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. These 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 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 by smooth muscle cell proliferation after flow cessation.

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. 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-126 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 Hessian 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 (Exz 147–1).

References

Key Words: atherosclerosis ■ microRNA ■ shear stress
Endothelial MicroRNA Tells Smooth Muscle Cells to Proliferate
Reinier A. Boon

Circ Res. 2013;113:7-8
doi: 10.1161/CIRCRESAHA.113.301636
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/113/1/7

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/