REVIEW

Editorial Process: Submission:07/15/2022 Acceptance:01/11/2023

Long Non Coding RNA in Triple Negative Breast Cancer: A Promising Biomarker in Tumorigenesis

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Abstract

Globally, Triple-negative breast cancer (TNBC) is an unsurpassed variant of breast cancer (BC) with a very high fatality rate, and disease burden. Nevertheless, the deficit of diagnostic markers and focused treatment are major hurdles for potent therapeutics. They are also the reason for bad outcomes and causes of a worse prognosis and a high rate of flare up in patients with TNBC diagnosis. Long non-coding RNAs (lncRNA) are a new class of molecules that have recently gained interest in healthcare management due to their potential as biomarkers for human diseases especially cancers. The growing interest in lncRNA in clinical practice has created an unmet need for developing assays to test lncRNA quickly and accurately for early diagnostics. These lncRNA modulate multiple stages of tumor development, including growth, proliferation, invasion, angiogenesis, and metastases, by controlling several genes and changing metabolic networks. Highly invasive phenotype and chemo resistance are prominent characteristics of TNBC subtypes that require accurate diagnostic and prognostic instruments involving lncRNA. This review focusses on the evolving purpose and coalition of lncRNAs in TNBC and accentuates their capable effects in diagnosis and treatment of cancer. Moreover, the extensive literature analysis of our review creates an opportunity in the translational application concerning the TNBC lncRNAs described until now. The depiction of lncRNAs enrolled in TNBC is comprehensive, and sufficient substantiation studies are the need of the hour to authenticate the current outcomes and create imminent upcoming of elemental research setting into clinical practice.

Keywords: Triple negative- breast cancer- lncRNAs- diagnostics- prognostics

Asian Pac J Cancer Prev, **24 (1)**, 49-59

Introduction

Breast cancer (BC) is the most common form of cancer and the leading cause of cancer death among women worldwide (Sung et al., 2021). Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer and accounts for 15-20% of all breast cancer cases worldwide. This subtype is characterized by the absence of estrogen (ER) and progesterone (PR) receptors and human epidermal growth factor (HER2/neu) receptor (Yin et al., 2020). In addition to radiotherapy and chemotherapy, surgery continues to be the main stay of therapy for TNBC. Due to the lack of effective therapy and treatment of TNBC patients, there is a greater risk of metastases, faster disease progression, and a shorter survival time associated with the treatments mentioned above (Keenan et al., 2020).

The most recent TNBC therapy techniques have yet to produce practical therapeutic effects. These techniques contribute to insufficient response due to the lack of biomarkers that determine which patient groups are most likely to respond to specific therapies (Medina et al., 2020). To our knowledge, no well accepted reliable biomarkers are available for the detection of TNBC. Therefore, the crucial need for a reliable, predictive biomarker may recognize patients with this aggressive and fast-growing tumor at an earlier stage to improve the prognosis. It will be necessary to classify these patients at an early stage, as they may benefit from adjuvant therapy and other targeted therapies. Unfortunately, in particular cases, there is no systematic approach to predict the outcome of the procedure. Therefore, it is essential to explore new, customized approaches and improve the TNBC results.

In neoteric years, treatment blueprint for TNBC

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have registered a huge amount of non-fulfilment in the establishment of drugs, until lately it has been offered to add molecular wide studies to recognise supplemental biomarkers for TNBC. Genomics and proteomics studies have enhanced molecular subtyping and cancer detection and predicted better patient outcomes. However, the simulation of the cellular effects of multiple molecular modifications on gene regulatory networks remains a major challenge. Often, selective molecular therapies do not always have therapeutic benefits to patients. These difficulties stem from the highly complex task of completely modelling the spectrum of cancer DNA, RNA, and protein interactions (Garrido-Castro et al., 2019). The extensive advance in cancer's precise genetic control reinforces us to reassess the basic effect of non-coding substances in the homo sapiens genome (Marotti et al., 2017).

The human genome sequence constitutes of two percentage genes which code protein and more than ninety percentage of human genomic sequence is transcribed into non-coding genes, resulting in a cumulative number of non-coding RNAs. According to the length of nucleotide sequence, non-coding RNAs (ncRNAs) can be classified as long non-coding RNAs (lncRNA), and small non-coding RNAs (sncRNA). MicroRNAs (miRNAs), small interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNA) are classified under small non-coding RNAs (sncRNA). The two primary non-coding RNAs, miRNAs (long 18-22 nucleotides) and lncRNA (transcripts longer than 200bp) , have emerged as critical cancer disease regulators (Guo et al., 2019). Due to their roles in human diseases, including cancers, long non-coding RNAs (lncRNA) have amplified interest in recent years.

LncRNA have very less to no protein-coding potential, predominantly act as cell controlling components and are documented to regulate many cellular processes. Dysregulation of lncRNA in different types of cancer is widely accepted as one of the most influential factors in tumour development (Chen et al., 2015). It inhibits tumour cell proliferation, resists growth inhibitors, and p revents the accumulation of mutations, among other effects. Several studies have recently elucidated the function of lncRNA in carcinogenesis, including cancer diagnosis, differentiation, and cancer spread monitoring, particularly for TNBC (Liu et al., 2020). They are involved in various biological processes such as cell proliferation, differentiation, remodelling of chromosomes, epigenetic regulation, transcriptional and post-transcriptional modifications.

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LncRNA can control many tumour development stages, including growth, proliferation, invasion, angiogenesis, and metastases (Tao et al., 2019). In this review, we will outline the biogenesis and mechanism of lncRNA in detail and, spotlight the functional approach of several lncRNA involved in TNBC and discuss their contribution to the diagnosis and therapeutic value of TNBC to the potential for their meaningful inclusion in clinical practice.

Molecular mechanism and function of long non-coding RNAs (lncRNA)

The discovery of several lncRNA has constituted a new milieu for diagnosing and predicting diseases, including carcinomas, over the last few years. The X-inactive–specific transcript (Xist) RNA was discovered in the early 1990s, a decade before the Human Genome Project (HGP) revealed that non-coding sequences make up the great bulk of the human genome. LncRNA are commonly defined as transcripts having more than 200 nucleotides but no protein-coding potential; this relatively arbitrates limit distinguishes small ncRNAs from lncRNAs (Kansara et al., 2020). LncRNA, on the other hand, are more similar to mRNAs than to other ncRNAs. First, the chromatin state of the lncRNA loci genome is similar to that of the mRNA loci genome, from which lncRNA are transcribed by RNA polymerase II (Pol II). LncRNA, like mRNAs, are frequently polyadenylated, 5′-coated, and spliced (Nagini, 2017). Although, relative to mRNAs, lncRNA transcripts have lower exons, are shorter and are expressed at a ten-fold lower level (Derrien et al., 2012).

The biological functions of lncRNA are classified according to their origin and mechanisms of action. LncRNA can act by cis-regulating or trans-regulating the target genes (Le et al., 2019). Also, multiple target genes may be regulated by a single lncRNA via different mechanisms (see Table 1). In particular, lncRNA can serve as platform to facilitate the formation of manifold protein structures, such as chromatin remodelling, which can be switched on to impact gene expression (Figure 1).

LncRNA functions as a ground rule for enhancing communications among DNA and proteins. They also act as enhancers that modulate expression of genes by employing suppressors of transcription, while loop forming of DNA and activation of transcription by protein structures of gene of target. LncRNA plays a protective role by acting as a trap and prevent the binding of proteins participating in transcription to their DNA targets or RNAs vital to miRNAs and thus stops the detrimental gene modulations (Kansara et al., 2020). Moreover, lncRNA enhance splicing of mRNA due to intron withholding by attaching to the mRNAs. The wide range of synergy among lncRNA ,nucleic acid and protein interactions enables lncRNA protein stabilization, protein complexes activation, and gene modulation all through the genome (Peng et al., 2017). With advances in analytical methods and high-throughput RNA sequencing, a significant number of lncRNA have been discovered (Zhang et al., 2016). However, in the development and evolution of TNBC, their expression profiles, methods, and related functions remain unknown.

Moreover, lncRNA in large numbers are deregulated in TNBC through oestrogen or progesterone receptor pathways (Zhang et al., 2016). Several lncRNAs was found to be associated with TNBC, such as LINC00993, which is significantly deregulated and corelated to gene expression of ER and ANKRD30A (Chen et al., 2020). Collina et al., (2019) and Beltrán-Anaya et al., (2019) found that HOTAIR expression is connected to primary

TNBC tumour tissues. Another study revealed that MALAT1 is higher in TNBC tissues and is linked with tumour proliferation, metastasis, and bad prognosis. Lin et al., (2017) recently showed that LINK-A is essential for the c signalling pathway induced by growth factor by channelizing activated breast tumour kinase (BRK) along with leucine-rich repeat kinase 2 (LRRK2) (Ebright et al., 2020). Similarly, HIF1 alpha degradation and Ser797 phosphorylation promote HIF1 alpha-p300 interaction under normal conditions, leading to HIF1 alpha goal gene activation20. Notably, LINK-A expression and the stimulation of the HIF1 alpha signalling pathway mediated by LINK-A could aid in treatment of TNBC (Lin et al., 2017).

It has also been demonstrated that lncRNA downregulation is associated with poor clinical outcomes. According to many recent studies, PVT1 is upregulated in clinical TNBC tumors (Li et al., 2018; Wang et al., 2018). MDA-231R overexpresse v v bed by GAS5 could increase TNBC's sensitivity to PTX (Zheng et al., 2020). FOXCUT can be a possible diagnostic and therapeutic marker of basal-like TNBC, another study has confirmed (Fan et al., 2019). By down-regulating lncRNA H19, lncRNA PTCSC3 inhibits TNBC cell proliferation (Yang et al., 2019). MIR100HG encourages the proliferation of cells and controls the CDKN1B gene to regulate the TNBC cell cycle by stimulating the FZD7 receptor, the upregulated AWPPH accelerates tumour growth in TNBC (N Wang et al., 2019). Recently, Rahman et al. [2018], have explored upregulation of lncRNA ERRLR01 levels in TNBC compared with BC ERα-positive patients.

LncRNA as predictive biomarkers

With the upcoming of many new drugs in the recent past, metastatic TNBC therapeutic environment has undergone a drastic change. However, to accomplish most desirable outcome from these drug therapies in clinical application remains a great challenge to the paucity of biomarkers for response and resistance prediction (i.e., predictive biomarkers). Its factual that there exists no unique analyte so far to fulfil the essential level of accurate diagnosis or prognosis in TNBC. Despite the above mentioned fact, this needs to be clarified for lncRNA, so by employing group of lncRNA, we anticipate to come about with markers with more clinical efficacy. Despite the increasing number of critical lncRNA speculated by sequencing of RNAs, there are limited number of fully identified and completely investigated lncRNA (Table 1). Thousands of lncRNA are expected to remain undetected due to the need to examine those resulting from overlapping protein-coding loci. Henceforth, the progress of TNBC can be analysed by these lncRNA as curative targets. In the ensuing sections, we elaborate the current lncRNA encoding with TNBC.

H19

LncRNA H19 (H19 Imprinted Maternally Expressed Transcript) is a transcription product of the H19 gene. The diverging expression of H19 can be evinced in different types of cancer cells including TNBC, it interacts with E2F1 and advocates cell cycle succession. The H19 expression is downregulated by PTCSC3 (Papillary thyroid carcinoma susceptibility candidate 3) in TNBC. TNBC cell invasion is prevented by lncRNA PTCSC3 which is negatively associated with lncRNA H19. The participation of PTCSC3 in signalling pathways such as STAT3 and WNT moderates the interaction with lncRNA H19 (Yang et al., 2019). In paclitaxel resistant TNBC patients, a positive association of lncRNA H19 was observed Wang et al., (2020), analysed the action of lncRNA H19 in carcinogenesis and metastases of BC and demonstrated H19/p53/TNFAIP8 axis as a favourable therapeutic outcome for BC, mainly for TNBC (N Wang et al., 2019). Li et al., (2020), also explained as such lncRNA H19 aids proliferation and spread via p53/TNFAIP8 pathway in TNBC . Taken together, H19 plays a significant role in TNBC progression, henceforth targeting H19 will provide a good therapeutic platform.

DANCR

DANCR is an carcinogenic lncRNA found on chromosome 4 that is also known as Anti-Differentiation Non-coding RNA (ANCR) (Braga et al., 2020). It is found in Small Nucleolar RNA host gene protein 13 (SNHG13), where it upregulates transcript 2 (AGU2). It was initially described as an unidentified function transcript whose expression in pluripotent stem cells in human mesenchyme (h MSCs) is dramatically increased during adipogenesis (Wang et al., 2017). It was later identified as non-coding anti-differentiation RNA, due to its role in promotion of epidermal progenitor cells maintenance and prevention of osteoblasts differentiation (Tao et al., 2019). Many Studies so far have highlighted the multiple carcinogenic functions of DANCR by means of various negative regulation targets contributing to the prognosis of certain cancers of human origin. For example, a bioinformatics study reported that lncRNA DANCR has a binding site for miR-216a-5p which can act as a potential therapy target (Zhong, et al., 2018).

However, another study reported that DANCR promotes essential integrant in the carcinogenic gene matrix by either mopping their subsequent miRNAs or by communicating with several regulatory proteins (Wu et al., 2020). The ability of DANCR to show up in tumor cells while also having a significant impact on cancer's ability to spread gives it strong potential as a therapeutic target for comprehensive cancer treatment. Furthermore, DANCR is an oncogene involved in PI3K/AKT activation and promotes phosphorylation of RXRA, and can potentially enhance TNBC tumorigenesis (Tao et al., 2019). A study indicates that DANCR is associated with TUFT1. The expression of DANCR is upregulated in women with triple-negative breast cancer, thus making them more likely to have TNBC (Zhong, et al., 2018). In summary, the ability of DANCR to show up in tumor cells while also having a significant impact on cancer's ability to spread gives it strong potential as a therapeutic target for comprehensive cancer treatment.

KLHDC7B

KLHDC7B was defined originally as a 3008-bp long expressed sequence tag (EST). The transcript undergoes

translation forming protein having 595 amino acids and a Kelch domain. The Kelch domain consists of Kelch motif ,which is a β-sheet of four strands and forms single part in a β-propeller arrangement (Beltrán-Anaya et al., 2019). KLHDC7B is enriched in the TNBC subtype's immunomodulatory, and its remodelling stimulates movement of the cell , proliferation , and prevents death of cells. The downregulation of lncRNA KLHDC7B by in silico analysis affirmed its association with bad survival outcome in patients with BC (Jeong et al., 2018). Similarly, one more study has also stated that the lncRNA KLHDC7B and STAR1 are upregulated in TNBC and notably correlated with modulation activity of gene in the signalling pathway of interferon in the course of carcinogenesis of Breast (Jeong et al., 2018). In conclude, KLHDC7B is highly expressed in TNBC and provides a predictive role in determining prognosis in such patients.

MNX1-AS1

As a recently identified lncRNA, MNX1-AS1 (Motor neuron and pancreas homeobox 1-antisense RNA1) has been found to be highly upregulated in several cancers of human mainly non-small cell cancer of lung, stomach cancer, even BC and many others indicating bad prognosis in patients with these cancers (Li et al., 2020). As per reports it stimulates cancer cell invasion and cell relocation in ovarian cancer. Recently, MNX1-AS1 was also found to promote the progression of colon cancer and lung cancer (Li et al., 2020). In another elaborative study lncRNA MNX1-AS1 expression was upregulated significantly in 95 TNBC patients when compared to adjacent normal breast tissue. Li et al., (2020) silenced MNX1-AS1 which reduced proliferation, invasion, and colony formation in TNBC while apoptosis was significantly induced. MNX1-AS1 increases Stat3 phosphorylation thus intensifying the interlinkage among p-JAK and Stat3 annotated using RNA pulldown assay, western blotting and RNA immunoprecipitation (RIP), which fastens TNBC growth (Li et al., 2020). Therefore, MNX1-AS1 can be targeted to improve the clinical benefits in patients having TNBC.

AFAP1-AS1

The AFAP1-AS1, a recently unearthed lncRNA, is the actin filament-associated protein 1 (AFAP1) antisense. This proto oncogene Src-binding partner executes the role in signalling cascade as an adaptor protein for Src family groups and other signalling proteins to the actin filament (Li et al., 2021). AFAP1-AS1 expression is positively associated in several cancers and linked with tumour morphology and staging of squamous carcinoma cells of oesophagus, lung, colon, and several others tumours for progression. In TNBC , AFAP1-AS1 expression is not properly regulated and related with bad prognosis and progressive phenotype of BC (Zhang et al., 2020). Nonetheless, knockdown of AFAP1-AS1 led to Ki-67 and matrix metalloproteinase downregulation. However, it upregulates the expression of Bax, thus leading to the suppression of tumour extension, albeit the particular targets of AFAP1-AS1 and the concerned signalling cascades in tumour growth and proliferation is yet to be defined. Yet other article substantiated that AFAP1-AS1 upregulation promoted extension and intrusion of TNBC cell by binding competitively to miR-145,sequentially, leading to MTH1 overexpression. Zhang et al., (2020) demonstrated overexpression of AFAP1-AS1 activates Wnt/β cantenin pathway promoting epithelial-mesenchymal transition (EMT) by enhancing the expression of C-myc. The positive association of AFAP1-AS1in TNBC, makes it a potential biomarker in TNBC.

MIR100HG

A study identified lncRNA MIR100HG regulates the p27 gene, which controls the cell cycle and, in turn, influences TNBC progression. As predicted by bioinformatics analysis, MIR100HG establishes an RNA–DNA triplex model that promotes cell proliferation and governs the CDKN1B gene to benchmark the cell synthesis in TNBC. The downregulation of MIR100HG halts G1 phase of cell cycle and decreases tumour invasion (Wang et al., 2018). This novel role of lncRNA MIR100HG in modulating TNBC progression might be a potential therapeutic benefit in such cancers (Wang et al., 2018). In contrast, another study revealed that MIR100HG knockdown inhibits tumour development in TNBC via miR-5590-3p/OTX1 axis. MiR-5590-3p inhibits TNBC growth and migration by targeting the *OTX1* gene, which is in charge for mammalian gland development and plays a role in the development of carcinoma of colon, rectum, urinary bladder, and hepatocellular origin (Chen et al., 2020). This novel role of lncRNA MIR100HG in modulating TNBC progression might be a potential therapeutic benefit in TNBC.

AWPPH

The lncRNA AWPPH (attributes to poor outcome in HCC) contributes to tumour growth in TNBC by upstreaming the FZD7 receptors of the WNT signalling pathway (Wang et al., 2018). AWPPH was found to be positively correlated with miRNA-21 in another study, TNBC patients' plasma levels of lncRNA AWPPH and miRNA-21 were found to be higher than healthy controls (Liu et al., 2019). Under carboplatin treatment, overexpression of this association caused cancer cell proliferation and increased cell viability in TNBC cells. In vitro studies have shown to regulate cell proliferation and chemo sensitivity in lncRNA AWPPH with miRNA-21 (Wang et al., 2018). Taken together, these key findings makes AWPPH a potential target in TNBC.

LINP1

LINP1(LncRNA In Non-Homologous End Joining Pathway 1) is coordinated by TP53. Therefore, TP53 and the TNBC-overexpressed Epidermal growth factor receptor (EGFR) regulating double-strand repair of the non-homologous end-to-end (NHEJ) pathway of DNA break are regulated by different lncRNA such as LINP1 (Zhang et al., 2016). TNBC exposure to radiotherapy can be improved by downregulating LINP1 (Zhang et al.,

2016). It has been stated that the LINP1 is an implicit lncRNA seeker that can play a role in apoptosis and damage feedback of DNA in TNBC (Zhang et al., 2016). Importantly, LINP1 can improve the activity of NHEJ by giving an arena for Ku80 and DNA-PKcs. After DNA break occurs, heterodimer consisting of the Ku80-Ku70 engages LINP1 to the destroyed DNA; LINP1 also balances the Ku80 and DNA-PKcs complex, enhancing the DNA repair activity mediated by NHEJ. Certain cells without LINP1 expression (e.g. MCF7) can undergo DNA repair through the NHEJ pathway, without the requirement of LINP1 for the NHEJ activity (Zhang et al., 2016). However, enforced expression of LINP1 in non-LINP1 expressing cells can augment NHEJ mediated DNA repair process. Essentially targeting and downregulating this implicit lncRNA LINP1 may provide a new therapeutic approach in TNBC.

MANCR

LncRNA MANCR (Mitotically-associated long non-coding RNA) is accountable for reduction in cell vi ability with a consequent rise in impaired DNA in TNBC. The increase in DDR and imperfect cytokinesis after the downregulation of MANCR, proposes the cytoprotective nature of MANCR in growth of TNBC (Kirsten et al., 2018). Transcriptome analysis, grounded on RNA sequencing (RNA-seq), after MANCR downregulation, expressed significant variations in the expression of transcripts greater than 2,000, and gene set enrichment analysis (GSEA) recognizes variations in different groups, concerned with cell cycle modulation (Tracy et al., 2018). In addition , in mitotic cells MANCR expression is maximum both in Real Time-qPCR and RNA in situ hybridization. Coherent in cell cycle regulation, MANCR-devoid cells possess a lesser mitotic index and increased defective cytokinesis and cell viability (Tracy et al., 2018). The lncRNA, MANCR, and aggressive BC genomic stability identify it as a capable treatment markers.

NEAT1

NEAT1 (Nuclear enriched abundant transcript 1) refers to be extensively expressed .in TNBC. An article has explored the carcinogenic part of NEAT1 in modulating cell death and cell programming. Reduction in NEAT1 expression with the help of shNEAT1 leads to sensitization of cells to chemotherapeutic drugs, decreases the stemness, and enhances cell death in TNBC (Shin et al., 2019). Therefore, variations in genes involved in apoptosis support chemotherapy-produced cell death, and regulation of non-coding RNAs leads to sensitization TNBC cells that are chemo-resistant. Another similar study has stated that lncRNA NEAT1 controls the proliferation and spread of BC cells by targeting CBX7 and RTCB (Li et al., 2021). Shin et al., (2019) explored that higher expression of lncRNA NEAT1 was linked with decreased mortality in BC patients. Moreover, lncRNA NEAT1 induced EMT and enhanced the growth and spread of BC cells by inhibiting miR-146b-5p expression. However, another study found that NEAT1 plays a role in chemo resistance and cancer stemness, implying that it could be used as a new clinical therapeutic target for TNBC patients, particularly drug-resistant (Shin et al., 2019).

ANKRD30A

ANKRD30A (also known as NY-BR-1 or B726P) encodes a DNA-binding transcription factor preliminarily seen in well-differentiated ER-positive and HER2-negative BC tumours. Also, ANKRD30A is recognised as a BC antigen in disseminated tumour cells (DTCs). It is at present very significant DTC biomarker denoting the presence of metastasis and a implicit marker for BC immunotherapy (Tracy et al., 2018). A study has validated a strong association between intergenic lncRNA LINC00993 and ANKRD30A gene expression. Both the genes are found on chromosome 10 adjacent to each other and are breast-specific. As per the study, structural features of ANKRDA30A indicate that it might interact with the LINC00993 as a transcription factor, showed mighty indication that expression of ANKRD30A gene may be epigenetic-target of the lncRNA LINC00993 (Tracy et al., 2018).

GATA3-AS1

GATA binding protein 3 antisense RNA 1 (GATA3-AS1) has been considered for therapy of advance stages of carcinoma in immunotherapy for the purpose of control of PD-1/PD-L1. However, it is not successful in few cancers as a result of "immune-escape". Nonetheless, the role of GATA3-AS1 in immune escape has been verified. Their downstream genes are regulated by, cytoplasmic lncRNA at the level of post transcription (Shin et al., 2019). A current study described if, PD-L1 through CSN5 was coordinated by GATA3-AS1 because an earlier study implied that CSN5 mediated the PD-L1 protein deubiquitinating level. A nearby GATA3-AS1 gene, GATA binding protein 3 (GATA3), was selected and detected (Shin et al., 2019). In the differentiation of T helper cells and the generation of functionally mature LTi cells, GATA3 has recently been documented as a regulator. This current study also elicited the role of GATA3-AS1 in controlling TNBC cell growth and metastasis and its underlying molecular mechanism (Shin et al., 2019).

HIF1 alpha

The hypoxia-inducible factor 1 alpha (HIF1A)-antisense RNA 2 (HIF1A-AS2) complex, linked to several cancers, including TNBC, plays a significant part in proliferation, metastasis, and multidrug resistance. Hydroxylation of proline instigates HIF-1α ubiquitination and decadence, which consequently leads to the decrease of the half-life of HIF-1 protein (Ebright et al., 2020). Recent studies have indicated that lncRNAs HIF1 alpha and AK124454 are linked with TNBC and are correlated with advanced disease and poor treatment outcomes. Both lncRNAs are greatly linked to G2-M arrest, that could be attributing to paclitaxel insensitivity in TNBC (Ebright et al., 2020). The stimulation of the HIF-1 pathway in breast cancer subtypes indicates that anaerobic pathways are entangled in HIF-1α management at the time of TNBC advancement. A study elucidated that HIF1A induces promyelocytic leukaemia protein (PML), which exerts pro metastatic function at multiple levels in TNBC metastatic

cascade (Ebright et al., 2020).

LINK-A

LINK-A is an intergenic lncRNA transcript of 1.5 kb, also known as NR015407 or LOC339535. Studies have described that LINK-A has been functionally correlated with worse prognosis and progression-free survival in TNBC malignancy patients (Lin et al., 2017). Another study has substantiated that LINK-A plays a vital part in HIF1 alpha cell signal transduction pathway mediated by growth factors. The expression levels of LINK-A in stage-III TNBC in ERPR+/HER2+, HER2-/ERPR+, and ERPR-/HER2+ breast cancer tissues, was highly significant than surrounding normal cell milieu, according to the study by Lin et al. [2016], pointing a affability of LINK-A with TNBC. It was also found that upregulated LINK-A is linked in TNBC with bad outcomes . Moreover LINK-As, are unique from other lncRNA, as they are situated by the side of cell membranes or in the cytoplasm. By activating the LINK-A-dependent signalling pathway, LINK-A could promote tumorigenesis in TNBC. Therefore, targeting LINK-A may give an optimal strategy to block the signaling pathway of HIF1 alpha in TNBCs. Whether LINK-As are constantly delivered into blood stream through cell death or emited through exosome pathways from TNBC cells requires detailing (Lin et al., 2017).

HOTAIR

HOTAIR is a non-coding transcript of 2.3 kb obtained from the HOXC homeotic gene cluster 12 intergenic region. HOTAIR was the rudimentary lncRNA to

Table 1. LncRNA as Predictive Biomarkers in Triple-Negative Breast Cancer (TNBC).

LncRNA	Role	Potential target	Clinical relevance	Reference
H19	upregulated	STAT3 and WNT Signalling pathway	Therapeutic target for metastases breast cancer, especially for TNBC	Li et al. 2020
DANCR	down regulation	PI3K/AKT	Potential therapy target for TNBC treatment	Tao et al. 2019
LINC00993	upregulated	Cell-cycle regulators	Diagnostics and therapeutic	Guo, et al. 2019
KLHDC7B	upregulated	Signalling pathway of interferon	Diagnostics and therapeutic	"Fredy 2019, Jeong 2018
MNX1-AS1	upregulated	p-JAK and Stat3	Upregulated in TNBC and correlated with poor survival outcome	Li et al. 2020
AFAP1-AS1	upregulated	Wnt/β cantenin pathway	Promotes TNBC cell proliferation and invasion	Zhang X et al. 2020
MIR100HG	upregulated	miR-5590-3p/OTX1 axis	Diagnostics and therapeutic of TNBC	Wang et al. 2018
AWPPH	upregulated	WNT Signalling pathway	Target able to promote tumor growth in TNBC by upregulating the FZD7 receptor	Wang et al. 2018
LINP1	upregulated	Ku80 and DNA-PKcs complex	Overexpressed and enhances double-strand DNA break repair in TNBC	Zhang et al. 2016
MANCR	upregulated	G2/M checkpoint	Potential therapeutic target of TNBC	Kirsten M et al. 2018
NEAT1	upregulated	miR-146b-5p	Therapeutic target for treating TNBC	Shin et al. 2019
ANKRD30A	upregulated	JAK/STAT	Potential target for immunotherapy of TNBC	ANKRD30A et al. 2015
GATA3-AS1	upregulated	PD-L1 protein	GATA3-AS1 in regulating TNBC cell growth and metastasis	Zhang et al. 2020
HIF1A	upregulated	alpha signalling pathway	Essential role in invasion, metastasis, and multidrug resistance	Ebright et al. 2020
LINK-A	upregulated	PI3K/GPCR; Akt; HIF1alpha	Promoting tumorigenesis in TNBC	Lin et al. 2016
HOTAIR	upregulated	Sox2 via miR-34a.	Diagnostics and therapeutic of TNBC	Collina et al. 2019
SNHG12	upregulated	STAT	Regulates cell proliferation, apoptosis and migration in TNBC	Wang et al. 2017
SnaR	down regulated	-	Inhibits cancer cell proliferation in TNBC patients	Niu et al. 2019
GAS5	upregulated	MDA-231R, miR-196a-5p	Diagnostics and therapeutic of TNBC patients	Zheng et al. 2020
PVT1	upregulated	KLF5/beta-catenin	Potential target for improving treatment of TNBC	Tang et al. 2018
POU3F3	upregulated	Caspase 9	Promote proliferation and inhibit apoptosis of cancer cells in triple-negative breast cancer	Yang et al. 2019
AC091043.1	upregulated	-	Strong diagnostic and prognostic value for predicting the existence of TNBC patients	Fan et al. 2019
FOXCUT	upregulated	β cantenin	Strong diagnostic and prognostic value for predicting the existence of TNBC patients	Fan et al. 2019
LINC00152	upregulated	PTEN axis	Overexpression predicts TNBC progression by affecting on stability of PTEN protein	Shen et al. 2018
LINC00993	upregulated	p53, and p21	Overexpression predicts a poor outcome of TNBC	Guo et al. 2019

cause malignancy and be linked to bad outcomes in BC (Cantile et al., 2020). HOTAIR expression in TNBC cells MDA-MB-231 and BT549 was greatly increased by oestrogen and promoted migration. HOTAIR concomitantly represses TNBC expressions of particular miRNA, incompletely reverses epithelial-mesenchymal transition (EMT), lowers the cancer stem cells, and hampers cell proliferation (Deng et al., 2017). According to Collina et al., (2019), HOTAIR expression is closely related to primary TNBC tumour tissues. This phrase is transcribed in an efficient manner using lapatinib and imatinib. This first one acts on EGFR/ErbB2, and the second one targets c-ABL, which binds to β-binding catenin's sites. Deng et al., (2017), also stated that Delphinidin-3-glucoside decreased HOTAIR expressions in TNBC cells both in vitro and in vivo. Many studies describe few concealed mechanisms connecting signalling modulation of HOTAIR in TNBC that can be utilised for treatment purpose (Zhang et al., 2020). This crucial mechanism of HOTAIR dysregulations provides current target for TNBC treatment.

SNHG12

Small nucleolar RNA host genes 12 (SNHG12), also known as LNC04080, is a lncRNA located at the p35.3 region on chromosome. It is ~1,867 bases long (7) and encodes four small nucleolar RNAs (SNORA66, SNORA61, SNORA16A, and SNORD99) from its spliced introns. Certain studies have indicated SNHG12 in many human cancers, including TNBC. The modified expression of SNHG12 has been linked with the survival, spread and expansion of tumour cells, influencing cancer patients' prognosis and mortality (Li et al., 2020). Current studies showed its participation in unfolded protein responses making it ideal as a therapeutic target (Li et al., 2020). Wang et al., (2017), utilized RNA sequencing to exploit the lncRNA expression profiles in TNBC and stated that upregulation of particular SNHG12 transcripts promotes growth inhibition and cell death in BC. SNHG12 levels were lowered considerably in BC. Hence, its downregulation may regulate cell invasion and spread (Li et al., 2020). Henceforth, SNHG12 can be a potent biomarker and a therapeutic drug target.

SnaR

RNA polymerase-III linked with nuclear factor 90 is transcribed by SnaR, a double-stranded lncRNA of 117nt (NF90). SnaR binds significant proteins connected by in vivo networking followed by immune-precipitation in multiple cellular functions, suggesting the likelihood that it has critical roles in controlling the initiation and progression of cancer (Niu et al., 2019). Several snaR transcripts are shared in the cytoplasm with ribosomes, and these regulatory functions are specific to the species and tissue in cell growth and gene translation. Niu et al. (2019), showed that lncRNA were strongly expressed in each cell line in BC cell lines based on molecular subtypes, snaR and ANRIL were identified as majorly increased in

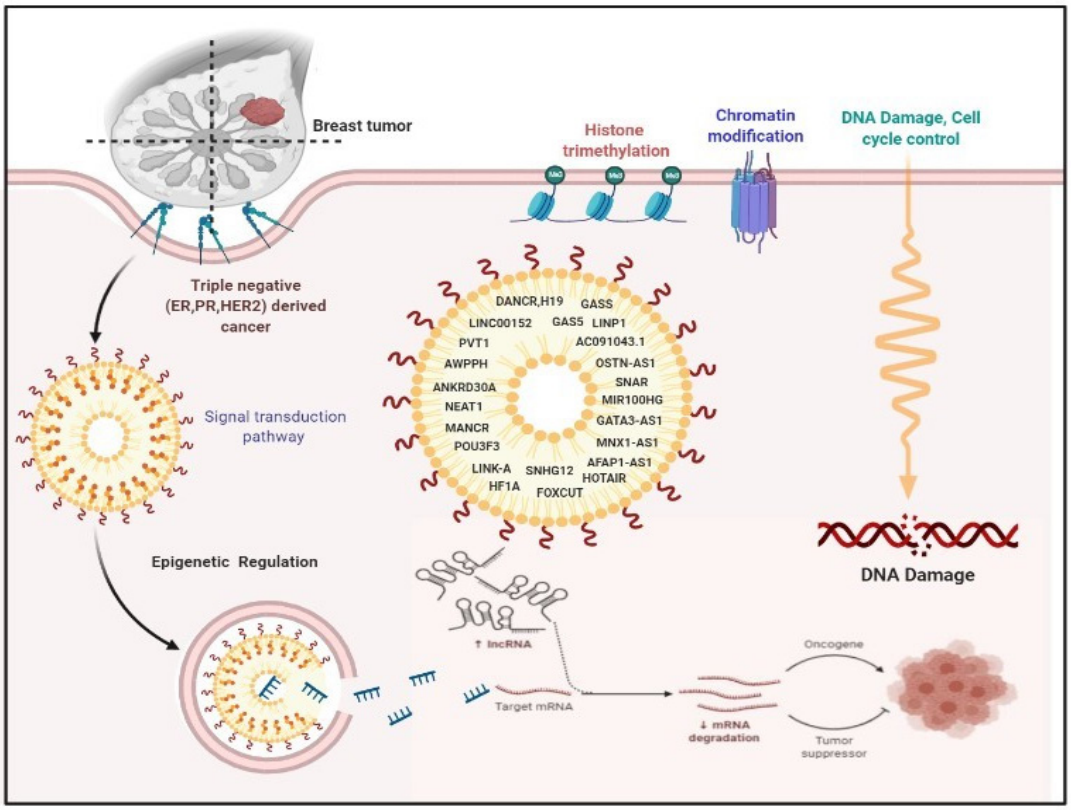

Figure 1. Triple-Negative Breast Cancer's lncRNA Mechanism. Understanding the mechanism of how lncRNA regulate transcription in breast cancer with regard to TNBC. The TNBC coregulatory factors are vital to the reactivation of histone trimethylation, chromatin modification, DNA damage, cell cycle control, and TNBC signalling in BC. This TNBC coregulatory network, which activates oncogenic genes while silencing tumour- suppressive ones, helps advance breast cancer.

MDA-MB-231 cell line and hormone receptor-expressing cell line (MCF7). Notably, snaR showed that the TNBC cells were highly expressed rather than in balance. After snaR-knockdown, the spread and metastasis of TNBC cells were considerably curbed. Hence, it would give a sweeping outcome the knockdown of snaR be therapeutically implied to TNBC.

GAS5

The growth-stasis specific transcript 5 (GAS5) lncRNA has been reported as a suppressor of TNBC development through inhibition of proliferation and invasion by competitively binding miR-196a-5p, therefore GAS5 may be a prognostic biomarker of TNBC. Li et al., (2018) showed that GAS5 expression promoted chemo sensitivity and apoptosis in TNBC cells. Aberrant methylation of the LncRNA promoter region is found to down-regulate LncRNA (Li et al., 2019). As a result, up-regulation of GAS5 can be inferred from unmethylation, which may make GAS5 a viable option for treating TNBC cells (Li et al., 2019).

PVT1

The plasmacytoma variant translocation 1 gene (PVT1) is a lncRNA that has carcinogenic role in several cancers. PVT1 is located ~50 kb downstream of MYC and is frequently co-amplified with MYC in colon, ovarian, lung, and BC. PVT1 was primarily identified to aid to tumorigenesis because of its subsequent translocations in mouse plasmacytomas (Li et al., 2018). PVT1 promotes KLF5/beta-catenin signalling to drive TNBC tumorigenesis. PVT1 is upregulated in clinical TNBC tumours. Recently a study reported that PVT1 prevented cell invasion, colony formation, and orthotopic xenograft tumour development (Wang et al., 2018). PVT1 binding with KLF5 causes KLF5 to stabilise and this elevates the BAP1 levels, which in turn promotes beta-catenin signalling, thus enhancing TNBC carcinogenesis (Li et al., 2018). PVT1 is significantly raised in TNBC patients. Also, in another study, PVT1 was found to promote drug resistance in the MDA-MB-231 cell line via preventing the degradation of Nrf2 (Li et al., 2018). Wang et al., (2018) identified PVT1 plays a major role in obesity-linked to breast cancer and accelerated MAM induced EMT, cell viability in TNBC cells via regulating p21.

POU3F3

The lncRNA POU3F3 (POU class 3 homeobox 3) was up-regulated in tumour tissues than in adjacent healthy tissues of TNBC patients (Yang et al., 2019). It has been stated that the lncRNA POU3F3 was significantly raised in TNBC patients than in healthy controls and negatively related with cleaved caspase 9 levels in TNBC patients only. Additionally, lncRNA POU3F3 may stimulate invasion and prevent death of cancer cells in TNBC (Li et al., 2019). Studies also noted that increased levels of lncRNA POU3F3 in plasma during diagnosis indicated bad prognosis and high mortality rate (Yang et al., 2019). Henceforth, lncRNA POU3F3 may play a pivotal role in predicting the disease prognosis in TNBC.

LINC00152

LINC00152 was called as cytoskeleton regulator RNA (CYTOR) and expressed in several cancers, including breast cancer. LINC00152, consisting of 677 base pairs , significantly elevated in TNBC tissues and several other cancers in relation to normal tissues multiple (Shen et al., 2019). Contemporary studies have illustrated, that YY1 modulated CYTOR, which in turn accelerated protein PTEN stability. YY1/LINC00152/PTEN axis provides crucial role in TNBC proliferation (Shen et al., 2019). Even though its role in TNBC proliferation is clear, further therapeutic application needs to be explored.

LncRNA as therapeutic targets in BC

As there is a paucity of knowledge about molecular targets for TNBC, chemotherapy is the only option for systemic treatment. Evolving studies showed that the expression of lncRNA provides a crucial part in the therapeutic resistance of TNBC, which necessitates understanding molecular regulation. Although lncRNA show very aggressive cancer activity, and their particular expression, as well as functionality, can help develop new ways to diagnose and treat TNBC, they have the potential to benefit basic research to be translated into clinical practice. Though there are only a few preclinical studies showing the potential of lncRNA in TNBC. Li et al., (2020) have shown that lncRNA H19 may be used as a therapeutic target for breast cancer, specifically TNBC since it causes carcinogenesis and metastasis.

In a study conducted by Tao et al., (2019), it was shown that the DANCR overexpressed in TNBC cells and is associated with the promotion of cell proliferation, invasion, and tumour- initiating cell characteristics. DANCR might function as a tumour promoter by targeting miRNA-216a-5p, which could potentially serve as a treatment target for TNBC. While LINC00993 is implicated in the formation and/or progression of TNBC, as reported by Guo et al., (2019). A second study was published revealing that the gene activity of TNBC is significantly associated with overexpression of KLHDC7B and can be exploited as a diagnostic and therapeutic option (Beltrán-Anaya et al., 2019). Li et al., (2020), have explored that the MNX1-AS1-> MNX1-AS2 of C7->C7 homolog is about 2.3 kbp long. Although they showed that the MIR100HG controls the p27 gene to govern the cell cycle, Wang et al., (2018), stated that it also impacts the course of TNBC, which they found to be associated with poor survival outcomes. AWPPH is known to upregulate the FZD7 receptor and accelerate tumor development in TNBC (Wang et al., 2018). Zhang et al., (2016), discovered that LINP1 expression was increased in TNBC and that this helped to repair double-strand DNA breaks. Manic disorder (MANCR) was shown to be elevated in tumour- cell genomic stability and can be identified as a potential therapeutic target of TNBC. NEAT1 upregulation enhanced the therapeutic utility of NEAT1 in the treatment of TNBC patients because it increased resistance to chemotherapeutic agents and cancer stemness (Shin et al., 2019). ANKRD30A is an upregulated target for TNBC treatment (FY Chen et al., 2020). In the article by Zhang et al., (2020), the GATA3-

AS1 was said to control cell proliferation and metastasis in TNBC.

Additionally, lncRNA are thought to be involved in various cellular processes, including those occurring in TNBC cells. The LINK-A protein is believed to help TNBC cells by making HIF1α more active and phosphorylated at the tyrosine 565 and serine 797 residues. Kirsten et al., (2018) explained that lncRNA MANCR had a substantial DNA damage inhibitory effect and regulated the integrity of the TNBC genome. Yang et al., (2019) has been reported that the upregulation of POU3F3 may stimulate invasion and prevent death of cancer cells in TNBC. However, the upregulation of PVT1 has been established as a new target for improving the treatment of TNBC (Li et al., 2018). Fan et al., (2019) stated that the upregulation of AC091043.1, LINC00993, LINC00152, and FOX CUT has strong diagnostic and prognostic value for predicting the existence of TNBC patients. Together, these research and current trials may provide a roadmap for the application of lncRNA in diagnostics and therapies in the context of TNBC.

Concluding Remarks and Future Perspectives

TNBC is a heterogenous pathological condition, and despite of numerous drug trials, TNBC patients lack a evident therapeutic effect. Therefore, TNBC is currently over and misdiagnosed since the available diagnostic and prognostic techniques are not very specific or sensitive. As a result, very sensitive biomarkers must be identified in order to properly stratify and treat these patients. LncRNA have currently been seen to play an eminent role in several cancers characteristics through interacting with other cellular macromolecules. Therefore, this study will provide insight into the roadmap of diagnostic and prognostics value for identification of aggressive and nonaggressive forms of TNBC apart, to help with stratification, management, and treatment options.

Understanding the mechanism of how lncRNA regulate transcription in breast cancer with regard to TNBC. The TNBC coregulatory factors are vital to the reactivation of histone trimethylation, chromatin modification, DNA damage, cell cycle control, and TNBC signalling in BC. This TNBC coregulatory network, which activates oncogenic genes while silencing tumour- suppressive ones, helps advance breast cancer.

AREAS COVERED

We review the key findings of the LncRNAs in TNBC, also emphasising primarily on their functional approach and molecular mechanisms.

HIGHLIGHTS

We have discussed the functional role and molecular mechanism of lncRNAs in TNBC and illuminated their potential implications in cancer diagnostics and therapeutics.

The characterizations of lncRNAs involved in TNBC is inadequate and validation studies are still required to authenticate the present results that would be the impending future of basic research setting into clinical practice (Li et al., 2018; Abdul-Rahman et al., 2018; Collina et al., 2019).

Author Contribution Statement

Conceptualization,G.G.,K.K.S.; methodology, G.G., K.K.S.; validation, G.G., K.K.S., S.M. S.S.; formal analysis, G.G., K.K.S.; resources, G.G.; data curation, all authors; writing—original draft preparation, G.G., K.K.S.; writing—review and editing, S.P., G.G., K.K.S.; visualization, ALL.; supervision, G.G., K.K.S. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

This work was realized in the framework of the international collaboration between All India Institute of Medical Sciences. Jodhpur, India and Federico II University, Italy.

Conflict of interest

The authors declare no conflict of interest.

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