

Original Analysis

# Investigating the structure and function of Long Non-Coding RNA (LncRNA) and its role in cancer



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## Article info

Received: 02 Mar 2022

Revised: 22 Jun 2022

Accepted: 12 Aug 2022

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## Keywords:

LncRNA, Molecular Reactions, Cancer, Therapeutic Target

## ABSTRACT

Cancer is one of the most complex and common diseases affected by many factors. In recent years, many studies have been conducted on the genetic characteristics of cancer, among which we can mention lncRNA Long Non-Coding RNAs, which effectively eliminate cancer tumors. LncRNAs are non-coding protein transcripts with a length of more than 200 nucleotides that react with other molecules through their unique structure and affect many cellular processes and chemical reactions in this way; they act as tumor suppressors and oncogenes in tumorigenic responses. On the other hand, lncRNAs play an essential role in cell proliferation, apoptosis, regulation of gene expression at different epigenetic levels of transcription, post-transcription, and interaction of molecules with other vital factors such as DNA, proteins, and other RNAs. Some lncRNAs can react with enzymes that change the state of chromatin and increase the transcriptional activity of some genes or turn off another group of genes. Also, lncRNAs are present in essential processes such as directing ribonucleoprotein complexes, regulating alternating processing, and maintaining the state of multipotency. Examining the function of lncRNAs has greatly impacted the early diagnosis and treatment of cancer cells. This review closely examines recent research on the use of lncRNAs in progression as clinical biomarkers and promising therapeutic targets in cancer.

## 1. Introduction

The Human Genome Project showed that only 2% of the human genome is dedicated to protein-coding genes; subsequent studies showed that more than 80% of active transcription regions depend on Non-Coding RNAs [1]. In general, Non-Coding RNAs are divided into 5 different groups:

Long-ncRNAs, Short-ncRNAs, tRNAs, rRNAs, and other RNAs (figure 1). ncRNAs are divided into two groups based on length: Short-ncRNAs and Long-ncRNAs [1, 2].

Short-ncRNAs include microRNA (miRNA) and PIWI-interacting RNA (piRNA), whose length is between 21 and 30 nucleotides, and small nuclear RNA (snRNA) and small nucleolar RNA (snoRNA),

whose length is between 30 and 170 nucleotides. Long-ncRNAs include enhancer RNA (eRNA), intra- and inter-genic RNA, sense RNA (sRNA), and antisense RNA (asRNA), which usually have a length of more than 200 nucleotides. Also, new types of RNA have been discovered by scientists, they were called circular RNA (circRNA), and research on them is progressing rapidly [1, 2].

In the last 15 years, new studies have been started in the field of ncRNAs, which clarifies their role in many diseases and effective mechanisms in cancer and the biological connection of cells [1]. In 2013, Zhou et al. estimated the total number of human lncRNAs to be 15,857 [2]. The production of these molecules is mostly influenced by transcriptional regulation, and some of them are

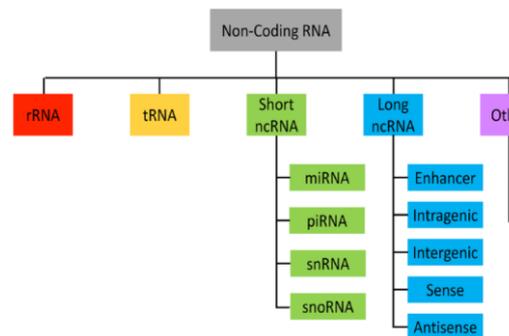
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transferred from the nucleus to the cytoplasm after processing. Some lncRNAs can produce small peptides, but most of them are never translated. There is a wide molecular relationship between lncRNAs, proteins, and miRNAs, which play an important role in gene expression and protein production [3]. This review article deals with the characteristics of lncRNAs in all types of cancers and the important implementation approaches of these molecules in the processes determining cell fate.



**Fig. 1.** Classes and types of ncRNA [1]. This figure is under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 2. lncRNAs

lncRNAs may exist in the cytoplasm or the nucleus and are transcribed by RNA polymerase II. Most of the lncRNAs are affected by the polyadenylation process and often have epigenetic marks and change the state of chromatin. lncRNAs are processed through their defined processing site motifs [3]. In general, lncRNAs are under the influence of special transcription factors, have a special expression pattern, and often have a low expression [4]. Many lncRNAs play an active role in cancer-related reactions. Table 1 shows several lncRNAs related to cancer types and their special characteristics.

### 2. 1. UORFs in lncRNAs

The upstream open reading frames (uORFs) in lncRNAs play an important role in regulating gene expression and stability of lncRNAs [6]. These uORFs are translated so that the transcribed lncRNAs survive ribosomal scanning and can perform their functions in the cytoplasm without the intervention of ribosomes. These uORFs can also direct factors to the ribosome. These uORFs can also affect RNA degradation pathways, such as degradation by non-sense mediated decay [7].

## 2. 2. Evolutionary lncRNAs

Many non-coding RNAs such as microRNA and snoRNA are highly conserved among different species. At the same time, lncRNAs are generally less conserved, which means that lncRNAs are more flexible than other RNAs against environmental changes. Today, it is known that lncRNAs can play an important role in the process of natural selection and evolution of organisms due to their flexible and semi-conserved properties [8].

## 2.3. Structural features of lncRNAs

lncRNAs do not have a special structure. They are usually shorter than protein-coding genes and have fewer exons. Transcription regulation, processing signals, and chromatin change patterns in them are similar to protein-coding genes [9]. Most lncRNAs have repetitive elements that play an important role in their function. Most of the lncRNAs are affected by the polyadenylation process. There are about 80 circular lncRNAs in humans. The stability of lncRNAs is done in two ways [10]:

1. helical structures of the 3'-end
2. Due to snoRNA molecules at both ends 3' and 5'

The secondary structure of lncRNAs is such that the more organized the lncRNAs are (the higher the amount of C and G), the more stable they are and the lower the expression level [11]. lncRNAs play an active and effective role in many reactions. Diagnosis and prognosis in cancer, metastasis, use as medicine, activity in alternating processing, maintaining multipotency, and role in cell cycle and apoptosis are among the things that are controlled by lncRNAs [12] (Figure 2).

## 2. 4. The expression level of lncRNAs

The comparison of lncRNAs and mRNAs shows that the amount of expression variation in lncRNAs is relatively higher. The expression level of lncRNAs in the testis and brain is higher than in other body organs [13]. Studies have shown that lncRNAs and mRNAs have the same half-life [14]. In general, lncRNAs can be found in a wide range of intracellular components, such as the nucleus and cytoplasm; for example, lncRNAs such as Xist, MALAT-1, and HOTTIP are located in the nucleus, and lncRNA SENCER in the cytoplasm [15]. Studies by Heesch et al., some lncRNAs exist in the nucleus, while most lncRNAs with important and vital functions are found in the cytoplasm and ribosomes [16].

**Table 1.** LncRNAs related to cancer types and their special characteristics [5]. This table is under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

lncRNA	Molecular reactions	Cancer phenotype	type of cancer	performance
HULC	Unknown	Unknown	Hepatocellular	Marker
PCA3	Unknown	Unknown	prostate	Marker
ANRIL/P15as	Connecting to the Polycomb Group 1 (PcG1) suppressor Connecting to the Polycomb Group 2 (PcG2) suppressor	Suppression of senescence by INK4A	Prostate/ Leukemia	Oncogene
HOTAIR	Connecting to the Polycomb Group 2 (PcG2) suppressor	Development of metastasis	Hepatocellular/ breast	Oncogene
MALAT1/NEAT2	Cooperation in nuclear formation and operations	Unknown	Prostate/ breast/lung/ colon	Oncogene
PCAT-1	Unknown	Strengthening cell proliferation/ BRCA2 inhibition	prostate	Oncogene
PCGEM1	Unknown	inhibition of apoptosis/ Strengthening cell proliferation	prostate	Oncogene
TUC338	Unknown	Strengthening cell proliferation and colony formation	Hepatocellular	Oncogene
uc.73a	Unknown	inhibition of apoptosis/ Strengthening cell proliferation	Leukemia	Oncogene
H19	Unknown	Development of growth and cell proliferation/ With long-term cell proliferation, its expression decreases	Hepatocellular/ breast	Oncogene/ Tumor suppressor
GAS5	binding to the glucocorticoid receptor	Induction of apoptosis and growth arrest/ Prevention of glucocorticoid receptor-mediated gene expression	breast	Tumor suppressor
linc-p21	Binding to ribonucleoprotein hnRNP-K	Mediation of P53 signaling/Apoptosis induction	Lymphoma/ Sarcoma/ lung	Tumor suppressor
MEG3	Unknown	Mediation of P53 signaling/ Inhibition of cell proliferation	Meningioma/ pituitary/ Leukemia/ Hepatocellular	Tumor suppressor
PTENP1	Unknown	Binding to PTEN repressor microRNAs	Prostate/ colon	Tumor suppressor

## 2. 5. Role of lncRNAs in cell cycle and apoptosis

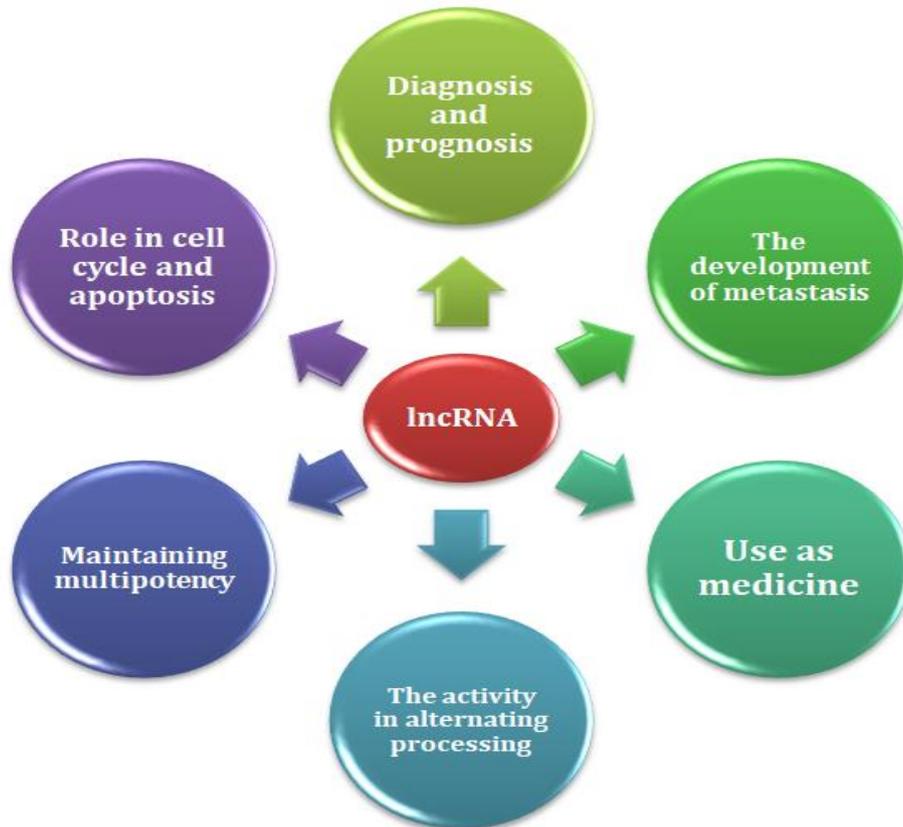
Apoptosis is programmed cell death and many factors are effective in its occurrence [17]. LncRNAs play an important role in controlling growth and apoptosis through cell cycle regulation. Gas5 (Growth arrest specific5) is one of the types of lncRNAs that accumulates in cells with growth arrest and sensitizes cells to apoptosis by

suppressing glucocorticoid-responsive genes [18]. Gas5 prevents the activation of anti-apoptotic genes by preventing the binding of glucocorticoid-reactive elements to their binding site in DNA and suppresses the transcriptional activity of this receptor (Figure 3 A) [19].

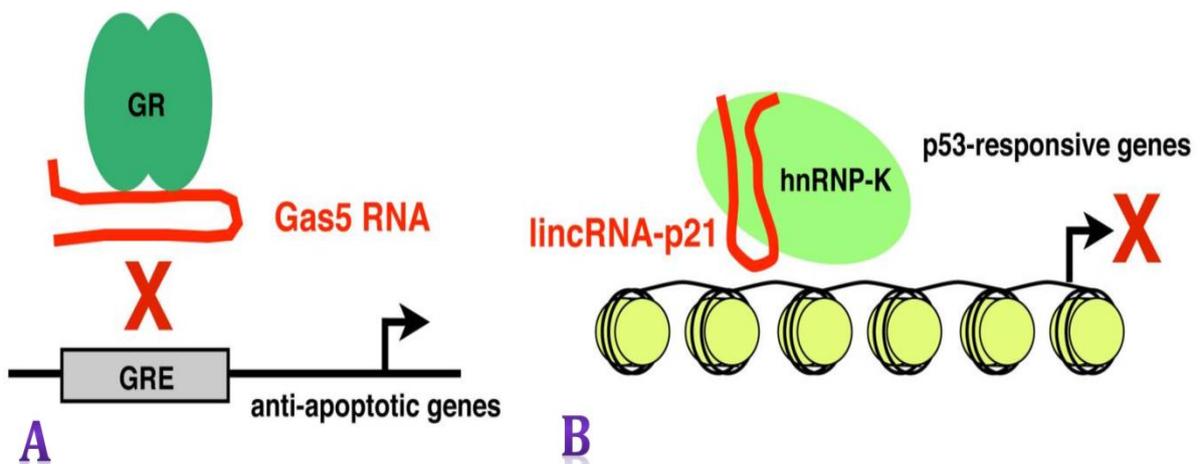
The P53 gene is one of the most famous tumor suppressor genes, which is mutated in more than

50% of human cancers. This gene plays an important role in tumor suppression by inducing apoptosis and stopping the cell cycle. LincRNA-P21 is activated by the P53 factor, plays an important role in the P53 pathway, and activates apoptosis. Suppression of transcription and deactivation of ribosomes in many nerve cells is done through the

binding of LincRNA-P21 to the nuclear ribonucleoprotein factor called hnRNP-K (Figure 3 B) [20].



**Fig. 2.** The roles of lncRNAs in diagnosis and prognosis in cancer, the development of metastasis, use as medicine, the activity in alternating processing, maintaining multipotency, and role in cell cycle and apoptosis



**Fig. 3.** A) Gas5 lncRNA suppresses the transcription of anti-apoptotic genes induced by glucocorticoid receptors and sensitizes the cell to apoptosis. B) LincRNA-P21 in binding with hnRNP-K suppresses the transcription of P53 responsive genes.

## 2. 6. The activity of lncRNAs in alternating processing and maintaining multipotency

LncRNA MALAT-1 (Metastasis-associated lung adenocarcinoma transcript 1) plays a vital role in the alternating processing of pre-mRNA. Since multiple proteins with non-overlapping functions are made in the alternating processing of an mRNA, MALAT-1 provides a molecular scaffold for the function of these proteins. MALAT-1 processes pre-mRNAs through the phosphorylation of SR proteins rich in serine, arginine, and threonine [21].

The ability of stem cells to transform into all three germ layers (endoderm, mesoderm, and ectoderm) is called multipotency. LncRNA-RoR, 26 LncRNAs, and two types of lncRNAs regulated by transcription factors Oct4 and Nanog, and LncRNA ANCR (Anti-differentiation non-coding RNA) are effective in maintaining multipotency [22].

## 2. 7. Application of lncRNAs as drugs

Since lncRNAs cause the absorption of microRNAs, they can be used as drugs to absorb microRNAs and proteins attached to them to enter the cell and return it to its normal state. This method can usually treat diseases such as cancer and return the cell to its original state [23]. PRNCR1 (prostate cancer-associated non-coding RNA 1) and PCGEM (prostate-specific transcript 1) react with androgen receptors and enhancer regions in DNA and increase the ability of transactivation by activating the oncogene factor. The results have shown that both of these lncRNAs can be suggested for treating advanced prostate cancer [24].

Urothelial Cancer Associated 1 (UCA1) is a lncRNA that has an inhibitory effect on cisplatin-induced apoptosis in bladder cancer cells and induces tumorigenesis. Therefore, they can be used as a new therapeutic target [25].

## 2. 8. The role of lncRNAs in the development of metastasis

Metastasis is a multi-stage genetic and epigenetic process that causes the development of malignant cells and the induction of secondary tumors in the body [26]. Some lncRNAs are

capable of inducing and developing metastasis through cascade regulation of metastasis and interaction with these factors [27].

MALAT-1 lncRNA was first identified in connection with metastasis and is located in the nuclear speckle. MALAT-1 controls the mRNA output of molecules involved in metastasis and carcinogenesis. Also, this lncRNA controls the cell cycle and organizes the extracellular skeleton [28].

H19 lncRNA is also involved in developing metastasis in bladder and breast cancer. Studies have shown that the expression of H19 in bladder cancer increases in the early stages of the tumor and is associated with metastasis in the later stages [29].

The role of HOTAIR has also been proven in the metastasis of breast cancer, gastric and intestinal stromal tumors, hepatocellular cancer, and lung cancer. Studies have shown that the expression of HOTAIR increases 2000 times in breast cancer samples. HOTAIR in gastric and intestinal stromal tumors along with the PRC2 factor, due to its special function, causes a significant decrease in the expression of 144 genes [30].

Also, using the RNA sequencing method in the study on 102 samples taken from prostate cancer, which was carried out to evaluate lncRNAs. These studies led to the identification of 121 transcripts with uncertain function, the expression of each of which was changed in benign and metastatic samples [5].

## 2. 9. Using lncRNAs for cancer diagnosis and prognosis

The discovery of lncRNAs is a key factor in cancer development and provides a new perspective for using these molecules as diagnostic and therapeutic targets. The number of lncRNAs used as biomarkers in diagnosis and prognosis is increasing every year, and some of them have been approved for clinical use. LncRNAs such as MALAT-1, HOTAIR, and ANRIL are expressed in a restricted manner in cancer and can be used as useful prognostic markers. Figure 4 shows a number of lncRNAs with diagnostic and prognostic applications in cancer [23].

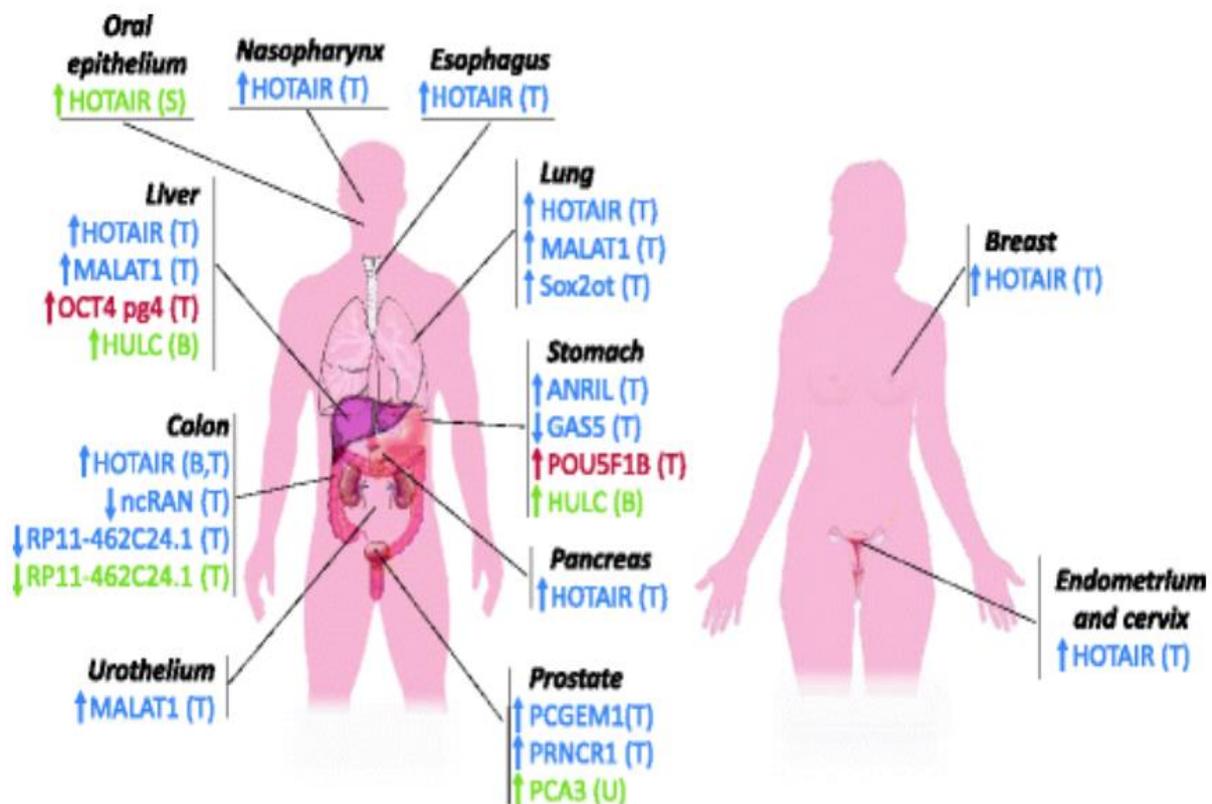


Fig. 4. Some lncRNAs used in cancer diagnosis and prognosis [23]

### 3. Conclusion

lncRNAs interact with other molecules through their molecular structure and thus affect many important cellular processes. The description of the function of lncRNAs in various cellular pathways is very extensive. With these interpretations, providing an accurate definition of lncRNAs is still controversial. Due to the complexity of the types and functions of these molecules among different species, it is still difficult to fully understand their activities. With the increasing tendency towards the study of lncRNAs, a deeper understanding of these molecules is gradually achieved. To further clarify the regulatory roles of these molecules, the emergence of RNA photography technologies with high operational power and tools for detecting binding patterns between lncRNAs with protein, RNA, and DNA with high resolution are needed.

lncRNAs have vital functions in controlling cells' growth, division, and differentiation, and disruption of the expression of these molecules plays an important role in cancer. However, a large proportion of cancer cases are related to the heredity effects of this disease, and the genetic components of cancer remain largely unknown. In recent years, the use of lncRNAs and agents created by them has developed an effective and effective approach to cancer treatment. Therefore,

it seems necessary to study the mechanisms of lncRNAs and the factors created by them.

Mechanisms of gene therapy are carried out to investigate lncRNAs in cancer treatment. Also, the review of bioinformatics algorithms to provide comprehensive explanations about the secondary structures of lncRNAs, identify interactions with other RNAs and proteins, and evaluate tissue characteristics and intracellular localizations, will strengthen our understanding of the regulation pathway of lncRNAs [14]. In general, the risk of cancer can be largely attributed to lncRNAs that are transcribed from the critical sites of cancer. It is hoped that with the progress in new biotechnology methods based on lncRNAs, a useful step will be taken in the direction of early diagnosis and effective treatment strategies.

### Abbreviations

asRNA: antisense RNA  
 circRNA: circular RNA  
 lncRNAs: Long Non-Coding RNA  
 miRNA: microRNA  
 piRNA: PIWI-Interacting RNA  
 sRNA: sense RNA  
 uORFs: upstream Open Reading Frames

### Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

### Informed Consent

The authors declare not to use any patients in this research.

### Ethics approval and consent to participate

No human or animals were used in the present research.

### Consent for publication

All authors read and approved the final manuscript for publication.

### Availability of data and material

All the data are embedded in the manuscript.

### Funding

There was not any financial support for this study.

### Author contributions

All authors are equally involved in the preparation of this manuscript and endorse the manuscript.

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Alsaedy HK, Mirzaei AR, Alhashimi RAH (2022) Investigating the structure and function of Long Non-Coding RNA (LncRNA) and its role in cancer. *Cellular, Molecular and Biomedical Reports* 2 (4): 245-253. doi:10.55705/cmbr.2022.360799.1062

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