Since their discovery in the 1990s, many microRNAs (miRs) have been found to control key cellular processes, many of which are relevant to the cardiovascular system. miRs regulate the expression of extensive networks of genes by binding to mRNA molecules in the cytoplasm to inhibit their expression. Therefore, it was quite a surprise when miRs were found in the blood or in the supernatant of cultured cells at relatively stable levels. These discoveries led to a vast amount of reports showing that circulating miRs can act as potential biomarkers for virtually all diseases, including cardiovascular disease. It was also soon discovered that extracellular miRs are not mere waste material but constitute an intercellular communication mechanism. Circulating miRs have been found inside protein complexes, high-density lipoprotein, low-density lipoprotein, and extracellular vesicles like shedding vesicles, exosomes, and apoptotic bodies, which not only prevent RNases from degrading the miRs but also may mediate delivery of the miRs to specific cell types. Intercellular communication through miRs secreted by endothelial cells in extracellular vesicles was recently shown to contribute to atheroprotective mechanisms.

Zhou et al. show in this issue of Circulation Research that miR-126 is secreted by endothelial cells in protein complexes on atheroprone stimuli. This miR is then taken-up by smooth muscle cells, where it inhibits the expression of proteins that normally keep the cells in a contractile and quiescent state (Figure). In previous studies, secreted miR-126 was implicated in atheroprotection when taken-up by endothelial cells, but the current study suggests that when miR-126 enters smooth muscle cells, atherosclerosis is enhanced. One important aspect of the current study by the Chien laboratory is that miR-126 is not secreted in vesicles, but rather in complex with argonaut proteins and likely other proteins, too. It is not clear how these miR-containing protein complexes are secreted by endothelial cells and how they enter smooth muscle cells, but these questions deserve further study.

An interesting finding of the study by Zhou et al. is that miR-126 is not transcriptionally regulated by laminar flow, which is consistent with the literature about mammalian miR-126. In fact, miR-126 levels do not alter at all in endothelial cells, despite convincing evidence that miR-126 is secreted under atheroprone conditions. These observations suggest that only a small fraction of endothelial miR-126 is secreted. However, when one takes into account that miR-126 is highly expressed in endothelial cells and is normally virtually absent in smooth muscle cells, transfer of even a small fraction of endothelial miR-126 to smooth muscle cells can have functional effects. Therefore, flow conditions specifically alter the secretion of miR-126 from endothelial cells. How atheroprone flow induces secretion of miR-126-containing protein complexes remains to be elucidated but likely involves proinflammatory signaling pathways known to be induced by atheroprone flow.

Transfer of these miRs to leukocytes could contribute to an additional aggravation of atherosclerosis. However, it has been shown that miR-126 inhibits the recruitment of monocytes and induces progenitor cell recruitment, processes considered to be antiatherosclerotic. Because inflammation is one of the hallmarks of atherosclerosis, it would be important to verify that blocking protein-bound miR-126 secretion also ameliorates atherosclerosis formation in a more inflammation-induced mouse model for atherosclerosis than the carotid artery ligation model used by Zhou et al.

The miR levels in the circulation can be conveniently measured and correlate well with diverse disease entities and therefore are extensively studied as potential biomarkers. The miR-126 levels in the plasma have been positively and negatively associated with various cardiovascular clinical entities. Even though the reported studies did not distinguish between miR-126 in protein complexes and vesicles, it was found that circulating miR-126 decreases during transcoronary passage, which could indicate an uptake of miR-126 by, for example, smooth muscle cells, thereby aggravating atherosclerosis. However, whether protein-bound miR-126 is also released into the circulation or whether it is just secreted to the basal side of endothelial cells into the intima is not known but highly likely, because miR-126 is found in protein complexes and vesicles in plasma.

The findings described in this issue of Circulation Research further improve our understanding of the pathophysiology of atherosclerosis and are of potential clinical relevance. Genetic deletion of miR-126 suppressed neointima formation in the carotid artery ligation mouse model, as characterized by smooth muscle cell proliferation after flow cessation.
Importantly, neointima formation could be induced in miR-126 knockout mice by injecting supernatant of cultured endothelial cells that contains protein-bound miR-126. Therefore, inhibition of transfer of miR-126 to smooth muscle cells could be a powerful tool to inhibit neointima formation in clinical settings. However, caution is necessary because vesicle-embedded miR-126 transfer to endothelial cells is atheroprotective. Inhibition of this process would putatively augment atherosclerosis and therefore should be avoided.

Disclosures

R.A. Boon is supported by the Hessien Ministry of Higher Education, Research, and the Arts (III L 4–518/17.004), and by the Excellence Cluster Cardiopulmonary Systems of the Deutsche Forschungsgemeinschaft (Exc 147–1).

References


Key Words: atherosclerosis ■ microRNA ■ shear stress
Endothelial MicroRNA Tells Smooth Muscle Cells to Proliferate
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Circ Res. 2013;113:7-8
doi: 10.1161/CIRCRESAHA.113.301636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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