

# **Circular RNA HIPK3: an emerging player in diabetes**

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With rapid global aging, the occurrence of diabetes mellitus (DM) and its associated complications, including diabetic retinopathy (DR), is also increasing. DR is one of the major complications of DM and a leading cause of visual impairment in developed countries (1). DR-induced visual impairment is usually accompanied by vascular hyperpermeability, inflammation, neovascularization, retinal ischemia, and vascular cell dysfunction (2-4), and it has become a primary cause leading to blindness. DR is characterized by abnormalities in either the structure or functionality of the retinal microvasculature (5). Due to the different proliferation statuses of retinal neovascularization, DR can be divided into proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR) (6,7) There are many hypotheses about the pathogenesis of DR. The most prominent one being that persistent hyperglycemia causes the formation of glycation end products, which activates the hexosamine pathway, which in turn triggers the apoptosis of retinal neurons. In addition, genetic susceptibility, immune response, inflammation, and disease have also been implicated in the onset of DR. DR has notable clinical and pathological features, and identifying biomarkers that can predict DR or therapeutic efficacy is crucial because of its complex pathogenesis and indistinct risk factors (8,9). With the accumulation of scientific data, the diagnosis and treatment of DR have improved significantly. However, there has been no substantial reduction in DR-related mortality. Therefore,

an effective treatment to improve the long-term survival and life quality of DR patients is urgently needed.

Non-coding RNAs (ncRNAs) include microRNAs (miRNAs) (10), long non-coding RNAs (lncRNAs) (11,12), and circular RNAs (circRNAs) (13). CircRNAs are mainly derived from exons or introns, which are generated by two kinds of splicing-exons reverse splicing of exons and introns (14). Unlike linear RNAs, circRNAs have neither 5' or 3' polarity nor a polyadenylate tail. They are closed loop structures that are not affected by RNA exonucleases, which makes them highly stable and non-degradable, and are abundant in the cytoplasm of eukaryotic cells. CircRNAs can function as a miRNA sponges to regulate miRNA activity by competitively binding to miRNA target sites, thereby decreasing or inhibiting their function and ultimately affecting the expression of the miRNA target genes (15,16). Recent evidence shows that circRNAs play a role in the occurrence and development of diabetes, atherosclerosis, nervous system disorders, cancers, and other diseases (17,18). Yang et al. (19) reported that the circRNA Circ-FBXW7 can translate proteins and plays an important role in glioma. This was the first report of a protein translated by a circRNA working synergistically with the protein expression products of the parent gene. Zeng et al. (20) found that circ-Amolt1 is highly expressed in the neonatal heart, where it promotes the phosphorylation and nuclear import of Akt1 through interaction with PDK1 and AKT1. This mechanism was further confirmed in cells in vitro as well as in an animal model of doxorubicin-induced cardiomyopathy. Moreover, Zhang *et al.* (21) demonstrated that circ-LARP4 can inhibit miR-424-5p competitively and regulate the LATS1 gene in the Hippo pathway, thereby contributing to the development of gastric cancer. These findings suggest that circRNAs could be robust molecular markers of diseases. An in-depth understanding of the mechanisms and functions of circRNAs will thus provide valuable insights into disease development, as well as identifying potential biological markers for disease diagnosis and prediction of therapeutic efficacy.

A recent article in Circulation by Shan et al. (22) suggests a novel role of circRNAs in the progression and development of DR. In this study, the authors explored the role of circRNA in retinal vascular dysfunction caused by diabetes and found that circ-HIPK3 is significantly elevated in diabetic retinal vascular disorders. Silencing or overexpression of circ-HIPK3 dysregulated the viability, proliferation, migration, and tube formation ability of retinal endothelial cells. Investigation of the molecular mechanism revealed that circ-HIPK3 competitively bound miR-30a-3p, miR-30d-3p, and miR-30e-3p to reverse the expression of their respective target genes, VEGF, FZD4, and WNT2, thus forming a new regulatory network comprising circRNAs-miRNAs-mRNAs that plays an important role in diabetic retinal vascular dysfunction. However, I consider the experimental design described for Figure 3D is flawed. The authors should design two categories of 3'-biotinylated miRNA duplexes: wild-type and one with a mutation in the circ-HIPK3 binding site. This investigation would powerfully support the conclusion of circ-HIPK3 sponging miR-30a-3p, miR-30d-3p, miR-30e-3p.

In brief, Shan *et al.* (22) clearly clarified the regulatory mechanism of the novel circRNA HIPK3 in diabetic proliferative retinopathy and provided a potential strategy for the therapeutic targeting of circ-HIPK3 in DR. CircRNA research has become more systematic and standardized with the rapid development of molecular biological information technology and in-depth RNA sequencing technology. The three most frequently used research tools in this field are molecular biological methods, genomic methods, and circRNA-specific databases. The circRNA-specific databases, including circ Base, circ2-Traits, and circ Net, contain information on nearly 100,000 circRNA sequences and can predict circRNA-miRNAmRNA interactions, which is invaluable for the systematic study of circRNAs. Thus, circRNAs have become novel diagnostic biomarkers and therapeutic targets for DR. However, identification and validation of novel functional circRNAs in vivo and in vitro are needed to explore the potential molecular mechanisms of diseases. Although accumulating evidence clearly supports the potential value of circRNAs in diagnosis and therapeutics of various diseases, their clinical applications remain unknown. It is believed that with the shift of research on circRNA and disease from the "hypothesis" stage to the "practice proof" stage, circRNAs will bring more surprises and breakthroughs for the medical and scientific communities.

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