LncRNAs: From Basic Research to Medical Application

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Abstract

This review aimed to summarize the current research contents about long noncoding RNAs (lncRNAs) and some related lncRNAs as molecular biomarkers or therapy strategies in human cancer and cardiovascular diseases. Following the development of various kinds of sequencing technologies, lncRNAs have become one of the most unknown areas that need to be explored. First, the definition and classification of lncRNAs were constantly amended and supplemented because of their complexity and diversity. Second, several methods and strategies have been developed to study the characteristic of lncRNAs, including new species identifications, subcellular localization, gain or loss of function, molecular interaction, and bioinformatics analysis. Third, based on the present results from basic researches, the working mechanisms of lncRNAs were proved to be different forms of interactions involving DNAs, RNAs, and proteins. Fourth, lncRNAs can play different important roles during the embryogenesis and organ differentiations. Finally, because of the tissue-specific expression of lncRNAs, they could be used as biomarkers or therapy targets and effectively applied in different kinds of diseases, such as human cancer and cardiovascular diseases.

Key words: lncRNA, molecular biomarker, therapy strategy, cancer, cardiovascular diseases

Introduction

The insights of the genome have changed overwhelmingly over the past decades. It has been a long time before we realize our unawareness of microcosm. There is no doubt that the advent of sensitive, high-throughput sequencing (NGS) has given rise to an unheard-of ability to detect novel transcripts [1]. Those “nonsense and dark materials of genome” unravel their mystery, play more important roles, and participate in various biological processes. However, those discoveries don’t mean the end, but seem to open a door to take us toward a more in-depth research on microcosm. Until now, except for messengers RNA (mRNA) and other functional RNAs, such as transfer RNA (tRNA), small nuclear RNA (snRNA), small nucleolar (snoRNA), and micro RNA (miRNA), we know very little on how lncRNAs function, how many different types of lncRNAs exist, or even whether most of them carry biological significance [1]. This review focused on the basic research of lncRNAs and their medical applications in human cancer and cardiovascular diseases.

Definition and classification of lncRNAs

The present definition of lncRNA, that is, a RNA molecule with a size longer than 200 nucleotides that is not translated into a protein, may be arbitrary without considering the following two issues [2]. 1) About the molecular size: A cutoff of 200 nucleotides was more based on the principle of RNA binding acid to silica columns during RNA purification [3]. While a protein coding gene (PCG) is usually defined as a transcript that contains an open reading frame (ORF) longer than 100 amino acids [4], thus a lncRNA might contain a longer ORF but not synthesize polypeptides. Besides, polypeptides shorter than 100 amino acids can be functional in organisms and are not outgrowth of canonical proteins [5]. 2) About the functions: The same RNA can contain both PCG and non-coding
functions [6]. Coding transcript can lose their ability to encode a protein, and noncoding transcripts can acquire a coding function [6]. Such above issues obscures a clear annotation of lncRNAs. The definition by Mercer et al is more moderate, who defined lncRNAs as RNA molecules that may function as either primary or spliced transcripts and could not be classified into known classes of small RNAs or structural RNAs [7]. Compared with small ncRNAs, such as miRNAs, which have been defined in more detail and comprehensively, the definition of lncRNA is still extensive with complex contexts. However, finally some difference has been made following an in-depth research of lncRNAs.

LncRNAs constitute various RNA molecules. It is difficult to classify them because of their broad spectrum of molecular splicing and cellular functions as a result of implementing different modes of action. The traditional classification is based on their locations of transcripts from genome, including five broad categories: (1) sense, (2) antisense, (3) bidirectional, (4) intronic, and (5) intergenic [8]. However, as new forms of lncRNAs were continually being found, the traditional classification of lncRNA could not cover the whole field and should be described in more detail. Sandre et al., who viewed it more widely, classified lncRNAs into eight categories: (A) divergent (pancRNA: They originate from the opposite strand of the same promoter region of protein coding gene as the adjacent) and convergent (They encoded on the opposite strands and facing each other); (B) intronic (They transcribed from an intron of another gene); (C) intergenic (They located distant from other genes, usually >10kb); (D) overlapping sense (They overlapped with other genes on the same strand) and overlapping antisense (They overlapped with other genes on the opposite strand); (E) enhancer RNA (They expressed as uni- or bidirectional transcripts); (F) miRNA host gene (Figure 1) [9]. Compared with the former classification, the latter described the relationship between lncRNA gene and their neighborhood gene in detail. However, they still belong to one criterion in essence. Following the development of new forms of lncRNAs, the classification needs to be continuously improved taking more criteria into account, such as their splicing modes or their final working mechanisms.

**Figure 1.** The classification of lncRNAs: (A) divergent (pancRNA: They originate from the opposite strand of the same promoter region of protein coding gene as the adjacent) and convergent (They encoded on the opposite strands and facing each other); (B) intronic (They transcribed from an intron of another gene); (C) intergenic (They located distant from other genes, usually >10kb); (D) overlapping sense (They overlapped with other genes on the same strand) and overlapping antisense (They overlapped with other genes on the opposite strand); (E) enhancer RNA (They expressed as uni- or bidirectional transcripts); (F) miRNA host gene [9].
Research methods and strategies of lncRNAs

Unlike miRNAs, which have been extensively studied, the research of lncRNAs is still in its infancy. The following sections discuss four research strategies of lncRNAs with several common methods for each strategy (Figure 3): (1) new species identification, (2) subcellular localization, (3) molecular interaction, and (4) gain of loss of function and (5) bioinformatics analysis.

New species identification

Although some difficulties exist in terms of lncRNA discovery because of tissues specificity and low expression levels, many kinds of methods still exist for identifying new lncRNAs, which were well reviewed by Kashi et al. [10]. Each kind of technology was used to certain purpose. Among them, RNA-seq might be the most wide-spread method used not only for RNA expression detection but also for novel lncRNA discovery [10]. Sometimes, because of limited samples sizes for RNA-seq, single-cell transcript sequencing were needed, including Smart-Seq, which allows the detection of alternative transcripts isoforms and single-nucleotide polymorphisms [11]; DP-Seq, which allows amplification of RNA from sample sizes as small as 50pg [10]; and Quartz-Seq, which reduces the background noise [12]. Besides, some methods could be used to map transcripts that are in the process of being degraded, including PARE-Seq [13], GMUCT [14], and Degradome-Seq [15], by which decapped transcripts are adapter ligated and reverse transcribed [10].

Subcellular localization

Fluorescence in situ hybridization (FISH) is a method for visualization the subcellular localization of a certain lncRNA. For example, MALAT1 has been visualized by RNA-FISH, which indicated that it is rich in nuclear speckles of cells in interphase and is concentrated in mitotic interchromain granule clusters [16]. RNA-FISH was used to verify that MIR99HG (MONC) and MIR100HG were located in the nucleus [17]. Furthermore, RNA-FISH could also be combined with DNA-FISH to validate co-localization of a transcript with chromatin sequences [10]. Alternatively, new recent technology of fluorescent in situ RNA sequencing (FISSEQ), which amplify cDNA in crosslinked cells and tissue samples [18], provide higher resolution and can identify a higher number of targets than RNA-FISH [10].

Molecular interaction

On the basis of the working mechanisms of lncRNAs, molecular interactions occur among RNA, DNA, and proteins. The related technologies can also be classified into three categories: (1) RNA–protein interaction: RNA immunoprecipitation is used to analyze and purify RNAs associated with specific proteins by directing antibodies against the target protein [10]. High-throughput sequencing cross-linking immunoprecipitation (HITS-CLIP/ CLIP-Seq) is another technique to analyze the
interaction between RNA and protein by cross-linking cell in vitro with UV light [10]. (2) RNA-DNA interaction: chromatin isolation by RNA purification (ChiRP) can analyze the relationship between RNA and chromatin by 20 nt-long biotinylated oligonucleotides which specifically recognize the target lncRNA [19]; RNA antisense purification (RAP) is another method which can be used to identify the genomic regions of chromatin that interact with RNAs using about 120nt long antisense RNA probes [20]; capture hybridization analysis of RNA targets (CHART) involves the purification of cross-linked protein, RNA, and DNA complexes by designing its probe on the region of potential open binding sites [10, 21]. (3) RNA and RNA interaction: rap-rna modification of the RAP method can provide a means to detect RNA-RNA interactions, even to distinguish the direct and indirect interaction between RNA transcripts by using different cross-linking methods [10]; Cross-linking, ligation and sequencing of hybrids (CLASH) is another technology for capturing direct RNA and RNA interaction by using UV cross-linking [22].

**Gain or loss of function**

Traditionally, if we want to learn about the function of a new molecule, we generally over-express or knock down the candidate target to investigate changes resulted by these means. LncRNAs could also follow the above methods. For example, using over-expression plasmid and siRNA (or shRNA) separately to up regulating and down regulating lncRNA, Cui et al., have verified that over-expression of HULC was able to accelerate lipogenesis in HepG2 and Huh7 cells, while HULC siRNA attenuate the lipogenesis in HepG2.2.15 cells [23]. For another, using the same methods, Nie et al., have found that knockdown of ANRIL expression could impair cell proliferation and induce cell apoptosis both in vitro and vivo [24]. In fact, in order to gain stable function of a gene, technology of lentivirus has been used for many years. Presently, although there has always been a dispute, exact gene editing technologies, such as CRISPR/CAS9 and NgAgo have emerged. Compared to the traditionally methods, they might be expected to realize the more accurate gene editing than any time in the past.

**Bioinformatics analysis**

The lncRNA databases have grown rapidly following with the research of lncRNAs. The database of lncRNAdb (http://www.lncrnadb.org/) is a famous long non-coding RNA research database that provides full comments on functional lncRNAs [25]. The present version is lncRNAdb 2.0 [26]. Another well-known ncRNA research database NONCODE (http://www.noncode.org) also provides full comments on lncRNAs, including expression and functions predicted by their computer software (ncFANs) [27]. Now the version has been updated to NONCODE v4 [28]. LNCipedia (http://www.lncipedia.org) provides the sequence and full comments on structures of human lncRNAs[29-30]. LncRNA disease (http://cmbi.bjmu.edu.cn/lncrnadisease) provides full comments of reported disease-related lncRNAs[31]. NRED (http://jsm-research.imb.uq.edu.au/nred/) provides the lncRNA expression information of human and mouse based on chip data [32]. ChiPBase (http://deepbase.sysu.edu.cn/chipbase/) provides the map of lncRNA, comprehensive identification, and annotation of the transcription regulation [33]. It also integrated lncRNAs identified by high-throughput RNA-seq, their expression profile and even the transcription factor binding sites identified by ChiP-seq experiment [33]. fRNAdb (http://www.ncrna.org/) collects non-code transcripts with or without comments from H-invitation, NONCODE and RNAdb database and provides searching function of four kinds of ncRNAs, including miRNAs, short ncRNAs, mid-size ncRNAs and lncRNAs [34]. Starbase (http://starbase.sysu.edu.cn/mirLncRNA.php) has set up the most comprehensive experimental support by CLIP-Seq for the regulation network of miRNA and lncRNA, Protein (RNA-binding protein) and lncRNA (includes lncRNA, pseudogene, circular RNA), competing endogenous RNAs (ceRNA) regulatory networks and provides prediction tools for a lncRNA function [35]. In fact, the section of bioinformatics analysis should not be summarized as a separate section because the context of each of the aforementioned sections could be permeated with biological information. Necessary information can be searched before studying a new function of a known lncRNA, or more information can be supplemented after the research on a new lncRNA.

**Working mechanisms of lncRNAs**

LncRNAs play important regulatory roles and participate in different levels of biological processes, such as chromatin remodeling, histone modification, and DNA methylation, and also serve as transcription factors or enhancers. The mechanisms underlying their functions can be summarized as interactions among RNA, DNA, and proteins (Figure 2). These interactions can be further summed up into two modes: (1) based on sequence hybridization and (2) based on secondary or tertiary structures.
**Figure 2.** The working mechanisms of lncRNAs. The present known working mechanisms of lncRNAs might be only a part of its all functions, just like several hubbles among all blowing group. A. ceRNA function of lncRNA: circRNA compete binding with miRNA to prevent miRNA binding with target mRNAs; B. Enhancer on/off: lncRNAs transcribed from an enhancer region interact with enhancer-promoter contact to inhibit the transcription of the protein-coding gene; C. lncRNAs acting as scaffold linking different proteins interaction; D. lncRNAs binding with proteins to prevent their actions; E. lncRNAs recruiting proteins, such as chromatin-modifying complexes to specific target sites in the genome; F. lncRNAs loop formation and transcription of the associated gene; G. lncRNA transcripts evicting proteins from chromatin, such as panceRNA prevent DNMT from methylating DNA in their promoter region, thereby ensuring mRNA transcription; H. Stabilizing of mRNA: lncRNA recruiting proteins to preventing degradation.

**Interaction based on specific sequence hybridization**

Some lncRNAs can mediate interactions by specific sequence hybridization with DNAs or other RNAs. For example, antisense intronic noncoding ras association domain family member 1 (ANRASSF1), which is transcribed in the antisense direction relative to the protein-coding mRNAs of the RAS association domain family member 1 (RASSF1) gene locus, could interact with genomic DNA, forming an RNA–DNA hybrid and regulating the expression of the sense gene at the pre-transcriptional level [36]. Phosphatase and tensin homolog pseudogene 1 antisense RNA (PTENP1-AS) may be an example of the RNA–RNA interaction. Because of the lack of a poly(A) tail, the stability and export to the cytoplasm of phosphatase and tensin homolog pseudogene 1 (PTENP1) is facilitated by interactions with PTENP1-AS, which has three variants: alpha, beta, and unspliced [37]. During this process, PTENP1-AS beta forms an RNA–RNA duplex with the PTENP1 transcript, altering its subcellular distribution and increasing its RNA stability [6], [37].

If the aforementioned examples of interaction between lncRNA and other RNAs are a universal phenomenon, the discovery of competing endogenous RNA (ceRNA) function of lncRNAs, which is of great biological significance, will not be surprising. LncRNAs can participate in the ceRNA network, by which lncRNAs cross talk with other RNAs by sharing the same miRNAs [38]. These exogenously expressed transcripts contain tandem repeats of miRNA response elements (MRE) sites that allow them to specifically bind a distinct miRNA or combination of miRNAs [39]. Once the miRNA(s) of interest is decoyed, it is unavailable to bind to its targets, leading to effective derepression of these transcripts [40], [41]. Such ceRNA function of lncRNAs has been well studied in human cancers. Metastasis-associated lung adenocarcinoma transcript 1(MALAT1) could sponge miR-145 to modulate the
radio-sensitivity of high-risk human papillomavirus (HR-HPV+) cervical cancer [42]. Liu S. et al., reported that MALAT1 could competitively bind with miR-124 to up-regulate the RBG2 expression, and then promote HR-HPV (+) cervical cancer cell growth and invasion [43]. HOX transcript antisense RNA (HOTAIR) could cross talk with erb-b2 receptor tyrosine kinase 2 (HER2kny) via miR-331-3p in gastric cancer [44]. Li JT. et al., identified that HOTAIR could suppress the miR-568 to up-regulate the expression of S100 calcium binding protein A1 (S100A), and then facilitates the metastasis of breast cancer [45]. The B-Raf proto-oncogene, serine/threonine kinase (BRAF) pseudogene 1 is a newly reported lncRNA that functions as a ceRNA for BRAF, in part by sponging miR-30a, miR-182, and miR-876[46].

Functions of IncRNAs during the embryogenesis and organ differentiation

IncRNA transcripts were found at all examined stages during the early differentiation process by a single-cell sequencing study [52]. Furthermore, in the following various differentiation periods, they might also act as important functions. In this section, we would like to discuss several IncRNAs involved in the embryogenesis and organ differentiation.

Imprinted genes are monoallelically expressed according to the parent of origin and are critical for embryogenesis [53]. H19 is a well-known imprinted gene, which is exclusively expressed from the maternal allele and governs normal embryogenesis [54]. Maternally expressed 3 (meg3) is another imprinted gene, which has effects on neighboring genes in cis and results in perinatal lethality [55].

X-chromosome inactivation (XCI) is also an interesting phenomenon during embryogenesis. Xist was found as an XCI gene in knockout mice two decades ago [56-57]. Lacking Xist could cause female mice die during the first half of gestation, while male mice were unaffected [9]. However, knockout female mice with a single X-chromosome (XO) lacking Xist could survive [9]. Thus, it can be explained by the failure to adjust the X-chromosome gene dosage and causes embryonic lethality [9].

There are so many kinds of IncRNAs related to various organ differentiations that we could not cover them all. However, we would like to focus more about on IncRNAs related to cardiovascular differentiation.

Fendrr is an example of IncRNAs demonstrated to play an essential role in cardiovascular differentiation and embryo survival [9]. Grote et al. have verified that loss of Fendrr lead to impaired differentiation of tissues derived from lateral mesoderm, the heart and the body wall, and eventually result in embryonic death [58-59]. Embryos lacking Fendrr lead to upregulation of some transcription factors which controlled lateral plate or cardiac mesoderm differentiation, coupled with a drastic reduction in PRC2 occupancy along with decreased H3K27 trimethylation and/or an increase in H3K4 trimethylation at their promoters [59].

Braveheart (Boht) has been verified as another cardiac-expressed IncRNA [60]. It epigenetically regulates cardiomyocyte differentiation [61]. It was cardiac-enriched approximately threefold than other tissues, but expressed similar with E14.5 embryos and adults; It was also not regulated late after
Medical applications of IncRNAs in human diseases

The best results of basic research are transforming the discoveries into diagnostic methods and therapeutic strategies for human diseases. Because of the tissue-specific characteristics of IncRNAs, they would be the next generation of biomarkers or targets for human diseases such as human cancer and cardiovascular diseases.

Biomarkers and therapy strategies for human cancers (Table 1)

IncRNAs, which isolated from tumor cells or circulating system, could provide readily-available, inexpensive and stable blood-borne diagnostics to more readily detect cancers and cancer subtypes[66]. Yang et al. analyzed eight kinds of IncRNAs in 240 patients with HCC and reported that highly upregulated in liver cancer (HULC) had a significant association with vascular invasion and was a positive factor for HCC overall survival and disease-free survival time [67]. They also reported that H19 was overexpressed in patients with hepatitis B [67]. Furthermore, they indicated that H19 and maternally expressed 3 (MEG3) were both considered to be risk factors for high alpha fetoprotein (AFP) level [67]. Tang J., et al have reported that compared with the traditional biomarkers of HCC (AFP), three IncRNAs (RP11-160H22.5, XLOC_014172 and LOC149086) might be the potential biomarker for the tumorigenesis prediction and XLOC_014172 and LOC149086 for metastasis prediction in the future [68]. Zhao et al., have reported that SPRY4 intronic transcript 1 (SPRY4-IT1) is an independent prognostic factor of overall survival in patients with urothelial carcinoma of the bladder (UCB) [69]. The work of Kristina P Sørensen.et al., firstly investigated the prognostic potential of IncRNA profiles for patients with breast cancer, which can distinguish metastatic patients from non-metastatic patients with sensitivity more than 90% and specificity of 64 to 65% [70].

Table 1. Working mechanisms and medical applications of IncRNAs in human cancer

| IncRNA | Working mechanisms | Medical applications |
|--------|--------------------|----------------------|
| ANRASSF1 | form an RNA/DNA hybrid and recruits PRC2 to the RASSF1A promoter[76] | Biomarker: breast cancer[77] |
| ANRIL | chromatin remodeling: CDKN2A/B [47], Kruppel-like factor 2 (KLF2) and p21 locus by interacting with PRC1 and PRC2 [24, 78] | Biomarker: acute lymphoblastic leukemia (ALL) [79], ovarian cancer [80], non-small cell lung cancer (NSCLC) [24] |
| H19 | 1. regulate Igf2 imprinting[81]; 2. miR-675 precursor[82-85]; 3. cellRNA function by sponging of let-7[86-88], miR-138[89], miR-200a[89]; 4. chromatin remodeling by binding mBD1[90]; 5. interact with Slug or EZH2 and regulate E-cadherin expression[91-92] | Biomarker: hepatocellular (HCC)[67] |
| MALAT1 (NEAT2) | 1. bind to unmethylated P2c2 promotes E2F1 SUMOylation, leading to activation of the growth-control gene program[96]; 2. cellRNA function by sponging of miR-145[42], miR-124[43], miR-205[97]; | Cancer therapy: BC-819[72], BC-821, siRNA and anti-miR* for lung cancer[93]; Cancer therapy: double promoter toxin vector P4-DTA-P3-DTA for pancreatic cancer, ovarian cancer and HCC[94-95]; Cancer therapy: DTA-H19 for unresectable pancreatic cancer[66, 75] |

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Because of the heterogeneity of human cancer, the personalized medicine for human cancer has been proposed for many years, and the precision medicine has become the most important field for cancer research and treatment. However, the etiologies of human cancer are so complex that the results need to be transformed by different levels of clinical trials. Several strategies of cancer therapy have been developed presently.

Treating cancer by interference of RNA expression has developed as a treatment modality because growth-promoting lncRNAs could be inactivated through antisense technologies [66]. LncRNAs could also function as mRNA or miRNA sponges to inhibit the growth-promoting, pro-tumorigenic signaling pathway so that synthetically-engineered lncRNAs may be employed through replacement therapy to inhibit tumor cells [71]. Dextran nanoparticles can deliver chemotherapy to the nucleus, which may be used to attach cytotoxic agents to lncRNAs [66]. The plasmid DTA-H19 was designed to express a diphtheria toxin subunit controlled by the H19 promoter [72], [73], which could be injected into tumor and lead to a H19-dependent activation of diphtheria toxin within the tumor [45]. Another emerging method is to increase the activity of...
tumor suppressor by neutralizing the inhibitory effects of lncRNAs through antisense oligo nucleotides [66]. These compounds, which are directly taken up by cells, can be injected subcutaneously without any delivery vehicle [66]. They can cross endosomal membranes and enter the nucleus to inhibit PRC2 interaction with lncRNAs[46]. These compounds could also cross the blood brain barrier without a lipid carrier [66].

**Biomarkers and therapy strategies in human cardiovascular diseases (Table 2)**

Although lncRNA in cardiovascular have not been researched as extensively and thoroughly as in human cancer, some research has indicated that lncRNA could be biomarkers for cardiovascular diseases. Kumarswamy et al., have validated mitochondrial lncRNA uc022bqs.1 (LIPCAR) as a novel biomarker of cardiac remodeling that predicts future death in patients with heart failure [74]. Myocardial infarction (MI) is another kind of important cardiovascular disease. Vausort et al., have verified about five kinds of lncRNAs as biomarkers for predicting the outcome of MI in about 414 patients, including hypoxia inducible factor 1A antisense RNA 2 (HIA1A-AS2), cyclin-dependent kinase inhibitor 2B antisense RNA 1 (ANRIL), potassium voltage-gated channel, KQT-like subfamily, member 1 opposite strand/antisense transcript 1 (KCNQ1OT1), myocardial infarction-associated transcript (MIAT), and MALAT1 [75]. Their results are summarized as follows: (1) HIA1A-AS2, CNQ1OT1 and MALAT1 were higher in patients with MI than in healthy volunteers (P<0.01), while levels of ANRIL were lower in patients with MI (P=0.003); (2) compared with patients with non-ST-segment-elevation MI, patients with ST-segment-elevation MI had lower levels of ANRIL (P<0.001), KCNQ1OT1 (P<0.001), MIAT (P<0.001), and MALAT1 (P=0.005); (3) levels of ANRIL were related to age, diabetes mellitus, and hypertension; (4) HIA1A-AS2 elevated in patients presenting within 3 h of chest pain onset than in patients presenting later; (5) ANRIL, KCNQ1OT1, MIAT, and MALAT1 were significant univariable predictors of left ventricular dysfunction as assessed by an ejection fraction ≤40% at 4-month follow-up; and (6) ANRIL and KCNQ1OT1 improved the prediction of left ventricular dysfunction by a model, including demographic features, clinical parameters, and cardiac biomarkers based on the multivariable and reclassification analyses [75].

**Conclusions**

In summary, we have separately discussed several items of lncRNAs, including their definition and classification, their related research methods and strategies, their possible working mechanisms, their function during embryogenesis and organ differentiation, their significance in human cancer and cardiovascular diseases. However, each section might have their limitations due to our unawareness of them. We could not make an exact definition for lncRNAs. And following with the discovery of new lncRNAs, we might be confronting with the difficulties from classifications. The present research methods could realize the interaction among RNA, DNA and protein, and provide important bioinformatics clues on basic research, we still need further techniques to reach a whole comprehension on lncRNA network mechanisms. We need not only learn about the real mechanisms of lncRNAs during embryogenesis and development, but also the novel changes in various kinds of diseases, and finally realize the destination of promoting human health by our knowledge.

| LncRNA  | Working mechanisms in cardiovascular diseases | Medical application |
|---------|-----------------------------------------------|---------------------|
| LIPCAR  | NA                                            | **Biomarkers:** cardiac remodeling predicts future death in patients with heart failure [74] |
| ANRIL   | NA                                            | **Biomarkers:** significant univariable predictors of left ventricular dysfunction [75] |
| KCNQ1OT1| NA                                            | **Biomarkers:** significant univariable predictors of left ventricular dysfunction [75] |
| MALAT1  | NA                                            | **Biomarkers:** significant univariable predictors of left ventricular dysfunction [75] |
| MIAT    | ceRNA: function by sponging of miR-150-5p [166] | **Biomarkers:** significant univariable predictors of left ventricular dysfunction [75] |
| MHRT    | Sequences Brg1 from its genomic DNA targets to prevent chromatin remodeling [167] | **Biomarkers:** myocardial infarction (MI) [168] |
| UCA1    | NA                                            | **Biomarkers:** Acute myocardial infarction (AMI) [169] |
| LncRNA-p21| Binding with MDM2 and release MDM2 repression of p53 [170] | NA |
| RNC8    | acts as a ceRNA, and forms a feedback loop with Kruppel-like factor 2 and miR-185-5p to regulate cell function, atheroprotective role in atherosclerosis [171] | NA |
| ROR     | promotes cardiac hypertrophy via interacting with miR-133 [172] | NA |
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Competing Interests

The authors have declared that no competing interest exists.

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