Microregulation of Plaque Neovascularization

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Angiogenesis, the formation of new blood vessels from preexisting ones, is an important phenomenon in various physiological processes, such as embryonic development and pathological conditions, including acute and chronic inflammatory processes, such as wound healing, rheumatoid arthritis, diabetic retinopathy, and tumor progression. Plaque neovascularization, first described by Koester more than 100 years ago, is thought to participate intimately in the growth and progression of human atherosclerosis. However, its pathophysiological significance is under debate. In atherosclerotic intima, newly formed blood vessels are distributed irregularly but ubiquitously at specific sites of medial disruption, especially in the plaque shoulder and atheroma. Furthermore, in coronary atherosclerosis, the intima and media of complicated plaques are infiltrated with a tumor-like mass of microvessels. In both cases, most of these vessels are immature and leaky, permitting inflammatory cell infiltration and influx of blood constituents.

It is now recognized that atherosclerosis is not merely a lipid disorder but also a chronic inflammatory disease. For instance, the endothelium of intimal capillaries shows increased E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 levels compared with the artery surface, which suggests a positive feedback loop between atherosclerosis and chronic inflammation, whereby new vessels deliver inflammatory cells that further promote angiogenesis. Angiogenesis and inflammation are independent biological processes, which are linked in response to injury. In acute inflammation, microvessels dilate and increase their permeability. Chronic inflammation of large blood vessels, observed atherosclerosis, is associated with proliferation of vasa vasorum. New vasa vasorum have been implicated in developing lesions and shown to occur as a response to tissue hypoxia, one of the most potent stimuli for angiogenesis, which occurs when the intima thickens. In addition, the inflammatory infiltrate (monocyte-derived macrophages and T-lymphocytes) produces a number of soluble factors (cytokines, chemokines, and growth factors) that influence endothelial cell (EC) behavior, supporting inflammatory cytokine-induced angiogenic programs. These processes are complex and require the orchestration of molecular and cellular events induced by both stimulatory and inhibitory signals. These processes include signals whose transduction pathways lead to specific programs of gene expression, as well as posttranscriptional and posttranslational modifications that assure an adequate response.

microRNAs (miRNAs) have emerged as critical regulators of gene expression acting predominantly at the posttranscriptional level by binding to partially complementary target sites in the 3'-untranslated regions of mRNA, which may result in translational repression, mRNA destabilization, or a combination of both processes. A growing body of literature has implicated endothelial miRNAs in the regulation of various physiological and pathological processes linked to angiogenesis and inflammation and that these miRNAs can be regulated dynamically in response to external stimuli.

The article in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology by Dentelli et al shows that the expression of miRNA mir-222 is downregulated in an inflammatory microenvironment containing interleukin 3 and basic fibroblast growth factor. Several studies have demonstrated that interleukin 3 and basic fibroblast growth factor are released by infiltrated T-lymphocytes in the atherosclerotic plaque, promoting neovascularization. Interestingly, previous reports have shown that in the context of different angiogenic or inflammatory stimuli, the regulation of miR-222 was not observed in ECs, indicating the participation of different transduction pathways on the regulation of miRNA expression. Consistently, the transcription of tissue-specific miRNAs is often modulated by the same master regulatory factors that regulate mRNA. In addition, following transcription, the primary miRNA undergoes further processing to generate the mature miRNA. Interestingly, different signaling pathways have been implicated in the modulation of miRNA activity by posttranscriptional regulation of the processing steps. It remains to be elucidated whether cytokine-mediated regulation of miRNAs occurs at the transcriptional level or at the level of their biogenesis.

The article by Dentelli et al identifies signal transducer and activator of transcription 5A (STAT5A) as a target for miR-222. Furthermore, they demonstrated that the upregulation of STAT5A due to interleukin 3/basic fibroblast growth factor-induced downregulation of miR-222 controls EC proliferation and migration and therefore facilitates intraplaque neovascularization during atherosclerosis. In fact, in advanced lesions, the authors found an increased proliferation rate of ECs lining vessels, which correlated with a diminished expression of miR-222. Furthermore, they showed that the upregulation of STAT5A due to interleukin 3/basic fibroblast growth factor-induced downregulation of miR-222 controls EC proliferation and migration and therefore facilitates intraplaque neovascularization during atherosclerosis. In fact, in advanced lesions, the authors found an increased proliferation rate of ECs lining vessels, which correlated with a diminished expression of miR-222. This miR-222 was previously shown to regulate EC migration and proliferation through the regulation of c-Kit. Interestingly, Dentelli et al show that miR-221 expression is also downregulated in EC incubated in the...
presence of interleukin 3 and basic fibroblast growth factor. However, the effects on proliferation and the regulation of STAT5 were specific for miR-222 despite the high homology of these 2 miRNAs. In summary, the recent findings by Dentelli et al identify miR-222 as a negative regulator of negrovascularization by posttranscriptional regulation of STAT5A.15

miRNAs are integrated into vast regulatory networks that impinge on a broad spectrum of biological events. Although we are far from a complete understanding of the endogenous functions of endothelial miRNAs, we now have tools to assess the potential contributions of miRNAs to discrete endothelial functions. Among these are a growing number of examples where endothelial miRNAs influence cell-signaling pathways that are central to both development and disease. Taking advantage of the sensitive nature of signaling pathways, miRNAs represent an elegant form of transcriptional control for both fine-tuning and dramatically altering the activity and output of cell signaling.

Plaque angiogenesis is believed to play a role not only in atherosclerotic plaque progression but also in destabilization, leading to plaque rupture.5 This idea is now the focus for pursuing antiangiogenic strategies for the treatment of patients with vascular disease.3,4,20 However, this strategy may hold more potential pitfalls than promises given the increased risk of atherothrombotic events seen with systemic antiangiogenic therapies.5

Identification of specific targets and functions for cytokine-regulated miRNA, together with the ability of miRNAs to affect multiple downstream effectors, might prove to be an advantage for miRNA-based therapeutic strategies and might overcome the limited therapeutic capacity of single-cytokine or single-gene therapy.

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