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Circular Rnas: Emerging Players in Coronary Artery Disease

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Editorial

In the cardiovascular research, it is a priority to identify novel candidates for the diagnosis, treatment, and prognosis of coronary artery disease (CAD) that remains, nowadays, the leading cause of death worldwide. At the present time, there is a great interest in the discovery of molecular biomarkers that may complement traditional cardiovascular risk scores in clinical decision-making as well as help to stratify patients for personalized therapeutic treatments (personalized medicine). With the development of next generation sequencing and bioinformatics technology, the interest in circular RNAs (circRNAs) has surfaced in the last few years. Notably, what was considered as "junk RNA" for two decades represents now one of the most attractive molecules. CircRNAs have been reported to play essential roles in physiological and pathological processes [1]. circRNAs can not only be found in different tissues [2,3], but also enriched in body fluids [4-6], such as blood, saliva, seminal fluid, supporting their potential use as clinical biomarkers.

CircRNAs are generated from exonic or intronic sequences, are conserved across species, and show tissue- specific expression. Because circRNAs form a covalently closed continuous loop, they are free of exonuclease-mediated degradation and more stable than most linear RNAs [7], which constitutes an enormous advantage from a clinical point of view. CircRNAs regulate gene expression through multiple mechanisms. Indeed, circRNAs can act as MicroRNA (miRNA) sponges, playing a competitive role in binding miRNA by post transcriptional regulation [8]. Additionally, circRNAs can also modulate transcription by interacting with nuclear small RNA or RNA polymerase II [9]. Furthermore, circRNAs can modulate RNA splicing by binding to transcription factors [10].

The diagnostic and predictive value of circRNAs in the field of cardiac disease is subject to ongoing research. Emerging clinical and experimental studies suggest that circRNAs can be potential key regulators in the initiation and development of CAD. Firstly, Burd et al. [11] found that circANRIL expression is associated with INK4/ARF transcription and atherosclerotic disease risk [11]. Interestingly, genetic variants in chromosome 9p21 (Ch9p21) locus, the most widely recognized and replicated genetic risk for CAD, can regulate ANRIL splicing and cANRIL production [11].

CircANRIL can confer atheroprotection by controlling ribosomal RNA (rRNA) maturation and modulation pathways of atherogenesis [12]. Specifically, circANRIL binds to Pescadillo homologue 1 (PES1), an essential 60S-preribosomal assembly factor, thus impairing exonuclease-mediated pre-rRNA processing and ribosome biogenesis in vascular smooth muscle cells and macrophages. Consequently, circANRIL induces nucleolar stress and p53 activation, resulting in the induction of apoptosis and inhibition of proliferation, which are key cellular functions in atherosclerosis [12].

In addition, reduced cANRIL expression can prevent coronary atherosclerosis by reducing vascular endothelial cells apoptosis and inflammatory factor expression [13]. In Song's study, the levels of total cholesterol, triglycerides, low density lipoprotein (LDL), interleukin-1 (IL-1), IL-6, matrix metalloproteinase-9 (MMP-9), C-reactive protein (CRP), Bax, and caspase-3, and rates of EC apoptosis were decreased in the low-expressed cANRIL group, while HDL (high density lipoprotein) levels and mRNA and protein expression levels of bcl-2 were increased. Conversely, the changes in expression levels in the over-expressed cANRIL group were the opposite of those in the low-expressed cANRIL group [13]. Hsa_circ_0003575 has also been found to regulate oxLDL induced vascular endothelial cells proliferation and angiogenesis, providing insight for the promising role of circRNAs in atherosclerotic disease [14]. Microarray analysis revealed the circRNA expression profiles of oxLDL treated human umbilical vein endothelial cells (HUVECs), and functional experiments confirmed the physiological function of hsa_circ_0003575 on endothelial cells. Moreover, bioinformatics analysis predicted the circRNA-miRNA-mRNA network as possible

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regulation mechanism [14].

Furthermore, in myocardal infarction (MI) mouse model, Cdr1as was also reported to be upregulated with increased cardiac infarct size [15]. Cdr1as functioned as a powerful miR-7a sponge in myocardial cells, and showed regulation on the protective role of miR-7a in MI injury, involving the function of miR-7a targets, such as poly (ADP-ribose) polymerase PARP and SP1 [15]. Interestingly, Zhao et al. first investigated the circRNA expression profiles in the peripheral blood of CAD patients to determine its correlation with the severity of CAD, and to test the potential of circRNAs as diagnostic biomarkers [16]. In this study, the authors explored circRNA signature in CAD patients and control individuals, and five significant differentially expressed circRNAs were selected for validation. After the validation in larger cohorts, hsa_circ_0124644 demonstrated its potential diagnostic value as a biomarker for the severity of CAD [16]. Subsequently, Pan et al. identified a network of nine circRNAs that regulate cation channel subfamily M member 3 (TRPM3) expressions by inhibiting hsa-miR-130a-3p in CAD patients [17]. TRPM3 is known to regulate proliferation and contractility of vascular smooth muscle cells in co-ordination with cholesterol and is potentially involved in therapeutic vascular modulation [18]. Furthermore, circRNAs might also be useful in aiding outcome prediction at early stages after MI, and thus supporting clinical decision-making [19]. Indeed, the expression levels of a MI-associated circRNA (MICRA), measured at reperfusion in peripheral blood samples of patients, have been found to predict left ventricular dysfunction after 3 to 4 months after acute MI [19]. Taken together, these studies reveal a novel potential for circRNAs in pathophysiological processes of CAD. However, much more studies are undoubtedly needed to better define their functional role in the diagnosis, treatment and prognosis of disease. Moreover, a better understanding of the molecular roles of circRNAs in the vascular biology may pave the way for the discovery of new therapeutic interventions.

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