New Ways to Dismantle a Ticking Time Bomb
MicroRNA 712/205 and Abdominal Aortic Aneurysm Development
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Abdominal aortic aneurysms (AAAs) are permanent dilations (>3 cm) of the abdominal aorta that are typically asymptomatic, and the discovery of these potentially deadly vascular lesions is almost always incidental. The most feared clinical consequence of AAA progression is acute rupture, which carries a mortality of 80%, and the number of deaths as a result of AAA rupture in the United States.1 However, this number is likely an underestimate because death from AAA rupture may not be readily identified without an autopsy. Sixty percent of patients with AAAs die of other cardiovascular causes, such as myocardial infarction or stroke, suggesting a relationship between AAAs and atherosclerosis. Predictors of AAA growth include diameter of the aorta at diagnosis, advanced age (>65 years), and active smoking.2 Currently, the only available effective treatment option is surgical repair, either via the traditional open approach or, more commonly, endovascular stenting. Furthermore, neither procedure is used in the early stages of the disease, and both carry potential operative risks. Although AAA disease is a common cause of morbidity and mortality in our aging society, it remains a somewhat understudied disease, with a paucity of information available regarding defined mechanisms of initiation and expansion. Importantly, no pharmacological treatment option has been found to prevent the formation of AAAs or effectively slow the growth of these ticking time bombs.

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In this dismaying scenario, the discovery of an entirely new method of epigenetic regulation of AAA biology through microRNAs and their recent validation as potential markers and modulators of pathological conditions provides new hope for innovative AAA therapy and identification. Inhibition or overexpression of a single microRNA can regulate numerous target genes involved in the coordination of complex pathophysiological processes and disease phenotypes in a wide variety of diseases. Many studies are now beginning to examine the potential of microRNAs as therapeutic and diagnostic entities.

The pathology of AAAs is characterized by progressive aortic dilation, promoted by an imbalance of vascular smooth muscle cell apoptosis versus proliferation, as well as extracellular matrix degradation versus synthesis. This disruption of vessel wall homeostasis is related in large part to localized transmural inflammation.3 Although previous studies on microRNA regulation in AAA disease have mostly focused on their role in smooth muscle cell apoptosis4 and protective profibrotic mechanisms in matrix remodeling,5,6 the article by Kim et al7 that appears in the current issue of ATVB identifies a novel and crucial role for microRNA 712 and its human homolog microRNA 205 in the aortic wall. They demonstrate that the angiotensin II–sensitive microRNAs 712/205 target the genes tissue inhibitor of metalloproteinase-3 (Timp3) and reversion-inducing cysteine-rich protein with kazal motifs (Reck), which they confirm as important contributors in murine AAA development by controlling aortic metalloproteinase activity and triggering a proinflammatory response through downstream extracellular matrix degradation in the vessel wall (Figure).

Of importance, they were able to correlate the findings of their experimental animal studies to alterations in microRNA expression in human AAA samples when compared with nonaneursymal control tissue. Although the authors concentrated primarily on the upregulation of microRNA 712/205 in endothelial cells, there were also significant alterations in the medial layer. In addition, both angiotensin II and microRNA 712/205 manipulation affected circulating leukocyte adhesiveness, further highlighting the therapeutic potential of targeting this pathway and implying other mechanisms at play. Notably, the in silico predicted target Lrp1 was not altered by microRNA 712/205 manipulation in the murine model, a common pitfall in microRNA studies. Future studies looking at microRNA 205

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Figure. Anti-microRNA (miR) 712/205 treatment limits murine abdominal aortic aneurysm development through derepression of Timp3 and Reck. AAA indicates abdominal aortic aneurysm; MMP, metalloproteinases; Reck, reversion-inducing cysteine-rich protein with kazal motifs; and Timp3, tissue inhibitor of metalloproteinase-3.
in human tissue will need to verify target regulation, including validated targets such as vascular endothelial growth factor A and connective tissue growth factor (which might well affect AAA biology) and will need to clarify potential interactions with more comprehensive patient clinical characteristics.

Treatment-directed studies using antagonists against microRNA 712 in the angiotensin II–induced AAA model revealed therapeutic potential for anti-microRNA 712, limiting AAA development by derepressing expression levels of Timp3 and Reck. As with other anti-microRNA treatments for cardiovascular disease, potential off-target effects in organ systems that assimilate systemically administered microRNA modulators to a much higher degree (eg, liver, kidney) would need to be taken into account when developing future therapeutic strategies for AAAs in humans. As with most studies of this sort to date, this work focused primarily on AAA prevention, rather than looking at efficacy in existing aneurysms.

Historically, the murine angiotensin II AAA model has been used in most studies that examine the therapeutic potential of microRNAs in AAA. This model has some limitations and features somewhat unique pathophysiology, including mural disruption and hematoma formation, with aneurysms positioned primarily in the suprarenal abdominal aorta (although human AAA disease is primarily infrarenal). Therefore, translational applicability to human use needs to be viewed with caution. However, the current work of Kim et al represents an important step toward the eventual goal of defusing these vascular threats.

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Disclosures
None.

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