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Long non-coding RNAs in breast cancer metastasis

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ABSTRACT

Breast cancer is the leading cause of cancer-related death among women. Recurrence of primary tumor and metastasis to distant body parts are major causes of breast cancer-associated mortality. The 5-year survival rate for women with metastatic breast cancer is only 25–30%. Breast cancer metastasis is a series of processes involved with EMT, invasion, loss of cell to cell adhesion, alteration in cell phenotype, extravasation, micro-environment of the tumor, and colonization to the secondary sites. Epigenetic modification is involved in the transformation of the distant stromal cell into a secondary tumor. LncRNAs, are one the key epigenetic modifiers, are the largest endogenous non-coding RNAs with approximate base-pair lengths from 200 nt to 100 kb. LncRNA plays a crucial role in breast cancer metastasis by sponging miRNA, by degrading or silencing specific mRNA, or else by targeting the enzymes and microprocessor subunits involved in the biogenesis of miRNA. LncRNA also alters the expression of several genes involved in breast cancer metastasis and modulating different cell signaling pathways. The goal of this review is to provide a better understanding of the role of lncRNA in the regulation of breast cancer metastasis. We also summarized some of the key lncRNAs that regulate the genes and signaling pathways involved in breast cancer invasion and metastasis.

1. Introduction

Breast cancer is the second leading cause of cancer-related death among women after lung cancer. About 15% of cancer-related death occurs in the age group of 20–59 years of women due to breast cancer. Breast cancer incidence has been increasing by 0.3% per year [1,2]. The major cause of mortality associated with breast cancer is the metastasis of the primary tumor spread into distant body organs. The most common metastatic organs are the lungs, liver, bones, and brain. Understanding the sequential events during metastasis is of utmost importance for the development of early biomarkers and therapeutics. The process of metastasis encompassing four major steps i.e. intravasation of tumor cells, survival in the circulation, extravasation, and establishment at the secondary sites. Before intravasation, tumor cells undergo three essential steps i. e migration, invasion and EMT through various signaling pathways regulated by genetic and epigenetic modifications.

Epigenetic modifications play a major role in breast cancer metastasis. The common epigenetic modifications are DNA methylation, histone modifications, and post-transcriptional gene regulation as well as PTMs by non-coding RNAs. The word 'ncRNA' is commonly hired for those RNAs which do not encode a functional protein, but as important as mRNA [3]. The human genome encodes about 20,000 functional genes, representing <2% of the total genome, and the rest of them are considered as 'junk DNA'. Current studies have proved that these 'junk DNA' transformed into biologically functional molecules and have some crucial regulatory effect on controlling two-third of the human transcriptional output [4]. ncRNA is one of the functional regulatory molecules encoded from this junk DNA. According to transcript size, ncRNAs are majorly categorized into small ncRNAs and lncRNAs. LncRNAs are the largest endogenous non-coding RNAs with approximate base-pair lengths of 200 nt to 100 kb.

In the human genome, more than 50% of transcripts functioned as lncRNAs, which do not carry any code for proteins but function directly as RNAs [5]. These newly discovered RNAs have been identified to have functional roles in a diverse range of cellular functions such as development, differentiation, and disease pathogenesis [6]. LncRNAs can be categorized into five groups concerning the nearest protein-coding transcripts: sense, antisense, bidirectional, intronic, and intergenic. Based on molecular mechanisms, lncRNA can be further classified into four sub-classes: guide, scaffold, signaling, and decoy molecules [7]. Current studies have revealed that by binding to a specific mRNA,

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Abbreviations

ARNILA	Androgen-receptor negatively induced lncRNA
ASOs	Antisense oligonucleotides
BrMs	Brain-metastatic derivatives
CASC2	Cancer susceptibility candidate 2
CCAT1	Colon cancer-associated transcript-1
ceRNA	competing endogenous RNA
CTC	Circulating tumor cells
DGCR8	DiGeorge syndrome critical region gene 8
ECM	Extracellular matrix
EMT	Epithelial-mesenchymal transition
eRNA	Enhancer RNA
EZH2	Enhancer of zeste homolog 2
GHET1	Gastric carcinoma highly expressed transcript 1
GSK3β	Glycogen synthase kinase 3β
HDACs	Histone deacetylases
HOST2	Human ovarian cancer-specific transcript 2
KLF4	Kruppel-like factor 4
LncRNAs	Long non-coding RNAs
MET	Mesenchymal-to-epithelial transition
MMP	Matrix metalloproteinases
mRNA	messenger RNA
ncRNA	non-coding RNA
NKILA	NF-KappaB Interacting LncRNA
PI3K	Phosphatidylinositol 3′ kinase, serine/threonine kinase
PRC2	Polycomb Repressive Complex 2
PTMs	Post-translational modifications
RNAi	RNA-mediated interference
shRNAs	short hairpin RNAs
siRNAs	small interfering RNAs
SYVN1	Synoviolin
TGF-β	Transforming growth factor-β
TICs	Tumor initiating cells
TNBC	Triple-negative breast cancer
TNM	Tumor-node-metastasis
Wnt	Wingless-type MMTV integration site family
XIST	X-inactive specific transcript

lncRNA reduces the protein expression encoded by the mRNA through degrading or silencing of the respective mRNA. LncRNAs also function as ceRNA which can sponging miRNA and inhibits the activity of miRNA. Furthermore, lncRNAs also can target the enzymes and microprocessor subunits involved in the biogenesis of miRNA, and hinder the production of mature miRNAs. In miRNA biogenesis, DGCR8 is an essential component of the Drosha complex which converts the pri-miRNAs into pre-miRNAs and then pre-miRNAs are released to the cytoplasm for further process. The expression of LncRNA TTN-AS1 has been associated with the expression of DGCR8. The upregulation of DGCR8 has been observed in TTN-AS1 overexpressed breast cancer cells. The overexpression of TTN-AS1 could enhance breast cancer cell migration and invasion by upregulating DGCR8 [8].

Similar to DGCR8, DICER is another important component involved in miRNA biogenesis. DICER is an endoribonuclease, converts pre-miRNAs into miRNA duplex in the cytoplasm and helps to produce the mature miRNAs. Some lncRNAs target DICER or pre-miRNA and hinder miRNA biogenesis which influences breast cancer metastasis. LncRNA LINC01787 binds pre-miR-125b and prevents to generate tumor suppressor miR-125b by inhibiting the binding of DICER to pre-miR-125b. As a result, overexpression of this oncogenic lncRNA LINC01787 promotes breast cancer cell proliferation, migration, and breast cancer xenograft growth *in vivo* by repressing the maturation of miR-125b [9]. LncRNA also can regulate the expression of DICER1 which leads to alter the expression of miRNAs and cause breast cancer invasion and metastasis. For example, tumor suppressor LINC00899 mainly functions as ceRNA for miR-425 and enhances DICER1. The upregulation of LINC00899 represses proliferation, migration, and invasion of breast cancer cells by inhibiting miR-425 [10]. Therefore, irregular expression of lncRNAs may lead to tumor initiation, growth, and metastasis in breast cancer [11]. Recently, lncRNAs have gained widespread attention and have been recognized to play a crucial role in various biological regulation. In this review, we have provided a comprehensive outline of the role of lncRNAs in breast cancer metastasis and discussed the molecular mechanisms behind their regulations. Further, these lncRNAs can be used as biomarkers or therapeutic targets for breast cancer therapy.

2. Breast cancer metastasis

Metastasis is a systematic consecutive process, where genetically trembling cancerous cells from the primary tumor, starting invasion, and migrate to the distant body organs through the blood and lymphatic vessels as shown in Fig. 1. With the help of the tissue microenvironment, the migrated cells proliferate at the secondary site and form the secondary tumor. Metastasis is responsible for more than 90% of cancer-related death [12,13]. Treatment of primary tumors with chemotherapeutics is easier compared to the metastatic secondary tumor. It has been observed that genetic and epigenetic factors play a key role in the transformation of the distant stromal cell into a secondary tumor. Among various mechanisms, EMT plays a major role in breast cancer metastasis [14].

2.1. Epithelial-mesenchymal transition

EMT is a reversible process where non-motile, polarized epithelial cells undergo a series of biochemical transformations and become motile non-polarized mesenchymal cells with invasive properties. These mesenchymal cells are resistant to apoptosis and also change the biosynthesis process of ECM components. Epithelium and mesenchyme are the basic phenotypes of tissues. The characteristics of epithelial cells are closely attached to the neighbor cells and apicobasal polarity via different sequential junctions such as tight junction, adherens junction, and desmosomes. Gap junction helps adjacent epithelial cells through protein channels for their direct communication. On the other side, mesenchymal cells are loosely bound to each other in the extracellular matrix and connective tissue next to epithelial cells. The morphology of the mesenchymal cell helps to travel to a specific target and initiates cell differentiation.

3. Long non-coding RNAs in EMT

In general, EMT is a central process involved in embryonic development, wound healing, and various pathophysiological conditions involved in tumor progression. EMT plays a crucial role in every stage of embryogenesis. In the primary stage of embryogenesis, EMT implicates the initiation of placenta formation and implantation of the embryo. Even at the later stage, gastrulation, where the delamination of neural crest cells from the dorsal neural tube occurs through EMT [15]. In embryonic development, EZH2, a histone-lysine N-methyltransferase enzymatic component of the PRC2, and epigenetic enzymes such as HDACs can regulate the expression of the genes responsible for development and differentiation. PRC2 is mainly required for the silencing genomic region (PRC-Response Elements or PRE) and repairing DNA double-strand breaks. EZH2, a histone methyltransferase and a catalytic component of PRC2 is mainly involved in tri-methylation of histone H3

at Lys 27 (H3K27me3) to regulate gene expression through epigenetic machinery [16]. EZH2 can regulate the invasion and aggressiveness of breast cancer by altering the expression of several genes involved in tumorigenesis and metastasis. Dickkopf WNT signaling pathway inhibitor 1 (DKK1), an inhibitor involved in the WNT signaling, is modulated directly by PRC2 through H3K27me3. Upregulation of lncRNA neuroblastoma associated transcript 1 (NBAT1) significantly deactivate DKK1 and induces migration and invasion of breast cancer cells by reducing the H3K27me3 level of the *DKK1* promoter. Simultaneously, tumor suppressor lncRNA NBAT1 suppresses the functions of EZH2 or PRC2 as well as reduces the PRC2-induced breast cancer cell invasion and migration [17]. In contrast to NBAT1, enforced expression of HOX transcript antisense RNA (HOTAIR) in epithelial cancer cells induces invasiveness and metastasis via prompting genome-wide re-targeting of PRC2 which leads to altering histone H3 lysine 27 methylation and gene expression [18]. HOTAIR specifically requires PRC2 to enhance breast cancer invasion and alters global gene expression. HOTAIR-induced PRC2 targeted genes are mainly *JAM2, PCDH10* and *PCDHB5* as well as HOTAIR is also recognized as positive a regulator of genes associated with cancer metastasis including *ABL2, SNAIL22*, and *LAMININ* [18]. *Homeobox A11 (HOXA11)*, another member of HOX gene clusters, is involved in embryonic development. Overexpression of lncRNA HOXA11-AS repressed the expression of HOXA11 mRNA and enhances cell proliferation, migration, and invasion of breast cancer cells [19]. Alteration in the expression of LncRNAs regulates the proliferation and metastasis of breast cancer, as compiled in Table 1.

Based on function, EMT has been categorized into three groups. Among them, type-I and II EMTs are mainly involved in the necessary physiologic functions of the body. Type-I EMT mostly occurs during embryogenesis where cells need to migrate to adjacent tissues in a direction to form new organs and tissues [14,20–22]. Type-II EMT is associated with events involved in the later stages of life such as wound healing, where fibroblasts repair or rebuild tissues [23]. Whereas, type-III is mainly involved in pathophysiologic alteration and it is closely associated with the progression of neoplasia cells which is regulated by epigenetic and genetic changes [21,24,25].

3.1. Role of long non-coding RNA in metastasis processes

Metastasis is a sequential process that includes a) local invasion, b) intravasation and circulation, c) extravasation, and d) colonization.

3.1.1. Invasion

The metastasis process starts by losing cell to cell adhesiveness through degrading the basement membrane of ECM and stromal layers. Few cells of primary tumor secrets proteases especially MMP which degrade ECM, sequential junctions, and finally integrin proteins such as vitronectin, collagen, fibronectin, fibrinogen, and laminin [26]. Therefore, tumor cells lose their cell to cell adherence, integrity, and start local invasion until it reaches near to the blood and lymphatic vessels as shown in Fig. 1. Metastasis is always organ and tissue-specific as well as it depends on some specific proteins present in tumor cells [12]. In this stage, alteration happened to EMT-transcription factors (EMT-TFs) and several transmembrane proteins belong to the cadherin family. These modifications indirectly reflect the changes in the phenotype of the epithelial cell to mesenchymal cells and initiate metastasis. Downregulation of E-cadherin, the most important transmembrane protein, shows the transformation of the epithelial cell to the mesenchymal cell and initiates the metastasis process. Mutation in E-cadherin is another reason for lobular breast cancer formation. E-cadherin is also associated with actin, a cytoskeleton protein, and α-catenin acts as a connector that ties E-cadherin to the actin through the help of β-catenin [27]. Loss of these cytoskeleton proteins promotes metastasis through the EMT pathway. In contrast, mesenchymal phenotype markers including N-cadherin and vimentin have an inverse correlation with E-cadherin. N-cadherin has the potential to form cysts in the mammary gland and progress in breast cancer malignancy [28]. Upregulation of N-cadherin and vimentin indirectly progress the adhesion of tumor cells to stromal cells and initiate the metastasis process.

The androgen-receptor negatively induced lncRNA (ARNILA) promotes EMT, invasion and metastasis *in vitro* as well as *in vivo*. ARNILA has been correlated with poor progression-free survival in TNBC patients [29]. ARNILA acts as a ceRNA for miR-204 and binds to 3′-UTR of *Sox4*, a known inducer of EMT. Upregulation of ARNILA enhances the expression of Sox4 protein which downregulate the expression of

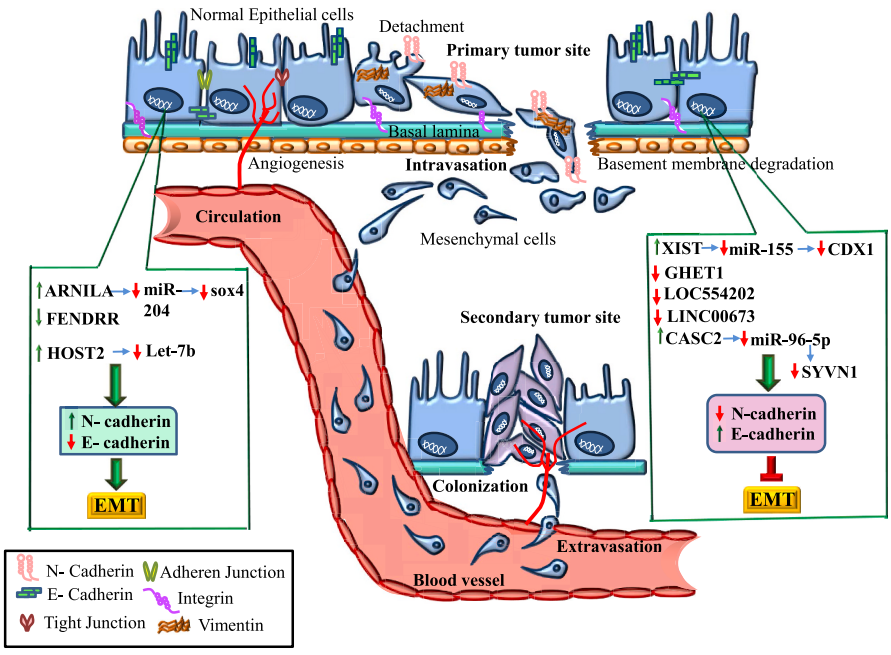

Fig. 1. LncRNAs in breast cancer metastasis. The process of metastasis involved with detachment, invasion, intravasation, circulation of cells from the primary tumor site and extravasation followed by colonization at the secondary tumor site. LncRNAs alter the expression of metastatic makers and thereby regulates the transition of epithelial to mesenchymal transition and *vice-versa*. By losing adherens junction, tight junction and E-cadherin expression epithelial cells transform into mesenchymal cells. In contrast, the expression of N-cadherin, integrin and vimentin is increased in these cells. After degrading the basement membrane, these mesenchymal cells travel to distant organs through blood vessels. After extravasation, tumor cells reaching to the secondary site and forming tumor by colonization. In secondary sites, angiogenesis provides the nutrients to the tumor cells to form a tumor.

Table 1
LncRNAs regulates invasion, migration, EMT, and metastasis of breast cancer cells.

LncRNAs	Dysregulation of lncRNA	Target	Effect on metastasis	Ref
TTN-AS1	Upregulation	↑ DGCR8	↑ migration and invasion	[8]
LINC01787	Upregulation	↓ pre-miR-125b	↑ proliferation and migration	[9]
LINC00899	Upregulation	↓ miR-425	↓ proliferation, migration, and invasion	[10]
NBAT1	Upregulation	↓ DKK1 ↓ EZH2 ↓ PRC2	↑ migration and invasion	[17]
HOTAIR	Upregulation	↑ PRC2	↑invasiveness and metastasis	[18]
ARNILA	Upregulation	↑Sox4 ↓E-cadherin ↑N-cadherin	↑ EMT, invasion and metastasis	[29]
	Downregulation	↓BCL2, ↓RAB22A, ↓SIRT1, and ↓FOXA1	↓ metastasis	[29]
H19	Downregulation	↓ miR-138	↓ proliferation, invasion, and migration	[30]
Linc-ITGB1	Downregulation	↓ N-cadherin ↓ vimentin ↑ E-cadherin	↓ EMT, invasion and migration	[33]
LINC01296	Downregulation	↑ Bcl-2/ caspase-3 pathway	↓ cell proliferation, metastatsis ↑ apoptosis	[34]
LINC00628	Upregulation	↑ Bcl-2/Bax/ Caspase-3 signal pathway	↓ proliferation, invasion, and migration ↑ apoptosis	[35]
XIST	Upregulation	miR-155	↓ growth, migration, and invasion	[36]
	Downregulation	↑ c-Met	↑ primary tumor growth ↑ stemness of tumor cells ↑ metastasis	[37]
GHET1	Downregulation	↓ N-cadherin, ↓ Vimentin ↑ E-cadherin	↓ cell proliferation, invasion, and migration	[39]
LINC00673	Downregulation	↓ B7-H6	↓ proliferation and metastasis	[40]
HOST2	Upregulation	↓ let-7b	↑ cell motility, migration, and invasion	[43]
CASC2	Upregulation	↓ miR-96-5p	↓ viability, migration and invasion	[44]
		↑ SYVN1	↑ apoptosis	
SNHG14	Downregulation	↑ miR-193a-3p	↓ invasion	[45]
LINC00115	Upregulation	↓ miR-7	↑ metastasis	[54]

E-cadherin but upregulates the expression of N-cadherin and thereby promoting metastasis of TNBC [29]. In contrast, the downregulation of ARNILA decreases the expression of miR-204 targeted proteins such as BCL2, RAB22A, SIRT1, and FOXA1 and inhibits breast cancer metastasis [29]. SOX4 is positively correlated with lncRNA H19 in breast cancer metastasis and negatively correlated with miR-138. miR-138 is also a direct target of H19 and SOX4. Therefore, the downregulation of H19 and overexpression of miR-138 repress the proliferation, invasion, and migration of breast cancer cells. H19 downregulates EMT markers and inhibits tumor growth *in vivo* by regulating miR-138 and SOX4. The silencing of H19 also promotes cell cycle arrest and apoptosis in breast cancer cells [30]. Overexpression of H19 also regulates let-7-mediated certain metastasis-promoting genes, including *c-MYC* [31]. MYC bound to evolutionarily conserved E-boxes close to the imprinting control region to stimulate the histone acetylation and transcriptional initiation of the H19 promoter, markedly prompting H19 expression [32]. Similarly, knockdown of linc-ITGB1 interrupts the EMT and reduces migration as well as invasion abilities of breast cancer cells by decreasing the expression of N-cadherin, vimentin, and increasing the expression of E-cadherin. Downregulation of linc-ITGB1 also induces cell cycle arrest at the G_0/G_1 phase, inhibits cell proliferation, and colony formation *in vitro* [33]. Consequently, the silencing of LINC01296 revokes cell proliferation, metastatic properties and induces apoptosis in breast cancer cells via the Bcl-2/caspase-3 pathway. Overexpression of LINC01296 correlates with larger tumor size, positive lymph node metastasis, and advanced tumor-node-metastasis (TNM) stage in breast cancer patients [34].

In contrast, overexpression of lncRNA LINC00628 suppresses the proliferation, invasion, and migration of breast cancer cells as well as promotes cell apoptosis via activating the Bcl-2/Bax/Caspase-3 signal pathway. The lower expression of LINC00628 also correlates with poor survival [35]. Similarly, overexpression of lncRNA X-inactive specific transcript (XIST) suppresses the growth, migration, and invasion of breast cancer cells by targeting miR-155. The 3′-UTR of *caudal-type homeobox 1 (CDX1),* a direct target of miR-155, can be modulated by XIST in breast cancer cells. Therefore, the XIST/miR-155/CDX1 axis plays a major role in breast cancer metastasis [36]. XIST has an inverse correlation with brain metastasis, but not with bone metastasis in primary breast cancer patients. The knockdown of XIST increases primary tumor growth and stemness of tumor cells as well as accelerates metastasis to the brain by activating c-Met. Silencing of XIST also enhances the secretion of exosomal microRNA-503 which activates M1-M2 polarization of microglia, which stimulates immune-suppressive cytokines in microglia and leads to suppress T-cell proliferation. Therefore, XIST influences the tumor microenvironment, signaling pathways involved in brain metastasis in breast cancer [37]. LncRNA breast cancer brain metastases (Lnc-BMs) is an important mediator to communicate between breast cancer cells and the brain microenvironment. The upregulation of lnc-BMs drives breast cancer brain metastases (BCBM) and enhances JAK2 kinase activity, which promotes STAT3 phosphorylation. In breast cancer cells, lncRNA-BM promotes STAT3-dependent expression of ICAM1 and CCL2, which mediates vascular co-option and recruitment of macrophages in the brain, respectively. These recruited macrophages in sequence produce oncostatin M and IL-6. Therefore, the lnc-BM/JAK2/STAT3/ICAM1 axis accelerates adhesion of breast cancer cells to brain capillaries and extravasation into the brain parenchyma, which eventually favors BCBM [38].

The LncRNA gastric carcinoma highly expressed transcript 1 (GHET1) is overexpressed in breast cancer. The overexpression of GHET1 has been associated with larger tumor size, advanced clinical stage, lymph node metastasis, and shorter overall survival rate [39]. Downregulation of GHET1 suppresses the expression of N-cadherin, vimentin, and upregulation of E-cadherin which decreases cell proliferation, invasion, and migration [39]. A similar alteration in the EMT signaling was also observed with the downregulation of lncRNA LINC00673. B7-H6 is a potential downstream target of LINC00673. The knockdown of LINC00673 could reduce breast cancer cell proliferation and metastasis via modulating EMT through suppressing B7-H6 at the transcriptional level [40]. Similar to LINC00673, knockdown of lncRNA LOC554202 inhibits breast cancer cell migration/invasion in both *in vitro* as well as *in vivo* breast cancer models [41]. The knockdown of endogenous FENDRR, a lateral mesoderm-specific lncRNA, significantly promotes breast cancer cell proliferation and migration as well as represses cellular apoptosis. The upregulation of FENDRR was found to be associated with reduced tumor growth in a xenograft model. Thus, lncRNA FENDRR plays a key role in the growth and development of breast cancer [42].

The LncRNA human ovarian cancer-specific transcript 2 (HOST2) enhances cell migration and invasion by regulating miR let-7b in breast cancer. Tumor suppressor miR Let-7b is involved in various mechanisms

including preventing cell adhesion, proliferation, and invasion. Additionally, Let-7b also controls the self-renewal capacity of embryonic stem cells and cancer cell proliferation and tumorigenicity. The upregulation of HOST2 might stimulate cell motility, migration, and invasion by hindering let-7b in breast cancer patients [43]. Similar to HOST2, upregulation of lncRNA cancer susceptibility candidate 2 (CASC2) represses the viability, migration and invasion, as well as induces apoptosis in breast cancer cells by reducing the miR-96-5p expression and enhancing expression of synoviolin (SYVN1). Overexpression of miR-96-5p in MDA-MB-231 cells increases cell viability, migration, and invasion, which is reversed by the upregulation of SYVN1. On the other side, lncRNA CASC2 may act as a ceRNA for miR-96-5p and controls the expression tumor suppressor *SYVN1,* which is one of the direct targets of miR-96-5p. Therefore, dysregulation of the CASC2/miR-96-5p/SYVN1 axis contributes a major role in breast cancer cell proliferation, migration, and invasion [44]. Similarly, lncRNA SNHG14 is also involved in cell proliferation and invasion of breast cancer cells and is also highly expressed in breast cancer tissues compared to adjacent ones. lncRNA SNHG14 is inversely correlated with tumor suppressor miR-193a-3p. Silencing of lncRNA SNHG14 increases the expression of miR-193a-3p and reduces the invasion capability of breast cancer cells [45].

3.1.2. Intravasation and circulation

After triumphing invasive property, tumor cells migrate from the primary tumor site into the first stromal site of the surrounding matrix and then cross the threshold to blood vessels. Entrance into blood vessels is the first step towards secondary tumor development in distant organs. Intravasation depends on the irregularity and malfunctioning effect of intracellular junction and cell to cell adherence of breast cancer cells. Depends on the abnormal activity of cell junctions and cellular attachments, a single cell from a primary tumor as well as multicellular clump travel in the blood and lymphatic vessels as CTCs [46]. The migration process of a single tumor cell and a cluster of tumor cells is different. In collective invasion, the leader cell with the help of membrane type 1 (MT1) MMP, forms a tube-like structure to cleave ECM. After breaking the ECM, it starts propagation into the other organs through blood or lymphatic circulation. On the other hand, single-cell migrates in two different ways such as by protease-independent amoeboid movement or by the protease-dependent mesenchymal movement. Protease-dependent migration depends on the action of MMPs to break the collagen fibrils of the basement membrane. Whereas, in the case of protease-independent migration, the collagenous barrier is broken down by the actino-myosin force of cancer cells [47]. Therefore, the action of breaking collagen boundaries is differing and depends on the type of cancer cells. EMT-TFs are regulated by different cell signaling pathways associated with metastasis at this stage. Wnt/β-catenin is the most crucial pathway for breast cancer metastasis. Besides, TGF-β and the PI3K/AKT also have significant control over the transformation of epithelial to mesenchymal phenotype. Alteration in these pathways leads to epithelial cells to lose cell to cell adhesion, apical-basal polarity, and cytoskeleton remodeling which induce the migration.

3.1.3. Extravasation

The circulatory tumor cells can spread into distant organs through the process called extravasation. At this phase, the tumor cells itself arrests the cell cycle and attaches to the base of the capillary. At the last stage of extravasation, tumor cells adhere to the capillary bed of distant organs from blood and lymphatic vessels as shown in Fig. 1. Some proteins are responsible for the extravasation process. For example, ICAM1 is one of the responsible factors for breast cancer cell adhesion to blood vessels of the brain and extravasation of metastatic lesions into the brain. Lnc-BM promotes STAT3-dependent expression of ICAM1. Therefore, knockdown of Lnc-BM represses the extravasation of breast cancer cells into brain parenchyma and also reduces the number and size of brain metastatic lesions. The silencing of Lnc-BM reduces micrometastases and macrometastases and enhances apoptotic marker in mouse brain tissues [38]. At same the time, the process of angiogenesis starting to provide nutrients to the tumor cells at the secondary sites. In contrast, tumor cells metastasizing to bone and liver encounter fenestrated sinusoids, which are permeable and do seem to impose minor

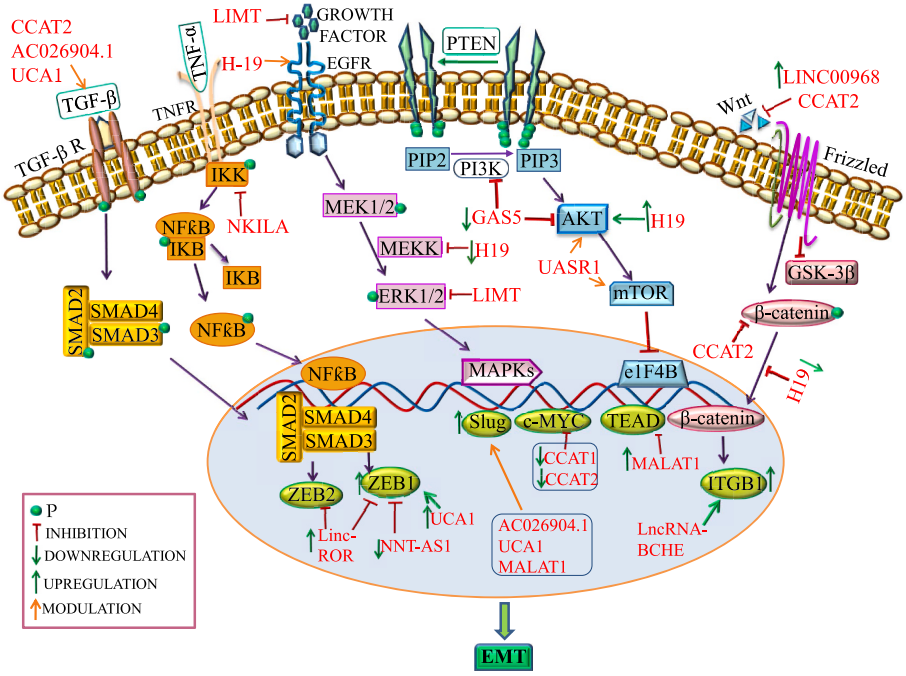

Fig. 2. LncRNAs in the regulation of multiple signaling pathways involved in the process of EMT. LncRNAs regulate breast cancer invasion and metastasis by targeting several proteins involved in downstream signaling pathways including TGF-β, NFkB, ERK1/2, PI3K/AKT and WNT, which are involved in the regulation of EMT.

obstacles to tumor cells [48]. To overcome such barriers, tumor cells secrete factors that modify distant microenvironments and help in extravasation. Distinct sets of factors are required for the extravasation of tumor cells at different secondary sites [46].

3.1.4. Colonization

This is the last stage in the metastasis process, where the situation is compared with the 'seed and soil' theory of Stephen Paget [49]. Because the migratory tumor cell (as seed) which needs a proper microenvironment at the distant organ (soil) to grow. This is the most delicate stage of secondary tumor growth. Several types of specialized cells such as immune cells, mural cells of the blood and lymph vessels, endothelial cells, and fibroblasts are involved in the eventual colonization at a distant site. These cells help unstable cancer cells to adopt a new microenvironment present at a distant site from that primary tumor [50,51]. The properties of self-renewal capacity of tumor cells is another important factor of successful metastatic colonization. Tumor initiating cells (TICs) can form macrometastases but it is not applicable for all types of cancer cells [52,53].

Angiogenesis plays a crucial role in this phase of migration and adaptation to a new environment. Angiogenesis is a crucial biological process involved to knob cellular stresses such as inflammatory process, genetic mutation, mechanical stress, and hypoxia. Angiogenesis related proteins involved in the fabrication of new blood vessels in migration as well as in the normal physiological condition of cells. KLF4 is one of the important members of the KLF family zinc finger transcription factors, involved in vascular inflammation, regulation of angiogenesis, and EMT. LncRNA LINC00115 suppresses the expression of KLF4, which is a direct target of miR-7 and regulates breast cancer metastasis. miR-7 prevents brain metastasis of breast cancer stem-like cells by modulating KLF4. But overexpression of LINC00115 stimulates breast cancer cell metastasis by directly inhibiting miR-7 [54,55].

The process of the vasculature for a tumor cell is different compared to the normal cell. Tumor cells have a very higher rate of proliferation compared to a normal cell, therefore, tumor cells require rapid and more supply of nutrients through blood vessels. The irregular vasculature sometimes also incapable to provide proper nutrients and oxygen to aberrant proliferating tumor cells which ultimately leads to hypoxia in the cell. To overcome the hypoxia incident, tumor cells generate pro-angiogenic factors such as HIF-1, which activates downstream target genes and angiogenesis-related proteins [56]. In the hypoxia condition, tumor promoter lncRNA BCRT1 (breast cancer-related transcript 1) is overexpressed by HIF-1α through direct binding with HRE1 on its promoter. Hypoxia also enhanced the expression of polypyrimidine tract binding protein 3 (PTBP3) and promotes cell proliferation, migration of breast cancer cells. Therefore, HIF-1α/lncRNA BCRT1/PTBP3 pathway plays a key role in breast cancer metastasis [57]. The upregulation of lncRNA H19 (producing 91H lncRNA) promotes the invasive and metastatic potential of breast cancer cells in hypoxia conditions. Similar to angiogenesis-related proteins, some chemokines are also involved in breast cancer metastasis. Breast cancer tissue highly expressed the chemokines (C-X-C motif) and its receptor 4 (CXCR4). Breast cancer metastasis also depends on the expression of CXCR12 and higher expression of CXCR12 increases metastatic properties of the breast cancer cell.

After metastasizing into the secondary sites, the tumor cells reverse back to their original epithelial phenotype by undergoing MET [58]. Merely, a fraction of disseminated tumor cells can be successful in completing the process of metastatic colonization by activating several self-renewal pathways after overcoming microenvironmental incompatibilities.

4. LncRNA in signaling pathways involved in metastasis

Dysregulation of signaling pathways plays a crucial role in breast cancer metastasis. LncRNAs can regulate the metastasis mechanism by targeting these signaling pathways. LncRNA targets several proteins and transcription factors involved in breast cancer metastasis as shown in Fig. 2.

4.1. TGF-β signaling

The TGF-β receptors are localized at tight junctions and directly interact with two important regulators of epithelial cells such as Par6 and Occludin [59,60]. Phosphorylation of Par6 by the TGF-β type II receptor leads to a loss of tight junctions and apical-basal polarity [59]. TGF-β signaling pathway also regulates several transcription factors such as Snail, Slug, SIP1, and Goosecoid through activation of Smads, which finally suppress the expression of E-cadherin [61,62]. LncRNAs AC026904.1 and Urothelial carcinoma associated 1 (UCA1) together upregulate the expression of Slug at both the transcriptional and post-transcriptional levels, exerting critical roles in non-canonical and canonical TGF-β-induced EMT. AC026904.1 and UCA1 are highly expressed in metastatic breast cancer and have poor upshot in breast cancer patients. Upregulation of UCA1 in breast cancer cells significantly enhances the expression of Slug and ZEB1 as well as reduces the expression of E-cadherin and initiating tumor metastasis. UCA1 functions as ceRNA, and has shown to induce Slug expression in breast cancer by inhibiting the expression of miR-1 and miR-203. Similarly, AC026904.1 might function as an eRNA to trigger Slug expression in breast cancer [63].

Smad is another important transcription factor involved in breast cancer metastasis. Type I serine-threonine kinase receptor (TβRI) is phosphorylated by type II serine-threonine kinase receptors (TβRII), and then stimulates Smads by binding TβRII and TβRI, respectively. As a result, cells begin to lose their attachment and adhesion with the neighboring cells. Mammary Tumor-Associated RNA 25 (MaTAR25), a nuclear enriched and chromatin-associated lncRNA interacts with purine-rich element binding protein B (PURB), and associate with a major downstream target, *Txensin 1 (Tns1),* to regulate breast cancer migration and invasion. Silencing of lncRNA MaTAR25 reduces focal adhesions, microvilli and reorganizes the actin cytoskeleton by down-regulating Tns1. Therefore, MaTAR25/PURB/Tns1 DNA complex plays a crucial role in breast cancer metastasis [64]. Similarly, Colon cancer-associated transcript 2 (CCAT2) is also highly expressed in breast cancer metastasis [65,66]. Higher expression of CCAT2 enhance proliferation, invasion, and migration in breast cancer cells by regulating the TGF-β signaling pathway [66]. Latent TGFβ-binding proteins (LTBPs) restrains metastasis by regulating the TGF-β signaling pathway. Especially, LTBP3, a protein that regulates TGFβ secretion and primary tumor invasion as well as metastasis [67,68]. LTBP3 is involved in the formation of the fibrillar extracellular matrix network [69]. The activity of this protein depends on the microenvironment of the primary tumor. Overexpression of LTBP3 promotes metastatic dissemination and poor outcomes in ER−/PR−breast cancer patients [70].

In another way, TGF-β initiates the Smad3 to bind to myocardin-related transcription factors (MRTFs) to stimulate the actin filament protein which plays a key role in EMT [71]. Another specialty of this pathway is the TGF-β prompts lncRNA activated by TGF-β (ATB) and changes the expression of EMT markers including E-cadherin, N-cadherin, and Vimentin in breast cancer cells. Overexpression of lncRNA ATB promotes EMT by the upregulation of ZEB1, Twist1, N-cadherin, Vimentin, and downregulation of E-Cadherin. In contrast, lncRNA ATB restores the expression of Twist1 by sponging miR-200c and enhances cell migration, invasion, and clonogenicity. Thereby, the lncATB/-miR200c/Twist1 axis plays a key role in breast cancer metastasis [72]. Most tumor-related studies had prompted that the TGF-β pathway works in partnership with Wnt, Notch, and receptor tyrosine kinase signaling pathways to succeed EMT in the progression of breast cancer metastasis.

4.2. Wnt/β-catenin signaling

The Wnt proteins activate a variety of signaling pathways involved in breast cancer metastasis. In the absence of Wnt, β-catenin separates from a multi-enzyme complex of APC, axin, and GSK3β. GSK3β phosphorylates Snail, Slug and N-terminal of β-catenin, which causes degradation of β-catenin through the ubiquitin-proteasome degradation pathway. However, in the presence of Wnt, the activity of GSK3 is inhibited, and that leads to stabilizing β-catenin to the nuclear localization. Aggregation of this stable β-catenin inside the nucleus of tumor cells causes the induction of EMT. Downregulation of lncRNA H19 stimulates the translocation of β-catenin from nuclear to cytoplasm in tamoxifen-resistant breast cancer cells as well as upregulates the expression of E-cadherin as well as vimentin in breast cancer cells. Therefore, knockdown of H19 represses EMT in tamoxifen-resistance breast cancer cells through the Wnt pathway [73]. Similar to H19, downregulation of lncRNA UCA1 enhances the tamoxifen sensitivity by impeding Wnt/β-catenin pathway in breast cancer cells whereas, overexpression of UCA1 stimulates EMT in breast cancer cells by activating Wnt/β-catenin signaling pathway [74,75]. Another lncRNA AC073284.4 might sponge miR-18b-5p to reduce the invasion, metastasis, and EMT by upregulating the dedicator of cytokinesis protein 4 (DOCK4) in paclitaxel-resistant breast cancer cells. Therefore, lncRNA AC073284.4 represses EMT and migration in breast cancer cells by regulating the miR-18b- 5p/DOCK4 axis [76].

Wnt2, a main Wnt ligand involved in vascularization and lncRNA LINC00968 regulates the Wnt2-mediated Wnt2/β-catenin signaling pathway through transcriptional repressor HEY1 in breast cancer. Upregulation of LINC00968 represses migration and invasion by obstructing the activation of the Wnt2/β-catenin signaling pathway and EMT in breast cancer cells [77]. In contrast, knockdown of novel lncRNA RUSC1-AS-N inhibits cell proliferation and metastasis in breast cancer cells by suppressing Wnt1 and β-catenin. However, Wnt signaling pathway activator Wnt agonist 1 can increase cell proliferation and metastasis by reversing the effects of RUSC1-AS-N knockdown [78].

Inside the nucleus, β-catenin functions as a coactivator of T-cell factor/lymphoid-enhancing factor-1 (TCF/LEF-1) to stimulate the transcription of Snail, Slug, and Twist, which in turn suppresses E-cadherin [79]. This pathway also increases the stability of Snail, Slug, and elevates the expression of oncogenes such as *c-MYC*, *cyclin D1* which promote metastasis and angiogenesis by regulating MMPs and VEGF. *c-MYC* also plays a key role in brain metastasis by enhancing the invasive growth of BrMs, macrophage infiltration, and GAP-junction formation between BrMs and astrocytes by upregulating connexin 43 (GJA1/Cx43). In contrast, upregulation of c-MYC makes brain-metastatic breast cancer cells (BrM-BCC) highly sensitive to TNF-related apoptosis inducing ligand (TRAIL)–induced apoptosis [80]. In addition to brain metastasis, c-MYC also has a correlation with several metabolic enzymes such as the M2 isoform of pyruvate kinase (PKM2). This glycolytic enzyme controls the expression of survivin by phosphorylating c-MYC at Ser62. Therefore, downregulation of PKM2 suppressed breast cancer cell proliferation and migration, which could be rescued by the upregulation of survivin. Besides, the downregulation of PKM2 also enhanced the sensitization of 4-hydroxytamoxifen (4OH-T) to breast cancer cells. The upregulation of PKM2 has been correlated with poor relapse-free survival in breast cancer patients treated with tamoxifen. Therefore, PKM2–c-MYC–survivin cascade plays a major role in the proliferation, migration, and chemoresistance of breast cancer cells [81]. c-MYC binds to the promoters of selected lncRNAs or targeting other transcription factors, enhancers, and suppressors. More recently, the interactions of c-MYC and lncRNAs have been compiled the role in cancer metastasis [82].

Colon cancer-associated transcript-1 (CCAT1) oncogenic lncRNA acts as a strong super-enhancer of *c-MYC* expression. CCAT1-L locus is localized at its transcription sites which is essential for intermediating the long-range chromatin interactions between *CCAT1* and *c-MYC* in conjunction with an enhancer of c-MYC. Therefore, knockdown of CCAT1-L reduced long-range interactions between the *MYC* promoter and its enhancers, which disclose the importance of lncRNA CCAT1 in gene regulation at the *MYC* locus [83]. Upregulation of CCAT1 has a correlation with TNM staging, differentiation grade, and lymph node metastases and has been associated with the poor survival of breast cancer patients [84]. Similar to CCAT1, irregular expression of CCAT2 could make an impact on the Wnt signaling pathway. Downregulation of CCAT2 reduces cell proliferation and invasion *in vitro* and also hinders tumorigenesis *in vivo* by decreasing the levels of β-catenin both in the cytoplasm and nucleus. The silencing of CCAT2 condenses the expression of downstream genes of the Wnt/β-catenin signaling such as *CCND1* and *c-MYC* [85]. MYC also activates lncRNA DC-STAMP domain-containing 1-antisense 1 (DCST1-AS1) which directly binds to miR-873-5p through Argonaute 2 and promotes the degradation of DCST1-AS1. As a result, the expression of insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1) and its downstream protein MYC, CD44, lymphoid enhancer-binding factor 1 (LEF1) is found to be upregulated. Therefore, the Knockdown of DCST1-AS1 inhibits TNBC cell proliferation and metastasis [86].

There is a correlation between increased Slug levels and reduced expression of the tumor suppressor *BRCA1*. *BRCA1* promotes EMT in basal-like breast cancers. Advanced studies confirm that SLUG as well as SNAIL directly suppresses *BRCA1* expression by hiring the chromatin-demethylase, LSD1, and binding to a series of E-boxes located within the *BRCA1* promoter and enhance breast cancer metastasis [87]. LncRNA high expressed in breast cancer (lncRNA-BCHE) is adjacent (<50 kb) to BRCA1 associated RING domain 1 (BARD1), which has been associated with the incidence of breast cancer. LncRNA-BCHE endorsed the migration and invasion of breast cancer cells, through regulating integrin subunit beta 1 (ITGB1) *in vitro*. ITGB1 plays an important role in the migration and invasion of breast cancer cells. Inversely, the down-regulation of ITGB1 moderately overturned the lncRNA-BCHE, which induces cell migration and invasion in breast cancer cells. Clinical investigation has revealed that the expression of lncRNA-BCHE also has a significant correlation with advanced clinical stage and lymph node metastasis [88].

4.3. Epithelial growth factor (EGF) and vascular endothelial growth factor (VEGF) signaling

EGF and VEGF are the most crucial factors involved in breast cancer progression and metastasis. Both of them have great functionality in the process of angiogenesis. Activation of human EGF receptor 2 (HER2; also known as ERBB2) in mammary epithelial cells has been associated with stimulating EMT in the tumor. In both mechanisms, transcription factors Twist and Snail are persuaded to repress the E-cadherin activity [14]. Another feature of the EGF pathway is endocytosis of E-cadherin which promotes EMT directly. EGF promptly decreases the expression of LncRNA Inhibiting Metastasis (LIMT), an inhibitor of cell migration and invasion, by augmenting histone deacetylation at the corresponding promoter. LIMT hinders ECM invasion of mammary cells *in vitro* and tumor metastasis *in vivo*. Suppression of LIMT symbolizes breast cancer patients diagnosed with either basal-like or HER2-enriched tumors and also predicted a relapse-free patient survival [89]. The 5′-region of LIMT is highly conserved in vertebrates and undergoes histone deacetylation after stimulation with EGF. Therefore, lncRNA LIMT is downregulated by EGF due to histone deacetylation at the respective promoter.

In general, lower expression of LIMT has been observed in the basal-like and HER2-enriched, two relatively aggressive subtypes of breast cancer. Recently, Risom et al. have shown the relationship between HER2 expression and MYC phosphorylation in $HER2^{+}$ breast tumors. The combination of deregulated MYC and amplified activated HER2 accelerates the tumorigenesis, metastasis of breast cancer cells. In addition to metastasis, MYC, and HER2-overexpressed tumors are also associated with decreased survival compared with HER2-overexpression

alone [90].

Tumor suppressor lncRNAs LIMT can hinder the ERK pathway and inhibits breast cancer metastasis [89]. Similar to LIMT, metastasis-associated lung adenocarcinoma transcript1 (MALAT1) functions as a metastasis driver and potential prognostic marker of patients diagnosed with ER-negative, lymph node-negative (LN) breast cancers. Overexpression of MALAT1 levels has been associated with poor prognosis. MALAT1 modulates the expression of genes associated with cell cycle progression and EMT in breast cancer cells. Overexpression of MALAT1 amplified expression of *VIM* and *WNT5A* increases the tumorigenic and metastatic properties of breast cancer cells. MALAT1 also regulates the expression of *SLUG*, a pro-EMT gene, by inversely modifying the interaction of miR-1 and in breast cancer cells [91]. Overexpression of MALAT1 suppresses breast cancer metastasis in the transgenic, xenograft, and syngeneic models by inactivating the prometastatic transcription factor TEAD [92]. The upregulation of MALAT1 prevents the association of TEAD with its co-activator YAP and TAZ to induce tumor progression and metastasis. In contrast, the downregulation of MALAT1 induces the expression of *ITGB4* and *VEGFA,* TEAD-targeted genes, and promotes breast cancer metastasis [92]. A lower expression level of MALAT1 promotes cell proliferation, tumor progression and metastasis of TNBC cells compared to hormonal-positive breast cancer cells [91]. MALAT1 is overexpressed in ER-positive breast cancer tissues and also associated with poor recurrence-free survival in tamoxifen-treated ER-positive breast cancer [93]. Wang et al. have shown that patients with higher expression of MALAT1 have a two-fold increase in the risk of tumor relapse compared to those with lower expression of MALAT1 [94].

In contrast to MALAT1, overexpression of lncRNA H19 involved in the progression and metastasis of cancers from different tissue origins. Oncogenic lncRNA H19 is a precursor of miR-675. H19-derived miR-675 targets ubiquitin ligase E3 family (c-Cbl and Cbl-b) through their coding sequences in breast cancer cells. Upregulation of H19/miR-675 downregulates the expression of both c-Cbl and Cbl-b which finally enhanced cell proliferation and migration *in vitro*, and increased tumor growth and metastasis *in vivo* through activation of EGFR in breast cancer [95].

4.4. AKT/mTOR signaling

AKT is a key activator of the Mammalian target of rapamycin (mTOR) signaling cascade by directly phosphorylating Ser 2448 of mTOR and by inhibiting of the TSC1/TSC2 complex via catalyzing Thr1462 phosphorylation of TSC2. The mTOR is a chief serine-threonine protein kinase that controls the proliferation, survival and migration of cells by triggering downstream effectors 4EBP1 and p70S6K as well as protein translation/synthesis. UNC5B antisense RNA1 (UASR1), novel lncRNA transcript, stimulates cell proliferation, and migration through activation of the AKT/mTOR signaling pathway. Therefore, knockdown of UASR1 reduces the level of pTSC2 pmTOR, and p4EBP1, involved in the cell cycle of breast cancer cells. Oncogenic UASR1 amplified pAKT (Thr308 and Ser473) in breast cancer cells and promotes cell proliferation and migration [96]. LncRNA growth arrest-specific transcript 5 (GAS5), a ceRNA can be complementing to miR-196a-5p. The upregulation of GAS5 downregulates the expression of miR-196a-5p and suppresses invasion through downstream FOXO1/PI3K/AKT signaling pathway in breast cancer. Since the upregulation of this ceRNA GAS5 impedes the phosphorylation of PI3K and AKT by enhancing the expression of FOXO1. In contrast, the ectopic expression of miR-196a-5p has shown the converse effect without altering the total expression of PI3K and AKT [97]. Similarly, the PI3K/Akt/GSK3β/Zeb2 axis also plays a key role in the activation of EMT in TNBC cells. ZEB2 is a direct target of lncRNA ZEB2-AS1 and by modulating PI3K/Akt/GSK3β/Zeb2 axis lncRNA ZEB2-AS1 can alter the metastatic nature of TNBC cells. In general, lncRNA ZEB2-AS1 is highly expressed in breast cancer specimens, especially in metastatic tumors and highly invasive cells. Overexpression of lncRNA ZEB2-AS1 has been correlated with the short survival of breast cancer patients [98].

4.5. Notch signaling

In hypoxia conditions, the Notch signaling pathway induces the expression of Snail 1. Hypoxia is a phase of angiogenesis and persists to the micrometastases stage of the EMT process. In the hypoxia condition, hypoxia factor-1 (HIF-1) is released and stabilizes the Snail 1. HIF-1 contains an unstable α-subunit and a stable β-subunit. Under hypoxic conditions, HIF-1α stabilizes and translocates into the nucleus, induces EMT by upregulating EMT-associated transcription activators or repressors, modulating EMT-associated signaling pathways, EMT-associated inflammatory cytokines, and epigenetic modulators [99]. The stimulation of the HIF-1α-mediated canonical hypoxia signaling leads to the upregulation of TWIST, SNAIL, ZEB1, and E12/E47 and accelerate EMT in breast cancer [79].

Higher expression of lncRNA linc-ROR also prevents the degradation of ZEB1 and ZEB2 by sponging miR-205 through the formation of an RNA-induced silencing complex (RISC) in the process of EMT. Similar to linc-ROR, lncRNA NNT-AS1 also regulates the expression of ZEB1. NNT-AS1 is transcribed in the inverse direction of nicotinamide nucleotide transhydrogenase (NNT) and doesn't intersect with NNT. NNT-AS1 is inversely correlated with miR-142-3p as NNT-AS1 and functions as ceRNAs by sponging to miR-142-3p. Alternatively, ZEB1 is also another target point of miR-142-3p and is positively controlled by NNT-AS1. Downregulation of NNT-AS1 hinders proliferation, migration and EMT formation of breast cancer cells by reducing the ZEB1 expression via targeting miR-142-3p [100]. In contrast, lncRNA linc-ZNF469-3 is overexpressed in lung-metastatic LM2-4175 TNBC cells and this overexpression of linc-ZNF469-3 boosting invasion capacity and stemness properties *in vitro* and lung metastasis *in vivo*. Overexpression of linc-ZNF469-3 sponging miR-574-5p and enhancing the expression of ZEB1, which has been correlated with tumor recurrence in TNBC patients with lung metastasis [101].

4.6. Ras-MAPK and NFκB signaling

Nuclear factor-κB (NF-κB), is a group of transcription factors, involved in inflammation, immunity, cell proliferation, differentiation, and survival [102]. Similar to the TGF-β pathway, NFκB and Ras-MAPK pathways also alter the EMT by targeting *Snail* [103]. *Snail1* is involved in reducing the expression of *E-cadherin* through NFκB pathways [104]. Similarly, the upregulation of *Snail2* also downregulates the expression of *E-cadherin* by activating the Ras-MAPK pathway [105]. HGF induces the Snail expression through the MAPK-independent pathway and also involves in the binding of early growth response factor-1 (EGR-1) to the *Snail1* promoter for initiation of EMT [106].

In breast cancer, NFκB promotes EMT with the help of insulin growth factor receptor (IGFR). IGF1R activation causes EMT in mammary epithelial cells as well as causes subsequent loss of the expression of E-cadherin, and gain in the expression of N-cadherin, vimentin, and fibronectin. LncRNAs control EMT by regulating the complex network of the signaling pathways. Irregular expression of NF-κB leads to a consequence of underlying inflammation in the tumor microenvironment which can promote cancer invasion and metastasis in breast cancer cells. NF-KappaB Interacting LncRNA (NKILA) is upregulated by inflammatory cytokines via NF-κB signaling. 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 invasiveness of breast epithelial cells and leads to metastasis and poor prognosis of breast cancer patients [107].

5. Conclusion

Breast cancer metastasis is the major cause of breast cancer-associated death among women. LncRNA is less explored epigenetic modifications involved in the regulations of breast cancer metastasis. For example, anti-metastatic lncRNAs can target oncogenes and inhibit metastasis whereas some prometastatic lncRNA reduce the expression of tumor suppressor genes and induce invasion and metastasis. LncRNAs can alter multiple signaling pathways and also regulate metastasis-related factors, such as cell adhesion molecules, extracellular matrix, and matrix metalloproteinases as well as able to alter the proteins, transcription factors involved in metastasis. Therefore, dysregulation of lncRNAs can promote breast cancer metastasis. Most of the time, metastasis occurs before diagnosis. Therefore, there is a requirement of diagnostic tools or prognostic markers to predict metastatic risk or stages of metastasis in breast cancer patients.

Many studies have addressed the use of lncRNA as an early biomarker for the diagnosis of breast cancer. The early detection of lncRNA can be developed as potential diagnostic tools as well as therapeutic targets for breast cancer therapy. Targeting lncRNA is a novel approach for cancer treatment. There are few techniques are developed to reduce the expression of oncogenic lncRNAs. Among them, ASOs, double-stranded RNAi especially siRNAs and shRNAs, genome engineering tools are major approaches to target lncRNAs [108]. ASOs are single-stranded antisense oligonucleotides with a DNA stretch that can reduce the expression of oncogenic lncRNAs by degrading lncRNAs, cleaving endogenous RNaseH1, or regulating RNA–protein interactions [109,110]. Locked nucleic acid Gapmers (LNA Gapmers), antagonists to natural antisense transcripts (NATs), and Mixer are some designed ASOs. This ASO can induce differentiation and inhibit breast cancer metastasis *in vivo* model by targeting *lncRNA MALAT1* [111]. Moreover, nanobodies, aptamers, RNA decoy, lncRNA regulatory elements are some new technologies to target lncRNAs. The role of these techniques to inhibit the expression of lncRNAs is discussed in some recent scientific reports [108,112]. Therefore, lncRNAs can be used as an early diagnostic tool as well as a therapeutic target for breast cancer metastasis.

Credit author statement

Priya Mondal: Conceptualization, Writing-Original Draft. **Syed Musthapa Meeran:** Conceptualization, Review, Editing and approval of the Final draft.

Declaration of competing interest

None.

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