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Review Article

MicroRNAs in abdominal aortic aneurysms

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ABSTRACT

The abdominal aortic aneurysm (AAA), representing 70% to 90% of all aortic aneurysms, is characterized by a widening of the diameter due to an irreversible weakening of the vascular walls. Risk factors include advanced age, male sex, smoking, hypertension, atherosclerosis, and genetic predisposition. From a pathophysiological point of view, AAA involves alterations in connective tissue proteins, chronic inflammation with the release of cytokines and matrix metalloproteinases, as well as changes in the extracellular matrix. MicroRNAs (miRNAs) have emerged as promising biomarkers and therapeutic targets in the regulation of gene expression and different specific signaling pathways in vascular pathologies. Among which some miRNAs have been highlighted such as: miR-29 and miR-27b-3p, involved in the degradation of the extracellular matrix and inflammatory processes during the progression of AAA. Some diagnostic methods such as computed tomography play a fundamental role, while some innovative therapeutic strategies, such as the inhibition of miRNAs, represent a leading role as possible diagnostic and therapeutic targets. A comprehensive approach includes surveillance and surgical treatment strategies to mitigate the progression and risk of AAA rupture, thus highlighting the relevance of miRNAs in the diagnosis and treatment of this pathology.

Keywords: Abdominal aorta, Aortic aneurysm, Abdominal aortic aneurysm, MicroRNA, Cardiovascular disease, Aorta

INTRODUCTION

Abdominal aortic aneurysm (AAA) represents 70-90% of all aortic aneurysms. It is most frequently located inferior to the renal arteries, and are defined as a widening in the diameter of the aorta greater than or equal to 30 millimeters, which can be measured by ultrasound or computed tomography.[1] These aneurysmal dilations may be a consequence of a weakening and irreversible dilation of the artery in its three layers of the vascular wall; intima, media and adventitia.[2] In the last 10 years, the number of deaths due to this pathology has increased by 25%. Some risk factors are attributed to it, such as advanced age, male gender, smoking, hypertension, atherosclerosis and genetic defects.[1] The pathophysiological processes in AAA formation have been described, among which changes in connective tissue proteins, chronic inflammation with subsequent release of cytokines and the activity of metalloproteinases, with early apoptosis and subsequent changes in connective tissue proteins, stand

out. connective tissue. In 2023, Mulati and collaborators investigated, in vivo and in vitro, some patterns involved in the differentiation and proliferation of smooth muscle cells along with structural changes generated in the extracellular matrix in the degeneration and subsequent dilation of the arterial wall.[3] However, the specific mechanisms attributed to the development of AAA have not been fully established, which is why molecular studies and their involvement in the formation and progression of these aneurysms have been delved into, where recent studies stand out. about microRNAs. In 2006, the Nobel Prize in Medicine was awarded to Doctors: Andrew Fire and Craig Mello, thanks to the discovery of RNA interference (RNAi) within these RNAs, also achieved the identification of microRNA (miRNA), siRNA (small RNA interference) and piwi-associated RNAs (piRNAs). In all of them, the capacity for gene silencing was identified through single chains in a complementary manner to messenger RNA (mRNA), recently generating interest in the role of its potential active participation in different vascular pathologies and the identification of possible therapeutic targets and biomarkers.[4]

MicroRNAs are a class of small non-coding RNAs that are responsible for regulating gene expression both in physiological conditions and in some pathologies. They play a role in cell production, differentiation, development, aging and apoptosis.[5] Some microRNAs play an important role in the development of AAA, among them the miR-29 family, which includes: miR-29a, miR29b and miR-29c, which have been linked to the decrease in the coding of some extracellular matrix proteins. such as elastin, fibrillin and collagen I and III. Boon et al demonstrated a higher concentration of miR-29 in the aorta, which led to greater destruction of the extracellular matrix and increased its susceptibility to dilation.[1] However, in a study carried out by Plana et al in which microRNAs were selected as possible biomarkers in AAA, they found that the miRNA most frequently associated with vascular pathologies is miR-27b-3p, showing a relationship with processes. inflammatory, lipid metabolism and angiogenesis. Having among its targets proteins involved in lipoprotein remodeling such as angiopoietin-like protein type 3 (ANGPTL3) and could even have implications in cholesterol homeostasis acting through targets such as low-density lipoprotein (LDL), which could provide an approach as possible biomarkers of the pathology.[6]

At the molecular level, miRNAs are highly stable, achieving greater handling through collection in fresh or fixed tissues, plasma, urine, saliva and serum. Achieving reproducible levels and making their quantification possible, which can turn them into useful diagnostic biomarkers, therefore can allow a comparison with the miRNAs present in samples from healthy patients versus patients with the pathology, evaluating their profiles and expression level. that miRNAs influence the expression of signaling pathways and genes; in addition, it was found that their inhibition in vivo using antiMicroRNAs, which are antisense oligonucleotides, was successful. The use of these antiMicroRNAs was initially described by Krutzfeldt et al, in which they sought to silence the MicroRNA-122 family that was found in large quantities in the liver of rats, after the intravenous administration of the antiMicroRNA specific for MicroRNA-122 family, a marked reduction in MicroRNA-122 levels was observed in tissues such as liver, lung, intestine, heart, skin, muscle, among others. Which represented an efficient and specific result that could be used as a therapeutic target.[7,8]

MiRNA AND AAA

MiRNAs derive from initial processing in the cell nucleus to finally complete their maturation in the cytoplasm, where they will perform their function. RNA polymerase II is responsible for transcription with the subsequent production of a long RNA molecule known as primary microRNA, forming a hairpin-stem-loop structure, which by means of the endonuclease RNAse III will be cut asymmetrically from the chains. at the base of the hairpin-shaped structure, resulting in a 60-70 nucleotide product known as pre-microRNA. The pre-microRNA will then be exported to the cytoplasm through active transport with the exportin-5 complex. Once it arrives and is released in the cytoplasm, the molecule is cut by the endonuclease RNase III, resulting in a double-stranded molecule known as microRNA duplex that, after the separation of one of the chains, will give rise to the mature microRNA to finally be incorporated into to the "RNA silencing complex" (Figure 1).[9] Although microRNAs have been associated with different inflammatory and pathological processes mentioned above, there is still much to explore about their role in vascular pathologies and AAAs. Initially, 5 miRNAs related to the possible formation of AAA have been described: miR-21, miR-24, miR-29b, miR-712 and miR-205.[10,11]

Table 1: MicroRNAs studied in vascular pathologies and their associations.

MicroRNA studied	Characteristics
MicroRNA-595	Its overexpression was associated with greater progression of abdominal aortic aneurysm.
MicroRNA-32	
MicroRNA-24	
MicroRNA-27b-3p	Its overexpression was more frequently associated with vascular pathologies with a relationship in angiogenesis and inflammatory processes. Furthermore, elevated levels were found in the plasma of patients with AAA regardless of the patients' risk factors.
MicroRNA-221-3p	
MicroRNA-29	Its overexpression was associated with a higher risk of suffering from thoracic aortic aneurysm in patients with aortic valves.

Continued.

MicroRNA studied	Characteristics
MicroRNA-103	Its overexpression was associated with a higher risk of coronary artery disease and peripheral artery disease.
MicroRNA-193a	
MicroRNA-486	
MicroRNA-582	
MicroRNA-3663	
MicroRNA-21	Its overexpression was associated with a protective factor against AAA progression, while its inhibition was associated with a higher risk of AAA formation.
MicroRNA-33a	Its inhibition in genetically modified rats was found to be an effective option that could be expanded in the management of AAA, through inflammatory suppression and changes in intracellular metabolism.
MicroRNA-33b	
MicroRNA 548n	It was found to be a method with high precision for the diagnosis of AAA that needs to be expanded with other studies.
MicroRNA-195-5p	The dysregulation of the following microRNAs was confirmed in tissue samples affected by Abdominal Aorta Aneurysm.
MicroRNA-133b	
MicroRNA-133b	
MicroRNA-1	
MicroRNA-103a-3p	
MicroRNA-146a-5p	

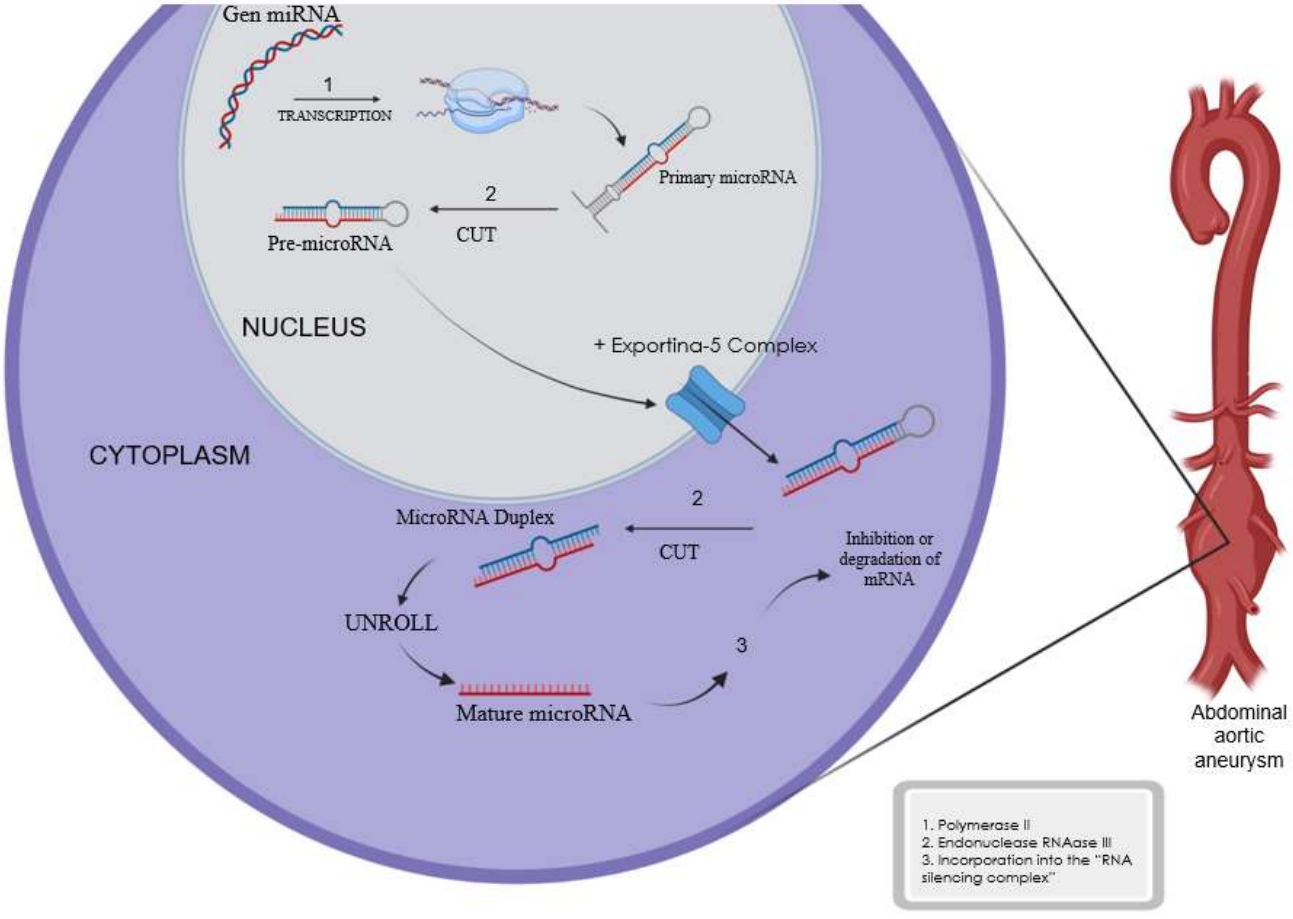

Figure 1: Biogenesis and formation of miRNAs.

In 2012, Pahl et al carried out the first study focused on the differential expression of miRNAs in AAA in humans using the comparison in healthy abdominal aorta tissue and tissue affected by abdominal aortic aneurysm in which they obtained an overexpression of miR-21 in those patients with AAA.[12] miRNA-21 was demonstrated through carotid injury models of its role in the regulation of smooth muscle cells in terms of their proliferation, through the inhibition of phosphatase and tensin homolog (PTEN). Likewise, it was found increased during the

progression of AAA. Its inhibition decreases its proliferative effects, leading to an increase in the size of the aneurysm.[13] Likewise, different studies have talked about miR-29 and its function in regulating the expression of different molecules, among which those of the extracellular matrix, such as collagen and elastin, play an important role. Likewise, its therapeutic inhibition was found beneficial for the improvement of the structure and integrity of the vascular wall. miRNA-29 not only acts on molecules of the extracellular matrix, but also targets the antiapoptotic protein BCL-1, which was also found to be decreased in studies carried out on mice with Marfan disease, where it was observed that an inhibition of miRNA-29 prevents apoptosis, which could contribute to the therapeutic effects of miRNA-29 inhibition. However, Boon et al found a relationship in those patients with overexpression of miRNA-29 with greater sensitization of the aorta for the formation of aneurysms and it was similarly observed in biopsies of thoracic aneurysms from patients with aortic valves.[14] The different findings related to microRNAs and their overexpression in tissues with vascular pathologies compared to healthy tissue as found in AAA, reinforce the importance of microRNAs in the pathophysiology of vascular disease. Furthermore, the study of its specific targets and gene regulation pathways represents diagnostic utility and potential therapeutic purposes.[1]

EPIDEMIOLOGY

The average age of prevalence in AAA is 65 years. In developed countries the prevalence and incidence of AAA has decreased significantly and is believed to be partially attributed to the decrease in smoking.[3] The risk of AAA is 1 in 17 for the general population and 1 in 9 for smokers. It was found that men have 6 times the risk of suffering from AAA than women, although it was described that there was a higher mortality due to AAA rupture in women.[15] Those men of Caucasian descent are at greater risk compared to those of African descent.[2]

DIAGNOSIS

Most AAA findings are diagnosed incidentally in those patients who underwent imaging in the abdominal region for any other reason. For the diagnosis of AAA, clinical examination may be useful when finding a pulsatile mass in the abdominal region, but very low sensitivity and greater limitations have been found in patients with high abdominal circumference. The usefulness of the use of ultrasound and computed tomography angiography has been described as first-line diagnosis. Computed tomography angiography is the gold standard for the diagnosis of AAA rupture, surgical planning and post-surgical follow-up. Ultrasound has been most usefully recommended in asymptomatic patients as screening and diagnosis, having high sensitivity and specificity. Magnetic resonance shares some of the characteristics of angiotomography, making it a viable and alternative imaging aid for those patients who cannot receive contrast or limitations in angiotomography. However, its availability and limitation must be considered depending on the patient.[2,3]

TREATMENT

The main goal of medical management includes slowing the growth of the aneurysm to decrease the risk of rupture. Therefore, periodic examination through ultrasound and angiotomography is sought to monitor growth. In addition to imaging monitoring, strict control of blood pressure, diabetes, dyslipidemia, smoking cessation, and control of other risk factors are of great importance. In the event that the patient meets the AAA criteria (Table 3), surgical management will be the most indicated. Endovascular repair is the repair recommended by international guidelines as the surgical management of choice, but for those patients not suitable for this type of management due to extension, anatomical site, among others. Open repair will be the most indicated option.[3]

Table 2: Most frequent symptoms due to compression of adjacent structures in AAA.

Structure affected	Symptoms
Duodenum	Threw up
Vena cava	Edema in lower extremities, venous thrombosis
Ureter	Hydronephrosis, kidney failure
Spinal cord	Lumbar pain, erosion of the vertebral body
Nerves	Radiculopathy in lower limbs

Table 3: Indications for surgical management in patients with AAA.

Classification	Characteristics
Fusiform aneurysm	Diameter >5 cm in women and >5.5 cm in men
Rapidly growing fusiform aneurysm	Growth greater than 0.5 cm in 6 months or 1 cm in 1 year
dilation form	Saccular dilation of the aneurysm
AAA with other associations	Associated with complications and/or symptoms

In recent years, interest in the relationship between microRNAs and different pathologies has attracted attention, leading to the development of new studies and clinical trials focused on the creation and understanding of possible therapeutic targets. Currently, the vast majority of drugs with a focus on microRNAs are still on clinical trials. To mention a few, the drugs Miravirsen and RG-101, designed for the management of hepatitis C, have stood out for their success in the results obtained.[16] The development of antiMicroRNAs has become popular in recent years due to their high affinity, small size and stability. Although they are still in development, the multiple doses necessary to achieve the required effect have been described.[8]

Kim et al demonstrated in mice that the angiotensin II-sensitive microRNA-712 and its homologue microRNA-205 stimulated the inflammatory activity of AAA, resulting in an increase in its development. Leaving this potential therapeutic target as a question to cover in the future.[11]

CONCLUSION

MicroRNAs have opened a door in the understanding of the pathophysiological processes related to abdominal aortic aneurysm, highlighting their potential usefulness as biomarkers and therapeutic targets that may be key in vascular pathology. Its ability to regulate gene expression and modulate specific signaling pathways in the formation and progression of AAA may offer new diagnostic and therapeutic opportunities. The new therapeutic strategies proposed, through the inhibition of microRNAs, demonstrate promise in mitigating the risk of rupture. However, it is of great importance to continue validating these biomarkers for their eventual integration into clinical practice.

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REFERENCES

1. Borek A, Drzymała F, Botor M, Augusciak-Duma AM, Sieroń AL. Roles of microRNAs in abdominal aortic aneurysm pathogenesis and the possibility of their use as biomarkers. Pol J Thoracic Cardiovasc Surg. 2019;16(3):124-7.
2. Kessler V, Klopf J, Eilenberg W, Neumayer C, Brostjan C. AAA Revisited: A Comprehensive Review of Risk Factors, Management, and Hallmarks of Pathogenesis. Biomedicines. 2022;10:94.
3. Mulatti GC, Joviliano EE, Pereira AH. Brazilian Society for Angiology and Vascular Surgery guidelines on abdominal aortic aneurysm. J Vasc Bras. 2023;22:e20230040.
4. López M, Ramdohr P. Premio Nobel de Fisiología o Medicina 2006: Descubrimiento del RNA de interferencia. Rev Chil Pediatra. 2006;77(6):553-6.
5. de Lucia C, Komici K, Borghetti G, Femminella GD, Bencivenga L, Cannavo A, et al. MicroRNA in Cardiovascular Aging and Age-Related Cardiovascular Diseases. Front Med. 2017;4:74.
6. Plana E, Gálvez L, Medina P, Navarro S, Miralles M. Estudio de selección de microRNA como posibles biomarcadores de aneurisma de aorta abdominal. Angiología. 2018:70(1):13-8.
7. Rico-Rosillo MG, Vega-Robledo GB, Oliva-Rico D. Importancia de los microARN en el diagnóstico y desarrollo de enfermedades. Rev Med Inst Mex Seguro Soc. 2014;52(3):302-7.
8. Krützfeldt J, Rajewsky N, Braich R, Rajeev KG, Tuschl T, Manoharan M, et al. Silencing of microRNAs in vivo with 'antagomirs'. Nature. 2005;438(7068):685-9.
9. Lamadrid-Romero M, Díaz-Martínez F, Molina-Hernández A. Los microRNA: una herramienta que podría ser usada como biomarcadores de la corticogenesis fetal. Perinatol Reprod Hum. 2014;28(3):146-53.
10. Maegdefessel L, Spin JM, Raaz U, Eken SM, Toh R, Azuma J, et al. miR- 24 limits aortic vascular inflammation and murine abdominal aneurysm development. Nat Commun. 2014;5:5214.
11. Kim CW, Kumar S, Son DJ, Jang IH, Griendling KK, Jo H. Prevention of abdominal aortic aneurysm by anti-microRNA-712 or anti-microRNA-205 in angiotensin II-infused mice. Arterioscler Thromb Vasc Biol. 2014;34(7):1412-21.
12. Cheuk BL, Cheng SW. Identification and characterization of microRNAs in vascular smooth muscle cells from patients with abdominal aortic aneurysms. J Vasc Surg. 2014;59(1):202-9.
13. Fernandez-Hernando C, Baldan A. MicroRNAs and Cardiovascular Disease. Curr Genet Med Rep. 2013;1(1):30-8.
14. Boon RA, Seeger T, Heydt S, Fischer A, Hergenreider E, Horrevoets AJ, et al. MicroRNA-29 in aortic dilation: implications for aneurysm formation. Circ Res. 2011;109(10):1115-9.
15. Joviliano EE, Ribeiro MS, Tenorio EJR. MicroRNAs and Current Concepts on the Pathogenesis of Abdominal Aortic Aneurysm. Braz J Cardiovasc Surg. 2017;32(3):215-24.
16. Bonneau E, Neveu B, Kostantin E, Tsongalis GJ, De Guire V. How close are miRNAs from clinical practice? A perspective on the diagnostic and therapeutic market. EJIFCC. 2019;30(2):114-27.

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