Bioorganic Chemistry 92 (2019) 103214

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

# The role of long noncoding RNA in major human disease

Xiaoli Zhang[a], Ruiyun Hong[b], Weiqiang Chen[a], Minwen Xu[b], Liefeng Wang[a,*]

[a] Department of Biotechnology, Gannan Medical University, Ganzhou 341000, China
[b] First Affiliated Hospital of Gannan Medical University, Ganzhou 341000, China

ARTICLE INFO

*Keywords:*
lncRNA
Chromosome dose compensation
Chromatin remodeling
Tumor
Aging related diseases

ABSTRACT

*Background:* Long noncoding RNAs (lncRNAs) are RNAs whose transcripts are longer than 200nt in length and lack the ability to encode proteins due to lack of specific open reading frames. lncRNAs were once thought to represent transcriptome noise or garbage sequences and a byproduct of RNA polymerase II (Pol II), and thereby ignored by researchers. In fact, lncRNA was involved in a wide variety of physiological and pathological processes in organisms. Comprehensive study of lncRNA does not only provide explanations to the physiological and pathological processes of living organisms, but also gives us new perspectives to the diagnosis, prevention and treatment of some clinical diseases. Therefore, the study of lncRNA is a very broad field of great research value and significance.

*Results:* This article reviews the function of lncRNAs and their role in major human diseases.

*Conclusions:* Numerous studies show that lncRNA might serve as a biomarker for diagnosis and prognosis of various diseases. Compared to conventional biomarkers, lncRNA seems to have a higher diagnostic and prognostic values, not only because of their tissue and disease specific expression patterns, but also due to their highly stable physical and chemical properties.

## 1. Introduction

LncRNAs were first discovered in the sequencing of a full-length cDNA library of mouse cells. According to whether RNA can encode proteins in living organisms or not, they can be classified as messenger RNAs with the ability to encode proteins and non-coding RNAs (ncRNAs) that do not have protein coding ability. Studies found that only 2% of the 3 billion base pairs that make up the human genome with the ability to encode proteins [1], while the remaining 98% of the RNA is non-coding RNA [2–4], which includes microRNAs (miRNA), snoRNAs, lncRNAs and circular RNAs (circRNAs). Most lncRNAs are structurally indistinguishable from encoded and processed mRNAs and are transcribed by Pol II. They have a methyl guanosine cap at their 5′ end and a polyA tail at the 3′ end (polyA) [5–7]. Nucleus lncRNAs are involved in epigenetic, trans transcriptional regulation of distal loci or cis-transcriptional regulation of adjacent loci. Cytoplasmic lncRNAs regulates the process of translation, stabilization and degradation of mRNA, and can act as a competitive endogenous RNA to target miRNAs and protein factors to inhibit their activity and promote mRNA translation [8–10]. In addition, lncRNA can also interact with RNA, DNA molecules and protein complexes to execute its function and regulate various physiological and pathological processes.

## 2. The functions of lncRNA

### 2.1. Differentiation and development

It is well known that lncRNA regulates cell differentiation and tissue development. For example, lncRNA can regulate the development of cardiomyocytes, stem cells, epithelial cells. Guttman M, *et al.* performed an unbiased functional analysis of lncRNA in mouse embryonic stem cells to demonstrate that their major role in intron-influencing gene expression is to bind chromatin proteins and affect the pluripotent state of stem cells. After knocking down lncRNA-ROR in stem cells, expression of pluripotency marker genes such as Oct4 and Nanog was downregulated, which affected cell proliferation [11]. Additional studies have demonstrated that lncRNA transcripts are found at all stages of mouse embryonic cell division, and maternal transcripts present in oocytes and zygotes contribute to early differentiation [12]. Fendrr is one of the rare examples of lncRNA that have been shown to play an important role in organ development and embryonic survival. This lncRNA interferes with impaired cardiac function, parietal cell development, and embryonic development. Fendrr interacts with chromatin-modifying complexes and DNA to alter the chromatin morphology of

*Abbreviations:* lncRNA, Long noncoding RNA; circRNAs, circular RNAs; XCI, X-chromosome inactivation; Xist, X-inactive specific transcript; HOTAIR, Homeobox (HOX) transcriptional antisense RNA; GACAT3, gastric cancer related transcriptional 3; APPAT, atherosclerotic plaque related transcriptional

* Corresponding author.
*E-mail address:* 469730795@qq.com (L. Wang).

https://doi.org/10.1016/j.bioorg.2019.103214
Received 27 February 2019; Received in revised form 20 August 2019; Accepted 20 August 2019
Available online 21 August 2019
0045-2068/ © 2019 Elsevier Inc. All rights reserved.

trans-specific target promoters, particularly mesodermal transcription factors, and affect development [13,14].

### 2.2. Chromosome dose compensation

In the early-stage of embryonic development, the sex chromosome-linked genes are selectively expressed in the same dose in both female and male individuals by means of silencing or up-regulation, ensuring that the X-chromosome-encoded proteins or other enzymes are balanced in quantity, and this genetic mechanism is called dose compensation [15]. The X chromosome is controlled by the X-chromosome inactive center (XIC) [16]. XIC can produce an approximately 20-kb lncRNA called *X-inactive specific transcript* (*Xist*) [17,18]. The *Xist* gene encodes *Xist* RNA and package the X chromosome to initiate the inactivation of the X chromosome. The expansion of the *Xist* RNA on the X chromosome leads to DNA methylation and histone modification, which are important for the establishment and maintenance of the X chromosome inactivation [19]. The mechanism of dose compensation varies among different species. Two X chromosomes in humans are randomly inactivated, and the gene expression of the X chromosome of the male *Drosophila* is up-regulated by 2-fold [19]. The dose compensation mechanism of *Caenorhabditis elegans* is to reduce the gene expression of the two female X chromosomes by half to maintain the balance of the X chromosome gene dosage between male and female [20].

### 2.3. Chromatin remodeling

In order to adapt to the dense structure of highly folded chromatin, eukaryotic organisms modify the chromatin structure by chromatin remodeling factors, thereby improving the accessibility of RNA polymerase and transcription factors on chromatin DNA, affecting transcriptional activity, and thus ensuring proper operation of various biological processes within the cell [21]. LncRNA can be a key regulator of the modification of gene-specific chromatin states during life activities. For example, *Xist* can recruit poly-comb repressor 2 (PRC2) to form Xist-PRC2 functional complexes targeting on the X-inactivation specific sites, and to catalyze the trimethylation of histone H3 lysine K27(H3K27), a gene silencing histone modification [16,22–24]. Human lncRNA *HOTAIR* is transcribed from the HOXC region and can also regulate the chromatin status by recruiting PRC2 and inhibit the expression of HOXD region genes [25]. Drosophila lncRNAs *roX1* and *roX2* bind to many regions on the X chromosome of male cells and are crucial for dose compensation on chromosomes 10 and 11 [26,27]. lncRNA *Evf2* is transcribed from the genomic region between Dlx5 and Dlx6, promoting SWI/SNF binding to enhancers. However, *Evf2* inhibited the remodeling activity of SWI/SNF and interfered with the upregulation of Dlx5/Dlx6. Thus, Dlx6 and Dlx5 expression was up-regulated in *Evf2* mutant mice. In another study, it was found that the binding of *Evf2* to BRG1 may be competitive by other RNAs with similar length, resulting in reduced remodeling activity [28–30].

### 2.4. Genome imprinting

The two alleles from both parents are subject to epigenetic modifications such as methylation and acetylation, resulting in offspring expressing only the parental or maternal allele, while the other allele is not expressed or expressed at very low level. This is called genomic imprinting. Genes involved in this process are called imprinted genes [31]. When the maternal allele is silenced, the imprinted gene will be expressed by the paternal allele, which is called maternal imprint. On the contrary, paternal imprint means the imprinted gene is expressed on the maternal allele. Imprinted genes often exist in clusters, and the occurrence of genetic imprinting often has tissue and development stage specificity. Recent studies have shown that genomic imprinting is closely related to the occurrence of tumors. Kang L-H, *et al.* first discovered that expression of lncRNA *IRAIN* was different in normal breast tissues and breast cancer tissues. This difference was associated with gene imprinting conversion phenomenon, involving in DNA methylation abnormality in the promoter region of parental allele of the *IRAIN* gene [31]. It is inferred that lncRNA *IRAIN* may act as a tumor suppressor gene, and the imprinting conversion is likely to be a way of inactivating the tumor suppressor gene and is expected to become a marker of prognosis and therapeutic target for the breast cancer.

The mechanism of lncRNA function is shown in Fig. 1. With increasing attention to lncRNAs, more and more lncRNAs are found to be involved in the occurrence and development of human diseases, and their role in major diseases is attracting more attention.

1. LncRNAs can bind to transcription factors and regulate target genes.
2. LncRNAs bind to the target site of the microRNA effect complex, causing it to lose its regulatory function.
3. LncRNAs specifically bind to regulatory proteins and participate in the formation of ribonucleoprotein complexes.
4. LncRNAs can recruit DNA target chromatin-modifying complexes.
5. LncRNAs are directly involved in the regulation and processing of their target mRNA—translational inhibition.
6. LncRNAs are directly involved in the regulation and processing of their target mRNA—shear splicing.
7. LncRNAs are directly involved in the regulation and processing of their target mRNA—degradation.

### 2.5. Long noncoding RNA and human disease

A genomic profiling (TCGA) study showed that in approximately 5,000 tumor samples, although approximately the same number of protein-coding genes and lncRNA genes were disordered, 60% of the lncRNAs showed specificity for only one tumor type [5]. The lncRNA has a lower abundance than mRNA and is less conserved in sequence, but it has a conserved secondary structure and shows stronger tissue and organ specificity [1,31]. It has been found that the expression or function abnormality of lncRNA is closely related to the occurrence of human diseases, specifically the abnormality in the sequence and space structure of lncRNA, the abnormality in the interaction with DNA and protein, abnormalities in expression levels, etc [32–34]. According to related reports, some lncRNAs can promote cell proliferation and promote the occurrence of tumor. while some lncRNAs inhibit cell overgrowth and reproduction to resist tumor formation and have high tissue and organ specificity [31]. Therefore, lncRNA has been suggested as a therapeutic target and biomarker for many diseases.

## 3. LncRNA and tumor

### 3.1. Cervical cancer

Recently lncRNAs have been shown to be involved in the regulation of many biological processes, such as abnormal transcription in tumor, cell proliferation, cell cycle regulation and apoptosis [35]. *MEG3* is an important tumor suppressor gene, which is down-regulated in cervical cancer. Researches showed that the methylation status of the *MEG3* promoter in two cervical cancer cell lines (HeLa and CaSki) was altered by using DNA methyltransferase inhibitor (5-Aza-CdR). The expression of *MEG3* in cervical cancer cells increased as the level of promoter methylation decreased and the proliferation potential of cervical cancer cells decreased [36]. In addition, the same study also demonstrated that lncRNA *MEG3* was significantly associated with tumor size and lymph node metastasis, and the receiver operating characteristic curve analysis showed that lncRNA *MEG3* had sufficient sensitivity and specificity to predict tumor size and lymph node metastasis. In addition, follow-up data indicated that low lncRNA *MEG3* expression was associated with the recurrence of cervical cancer and lower overall survival [36]. *Homeobox* (*HOX*) *transcriptional antisense* RNA (*HOTAIR*) is highly

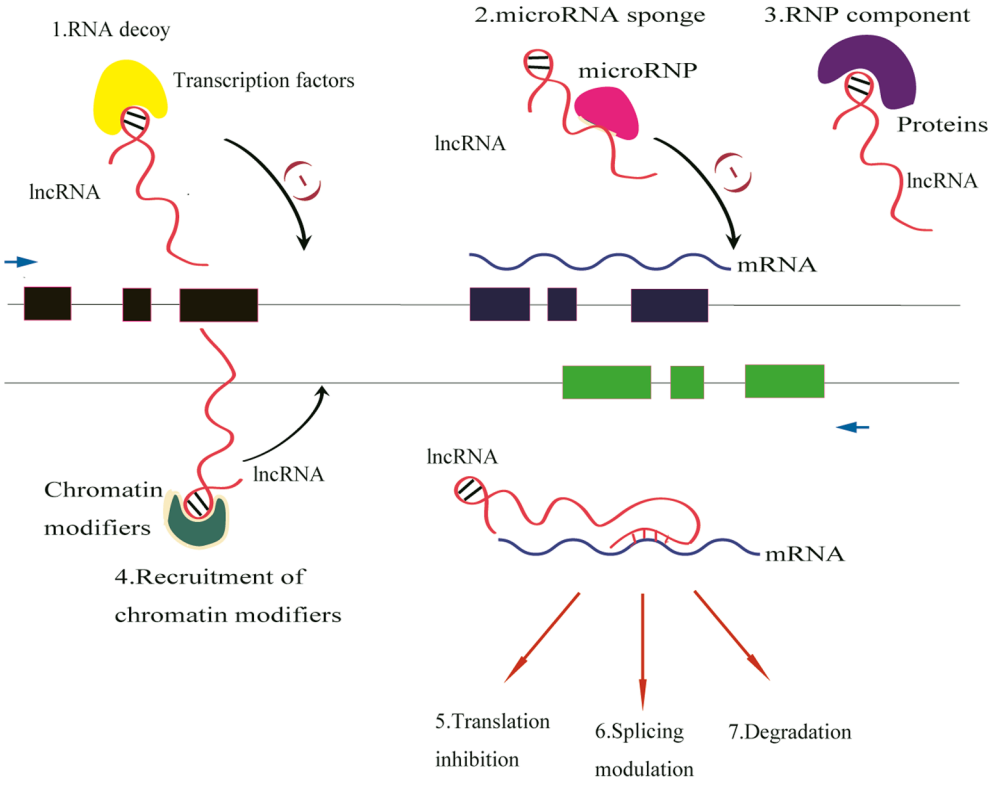


**Fig. 1.** Mechanisms of lncRNA function. (Wenqian Hu, et al., EMBO reports, 2012).

up-regulated in several types of cancers. In order to study the expression and possible function of *HOTAIR* in cervical cancer cells, Zhang Y, *et al.* investigated the relationship between gene expression of *HOTAIR* in different cell lines and cell migration/invasion. The results showed that the expression of *HOTAIR* was significantly up-regulated in cervical cancer cells. The inhibition of *HOTAIR* expression in HeLa cervical cancer cells would suppress cell proliferation, migration and invasion [37]. With the deepening of research, increasing lncRNAs might be found to be related to the incidence of cervical cancer, which will also help researchers to further understand the pathogenesis of cervical cancer and find appropriate treatment methods.

### 3.2. Non-small cell lung cancer

LncRNA *GACAT3* co-expresses with many known oncogenic genes in different solid tumors and has a carcinogenic effect in many malignant tumors. Recent studies have shown that the level of *GACAT3* is closely related to the clinical parameters of many cancers, such as recurrence and survival rate [38,39]. Yang X, *et al.* performed RNA and protein expression analysis on non-small cell lung cancer tissues (40 adenocarcinomas and 22 squamous cell carcinomas) and adjacent tissues, and confirmed that lncRNA *GACAT3* was significantly up-regulated in lung cancer tissues and protected lung cancer cells from radiotherapy. LncRNA *GACAT3* may be a potential biomarker for evaluating the curative effect and prognosis of lung cancer. However, the role of lncRNA *GACAT3* in non-small cell lung cancer and its potential mechanism for regulating the radio-sensitivity of non-small cell lung cancer still need to be elucidated [40]. lncRNA *GAS5* is a newly-discovered lncRNA that can regulate cell cycle and cell proliferation. Zhang X-J, *et al.* analyzed the expression of lncRNA *GAS5* in lung cancer tissue specimens and normal lung tissue adjacent to cancer in 50 patients with non-small cell lung cancer. Combined with the correlation of clinicopathological parameters, lncRNA *GAS5* showed a low expression in the tumor tissue of non-small cell lung cancer, and was negatively associated with the diameter of non-small cell lung cancer, the clinical stage of tumor and lymph node metastasis, which are markers of poor prognosis [41]. Although no specific lncRNA has been found to be associated with lung cancer, it can be seen from the above that lncRNA should play a role in the early diagnosis, treatment and prognosis evaluation of lung cancer.

### 3.3. Breast cancer

*BANCR* was a 693 bp lncRNA originally found in melanoma cells by Flockhart [42]. It is aberrantly expressed in various cancers such as lung cancer, hepatocellular carcinoma, and colorectal cancer, and can regulate cell proliferation, migration, and invasion [43]. Lou K-X, *et al.* found that lncRNA *BANCR* was up-regulated in breast cancer tissues and was significantly associated with tumor lymph node metastasis (TNM) staging and prognosis of patients, suggesting this lncRNA might promote the development of breast cancer. Both wound healing and trans-well migration experiments showed that downregulation of lncRNA *BANCR* can inhibit the proliferation, invasion and metastasis of breast cancer cells via the inhibition of epithelial mesenchymal transition (EMT) process and the expression of MMP-2 and MMP-9 in the cells. Therefore, lncRNA *BANCR* could serve as a molecular marker and therapeutic target for breast cancer diagnosis and prognosis evaluation [44]. In addition, high expression of lncRNA *NORAD* was found to promote TGF-β signaling in breast cancer cells. TGF-β signaling regulates cell proliferation, differentiation, apoptosis, wound repair, and immune function, and is involved in malignant progression of breast cancer by promoting epithelial mesenchymal transformation [45,46]. Zhou *et al.* found that lncRNA *NORAD* expression was increased in breast cancer cells, and when *NORAD* was knocked down in breast cancer cells, TGF-β and its downstream factor RUNX2 were also down-regulated, suggesting that *NORAD* can be involved in breast cancer progression by regulating the TGF-β signaling pathway [45].

These studies suggest that lncRNA is indeed widely involved in the pathogenesis of tumors, and the development of a new lncRNA-based diagnostic technique and a targeted therapeutic strategy for tumors

**Table 1**
LncRNA involvement in human diseases.

| LncRNA | Cellular localization | Physiological/pathological | Mechanism | References |
|---|---|---|---|---|
| MALAT1 | Nucleus | Cancer, Cardiovascular disease | Post transcriptional | [62–64] |
| CDKN2B-AS | Nucleus | Hypertension, Cancer | Histone modification | [55,65] |
| HOTAIR | Nucleus | Cancer, skeletal development | Histone modification | [37,66–68] |
| NORAD | Cytoplasm | Cancer | Post transcriptional | [45,46] |
| P21 | Nucleus | Cancer, Cardiovascular disease | Transcription | [53] |
| H19 | Nucleus | Cardiovascular disease, muscle differentiation | DNA methylation | [49–52] |
| MIAT | Nucleus | Myocardial infarction, brain development | Post transcriptional | [60,61,69] |
| MEG3 | Nucleus | Cancer | Histone modification, DNA methylation | [36,70,71] |
| GACAT3 | Nucleus | Cancer | | [38–40] |
| BANCR | Cytoplasm | Cancer | | [42–44] |
| GAS5 | Cytoplas, Nucleus | Cancer, Hypertension | | [41,72] |

seem very promising. With the development of research, targeting lncRNA may be the main treatment strategy for cancer in the future. In this paper, only some lncRNA involved in tumor diseases were listed and summarized in Table 1.

## 4. Long noncoding RNA and cardiovascular diseases

### 4.1. Atherosclerosis

The progression of atherosclerosis includes the following steps: formation of vascular endothelial injury, formation of fatty streaks, and formation of atherosclerotic plaques. Cell adhesion, angiogenesis, cell proliferation, apoptosis and ischemic hypoxia response are all regulated by the expression of related genes [47,48]. Recently, some studies reported that lncRNA plays a key role in the regulation of atherosclerosis. LncRNA *H19* is transcribed from *H19/IGF2* gene, which is located on human chromosome 11p15.5 [49,50]. J.-X. PAN found that H19 was highly expressed in the serum of ApoE$^{-/-}$ atherosclerotic mice and atherosclerotic patients [51]. Overexpression of *H19* in vascular smooth muscle cells leads to increased proliferation and decreased apoptosis. Li *et al.* reported that H19/ miR-675 can inhibit the apoptosis of cardiac myocytes [52]. The results suggest that *H19* may be a key factor in inhibiting apoptosis. In order to further explore the regulatory mechanism of *H19* in atherosclerosis, J.-X. PAN measured the expression of p38 and p65 after the overexpression of *H19*, and found that p38 and p65 were both highly expressed in vascular smooth muscle cells, and they were key factors of MAPK and NF-κB signaling pathways, suggesting that lncRNA *H19* may regulate the occurrence of atherosclerosis through MAPK and NF-κB signaling pathways [51]. LncRNA *P21* was initially identified as a direct transcription target of P53, which plays an important role in the pathogenesis of atherosclerosis. Wu *et al.* reported that lncRNA *P21* could feedback regulate the P53 pathway and affect the proliferation and apoptosis of ApoE$^{-/-}$ mouse vascular smooth muscle cells [53]. Ballantyne *et al.* found that lncRNA *SMILR* can regulate the proliferation of vascular smooth muscle cells and is highly expressed in unstable atherosclerotic plaques [54]. The above studies showed that lncRNA can be involved in the pathogenesis of atherosclerosis by regulating the proliferation and apoptosis of vascular smooth muscle cells, suggesting that these lncRNA can be used as potential targets for the diagnosis and treatment of atherosclerosis.

### 4.2. Hypertension

Hypertension is affected by a variety of diseases, heredity and environment factors. Neurohumoral regulation is widely accepted as the pathogenesis of hypertension. Jin *et al.* found that lncRNA *AK098656* was highly expressed in vascular smooth muscle cells of patients with hypertension, which promoted the proliferation and migration of vascular smooth muscle cells, and the transition from contraction type to secretion type. In addition, *AK098656* can directly bind to the specific contractile protein of vascular smooth muscle cells, the important components of myosin heavy chain-11 and extracellular matrix fibrin-1, and reduce the level of these proteins through protein degradation, narrowing the resistance arteries to promote the occurrence of hypertension. *AK098656* transgenic rats showed the onset symptoms of hypertension, with increased secretory-type smooth muscle cells, narrowed arteries and slight myocardial hypertrophy, which was similar to the early pathophysiological changes in hypertension [55]. These data show that *AK098656* can promote the occurrence and development of hypertension. Yang *et al.* injected sodium aescinate into the tail vein of rats with spontaneous hypertension and found that sodium aescinate reduced the tail blood pressure of rats with spontaneous hypertension by regulating the increase of nitric oxide synthase through lncRNA *AK094457* [56]. Bayoglu B *et al.* evaluated the expression difference of lncRNA in the heart tissues of spontaneous hypertension rats and control rats using microarray method, and the enrichment analysis results showed that the lncRNA *CDKN2B-AS1* polymorphism may be the cause of the increase of systolic blood pressure in hypertension patients [57]. All the above studies showed that lncRNA was involved in the pathogenesis of hypertension.

### 4.3. Myocardial infarction

Myocardial infarction is the most serious heart disease with the highest morbidity and mortality, and inflammatory reaction and myocardial cell apoptosis are the main characteristics of myocardial infarction, which can eventually lead to myocardial dysfunction and heart failure [58]. Activation of NF-κB elevated the inflammatory response in myocardial injury, and blocking the NF-κB signaling pathway protects the heart from ischemic injury and inflammation [59]. *MIAT* was first identified as a lncRNA associated with myocardial infarction, which was significantly up-regulated in patients with myocardial infarction [60]. Li *et al.* found that MIAT is mainly expressed in cardiac fibroblasts, and the down-regulation of MIAT can inhibit myocardial apoptosis and reduce the infiltration of myocardial inflammatory cells, thus improving cardiac function. Further studies showed that down-regulation of MIAT in myocardial fibroblasts also inhibited the activation of NF-κB signaling pathway [61], suggesting that downregulation of MIAT may reduce myocardial apoptosis and inflammatory cell infiltration by inhibiting the activation of NF-κB signaling pathway, thereby alleviating myocardial infarction injury and protecting cardiac function. Biological morphological analysis showed that lncRNA *MALAT1* shared the miRNA response element with the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) of miR-320, which was the direct target gene of miR-320, and miR-320 was closely related to myocardial remodeling after myocardial infarction [62]. Hu *et al.* found that knockdown of *MALAT1* in acute myocardial infarction mice can reduce myocardial cell apoptosis, possibly because MALAT1 reduces myocardial cell apoptosis by regulating miR-320 to inhibit PTEN expression [63].

The above studies have shown that lncRNA indeed widely participate in the onset of cardiovascular disease and plays an important role

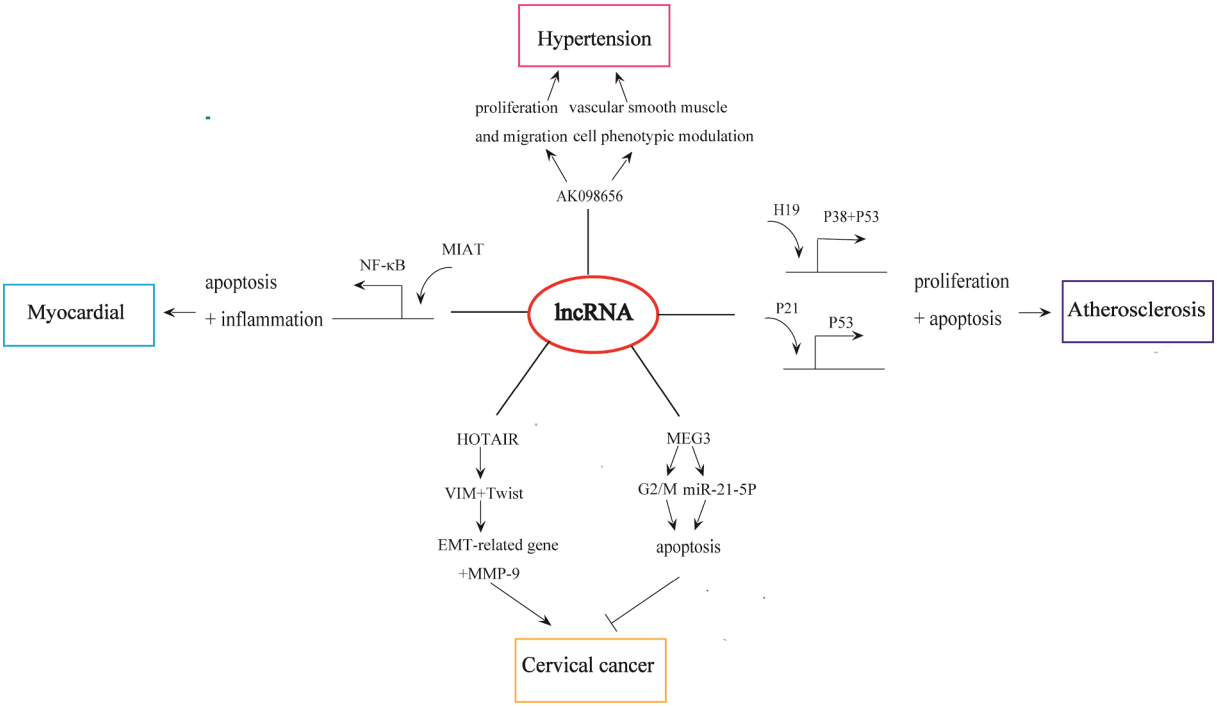


**Fig. 2.** The role of long noncoding RNA in major human disease.

in the course of illness. There are a lot of researches in succession, believe in the future, the role of lncRNA in cardiovascular disease will be further elaborated, and it might very well serve as biomarkers of disease diagnosis and therapeutic target widely used for clinical treatment. In this paper, only some lncRNA involved in cardiovascular diseases were listed and summarized in Table 1.

## 5. Conclusions

So far, at least 270,044 lncRNA genes have been classified, but only a small number of transcripts are known in terms of structure, function, and their impact on disease development (Fig. 2). In the study of noncoding RNA, the research on miRNA is the most thorough, while the research of lncRNA is only the tip of the iceberg. Furthermore, the advanced structure, function and molecular mechanism of lncRNA are still not very clear. Therefore, more research and technology applications are needed to explore this mysterious treasure.

Numerous studies show that lncRNA is expected to be a marker for diagnosis and prognosis of various diseases, but these studies results lack consistency. For example, as an important tumor suppressor gene, the expression of lncRNA MEG3 is decreased in breast cancer, lung cancer, cervical cancer and so on [36,73]. But there were contradictory experimental results in osteosarcoma. Wang et al. showed that MEG3 is highly expressed in osteosarcoma cell lines, and knockdown of MEG3 inhibits cell growth and metastasis and induces osteosarcoma cell apoptosis [74]. However, Liu et al. showed that the expression of MEG3 in plasma of colon cancer patients also showed an upward trend [75]. In addition, MEG3 have been found that the expression is decreased and predicts a poor prognosisin in colon cancer tissues [76]. Tumor formation is characterized, not only by the infinite proliferation of tumor cells, but also by many biological processes such as genomic mutations, DNA damage, and DNA methylation. LncRNAs may act as important post-transcriptional regulators in these processes, regulating tumor development. For the development of cardiovascular disease, lncRNA may regulate the proliferation, migration, phenotypic shift of vascular smooth muscle cells and affecting the activation of NF-κB signaling pathway.

LncRNA have great potential for development as novel biomarkers. The reliable, accurate and sensitive detection of the lncRNA candidates is a prerequisite for their use as biomarkers in clinical applications. Some lncRNAs seem to show higher diagnostic and prognostic values than conventional biomarkers, not only because of their physical and chemical properties. lncRNA as a diagnostic biomarker is further highlighted by its associations with exosomes. The lipid bilayer membrane structure of the exosomes makes them resistant to ribonuclease attack in the blood, so that lncRNA is not easily degraded and can be stably present in body fluids [77]. Future researches may be to assess its expression levels in serum of cancer patients to replace invasive biopsy with liquid biopsy. The detection of biomarkers in the serum of cancer patients can greatly alleviate the suffering of patients, and the application prospect is very broad.

## Acknowledgements

We thank Dr. Zhiping Liu for helpful comments.

## Declaration of Competing Interest

The authors declare that they have no competing interests.

## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Consent for publication

Not applicable.

## Ethics approval and consent to participate

Not applicable.

## Funding

This work was partially supported by National Natural Science Foundation of China (31660256) to L. Wang.

## Authors' contributions

Xiaoli Zhang, Ruiyun Hong, Weiqiang Chen, Minwen Xu and Liefeng Wang wrote the manuscript. All authors read and approved the final manuscript.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103214.

## References


[1] Y. Feng, Y. Fan, C. Huiqing, et al., The emerging landscape of long non-coding RNAs, Yi Chuan. 36 (5) (2014) 456–468.
[2] M.N. Cabili, C. Trapnell, L. Goff, et al., Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses, Genes Dev. 25 (18) (2011) 1915–1927, https://doi.org/10.1101/gad.17446611.
[3] Z. Wang, X. Li, The role of noncoding RNA in hepatocellular carcinoma, Gland Surg. 2 (1) (2013) 25–29, https://doi.org/10.3978/j.issn.2227-684X.
[4] J.R. Ecker, W.A. Bickmore, I. Barroso, et al., Genomics: ENCODE explained, Nature 489 (7414) (2012) 52–55, https://doi.org/10.1038/489052a.
[5] S.U. Schmitz, P. Grote, B.G. Herrmann, Mechanisms of long noncoding RNA function in development and disease, Cell. Mol. Life Sci. 73 (13) (2016) 2491–2509, https://doi.org/10.1007/s00018-016-2174-5.
[6] M.B. Clark, J.S. Mattick, Long noncoding RNAs in cell biology, Semin. Cell. Dev. Biol. 22 (4) (2011) 366–376, https://doi.org/10.1016/j.semcdb.
[7] J.B. Heo, Y.S. Lee, S. Sung, Epigenetic regulation by long noncoding RNAs in plants, Chromosome Res. 21 (6–7) (2013) 685–693.
[8] J. Viereck, T. Thum, Circulating noncoding RNAs as biomarkers of cardiovascular disease and injury, Circ Res. 120 (2) (2017) 381–399, https://doi.org/10.1161/CIRCRESAHA.116.308434.
[9] A. Diaz-Lagares, A.B. Crujeiras, P. Lopez-Serra, et al., Epigenetic inactivation of the p53-induced long noncoding RNA TP53 target 1 in human cancer, Proc. Natl. Acad. Sci. U. S. A. 113 (47) (2016) E7535–E7544.
[10] T. Hung, Y. Wang, M.F. Lin, et al., Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters, Nat. Genet. 43 (7) (2011) 621–629, https://doi.org/10.1038/ng.848.
[11] M. Guttman, J. Donaghey, B.W. Carey, et al., lincRNAs act in the circuitry controlling pluripotency and differentiation, Nature 477 (7364) (2011) 295–300, https://doi.org/10.1038/nature10398.
[12] L. Yan, M. Yang, H. Guo, et al., Single-cell RNA-Seq profiling of human preimplantation embryos and embryonic stem cells, Nat. Struct. Mol. Biol. 20 (9) (2013) 1131–1139, https://doi.org/10.1038/nsmb.2660.
[13] P. Grote, B.G. Herrmann, The long non coding RNA Fendrr links epigenetic control mechanisms to gene regulatory networks in mammalian embryogenesis, RNA Biol. 10 (10) (2013) 1579–1585, https://doi.org/10.4161/rna.26165.
[14] P. Grote, L. Wittler, D. Hendrix, et al., The tissue-specific lncRNA Fendrr is an essential regulator of heart and body wall development in the mouse, Dev. Cell. 24 (2) (2013) 206–214, https://doi.org/10.1016/j.devcel.2012.12.012.
[15] D. Bachtrog, Y-chromosome evolution: emerging insights into processes of Y-chromosome degeneration, Nat. Rev. Genet. 14 (2) (2013) 113–124, https://doi.org/10.1038/nrg3366.
[16] T. Kondo, S. Plaza, J. Zanet, et al., Small peptides switch the transcriptional activity of shavenbaby during drosophila embryogenesis, Science 329 (5989) (2010) 336–339, https://doi.org/10.1126/science.
[17] B.D. Adams, C. Parsons, L. Walker, et al., Targeting noncoding RNAs in disease, J. Clin. Invest. 127 (3) (2017) 761–771, https://doi.org/10.1172/JCI84424.
[18] S.T. Rocha, E. Heard, Novel players in X inactivation: insights into Xist-mediated gene silencing and chromosome conformation, Nat. Struct. Mol. Biol. 24 (3) (2017) 197–204, https://doi.org/10.1038/nsmb.
[19] Y.Y. Wang, M. Chen, B. Li, Dosage compensation mechanism of X chromosome, Yi Chuan. 34 (8) (2012) 977–984.
[20] J.C. Lucchesi, M.I. Kuroda, Dosage compensation in Drosophila, Cold Spring Harb Perspect Biol. 7 (5) (2015).
[21] J. Zhao, B.K. Sun, J.A. Erwin, et al., Polycomb proteins targeted by a short repeat RNA to the mouse X chromosome, Science 322 (5902) (2008) 750–756, https://doi.org/10.1126/science.1163045.
[22] A. Wutz, T.P. Rasmussen, R. Jaenisch, Chromosomal silencing and localization are mediated by different domains of Xist RNA, Nat. Genet. 30 (2) (2002) 167–174.
[23] J.H. Yoon, K. Abdelmohsen, M. Gorospe, Posttranscriptional gene regulation by long noncoding RNA, J. Mol. Biol. 425 (19) (2013) 3723–3730, https://doi.org/10.1016/j.jmb.
[24] J.L. Rinn, M. Kertesz, J.K. Wang, et al., Functional demarcation of active and silent chromatin domains in human HOX, loci by noncoding RNAs, Cell 129 (7) (2007) 1311–1323.
[25] R.S. Young, A.C. Marques, C. Tibbit, et al., Identification and properties of 1,119 candidate lincRNA loci in the Drosophila melanogaster genome, Genome Biol. Evol. 4 (4) (2012) 427–442, https://doi.org/10.1093/gbe/evs020.
[26] I.A. Ilik, J.J. Quinn, P. Georgiev, et al., Tandem stem-loops in roX RNAs act together to mediate X chromosome dosage compensation in Drosophila, Mol. Cell. 51 (2) (2013) 156–173, https://doi.org/10.1016/j.molcel.
[27] D.P. Barlow, M.S. Bartolomei, Genomic imprinting in mammals, Cold Spring Harb. Perspect. Biol. 6 (2) (2014).
[28] A.M. Bond, M.J.W. Vangompel, E.A. Sametsky, et al., Balanced gene regulation by an embryonic brain ncRNA iscritical for adult hippocampal GABA circuitry, Nat. Neurosci. 12 (8) (2009) 1020–1027, https://doi.org/10.1038/nn.2371.
[29] I. Cajigas, D.E. Leib, J. Cochrane, et al., Evf2 lncRNA/BRG1/DLX1 interactions reveal RNA-dependent chromatin remodeling inhibition, Aug 1, Development 142 (15) (2015) 2641–2652, https://doi.org/10.1242/dev.126318.
[30] A. Minajigi, J.E. Froberg, C. Wei, et al., A comprehensive Xist interactome reveals cohesin repulsion and an RNA-directed chromosome conformation, Science 349 (6245) (2015), https://doi.org/10.1126/science.aab2276aab2276.
[31] L. Kang, Study on imprinting expression and the roles of a novel long non-coding RNA IRAIN in breast cancer http://cdmd.cnki.com.cn/Article/CDMD-10183-1015588012.htm. Accessed 5 May 2015, 2015.
[32] S. Diederichs, The four dimensions of noncoding RNA conservation, Trends Genet. 30 (4) (2014) 121–123, https://doi.org/10.1016/j.tig.2014.01.004.
[33] P. Ji, S. Diederichs, W. Wang, et al., MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer, Oncogene 22 (39) (2003) 8031–8041.
[34] V. Srikantan, Z. Zou, G. Petrovics, et al., PCGEM1, a prostate-specific gene, is overexpressed in prostate cancer, Oct 24, Proc. Natl. Acad. Sci. U. S. A. 97 (22) (2000) 12216–12221.
[35] E. Lau, Non-coding RNA: Zooming in on lncRNA functions, Sep, Nat. Rev. Genet. 15 (9) (2014) 574–575, https://doi.org/10.1038/nrg3795.
[36] J. Zhang, Z. Lin, Y. Gao, et al., Downregulation of long noncoding RNA MEG3 is associated with poor prognosis and promoter hypermethylation in cervical cancer, J. Exp. Clin. Cancer Res. 36 (1) (2017) 5, https://doi.org/10.1186/s13046-016-0472-2.
[37] Y. Zhang, X. Cheng, H. Liang, et al., Long non-coding RNA HOTAIR and STAT3 synergistically regulate the cervical cancer cell migration and invasion, Chem. Biol. Interact. 25 (286) (2018) 106–110, https://doi.org/10.1016/j.cbi.
[38] C. Ding, Z. Yang, Z. Lv, et al., Long non-coding RNA PVT1 is associated with tumor progression and predicts recurrence in hepatocellular carcinoma patients, Oncol. Lett. 9 (2) (2015) 955–963.
[39] Y. Takahashi, G. Sawada, J. Kurashige, et al., Amplification of PVT-1 is involved in poor prognosis via apoptosis inhibition in colorectal cancers, Br. J. Cancer 110 (1) (2014) 164–171, https://doi.org/10.1038/bjc.
[40] X. Yang, W. Zhang, S.Q. Cheng, et al., High expression of lncRNA GACAT3 inhibits invasion and metastasis of non-small cell lung cancer to enhance the effect of radiotherapy, Eur. Rev. Med. Pharmacol. Sci. 22 (5) (2018) 1315–1322, https://doi.org/10.26355/eurrev_201803_14473.
[41] X. Zhang, H. Tang, F. Liu, Expression of long non-coding RNA Gas5 and its significance in non-small cell lung cance, 2015. http://www.cnki.net, Accessed 8 Feb 2015.
[42] R.J. Flockhart, D.E. Webster, K. Qu, et al., BRAFV600E remodels the melanocyte transcriptome and induces BANCR to regulate melanoma cell migration, Genome Res. 22 (6) (2012) 1006–1014, https://doi.org/10.1101/gr.140061.112.
[43] L. Hu, M. Li, L. Pu, et al., The different prognostic value of long non-coding RNA BANCR in human cancers, Minerva Med. 108 (1) (2017) 97–100, https://doi.org/10.23736/S0026-4806.
[44] K.X. Lou, Z.H. Li, P. Wang, et al., Long non-coding RNA BANCR indicates poor prognosis for breast cancer and promotes cell proliferation and invasion, Eur. Rev. Med. Pharmacol. Sci. 22 (5) (2018) 1358–1365, https://doi.org/10.26355/eurrev_201803_14479.
[45] Ke Zhou, Qin Ou, Geng Wang, Wenqi Zhang, Yin Hao, Wenfang Li, High long non-coding RNA NORAD expression predicts poor prognosis and promotes breast cancer progression by regulating TGF-β pathway, Cancer Cell. Int. 19 (1) (2019), https://doi.org/10.1186/s12935-019-0781-6.
[46] R.J. Akhurst, A. Hata, Targeting the TGFβ signalling pathway in disease, Nat. Rev. Drug. Discov. 11 (10) (2012) 790–811, https://doi.org/10.1038/nrd3810.
[47] M. Rafieian-Kopaei, M. Setorki, M. Doudi, et al., Atherosclerosis: process, indicators, risk factors and new hopes, Int. J. Prev. Med. 5 (8) (2014) 927–946.
[48] L. Chen, H. Yao, J.Y. Hui, et al., Global transcriptomic study of atherosclerosis development in rats, Gene 592 (1) (2016) 43–48, https://doi.org/10.1016/j.gene.2016.07.023.
[49] A.N. Kallen, X.B. Zhou, J. Xu, et al., The imprinted H19 LncRNA antagonizes Let-7 MicroRNAs, Mol. Cell. 52 (1) (2013) 101–112, https://doi.org/10.1016/j.molcel.2013.08.027.
[50] A. Keniry, D. Oxley, P. Monnier, et al., The H19 lincRNA is a developmental reservoir of miR-675 that suppresses growth and Igf1r, Nat. Cell. Biol. 14 (7) (2012) 659–665, https://doi.org/10.1038/ncb2521.
[51] J.X. Pan, LncRNA H19 promotes atherosclerosis by regulating MAPK and NF-kB signaling pathway, Eur. Rev. Med. Pharmacol. Sci. 21 (2) (2017) 322–328.
[52] X. Li, H. Wang, B. Yao, et al., lncRNA H19/miR-675 axis regulates cardiomyocyte apoptosis by targeting VDAC1 in diabetic cardiomyopathy, Sci. Rep. 31 (6) (2016) 36340, https://doi.org/10.1038/srep36340.
[53] M.D. Gengze Wu, LincRNA-p21 regulates neointima formation, vascular smooth muscle cell proliferation, apoptosis, and atherosclerosis by enhancing p53 activity, Circulation 130 (17) (2014) 1452–1465, https://doi.org/10.1161/CIRCULATIONAHA.114.011675.
[54] M.D. Ballantyne, K. Pinel, R. Dakin, et al., Smooth muscle enriched long noncoding RNA(SMILR)regulates cell proliferation, Circulation 133 (21) (2016) 2050–2065, https://doi.org/10.1161/CIRCULATIONAHA.115.021019.
[55] L. Jin, X. Lin, L. Yang, et al., AK098656, a novel vascular smooth muscle cell-dominant long noncoding RNA, promotes hypertension, Hypertension 71 (2) (2018) 262–272, https://doi.org/10.1161/HYPERTENSIONAHA.117.09651.

[56] Y. Yang, P. Xi, Y. Xie, et al., Notoginsenoside R1 reduces blood pressure in spontaneously hypertensive rats through a long non-coding RNA AK094457, Int. J. Clin. Exp. Pathol. 8 (3) (2015) 2700–2709 Mar 1, eCollection 2015.
[57] B. Bayoglu, H. Yuksel, H.A. Cakmak, et al., Polymorphisms in the long non-coding RNA CDKN2B-AS1 may contribute to higher systolic blood pressure levels in hypertensive patients, Clin. Biochem. 49 (10–11) (2016 Jul) 821–827, https://doi.org/10.1016/j.clinbiochem.2016.02.012.
[58] F. Garmaroudi, B. McManus, J. David, et al., Inflammation in myocardial diseases, Circ. Res. 110 (1) (2012) 126–144, https://doi.org/10.1161/CIRCRESAHA.111.243170.
[59] N. Toshiyuki, O. Junichi, S. Aya, et al., Deletion of apoptosis inhibitor of macrophage (AIM)CD5L attenuates the inflammatory response and infarct size in acute myocardial infarction, Apr 4, e002863, J. Am. Heart Assoc. 5 (4) (2016), https://doi.org/10.1161/JAHA.115.002863.
[60] N. Ishii, K. Ozaki, H. Sato, et al., Identification of a novel non-coding RNA, MIAT, that confers risk of myocardial infarction, J. Hum. Genet. 51 (12) (2006) 1087–1099.
[61] X. Li, J. Zhou, K. Huang, Inhibition of the lncRNA Mirt1 attenuates acute myocardial infarction by suppressing NF-κB activation, Cell. Physiol. Biochem. 42 (3) (2017) 1153–1164, https://doi.org/10.1159/000478870.
[62] C. Li, J. Shi, Z. Yu, MiR-320 promotes B cell proliferation and the production of aberrant glycosylated IgA1 in IgA nephropathy, J. Cell. Biochem. 119 (6) (2018) 4607–4614, https://doi.org/10.1002/jcb.26628.
[63] H. Hu, J. Wu, D. Li, et al., Knockdown of lncRNA MALAT1 attenuates acute myocardial infarction through miR-320-Pten axis, Biomed. Pharmacother. 106 (2018) 738–746, https://doi.org/10.1016/j.biopha.2018.06.122.
[64] T. Gutschner, M. Hammerle, M. Eissmann, et al., The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells, Cancer Res. 73 (3) (2013) 1180–1189, https://doi.org/10.1158/0008-5472.CAN-12-2850.
[65] H. Yuqi, X. Bo, L. Yuanhua, et al., LncRNA CDKN2B-AS1 promotes tumor growth and metastasis of human hepatocellular carcinoma by targeting let-7c-5p/NAP1L1 axis, Cancer Lett. 28 (437) (2018) 56–66, https://doi.org/10.1016/j.canlet.2018.08.024.
[66] J.L. Rinn, M. Kertesz, J.K. Wang, et al., Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs, Cell 129 (7) (2007) 1311–1323.
[67] L. Li, B. Liu, O. Wapinski, et al., Targeted disruption of hotair leads to homeotic transformation and gene derepression, Cell. Rep. 5 (1) (2013) 3–12, https://doi.org/10.1016/j.celrep.2013.09.003.
[68] P. Schorderet, D. Duboule, Structural and functional differences in the long non-coding RNA, hotair in mouse and human, PLoS Genet. 7 (5) (2011), https://doi.org/10.1371/journal.pgen.1002071 May, e1002071.
[69] J. Aprea, S. Prenninger, M. Dori, et al., Transcriptome sequencing during mouse brain development identifies long non-coding RNAs functionally involved in neurogenic commitment, EMBO J. 32 (24) (2013) 3145–3160, https://doi.org/10.1038/emboj.2013.245.
[70] X. Wang, Z. Wang, J. Wang, et al., LncRNA MEG3 has anti-activity effects of cervical cancer, Biomed. Pharmacother. 94 (2017) 636–643, https://doi.org/10.1016/j.biopha.2017.07.056.
[71] W. Peng, S. Si, Q. Zhang, et al., Long non-coding RNA MEG3 functions as a competing endogenous RNA to regulate gastric cancer progression, J. Exp. Clin. Cancer Res. 8 (34) (2015) 79, https://doi.org/10.1186/s13046-015-0197-7.
[72] Y.N.Z. Wang, K. Shan, M.D. Yao, et al., Long noncoding RNA-GAS5: a novel regulator of hypertension-induced vascular remodeling, Hypertension 68 (3) (2016) 736–748, https://doi.org/10.1161/HYPERTENSIONAHA.116.07259.
[73] Y. Xia, Z. He, B. Liu, et al., Downregulation of Meg3 enhances cisplatin resistance of lung cancer cells through activation of the WNT/β-catenin signaling pathway, Mol. Med. Rep. 12 (3) (2015) 4530–4537, https://doi.org/10.3892/mmr.2015.3897.
[74] Y. Wang, D. Kong, Knockdown of lncRNA MEG3 inhibits viability, migration, and invasion and promotes apoptosis by sponging miR-127 in osteosarcoma cell, J. Cell. Biochem. 119 (1) (2018) 669–679, https://doi.org/10.1002/jcb.26230.
[75] H. Liu, D. Ye, A. Chen, et al., A pilot study of new promising non-coding RNA diagnostic biomarkers for early-stage colorectal cancers, Clin. Chem. Lab. Med. 57 (7) (2019) 1073–1083, https://doi.org/10.1515/cclm-2019-0052.
[76] D.D. Yin, Z.J. Liu, E. Zhang, et al., Decreased expression of long noncoding RNA MEG3 affects cell proliferation and predicts a poor prognosis in patients with colorectal cancer, Tumour. Biol. 36 (6) (2015) 4851–4859, https://doi.org/10.1007/s13277-015-3139-2.
[77] R. Zhou, K.K. Chen, J. Zhang, et al., The decade of exosomal long RNA species: an emerging cancer antagonist, Mol. Cancer. 17 (1) (2018) 75, https://doi.org/10.1186/s12943-018-0823-z.