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Circular RNA in Cardiovascular Diseases

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Abstract: Circular RNA (circRNA) is a type of RNA molecule mainly formed by a covalent bond. There is a large number of circRNA in vivo, which has tissue and cell specificity. Research related to this shows that circRNA plays an essential role in the pathogenesis, diagnosis and treatment of cardiovascular diseases. This review summarizes the research of circRNA in biosynthesis and function, studies the role of circRNA in cardiovascular diseases, and proposes a new method for diagnosing and treating cardiovascular diseases.

Keywords: circular RNA; cardiovascular disease; cardiovascular system; mechanism.

Introduction

In 1976, it was found that there were viroids in some plants, which were made up of circular RNA (circRNA) and caused infectious diseases to plants [1]. Subsequently, several studies [2-4]. carrying out in-depth research on this observed the presence of circRNA in the human cytoplasm using electron microscopy. Although circRNA was observed by electron microscope, no attention was paid to it because of its low expression. Only when circRNA was ubiquitous in different plants and animals was recognized that circRN

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A was of great significance to organisms and plants. It has been found that circRNA exists in many tissue s and organs and has a wide distribution and strong stability [4-5]. Unlike traditional linear RNA, circRNA cannot easily be degraded by exonuclease. Thus, it has a more stable performance. CircRNAs can play a r egulatory role in genes and participate in various pathological processes. At present, circRNA plays an im portant role in a series of cardiovascular diseases such as atherosclerosis and myocardial infarction. There fore, this paper reviews the relationship between circRNA and cardiovascular diseases, aiming to provide new ideas and targets for diagnosis and treatment of cardiovascular diseases [6-8]. Zhao, 2019, also highli ghted the significance of circRNAs in the context of its biological formation, mechanisms performed by it , and its functional attributes 2020[102].

1. Classification of circRNAs

CircRNAs were previously thought to be non-coding molecules produced by splicing errors. Recently, evi dence shows that circRNAs are widespread and diverse in eukaryotic cells. Because of the lack of toucha ble end, circRNAs can avoid degradation by exonuclease; therefore, they are more stable than linear RNA . However, the formation mechanism and cellular function of circRNAs are not clear. As a member of no n-coding RNAs, circRNAs have a unique covalent closed-loop structure, making them different from othe r non-coding RNAs, such as long non-coding RNAs (lncRNAs) and micro RNAs(miRNAs). High throug hput sequencing technology has detected a large number of circRNAs with different lengths and types. Se quencing data analysis shows that they are expressed explicitly in developmental stages and are conservat ive between mice and humans. The latest research shows that circRNAs have many biological functions a nd play an important role in many diseases. VO *et al.* found that in more than 2000 tumour samples, the t otal amount of circRNA was generally reduced compared with adjacent normal tissues [9-12].

With the development of sequencing technology, several types of circRNAs have been found and identifi ed, mainly including four subtypes: exon type circRNAs (ecircRNAs), which mainly come from one or m ore exons; ring intron type circRNAs (lincRNAs), which only contain introns; exon-intron type circRNAs (eicircRNAs), which are composed of exons and introns; tRNA intron type circRNAs Na (tricRNAs) whi ch is formed by splicing the introns of pre tRNA. So far, most of the identified circRNAs are ecircRNAs. As shown in Figure 1A below is a lasso-driven cyclization. When pre-mRNA is spliced, the splicing rece ptor of the upstream exon and the downstream donor is close to producing a lasso structure containing the exon and the intron. After the intron in the lasso structure is removed, the exon is connected by the phosp hodiester bond to form ecircRNAs.

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Furthermore, 1B shows the cyclization driven by RNA binding protein (RBP). RBPs can promote the inte raction between upstream intron and downstream intron and finally produce ecircRNA. Figure 1C shows t he cyclization driven by base pairing. The upstream intron and downstream intron are based on the seque nce complementary pairing of reverse repeat and complementary, and the intron is removed or retained to form eiciRNA or eiciRNA respectively.Fig. 1D shows the formation of circRNA [13]. The formation of cir cRNA mainly depends on a 7 NT Gu enrichment element and an 11 NT C enrichment element to avoid its de branching and degradation by exonuclease.

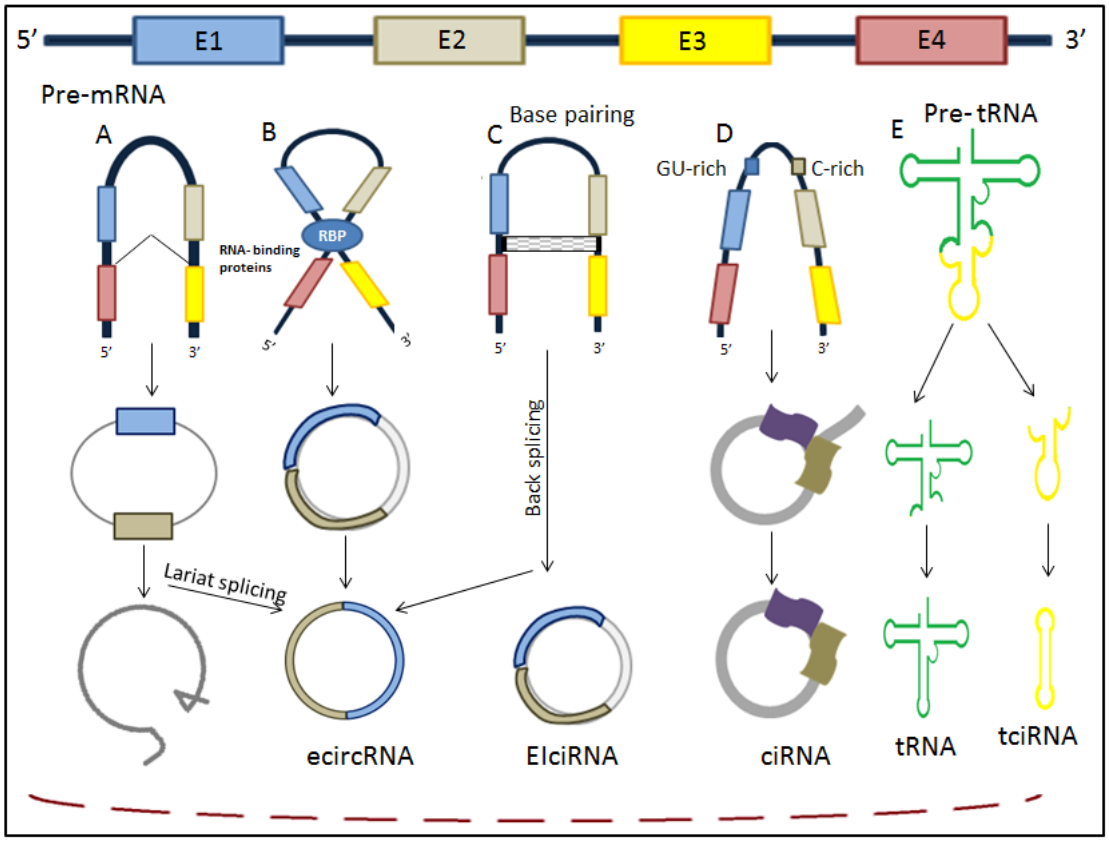

Figure 1: Formation of tricRNA

TRNA cleavage enzyme divides pre tRNA into two parts, one of which forms tricRNAs through 3 '- 5' phosphate diester bond, the other produces tRNAs

2. The mechanisms of circRNAs

The mechanisms of circRNAs in human cancer are diverse, including miRNA sponges, epigenetic regulat ion, regulating gene splicing or transcription, translating into proteins or peptides and interacting with pro

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teins. According to the target genes of circRNAs, there are two types: one is to regulate its host gene; the other is to target other genes [14].

2.1 As miRNA Sponges:

Currently, the main research direction of circRNAs is to use circRNAs as miRNA sponges or to translate t hem into short peptides to play their functions [15].

As shown in Figure 2D, circRNAs can affect the expression of genes by adsorbing miRNAs. For example , CIRC HIPK3 can adsorb miR-7 and reverse the proto-oncogenes (EGFR, YY1, FAK, IGF1R) targeted b y miR-7, thus promoting the progress of colorectal cancer [16-17].

With the development of deep ribosome sequencing and mass spectrometry, many studies have recently i dentified and confirmed that some non-coding RNAs (including circRNAs) can encode proteins or small peptides. As shown in Figure 2F, for example, circRNAs derived from linc-pint can encode short peptides with 87 AA, which can directly interact with polymerase related factor complex (paf1c), thus, inhibiting t he transcription of extension of a variety of cancers genes. CircRNA FBXW7 can also encode tumour rela ted protein FBXW7-185aa, which can resist the stability of c-myc protein induced by USP28, thus reduci ng the half-life of c-myc protein; short peptide SHPRH-146aa encoded by circ-SHPRH can mediate the u biquitination and degradation of PCNA [18].

2.2 Epigenetic and post-translational regulation:

CircRNAs can also play an important role in epigenetic regulation and post-translational regulation. For e xample, in Figure 2c, circna fecr1 originated from FLI1 gene can interact with FLI1's promoter, and gener ate extensive demethylation in the CpG island region of FLI1 gene by recruiting demethylase Tet1. At the same time, circRNA fecr1 can be combined with the promoter region enriched in h3k27ac of DNMT1 ge ne, thus inhibiting the expression of methyltransferase DNMT1 gene. As shown in Fig. 2E, circRNAs can regulate their activity or affect their expression by binding proteins. For example, circ-foxo3 can bind M DM2 and p53. When circ-foxo3 binds MDM2, it can enhance its polyubiquitin effect on p53, promotep53 degrade through the proteasome pathway [19].

2.3 Regulation of expression of the host genes:

Furthermore, circRNAs can also regulate the expression of their host genes.

As shown in Figure 2 below, the formation of circRNAs can compete with linear RNAs for their common pre mRNA, thus affecting the abundance of linear RNAs. The circRNAs containing introns, introns can i nteract with U1 snRNP through RNA-RNA interaction and then combine with pol II transcription comple xes, interacting to enhance the expression of their maternal genes [20].

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2.4Translation of circRNA into proteins:

In addition to its function at the RNA level, circular RNA has been reported to translate into proteins like linear mRNA molecules. For example, hepatitis δ, a circular RNA molecule in the hepatitis B virus, can e ncode a virus-related protein and play a role in the occurrence of diseases. However, at present, this pheno menon is only observed in viruses. The circular RNA molecules containing ATG initiation codon in eukar yotes can be recognized by ribosomes like linear mRNA for protein translation.

2.5 Translation of proteins:

CircRNA has been considered as non-coding RNA since it was found. The vast majority of circRNAs are derived from different protein-coding sequences and open reading frames, ubiquitous in the cytoplasm. T herefore, researchers have long believed that circRNA has the potential to translate proteins. As early as 1 995, there was a literature report on circRNA. It is believed that some circRNA can effectively translate p roteins. Circ-fbxw7 is a circRNA formed by cyclizing exon 3 and exon 4 of the tumour suppressor gene F bxw7. It can translate a 185 amino acid protein fbxw7-185aa. Fbxw7 regulates the stability of proto-onco gene c-myc through ubiquitination. At the same time, fbxw7-185aa can cooperate with Fbxw7, reduce the expression of c-myc, and promote the ubiquitination and degradation of c-myc, thus inhibiting the occurr ence of glioma. These studies break the understanding that circRNA is non-coding RNA, and have a new understanding of circRNA. However, through the translation of exogenous circRNA, there is direct evide nce that endogenous circRNA can also be translated.

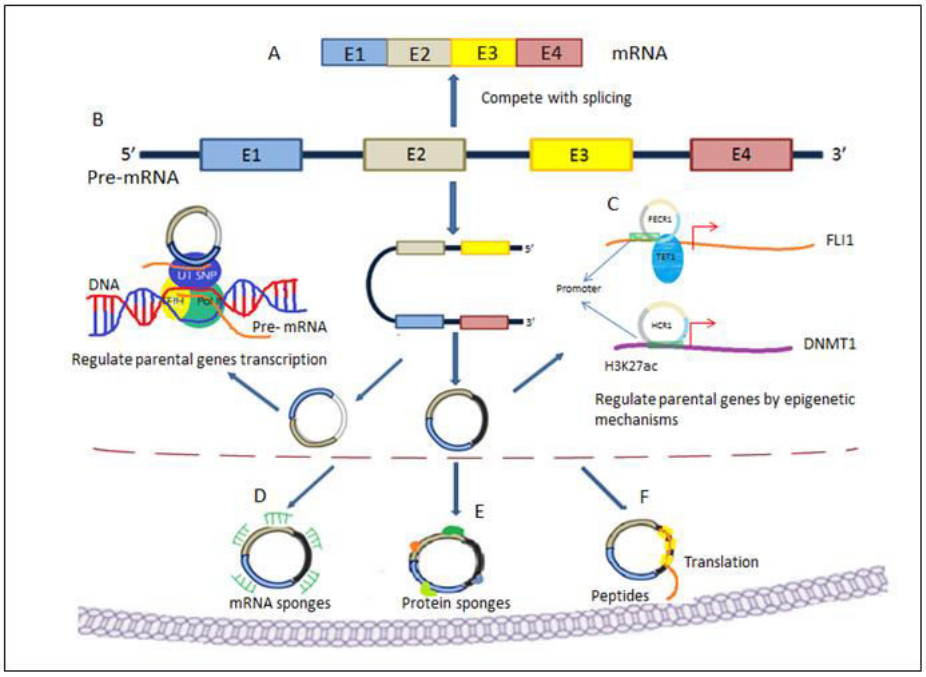

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Figure 2: The formation of circRNAs process

3. Functional significance of CircRNAs

CircRNA mainly exists in the cytoplasm and has been found in exosomes of the culture medium. CircRNA is related to the development of tissues and organs and may play a role in various disease processes. Its function is still largely unknown:

(1) A few circRNAs act as "sponges" of miRNA;

(2) Some circRNAs can "sponge" other factors, such as RNA binding proteins

(3) A large number of circRNA may have other unknown regulatory functions;

(4) Increased evidence suggests that circRNA may not be a real non-coding RNA type, at least some of which are translatable [20-21].

Although many circRNAs may have biological functions, it is still likely that a large number of circRNAs may be insignificant by-products of the splicing of precursor mRNA [22].

3.1 CircRNA protein interaction

Some of the endogenous cytosolic circRNA can be used as scaffolds to regulate protein-protein interaction. Some RNA binding proteins (RBPs) can combine with circRNA to form competition between circRNA and its homologous mRNA, in which RBP affects translation. Moreover, our review of the available studies noted that some circRNA could regulate the expression of its binding protein by regulating protein-protein interaction [23].

3.2 Detection of circRNA protein interaction

The global bioinformatics analysis of circRNA sequence showed that there was no enrichment in the binding sites of RBP compared with linear mRNA. However, the third-order structure of circRNA may have more influence on protein binding than linear RNA sequence. So far, the interaction between circRNA and protein has been analyzed mainly by RNA pull-down assay or RNA immunoprecipitation (RIP) [24].

The probe for reverse splicing point is the unique sequence element of circRNA. (1) In RNA pull-down assays, RNA is pulled down by probes to allow an analysis of related proteins. The use of circRNA overexpression and silencing techniques will help identify RNA protein interactions by quantitatively comparing pull-down circRNA with specific pull-down proteins [25].

(2) RNA binding protein immunoprecipitation assay (RIP) followed by circRNA sequencing is another feasible strategy for analyzing circRNA protein interaction.

(3) RNase protection assay (RPA) is an effective method to detect RNA and RNA fragments in cell extracts. RPA can also be used to map protein RNA interactions.

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(4) Microscopically analyzing the co-location of circRNA and protein is another strategy to identify t he interaction between circRNA and protein [26].

3.3 Dynamic circRNA protein interaction

There is sufficient evidence showing that circRNA expression is dynamic and allows for different spatial and temporal expression profiles. CircRNA may form different third-order models, which prefer to bind s pecific proteins. Some third-order models may exist dynamically in some tissues and cells, resulting in dif ferent affinities with binding proteins. Because of the strong influence of solvent and metal ions on the dy namic third-order structure of circRNA, the main third-order structure of circRNA may be different in diff erent cell lines, tissues and development stages [27-30].

3.4 RNA protein interaction affects the dynamic expression of circRNA and protein

CircRNA binding proteins play a key role in the regulation of circRNA synthesis and degradation. It has been shown that RNA circulation is promoted by complementary sequences and regulated by specific RN A binding proteins. RNA protein interaction can also promote the formation of circRNA by stabilizing co mplementary sequences or by inhibiting canonical splicing. RBP can be used as an activator or inhibitor o f circRNA formation and regulate the expression level of circRNA. Because of the high stability of circR NA and its assumed resistance to exonuclease degradation, there may be cellular mechanisms controlling the level of circRNA [31]. At least some degradation pathways of circRNA can be mediated by endonuclea se cleavage. RNA protein interaction affects protein expression, function and biogenesis.

3.5 CircRNA for targeted therapy

Our recent studies have shown that the conjugation of circular RNA expression plasmids with nanoparticl es is a useful method for the delivery of circular RNA. Because nanoparticles cannot enter the nucleus, th e treatment can only focus on exon cyclic RNA, which is mainly detected in the cytoplasm [32]. Because of its high delivery efficiency, siRNA or AON delivery will be a valuable method in the future.

4. CircRNA and cardiovascular diseases

CircRNA is a kind of RNA with a ring structure composed of covalent bonds. The main method for RNA detection is to isolate linear RNA molecules with polyadenylate tail (Polya) structure. In recent years, to i dentify circRNA by genes, after extracting the total RNA, the researchers remove the ribosome RNA and linear RNA to extract and sequence the circRNA, from which a variety of circRNA can be detected [33]. Th e regulatory role of circRNA runs through the whole process of gene regulation, from mRNA transcriptio

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n splicing to RNA degradation and translation. There are two screening methods widely used; one is sequ encing by high throughput, the other is sequencing analysis by chips [34-36].

The changes of circRNA in cardiovascular diseases are shown in Table 1[37].

Table 1:circRNA changes in cardiovascular disease

Disease	Detection mode	Detection objects	Sample	CircRNA Expression cha nge
Acute myocar dial infarction	Chip detection	Myocardial infarctio n patients	Plasma	Upregulation of 73 circRN As Downregulation of 87 circR NAs
Myocardial fibrosis	Chip detection Chip detection	Diabetic mice Diabetic mine	Myocardi al tissue Myocardi al tissue	Upregulation of 45 circRN As Downregulation of 31circR NAs Upregulation of 24circRNA s Downregulation of 19 circR NAs
Coronary arte ry disease	Chip detection	Patients with coronar y artery disease	Peripheral blood	Upregulation of 12 circRN As Downregulation of 10 circR NA
Diabetes	Chip detection	Diabetic retinopathy	Serum	Upregulation of 30 circRN As
Heart failure	Chip detection		Myocardi al tissue	Upregulation of 29 circRN As Downregulation of 34circR NAs
Chronic total o cclusion pulmo nary hyperten sion	Chip detection	Chronic total occlusi on pulmonary hypert ension	Peripheral blood	Upregulation of 122 circRN As Downregulation of 229circ RNAs

At present, the role of circRNA in cardiovascular disease is still incomplete, and there are few studies in t his area. We need to know the role of circRNA in cardiovascular disease to find the relevant treatment me asures. [38]. Wilson *et al.* sequenced circRNA in human heart, mouse heart, and human embryonic stem cel l differentiated cardiac tissue and found 15318 and 3017 circRNA in human and mouse hearts. The expres sion level of these circRNAs is consistent with that of their homologous linear RNAs. The genes correspo

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nding to the highest content of circRNAs are also cardiac tissue-specific genes, such as titin, RyR2 and D MD genes [39].

4.1CircRNA and heart failure

Mir-223 is a positive regulator of cardiac hypertrophy. Apoptosis suppressor with card (ARC) is the down stream target of mir-223, and the cardiac hypertrophy response of arc transgenic mice is decreased. Heart-related circular RNA (HRCR) is a recently reported cardiac circRNA, which acts as a "sponge" of miR-22 3, directly combines with miR-223, inhibits the activity of miR-223, and thus increases the expression of ARC. The overexpression of Hrcr in cardiomyocytes and mice showed a decreased cardiac hypertrophy [3 9-42]. These findings reveal a new regulatory pathway and therapeutic target of cardiac hypertrophy/heart f ailure composed of circular, mir-223 and arc. Werfel *et al.* constructed a library for RNA sequencing by r emoving ribosomal RNA, and analyzed the expression of circRNA in the heart of humans, mice and rats a t different stages of development or physiological and pathological states. The results showed that the tota l expression of circRNA in human cardiac tissue was higher than that of rats and mice [43]. The rats were d ivided into the newborn rat's group and the adult rat's group. There were significant differences between t he two groups in the circRNA expression of slc8a1, TTN, eya3 and scmh1 genes. Humans and mice were divided into heart failure group and non-heart failure group [44]. It was found that the number and types of circRNA in the heart failure group were higher than those in the non-heart failure group. For example, the expression of circRNA corresponding to slc8a1 and TTN genes in the heart failure group increased signif icantly. In particular, the ryanodine receptor 2 (RyR2) genes exist in human heart tissue, corresponding to more than 100 subtypes of circRNA [45]. In conclusion, circRNA is closely related to the physiological an d pathological process of heart, especially the genes corresponding to several differentially expressed circ RNA molecules, such as slc8a1, TTN, RyR2, eya3, etc., which can be used as ideal candidate genes for fu rther study of heart failure [46-49].

4.2CircRNA and CAD

It is reported that compared with the healthy control group, the plasma endothelial cells of CAD patients a re rich in endothelial cells. MiRNAs (miR-126, mir-92a and miR-17) were collected from smooth muscle cells (SMCs). MiR-145 and inflammation-related miR-155 were significantly decreased. Another study e xamined157 different miRNA microarrays which were detected in peripheral blood mononuclear cells of CAD patients [50-51]. The results showed that mir-135a increased and mir-147 decreased significantly in C AD patients, and the ratio can be used in CAD diagnosis. This study further confirmed that increased the l

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evel of mir-134, 198 and mir-370 may help to distinguish unstable angina patients from stable angina pati ents. It is suggested that circulating miRNAs can be used to predict acute coronary syndrome in patients with angina pectoris[52]. Sun et al. Used QRT PCR to detect 31 cases of CAD, and plasma miR-126 was d etected in 36 non-CAD patients. However, it was found that the expression of miR-126 was increased in p atients with elevated low-density lipoprotein cholesterol (LDL-C) and decreased in patients with low-dens ity lipoprotein cholesterol (LDL-C), suggesting a specific correlation between miR-126 and lipid metaboli sm. In addition, mir-149 was found to be associated with an increased risk of CAD in the Chinese Han po pulation [53-56].

Serum miR-31 was abnormally elevated in patients with CAD restenosis compared with patients without CAD restenosis. Compared with the healthy control group, circulating blood mir-133a and mir-208a level s were up-regulated in patients with stable coronary artery disease, while miR-126, miR-17 and mir-208a were up-regulated-The levels of 92a and miR-155 decreased significantly, and miR-214 was found to be b eneficial to CAD-Patient. This may be a promising biomarker for severe CAD; the loss of its protection m ay increase placental growth factors and the deterioration of atherosclerosis. Recently, the result of severa l studies showed that the miR-122 and mir-370 tables were circulated. It may be related to the severity of CAD. The expression level was positively correlated with TC, TG and LDL-C levels. All in all, follow M iRNAs can improve the diagnosis of CAD [57-58].

4.3 CircRNA and myocardial fibrosis

Tang *et al.* found that circRNA 000203' upregulated in the myocardium of diabetic mice and Ang-II induc ed mice cardiac fibroblasts. CircRNA_000203 has two potential binding areas for microRNA-26b-5p (mi R-26b-5p), which shows the anti-fibrotic effect targeting I collagen and connective tissue. In availability o f a higher number of circRNA_000203 could obliterate the anti-fibrotic effect of miR-26b-5p in cardiac fi broblasts. Thus circRNA_000203promotes the proliferation of cardiac fibroblasts by blocking the functio n of miR-26b-5p. It has also been found that circacta2, as a cecRNA, inhibits the mir-548f-5p pair.

4.4CircRNA and diabetic cardiomyopathy

It has been proved that diabetes mellitus can cause changes of myocardial structure and function in varyin g degrees, which will lead to cardiac hypertrophy and myocardial fibrosis. Tang *al.* the circRNA in mouse cardiac tissue found 76 different circRNA expressions, 45 of which were up-regulated and 31 of which w ere down-regulated [58-62]. At the same time, the researchers selected the up-regulated circRNA00203 and f ound that there are two binding sites between circRNA000203 and mir-26b-5p [63-65]. Overexpression of ci rcRNA 000203 in cardiac fibroblasts will lead to up-regulation of the downstream target fibrosis-related g

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enes COL1A2 and CTGF of mir-26b-5p. Therefore, cir-crn000203 may be a new target for the treatment of myocardial fibrosis in diabetic cardiomyopathy [65-67].

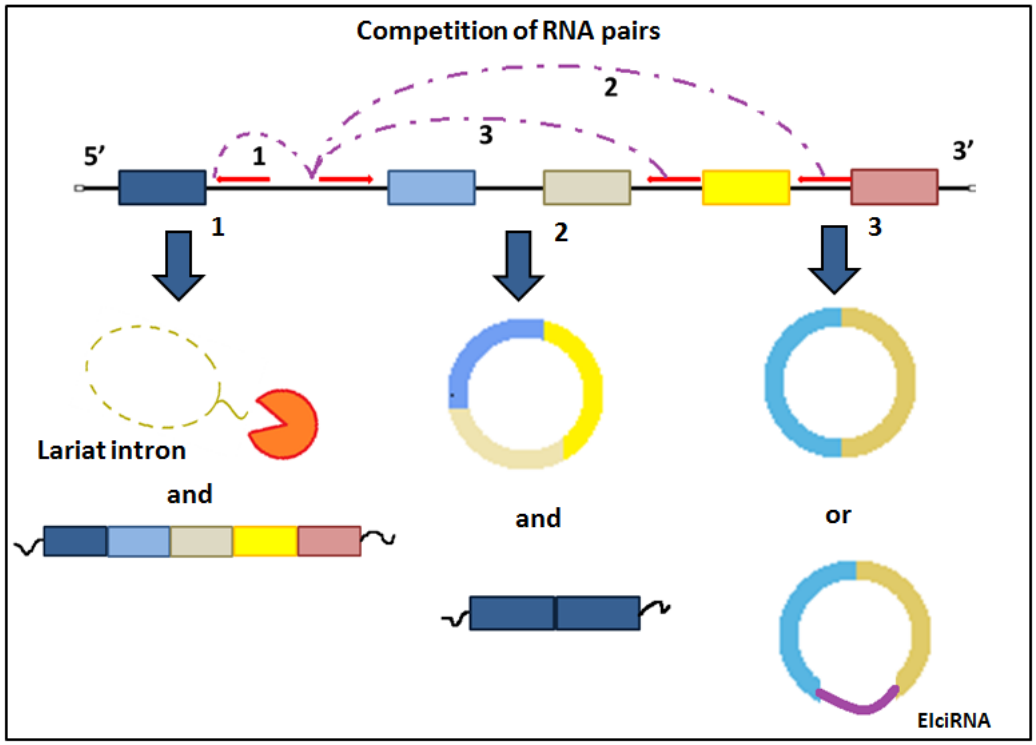

Figure 3: The categories exon derived circular RNAs

Conclusion

The mortality of cardiovascular disease is high, and treatment and nursing are complex. In addition to con ventional treatment, gene therapy technology can also be used to treat cardiovascular disease. The use of disease-specific antisense miRNA molecules to inhibit disease has entered the clinical trial stage. At the molecular level, the antisense nucleotide chain of miRNA can improve the affinity between miRNA and c ells to achieve the purpose of treatment. For LNA gapmers technology, the direct target is lncRNA. After the target is combined with lncRNA, RNA endonuclease can be activated rapidly to degrade lncRNA. Unl ike miRNA and lncRNA, circRNA can resist ribonuclease endonuclease, so it cannot be degraded by ribo nuclease endonuclease, remaining stable in vivo. Therefore, for circRNA, it may become a new method o f gene therapy.

CircRNA can combine with miRNA to inhibit the expression of the target gene. Foreign media reports ha ve confirmed that circRNA molecules can target miR-122, which is closely related to the hepatitis C virus

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, to inhibit the formation of the virus and achieve the purpose of disease treatment. CircRNA can also play a role by regulating gene expression, protein translation, production and other mechanisms. Therefore, th e synthetic circRNA may also target genes or proteins and directly affect diseases. In recent years, it has b een shown that circRNA can play an essential role in the regulation of cardiovascular diseases and achiev e the goal of treating cardiovascular diseases [68]. However, the current understanding of the biological fun ction of circRNA needs further study, and there is limited knowledge of its biosynthesis and degradation process.

In conclusion, circRNA is considered to be an abnormal splicing product. Currently, some studies suggest that circRNA can play an important role in gene therapy, particularly in a series of cardiovascular disease s such as atherosclerosis, myocardial infarction and myocardial fibrosis. However, the mechanism of circ RNA in cardiovascular diseases is not much clear, and there are still many gaps of knowledge. It is necess ary to strengthen the relevant research and explore the mechanisms of circRNA in cardiovascular diseases to find a new target of cardiovascular disease treatment and diagnosis.

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