Crippling of Krüppel (-Like Factor 2) by Bad Flow Portends a miRky Day for Endothelial Function

Kaikobad Irani, MD

K

rüppel-like Factor 2 (KLF2) is a 38-kDa transcription factor that is highly expressed in the vascular endothelium. The enormous attention that KLF2 has received in recent years is well deserved, because experimental evidence has shown that it is a vital protein that, via transcriptional and nontranscriptional targets, mediates a host of endothelial functions. These include inhibition of vascular inflammation and attendant atherosclerosis, maintenance of an antithrombotic endothelial surface, stimulation of endothelial nitric oxide synthase expression and vascular nitric oxide production, inhibition of hypoxia-stimulated angiogenesis, and promotion of prenatal vasculogenesis, among others. It is not surprising, therefore, that regulation of endothelial KLF2 expression has been the subject of intense investigation.

KLF2 mRNA by RNA-binding proteins is yet another mechanism through which laminar shear induces endothelial KLF2. Despite this substantial knowledge about the regulation of KLF2 by shear forces, translational regulation, in particular, by microRNAs, has not been reported.

MicroRNAs (miRs) are noncoding RNAs that, by binding to mRNAs, inhibit translation or lead to degradation of those mRNAs. In the current issue of Circulation, Wu et al\(^{10}\) show, for the first time, that a specific miR (miR-92a) expressed in the endothelium targets KLF2 mRNA, and miR-92a impairs pulsatile flow-induced endothelium-dependent relaxation. That shear forces result in up- or downregulation of miRs is not new. In comparison with static conditions, pulsatile and unidirectional laminar shear changes the expression profile of miR expression in endothelial cells, leading to the upregulation of miRs targeting regulators of the cell cycle and the Akt kinase-endothelial nitric oxide synthase pathway, resulting in endothelial cells that are growth arrested and protected from apoptosis.\(^{11-13}\) On the other hand, oscillatory shear results in a different miR expression profile that induces an inflammatory phenotype in endothelial cells.\(^{14}\) Despite this prior work, the work by Wu et al in this issue of Circulation adds a new and important dimension by identifying KLF2 as a target of shear stress-regulated miRs and showing that miR-92a, by targeting KLF2, inhibits laminar shear-stimulated expression of vasodilatory and antithrombotic genes.

As alluded to in the article by Wu et al,\(^{10}\) miR-92 is not a newcomer to the field. Prior elegant work has shown that endothelial miR-92a, upregulated in the context of tissue ischemia, inhibits angiogenesis and neovascularization.\(^{15}\) Interestingly, among the mRNAs directly or indirectly downregulated by miR-92a were those of endothelial nitric oxide synthase, thrombomodulin, and SIRTUIN1.\(^{15}\) The former two are transcriptionally upregulated by KLF2, whereas SIRT1 induces KLF2.\(^{16}\) These findings, taken together with those reported by Wu et al, strongly suggest that downregulation of at least some of the genes during ischemia occurs because miR-92a directly targets KLF2. They also hint at additional indirect mechanisms through which miR-92a may repress KLF2, such as downregulation of SIRT1.

The finding that KLF2 is a target of miR-92a is, for the most part, consistent with its described roles in the endothelium. However, it is somewhat problematic to reconcile this finding with prior observations that both miR-92a\(^{15}\) and KLF2\(^{17,18}\) inhibit angiogenesis in the setting of ischemia or hypoxia. Nevertheless, the role of KLF2 in inhibiting angiogenesis is sufficiently controversial, with some reports showing that it is required for vasculogenesis in the embryo,\(^{19}\) to allow one to conclude that in specific physiological or pathophysiological contexts, other than ischemia or hyp-
oxia, miR-92a-mediated repression of KLF2 may play a part in impairing angiogenesis.

MicroRNA-92a is a member of the polycistronic miR-17∼92 cluster on human chromosome 13. Members of this cluster share a common transcript. Oncogenic transcription factors, including c-myc and N-myc, promote transcription of this cluster.20,21 In accordance with its induction by these transcription factors, the miR-17∼92 cluster is highly expressed in several solid and hematologic malignancies.21,22 A detailed and systematic analysis of expression of this cluster in atherosclerotic vessels (or regions of vessels subjected to nonlaminar oscillatory shear) has not been undertaken, but is one that is begging to be done. Despite the lack of such information, there is emerging evidence that this miR cluster (or members of it) may play a part in the pathogenesis of atherosclerotic vascular disease, or at least serve as a marker for such disease. A recent report shows that miR-92a expression in the circulating plasma is decreased in patients with stable coronary artery disease in comparison with healthy controls.23 Taken in the context of the findings by Wu et al, this decrease in miR-92a in atherosclerotic vascular disease may at first look seem paradoxical, but could be explained on the basis of diminished endothelial progenitor cells, or a highly dysfunctional end-stage endothelium that is associated with advanced atherosclerosis. It would be more revealing to determine the temporal pattern of expression of miR-92a during the slow development of atheromatous disease, starting from the earliest phases of endothelial dysfunction and plaque formation, and correlating this expression to that of KLF2.

Given the importance of HDAC in regulating endothelial KLF2 expression,24 an important question that surfaces from the current work is the role that chromatin modification, in particular, by HDAC, may play in flow-mediated miR-92a expression. Laminar flow-induced KLF2 expression is, in part, mediated by deinhibition of HDAC5-mediated KLF2 repression.7 Whether, in the context of flow, HDAC5, or other HDAC, regulate the expression of the miR-17∼92 cluster in endothelial cells is not known. However, the treatment of breast cancer cells, which express this cluster, with a pan-HDAC inhibitor down-regulates at least some of its members.25 This raises the intriguing possibility, and one that is not too far-fetched, that athero-protective pulsatile flow suppresses expression of the miR-17∼92 cluster by inhibiting HDAC5 (or possibly other HDAC), thus promoting endothelial KLF2 expression.

In conclusion, the current work by Wu et al is ground-breaking with respect to identifying KLF2 as a direct target of miR-92a, showing that miR-92a is differentially expressed in response to pulsatile and oscillatory shear forces, and miR-92a expression plays an important part in inhibiting flow-induced endothelium-dependent vasorelaxation. Only further studies will tell how shear forces govern miR-92a expression, and whether this expression contributes to the pathogenesis of atherosclerosis in arterial segments exposed to disturbed flow.

Acknowledgments
Dr Irani apologizes to all whose important work related to this subject could not be cited in the interest of space.

Disclosures
None.

Sources of Funding
Dr Irani is supported by the National Institutes of Health (HL070929, HL098892, HL094959, HL065608), the American Heart Association (0655467U), and the Heart and Vascular Institute of UPMC.

References


Key Words: Editorials | endothelium | microRNA | vascular function | vasodilation
Crippling of Krüppel (-Like Factor 2) by Bad Flow Portends a miRky Day for Endothelial Function
Kaikobad Irani

Circulation. 2011;124:541-543
doi: 10.1161/CIRCULATIONAHA.111.043299
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/124/5/541

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation 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 is online at:
http://circ.ahajournals.org//subscriptions/