Editorial

Emerging Novel Biomarkers for Arteriosclerosis Obliterans

Takahiro Horie, Takeshi Kimura and Koh Ono

Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

See article vol. 23: 196-206

Arteriosclerosis obliterans (ASO) is one of the most common peripheral vascular diseases and is considered as a form of atherosclerosis. Risk factors of ASO include age, male gender, smoking, hypertension, hyperlipidemia, diabetes mellitus (DM), chronic renal failure, and hyperhomocysteinemia. Although several therapeutic approaches such as surgery, endovascular interventions, and pharmacological treatments are progressing, ASO remains a major cause of limb loss worldwide and has a high mortality rate even if symptoms such as intermittent claudication are free¹⁾. Therefore, early diagnostic methods, before symptoms become evident, and new therapies for ASO are required.

MicroRNAs (miRNAs; miRs) are endogenous, small (20–22 nucleotides), non-protein-coding RNAs. miRNAs bind to the 3' untranslated region (UTR) of the specific mRNAs on the basis of sequence complementarity and inhibit translation or promote mRNA degradation^{2, 3)}. Initially, miRNAs were discovered in *Caenorhabditis elegans*^{4, 5)} and were later found to be evolutionarily conserved⁶⁾. Approximately 2,500 miRNAs have been identified in humans till date. Many studies have demonstrated that miRNAs play significant roles physiologically and pathophysiologically and some miRNAs also significantly impact metabolism and lipid homeostasis^{7, 8)}. Moreover, miRNAs are present and enriched in blood, and circulating miRNAs have been proposed as biomarkers for various cancers, cardiovascular diseases, and metabolic disorders, including DM⁹⁾.

In this study, He *et al.* identified certain miRNAs in plasma as novel biomarkers for ASO¹⁰⁾. They screened

miRNAs by microarray using plasma of control and ASO patients and confirmed using quantitative PCR that some miRNAs were altered in both the plasma and tissues. Among them, miR-4284 and miR-4463 were altered at the early stages of ASO and the alterations were observed even at the later stages. miR-4306 and miR-221-3p gradually decreased with the increasing stages of ASO. Furthermore, miRNA expression patterns in ASO patients with type 2 diabetes mellitus (T2DM) and the effects of homocysteinemia, cystatin C, and smoking on these miRNAs were analyzed. They concluded that plasma miR-4284 and miR-4463 levels could be novel early diagnostic biomarkers for ASO.

However, some questions remain unanswered. One is that the functional roles of these miRNAs for ASO formation are still unknown, although potential target genes of miRNAs were listed using bioinformatics analyses in this study. The actual target genes of miRNAs and the kinds of cells that express and secrete these miRNAs remain unknown. Moreover, the function of miRNAs in cell to cell communication is unclear. These questions are important because the modulation of these miRNAs could be a potential therapeutic approach for ASO. In this study, the expressions of miRNAs changed when ASO patients had T2DM; miR-4284 was not altered in ASO with T2DM; and miR-4463 was decreased in ASO only, on the contrary, increased in ASO with T2DM. Because DM is one of the most frequent risk factors of ASO and ASO patients often have DM, elucidation of the underlying mechanism of the discrepancy will be necessary for using miR-4284 and miR-4463 as biomarkers.

In this study, the expressions of miR-4284 and miR-4463 were altered at the Stage I of ASO (Fontaine classification); therefore, these circulating miRNAs can be novel biomarkers for the early diagnosis of ASO. Large scale studies in the future will support and strengthen the usefulness of these circulating miRNAs for ASO diagnosis.

Address for correspondence: Takahiro Horie, Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, 54 Shogoinkawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan

E-mail: thorie@kuhp.kyoto-u.ac.jp

Received: October 20, 2015

Accepted for publication: October 27, 2015

Disclosures

None.

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