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ORIGINAL RESEARCH ARTICLE

Research progress on the relationship between long chain noncoding RNA and cardiovascular disease

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ABSTRACT

Long non coding RNA (lncrna) is a highly conserved non coding RNA (ncRNA) with a length of more than 200 nucleotides. Studies have found that lncrna is closely related to transcriptional regulation, post transcriptional regulation and apparent regulation, and thus participates in the regulation of cardiovascular physiology and pathophysiology. This article summarizes the current biological characteristics of circulating lncrna, the value of lncrna as a potential biomarker of cardiovascular diseases and the future prospects of therapeutic methods.

Keywords: long chain noncoding RNA; cardiovascular disease; research progress

1.Introduction

Long non coding RNA (lncrna) plays a key role in transcription, post transcriptional regulation and chromatin modification. Many studies have found that lncrna is associated with myocardial injury and cardiovascular disease, indicating that lncrna is of great significance to the occurrence and development of cardiovascular disease. This paper reviews the biological characteristics of circulating lncrna and the research progress on the relationship between lncrna and cardiovascular diseases such as atherosclerosis, myocardial infarction, heart failure, cardiac hypertrophy, hypertension, arrhythmia, etc.

2. Discovery, classification and mechanism of ncRNA

Genomic studies have found that less than 2% of mammalian genes are translated into proteins, and most of the rest are non coding RNA (ncRNA) without coding function. Previously, ncRNA was regarded as a kind of "garbage" in genetic transcription and has no function [1-2]. With the deepening of research, it was found that tRNA and rRNA participate in gene expression, and small nuclear RNA (snRNA) exists together as structural non coding RNA. In recent years, microRNA (miRNA), circular RNA (circrna), small interfering RNA (siRNA) and lncrna have gradually come into people's attention, and they have been found to play

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an important regulatory role in cells [3]. Lncrna has stronger regulatory ability and tissue specificity than protein genome, and is the most important component of ncRNA [4].

Lncrnas are non coding RNAs with transcripts greater than 200 nucleotides. Like messenger RNAs (mRNAs), they are usually transcribed by RNA polymerase II, further spliced and polyadenylated, but they have no or very low coding ability. According to the position of lncrna in gene sequence compared with mRNA, it can be divided into the following six categories: (1) between genes, lncrna is a transcript located in the genomic interval of two amino acid coding gene sequences; (2) Intron lncrna is transcribed from intron of amino acid coding gene sequence; (3) Bidirectional lncrna is located in the opposite chain of the protein coding gene, close to the promoter region and within the genome of 1 KB; (4) Enhancer lncrna, usually located in the enhancer region less than 2 kb; (5) Sense lncrna, located on the same chain of coding gene, overlaps one or more introns and exons; (6) Antisense lncrna, located on the reverse chain of the coding sequence gene, overlaps one or more introns and exons [5]. Although some lncrnas have been proved to be conservative in evolution, a large number of lncrnas do not show the same level of conservative constraints as protein coding transcripts [6]. Many lncrnas are located in synthetic genomic regions and display conservative expression patterns between species in a cell type specific manner because their regulatory and promoter elements are similar [7-8]. Lncrna has population specificity and strong specificity between cells. Because lncrna has a relatively long base sequence, it can complete a variety of RNA RNA RNA interactions and form a complex three-dimensional space. Its unique physical configuration enables lncrna to establish nuclear domains with target genes and combine proteins to form RNA DNA protein complexes [9]; the open single stranded RNA sequence enables lncrna to perform its basic functions by combining with other base sequences [10]. Therefore, lncrna can weaken or trigger the transcriptional regulation of genes through a variety of mechanisms.

Lncrna interacts with proteins to form protein complexes. According to their cellular localization, lncrna can be used as a chromatin modifier to modify specific sites of chromatin [11]; as a signal molecule, it regulates cell processes and separates the molecular decoration of proteins from chromatin [12]. Intranuclear lncrnas also participate in the regulation of chromatin, recruit epigenetic modification factors to specific sites through direct interaction with genomic DNA [13], and some lncrnas bind to adjacent genomic sites to initiate genomic imprinting [14]. Through direct RNA interaction, lncrna regulates protein transcription by regulating protein stability [15], translation [16] and splicing [17]. By indirectly regulating the transcription level, lncrna has also been proved to be able to isolate miRNAs from endogenous targets and act as a molecular sponge [18]. Lncrna can also regulate its target gene after transcription, and indirectly act as a precursor of miRNA. It can not only regulate its target gene lncrnas, but also encode short peptides [19]. In conclusion, lncrna mainly exists in the nucleus and can play a synergistic role with a variety of nuclear proteins to regulate gene sequence expression in the epigenetic direction. Lncrna in cytoplasm can regulate protein orientation, mRNA stability and translation. Although the list of lncrnas expressed by active cells is steadily growing, the understanding of functional lncrnas is still very limited.

3. Biological function of cardiac specific lncrna

By using large-scale transcriptome sequencing technology (RNA SEQ), gene expression profiles of various types of cells in the cardiovascular system were analyzed in the heart development process, adult healthy heart, myocardial infarction, pressure overload and other models. Thousands of heart specific lncrnas have been found, and it was found that the relative expression of heart specific lncrnas in embryonic and adult hearts was quite different, but there was little difference between adult heart and disease models, these results suggest that cardiac specific lncrna plays a key role in cardiac development. Cardiac development involves the

biological process of simultaneous differentiation of multiple types of cells, in which the precise temporal and spatial regulation of gene sequence expression is involved [20-21]. Lncrnas that play a key role in heart development include bvht (Braveheart), fendrr (Federal -lethal non coding development regulatory RNA) and kcnqlot1 [22-24]. To understand the physiological role of cardiovascular lncrna in the process of development and disease, and to clarify whether their regulatory function is cis or trans mechanism, it is usually necessary to regulate the expression of lncrna experimentally.

3.1. Kcnqlot1 and heart development

KCNQ1 is a gene encoding k+ channel. It was originally imprinted gene, but became a double stranded allele during heart development. Lncrna kcnqlot1 was formed by antisense transcription of intron 11 of KCNQ1 gene. In September, 2012, korostowski et al. [22] proposed that, especially in the heart, kcnqlot1 can also be converted to biallelic gene expression, and has the same time window as KCNQ1 expression; further studies showed that the level of KCNQ1 imprinted gene did not depend on the transcription of kcnqlot1 in the early stage of cardiac development, but there was a significant correlation in the late stage of cardiac development. And kcnqlot1 can regulate the expression of KCNQ1. At 16.5 days of embryonic stage, the level of KCNQ1 in k-mice was significantly higher than that in wild-type mice. In addition, they found that the increase in KCNQ1 levels was accompanied by an abnormal three-dimensional chromatin structure. Their research shows that kcnqlot1 regulates the relative expression of KCNQ1 by modifying chromatin variability and regulating enhancers.

3.2. Bvht and cardiac development

Klattenhoff et al. [12] of the Massachusetts Institute of technology found that mouse specific lncrnaak143260, abbreviated as bvht, was found on chromosome 18 of mice, which was crucial to heart development. Bvht began to express in the early stage of mouse embryonic stem cell development, and the relative expression was also high in the adult heart. They found that depletion of bvht in mouse embryonic stem cells resulted in the loss of beating cardiomyocytes and the failure to activate the cardiac transcription factor system, including Nkx2.5 and mep1 (a marker of cardiovascular progenitor cells, which determines the final type of all cardiac cells). Through transcriptome analysis, it is believed that bvht plays a role in the upstream of cardiac mep1 to induce its expression and guide the correct activation of cardiac gene regulation system. They also observed that bvht interacts with Suz12, a component of the Polycomb inhibition complex, thereby promoting histone H3 lysine 27 methylation and participating in the regulation of cardiac epigenetics. In addition, neonatal cardiomyocytes depleted of bvht showed abnormal myofibrils and decreased expression of a-myosin and b-myosin heavy chain [12].

3.3. Fendrr and heart development

Shortly after the discovery of bvht, grote et al. [23] reported another kind of lncrna fendrr with a length of 2397 BP, which was enriched in mesoderm and was extremely important for the development of mouse heart and body surface. Fendrr is differentiated and transcribed from the gene foxf1, which is specifically expressed in the mesoderm of the lateral plate and produces heart and parietal muscle. They found that the absence of fendrr in mice caused damage to the development of heart and body wall, caused myocardial dysfunction, and finally increased the embryonic mortality rate around e13.75. It was also found that the deletion of fendrr in mice increased the relative content of Nkx2.5 and GATA6 (transcriptional sequence of cardiac development) of E8.5 in early embryo. Similar to bvht, fendrr epigenetically regulates some transcription factors of cardiac development, including GATA-6, nkx2-5, foxf1, tbx3, iRX3 and Pitx2.

However, the loss of fendrr increased the methylation status of h3k4me3 on Nkx2.5 and GATA6 promoters, resulting in decreased target gene expression. Their results show that, like bvht, fendrr regulates the expression of cardiac transcription

factors through epigenetics and plays a crucial role in cardiac development.

4. Circulating lncrna and cardiovascular disease

The research progress of circulating lncrna as a cardiac biomarker is slow. Lncrna is unstable in body fluid, and most lncrnas are stable in neuroblastoma cell lines. Therefore, lncrna provides a very useful method for epigenetic research in the occurrence and prognosis of cardiovascular diseases.

4.1. Lncrna and atherosclerosis

Inflammation is a kind of self-defense response of living body to resist trauma and infection. Atherosclerosis is the basis of many cardiovascular and cerebrovascular diseases, and it is a complicated chronic inflammatory process [24]. Several recent studies have shown that lncrna plays a key role in the pathogenesis of atherosclerosis.

Ang362

It is known that the growth of vascular smooth muscle cells (VSMC) plays an indispensable role in the development of atherosclerosis. Recent studies [25] have shown that the positive regulation between lncrna and miRNA is related to the proliferation and hypertrophy of VSMCs, thus promoting atherosclerosis. It was found that lncrna-ang362 was similar to mir-221/222, and was co transcribed with mir-221/ 222 in VSMCs. After ang Ⅱ treatment, ang362 and mir-221/222 in circulation increased in a time-dependent manner. Down regulation of ang362 decreased the expression of mir-221/222 and MCM7 (related to the beginning of DNA replication and cell cycle), and also hindered the proliferation of VSMCs. Although it is still unclear whether MCM7 is a possible target of mir-211/222, lncrnaang362 can positively regulate MCM7 and mir-221/222.3, thereby aggravating vascular dysfunction caused by Ang Ⅱ and promoting the formation of atherosclerosis [25].

ANRIL(anti-sense noncoding RNA in the INK4 Locus)

In february2013, congrains et al. [26] of Osaka University in Japan reported that knocking down anril (lncrna encoded by chromosome 9p21) in aortic VSMC with small interfering RNA would reduce cell proliferation, and specifically knock out different anril exons 1 and 19 with small interfering RNA, resulting in significant changes in gene expression of pathways related to atherosclerosis in the body. In july2013, holdt et al. [27] reported that overexpression of anril can increase cell adhesion, promote cell proliferation and reduce apoptosis, which are important mechanisms for the development of atherosclerosis. Further research found that the promoter structural region of anril specific gene sequence is rich in Alu gene sequence, which is very important for transcriptional regulation and atherogenic mechanism. These studies demonstrate that anril is significantly associated with the development and severity of atherosclerosis.

RP5 -833A20.1

Lncrna rp5 -833a20.1 exists in intron 2 of nuclear factor IA (NFIA) gene sequence, and the transcription direction is opposite to that of NFIA. Lncrna rp5-833a20.1 negatively regulates the mRNA and protein content of NFIA, which is the target of mir-382-5p. The decrease of NFIA protein expression is caused by the overexpression of rp5-833a20.1, which aggravates the inflammatory response and lipid accumulation of THP-1 macrophages, while hsmir-382-5p inhibitor can completely delay the lipid deposition and inflammatory response [28]. However, the genetic correlation between mir-382-5p and rp5-833a20.1 is still rarely explored and needs to be further solved.

4.2. Lncrna and myocardial infarction (MI)

Mi is a common fatal cardiovascular disease. Although some progress has been made in recent years, the molecular mechanism of MI is still not fully elucidated. At present, it has been confirmed that miRNA is involved in the occurrence and development of MI, and miRNA based therapies may play a role [29], but there are few studies on the

main role of lncrna in the occurrence of MI. Some single nucleotide polypeptide (SNP) analysis showed that lncrna was associated with MI.

MIAT(MI -associated transcript)

In october2006, ishii et al. [30] of Japan found 6 SNPs in Miat. They first identified the susceptibility site of acute myocardial infarction on chromosome 22q12.1, and found a new gene, miat. Next, they found that Miat was composed of five exons, and further experiments proved that Miat did not encode any products. In addition, in vitro functional analysis showed that one SNP in exon a11741g increased the transcriptional level of Miat compared with the normal allele, while the other five SNPs did not show transcriptional differences. Their analysis suggests that SNP changes the expression of Miat, which may be related to the pathogenesis of MI.

KCNQ1OT1

In September, 2014, vausort m et al. [31] found that the levels of lncrna hypoxia inducible factor 1A antisense RNA 2, member 1 reverse strand/ antisense transcript 1 (kcnq1ot1) and metastasis related lung adenocarcinoma transcript 1 were higher in the peripheral blood of MI patients than those of healthy volunteers. Patients with ST segment elevation Mi had lower levels of anril, kcnq1ot1, miat, and metastasis related lung adenocarcinoma transcript 1 than patients with non ST segment elevation MI.

4.3. Lncrna and heart failure (HF)

HF is a syndrome in which various cardiac structural or functional diseases cause ventricular filling or ejection capacity damage. It is the critical and terminal stage of many cardiovascular diseases, and is often complicated by myocardial infarction, cardiomyopathy and myocarditis. Although the level of diagnosis and treatment continues to improve, hF is still a serious health care problem. Although significant progress has been made in protein-mediated transcriptional regulation and signaling pathways, the breakthrough in the key diagnosis and treatment of the disease has not been achieved. In recent years, the detection results of a large number of lncrnas and the multiple regulatory roles of ncRNA in gene expression may provide some clues [32].

NRF(Necrosis-related factor)

Wang et al. [33] found an lncrna, nRF, in the establishment of mouse ischemia-reperfusion model, which is an endogenous lncrna that interacts with mir-873 in the cytoplasm. Research [32] found that NRF knockout can increase the expression of mir-873 and reduce the expression level of ripk3 and ripk1, the downstream targets of mir-873 (pipk1 and ripk3 participate in H2O2 induced mouse cardiomyocyte necrosis), resulting in a sharp reduction in myocardial necrosis. They found that NRF could be regulated at the transcriptional level, and p53 binding sites were detected in the promoter region of NRF. H2O2 increased the association between NRF promoter and p53. Chip detection further showed that p53 increased the activity of NRF, thereby affecting downstream factors. Functional assay showed that p53 knockout could reduce cell necrosis and inhibit the activity of NRF promoter on H_2O_2. The expression of mir-873 increased and the level of ripk1/ripk3 decreased, which was also caused by the down-regulated p53 level. These results elucidate the regulatory relationship of LNC RNA mirnamrna axis in the process of cardiomyocyte necrosis, and provide a basis for exploring potential therapeutic targets for myocardial dysfunction.

LIPCAR

Lipcar is a long-chain non coding RNA from mitochondria. Lipcar may be involved in mediating mitochondrial pathways, such as oxidative phosphorylation. Mitochondrial dysfunction leads to a variety of cardiovascular diseases, especially coronary atherosclerotic heart disease and heart failure. In 2014, kumarswamy research team found that [34], lipcar in plasma was significantly positively correlated with the degree of left ventricular remodeling after myocardial infarction. Subsequently, the research team also found that the plasma lipcar level increased in the plasma of

patients with chronic heart failure 1 year after chronic heart failure and myocardial infarction, which could predict the survival rate of patients with heart failure. It is preliminarily found that lipcar is related to the decline of left ventricular diastolic function and the occurrence of ventricular remodeling, but the significance and function of lipcar need to be comprehensively explored.

4.4. Lncrna and arrhythmia

Arrhythmias, especially malignant arrhythmias, are related to the morbidity and mortality of cardiovascular diseases. Genetic factors are related to the occurrence and progression of arrhythmias, including neurometabolism, dysfunction of ca2+ regulation, and remodeling of cardiac structure and electrical pathways [35]. Therefore, the targeted markers for diagnosis, treatment and prognosis of arrhythmias that will be found are of great significance to control this situation and prevent sudden cardiac death.

Research [36] found that lncrna can affect the progress of atrial fibrillation (AF) by regulating different mRNAs. Lncrna-ak055347 promotes the pathogenesis of AF by regulating mss51, cYP450 and ATP synthase. Up regulation of mir208b could inhibit the expression and function of SERCA2, cacnb2 and cacna1c during atrial remodeling. Lncrna interacts with miRNA and its specific mRNA, resulting in electrical remodeling in the development of AF. On TCON_ Among the 5 rabbits in the 00075467 gene knockout group, 3 rabbits induced atrial fibrillation and silenced TCON_ 00075467 can significantly reduce L-type calcium current (ICAL), effective refractory period (AERP) and action potential (APD) of primary atrial myocytes, revealing the inhibition of TCON_ The content of 00075467 is related to the occurrence of atrial fibrillation [35].

4.5. Lncrna and cardiac hypertrophy

Persistent cardiac hypertrophy is often accompanied by maladaptive cardiac remodeling, resulting in decreased compliance and increased risk of heart failure. Maladaptive cardiac hypertrophy is considered to be associated with the development of HF. In february2014, wang et al. [37] of China Institute of zoology showed that lncrna CHRF (cardiac hypertrophy related factor) was involved in the pathological process of cardiac hypertrophy induced by Ang Ⅱ targeted gene mir-489. CHRF reduced the level of mir-489 by acting as an endogenous sponge of mir-489.

4.6. Lncrna and dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a heart disease characterized by ventricular enlargement and impaired systolic function, which often leads to congestive heart failure. Heredity plays an important role in the pathological changes of dilated cardiomyopathy. In 2009, friedrichs et al. [38] identified a genomic region (5q31.2–3), which has alleles for the risk of dilated cardiomyopathy in Caucasians. The steroid receptor RNA activator (SRA) gene simultaneously produces steroid receptor RNA activator protein and several non coding SRA transcripts. Knockout of sra1 in this region can cause ventricular systolic dysfunction in zebrafish, revealing the relationship between sra1 and dilated cardiomyopathy.

4.7. Lncrna and hypertension

Hypertension is one of the most common cardiovascular diseases. However, the molecular mechanism of the occurrence and development of hypertension has not been fully explained. Oxygen free radicals have been implicated in vascular endothelial function and pregnancy induced hypertension [39]. Recent studies [40] have shown that lncrna plays a certain role in the occurrence and development of hypertension. It has been found that malat1 can regulate vascular growth and endothelial cell function. SENCR is considered as a new type of lncrna enriched in vascular cells, which is related to the phenotype of smooth muscle cells [41]. Another study [42] found that 749 differently expressed lncrnas were found between Dahl salt sensitive rats and essential hypertensive rats. However, the study on the effect of lncrna on hypertension is only in its infancy.

4.8. Lncrna and aneurysm

Aneurysms are characterized by vascular wall thinning and pathological widening. They often occur in large arteries and can lead to death after rupture. MicroRNA is involved in the formation of aneurysms [43], but the study on the relationship between lncrna and aneurysms is in the preliminary stage. It has been reported [44-45] that whole gene correlation studies have determined that anril has genetic susceptibility gene loci related to abdominal aortic aneurysm. Foroud et al. [46] confirmed that anril can be used as a risk factor for intracranial aneurysms through genome association research. However, the function of anril in aneurysms is still unclear, which needs to be verified by more functional experiments.

5. Summary and Outlook

The basic function of lncrna has been the focus of life science and medical science research in recent years, and it has developed very rapidly. It is very important to identify specific lncrnas for the diagnosis and treatment of diseases. So far, a variety of lncrnas have been found to be related to the physiological and pathophysiological processes of cardiovascular diseases such as heart failure, coronary heart disease, myocardial infarction and arrhythmia. Although only a few studies have clarified the mechanism of action of lncrna, lncrna can participate in the occurrence and development of cardiovascular diseases in a variety of ways. It can be predicted that more and more lncrnas will be found through further systematic and comprehensive research. Clarifying the complex regulatory mechanism and functional targets of lncrnas will provide the latest means for clinical diagnosis and treatment of cardiovascular diseases.

Conflict of interest

The authors declare no conflict of interest.

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