



Function and clinical potential of miRNA-29 family in thoracic aortic aneurysm

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Comment on: Jones JA, Stroud RE, O'Quinn EC, *et al.* Selective microRNA suppression in human thoracic aneurysms: relationship of miR-29a to aortic size and proteolytic induction. *Circ Cardiovasc Genet* 2011;4:605-13.

Received: 17 December 2018; Accepted: 30 December 2018; Published: 03 January 2019.

doi: 10.21037/ncri.2018.12.02

View this article at: <http://dx.doi.org/10.21037/ncri.2018.12.02>

Thoracic aortic aneurysm (TAA) represents the 15th leading cause of death in patients greater than 65 years (1). The incidence of TAA is estimated to be around 10 per 100,000 person-years and is approximately equal in men and women (2).

TAA is characterized by the progressive dilatation of the thoracic aortic wall (3). The pathological enlargement of the aorta is caused by a maladaptive remodeling of the vessel in response to stress and physiological stimulus. This results in the degradation of critical extracellular matrix (ECM) components principally mediated by the matrix metalloproteinases (MMPs), leading to the loss of mechanical strength and integrity, aortic dilation and dissection (3).

Despite the progressive dilatation, aortic aneurysm usually remains asymptomatic until dissection occurs. Thus, the discovery and monitoring of TAAs are doubtless crucial.

At present, the diameter of the aorta represents the major clinical risk criterion used in combination with other risk factors (e.g., family history of dissection, presence of bicuspid aortic valve, presence of coarctation, root phenotype) to predict complications. However, the size criterion is an imperfect predictor of aortic dissection in many patients who suffer complications at smaller diameters (4). Consequently, additional predictors (e.g., imaging, genetic and biological markers) are required for understanding the molecular mechanisms underlying TAA in order to identify personalized therapeutic and surgical strategies (5).

With the development of high-throughput sequencing technologies, there is an increasing interest in several classes of non-coding RNAs (ncRNAs) as crucial players in the regulation of disease-relevant genes.

In particular, microRNAs (miRNAs) have emerged as central regulators of heart and promising biomarkers in a wide range of cardiovascular diseases (6-8).

miRNAs are highly conserved, non-coding RNAs of 21 to 25 nt, which can negatively modulate mRNAs at the post-transcriptional level by binding to target sequences within the 3' untranslated region (3' UTR). Thanks to their ability to target thousands of mRNA molecules, miRNAs may control the expression of several components of signal transduction at multiple levels (9).

During the last years, interest has grown in understanding the function and clinical potential of miRNAs in the pathogenesis of aortic aneurysm and dissection.

In particular, miRNA-29 family, including miRNA-29a, miRNA-29b and miRNA-29c, has been the most studied in TAA development and progression. They are important regulators of ECM homeostasis, with gene targets in elastin (ELN) (10), several collagens and MMPs (11).

In 2011, the first in-depth characterization of miRNAs in TAA disease revealed the dysregulation of 74 miRNAs (18 miRNAs up-regulated, 56 miRNAs down-regulated) (12). Among them, miRNA-29 family was found to have a key role in the regulation of mitogen-activated protein kinase (MAPK) signaling and focal adhesion pathways, known to be linked to TAA disease (12).

The elevated expression levels of miRNA-29b was further associated with a down-regulation of numerous ECM components in the aortas of mice (13). In a similar context, the blockade of miRNA-29b has been shown to prevent early aneurysm development, cell apoptosis, and ECM deficiencies in *Fbn1C1039G/+* Marfan mouse model (14).

More recently, the dysregulation of miRNA-29c

expression profile in TAA tissues has also indicated the potential of such miRNA as a critical factor that trigger molecular pathways of aneurysmal transformation (15).

In an effort to better elucidate the role of miRNA-29 family in TAA development, Jones and colleagues (16) have been among the first research group to examine the expression of miRNA-29a in aortic tissues from patients with TAA compared with normal aortic specimens.

In their elegant study, the authors observed a decreased expression of miRNA-29a in TAA disease and confirmed these findings by microarray analysis. A significant relationship between miRNA-29a expression and aortic diameter was identified; as miRNA level decreased, aortic diameter increased.

In accordance with the biological function of miRNAs, the authors observed a significant reduction of miRNA-29a, knowing that many of the putative mRNA targets increase in response to the extent of disease. The dynamic changes in miRNA levels probably occur during TAA progression and the subsequent block of translational repression may play an important role in modifying the mechanisms of vascular remodeling (16).

In the second part of the study, through the use of bioinformatics tools and *in vitro* validation, members of MMP family have been examined as potential targets for miRNA-29a. MMP-2 emerged as one of the target for miRNA-29a, supporting earlier studies that have identified such miRNA as a key regulator of MMP-2. Notably, the loss of aortic miRNA-29a expression may induce the elaboration of MMP-2 translation within the developing aneurysm and may recognize a possible mechanism by which MMP-2 protein induction occurs in the course of the TAA pathogenesis (16).

The main limitation of the present study is that each miRNA, such as miRNA-29a, may affect several mRNA targets, many of which may be involved in TAA development. The dysregulation of these putative genes may be harmful for the function and structure of the thoracic aorta (16).

Nevertheless, the study by Jones and colleagues (16) supports the notion that the loss of a specific miRNA during TAA development may have a crucial role in worsening pathological remodeling by eliminating inhibitory signals that reduce MMP production. Moreover, the altered expression of miRNA profiles may be extended to pave the way for the development of biological assays in order to define the phases of disease progression, informing of the best time of surgical intervention or the probability of aortic

dissection (16).

However, in a more recent study by the same group, miRNA-29a has not emerged as circulating biomarker that could be useful in personalized medicine strategies to distinguish etiological subtypes of aneurysm disease (9).

Therefore, further research is warranted to validate the biological and clinical relevance of miRNA-29 family in TAA disease, thus providing novel and efficient molecular targets for potential diagnostic, prognostic and therapeutic applications.

Acknowledgments

The author thanks the Genetics and Molecular Epidemiology Research Group led by Dr. Maria Grazia Andreassi.

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Dr. Qiying Dai (Metrowest Medical Center, Framingham, USA).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/ncrj.2018.12.02>). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/ncr.2018.12.02

Cite this article as: Borghini A. Function and clinical potential of miRNA-29 family in thoracic aortic aneurysm. *Non-coding RNA Investig* 2019;3:1.