TITLE:
MicroRNA-133a in the development of arteriosclerosis obliterans

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Peripheral artery disease (PAD), specifically atherosclerotic disease leading to peripheral artery obstruction, may be silent or present with a variety of symptoms and signs indicative of extremity ischemia. The clinical manifestations of PAD are due to a lack of blood flow to the musculature relative to its metabolism, which results in pain in the affected muscle groups. Risk factors for PAD are similar to those that promote the development of coronary atherosclerosis. Other risk factors include male gender, black ethnicity, a family history of atherosclerosis, smoking, hypertension, hyperlipidemia, and homocysteinemia. Currently, pharmacologic therapies used in the treatment of patients with lower extremity PAD are primarily aimed at improving symptoms or slowing the progression of the disease.

MicroRNAs (miRNAs; miRs) have been shown to be further layer of gene regulation, and it is not surprising that they are also involved in the development of arteriosclerosis obliterans. miRNAs are endogenous, small (approximately 18-25 nucleotides in length), non-protein-coding RNAs present in almost all organisms. miRNAs bind to the 3'-untranslated region (UTR) of specific mRNAs according to the complementarity of their sequences and inhibit translation or promote mRNA degradation. miRNAs were initially discovered in Caenorhabditis elegans and were later found to be evolutionarily conserved. More than 60% of human protein-coding genes have been under selective pressure to maintain pairing with miRNAs, and so far, approximately 2,500 miRNAs have been identified in humans.

In this study, Li et al. have demonstrated that miR-133a was clearly detected in smooth muscle cells in human arteries, and its expression was significantly reduced in arteriosclerosis obliterans (ASO) arteries compared with normal arteries. Down-regulation of miR-133a enhanced the proliferation and migration of human arterial smooth muscle cells (HASMCs) induced by platelet-derived growth factor-BB. Moreover, they also demonstrated that RhoA is one of the targets of miR-133a, although the seed sequence does not match well with its potential binding site in the RhoA 3'-UTR. Overexpression of RhoA attenuated miR-133a-induced anti-proliferative and anti-migratory effects on HASMCs. These results indicated that miR-133a may be a preventive factor against ASO.

It is still unknown which factors reduce the expression of miR-133a and whether down-regulation of miR-133a is related to phenotypic changes in smooth muscle cells. These points should be clarified in future experiments.

Many miRNAs share similar seed sequences, and they are referred to as an miRNA ‘family’. There are three different miRNAs in the miR-133 family, miR-133a, -133b, and -133c. Usually, these miRNA families work in a coordinated fashion by complementary binding to the 3'-UTRs of the same genes. In this case, it seems that binding of miR-133a does not necessarily occur between its seed sequence and the RhoA 3'-UTR. Thus, other family members are unlikely to affect RhoA in smooth muscle cells. However, on the contrary, this kind of ‘non-specific’ binding may occur between a number of miRNAs and mRNAs and it may confuse the understanding of miRNA-based biology.

This study demonstrated that the miR-133a
miR-133a expression may affect the proliferation and migration of HASMCs via RhoA, and the down-regulation of miR-133a may be involved in ASO. Up-regulation of miR-133a could be a promising new approach for the prevention or treatment of ASO in the future.

**Conflicts of Interest**

None.

**References**

6. Lewis BP, Burge CB, Bartel DP: Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell, 2005; 120: 15-20

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**Fig. 1.** Schematic overview of the function of microRNA (miR)-133a

miR-133a expression may affect the proliferation and migration of human arterial smooth muscle cells (HASMCs) via RhoA, and the down-regulation of miR-133a may be involved in arteriosclerosis obliterans (ASO).