Kruppel-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.

miR-92a, 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. Interestingly, among the mRNAs directly or indirectly down-regulated by miR-92a were those of endothelial nitric oxide synthase, thrombomodulin, and SIRTUIN1. The former two are transcriptionally upregulated by KLF2, whereas SIRT1 induces KLF2. 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 and KLF2 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, 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. In accordance with its induction by these transcription factors, the miR-17–92 cluster is highly expressed in several solid and hematologic malignancies. 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. 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, 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 deinnhibition of HDAC5-mediated KLF2 repression. 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. 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.

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None.

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Kaikobad Irani

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