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RAPID COMMUNICATION

Identification of hsa_circ_0092576 regulatory network in the pathogenesis of coronary heart disease

Cardiovascular diseases (CVDs) are responsible for 30% of all deaths globally. Coronary heart disease (CHD), is the most common form of CVD, accounting for 46% of male and 38% female cardiovascular deaths.[1] CHD is characterized by chronic inflammation and endothelial injuries in coronary arteries, and subsequent development of atherosclerotic plaques which eventually leads to myocardial ischemia.[2] CHD is influenced by both genetic and environmental factors, and is prevalent in all parts of the world.[3] Regulatory non-coding RNAs (ncRNAs) e.g., long-chain ncRNAs, circRNAs, and miRNAs, are involved in the regulation of approximately 60% of protein-coding genes. Thus, ncRNAs partake in the regulation of many cellular processes. Dysregulation of ncRNAs is a major underlying event in the pathogenesis of many diseases.[4] Despite the vast information about CHD, frequency of the disease is still rising. Therefore, a study on the role of ncRNAs in CHD pathology is necessary to expand the understanding of molecular basis of the disease and pave way for its new diagnostic and treatment approaches. We demonstrated that hsa_circ_0092576 and its target miRNAs are vital in the regulation of genes related to CHD pathology, and thus could be promising biomarkers of the disease.

In this study, bioinformatics tools were used to evaluate the role of hsa_circ_0092576 in the pathogenesis of CHD (Supplementary File 1). These results showed that hsa_circ_0092576 participated in the initiation and progression of CHD via the sponging action on the target miRNAs including miR-548c-3p, miR-495–3p, miR-7-5p, miR-186–5p, miR-203a-3p, miR-21–5p and miR-145–5p. Several reports have linked the expression of circRNAs with heart-related diseases. However, this is the very first study that relates the importance of the regulatory effect of hsa_circ_0092576 in the pathogenesis of CHD. The higher number of up-regulated genes observed in CHD was the consequence of the up-regulation of hsa_circ_0092576. It acts as a competing endogenous RNA (ceRNA) and characteristically sponges miRNA and diminishes its regulatory action on the target genes, resulting in increased expression of the genes.

The functional enrichment analysis of differentially expressed miRNA target genes (miR-DEGs) revealed the involvement of miR-548c-3p, miR-495–3p, miR-7-5p, miR-186–5p, miR-203a-3p, miR-21–5p and miR-145–5p in the pathogenesis of CHD via the regulation of genes necessary for protein phosphorylation, cell proliferation, circadian rhythm, and vascular endothelial growth factor production (Table S1). Dysregulation of protein phosphorylation could lead to heart-related disease. Human heart failure in particular, which could be the consequence of CHD, has been linked to the low level of thin-filament protein phosphorylation. miR-495–3p, miR-7-5p, miR-21–5p and miR-145–5p were significantly involved in the regulation of protein phosphorylation. Circadian rhythm is one of the underlying mechanisms of cardiovascular physiology, and its disturbances increase the risk of developing cardiac problems and adverse cardiovascular events. Our results demonstrated the involvement of miR-548c-3p-DEGs in the circadian rhythms, predicting the role of miR-548c-3p in cardiovascular physiology via the regulation of *CREB1, NAMPT, NRIP1,* and *ID3*. VEGF plays a vital role in angiogenesis and atherosclerosis, hence associated with heart-related diseases. The involvement of miR-548c-3p and miR-7-5p in the production of VEGF via the regulation of target *IL6ST, PTGS2 and HIF1A* was predicted in the present study. This could be seen as another mechanistic way by which hsa_circ_0092576 and its target miR-548c-3p and miR-7-5p have been connected to the pathogenesis of CHD. Among the miRNAs, miR-548c-3p showed the highest degree of association with cellular functions related to CHD pathology. To the best of our knowledge, this is the first

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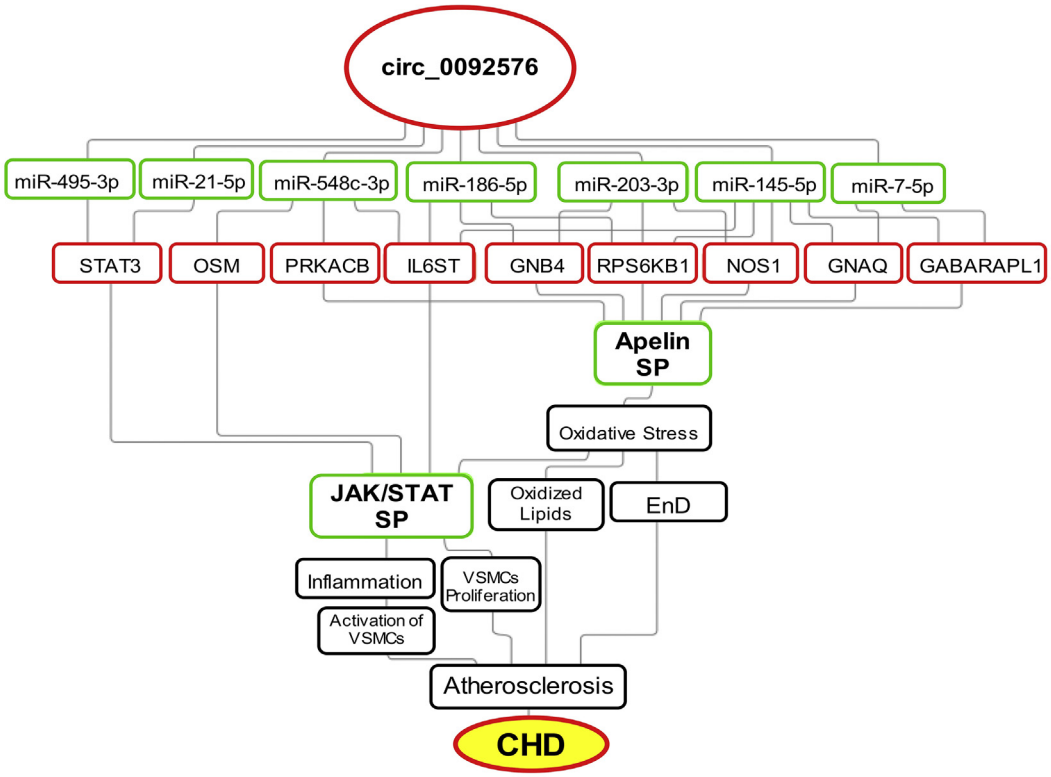

Figure 1 Proposed model for the role has_circ_0092576 in the pathogenesis of CHD. SP, signaling pathway; EnD, endothelial dysfunction; VSMCs, vascular smooth muscle cells; CHD, coronary heart disease.

report that demonstrates the participation of miR-548c-3p in CHD pathology.

The KEGG pathway analysis revealed the role of hsa_circ_0092576 and/or its target miRNAs in the regulation of signaling pathways and other cellular processes related to CHD (Table S2). These include MAPK, TGF-beta, JAK/STAT, Apelin, mTOR, PPAR, FoxO, PI3K-AKT, VEGF, and Relaxin signaling pathways. Other affected pathways relevant to CHD include atherosclerosis, insulin resistance, platelet activation, cardiac muscle contraction, vasopressin regulated water reabsorption as well as aldosterone synthesis and secretion. JAK/STAT pathway is implicated in a variety of cardiac pathologies and contributes to both adaptive and maladaptive responses thus protective and harmful effects on cardiomyocytes. The involvement of a significant number of miR-DEGs in JAK/STAT is an indication of the regulatory effect of hsa_circ_0092576 or its target miRNAs on the signaling pathway. Up-regulation of genes in the JAK/STAT signaling pathway and atherosclerosis process was observed. This supports the fact that activation of the JAK/STAT signaling pathway is critical in the initiation and progression of atherosclerosis.

Our data indicated a significant number of miR-DEGs were associated with the Apelin signaling pathway. The pathway is usually expressed in the cardiovascular system and identified as an essential process for cardiovascular homeostasis. The activated Apelin signaling pathway elicits a variety of physiological processes, e.g., fluid homeostasis, endocrine stress response, regulation of blood pressure, angiogenesis, cardiac contractility, and energy metabolism. On the other hand, the pathway also takes part in the pathology of many diseases. Apelin may act as a prominent Atheros-protective marker against the development of CHD. The involvement of miR-DEGs in the Apelin signaling pathway indicated the role of hsa_circ_0092576 or their target miRNAs in the pathogenesis of the disease. The up-regulated hsa_circ_0092576 sponges the target miRNAs and inhibits the miRNAs suppression effect on the target genes, resulting in the up-regulation of the genes. Apelin may have beneficial or harmful effects in the development of atherosclerosis. It may contribute to atherogenesis by mediating oxidative stress, thus a detrimental effect. Conversely, Apelin can slow down atherosclerosis by inhibiting angiotensin II, thus a beneficial effect.

miRNA:mRNA homology analyses are fundamental in predicting the potentials of miRNA to efficiently bind to the target sequence and regulate its expression. In the present study, many duplexes possess MFE values of $\leq$ -27 kcal/mol (Table S3), which are comparable to the MFE value for the hybridization of let-7 and 3′UTR of the *C. elegans*. CELF35-1, identified as one of the best-known duplexes of let-7.[5] However, miRNA:mRNA duplex attain stable and perfect interaction if the MFE value $\leq$ -30 kcal/mol. The duplexes of miR-145−5p:RPS6KB1, miR-145−5p:NOS1 and miR-145−5p:APLNR

possessed the lowest MFE value of < -30 kcal/mol, thus predicted to have a stable and perfect hybrid. It is therefore predicted that miR-145−5p could efficiently regulate the expression of *RPS6KB1*, *NOS1* and *APLNR*.

Based on the present data, a model was proposed to explain the role of hsa_circ_0092576 and its target miRNAs in the pathogenesis of CHD (Fig. 1). It was predicted that hsa_circ_0092576 can effectively sponge the target miRNAs thereby suppressing their inhibitory effect to their respective target genes of JAK/STAT and Apelin signaling pathway including *IL6ST STAT3*, *OSM*, *PRKACB*, *NOS1*, *RPS6KB1*, GABARAPL1, GN*AQ* and *GNB4*. Consequently, the expression of genes was enhanced, and the pathways were activated. This event enhanced the vascular inflammation which eventually resulted in atherosclerosis via the activation and proliferation of vascular smooth muscles cells (VSMCs). Similarly, the active Apelin signaling pathway promoted atherogenesis by mediating oxidative stress in the vascular tissues, thereby causing endothelial injury and accumulation of oxidized lipids, which result in the development of atherosclerosis. Ultimately, CHD developed due to atherosclerotic plaque in the artery. Conclusively, it is suggested that hsa_circ_0092576 and/or its target miRNAs most importantly miR-145−5p play a significant role in the pathogenesis of CHD by implicating the Apelin and JAK/STAT signaling pathways, thus could be considered potential biomarkers of the disease. An intensive study to evaluate the feasibility of hsa_circ_0092576 and its target miR-145−5p as a biomarker of CHD will aid in the development of new and possibly better diagnostic or therapeutic approaches to the disease.

Conflict of interests

Authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2021.12.027.

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