

## The role of long, non-coding RNA in the biology of tumors

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### ABSTRACT

One of the most significant events in recent years in the field of molecular biological research has been the recognition of the biological significance of non-coding ribonucleic acid (RNA). It turned out that a significant part of the non-coding part of the genome, which constitutes 98% of the genome, is rewritten. In addition to small RNAs (such as microRNAs (miRNA)), long non-coding RNAs (lncRNAs), which are a large group of non-coding RNAs (ncRNAs) over 200 nucleotides in length, have been discovered. They play a role in the regulation of a number of basic molecular processes (cell division, chromatin function, microRNA activity, etc.). Many of these long non-coding RNAs were expressed in tumors compared with healthy tissues, for example, H19, HOX antisense intergenic RNA HOX (HOTAIR), Metastasis Associated Lung Adenocarcinoma Transcript 1 (MALAT1). A large amount of evidence revealed their roles at all stages of carcinogenesis and in modulating metastasis through regulatory networks. Aberrant expression of lncRNAs has been observed in cancer patients. In this context, lncRNAs can regulate the main characteristics of cancer cells by controlling gene expression programs associated with their suppressive and oncogenic functions. Therefore, they can be excellent biomarkers and therapeutic targets for tumors.

**Keywords:** genome, long non-coding RNA, tumor, miRNA.

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## Роль длинных некодирующих РНК в биологии опухолей

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### РЕЗЮМЕ

Одним из наиболее значительных событий в последние годы в области молекулярно-биологических исследований стало признание биологической значимости некодирующих РНК. Оказалось, что значительная часть некодирующей части генома, которая составляет 98%, перезаписана. Помимо небольших РНК (таких как микроРНК) известно о длинных некодирующих РНК (lncRNAs), которые являются большой группой некодирующих РНК (ncRNAs) длиной более 200 нуклеотидов. Они играют роль в регуляции ряда основных молекулярных процессов (деление клеток, функция хроматина, активность микроРНК и т.д.). Многие из этих длинных некодирующих РНК были экспрессированы

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в опухолях по сравнению со здоровыми тканями, например H19, HOTAIR, MALAT1. Большое количество исследований выявило их роль на всех стадиях канцерогенеза и в модулировании метастазирования через регуляторные сети. Была замечена aberrantная экспрессия lncRNAs у больных раком. В этом контексте lncRNAs могут регулировать основные характеристики раковых клеток, контролируя программы экспрессии генов, связанные с их супрессивными и онкогенными функциями. Следовательно, они могут быть отличными биомаркерами и терапевтическими мишенями при лечении опухолей.

**Ключевые слова:** геном, длинная некодирующая РНК, опухоль, микроРНК.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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## INTRODUCTION

In recent years, we have witnessed radically new directions in the field of molecular biology. Among them, a new interpretation of the world of ribonucleic acids (RNA) is of great importance, in which new regulatory mechanisms led to the discovery of previously unknown aspects of the genome, cells, and organism [1, 2]. The wider use of bioinformatics methods is significant in expanding our knowledge. In addition to protein-based messenger RNAs (mRNAs), RNAs that do not encode proteins are becoming increasingly important. Epigenetic pathways that are not associated with a change in the nucleotide sequence play a primary role in the molecular mechanisms of these molecules. Among non-coding RNAs, there is growing evidence of the importance of small RNAs, including microRNAs (they are mature, 18–24 nucleotide single-stranded RNA fragments: important elements of post-transcriptional regulation). Their various expressions have been described in many diseases, and the role of miRNAs in the molecular biological aspects of neoplasms has already been proven [3]. In addition to microRNAs, it is known that a number of other small RNAs play a key role in supporting basic molecular processes, such as splicing during mRNA maturation, telomere maintenance, centromere control, and genome stability. The former “central dogma” of molecular biology has been changed in several respects, and the role of RNA in the regulation of cell and genome functions can be shown at many levels [2]. One of the most shocking results of the next generation sequenc-

ing methods, which revolutionized research in the field of molecular biology (deep sequencing), was that a significant part (70–90%) of the non-coding part of the genome is transcribed into RNA [4, 5]. For example, an RNA aggregate transcribed from the mouse genome (transcript) may consist of 180,000 RNA molecules, of which only 20,000 encode proteins [1]. The functions of most non-coding RNAs are currently largely unknown. Non-coding RNAs can mainly be divided into two groups: small RNAs (microRNAs, transport RNAs associated with PIWI RNAs, telomeric RNAs associated with the RNA promoter, small nucleolar RNAs, etc.); and a class of long non-coding RNAs up from a size of 200 nucleotides. Although there is a lot of data on small RNAs, especially microRNAs, much less is known about the importance of long non-coding RNAs [5–7]. In this short review article, we are trying to present a very new and rapidly developing direction. Unfortunately, for most of the terms mentioned, there are currently no Russian equivalents, so we used English terminology.

## CHARACTERISTIC OF lncRNAs

The biological function of several lncRNAs, which play a role in the regulation of basic molecular biological processes, is described. They include regulation of gene expression and genome function, which can be positively and negatively affected by protein binding, including transcription factors, to affect chromatin structure and function. Regulation of the ratio of transcriptionally active euchromatin to inactive heterochromatin, modification of histone proteins (including methylation and phosphoryla-

tion) give greater importance to lncRNAs. They can participate in these processes as molecular scaffolds [5]. In addition, lncRNA genes express themselves weaker than the coding genes, and their expression is particularly specific for certain tissues. Depending on their position relative to the coding genes, lncRNA can be divided into two broad categories: intergenic lncRNAs and intragenic lncRNAs. Intergenic localized by definition in unannotated regions of the genome are commonly referred to as lincRNA. On the other hand, intragenic lncRNAs can be subdivided depending on how they overlap the coding genes or their orientation in relation to them (antisense, intron, etc.). Many lncRNAs have an antisense sequence complementary to other sequences, and it is also known that some of the promoters that regulate gene expression also allow bidirectional transcription [4]. The binding of antisense lncRNA to complementary RNA can lead to the formation of double-stranded RNA, which is the fundamental substrate for the RNA interference process and can lead to the appearance of small interfering RNA (siRNA) during the general maturation of miRNAs. SiRNAs, like their endogenous analogues, have a mechanism similar to miRNAs for post-transcriptional regulation of gene expression [4]. In humans, the number of lncRNAs is estimated to a range from 5,000 to 7,000, but it is expected that this number will increase in the future [8]. However, the number of experimentally confirmed and known functions of lncRNAs is only about 100 [9]. One of the first known lncRNAs was XIST (X inactive specific transcript), responsible for inactivation of the X chromosome. XIST binds to proteins, of which the protein group PRC (polycomb repressor complex) should be noted. Modification of histones and chromatin leads to inactivation of the X chromosome. PRC proteins also play a role in the regulation of chromatin structure due to the expression of lncRNAs [10].

## THE FUNCTIONS OF lncRNAs IN PHYSIOLOGICAL PROCESSES

lncRNAs mainly act by modulating gene expression [11]. This function can be performed locally when lncRNAs act on neighboring genes in the cis-position, or distally when their functions are performed regardless of the location of the target genes. In particular, there is a class of lncRNA with enhancer-like activity that can transcriptionally activate neighboring genes [12]. More generally, studies of the functions of lncRNAs have shown that they are potentially involved in various biological processes in mammals [11]. These processes include, for example, maintaining the pluripotency of embryonic stem cells, cell differentiation, cell cycle regulation, and the immune response. lncRNAs can regulate gene expression through various mechanisms. The molecular aspects of these mechanisms have been described in detail in a recent review [11]. lncRNAs can potentially bind DNA, proteins or other RNAs, forming networks and, thus, providing an interaction between different functional molecules. Some lncRNAs can change the chromatin context near their target genes by a set of transcription factors, histone modification factors, thereby stimulating or inhibiting the transcription of target genes, depending on the context. Among the lncRNAs that were functionally characterized, XIST, which gene is located on the X chromosome [13], is directly involved in the inactivation of the X chromosome in women. After transcription, XIST is retained in the nucleus and covers the inactive X chromosome. In addition, it interacts with the Polycomb 2 inhibitor complex (PRC2), which makes it possible to purposefully recruit this complex and thereby contributes to maintaining the inactivation of the X chromosome [13]. Interestingly, XIST, in turn, is regulated by other lncRNAs, such as TSIX (Transcription silencing inactivation of X) and XITE (X-inactivation intergenic transcription element) [13]. Other lncRNAs, such as AIRN, H19, and KCNQ1OT1, also participate in the inactivation of gene expression through their association with chromatin-associated inhibitor complexes. HOTAIR lncRNA, whose gene is located in the HOXC locus, will serve as a framework for the PRC2 and LSD1 complexes (lysine-specific demethylase 1), two complexes associated with transcription inhibition, and facilitate their recruitment within the HOXD locus [14, 15]. In contrast, Mistral and HOTTIP lncRNAs will facilitate the expression of HOXA genes by recruiting the WD5 / MLL epigenetic complex [16, 17]. lncRNAs are also significantly involved in post-transcriptional processes associated with mRNA biogenesis, such as splicing, transport, translation, and mRNA degradation. For example, UCHL1-as, an antisense lncRNA that partially overlaps the 5' end of the UCHL1 gene, promotes translation of the mRNA of the UCHL1 gene [18]. In addition, lncRNAs can act as "sponges" to prevent miRNAs from binding to their mRNA targets. CDR1-as /

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ciRS-7 (sponge for miR-7), circular lncRNA expressed in humans, has 70 binding sites for miR-7 [19, 20]. In addition, some non-coding RNAs, called enhancer RNAs (eRNAs), are formed from distal cis-regulatory elements [12]. Currently, the role of these eRNAs in the transcriptional activity of the target gene has not yet been determined, since they can also be simply by-products of active regulatory elements. In this sense, it has recently been demonstrated that divergent transcribed lncRNA / mRNA pairs reflect a specialized transcriptional regulation mechanism involving bidirectional promoters.

### **lncRNAs IN TUMORS**

lncRNAs can affect many aspects of tumor formation, such as stimulating cell division, eliminating effects that inhibit cell growth, inducing unlimited ability to replicate, stimulating invasion and metastasis, enhancing neovascularization and inhibiting apoptosis [8]. One of the earliest identified lncRNAs with biological significance in the tumor was H19. H19 is 2.3 kb lncRNA. This is a highly conserved imprinted gene that is expressed only in the maternal allele. This phenomenon, in which the alleles of the father and mother behave differently and only one allele is expressed, is called genomic imprinting. Another important gene involved in the H19 regulatory system is IGF-2, an insulin-like growth factor type 2, which is expressed only in the paternal allele. Increased expression of IGF-2 has been reported in several tumors, including adrenal cancer. In Beckwith-Wiedemann syndrome (hemihypertrophy, neonatal hypoglycemia, omphalocele, adrenal cancer, etc.), increased expression of IGF-2 is a fundamental indicator [21]. Increased expression of H19 is observed in cancer of the bladder, breast and hepatocellular carcinoma. It has been shown that the proto-oncogene c-myc stimulates H19 expression [22]. A close relationship between large and small non-coding RNAs is indicated by the fact that the first exon H19 encodes miRNA-675, which inhibits mRNA, the tumor suppressor Rb (retinoblastoma) [23, 24]. However, in many experiments, a decrease in H19 expression was associated with an increase in the tumor [6].

SRA (steroid receptor RNA activator), identified as a co-activator of steroid receptors (estrogen, progesterone, glucocorticoids and androgens), is also lncRNA. It has a transactivation effect through its AF-1 domain. Breast tumors have been shown to have increased SRA expres-

sion, which may play a role in tumor formation [25]. However, recent evidence suggests that SRA can not only function as lncRNA, but also can encode a transcriptional protein. The formation of non-coding and protein-coding RNA can be controlled by alternative splicing [26]. In the regulation of cell division in the aging process of cells, telomeres located at the end of chromosomes and the telomerase enzyme that regulates their length are of great importance. The telomerase enzyme complex itself also contains non-coding RNA called TERC (telomerase RNA component) and TERT (telomerase reverse transcriptase) activity. According to recent data, another lncRNA also plays a role in regulating telomerase activity called TERRA (telomeric repeat-containing RNA). Some evidence suggests that TERRA expression in tumor cells is reduced and that increasing TERRA expression may be a possible method of inhibiting tumor growth [27].

Among lncRNAs involved in metastatic processes, HOTAIR and MALAT1 should be distinguished. The expression of HOTAIR in primary and metastatic breast cancer is significantly increased [28]. Increased HOTAIR expression can be assessed as a prognostic signal associated with metastasis and decreased survival [6, 28]. PRC2, already mentioned in the XIST case, plays a role in its molecular mode of action. The PRC2 complex inhibits the transcription of a number of genes, including the fundamental processes of cell division and differentiation [29]. HOTAIR binding to PRC alters the inhibitory effect of PRC, restraining the inhibition of several genes' transcription. Increased expression of lncRNA MALAT1 (metastasis associated lung adenocarcinoma transcript 1) was observed in non-small cell lung cancer [30]. In addition to non-small cell lung cancer, increased expression was observed in cancer of the prostate, breast, liver and uterus. MALAT1 is important for the regulation of cancer cell invasiveness, but its exact mechanism of action is unknown. Some data suggest that mRNA maturation may play an important role in alternative splicing processes [31]. Like XIST and HOTAIR, ANRIL (antisense non-coding RNA in the INK4 locus) also binds to the PRC complex. Significance in the biology of tumors of the INK4b-ARF-INK4a locus is indicated by its deletion in several tumors [32]. ANRIL inhibits the expression of several genes (including tumor suppressor genes p15 and p21) through complexes of PRC1 and PRC2 [33, 34].

MEG3 was the first lncRNA originally identified as a tumor suppressor. Like H19, MEG3 has only the maternal allele [35]. By analogy with H19, one can also interpret that MEG3 encodes miR-770, whose gene is located in the intron at the 3'-end of RNA [36]. MEG3 is most strongly expressed in pituitary and brain tissues, and its expression in pituitary adenomas is associated with increased methylation of the regulatory region of MEG3 expression [35]. Activation of p53 pathways is a priority in the suppressor effect of MEG3. P53 itself induces the expression of certain lncRNAs, among which the tumor suppressor lncRNA-p21 should be noted [37]. GAS5 (growth-arrest specific 5) is another tumor suppressor. Like the previously mentioned SRA, GAS5 also plays a role in the regulation of glucocorticoid receptor activity, by inhibiting glucocorticoid activity [38, 39]. Increased expression of GAS5 leads to inhibition of cell proliferation in breast and prostate cancer cell lines [40]. Apparently, an extremely interesting molecular mechanism is that lncRNAs can bind complementary miRNAs and, thus, inhibit their action ("sponge" miRNA). MicroRNA binding is also tested for inhibition of the action of miRNAs with artificial nucleic acids, since several miRNAs can be inhibited simultaneously [41]. An example is lncRNA HULC (highly upregulated in liver cancer), which exhibits increased expression in hepatocellular carcinoma [42]. A mechanism similar to HULC-mediated miRNA inhibition has been described for tumor suppressor PTEN (phosphatase and tensin homolog). PTEN, a tumor suppressor gene, has the pseudogen PTENP1. PTENP1 and PTEN compete for binding of inhibitory miRNAs. Under normal conditions, lncRNA PTENP1 allows expression of PTEN by binding of miRNAs [43]. However, in tumors, somatic miRNA binding sites result in a loss of ability to bind PTENP1. Therefore, the expression of PTEN is reduced, which can lead to an increase in tumor growth [44]. lncRNA, called  $\alpha$ HIF, plays a central role in the regulation of HIF1 $\alpha$  (hypoxia-induced factor 1 $\alpha$ ) specifically in neovascularization processes.  $\alpha$ HIF is an antisense lncRNA that is complementary to the 3' untranslated portion of HIF1 $\alpha$  mRNA. Increased expression of  $\alpha$ HIF leads to inhibition of HIF1 $\alpha$  and thereby to inhibition of angiogenesis [45]. The expression of  $\alpha$ HIF has been described in many tissues and, interestingly, its expression in breast cancer is a poor prognostic factor [46].

## THE MOLECULAR MECHANISM OF lncRNA IN TUMOR METASTASIS

The metastatic cascade is a coordinated sequence of cell-biological events that includes local cell invasion and allows cancer cells to exit the primary site, develop new blood vessels (angiogenesis), migrate and penetrate the microenvironment, perform intravation and extravasation, survive in circulation and colonize distant organs [47]. There is increasing evidence for the role of lncRNAs at every stage of metastasis. Let us examine the role of lncRNAs in cell invasion.

## lncRNA IN CELL INVASION

In order to spread to distant organs, cancer cells must separate from the primary tumor using extracellular proteases to destroy the extracellular matrix (ECM) and invade the adjacent parenchyma. Then metastasis occurs when invasive cancer cells enter the blood and lymph vessels, pass through the bloodstream and enter the endothelium, eventually settling in a distant organ and creating a secondary tumor [48]. The epithelial-mesenchymal transition (EMT) is one of the central and important processes that allows epithelial cells to acquire migration ability and penetrate into tissues and organs [49, 50]. EMT is performed by activating a number of transcription factors (EMT-TF), mainly the ZEB, SNAIL, and TWIST families [51]. Many research groups have reported that lncRNAs are the main regulators of invasion. We summarized the most thoroughly studied lncRNAs involved in the regulation of EMT-TF to stimulate metastasis. Several lncRNAs, including lncRNA-ATB21 and HOTAIR, function as miRNAs to modulate ZEB and SNAIL levels in cancer [52]. Other lncRNAs are also involved in the epigenetic regulation of EMT-TF expression, such as TRERNA1 as an enhancer of the recruitment of SNAIL and ZEB1-AS1p300 to the ZEB1 promoter [53, 54]. lncRNAs also function through RNA and protein interactions to regulate metastasis. For example, GAPLINC stimulates the expression of SNAIL2 by binding to PSF and the NONO protein [55]. In addition to the regulation of SNAIL and ZEB, Hu et al. revealed more than 99 lncRNAs involved in EMT processes induced with TWIST [56]. Detailed mechanisms of how lncRNAs bind to TWIST / EMT signaling pathways have also been confirmed by other groups of scientists. TWIST binds to lncRNA HOTTIP, which recruits and directs WDR5 to the HOX cluster and

induces HOXA9 expression [57]. High levels of HOXA9 correlate with an aggressive cellular phenotype in prostate cancer. It was shown that in addition to direct binding to TWIST, lncRNA CHRF regulates the TWIST / EMF signaling pathway, acting as miR-489 [58]. CHRF inhibits the expression of TWIST and further inhibits the progression of EMF in CRC [58].

## DIAGNOSTIC AND THERAPEUTIC VALUE OF lncRNAs

The role of miRNAs in the diagnosis of tumors is confirmed by several experimental results. Their applicability is greatly enhanced due to their stability, so that they can be safely detected not only in frozen tissue samples, but also in body fluids and secretions. lncRNAs, despite their larger size, can also be found in body fluids, such as, for example, in blood samples of patients with hepatocellular carcinoma (HULC) [41]. The detection of PCA3 (prostate cancer gene 3) in urine has been described in some studies as a more sensitive biomarker compared to the prostate-specific antigen (PSA) [59]. Detection of some lncRNAs in tissue has a predictive value. For example, in hepatocellular carcinoma, increased MALAT1 expression is associated with poor prognosis and decreased survival after liver transplantation [60]. Although we are just beginning to learn the biology of lncRNAs, and there are many more questions that need to be clarified, it is possible that they may become a therapeutic target in the future, based on their significance in tumor biology.

## CONCLUSION

Thus, acquaintance with long non-coding RNAs is a new chapter in research in the field of molecular biology of tumors, which contributes to a better understanding of tumor development processes. Clarification of the functions and mechanisms of these lncRNAs in biological systems under normal and pathological conditions may lead to potential opportunities for the identification of biomarkers and new therapeutic targets for tumors. To date, only a very small number of lncRNAs have been studied for their effect on the pathological process of neoplasms. Studies on lncRNAs require more sensitive detection methods than those on proteins and other RNAs due to lncRNAs lower expression. With an increased understanding of the role of lncRNAs in tumor biology, we can expect to

identify new diagnostic biomarkers in the future. A clear understanding of how lncRNAs regulate many mechanisms in metastasis may lead to the emergence of new therapies for cancer patients. The lncRNA research area is expected to continue to improve in the near future.

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