Therapeutic strategies aiming at enhancing disease-induced downstream signaling networks and cell function, targeting a miRNA because one miRNA controls the fate of many genes modulating age-related diseases, including vascular and metabolic systems. MicroRNAs (miRNAs) are 22-nucleotide to 24-nucleotide noncoding RNAs that posttranscriptionally regulate expression of multiple target genes. They function via non-perfect base-pairing with complementary sequences within the 3'-untranslated region of messenger RNAs, leading to degradation or translational repression. Increasing evidence suggests an important role of miRNAs as epigenetic regulators of age-related diseases, including vascular and metabolic diseases. Gene expression, cell-type-specific function, and cell–cell communication are regulated by miRNAs, which emerge as important regulators of the cardiovascular system. Because 1 miRNA controls the fate of many genes modulating signaling networks and cell function, targeting a miRNA might be a promising strategy to treat atherosclerotic disease. Therapeutic strategies aiming at enhancing disease-induced downregulated vascular miRNAs or inhibition of upregulated miRNAs have opened a new area of preclinical research to treat vascular inflammation and disease.

Activation and nuclear translocation of the transcription factor nuclear factor-κB (NF-κB) induce the expression of multiple proinflammatory cytokines and adhesion molecules in the endothelium, promoting the initiation and progression of vascular inflammation, atherosclerosis, and metabolic syndrome. Targeting NF-κB has been regarded as a promising therapeutic strategy to reverse chronic vascular inflammation and prevent atherosclerotic disease. Blockade of the endothelial cell NF-κB pathway additionally prevents age-related insulin resistance and vascular senescence and prolongs life span in mice.

In this issue of Circulation Research, Sun et al report that systemic delivery of miR-181b inhibits NF-κB activation, vascular inflammation, and atherosclerosis in apolipoprotein E–deficient mice (Figure). It has been reported previously by the same group that miRNA-181b regulates NF-κB–mediated vascular inflammation by targeting importin-α3, a protein that is required for nuclear translocation of NF-κB. Increased expression of miR-181b leads to decreased expression of its target importin-α3 and subsequently inhibits the NF-κB signaling pathway. Proinflammatory stimuli and high-fat diet repress miR-181b expression in murine tissues, such as the aorta. These findings in small animal models were extended by showing that circulating miR-181b levels were reduced in patients with inflammatory diseases, including sepsis and...
coronary artery disease.6,8 Of note, circulating miR-181b levels were also reduced in the elderly,7 suggesting that aging, which is a major risk factor for atherosclerosis, also impairs the expression of this atheroprotective miRNA in humans.

Systemic intravenous delivery of liposomally encapsulated miR-181b mimetics for 12 weeks inhibited atherosclerotic lesion formation in apolipoprotein E–deficient mice and reduced NF-κB activation, as elegantly shown in reporter mice.3 Inhibition of NF-κB activation was associated with a reduction of proinflammatory gene expression (such as tumor necrosis factor-α and interleukin-1β) and decreased expression of the endothelial adhesion molecules vascular cell adhesion molecule-1, intracellular cell adhesion molecule-1, and E-selectin.5 Consequently, miR-181b treatment decreased leukocyte recruitment and accumulation in the vessel wall.3 These effects seem to be mediated via the repression of importin-α3, which blocks the import of NF-κB from the cytoplasm to the nucleus. Interestingly, the effects seem to be endothelial-specific because nuclear translocation of NF-κB in leukocytes does not involve importin-α3, but rather importin-α5, which miR-181b does not target. However, miR-181 family members are highly expressed in inflammatory cells and the systemic delivery of miR-181b mimics profoundly increased the expression of miR-181b in peripheral blood mononuclear cells. Therefore, a more detailed assessment of miR-181b effects on inflammatory cells, which may occur independently of NF-κB, may be needed to finally determine the functional contributions of inflammatory cell–expressed miR-181b in atherosclerosis.

The study by Sun et al5 confirms previous reports supporting the role of endothelial cell NF-κB signaling pathway in atherogenesis and atherosclerosis.8 It is tempting to speculate that restoration of miR-181 expression, which is downregulated by aging, may additionally inhibit NF-κB–mediated age-related insulin resistance and vascular senescence.4 Translating these experimental advances into therapy might provide an interesting option to treat patients with atherosclerotic disease. However, treatment of chronic diseases, such as atherosclerosis with miRNAs, needs to be established and may be particularly challenging when aiming at overexpressing miRNAs. Whereas the inhibition of miRNAs by locked nucleic acid–modified antisense miRNAs was successfully and safely achieved in first phase 2a clinical trials for a period of 5 weeks,5 overexpression of miRNAs has been more challenging. The current study by Sun et al5 shows that systemic intravenous injection of mixtures of miR-181b mimics with lipofectamine effectively delivered miR-181b to the aortic intima and to peripheral blood mononuclear cells, but not to the aortic media/adventitia. The generally known high uptake of miRNAs to the liver did not result in liver toxicity during a treatment of 12 weeks. However, whether long-term treatment of intravenously infused miRNAs mimics can be safely and effectively performed needs to be further investigated.

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References

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