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Review Article

CircRNA-mRNA-miRNA Interaction Network's Part in Diabetes

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Abstract

A neoteric transcript called circular RNA (circRNA) functions as a sponge for miRNAs to regulate gene expression. Recently discovered, the dysregulation of this circRNA-miRNA-mRNA connection is linked to illness development and progression. Studies have shown that this regulatory network controls the pathophysiology of vascular disorders through the regulation of endothelium dysfunction. Endothelial dysfunction is caused by imbalances or disruptions of the vasodilation and vasoconstriction components as a result of alterations in oxidative stress, inflammatory markers, and nitric oxide signalling. In order to create atherosclerotic lesions, these abnormalities prevent blood from passing through the endothelium barrier. We now have a better understanding of the intricate regulatory network underlying endothelial dysfunction because to advances in high-throughput methods like genome and RNA sequencing (Tela et al., 2016).

Keywords: Trans-acting proteins, Vasoconstriction, RNA sequencing, Development and progression

INTRODUCTION

The majority of non-protein-coding RNAs have a variety of roles in cellular homeostasis that are currently being uncovered. Circular RNAs (circRNAs) are being recognised as non-coding transcripts that play a significant part in the onset and progression of several physiological and pathological disorders. We have been able to uncover numerous circRNA regulatory mechanisms, one of which is microRNA (miRNA)-mediated control, thanks to developments in high-throughput RNA sequencing and bioinformatics tools. In addition to directly affecting mRNA transcription, circRNAs can indirectly regulate the expression of their targets via sponging miRNAs or RNA-binding proteins. Numerous disorders, including diabetes, have circRNA-miRNA-mRNA interaction networks that are dysregulated, according to research (Desai et al., 2008). The aetiology of diabetes and its consequences are linked to this complex system. Circular RNAs (circRNAs), an endogenous class of macromolecules with cell- and tissue-specific expression patterns, are present in eukaryotes. Particular cis-acting elements and trans-acting proteins control their synthesis. According to Sanger and his colleagues' classifications, the viroid has both single-stranded and molecules of covalently closed circRNAs. CircRNAs were initially discovered in infections (Iniobong et al., 2019). In contrast, Hsu published a second research in 1979 that included information on RNA that had no free ends and circularity that was independent of associated proteins. Around 2010, there was a spike in circRNA study due to advancements in RNA sequencing techniques and the development of numerous analytical procedures, which revealed that metazoans express thousands of circRNAs. CircRNAs are mostly produced by the process of back-splicing, in which a splice donor from a downstream exon connects to an upstream splice acceptor (Sudakin 2005). CircRNA is thought to play a part in transcription regulation, the sponging of microRNA, and potential disease biomarkers. The circRNAs may bind to RNA-associated proteins to form RNA-protein complexes and act as miRNA sponges. Additionally, circRNAs and miRNAs are thought to work together to regulate gene expression at the transcriptional or post-transcriptional level, and circRNAs may have an impact on how miRNAs operate in the growth of tumours. Numerous studies have shown the relevance of circRNA in illness prevention and therapy as well as the function it plays in cell ageing, proliferation, and apoptosis. Although they

are often produced at low levels, circRNAs are linked to the physical and biological progression of illnesses such nervous system degeneration, cancer, heart disease, etc. CircRNAs are numerous and persistent in sputum, extracellular fluid, and potentially serum microvesicles, indicating that they may represent biomarkers (Farshid 2015). Due to variances in protein expression activity in tissue-specific settings and activation by tumour cells, circRNAs have piqued a great deal of interest due to their exceptional distinctiveness and biocompatibility and are being investigated as a potential biomarker in reducing disease and therapy (Chaudhry et al., 2014).

Diabetes mellitus (DM), a primary metabolic and endocrine illness brought on by persistent hyperglycemia as a result of insulin resistance, is an epidemic that is spreading quickly. Approximately 463 million individuals worldwide are thought to have diabetes; this figure is projected to rise to 578 million by 2030 and 700 million by 2045. The two main diabetes-related variables that obstruct additional vascular problems are insulin resistance and endothelial dysfunction. End-organ damage comes from unbalanced growth factor secretion produced from the endothelium. In addition to insulin resistance, the deterioration of the endothelium is also brought on by factors such as the production of free fatty acids and lipid toxicity, oxidative stress, and dyslipidemia (Madhumathi et al., 2020). Vascular problems in diabetic patients, such as nephropathy, retinopathy, and cardiomyopathy, have significant symptoms and a short life span. The body is exposed to substances that, by transferring unpaired free electrons, create reactive oxygen species (ROS), which lead to the oxidation of cellular components. Exogenous antioxidants that can neutralise these species are obtained by the body through the food as a kind of defence. Oxidative stress, which results from an imbalance between ROS and antioxidants, causes pathological illnesses like diabetes. Additionally, studies have revealed the role that epigenetic regulators play in the development of diabetes (Xinkuan et al., 2016).

The development of new sequencing technology has aided in our understanding of how the human genome is translated into RNAs, only 1-2% of which have been identified to encode for proteins.8 For a long time, these noncoding RNA (ncRNA) transcripts—transcripts that do not encode proteins—were called "junk"; subsequently, they were identified as a highly conserved functional molecule that controls gene expression in a variety of ways. Small noncoding RNAs (sncRNA) and long noncoding RNAs (lncRNA) are two general categories for ncRNAs based on size. Small interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), and microRNAs are examples of transcripts that fall under the category of non-coding RNAs (sncRNAs), while promoter-associated transcripts (PATs), enhancer RNAs (eRNAs), and circular RNAs (circRNAs) fall under the category of long non-coding RNAs (lncRNAs). Circular lncRNAs, also known as circRNAs, have recently attracted the attention of scientists and are the subject of intense investigation due to their regulatory function in cellular signalling. CircRNAs were previously unknown, but developments in genome sequencing, transcriptional profiling, computational techniques, and structural biology have helped us to understand the role that they play in the pathophysiology of a number of disorders, including diabetes. Researchers have discovered that circRNA functions as a sponge for its endogenous partner, the miRNA, and hence plays a significant role in the development of diabetes and its consequences. For instance, Zhou et al. discovered circRNA 010567, a new circRNA that targets and upregulates TGF-b1 expression by sponging miR-141, therefore fostering myocardial fibrosis (Proudfoot 2009).

The introns surrounding the up to five exons in circRNA are three times longer than in their linear form. Numerous complementary Alu repeats have been found in the intronic region, which makes it easier for the splice site to detect one another and encourage circularization.16 They are resistant to exonucleases, such as those mediated by ribonuclease R (RNase R), because of their closed-loop structure, which excludes 50 and 30 regions with a poly-A tail and cap region.Since RNase R degradation can degrade linear RNA and its poly-A tail, it can effectively distinguish between the closed-loop character of circRNA and its linear variants. Due to the absence of their linear counterparts' 50 cap and 30 tails, circular RNAs are resistant to RNA degradation. By having inverted repetitions of long introns that border the genomic structure of long exons and by reversely attaching Alu elements to RNA helicases, DExH-Box Helicase 9 (DHX9), circRNA production is enhanced. The synthesis of circRNA via back-splicing takes place in normally developing cells as a result of NF90/NF110 binding to A/U-rich regions in the intronic region. Muscle bind (MBL), RNA-binding protein quaking I (QKI), and heterogeneous nuclear ribonucleoprotein L (HNRNPL) are additional factors that encourage the back splicing of circRNA. According to reports, QKl brings two cyclic sites closer by binding to both flanking ends of introns and joining the cyclic exons, whereas MBL improves circMBL back splicing by binding to pre-mRNA and lowering the levels of MBL (Olusegun et al., 2019).

CONCLUSION

In this conclusion, we have examined the research on the network of interactions between circRNA, miRNA, and mRNA in diabetes and its consequences. Noncoding RNA research has recently attracted more interest in the realm of disease biology. It is noteworthy that further research is being done to clarify the miRNA sponge's mechanism. Numerous studies have shown that miRNAs have inhibitory effects and that these effects are closely correlated with a number of illnesses, including diabetes. As a result, the scientific community has begun to show interest in exogenous tools such artificial miRNA mimics and agomiRs that attach to the 30 UTR to alter the expression of native genes. A few researchers additionally concentrate on the miRNA's upstreams to prevent its expression. One of them, circRNA, primarily functions as a protein sponge or miRNA. Holdt et

al. have studied the potential therapeutic applications of circRNAs. The circRNAs can be chemically created or altered to act as miRNA mimics by adding photolabile linkers to RNA ligases or ribozymes. This could stop circRNAs from linearizing and becoming increasingly inactive. Additionally, covering circRNAs with proteins or applying chemical alterations to enhance stability and binding affinity facilitate identification of the system. However, it is challenging to deliver any naked RNA and determine its half-life in any biological system. Most of the circRNAs' physiological roles have not yet been determined, although they may disclose some of their protein counterpart-like properties. Exonic circRNAs are significant found circRNAs that operate as miRNA sponges to mitigate and reverse the alterations brought on by miRNAs. Intronic circRNAs' function has received little attention. Numerous breakthroughs in circRNA research might be predicted in the near future because to advancements in RNA technology.

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