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Editorial

Circular RNA as a Possible Novel Biomarker for Kawasaki Disease

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▸ See the article "Analysis of Circular RNAs in the Coronary Arteries of Patients with Kawasaki Disease" in volume 8 on page 50.

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Kawasaki disease (KD) is an acute febrile vasculitis of unknown cause that predominantly affects children less than 5 years of age. Because of the potential for coronary arterial lesion, it is now the most common cause of acquired heart disease in developed countries.[1] Although there are laboratory and clinical findings to diagnose KD, there is no single diagnostic parameter which enables early diagnosis. Since the development of coronary artery lesion is related to delayed treatment, early detection is highly important, especially in case of incomplete KD.

Circular RNAs (circRNAs) are an emerging novel class of noncoding RNAs with various cellular and molecular functions.[2] Noncoding RNAs are a group of functional RNAs that do not encode proteins and they are known to be involved with diverse regulatory processes in cells. Due to the unique nature of origin of genes and the closed molecular structure of RNA, circRNAs can function as a molecular sponge to sequester microRNAs (miRNAs) and prevent miRNA-mediated post-transcriptional gene regulatory pathways.[3] Several lines of evidence support the role of circRNAs in the regulation of transcriptional activation or suppression through the recruitment of epigenetic modulators or transcription factors.[4] circRNAs can also serve as a molecular adaptor to modulate protein–protein interactions.[2] A recent investigation on the function of circular antisense non-coding RNA in the INK4 locus (circANRIL) showed its role in the inhibition of maturation of ribosomal RNAs, expanding the knowledge of cellular functions of circRNAs.[5]

It is becoming clear from several reports that dysregulation of circRNA expression is associated with the development of several human diseases. Pathogenic roles of circRNAs are implicated in neurological diseases, cardiovascular diseases, and cancer progression.[2] A specific subgroup of circRNAs in endothelial cells is upregulated by hypoxic stresses.[6] In addition to RNA binding motif protein 20 (RBM20)-regulated circularization of human *TITIN* gene during its expression in cardiomyocytes (dilated and hypertrophic cardiomyopathy), the expression of circANRIL was found in atherosclerotic plaques, aneurysm and several primary cells including peripheral monocytes, endothelial cells, adventitial fibroblast and smooth muscle cells.[5] As such, circRNAs and their interactions as a regulatory circuit have become potential therapeutic and diagnostic targets in various diseases.[2]

Changes in the level of cirRNAs and miRNAs were suggested as an underlying mechanism of coronary heart disease as co-expression of circRNAs-miRNAs regulates multiple cellular pathways and molecular biological processes related to coronary heart disease.[7] In spite of the link between KD and coronary heart disease, investigations on the clinical connections between circRNAs and the pathogenesis of KD are largely lacking. Recent studies by Wu et al.[8] showed that the expression of circANRIL in KD patients (n=56) can be recovered upon the disease treatment. In contrast, the serum level of hsa_circ_0123996 was high in the KD patients before the treatment compared to healthy cohorts. Therefore, this bidirectional molecular signature could be a potential biomarker for early diagnosis of KD. In the current issue, Kim[9] re-analyzed publicly available RNA-Seq data from the Gene Expression Omnibus (GEO) dataset and showed that 5 circRNAs in coronary tissue but not in the blood of KD patients recovered their levels to normal upon the disease treatment. Although the resource for a biorepository of coronary tissues from 7 KD patients (3 untreated, 4 treated) and the status of individual coronary artery in these patients are not known, these initial observations are interesting and significant enough to put circRNAs as target molecules in translational research in KD pathogenesis. Although the conclusions from this study need further validations using a larger sample size, the study by Kim[9] opens up a new paradigm in connecting circRNAs to the KD pathogenesis and suggests circRNAs as a novel biomarker for KD. This study also suggests that comparative analyses of circRNAs between normal coronary and coronary lesion groups can identify risk factors for coronary artery lesion in KD patients. Further investigations on the clinical relevance of circRNAs will be needed using well-defined and systemic classifications of clinical features associated with KD pathogenesis and prognosis.

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