Long Noncoding RNAs as Players in Breast Tumorigenesis

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Contents

Abstract Comprehensive analysis of the mammalian genome uncovered the discovery of pervasive transcription of large RNA transcripts that do not code for proteins, namely, long noncoding RNAs (lncRNAs). LncRNAs play important roles in the regulation of gene expression from integration of chromatin remodeling complexes to transcriptional and posttranscriptional regulation of protein-coding genes. Application of next-generation sequencing technologies to cancer transcriptomes has revealed that aberrant expression of lncRNAs is associated with tumor progression and metastasis. Although thousands of lncRNAs have been shown to be dysregulated in different cancer types, just few of them have been fully characterized. In this book chapter, we

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aim to highlight recent findings of the mechanistic function of lncRNAs in breast cancer and summarize key examples of lncRNAs that are misregulated during breast tumorigenesis. We have categorized breast cancer–associated lncRNA according to their contribution to tumor suppression or tumor progression based on recent studies. Because some of them are expressed in a specific molecular breast cancer subtype, we have outlined lncRNAs that can potentially serve as diagnostic and prognostic markers, in which expression is linked to chemotherapy resistance. Finally, we have discussed current limitations and perspectives on potential lncRNA targets for use in therapies against breast cancer.

Keywords Long noncoding RNA (lncRNA) · Gene expression regulation · Breast cancer · Metastasis · Chemoresistance

1 Introduction

Over the last decades, the development of high-throughput technologies has changed the perception of the central dogma stating that genetic information inscribed in DNA is transcribed into RNA and afterward translated into proteins. Indeed, transcription is not limited to protein-coding genes but is pervasive throughout the genome. Hence, tens of thousands of transcripts with biological function do not code for proteins. These transcripts are collectively known as noncoding RNA (ncRNA). Transfer RNA (tRNA) and ribosomal RNA (rRNA) were among the first ncRNAs to be identified. Both are highly abundant and mostly function in translation regulation. More recently, regulatory ncRNAs with key roles in cellular homeostasis have been described. These ncRNAs vary in localization and function, and an arbitrary size cutoff distinguishes two groups: small noncoding RNA (sncRNA) and long noncoding RNA (lncRNA). These sncRNAs include the small interfering RNA (siRNA), microRNA (miRNA), and PIWI-interacting RNA (piRNA), which have been well reviewed elsewhere (Okamura and Lai 2008; Gebert and MacRae 2019).

LncRNAs are noncoding transcripts that are more than 200 nucleotides in length. They share common characteristics with messenger RNAs (mRNAs). For instance, lncRNAs are transcribed by RNA polymerase II; many of them present a 5′ cap, undergo splicing, and are polyadenylated at their 3′ ends. LncRNAs were initially considered to be transcriptional noise. However, recent studies have shown that they are conserved in a cell-type-specific manner and can vary in response to environmental stimuli and during development, supporting their biological significance. Although lncRNAs can be found in both cytoplasm and nucleus, they are enriched in the later one, where they modulate transcription of genes *in cis*, located at or adjacent to their locus, and *in trans*, located on different genomic loci or in distal chromosomes. Furthermore, the transcription of lncRNAs can affect the transcription of

neighboring genes, representing a limitation for their study as such regulation is independent of the RNA product.

Based on their position relative to the nearest protein-coding gene, lncRNAs can be classified into different groups: (a) long intergenic ncRNAs (lincRNAs), which do not overlap in close proximity to protein-coding genes; (b) antisense lncRNAs, transcribed from the antisense strand of a protein-coding gene; (c) sense-overlapping lncRNAs, which overlap with at least one intron/exon of different protein-coding genes in the sense RNA strand; and (d) bidirectional lncRNAs, transcribed from a promoter of a protein-coding gene, yet in the opposite direction. LncRNAs can also be classified based on the functionality of the genomic region by which the lncRNA is encoded. For instance, enhancer RNAs (eRNAs) are bidirectionally transcribed from active enhancers (Lai and Shiekhattar 2014).

LncRNAs can serve to recruit chromatin-modifying complexes to specific loci to achieve appropriate temporal and spatial gene regulation by activating or inactivating transcription. Hence, many lncRNAs have been shown to interact with polycomb repressive complexes 1 and 2 (PRC1 and PRC2) to silence target genes (Achour and Aguilo 2018). In addition, an increasing number of lncRNAs regulate gene expression by directly interacting with transcription factors and recruit them to their DNA target site. LncRNAs can also act as competitors for the binding of DNA response elements of transcription factors and act as inhibitors of their transcriptional activation activity. For instance, glucocorticoid receptor can bind both DNA and lncRNA *GAS5* through its DNA-binding domain (Kino et al. 2010). Others affect RNA processing events such as pre-mRNA splicing, mRNA export, localization, translation, and stability, by directly interacting to RNA-binding proteins (He et al. 2019). Such mechanism would confer an energetic and dynamic advantage to cells, as RNAs are less expensive and more rapidly produced than proteins. LncRNAs can recognize specific targets by directly binding to genomic DNA through R-loops and/or RNA-DNA triplex structures (Chu et al. 2011). In addition, recent studies have proposed that lncRNAs with common miRNA-binding sites can act as molecular "sponges," thereby activating the transcription of those miRNA targets (Salmena et al. 2011).

LncRNAs regulate cellular homeostasis, dysregulation of which may impact normal cellular function, and lead to tumor development and metastasis. Indeed, many lncRNAs have been shown to influence the different hallmarks of cancer by either sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, or activating invasion and metastasis. In this book chapter, we have provided an overview of the current state of lncRNAs in breast cancer, with a particular focus on lncRNAs that impact cell growth, invasion, and metastasis. Based on their contribution to the activation or repression of oncogenic pathways, lncRNAs can be classified as oncogenic or tumor suppressor genes, respectively. Some key examples are summarized here. We have also highlighted the role of lncRNAs in chemotherapy resistance and the possibility of using oncogenic lncRNAs as novel prognostic markers and therapeutic targets for breast cancer.

2 LncRNAs and Breast Cancer Molecular Subtypes

Breast cancer is one of the most common malignant tumors in women and is the leading cause of morbidity and mortality for women worldwide (Torre et al. 2015). Breast cancer is a heterogeneous disease that can be classified into various subtypes based on molecular, histological, and clinical characteristics, with different clinical implications and treatment responses. Based on the presence of hormone receptors (progesterone (PR) and estrogen (ER)) and epidermal growth factor receptor type 2 (HER2) defined by immunohistochemistry staining, tumors are classified into four subtypes: luminal A, luminal B, HER2-positive (harboring an *ERBB2* amplification), and triple-negative (Table 1). Global gene expression studies of breast carcinomas distinguished five tumor subclasses, which mapped to the IHC-defined subtypes, except for the normal-like tumors, which share similar hormonal status with the luminal A but are characterized by normal breast tissue profiling and worse prognosis (Sorlie et al. 2001). Later, the PAM50 assay, in which the expression of 50 genes is assessed, was developed to further characterize the distinct subtypes (Parker et al. 2009).

Several studies have shown that lncRNAs are highly correlated with breast cancer subtypes achieving greater specificity than the protein-coding genes. Cluster analysis of unsupervised lncRNA expression retrieved from a large cohort of breast cancer patients from The Cancer Genome Atlas Portal (TCGA) revealed four subgroups that highly correlated with the defined PAM50 subtypes. Overall, 370 lncRNAs were overexpressed in the basal-like (cluster I), 220 were overexpressed in the HER2-positive (cluster II), 339 in luminal A (cluster III), and 279 in luminal B (cluster IV) breast cancer subtypes (Su et al. 2014). Another study identified a lncRNA molecular subtype-specific signature consisting of 42 lncRNAs (36 upregulated and 6 downregulated) for luminal A, 9 (8 upregulated and 1 downregulated) for luminal B, 14 (8 upregulated and 6 downregulated) for $HER2^{+}$, and 74 (28 upregulated and 46 downregulated) for the basal-like subtype

Table 1 Definition of breast cancer subtypes

BC subtype	Luminal A	Luminal B	HER-2	Basal
Molecular characteristics	ER/PR positive HER2/neu negative low Ki-67 (<14%)	ER/PR positive HER2/neu positive or negative high Ki-67 (≥14%)	ER/PR negative HER2/neu positive Ki-67	ER/PR negative HER2/neu negative Ki-67
Prevalence of invasive cancer	50%	20%	15%	~15%
Outcome	Favorable prognosis	Poor prognosis	Poor prognosis	Poor prognosis

Immunohistochemical phenotype of molecularly defined breast cancer subtypes based on the presence of *ER* estrogen receptor, *PR* progesterone receptor, *HER-2* human epidermal growth factor-2, and *Ki 67* proliferation index. The prevalence of invasive cancer and the outcome are also indicated

(Van Grembergen et al. 2016) (Fig. 1). In addition, overexpression of lncRNAs *CTD-2015G9.2*, *CTD-2527I21.15*, *LINC00393*, *LINC001198*, *RP11-10A14.5*, and *RP11-19E11* was highlighted in the basal-like subtype (Bradford et al. 2016). Although thousands of lncRNAs regulated by estrogen signaling have been identified in MCF7 human breast carcinoma cells, a three-lncRNA signature, including *PTPRG-AS1*, *LINC00324*, and *SNHG17*, was associated with the ER-positive and ER-negative subtypes of breast cancer (Zhao et al. 2014a).

3 Metastatic Breast Cancer

Metastasis occurs when cancer cells spread to other tissue sites and organs from the primary tumor and reach the blood circulation, the extracellular matrix, and the stroma. Invasion and metastasis of breast cancer target primarily the lungs and are generally the cause of death of breast cancer patients. LncRNAs participate in the invasion and metastasis of breast cancer by regulating cell adhesion molecules (CAM), extracellular matrix (ECM), and matrix metallo-proteinases (MMPs). For instance, in breast cancer cell lines, lncRNA *MALAT1* directly repressed the expression of tenascin Xb, an ECM protein that has been shown to have antimetastatic properties (Arun et al. 2016). Nevertheless, as discussed below, the role of lncRNA *MALAT1/Malat1* in breast tumorigenesis remains controversial. A large number of lncRNAs, including *SNHG12*, *HULC*, *ANCR*, and *BANCR* (Shi et al. 2016; Li et al. 2017b; Wang et al. 2017; Lou et al. 2018), have been shown to upregulate the expression of MMPs, thereby affecting cell-cell and cell-matrix interactions and promoting cellular migration and invasion. LncRNAs can also exert antimetastatic function through MMPs. Indeed, the overexpression of the tumor suppressor lncRNA *MEG3* decreased cell growth, invasion, and angiogenesis of breast cancer cells through downregulation of MMP-9 (Zhang et al. 2017a).

LncRNAs may influence cancer development by dysregulating multiple signaling pathways, such as p53, Bcl-2/Bax, or KLF4-KRT6/13, among others, thus affecting apoptosis, chemoresistance, radioresistance, and angiogenesis. For instance, it has been shown that lncRNA *LINP1* promoted metastasis and epithelial-to-mesenchymal transition and its overexpression in breast cancer cells correlated with the low sensitivity of the cells to 5-fluorouracil and doxorubicin through the inhibition of pro-apoptotic protein Bax (Liang et al. 2018).

During the process of epithelial-to-mesenchymal transition (EMT), epithelial cancer cells lose their defining epithelial features and gain a mesenchymal phenotype, which is critical for cell migration and invasion. The transition from epithelial to mesenchymal state is conducted by the repression of cell adhesion proteins such as E-cadherin; the increased expression of mesenchymal markers such as N-cadherin, vimentin, fibroblast-specific protein 1, and fibronectin; and the remodeling of the ECM and MMP. Transforming growth factor-β (TGF-β) signaling has been shown to be a major inducer of EMT and to facilitate breast cancer metastasis. Several studies have shown that lncRNAs can mediate TGF-β signaling.

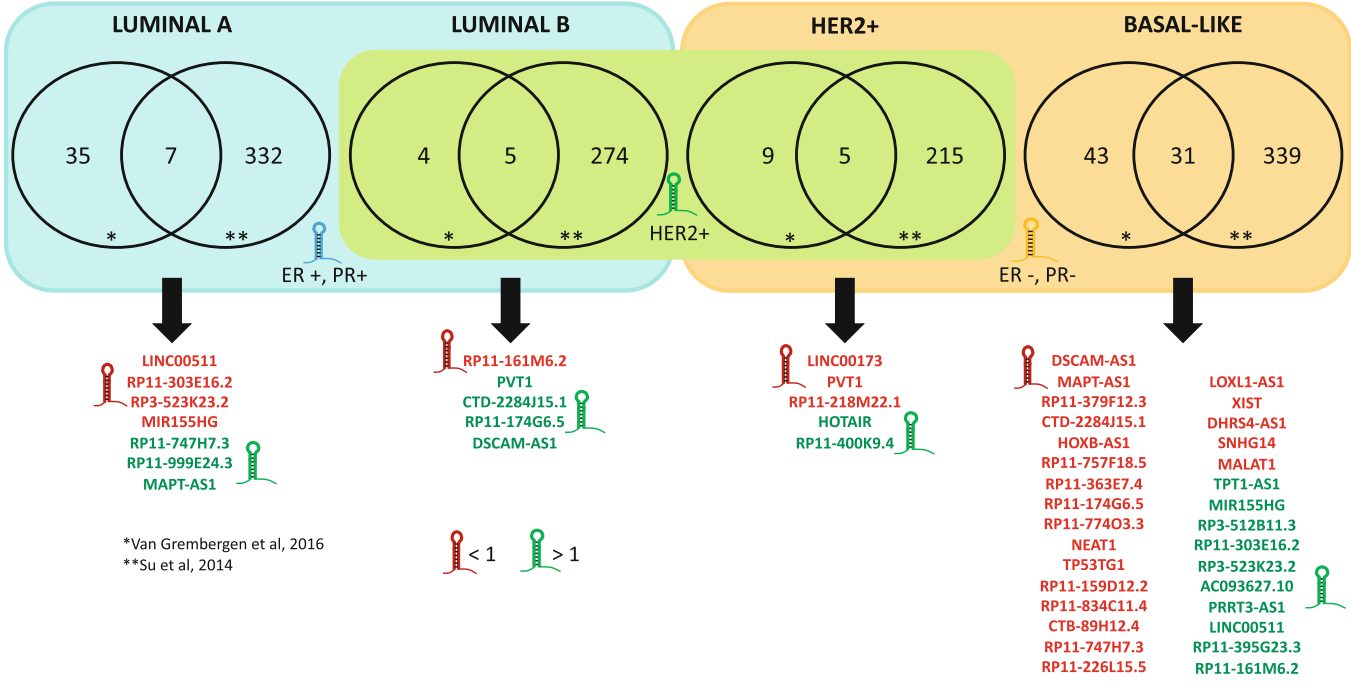

Fig. 1 Venn diagram depicting the lncRNAs that are differentially expressed in the breast cancer molecular subtypes. Data are retrieved from Van Grembergen et al. (2016) (∗) and Su et al. (2014) (∗∗). Common dysregulated lncRNAs are shown in red (downregulated) and green (upregulated). Fold change = 1.5 and FDR < 0.05. The blue, green, and orange rectangles group the subtypes based on the expression of ER, PR, and HER2. ER+/PR+ in blue (luminal A and luminal B), HER2 amplification in green (luminal B and HER2+), and ER-/PR- in orange (HER2+ and basal-like). *ER* estrogen receptor, *PR* progesterone receptor, *HER2* epidermal growth factor receptor type 2

Genome-wide lncRNA profile in mouse mammary gland epithelial cells has identified a signature of differentially expressed lncRNAs upon TGF-β induction of EMT. *LncRNA-HIT* was one of the top upregulated lncRNAs, playing a central role in TGF-β-induced EMT, cell migration, and invasion. Hence, depletion of *lncRNA-HIT* could reverse the process of EMT-associated gene expression of E-cadherin and vimentin (Richards et al. 2016). Moreover, lncRNAs can also activate TGF-β signaling pathway to promote EMT. For instance, lncRNA *ROR*, *CCAT2*, and *NORAD* have been shown to promote breast cancer metastasis by upregulating critical factors in the TGF-β signaling pathway (Cai et al. 2015; Hou et al. 2018; Zhou et al. 2019).

EMT is associated with the increased enrichment of cancer stem cells (CSCs). CSCs constitute a subpopulation of cancer cells that have the properties of self-renewal and are responsible for tumor initiation, formation, and recurrence. In breast tumors, this population of cells, exhibiting a $CD44^{+}/CD24^{-/low}$ phenotype with high ALDH activity ($ALDH^{+}$), is known as breast CSCs (BCSCs). *HOTAIR* has been shown to indirectly repress miR-7 through inhibition of the tumor suppressor *HoxD10*, maintaining the EMT process and the pool of BCSCs (Zhang et al. 2014). In addition, other lncRNAs such as *linc00617*, *ROR*, and *H19*, to name a few examples, have been described to promote the stem cell characteristics of BCSC (Hou et al. 2014).

4 Examples of LncRNAs in Breast Tumorigenesis

A large number of lncRNAs have been shown to play a role in breast cancer. However, the role and regulatory mechanisms of the vast majority of these transcripts is still elusive. We have summarized the function of some of the well-characterized oncogenic and tumor suppressor lncRNAs in breast tumorigenesis and metastasis below and in Fig. 2.

4.1 X-Inactive-Specific Transcript (XIST)

Although *X-inactive-specific transcript (XIST)* plays a central role in the initiation of X chromosome inactivation (XCI) during early development (Brown et al. 1992; Penny et al. 1996), lncRNA *XIST* is also expressed in adult females. X chromosome abnormalities contribute to the pathogenesis of breast cancer. For instance, duplication of the active X chromosome and loss of Xi has been frequently observed in the triple-negative breast cancer subtype, which leads to overexpression of a small subset of X-linked genes (Rakha et al. 2008). *XIST* expression correlated with the loss of the heterochromatic X chromosome or Barr body in somatic cells, a strong cytological marker of the inactive X chromosome (Xi) (Pageau et al. 2007). *BRCA1*, a tumor suppressor required for the cellular response to DNA damage and

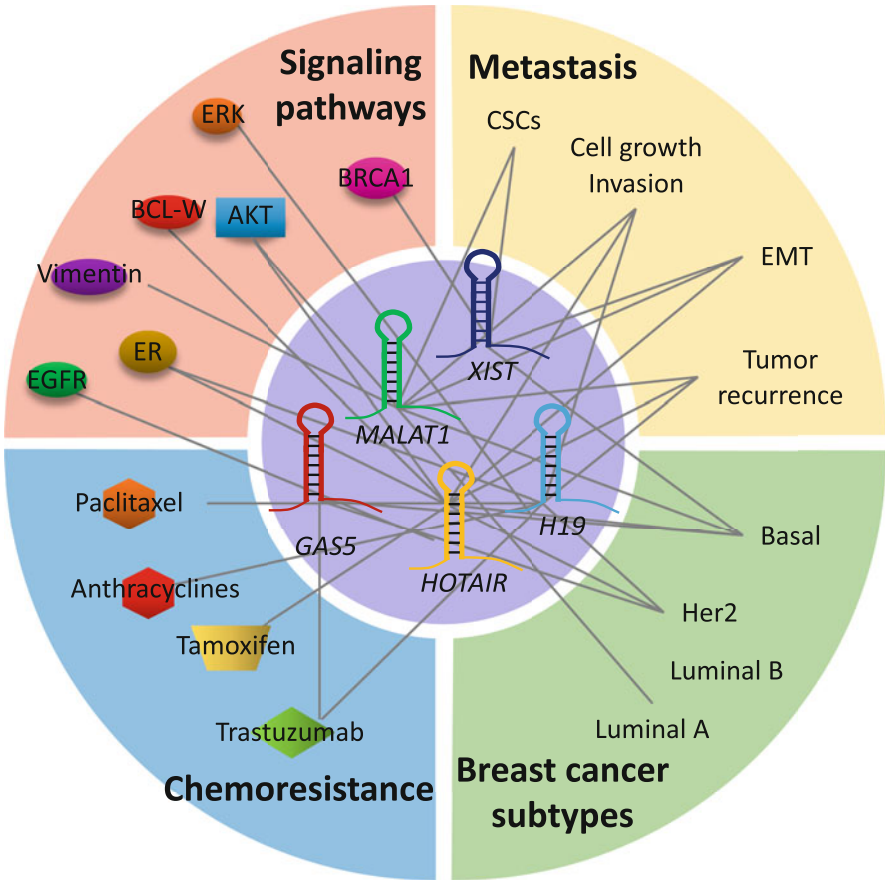

Fig. 2 Network of five common lncRNAs linked to metastasis and chemoresistance in breast cancer. LncRNAs are important factors that alter a plethora of signaling pathways. LncRNAs *XIST*, *MALAT1*, *H19*, *GAS5*, and *HOTAIR* play roles in chemoresistance and are involved in metastasis and tumor recurrence, epithelial-to-mesenchymal transition (EMT), and cancer stem cells (CSCs). The gray lines represent the association of the lncRNAs to the signaling pathways, chemoresistance, breast cancer subtypes, and metastasis

homologous recombination (Scully and Livingston 2000), physically associated with lncRNA *XIST* to maintain a proper Xi heterochromatin superstructure. Furthermore, loss of lncRNA *XIST* was associated with a *BRCA1* deficiency in sporadic basal-like cancers (Richardson et al. 2006). However, the role for BRCA in regulating the maintenance of facultative heterochromatin mediated by *XIST* has been controversial, and subsequent studies revealed that lncRNA *XIST* functioned independently of *BRCA1* in XCI (Sirchia et al. 2005; Xiao et al. 2007). Dysregulated expression levels of *XIST* have been associated with breast cancer where it has been shown to act as a tumor suppressor. Hence, depletion or overexpression of *XIST* resulted in increased or decreased levels, respectively, of AKT phosphorylation and

cell viability (Huang et al. 2016). In addition, lncRNA *XIST* was significantly downregulated in brain, but not bone, metastatic tumors from patients with breast cancer. Decreased expression of *XIST* stimulated EMT and activated c-Met via MSN-mediated protein stabilization, which resulted in the promotion of stemness in the tumor cells (Xing et al. 2018).

4.2 H19

H19 encodes a capped, spliced, and polyadenylated noncoding lncRNA, which is predominantly cytoplasmic (Brannan et al. 1990). The oncofetal lncRNA *H19* is expressed in the embryo, is downregulated at birth, and then reappears in tumors, where it is actively involved in all stages of tumorigenesis, from translational deregulation and genomic instability through enhanced proliferation and metastasis. Indeed, lncRNA *H19* is overexpressed in almost every human cancer, where it is frequently associated with poor prognosis (Raveh et al. 2015). In addition, *H19* acts as molecular sponge of the tumor suppressor *let-7* microRNA, limiting its bioavailability and leading to increased cell proliferation (Kallen et al. 2013). LncRNA *H19* has been described to be overexpressed in 70% of breast cancers where it exerts tumorigenic functions through different mechanisms. For instance, *H19* overexpression conferred proliferation advantage to tumor cells via positive regulation by E2F1 (Berteaux et al. 2005). Furthermore, *H19* upregulated tyrosine kinase receptors and its downstream AKT and ERK signaling pathways to promote breast tumorigenesis (Vennin et al. 2015).

4.3 HOX Transcript Antisense Intergenic RNA (HOTAIR)

HOX transcript antisense intergenic RNA (*HOTAIR*) is transcribed from the antisense strand of the *HOXC* locus on chromosome 12. LncRNA *HOTAIR* undergoes splicing and is polyadenylated (Rinn et al. 2007). *HOX* genes encoding transcription factors are clustered in four loci *HOXA-HOXD*. During development of vertebrates, *HOXA-HOXD* expression follows a spatial and temporal order along the body and the appendicular axis (Forlani et al. 2003). LncRNA *HOTAIR* has been shown to act *in trans* and repress *HOXD* cluster of genes by recruiting PRC2. In breast cancer, *HOTAIR* is overexpressed in both primary and metastatic tumors, and its expression in primary tumors correlates with later metastases, patient prognosis, and death. LncRNA *HOTAIR* promotes the reorganization of PRC2 occupancy on target genes, including progesterone receptor and protocadherin, which repressed their expression. A specific subunit of the PRC2 complex, enhancer of zeste homolog 2 (EZH2), has been found to be associated with *HOTAIR* expression and therefore with invasion and metastasis. Overexpression of lncRNA *HOTAIR* in the highly invasive breast cancer cell line MDA-MB-231 led to lung metastasis after tail vein xenograft

in mice. In contrast, knockdown of EZH2 showed an absence of metastasis to the lungs, thus confirming that EZH2 mediated the metastatic function of *HOTAIR* (Gupta et al. 2010). *HOTAIR* is an estrogen-responsive gene being its expression linked to ER in breast cancer (Bhan et al. 2013). Its promoter contains multiple estrogen response elements, which are targeted by ER and ER co-regulators in the presence of estradiol to induce *HOTAIR* transcription and contribute to breast cancer progression. In addition, a recent study has shown that overexpression of *HOTAIR* upregulated the expression of the apoptosis inhibitor Bcl-w in breast cancer. Bcl-w has been shown to promote migration, invasion, and therapy resistance of cancer cells. Mechanistically, lncRNA *HOTAIR* acted as a sponge for miR-206, which is known to inhibit Bcl-w expression, thereby facilitating the proliferation of breast cancer cells (Ding et al. 2017).

4.4 Metastasis-Associated Lung Adenocarcinoma 1 (MALAT1)

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*, also known as *nuclear-enriched abundant transcript 2* or *NEAT2*) is highly conserved through evolution, and is among the most abundantly expressed lncRNAs in normal tissues (Hutchinson et al. 2007). *MALAT1* is posttranscriptionally processed by RNAses at its 3′-end, generating a *MALAT1-associated small cytoplasmic RNA* (mascRNA), with unknown function, and a long nuclear transcript localized in nuclear speckles which was shown to regulate alternative splicing. However, *Malat1* knockout mice were viable and fertile and displaced no global difference in alternative splicing compared to their wild-type counterparts (Zhang et al. 2012).

MALAT1 was first discovered as a prognostic marker in non-small cell lung cancer patients, but later studies have shown that lncRNA *MALAT1* is dysregulated in a broad range of malignant tumors, including breast cancer, and its function has been directly linked to cancer progression and metastasis. *MALAT1* is highly expressed in primary breast tumors, and its expression levels have been shown to be positively correlated with lymph node size, ER expression, tumor stage, and histological grade (Gutschner et al. 2013). In addition, *MALAT1* overexpression correlated with decreased survival in lymph node-negative patients of the HER2- and triple-negative breast cancer subtypes (Jadaliha et al. 2016). Overall, these studies suggested that *MALAT1* could be used as a diagnostic and prognostic marker for breast cancer. *MALAT1* promoted cell proliferation, tumorigenesis, and metastasis of triple-negative breast cancer cells, despite having a comparatively lower expression level than ER- or HER2-positive breast cancer cells. Furthermore, downregulated *MALAT1* expression after treatment with high concentration of 17-β-estradiol inhibited cell growth, invasion, and metastasis of both ERα-positive and ERα-negative cell lines (Zhao et al. 2014b). More recently, an antisense transcript coexisting in the *MALAT1* locus termed *TALAM1* has been shown to synergize with

MALAT1 during tumorigenesis in aggressive breast cancer (Gomes et al. 2019). In support to the functional role of lncRNA *MALAT1* in regulating breast tumorigenesis, it has been reported that ablation or depletion of *Malat1* in the MMTV (mouse mammary tumor virus)-PyMT mouse mammary carcinoma model resulted in decreased tumor growth, differentiation into cystic tumors, and reduction in metastasis. Mechanistically, depletion of *Malat1* led to alterations in gene expression and splicing of signatures correlating with differentiation and pro-tumorigenic signaling pathways (Arun et al. 2016). Nonetheless, opposite observations of *MALAT1* in tumorigenesis have also been reported, and ablation of *Malal1* in mice did not impact global gene expression or alternative splicing (Zhang et al. 2012). However, this work has shown that *Malat1* neighboring genes were dysregulated in *Malal1* knockout mice, which raises the question to re-evaluate if the in vivo tumorigenic effect of *Malat1* lncRNA observed by other studies was a consequence to *Malat1* deletion or if the deletion of *Malat1* suppressed regulatory sequences of those genes. Indeed, later studies using targeted insertional inactivation of *Malat1* in MMTV-PyMT mice, for which lncRNA *Malat1* was directly targeted and not its neighboring genes, observed an opposite phenotype and showed that loss of *Malat1* induced metastasis. Rescue experiments and overexpression of *Malat1* in mice also validated that *Malat1* is a suppressor of breast cancer lung metastasis (Kim et al. 2018). In agreement with the tumor suppressor role of *MALAT1* lncRNA, lower expression of *MALAT1* in breast cancer patients was associated with shorter relapse-free survival. Furthermore, depletion of *MALAT1* in breast cancer cell lines induced an EMT program and enhanced cell migration and invasion by activating phosphatidylinositide-3 kinase-AKT signaling (Xu et al. 2015). Overall, several studies have reported contradictory effects of *MALAT1* in breast cancer metastasis; therefore, the function of lncRNA *MALAT1* still remains unclear and its roles must be more carefully dissected.

4.5 Growth Arrest-Specific Transcript 5 (GAS5)

Growth arrest-specific transcript 5 (*GAS5*) comprises 12 exons that due to the presence of alternative 5′-splice donor sites in exon 7 yield two mature lncRNAs, termed *GAS5a* and *GAS5b*. Within its introns, the gene encodes 10 box C/D snoRNAs which participate in the 2'-O-methylation of ribosomal RNA (rRNA) (Smith and Steitz 1998). LncRNA *GAS5* is highly expressed in growth-arrested cells from which it was isolated after screening of tumor suppressor genes that accumulate upon lack of nutrients and growth factors (Schneider et al. 1988). LncRNA *GAS5* acts as a tumor suppressor in several types of human cancer, including breast cancer, by both facilitating growth arrest and promoting apoptosis. Depletion of lncRNA *GAS5* in triple-negative and ER-positive cell lines attenuated cell responses to apoptotic stimuli, including classical chemotherapeutic agents (Pickard and Williams 2014). LncRNA *GAS5* is significantly low expressed in multiple cancers, with expression levels related to both clinicopathological

characteristics and patient prognosis. For instance, lncRNA *GAS5* could serve as a novel early diagnostic biomarker for breast tumorigenesis as it is already downregulated in stages I and II of breast cancer (Mourtada-Maarabouni et al. 2009). Furthermore, *GAS5* can also be used to assess the prognosis evaluation for breast cancer patients after surgery (Han et al. 2016). In addition, downregulation of lncRNA *GAS5* leads to trastuzumab resistance in HER2-positive breast cancer, indicating that *GAS5* could be a candidate drug target for this breast cancer subtype (Li et al. 2016a).

5 LncRNAs Associated with Chemotherapy Resistance

Over the past few years, substantial advances in the treatment of breast cancer, involving the use of cytotoxic drugs, hormonal and targeted therapies, and immunotherapeutic agents, have decreased the mortality rate. Furthermore, a better understanding of the heterogeneity of breast cancer has led to the development of more effective therapies and individualized approaches to target specific molecular subtypes. Although in the majority of patients clinical responses are observed, the presence of primary and acquired resistance to chemotherapy treatment remains a significant common challenge that results in therapeutic failure. Recently, lncRNAs have emerged as key players in breast cancer drug resistance.

Endocrine therapy has proved to be one of the most effective treatment modality against ER-positive tumors. Tamoxifen, a partial nonsteroidal estrogen agonist is the prototype of the selective ER modulator family, and acts as a competitive inhibitor of estradiol in the estrogen receptor (Lumachi et al. 2011). Several lncRNAs have been shown to contribute to tamoxifen resistance by influencing different mechanisms. For instance, lncRNA *HOTAIR* is directly repressed by ER and, thus, upregulated upon the blockade of ER signaling, either by hormone deprivation or by tamoxifen treatment. Elevated lncRNA *HOTAIR* increased ER protein level and thus ER occupancy on the chromatin, enhancing ER transcriptional program (Xue et al. 2016). LncRNA *ROR* is also involved in tamoxifen resistance in ER-positive tumors. Hence, inhibition of lncRNA *ROR* reversed resistance to tamoxifen by inducing autophagy in breast cancer (Li et al. 2017a). Furthermore, downregulated lncRNA *ROR* could enhance the sensibility of breast cancer cells to tamoxifen by increasing and decreasing miR-205 and ZEB1/2, respectively (Zhang et al. 2017b). In addition, lncRNA *urothelial carcinoma-associated 1* (*UCA1*) conferred resistance to tamoxifen by activating the mTOR signaling pathway and by sponging miR-18a, a negative regulator of HIF1α (Li et al. 2016b).

Achieving a blockade of HER2 receptors with antibody-drug conjugates such as trastuzumab has been shown to improve the poor prognosis associated with HER2-positive metastatic tumors. However, trastuzumab resistance has become prevalent in recent years, and it is the leading cause of mortality in the HER2-positive breast cancer subtype. The role of TGF-β-induced EMT in trastuzumab resistance is well established. LncRNA activated by TGF-β (*lnc-ATB*), a mediator of TGF-β signaling,

has been described to predispose breast cancer patients to EMT and trastuzumab resistance by competitively binding miR-200c and upregulating the oncogenes *ZEB1* and *ZNF217* (Shi et al. 2015). On the contrary, downregulation of lncRNA *GAS5* led to trastuzumab resistance in HER2-positive breast cancer. *GAS5* suppressed cancer proliferation by acting as a molecular sponge for miR-21, leading to the derepression of PTEN (Li et al. 2016a).

Cytotoxic chemotherapy is used during adjuvant systemic therapy, administrated after breast cancer surgery regardless of the breast cancer subtype, to prevent distant recurrence of the disease. Anthracyclines, such as doxorubicin and epirubicin, and/or taxanes, including paclitaxel and docetaxel, are the current cytotoxic agents used for both early and advanced stages of breast cancer (Hernandez-Aya and Gonzalez-Angulo 2013). Several studies have shown that lncRNA *H19* confers chemotherapy resistance in breast cancer. ERα upregulated the expression of *H19,* which is associated with paclitaxel resistance. Hence, in ERα-positive breast cancer cells, lncRNA *H19* attenuated cell apoptosis by inhibiting transcription of pro-apoptotic genes by recruiting polycomb factors at their promoters (Si et al. 2016). In doxorubicin-resistant breast cancer cells, *H19* was significantly upregulated, which led to the upregulated expression of *CUL4A* and *ABCB1*/MDR1, contributing to the cell resistance of multiple chemotherapeutic agents (Zhu et al. 2017).

Triple-negative breast cancer does not express conventional therapeutic targets and is the only type of malignant breast cancer for which no targeted therapy is available, with cytotoxic chemotherapy being the main treatment. Several lncRNAs have been shown to be involved in chemoresistance of these patients limiting the options for treatment. For instance, lncRNA *ferritin heavy chain 1 pseudogene 3* (*FTH1P3*) expression is enriched in paclitaxel-resistant breast cancer tissue samples, promoting cellular proliferation by targeting miR-206/ABCB1 axis (Wang et al. 2018). LncRNA *HIF1A-AS2* and *AK124454* have been shown to promote cell proliferation and invasion and were also contributing to paclitaxel resistance in triple-negative breast cancer patients (Jiang et al. 2016). Epidermal growth factor receptor (EGFR) and the non-receptor tyrosine kinase c-ABL are frequently overexpressed in triple-negative breast cancer to enhance proliferation, survival, invasion, and metastasis of cancer cells (Corkery et al. 2009). Co-treatment with clinically validated inhibitors of EGFR and c-ABL blocked β-catenin nuclear expression, which resulted in repression of the lncRNA *HOTAIR*. Consistently, *HOTAIR* expression and cellular growth could be restored by forcing the expression of β-catenin in the presence of both drugs. Furthermore, depletion of *HOTAIR* alone phenocopied the dual treatment in growth suppression (Wang et al. 2015).

6 LncRNAs in Diagnostic, Prognosis, and Therapies in Triple-Negative Breast Cancer

Due to the lack of early detection biomarkers and hormonal or targeted therapies, triple-negative breast cancer is the most aggressive subtype. As a consequence, patients with triple-negative breast cancer usually suffer from distal recurrence and, hence, have a poor prognosis. Therefore, the identification of potential biomarkers for prognoses and novel therapies is urgently needed. A number of lncRNAs have been associated with clinical diagnosis and survival outcome in patients with triple-negative breast cancer, thus serving as novel predictors for tumor diagnosis and prognosis. For instance, the expression of the lncRNAs *ANRIL*, *UCA1*, and *HIF1A-AS2* was increased in the plasma of patients with triple-negative breast cancer in comparison to patients with other breast cancer subtypes (Liu et al. 2017). LncRNA *NEAT1* was also found to be overexpressed in blood samples of patients with triple-negative breast cancer compared to the other subtypes. Knockdown of *NEAT1* led to a decrease of stemness and an increase in chemotherapy sensitivity, supporting the use of *NEAT1* as a target for triple-negative breast cancer (Shin et al. 2019). Another example is the analysis of microarray expression profiles from 473 breast cancer patients, of which 12 lncRNAs have been identified as either upregulated or downregulated in patients with tumor recurrence (Zhou et al. 2016). Therefore, those lncRNAs may be used as a prognostic signature for breast cancer patients to predict the tumor recurrence and recurrence-free survival.

Despite our current understanding of lncRNA function in breast cancer is limited, and controversies still remain in the field, several studies have highlighted the use of lncRNAs in cancer therapy. Antisense oligonucleotides (ASOs) are single-stranded oligonucleotides that are complementary to a target sequence which induces its RNA degradation by RNase H. They offer advantages over siRNA targeting, as ASOs show fewer off-target effects and higher specificity. ASOs targeting lncRNA *Malat1* in the mouse MMTV-PyMT carcinoma model resulted in a decrease of the tumor growth and lung metastasis (Arun et al. 2016). More recently, a novel tool using ASO has been developed to target *MALAT1* in lung cancer cells, but one could think of its application in breast cancer. This new technology uses functionalized gold nanoparticles conjugated with positively charged TAT peptides to stabilize the negatively charged ASO and guide it to the cell nucleus where it can specifically target *MALAT1* (Gong et al. 2019). This novel method to target lncRNA *MALAT1* showed a significant reduction of the migration capacity of cells in vitro and of the formation of tumors in a mouse model. The use of small molecules which target specific lncRNA-protein interactions to finely tune gene expression and modify chromatin state may represent a novel therapeutic approach in cancer. Hence, targeting chromatin-modifying enzymes through interacting lncRNAs would increase the specificity of such compounds and provide reversible regulation at non-catalytic domains of the protein. For instance, a small molecule compound (AC1Q3QWB) has been identified as a selective and efficient disruptor of

HOTAIR-EZH2 interaction, resulting in blocking PRC2 recruitment and increasing the expression of tumor suppressor genes in breast cancer (Li et al. 2019). Furthermore, treatment of breast cancer cell lines with a peptide nucleic acid-based approach that also blocked *HOTAIR*-EZH2 interaction decreased invasion and increased chemotherapy sensitivity (Ozes et al. 2017). Although the application of these approaches against lncRNA function is still in its infancy, it proves to be an exciting area to explore for novel therapeutic targeting of breast cancer.

7 Conclusion and Future Perspectives

Over the past few years, high-throughput sequencing analysis has highlighted the importance of lncRNAs in cellular homeostasis by playing essential roles in gene expression regulation. LncRNAs have been implicated in several processes including epigenetic control, RNA processing, stability, and translation, but knowledge of the precise mechanisms of action is still in the early stages. A limited number of well-characterized lncRNAs have given important clues about the biology of lncRNA in cancer revealing their function as tumor suppressors or pro-oncogenes, depending on how they influence tumorigenesis. In breast cancer, aberrant expression of lncRNAs has been shown to promote tumor growth and metastasis through sustaining proliferation and cell cycle progression, promoting migration, invasion, and EMT transition, and regulating cell stemness, among others. LncRNA gene signatures have been associated with different breast cancer subtypes and clinical outcomes, suggesting their potential as attractive therapeutic targets and novel molecular biomarkers for breast cancer. Therefore, a better understanding of the biology and functional mechanisms of lncRNA in cancer could pave the way for novel anticancer therapies in the future.

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