Battle of the Bulge
miR-195 Versus miR-29b in Aortic Aneurysm

Joshua M. Spin, Philip S. Tsao

Abdominal aortic aneurysm (AAA) is a potentially lethal condition, capable of progressing to acute rupture—a catastrophic event with an 80% mortality risk. A conservative estimate places annual deaths because of AAA in the United States at ≈15,000, although the actual burden is likely higher. These dilations are typically found within the infrarenal aortic segment but are only rarely symptomatic, causing them to remain undiscovered until they are either identified through coincident imaging or rupture occurs. Among the risk factors for AAA are male sex, advanced age, genetic predilection, and a history of tobacco use. No pharmacological approach in humans to identify any differentially regulated miR has successfully decreased AAA expansion or prevented rupture. Although surgery and endovascular stent grafting are highly effective in preventing death from larger AAAs, they are complex procedures with multiple potential complications. How then, might the battle against AAA be better waged?

MicroRNAs are intricately woven into a web of epigenetic pathophysiologic regulation. Modulation of any given microRNA can alter the expression of dozens of target genes, including entire functional gene networks, thereby affecting the progression of a wide array of disease phenotypes. In recent reviews examining the role of microRNAs in AAA, we noted their remarkable potential, both to improve risk stratification and diagnosis and to alter vascular disease therapeutically. In this vein, exciting findings have been published for several microRNAs including miR-21, miR-26a, the miR-17-92-cluster, miRs-221/222, miR-133, miR-126, miR-143/145, miR-146a, miR-155, and miR-29b.3,4 Of these candidates, the last (miR-29b) seems particularly promising. Remodeling of the extracellular matrix within the aortic adventitia and media is crucial for AAA progression, characterized by elastin fragmentation and loss and increased collagen turnover. miR-29b targets include numerous collagen genes and elastin. Furthermore, miR-29b modulation in vitro and in vivo can alter matrix metalloprotease (MMP) activity. miR-29b is differentially regulated in animal models of aneurysm and in human AAA tissue, and inhibition of miR-29b in murine models of AAA and Marfan syndrome has led to diminished aneurysm progression (while overexpression increases aneurysm growth and rupture rate).5-7

In this issue of Circulation Research, Zampetaki et al examined miR-195, a member of the miR-15 family known to share many of the same targets as miR-29b.8,9 They found that miR-195 (alone of the miR-15 family) was increased in aneurysmal aortic tissue from angiotensin II–treated apolipoprotein E–deficient mice. Angiotensin II has previously been shown to induce or inhibit miR-15a, -15b, -16-1, and -16-2 in either rat or human smooth muscle cells, but not miR-195.10,11 Furthermore, although significant downregulation of miR-15a, miR-195, and miR-497 has been observed in tissue from dissected human thoracic aorta compared with normal aorta, Pahl et al’s expression profiling of human AAA tissue did not identify any differentially regulated miR-15 family members.12,13 In human aortic smooth muscle cells, miR-195 mimic was able to suppress elastin expression, but unlike miR-29b, caused a nonsignificant increase in MMP9 activity and an increase in MMP2 expression. The authors then performed proteomic studies of human smooth muscle cells, confirming that miR-195 regulates numerous extracellular matrix elements, although not to the same extent as miR-29b (especially in terms of collagen repression).

More disappointing were attempts at in vivo inhibition of miR-195 in the mouse AAA model. Although clear suppression of miR-195 in the aorta was achieved, correlating with increases in expression of elastin and collagens, there was no significant impact on aneurysm progression or subject survival (no in vivo miR-195-mimic experiments were performed). Immunohistochemistry showed increased Mmp9 expression in anti-miR-195–transfected aortae. In contrast, and confirming published data using the same model, anti-miR-29b led to improved survival and slowed aortic growth. Maegdefessel et al also demonstrated that systemic anti-miR-29b lowered MMP2 and MMP9 activity and expression in vivo.

Zampetaki et al9 noted that antagonimiR-29b had minimal effects on miR-29b levels in an aortic isograft model. This supports the conclusion in Maegdefessel et al7 that locked nucleic acid (LNA)-anti-miR-29b is not readily taken up by uninjured vessel wall. However, in both studies, uptake within the affected suprarenal aorta (angiotensin II murine model) was sufficient to alter disease progression and target expression. In contrast, anti-miR-195 diffused more readily into uninjured vasculature but did not abrogate disease. This is unusual, as in our experience intact endothelium often resists LNA-miR uptake. The authors attribute the contrasting in vivo results between anti-miR-195 and anti-miR-29b to their inverse regulatory effects on MMP activity. Given the known association between MMP activity and AAA severity and progression, this may well be the case.14

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Division of Cardiovascular Medicine, Stanford University School of Medicine, CA.

Correspondence to Philip S. Tsao, PhD, Division of Cardiovascular Medicine, Stanford University School of Medicine, 300 Pasteur Dr, Stanford, CA 94305-5406. E-mail ptsao@stanford.edu

(Circ Res. 2014;115;812-813.)

© 2014 American Heart Association, Inc.

Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESHA.114.305233

812
Spin and Tsao

miR195 vs miR29b in AAA Management

813

Interestingly, in addition to its role in extracellular matrix regulation, miR-195 is a known tumor suppressor, which has been shown to inhibit growth and proliferation, promote apoptosis, and inhibit cellular migration in various tissues and cell types. In contrast another microRNA—miR-21—inhibits tumor suppressors, eliciting the opposite cellular responses from those attributed to miR-195, and pre-miR-21 administration has significantly curtailed murine AAA growth. It might have been expected that anti-miR-195 would, therefore, have similar effects. However, miR-195 is also known to suppress angiogenesis. Angiogenesis inhibition is believed to limit AAA progression, which might, therefore, have further undermined the effectiveness of anti-miR-195.

Zampetaki et al. suggest an intriguing role for miR-195 as an AAA biomarker, which miR-29b is unlikely to match (as it was barely detectable in human plasma samples). Circulating microRNAs are stable in human blood and detectable and measurable with high sensitivity and specificity, suggesting that they might make effective AAA biomarkers. Clinical studies have demonstrated changes in microRNA levels in association with cardiovascular disease phenotypes, although these have often been underpowered or lacking in matched controls. The authors examined 16 microRNAs in plasma from 73 participants from an aneurysm screening program, finding that miR-195 was inversely correlated with aneurysm size and disease classification. Although 4 other miRs also showed such association, they were closely correlated with miR-195, and after proper adjustment their association with aortic size diminished. Intriguingly, miR-133a and miR-145 emerged as significant after adjustment for miR-195, suggesting that further studies involving a comparison approach might yield a robust biomarker panel. As in the work cited above, the sample size queried was small for a biomarker study, and these findings will require extensive verification and replication in larger data sets to prove clinical utility.

Despite the similar target profiles of miR-29b and miR-195, it remains to be seen whether the first may someday triumph on the field of therapeutic AAA abrogation and whether the latter will fulfill its promise as a predictive biomarker of AAA progression.

Sources of Funding

This work is supported by research grants from the National Institutes of Health (1P50HL083800-01; 1H1-105299 and 1H1L122939 to P.S. Tsao).

Disclosures

None.

References


Key Words: Editors ● aortic aneurysm, abdominal ● extracellular matrix ● microRNAs
Battle of the Bulge: miR-195 Versus miR-29b in Aortic Aneurysm
Joshua M. Spin and Philip S. Tsao

Circ Res. 2014;115:812-813
doi: 10.1161/CIRCRESAHA.114.305233

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/115/10/812

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