During life, our arteries with their 3 layers, numerous curvatures, branch points, and bifurcations, are continuously exposed to different flow and shear stress conditions. At branch points and bifurcations, especially oscillatory shear stress activates the endothelium, making these arterial sites prone to develop atherosclerosis.\(^1,\)\(^2\) The subendothelial deposition and subsequent modification of lipids, such as low-density lipoprotein (LDL), further enhances this vascular inflammation. Along with endothelial activation, both the innate and adaptive immune system come into play, resulting in further recruitment of leukocytes and formation of atherosclerotic plaques.\(^1,\)\(^2\)

**Article, see p 434**

To keep the development of atherosclerosis under control, our arteries are subjected to a tight regulation to maintain their homeostasis. Regulatory RNAs, including micro-RNAs, are powerful post-transcriptional mediators that control vascular homeostasis, and their deregulation can result in aggravation of endothelial dysfunction and aggravation of vascular disease. Micro-RNAs can therefore be considered as potential novel therapeutics to treat cardiovascular disease.\(^3\)

In this issue of *Circulation Research*, Loyer et al\(^1\) performed an elegant screening to identify micro-RNAs affecting atherosclerosis, the so-called atheromiRs, in endothelial cells. The authors selected the atheromiRs in vitro settings using human umbilical vein endothelial cells based on 2 criteria that are highly relevant for the pathogenesis of atherosclerosis: (1) miRs that exhibit a change in expression by exposure to oxidized LDL (oxLDL) under low shear stress and (2) miRs that are not affected by oxLDL exposure under high shear stress conditions. The miR that was most dysregulated and fulfilled these criteria was miR-92a, which was highly expressed in atherosclerosis-prone regions in normocholesterolemic ldlr\(^{-/-}\) mice compared with atherosclerosis-resistant regions in normocholesterolemic ldlr\(^{-/-}\) mice. Expression of KLF2 and KLF4 is mediated by not only endothelial cells but also smooth muscle cells that were exposed to oxLDL, Loyer et al\(^1\) showed in vivo evidence for the importance of atheromiR-92a expression.

Interestingly, a recent report showed that KLF2 is downregulated by LDL, and that the repression of KLF2 is mediated by both DNA and histone methylation,\(^8\) suggesting that the oxLDL-induced repression of KLF2 is not solely mediated by miR-92a, but that other epigenetic phenomena also play an important role. Both endothelial KLF2 and KLF4 have been shown to be atheroprotective.\(^8,\)\(^9\) However, the atheroprotective effect of KLF2 and KLF4 is mediated by not only endothelial cells but also myeloid cells.\(^11,\)\(^12\) Because miR-92a is not expressed in oxLDL-exposed macrophages, other factors than miR-92a must regulate KLF2 and KLF4 expression in myeloid cells.

Of particular interest, the authors identified a novel target of miR-92a, Suppressor Of Cytokine Signaling 5 (SOCS5),...
SOCS5 was specifically targeted by miR-92a in endothelial cells under low shear stress conditions and on exposure of ox-LDL. The function of SOCS5 is not yet clear, but it is thought to act as a tumor suppressor and was shown previously to act as an inhibitor of janus kinase/signal transducer and activation of transcription pathways in endothelial cells. Here, Loyer et al. show that inhibition of SOCS5 by siRNA increases monocyte chemoattractant protein-1 and interleukin-6 release without affecting KLF2, KLF4, and NOS3 levels, indicating that SOCS5 indeed directly protects against endothelial activation and inflammation. In which stages of atherosclerosis development the miR-92a-SOCS5 pathway plays its most prominent role still warrants further investigation.

In the current article, miR-92a plays a predominant role in endothelial cell biology in low shear stress conditions and when selectively exposed to oxLDL. However, in other diseases, miR-92a plays an important role in re-endothelialization, angiogenesis, and inflammation. In a model of neointima formation, re-endothelialization after wire injury was enhanced and neointima formation was reduced on inhibition of miR-92a. When miR-92a was blocked using an antagonim in mouse models of acute limb ischemia and myocardial infarction, angiogenesis was improved, and tissue recovery was enhanced. Similarly, when miR-92a was blocked by a locked nucleic acid-modified anti-miR in a pig model of myocardial infarction, infarct size was significantly reduced by increased angiogenesis and a reduction in inflammation.

Circulating members of the miR-17 to 92 cluster, and especially miR-92a, have been shown to be potent biomarkers for cardiovascular disease. miR-92a levels were strongly associated with coronary artery disease in humans. Moreover, miR-92a was found to be highly expressed in circulating Annexin+ CD31+ microparticles of these patients, suggesting an endothelial origin of this biomarker.

In conclusion, Loyer et al. make an important observation that miR-92a is a powerful lipid-driven atheromiR, which may be a promising therapeutic target in atherosclerosis. Not only do Loyer et al show the importance of modulation of KLF2 and KLF4 in atherosclerosis by miR-92a, but they also identify SOCS5 as a novel target for miR-92a in the endothelium (Figure). These combined regulatory effects of miR-92a in endothelial activation make it thus an important regulator of atherosclerosis development.

Together with the data available on the role of miR-92a in cardiovascular disease, this article shows the potential of miR-92a to be used both as a diagnostic and therapeutic target in atherosclerotic disease. Because this miRNA seems to particularly act on the endothelium in atherosclerosis-prone areas, both systemic and local therapeutic approaches using miR inhibitors could be of interest in both preventing atherosclerotic disease and minimizing tissue loss on infarction when atherosclerotic disease is irreversible.

Sources of Funding
We acknowledge the support from the Netherlands CardioVascular Research Initiative: “the Dutch Heart Foundation, Dutch Federation of University Medical Centres, the Netherlands Organisation for Health Research and Development, and the Royal Netherlands Academy of Sciences” for the GENIUS project “Generating the best evidence-based pharmaceutical targets for atherosclerosis” (CVON2011-19) to E. Lutgens and M.P.J. de Winther. M.P.J. de Winther and E. Lutgens are supported by the Humboldt Foundation (Sojja Kovalevskaja grant to E. Lutgens), the Deutsche Forschungsgemeinschaft (SFB1054 to E.L.), the Netherlands Organization for Scientific Research (VICI grant to E. Lutgens) the Netherlands Heart Foundation (established investigator grant to M.P.J. de Winther and E. Lutgens).

References


**Key Words:** Editorials ■ antagomir-92a ■ atherosclerosis ■ endothelium ■ oxidized low-density lipoprotein
MiR-92a: At the Heart of Lipid-Driven Endothelial Dysfunction
Menno P.J. de Winther and Esther Lutgens

Circ Res. 2014;114:399-401
doi: 10.1161/CIRCRESAHA.114.303125
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 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/114/3/399

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/