, SMO translocation to the primary cilium occurs, starting a signaling cascade that causes SUFU to separate from GLI proteins. The transcription of Hh target genes is then encouraged by activated GLIs, which include GLI1 (activator), GLI2 (repressor and activator), and GLI3 (repressor), which translocate to the nucleus. Cell cycle regulation (Cyclin D1/2), proliferation (PDGFR, MYC), apoptosis (BCL2), angiogenesis (VEGF, ANG1/2), epithelial-mesenchymal transition (MMP9, SNAIL), and stem cell regulation (NANOG, SOX2) are just a few of the cellular processes that these genes are involved in. In addition, GLI proteins are phosphorylated by GSK3β, casein kinase 1, and protein kinase A in the cytoplasm, which exposes them to proteasome degradation. The Hedgehog signaling pathway is regulated by lncRNA-miRNA interactions, which affect breast cancer cell survival, differentiation, and proliferation.[139] Understanding the intricate crosstalk between lncRNAs and other components within these pathways provides valuable insights into the molecular landscape of breast cancer. Targeting specific lncRNAs may offer novel therapeutic strategies for breast cancer treatment by modulating these critical signaling pathways and impeding tumorigenesis.

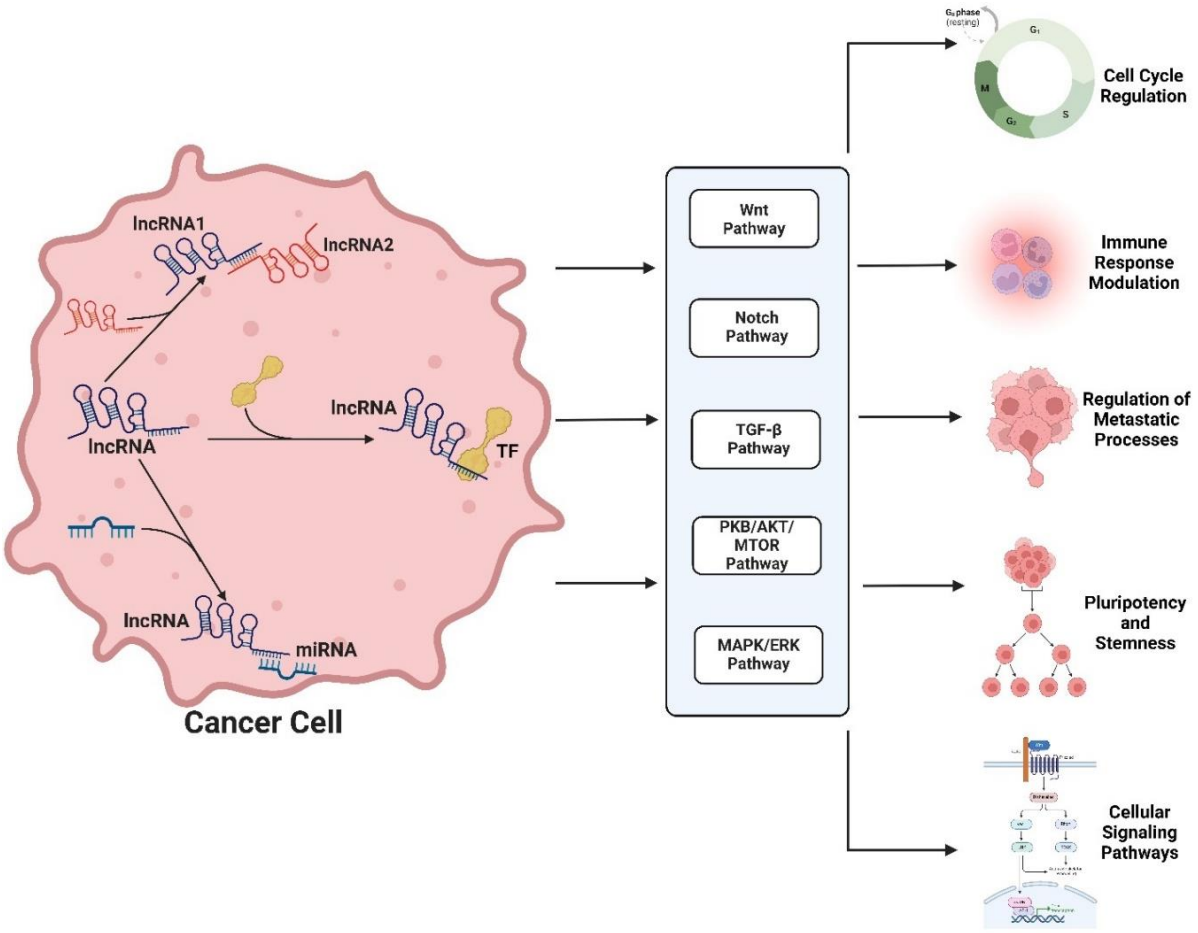

Figure 4. Graphical Abstract of Regulatory Interplay of lncRNAs in Breast Cancer Progression.

The summary of intracellular interactions by lncRNAs and the associated pathways in breast cancer progression is shown as a graphical abstract in Figure 4.

lncRNA-Based Breast Cancer Therapeutics

RNA therapeutics gained more attention and funding since the early 2000s, when RNA interference (RNAi) and small interfering RNA (siRNA) were discovered to be effective in silencing human genes.[140] In 1998, Vitravene, an ASO, was approved as the first RNA-based medication; however, it was later withdrawn because of low demand.[141] lncRNAs' involvement in a variety of cellular functions, including drug resistance mechanisms frequently observed in triple-negative breast cancer (TNBC), has made them promising targets for breast cancer treatment.[142] These molecules are important players in the development of cancers because they can predict and modify chemoresistance. Creating novel treatment approaches for breast cancer requires an understanding of the regulatory mechanisms of lncRNAs.

LncRNAs have a lot of potential as breast cancer treatment targets. Different targeting strategies, such as transcriptional inhibition, post-transcriptional inhibition, and modulation of lncRNA genomic loci, are made possible by the diverse functional repertoire of lncRNAs.[143] These strategies could lead to more personalized and effective treatment options for breast cancer patients. Companies such as Moderna and Pfizer/BioNTech have developed mRNA vaccines against SARS-CoV-2, which are a significant advancement in RNA therapeutics.[144] A number of siRNA medications, such as inclisiran for hypercholesterolemia and patisiran for hereditary transthyretin-mediated amyloidosis, have received approval. Patients with hereditary transthyretin amyloidosis were the first to undergo CRISPR-based in vivo gene editing therapy using Cas9 mRNA and guide RNA.[145] LncRNAs have a potential role in therapeutics because they can be used as diagnostic biomarkers, prognostic factors, and potential therapeutic targets. lncRNAs have high tissue and cell-type specificity and are aberrantly expressed in breast cancer, they are appealing as diagnostic biomarkers.[146] As prognostic factors and targeted therapeutic targets, they might support individualized treatment plans. lncRNAs have been linked to several cellular processes, including migration, apoptosis, angiogenesis, and proliferation, and hence can be potential therapeutic targets. LncRNAs have also shown promise in therapeutic approaches to Breast cancer. RNA was first investigated as a potential therapeutic target in the

early 1980s with the creation of antisense oligonucleotides (ASOs) that could prevent protein synthesis.[147] ASOs are powerful for lncRNA targeting, and in preclinical models, they appear to be able to slow the growth of tumors. For example, MALAT1 ASOs have been reported to reduce tumor growth in a preclinical mouse model for breast cancer.[148]

On the other hand, an approach called Locked Nucleic Acid (LNA) Targeting is also being considered as a potential strategy**.** Targeting lncRNA PVT1 with locked nucleic acid (LNA) increased the sensitivity of ovarian cancer cells to chemotherapeutic agents. It is possible that breast cancer could benefit from this strategy as well.[142] The inhibition of cancer metastasis in breast cancer models has been demon strated by antisense oligonucleotide-conjugated nanostructures that target the long noncoding RNA MALAT1.[148] Using lncRNA-based combination therapy to treat breast cancer may be a promising way to overcome drug resistance. Combining lncRNA-targeted therapies with conventional chemotherapy could potentially improve outcomes.[149]

miRNA and siRNA therapeutics have become effective for modifying gene expression in a variety of diseases. Through the restoration of tumor-suppressive functions, inhibition of viral replication, or silencing of particular disease-associated genes, these therapies demonstrate the accuracy and adaptability of RNA-based interventions in treating a wide range of medical conditions.[150] LncRNAs have the potential to enhance patient outcomes and facilitate earlier intervention. LncRNAs are great candidates for lineage-specific gene therapy because of their tissue-specific expression, which may lessen off-target effects in non-cancerous cells.[151] Chemical modifications to the RNA structure are widely used to enhance stability. These include changes to individual bases, the phosphate linkage, and the ribose sugar (particularly at the 2' position). To improve their resistance to degradation and lessen off-target effects, siRNAs frequently go through significant modifications. The degree of modification must be carefully balanced, though, because too many changes can affect the RNA's functionality, particularly for larger mRNAs that require efficient ribosome translation.[152] In order to safeguard RNA molecules and promote their cellular uptake, a number of delivery methods have also been investigated.[153] These include the use of viral vectors, complexation with cationic polymers, and encapsul ation in lipid nanoparticles. The objectives of each strategy are to prevent the RNA from degrading, lessen its negative charge, which prevents cellular entry, and encourage targeted delivery to particular tissues or cell types.[154]

Clinical trials involving lncRNAs in breast cancer typically fall into Biomarker Studies, Therapeutic Targeting, Combination Therapies, Diagnostic and Prognostic Tools, and Mechanistic Studies. Several ongoing clinical studies in various parts of the world are primarily focused on lncRNAs and their involvement in breast cancer. One such study is being carried out in China. This study began in 2016 and is still being carried out to validate the efficacy of the mRNA-lncRNA signature and evaluate the efficacy and safety between docetaxel combined with doxorubicin (epirubicin) and cyclophosphamide, followed by gemcitabine combined with cisplatin and doxorubicin (epirubicin) combined with cyclophosphamide, followed by docetaxel for high-risk triple-negative breast cancer predicted by the integrated signature.[155] A study carried out by Ain Shams University aims to provide information about the role of LINC00511 SNPs (rs11657109, rs17780195, or rs9906859, rs4432291, and rs1558535) in breast cancer susceptibility in the Egyptian population. The eligibility criteria for the study included histo pathologically confirmed primary BC patients and the patient age group (adult female BC patients, 20-70 years). The study used several biochemical and statistical analyses to determine and validate that genetic variations such as single nucleotide polymorphisms (SNPs) in lncRNAs are associated with cancer.[156] In Lebanon, an innovative clinical trial applies a comprehensive strategy to study the complex interplay of biomarkers, immune responses, angiogenesis, and proliferation in solid tumor progression. The study investigates LncRNA for its potential as a prognostic and predictive biomarker. The investigation began with colorectal cancer and extended to other solid cancers, including lung, ovarian, and breast cancers. Patients were stratified into carriers or non-carriers of the risk allele, forming the foundation for precision-driven treatments. The study integrates precision medicine, biomarker-driven therapies, and a comprehensive understanding of the molecular basis of tumor progression, including thromboembolism. This approach offers a promising avenue for the development of personalized and effective treatments for various solid tumors, emphasizing not only efficacy and safety but also the overall effectiveness of the proposed therapeutic interventions.[157]

Another study conducted by Lebanese University aims to assess biomarkers and their related polymorphisms in the context of cancer-associated thromboembolism, with a particular focus on their interaction with the immune system. The roles of immune checkpoints, inflammatory and angiogenesis factors, as well as circulating immune cells. Additionally, the investigation extends to the exploration of lncRNAs, and genes associated with the coagulation vascular system. Initially, these aspects were evaluated in the context of colorectal cancer, with the intention of expanding research to other solid tumors. The study seeks to contribute to our understanding of the intricate connections between LncRNA, coagulation-related biomarkers, thrombo embolism, immune responses, and cancer, using solid tumors as a representative example. By shedding light on these complex interactions, it aims to identify potential

biomarkers that can guide risk assessment and treatment decisions, ultimately improving the management of cancer patients.

The identification of these biomarkers and genetic factors holds the potential to revolutionize therapeutic approaches for patients with cancer-associated thrombo embolism, shedding light on their chemotherapy resistance. The effectiveness of combining immunotherapy with targeted inhibitors like Palbociclib and anticoagulants such as Rivaroxaban, among other potential interventions.[158]

However, there are various challenges involved. Some of them have been discussed. LncRNA-based therapies have not been extensively used in clinical settings, despite their important role in drug resistance.[159] Difficulties include toxicity concerns, problems with lncRNA delivery, financial implications, and the requirement for additional clinical research.[160] Depending on the lncRNA, there could be several target genes. These effects could have unexpected consequences or reduce the effectiveness of lncRNA-based treatments.[161] Effective delivery strategies are essential for the clinical treatment of breast cancer patients with long noncoding RNAs to be successful. To minimize side effects and optimize therapeutic benefits, precise and efficient delivery mechanisms are crucial.[161] The intricate networks of regulation involving proteins, miRNAs, and lncRNAs may result in unintentional interactions that impact cellular functions outside of the intended targets and may have unanticipated side effects.[162]

Conclusion

The complex network of regulatory proteins, miRNAs, and lncRNAs is essential to the development of breast cancer. The numerous roles that lncRNAs play in the development, invasion, and metastasis of breast cancer have been examined in this work, along with their potential as therapeutic targets. Because lncRNAs can interact with one another, a complex web of regulatory interactions is formed that greatly accelerates the development of breast cancer. These interactions can enhance the growth, survival, and dissemination of cancer cells by modifying the tumor microenvironment, influencing cellular pathways, and modulating gene expression. Breast cancer's molecular mechanisms rely heavily on protein network as well as on lncRNA pathways. The interactions and context of these molecules determine whether they function as tumor suppressors or oncogenes. Through their impact on crucial signaling pathways like PI3K/AKT, Wnt/β-catenin, and NF-κB, lncRNAs trigger actions that result in unchecked cell proliferation and resistance to apoptosis, ultimately aiding in the development and advancement of breast cancer. The interaction of miRNAs and lncRNAs adds another level of regulatory complexity. LncRNAs can act as "sponges" for miRNAs, offering a new way to indirectly control gene expression. However, there are still challenges in delivering these therapies effectively. RNA is unstable and has trouble crossing cell membranes. To address this, researchers are exploring advanced delivery systems like nanoparticles and exosomes to improve how well the therapies reach their targets. RNA therapies also show promise in overcoming drug resistance in diseases like breast cancer. They can target genes that traditional small molecule drugs have trouble affecting. By combining lncRNA targeting with standard treatments, there is a hope to create more personalized and effective treatment strategies. lncRNAs have emerged as promising targets for breast cancer therapeutics due to their tissue-specific expression and dysregulation in cancer tissues. Their unique expression patterns in different cancer subtypes and stages make them valuable for early detection and monitoring disease progression. Furthermore, lncRNAs are involved in regulating key signaling pathways and cellular processes in breast cancer, making them attractive targets for therapeutic intervention. Preclinical studies have demonstrated the efficacy of targeting lncRNAs using various approaches, such as antisense oligonucleotides and RNA interference techniques. These strategies have shown promise in inhibiting tumor growth, enhancing drug sensitivity, and modulating immune responses in breast cancer models. Additionally, ongoing research is exploring the potential of lncRNA-based signatures to guide treatment decisions and predict therapy responses in high-risk breast cancer patients. While other RNA-based therapies like miRNA, siRNA, and antisense oligonucleotides have already reached the market and clinics, there is a high possibility that the extensive research carried out currently in relevance to lncRNAs will soon bring a wide array of lncRNA-based therapies to clinics in the forthcoming years. This progress is expected to lead to more personalized and effective treatment strategies for breast cancer patients. Ongoing efforts to overcome these challenges and further studying the complex functions of lncRNAs in breast cancer biology are likely to pave the way for innovative therapeutic approaches in the near future.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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