JCOMS

http://journalofcoms.com

Journal of

Current Oncology and Medical Sciences

Vol. 1, No.2

Review Free Access

Variable performance of lncRNA in breast cancer

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Abstract

Introduction: Breast cancer, is one of most frequent cancers across women, is recognized as a diverse and difficult disease that continues to be a serious public health problem. Long non-coding RNAs have already attracted a lot of interest as a result of the advancement of next-generation sequencing methods. Various studies indicate that long non-coding RNAs play an essential part in tumor growth. Even though the biological purpose and molecular processes of long non-coding RNAs are still unknown, modern data has shown that a variety of long non-coding RNAs express inappropriately in malignancies, particularly breast cancer. This review highlighted the most recent research on long non-coding RNAs in breast cancer, with an emphasis on the many molecular functions of regulatory long non-coding RNAs.

Keywords: Breast cancer, Long non-coding RNA, Cell proliferation, Molecular mechanisms

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Received: 2021.11.17, Accepted: 2021.12.20

Introduction

The cancer susceptibility is to some extent due to the inheritance of significant genetic factors that vary depending on the type of cancer. Breast cancer is one of the most common causes of death in women, especially in industrialized countries (1). Breast cancer screening allows early detection of malignancy and ultimately reduced mortality. Although a variety of imaging techniques are commonly used to screen for breast cancer, they often lack sufficient sensitivity and diagnostic specificity (2). Therefore, access to appropriate, reliable, accurate, non-invasive, as well as cost-effective diagnostic methods is needed to identify breast tissue abnormalities. ncRNAs involved in cancer have been identified by a variety of techniques, including expression microarrays, tiling arrays, methylation analysis and next-generation sequence (3).

Biogenesis and roles of lncRNA in BC

One of the most influential factors in the development of cancer that is widely studied today is the genes that regulate cancer pathways. Recent advances in RNA biology show that non-coding RNAs are essential molecules (4). They have specific regulatory functions in the formation and progression of diseases, especially cancer. To organize the processes of lncRNA activity, numerous categorization systems have been developed. One of them categorizes lncRNAs into four items including signal, decoy, scaffold and guide (Figure 1).

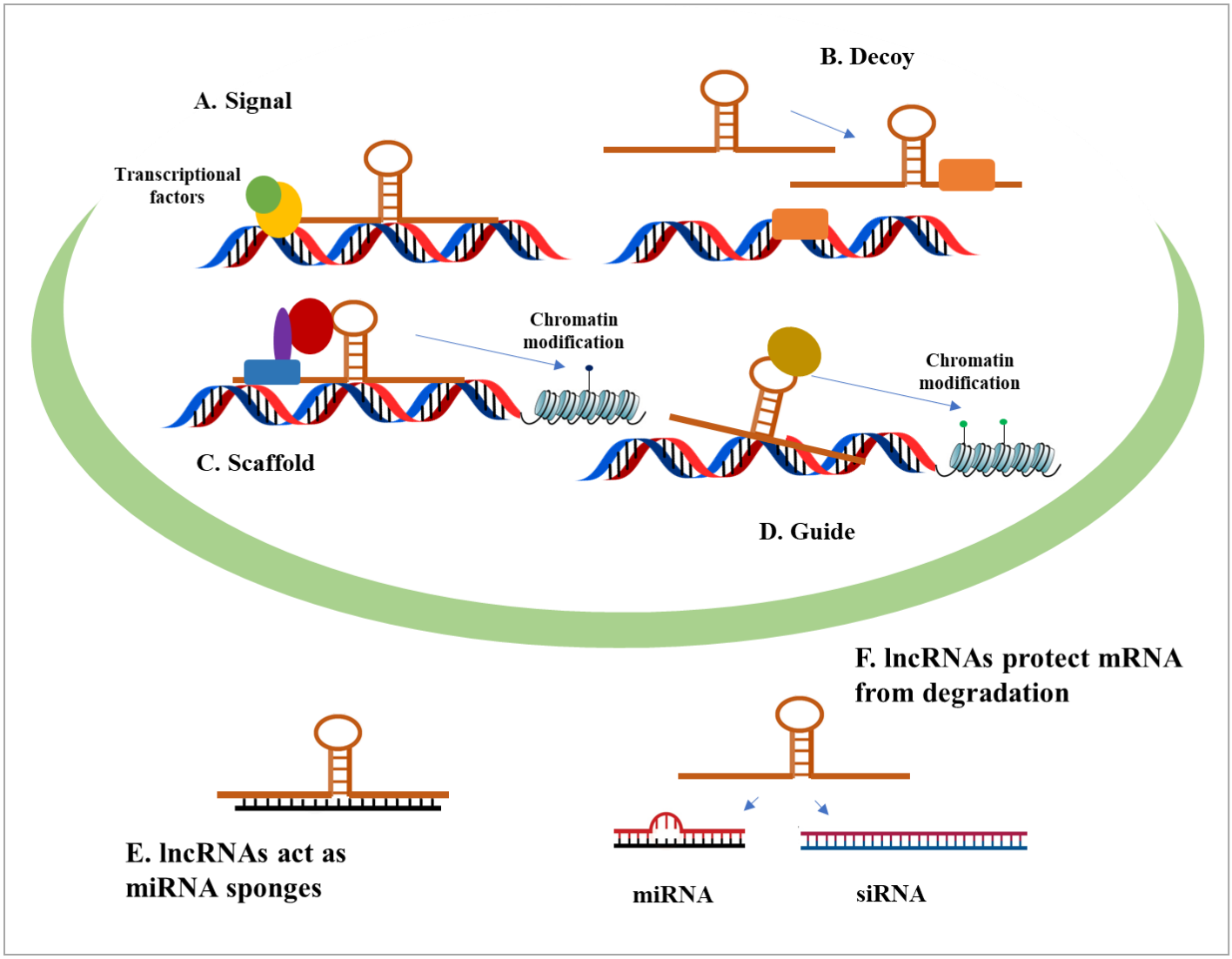

Figure 1. Roles of long noncoding RNAs (lncRNAs).

Breast cancer is the leading cause of death in women's health. Despite improvements in gene regulation of breast cancer, and even individualized therapies are being developed based on four molecular types (Luminal A, Luminal B, Her2 positive, and triple-negative breast cancer (TNBC)), but still failing to decrease the occurrence and overall death rate. Numerous long noncoding RNAs (lncRNAs) have been linked to breast cancer (3, 5). LncRNAs are a kind of ncRNA transcript that regulates gene expression at the transcriptional, translational, and post-translational stages; nevertheless, lncRNAs do not produce peptides or proteins, while being essential for cell types to work properly. LncRNAs perform their tasks in a variety of ways, such as interchromosomal contact mediation, functioning as sponges for endogenous RNAs, controlling mRNA decay, and altering epigenetic modifications that are steered to their destinations, among others (4, 6, 7). As a result, any variation in lncRNA expression levels can result in a variety of disorders, notably cancer (8). There is also abundant awareness that lncRNAs may control gene expression at the post-transcriptional stage. MiRNAs function as post-transcriptional controls of their messenger RNA (mRNA) targets via mRNA degradation as essential cytoplasmic controllers. There are a vast number of LncRNAs (9, 10). However, the transcripts of numerous forms of LncRNAs are not stable across specimens with comparable genetic links, and only around 200 types of LncRNAs have been studied in detail thus far. As a consequence, researchers are wondering if all LncRNAs have biological activities, and further study is needed to solve this topic. The majority of lncRNAs are found in the nucleus and chromatin, where they govern DNA sequences and are engaged in transcriptional regulation with various activities in the cytoplasm, while a subset of molecules is found in the cytoplasm as circulating lncRNAs, which are conveyed by exosomes (11).

LncRNAs can interact with a wide range of molecules, comprising transcription factors, mature mRNAs, chromatin-modifying complexes, RNA-associated proteins, DNA, nascent RNA transcripts, microRNA, and chromatin. LncRNA transcripts can bind to active proteins and determine their precise location (12). As a result, lncRNAs play critical roles in regulating gene expression at the epigenetic, transcriptional, and post-transcriptional stages. Different lncRNAs have been identified and studied in breast cancer that is involved in various processes of tumor formation, proliferation and cell migration. For example, ATB, HOXA-AS2 and CCAT2 increase expression in tumor tissues compared to margin tissues, resulting in increased proliferation, cell migration, and metastasis (13) (Table 1).

lncRNAs	Rols	Ref
NKILA	Epithelial mesenchymal transition	(14)
XIST	Cell growth and metastasis	(15)
PTENP1	Migration and proliferation	(16)
ANCR	Metastasis and invasion	(17)
MEG3	Epithelial-mesenchymal transition and proliferation	(18)
PDCD4-AS1	Progression	(19)
MAGI2-AS3	Cell growth	(20)
Lnc015192	Epithelial-mesenchymal transition, invasion and migration	(21)
GACAT3	Proliferation	(22)
CHET1	Invation, proliferation and migration	(23)
TUG1	Apoptosis, migration and proliferation	(24)
PVT1	Proliferation	(25)
ATB	Epithelial mesenchymal transition	(26)
NNT-AS1	Progression	(27)
NEAT1	Metastasis	(28)
UCA1	Metastasis	(29)

Retinoblastoma tumor suppressor (RB) is an important regulator of the cell cycle and a large number of processes associated with tumor growth. Functional inactivation of RB has been identified sporadically in many human tumors, which is involved in the onset or progression of the disease. Numerous studies have now shown that the disappearance of this tumor suppressor creates a selective vulnerability that can be therapeutically targeted and thus provide an accurate approach to exploiting RB deficiency (30, 31).

RB is believed to be inactivated as a result of two different mechanisms in breast cancer. One of these mechanisms is the loss of RB gene as a result of homozygous deletion in breast cancer of triple-negative type and the second pathway is through phosphorylation by CDK4/6 (32).

HOTAIR expression is significantly increased in breast tumors, and measuring its levels is a defining indicator in the diagnosis of primary breast tumors, the likelihood of metastasis occurring, and patient survival. LncRNAs are categorized into two groups based on their involvement in the development of BC, those that stimulate the development of BC and those that hinder the development of BC (33). The role of HOTAIR in breast cancer metastasis has been demonstrated. By targeting the PRC2 set and directing it to a specific gene set, it reinforces the expression patterns that promote aggression and migration. HOTAIR expression is increased 2,000-fold in metastatic breast cancer specimens (1, 34).

The function of H19 has also been demonstrated in the development of metastases, including in breast cancer. SNP rs2107425 in the intron 1 of H19 gene is significantly associated with short-term survival without metastasis (35).

Whether they stimulate or hinder the formation of BC, their mechanism of action typically encompasses the following aspects, influence BC cell proliferation and apoptosis, influence BC cell invasion and influence BC cell treatment resistance (36).

Several LncRNAs stimulate the growth of BC, and their roles have been studied in the preliminary stage. It aids in the development of more effective methods for diagnosing BC, determining its prognosis, forecasting its origin, and interfering with therapy. Mechanisms associated to these LncRNAs will be discussed in detail below (37).

Up to this point, many LncRNAs that limit BC formation have already been thoroughly investigated. They have been shown to primarily impede BC formation by reducing proliferation or promoting apoptosis (38).

Negatively affecting BC cell migration and invasion

Researchers discovered a novel LncRNA called NF-KappaB associating LncRNA (NKILA). It is elevated by NF-B and connects to NF-B/IB to form stable composites that effectively cover the phosphorylated structural regions of IB. As a result, IKK (IB kinase) triggered IB phosphorylation and NF-B activation (39). Furthermore, NKILA may inhibit excessive NF-B activation in mammary epithelial cells in response to inflammatory stimuli. NKILA may increase apoptosis and decrease invasion in MDA-MB-231 cells. To summarize, NKILA may limit BC proliferation and metastasis via suppressing NF-B function (40).

As a result, certain lncRNAs may hinder the genesis and maintenance of BC. In respect of function, it primarily inhibits the genesis and growth of BC by lowering proliferation of BC cells, encouraging apoptosis of such cells, and preventing cell invasion and metastasis (41). Nonetheless, few LncRNAs have now been identified to be efficient for suppressing BC, and even fewer were studied in terms of their reaction mechanisms (42).

Conclusion

Previously assumed to be transcriptional background, lncRNAs, like miRNAs, are now generally recognized as key regulators of gene expression and cancer. The lncRNAs are prospective strategies for human cancer detection, treatment, and therapy. Surprisingly, abnormal lncRNA expression is linked to breast cancer. In contrast to protein-coding mRNAs and miRNAs, our comprehension of lncRNAs is still in its early stages. There is a major gap in the understanding of lncRNAs. It's unclear if aberrant lncRNA expression is a factor or a result of carcinogenesis. As a result of the growing amount of lncRNAs discovered, their biological activities and methods of action in cancer deserve additional investigation. There are a lot of lncRNAs in the bloodstream. Nevertheless, research into circulating lncRNAs in cancer is still in its initial phases. A considerable study is required before circulating lncRNAs may be used as diagnostic, prognostic, or therapeutic indicators. Finally, the identification of lncRNAs has led to advances in cancer study. lncRNAs have the potential to play a key role in cancer screening, prognosis, and treatment advancement, aiding patients with breast cancer and others.

Author contributions

SV, **FN**, **MKh**, and **HEK** wrote and compiled this article. **SV** wrote and edited the manuscript comprehensively. All authors confirmed the final version of the paper.

Conflict of interest

The authors declare that they have no conflicts of interest.

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