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Long non-coding RNAs: Functional regulatory players in breast cancer

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A B S T R A C T

Historically, the long-held protein-centered bias has denoted 98% of the human genome as 'Junk' DNA. However, the current work has shifted the perception of such 'junk' transcriptional products to functional regulatory molecules. The recent surveillance of the human transcriptome has highlighted the pivotal role of such non-coding RNA (ncRNA) molecules in diverse physiological and pathological conditions. Long non-coding RNA (lncRNA) is a recent class of ncRNA molecules that is still in its infancy stage. The main focus of this review is to unravel the importance of lncRNAs in the most prevalent malignancy among females which is Breast Cancer (BC). A specific focus on lncRNAs as prognostic markers among BC patients showing molecular subtype heterogeneity was also tackled in this review. Finally, the functional and the mechanistic roles of such booming ncRNA molecules in shaping the fate of the BC progression have been highlighted.

1. Introduction

1.1. Breast cancer (BC)

Breast cancer (BC) is the 2nd most common malignancy among both sexes where only lung cancer comes on top of it [1]. Yet, it is the most common malignancy among females, thus represents a top biomedical research priority [1]. The dilemma of BC mainly arises from its multiple subtypes that are manifested in a wide variety of clinical, pathological and molecular profiles and consequently having variable responses to treatment[2].

BC is one of the most heterogeneous solid tumors where it was hypothesized that this heterogeneity evidenced in breast tumors could be the reason beyond the resistance towards conventional protocols experienced by a large number of BC patients [3]. Moreover, it spots specific BC subtypes as one of the most complex and challenging types of malignancies to diagnose and treat (Table 1) [2].

Triple Negative Breast Cancer (TNBC): The real obstacle

Massive parallel sequencing confirmed an unexpected level of heterogeneity among Triple Negative Breast Cancer (TNBC) patients in particular. Of note, tumors of TNBC patients are reported to be the most aggressive as they are portrayed by high histological grade, scant stromal content, elevated mitotic count, central necrosis and pushing margins of invasion [4,5]. Thus, TNBC patients have the highest percentage of early local relapse, especially between the 1st and 3rd year post-diagnosis [6]. Consequently, patients with TNBC have inferior disease free survival (DFS) and overall survival (OS) as compared to age and grade matched non-TNBC patients [5,7]. Thus, a new era of research should be directed to identify actionable targets dedicated to this hard-to-treat group of BC patients.

1.1.1. What are the molecular drivers underling BC?

Molecular pathogenesis studies also support the heterogeneity concept of BC. They refer to BC as a collection of diseases with variable molecular underpinnings that modulate therapeutic responses, disease-free intervals, and long-term survival of BC patients [8].

Moreover, condensed 'omics' technologies have also led to the identification of some potential actionable molecular features in some TNBC cases such as germline BRCA1/2 mutations or 'BRCAness', the presence of androgen receptor, and other rare genomic alterations. Yet, whether these alterations are molecular 'drivers' or not, this has not been clearly identified [9]. Yet, it is very disappointing that despite all current efforts directed towards BC research, the molecular basis of such malignant transformation process has remained unknown and considered as one of the most challenging aspects of the disease [10]. In an attempt to reach a true personalized BC therapy, a more comprehensive analysis and evaluation of the molecular characteristics of the disease in each individual patient is required, together with an understanding of the contributions of specific genetic and epigenetic alterations (and their combinations) are definitely required to reach the goal of personalized management of BC patients [8]. Fig. 1 summarizes some of the altered molecular circuits underlying the pathogenesis of BC such as JAK/STAT, PI3K/AKT/mTOR and RAS/RAF/MAPK signaling pathways [11]. It is very important to

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Table 1
Molecular classification of breast cancer and their current therapeutic options [126–128].

Molecular subtype	Biomarker profile	Adjuvant therapeutic strategy
Luminal A	ER^+ and/or PR^+, $HER\text{-}2^-$, and low Ki-67 (< 14%)	Endocrine therapy solely in most of the cases Combination therapy: (only in case of large tumor burden (4 or more positive LN, T3 or higher) or grade 3) Endocrine therapy with Chemotherapy
Luminal B	ER^+ and/or PR^+ and $HER\text{-}2^+$ (luminal-HER2 group)	Combination therapy: Endocrine therapy, Chemotherapy and Anti-HER-2 treatment
Luminal B-like	ER^+ and/or PR^+, $HER\text{-}2^-$, and high Ki-67 (≥14%)	Combination therapy: Endocrine therapy and Chemotherapy
HER-2	ER^-, PR^-, and $HER\text{-}2^+$	Combination therapy: Chemotherapy and Anti-HER-2 treatment
Triple Negative Breast Cancer (TNBC)	ER^-, PR^- and $HER\text{-}2^-$	Chemotherapy only

LN: Lymphnode; ER: Estrogen Receptor; PR: Progesterone Receptor; HER-2: Human Epidermal growth factor-2; Ki-67: Proliferation index.

note that all those oncogenic signaling cascades are drawn down-stream a set of aberrantly expressed tyrosine kinase receptors such as insulin like growth factor-1 receptor (IGF-1R), EGFR and HER-2 receptors or cytokines receptors such as interlukin-1 (IL-1) and TNF-α or chemokine receptors such as C—C chemokine receptor type 7 (CCR7) and C-X-C chemokine receptor type 4 (CXCR4) as presented in Fig. 1. Moreover, Fig. 1 also represents the available drugs used to molecularly target BC through blocking one of the oncogenic drivers of BC such as Lapatinib inactivating EGFR and HER-2 receptors, Sorafenib blocking the RAS/RAF signaling cascade and Bortezomib blocking the activation of NF-κB. However, an unpredictable mechanism of resistance to such molecular weapons was observed. A compensatory activation of the other parallel signaling pathways usually occurs. Hence, targeting a single point in such convoluted circuits induces compensatory activation of an up- and/or down-stream corresponding oncogenic pathways resulting in drug resistance [12,13]. However, a multi-functional player which has the ability to repress several proteins rather that a single one, and consequently shuts down several deregulated pathway simultaneously would be very effective [14].

But the question now is: Is there a multi-functional upstream regulator that could simultaneously tune more than one player in such inter-wined signaling cascades starting from the receptors and their ligands ending up to the oncogenic transcription factors ?

Fortunately, the answer of this question is definitely “yes” where those multi-functional tuners are endogenously expressed within our human cells and known as non-coding RNAs (ncRNAs).

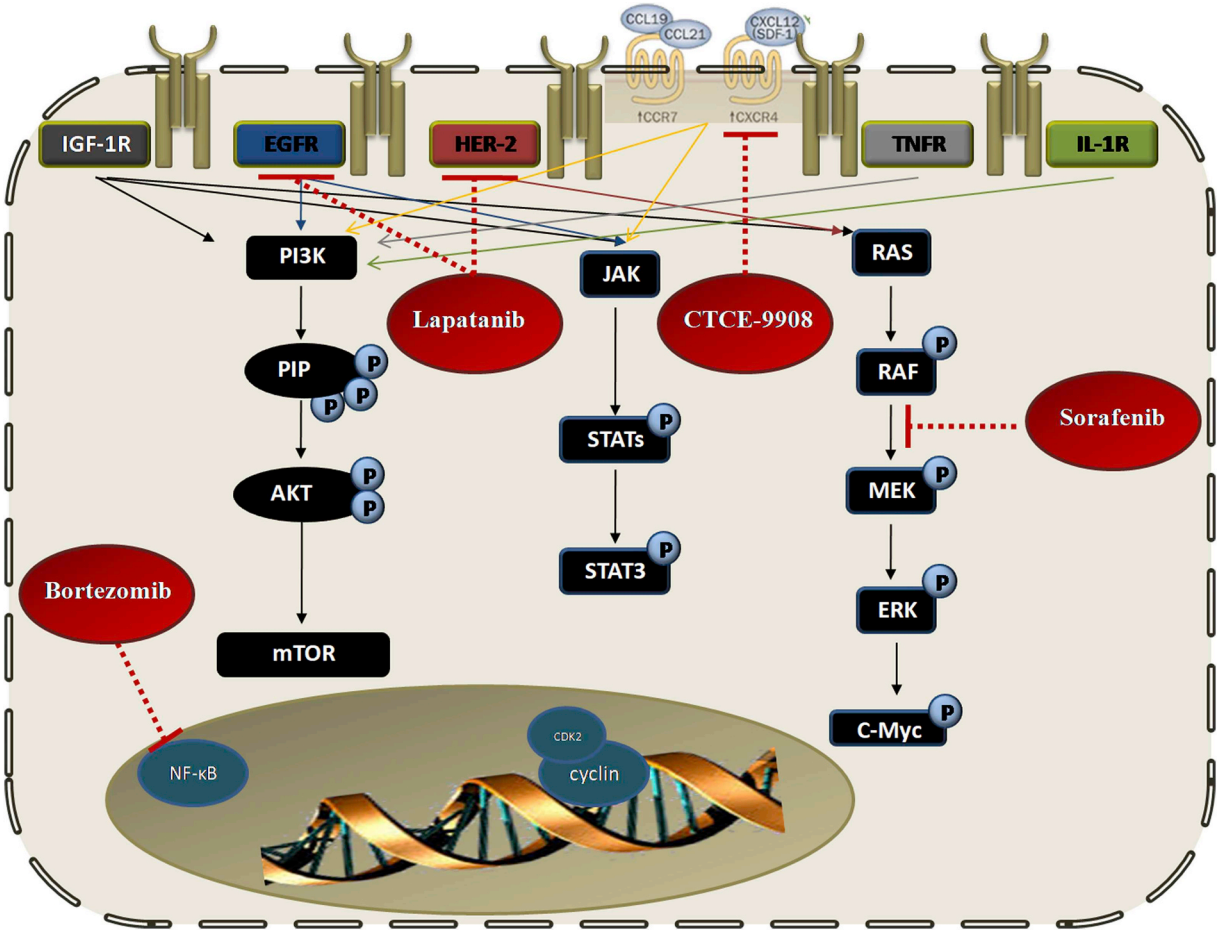

Fig. 1. Molecular signaling pathways underlying breast cancer.

1.2. Non-coding RNAs

From birth to death, the genetic material is convolutedly regulated; the human body highly modulates the amount and timing of expressing vital cellular proteins in a securely regulated manner that allows the cells to produce the gene products only when needed. This regulatory process occurs at any step throughout the genetic expression process, starting from RNA transcription to post-translational modifications of proteins. Historically, regulators of gene expression were known to be factors affecting DNA methylation, histone modification or specific transcription factors. However, over the last few years, non-coding RNAs (ncRNAs) have emerged as prominent class of gene regulatory molecules [15].

Current work has shifted the perception of ncRNAs from 'junk' transcriptional products to functional regulatory molecules. ncRNAs could potentially modulate different cellular processes including chromatin re-modeling, transcription, post-transcriptional modifications and most importantly regulate several signal transduction pathways through having hundreds of simultaneous targets as mentioned before, thus nominating ncRNAs to play a key role in different pathological conditions [16]. ncRNAs has been classified into 2 main categories according to their length: short ncRNA molecules (< 200 nucleotide (nt)) and a recent class known as long ncRNAs (lncRNAs) (≥200 nt) that will be the main focus of this review [17].

1.2.1. Short non-coding RNA

Short ncRNAs are extensively studied and reviewed [18–20]. Short ncRNAs are sub-classified into several sub-classes such as: microRNAs (miRNA), short interfering RNAs (siRNA), piwi interacting RNAs (piRNA) and small nuclear RNAs (snoRNA) [17]. Different classes of short ncRNAs showed pivotal epigenetic roles in modulating several epigenetic regulatory circuits in normal physiological and pathological conditions as shown in Table 2 [14,21–23].

1.2.2. Long non-coding RNAs (LncRNAs)

Previously, lncRNAs were considered as “dark matter” or “transcriptional noise” of the human genome with no biological functions [24]. However, the recent surveillance of the human transcriptome has highlighted their pivotal role in diverse physiological and pathological conditions [25]. Unlike miRNAs, lncRNAs are mRNA-like transcripts ranging in length from 200 to 200 kb nucleotide, yet poorly conserved species [26]. A detailed comparison between miRNAs, siRNAs and lncRNAs is shown in Table 3.

The total number of lncRNAs continues to ascend, catalyzed by deeper and more sensitive RNA sequencing techniques, improved epigenomic technologies and computational prediction techniques [27,28]. According to the most recent reports from Encyclopedia of DNA Elements (ENCODE) Project Consortium (GENCODE release 28), it was reported that the human genome encodes for more than 120,000 distinct lncRNA transcripts [29]. However, there are still a lot of missing information about the mechanistic role of such new class of ncRNAs, highlighting the infancy of the field is terms of functional characterization.

Such growing ranks have motivated researchers to focus on understanding the questionable roles of lncRNAs in cancer biology [30]. Myriad studies have reported de-regulated lncRNA expression across numerous cancer types suggesting that aberrant lncRNA expression may be a major contributor to tumorigenesis [31,32] and especially BC [33–35] which is the main focus of this review.

1.2.2.1. Nomenclature of LncRNAs. The nomenclature of lncRNAs is extremely variable [36]. Some lncRNAs are named according to their molecular role such as PRAL (P53 Regulation-Association Long Non-Coding RNA), or based on their relative expression in specific cancer such as HULC (Highly upregulated in liver cancer). While on the other hand, some are named according to their genomic location such as HOTAIR (Hox antisense intergenic RNA) [37].

1.2.2.2. Biogenesis of lncRNAs. LncRNAs biogenesis is quite complicated. LncRNAs share mRNAs in several characteristics especially in their transcriptional and processing steps [25]. Most of lncRNAs are transcribed by RNA polymerase II, the majority of them are spliced, polyadenylated and 5′-capped [25]. Yet, some lncRNAs are not adenylated.

Yet, lncRNAs also show a lot of differences that distinguish them from protein-coding mRNAs. Several reports have showed that lncRNAs are of lower expression levels than protein-coding genes; however, they exhibit a more cell type-specific pattern [38]. Moreover, most lncRNAs are localized in the nucleus unlike mRNAs [39]. LncRNAs originate from intronic, exonic, intergenic, intragenic, promoter regions, 3′- and 5′-UTR, and enhancer sequences and are sometimes bidirectional transcripts. In particular, a large group of lncRNAs is antisense to known protein-coding transcripts that are also referred to as natural antisense transcripts (NATs) [40,41]. NATs are divided into two subtypes: cis-NATs, which are transcribed from opposite DNA strands at the same genomic loci; and

Table 2
Different sub-classes of short non-coding RNA molecules.

Class of ncRNA	Description	Functional Role	References
MicroRNAs (miRNA)	• Single stranded RNA molecules with 22–25 nucleotides in length. • Known as master-regulators of the genome. • Post-transcriptionally regulate the expression of almost 60% of genome. • It acts in a Dicer-dependent manner.	• The post transcriptional regulation of its targets depends on base pair complementarity: **Perfect complementarity:** Results in Ago-catalysed cleavage of target mRNA **Imperfect complementarity:** Results in translational repression (reducing protein levels of target genes without affecting their transcript levels). • miRNAs are functionally implicated in various pathological conditions such as cancer progression.	[10,12,14–16]
Small interfering RNA (siRNAs)	• Double stranded RNA molecules with 21–23 nucleotides in length. • Post-transcriptional silencing of coding genes • It acts in a Dicer-dependent manner.	• siRNA guide strand is used to trigger post-transcriptional gene silencing through Watson-Crick base pair interactions with the target mRNA. • It is currently involved in the treatment of several malignancies (pre-clinical studies)	[16–19]
Piwi interacting RNA (piRNA)	• Double stranded RNA molecules with 26–30 nucleotides in length. • RNAs present in clusters of repetitive sequence within genome	• They were discovered because of their direct association to piwi-proteins which is involved in the gametogenesis. • It directly affects DNA methylation in germ cells. • Possible role in silencing retro-transposable elements within the genome. • Association between piRNAs and different pathological conditions has not been revealed yet.	[6,16,20]
Small nucleolar RNA (snoRNA)	• Double stranded RNA molecules with 60–300 nucleotides in length. • Localized in the nucleolus	• Implicated in the maturation of other RNA molecules (coding and non-coding) through guidance of chemical modifications targeting such asrRNAs, tRNAs and snRNAs.	[6,16,21]

Table 3
Detailed comparison between miRNAs and lncRNAs.

Molecular Feature	lncRNAs	miRNAs	siRNAs
Size	≥200 nucleotide	18-25nucleotide	21-23 nucleotide
Physiological Function	Regulators of endogenous coding and non-coding genes	Regulators of endogenous coding genes	Defenders of genome integrity in response to foreign or invasive nucleic acids such as viruses, transposons, and transgenes
Location	1 Exonic 2 Intronic 3 Intergenic	1 Exonic 2 Intronic 3 Intergenic 4 Intergenic 5 Overlapping	siRNA is likely formed by two perfectly complementary RNA molecules transcribed from two different promoters (remained to be explored)
Source	Multiple ways according to its location	Primary microRNA	(Double stranded RNA) Viral RNAs Hairpin RNAs Gene/Pseudo-gene duplex Transgene Transcript Convergent Transcripts Repeat associated transcripts
Tissue Specificity	High	Low	Unkown
Target mRNA	Multiple	Multiple	Single
Transcription	Mostly RNA Polymerase II (In some cases RNA Polymerase III)	Mostly RNA Polymerase II (In some cases RNA Polymerase III)	Double stranded RNA that is only processed by DICER
5′ Capping	Yes	Yes	No
Poly-Adenylation	Yes	Yes	No
Splicing	Yes	Yes	No
Translation	Rarely produce some peptides	No	No
Molecular Mechanism of Action	1 Chromatin remodeling 2 Transcriptional regulation 3 Post-transcriptional regulation 4 Act as precursors for siRNAs	1 Translational repression 2 mRNA degradation 3 In rare cases, Endonucleolytic cleavage occurs (in case of perfect complementary)	Endonucleolytic cleavage of mRNA
Complementarily	Depends on its mechanism of action and its target	Partial complementary to its target mRNA is enough, typically targeting 3'UTR of mRNA	Perfect Complementary is required to mediate its function
Interactions with other ncRNAs	1 Sponge/decoy miRNAs 2 Generate miRNAs 3 Compete with miRNAs for interaction with target mRNAs	1 Trigger lncRNAs decay 2 Compete with lncRNAs for interaction with mRNAs	Unknown
Clinical Applications	1 Therapeutic agent 2 Drug target 3 Diagnostic tool 4 Prognostic tool	1 Therapeutic agent 2 Drug target 3 Diagnostic tool 4 Prognostic tool	1 Therapeutic agent
Stability as therapeutic agent	Unstable	Unstable	Unstable
Delivery as therapeutic agent	Difficult	Difficult	Difficult
Selectivity and Potency	Unspecific and potent	Highly specific and potent	Highly specific and potent

trans-NATs, which are transcribed from distal loci. Notably, many cancer relevant genes produce antisense lncRNAs [42].

1.2.2.3. Mechanism of action. LncRNAs have their own functional attributes due to their secondary structures [36]; they usually have stem-loop secondary structures [43]. LncRNAs utilize a large arsenal of mechanisms to regulate gene expression to affect diverse biological functions [42]. According to their functions, lncRNAs roughly fall into 3 main categories which are (1) transcriptional regulators, (2) post-transcriptional regulators, and (3) other regulatory functions displayed by a unique interplay between lncRNAs and miRNAs [25].

In contrast to miRNAs, lncRNAs interact with other biological macromolecules such as RNA, DNA, and protein, and other decisive factors in promoting the normal functions of normal cells [36]. Digging deeper to understand the molecular mechanism by which lncRNAs could affect their prey whether it is RNA, DNA or proteins; some lncRNAs were found to act as molecular signals or inducers of the transcriptional activity of its targets [44]. While other lncRNAs act as a decoy, binding and titrating away a protein target, but does not exert any additional functions. Another class of lncRNAs acts as a guide strand where it binds to its target proteins and then directs the localization of ribonucleoprotein complex to specific targets. Other lncRNAs act as scaffold where it serves as central platform to bring multiple proteins together to form ribonucleoprotein complexes [45].

1.2.3. LncRNAs: central players in the battle against malignancy

As previously highlighted, ncRNAs have a versatile ability to shut-down an array of oncogenic signaling cascades simultaneously and thus having the potential to play a central role in the process of carcinogenicity. In terms of oncology, miRNAs are the well-studied class of short ncRNAs while lncRNAs are not well-plotted in the puzzle of oncology which will be the main goal of this review (to spot lncRNAs as pivotal pieces in the puzzle of cancer and in BC in particular) [46].

As recently reported by Wang et al. and de Oliveira et al. lncRNAs hold a lot of promises in the field of oncology through revealing a lot of the hidden cancer biology aspects and also pave a road for better diagnosis and treatment [32,47]. Aberrant expression of lncRNAs may confer capacities for tumor initiation, growth, and metastasis in cancer cells, thus leading to a differential prognosis between patients [48]. The mechanisms by which lncRNAs contribute to the regulatory networks that underpin cancer development are diverse [49]. LncRNAs showed a functional involvement in several fundamental processes such as apoptosis, proliferation, migration, cell-cycle regulation, DNA damage response, survival, self-renewal, and metastasis through either

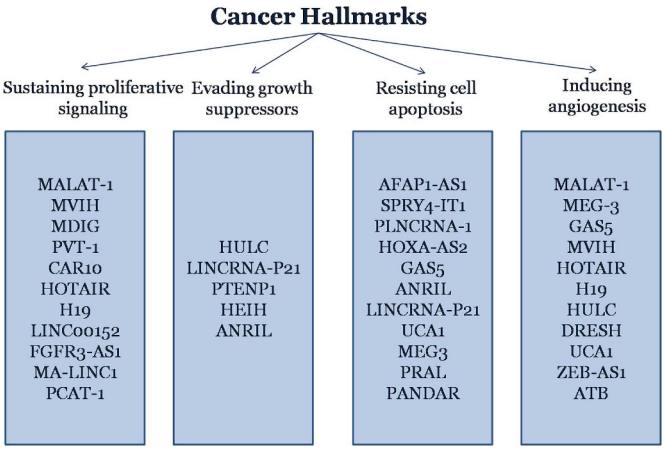

Fig. 2. Association of long-non-coding RNA molecules with different hallmarks of cancer.

transcriptional or post-transcriptional regulation in several cancers as summarized in Fig. 2 [50].

1.2.4. Portraying BC with lncRNAs

Recently, the research of lncRNAs in BC was gradually revealed and the related mechanisms were slightly unveiled [47]. It was reported that lncRNAs are involved in mammary gland development and consequently BC evolution [51]. It is also worth mentioning that some researchers also reported the potential role of lncRNAs to act as diagnostic and prognostic markers and therapeutic targets or therapeutic tools in BC. Recently, lncRNAs' differential expression was found to potentially distinguish between different subtypes of BC such as TNBC from non-TNBC patients [52]. Table 4 shows lncRNAs involved in BC progression with more clinically relevant ones described below.

1.2.4.1. Oncogeneic lncRNAs in BC

1.2.4.1.1. HOX transcript antisense intergenic lncRNA (HOTAIR). HOTAIR is located on chromosome 12q13.13. It is transcribed from the HOXC locus and epigenetically acts as a repressor of HOXD gene [53]. HOTAIR has been highly associated with metastasis in several solid malignancies such as liver cancer [54], pancreatic [55], lung [56], and BC [57]. In BC in particular, HOTAIR is the first reported oncogeneic lncRNA that provides a powerful indication for tumor aggressiveness and metastases [58]. Its expression level was positively correlated with poor prognosis and lymph node metastasis [59]. On the cellular level, HOTAIR was found to induce TNBC cell lines' migration and invasion capacities [59]. In view of the importance of HOTAIR in TNBC, it was reported that HOTAIR knock-down is essential to get the desired therapeutic effects of the combination therapy of lapatinib and imatinib [60,61]. These reports elucidate some unidentified mechanisms in TNBC that is directly linked with HOTAIR regulation opening new avenues for great therapeutic benefits.

1.2.4.1.2. Non-homologous end joining pathway 1 (LINP1). The non-homologous end joining pathway 1 (LINP1) is another lncRNA that is classified as an oncogenic lncRNA in several cancers such as protstate cancer [62], cervical cancer [63] and BC [64]. Its chromosomal location is 10p14. Several reports support *LINP1* over-expression in BC patients with different subtypes [64–66]. In a similar manner to *HOTAIR,* it was reported that blocking *LINP1* in BC cells is essential to increase the sensitivity of tumor cells to radiotherapy [47].

1.2.4.1.3. Metastasis associated lung adenocarcinoma transcript 1 (MALAT1). MALAT1 is an oncogenic lncRNA that exhibit its tumor promoting effects in several cancers including BC [67–70]. Its chromosomal location is 11q13. It was initially reported to be highly upregulated in invasive non-small cell lung carcinoma (NSCLC) [71]. MALAT1 is a nuclear lncRNA that is highly conserved among mammals [72]. Functionally, MALAT-1 was found to act as a potent inducer PI3k/AKT/mTOR and Wnt/β-catenin pathways in several solid malignancies including BC [73]. Moreover, some researchers had focused on its ability to sponge some miRNAs regulating the cell cycle such as miR-101, miR-217 demonstrating MALAT1 as a competing endogenous lncRNA sequestering other small ncRNAs [74]. Focusing on BC in particular, it has been repeatedly reported through several *in vivo* and *in vitro* studies that MALAT1 promotes proliferation, tumor development and metastasis of BC [67,68,75]. In addition, the expression level of MALAT1 was reported to have a high prognostic value as it was negatively correlated to the survival of ER negative, lymph node negative patients of the HER-2 and TNBC molecular subtypes [76]. It is also worth mentioning that a recent study showed very promising results of MALAT1 antisense nucleotides in suppressing BC development in xenograft luminal B mouse models [77]. Collectively, these studies highly propose MALAT1 as a core signaling molecule promoting BC development and progression and consequently a potential therapeutic target for several BC subtypes [78].

1.2.4.1.4. Highly up-regulated in liver cancer (HULC). The lncRNA HULC is chromosomally located at 6p24.3. It is the first lncRNA with highly specific upregulation in liver cancer [79]. HULC expression and functional activities are not only restricted to liver cancer, however, it is also overly expressed in several cancers such as colorectal carcinoma [80,81], oral squamous cell carcinoma [82], gastric carcinoma [83] and BC [84]. Functionally, HULC was found to act as an endogenous sponge that downregulates an array of miRNAs such as miR-372, miR-186 and miR-200a-3p [85,86]. In TNBC, HULC was found to be significantly upregulated in TNBC patients and cell lines. Moreover, Shi and his colleagues recommended HULC as an independent poor prognostic factor in TNBC patients [84].

1.2.4.1.5. CDKN1A antisense DNA damage activated RNA (PANDAR). The lncRNA *PANDAR* is located at 6p21.2 which is approximately 5 kilobases upstream of the CDKN1A transcription start site and was induced upon DNA damage [87]. On the functional level, *PANDAR* plays a pivotal role in regulating the apoptotic process in several types of malignancies. It acts as an oncogenic lncRNA through inhibiting the expression of several proapoptotic genes through interaction with the transcription factor *NF-YA* [88]. Recently, PANDAR was reported to control the entry and exit into and out of the senescence status [87]. PANDAR abnormal expression level has been reported in various cancers such as hepatocellular carcinoma, gastric cancer, thyroid cancer, acute myeloid leukemia and BC [89–91]. In a study performed by Sang et al., they clearly shown that PANDAR is markedly up-regulated in BC patients and cell lines and that the knockdown of PANDAR reduced cell growth and colony formating ability of BC cells. Mechanistically, the knock down of PANDAR led to the G1/S arrest mainly through affecting P16 promotor activity [87].

1.2.4.1.6. LincRNA-regulator of reprogramming (lincRNA-RoR). The regulator of reprogramming (ROR or linc-RoR) was first identified in induced pluripotent stem cells [92]. RoR is ~2.6 kbp and is located on 18q21.31. RoR is an oncogenic lincRNA that is highly expressed in self-renewing human embryonic stem cells and various cancer cells such as hepatocellular carcinoma [93], endometrial cancer [94], pancreatic cancer [95] and BC [96–98]. In several contexts, there is a positive correlation between the expression level of RoR and the undifferentiation degree of the carcinoma tissues [99]. Functionally, lincRoR has been proven to act as a multi-functional player in several cancers. For instance, lincRoR was found to promote the epithelial–mesenchymal transition [98], enhance the hypoxia resistance of the tumor tissue [100], and reduce the sensitivity of the tumor to chemotherapy [99]. RoR is also a well-known negative regulator of the p53 pathway [101]. Nonetheless, RoR acts as a competing endogenous lncRNA with several tumor suppressor miRNAs such as miR-145, miR-205, and miR-124 thus abrogating

Table 4
Functionally characterized lncRNAs in BC.

LncRNA	Chromosomal Location	Expression Profile	Tumor suppressor or Oncogene	Molecular Function
H19	11p15.5	Upregulated	Oncogene	Sponge Let-7 family miRNAs miRNA precursor for miR-675-3p
HOTAIR	12q13.13	Upregulated	Oncogene	Molecular scaffold Epigenetic gene silencing
CCAT1	8q24.21	Upregulated	Oncogene	Sponge Let-7 family miRNAs
MALAT-1	11q13.1	Upregulated	Oncogene	Activates ERK/MAPK pathway Induces expression of *B-MYB* Promotes EMT by activating Wnt signaling Sponge miR-1; miR-101; miR-217
PVT1	8q24.21	Upregulated	Oncogene	Promotes KLF5/β-catenin signaling pathway
MVIH	10q22 at RPS24	Upregulated	Oncogene	Promotes cellular proliferation, cell cycle progression and inhibiting apoptosis
BCAR4	16p13.13	Upregulated	Oncogene	Required for noncanonical Hedgehog/GLI 2 signal transduction pathways
LINC00152	2p11.2	Upregulated	Oncogene	Promotes cellular proliferation, migration and invasion
PCAT-1	8q24.21	Upregulated	Oncogene	Post-transcriptional repression of the *BRCA2* 3′UTR
CCAT2	8q24.21	Upregulated	Oncogene	Regulation of Wnt/β-catenin signaling pathway
UCA1	19p13.12	Upregulated	Oncogene	Sponge miR-26a; miR-184; miR-203; miR-129 Regulation of KLF4-KRT6/13 signaling pathway
Z38	unknown	Upregulated	Oncogene	Unknown
SPRY4-IT1	5q31.3	Upregulated	Oncogene	Unknown
HULC	6p24.3	Upregulated	Oncogene	Sponge miR-186 and miR-372 Repress the expression of P18
ANRIL	9p21.3	Upregulated	Oncogene	Sponge miR-199a
AFAP1-AS1	4p16.1	Upregulated	Oncogene	Unkown
UCA1	19p13.12	Upregulated	Oncogene	Affects Wnt/β-Catenin Pathway Affects mTOR signaling Pathway Sponge miR-181a; miR-182; miR-122-5p
SPRY4-IT1	5q31.3	Upregulated	Oncogene	Targets ZNF703
LINP1	10p14	Upregulated	Oncogene	Molecular scaffold
lincRNA-RoR	18q21.31	Upregulated	Oncogene	miRNA sponge
AK058003	Unknown	Upregulated	Oncogene	Regulating γ-synuclein gene (SNCG) expression
LINK-A	Unknown	Upregulated	Oncogene	Regulation of HIF1α signaling pathway
DSCAM-AS1	21q22.2	Upregulated	Oncogene	Unknown
HOXA-AS2	7p15.2	Upregulated	Oncogene	Sponge miR-520c-3p
ATB	Unknown	Upregulated	Oncogene	Promotes epithelial-mesenchymal transition by upregulating the miR-200c/Twist1 axis
XIST	Xq13.2	Upregulated	Controversial	X-chromosome silencing
PANDAR	6p21.2	Upregulated	Controversial	Regulation of G1/S transition
LOC554202	9p21.3	Controversial	Controversial	Activation of specific caspase cleavage cascades
NBAT-1	6p22.3	Downregulated	Tumor supressor	Mediating transcriptional silencing
EPB41L4A-AS2	5q22.2	Downregulated	Tumor supressor	Unknown
FGF14-AS2	13q33.1	Downregulated	Tumor supressor	Unknown
BC040587	3q13.31	Downregulated	Tumor supressor	Unknown
GAS5	1q25.1	Downregulated	Tumor supressor	Interaction with mTOR signaling pathway
LINC00472	6q13	Downregulated	Tumor supressor	Unknown
MA-LINC1	5q31.3	Downregulated	Tumor supressor	Vital regulator of cell cycle
LINCRNA-P21	Unknown	Downregulated	Tumor supressor	Regulates P21 mRNA and protein levels
PTENP1	9p13.3	Downregulated	Tumor supressor	Upregulates PTEN via its ceRNA interaction on miR-19b
PLNCRNA-1	21q22.12	Downregulated	Tumor supressor	Induces Apoptosis Upregulates TGF-β1 Downregulates PHGDH
MEG3	14q32.2	Downregulated	Tumor supressor	Sponge miR-21; miR-421 Activation of P53

their tumor suppressive actions and promotes cancer development and progression [94,97,102]. In BC, lincRoR is significantly upregulated in several BC patients and cell lines [103]. In a recent study performed by Hou and his colleagues, it was found that lincRoR expression is correlated with BC patients' poor prognosis and recommends the blocking the functional activity of linc-ROR may represent a possible therapeutic strategy [104].

1.2.4.2. Tumor suppressor lncRNAs in BC

1.2.4.2.1. Growth arrest-specific 5 (GAS5). Tumor suppressor lncRNAs in BC are still in its infancy stage where very few lncRNAs were characterized as tumor suppressors such as growth arrest-specific 5 (GAS5). *GAS5* is localized at 1q25.1. GAS5 is downegulated in several solid malignancies such as pancreatic [105], colorectal [106], lung [107], liver [108] and breast cancers [69,109,110]. Recently, GAS5 has been extensively studied in terms of BC where it was reported to act as a tumor suppressor lncRNA through sequestering several oncogenic miRNAs such as miR-221/222 [109], miR-196 [111]. Moreover, GAS5 level was found to act as an important determinant for drug resistance in BC where low leveled of GAS5 was found to be responsible for tamoxifen [112] and dendrosomal curcumin resistance [113] in BC cells. GAS5 is down-regulated in BC tissues and its low levels was directly associated with poor prognosis of BC [114]. GAS5 is also known as a prominent cell cycle regulator that accumulates the cells in growth arrested state [115].

1.2.4.2.2. Neuroblastoma associated transcript 1 (NBAT-1). Neuroblastoma associated transcript-1 (NBAT-1) is located at 6p22.3. It is known as a tumor suppressor lncRNA that is downregulated in several cancers such as lung cancer [116], ovarian cancer [117], renal cell carcinoma [118] and BC [119]. Its expression level was found to be associated with poor survival of BC patients and lymph node metastases [119]. However, the detailed mechanism of action responsible for the tumor suppressive actions in BC still needs further investigations.

1.2.4.2.3. Maternally expressed 3 (MEG3). MEG3 is chromosomally located at 14q32.2. It is down-regulated in several malignancies such as prostate cancer [120], oral cell carcinoma [121] and BC [122]. In BC patients, MEG3 was directly associated with the overall-survival of patients thus highlighting its high prognostic value in BC [123]. It has been reported to act as a tumor suppressor lncRNA through acting as a sponge to several miRNAs such as miR-9 [120], miR-494 [120], miR-21 [121] and miR-29 [124]. In BC, MEG3 was found to act as a tumor suppressor lncRNA through increasing p53 expression level through increasing the nuclear factor κB (NF-κB) expression level [122]. Moreover, it was also found to repress PI3K/AKT/mTOR pathway and thus repressing the oncogenic behavior of the overly expressed miR-21 in BC cells [125].

2. Conclusion

In conclusion, this review highlights the current knowledge about lncRNAs in BC. lncRNAs has been classified into oncogenic lncRNAs and tumor suppressor lncRNAs in BC. However, still further information and detailed studies are required to draw the full picture of lncRNAs in BC. Yet, the current information highly proposes lncRNAs as aggressive tumor-promoting factors and consequently their inhibition would be able to harness BC progression efficiently. Therefore, targeting such cantankerous oncogenic lncRNAs may serve as a favorable strategy with promising therapeutic potential in BC. However, due to the lack of experimental data, an interpretation of these findings concerning the tumor suppressors' lncRNAs is difficult and not connected to an appropriate biological context yet, thus highlighting a very critical gap in the field of lncRNAs that may hold a lot of great promises and therapeutic candidates for BC patients.

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