Endothelial MicroRNA Tells Smooth Muscle Cells to Proliferate

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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 also was 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.

The miR-126 levels in the plasma have been positively and negatively associated with various cardiovascular clinical entities and therefore are extensively studied as potential biomarkers. 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. Furthermore, secretion of other protein-bound miRs by endothelial cells might additionally contribute to the proatherosclerotic effects on smooth muscle cells.

Smooth muscle cells are the predominant cell type in the normal vessel wall; however, under atheroprone conditions, significant influx of inflammatory cells occurs. The miRs that are secreted on the basal side of endothelial cells, including miR-126, therefore also could be taken-up by leukocytes. Transfer of these miRs to leukocytes could contribute to an additional aggravation of atherosclerosis. However, it has been shown 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
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References

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