

miRNA Regulation in Atherosclerotic and Non-Atherosclerotic Aortic Aneurysms

Subjects: Pathology

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Aortic aneurysms are a serious health concern as their rupture leads to high morbidity and mortality. Abdominal aortic aneurysms (AAAs) and thoracic aortic aneurysms (TAAs) exhibit differences and similarities in their pathophysiological and pathogenetic features. AAA is a multifactorial disease, mainly associated with atherosclerosis, characterized by a relevant inflammatory response and calcification. TAA is rarely associated with atherosclerosis and in some cases is associated with genetic mutations such as Marfan syndrome (MFS) and bicuspid aortic valve (BAV). MFS-related and non-genetic or sporadic TAA share aortic degeneration with endothelial-to-mesenchymal transition (End-Mt) and fibrosis, whereas in BAV TAA, aortic degeneration with calcification prevails. microRNA (miRNAs) contribute to the regulation of aneurysmatic aortic remodeling. miRNAs are a class of non-coding RNAs, which post-transcriptionally regulate gene expression.

Keywords: abdominal aortic aneurysm ; thoracic aortic aneurysm ; atherosclerosis

1. Introduction

The aorta is the largest arterial blood vessel in the body. It is subjected to high pressure when a large volume of blood is pumped out of the heart with each contraction, exposing it to the risk of wall degeneration and aneurysms ^[1]. The latter are categorized in two main types: thoracic aortic aneurysms (TAAs) and abdominal aortic aneurysms (AAAs) ^[2]. Aortic aneurysms are often asymptomatic until the aortic media undergoes dissection or rupture, with a high degree of morbidity and mortality ^[3]. Currently, the available pharmacological treatments for aortic aneurysms are not specific and aim to delay disease progression and surgical intervention ^[3]. TAAs and AAAs have different developmental origins as well as pathogenetic factors that induce different structural degeneration of the aortic wall ^[3]. Atherosclerosis and chronic inflammation are associated with AAAs ^[3], whereas TAAs are characterized by an increased accumulation of proteoglycans ^[4]. The histopathological abnormality of TAAs is named cystic medial degeneration, characterized by loss of smooth muscle cells (SMCs) and elastic fiber degeneration that leads to a weakened wall and the consequent high risk of dilatation and aneurysm formation ^{[4][5]}. Cystic medial degeneration occurs normally with aging, in particular in the presence of hypertension ^[3]. As mentioned above, AAAs are often associated with atherosclerosis, but as for TAAs, AAAs show SMC loss and fragmentation of elastic fibers ^[4]. Smoking, male sex, advanced age and atherosclerosis are mostly associated with AAAs and some sporadic (non-genetic) TAAs ^[1]. In fact, the majority of sporadic TAAs are mainly associated with hypertension and aging. However, there are some TAAs associated with genetic conditions, such as Marfan syndrome (MFS) and bicuspid aortic valve (BAV) ^[6]. All genetic TAAs occur at an early age but their underlying pathogenetic mechanisms can be very different. In fact, MFS TAAs display fibrosis ^[7], whereas BAV TAAs show mainly calcification ^[8].

2. Vascular Remodeling in Abdominal Aortic Aneurysms

As mentioned above, AAAs are often associated with atherosclerosis, and some evidence suggests that their formation starts from occlusive disease ^[9]. In particular, the formation of atheroma in the abdominal aorta starts in the subendothelial intimal space of medium- and large-sized arteries, through a multistep process. First, the inflammatory stimulus induces endothelial dysfunction and permeabilization with the consequent formation of a fatty streak. The latter evolves into an atheromatous or fibroatheromatous plaque that can rupture and provoke thrombosis ^[10]. During this process, endothelial cells increase the expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 and reduce nitric oxide synthesis ^[10]. The increased expression of those molecules leads to a recruitment of monocytes to the site of injury. Macrophages and T lymphocytes, in turn, express growth factors, cytokines and matrix metalloproteinases (MMPs) that stimulate the migration and proliferation of aortic SMCs into the tunica intima and the

formation of atherosclerotic plaque with the accumulation of foam cells. ^[10]. With time, SMCs and inflammatory cells undergo apoptosis, contributing to the development of atherosclerotic lesions ^{[11][12][13]}. Crystallized calcium concentrates around the apoptotic bodies derived from dead SMCs, leading to aortic micro-calcification ^[3].

3. Phenotypic Alterations and Vascular Remodeling in Thoracic Aortic Aneurysms

In contrast to AAAs, TAAs are rarely associated with atherosclerosis and are divided into two main categories: sporadic (non-genetic) and genetic TAAs ^[14]. Sporadic TAAs may occur with aging, and their progression is accelerated by hypertension ^[14]. In young patients, TAA formation is associated with genetic conditions such as MFS and BAV.

Similarly to AAAs, TAAs are characterized by an extensive remodeling of the ECM ^[15]. Endothelial dysfunction is also present in TAAs, but the formation of fibro-atherosclerotic plaque is rarely evidenced ^[16]. In addition, endothelial cells can undergo endothelial-to-mesenchymal transition (End-MT), a process in which cells switch from an endothelial to a mesenchymal phenotype, losing cell-to-cell contact and cell polarity ^[17]. The main pathway responsible for the End-MT is the canonical Transforming Growth Factor β (TGF- β) signaling in association with NOTCH and Wnt/ β catenin signaling ^[8] ^{[17][18]}. End-Mt has been observed in sporadic TAAs but appears to be more accentuated in MFS TAAs ^[7]. At the same time, SMCs in the tunica media can dedifferentiate in myofibroblasts, switching from a contractile phenotype to a proliferative/synthetic one. Myofibroblasts deposit alcianophilic material like Glycosaminoglycans (GAGs) and collagen, determining fibrosis ^[19]. This process is well evidenced in sporadic TAAs and strongly exacerbated in MFS TAAs ^[7]. SMCs can also acquire an osteoblast-like phenotype, promoting calcification, especially in BAV TAAs ^{[8][20]}. Those alterations are associated with the deregulation of NOTCH and BMP signaling ^{[21][22]}.

4. miRNAs' Biogenesis and Their Role in Aortic Remodeling

In the last few decades, many studies have demonstrated that about 97% of the human genome consists of non-coding sequences that are not transcribed in mRNAs but in non-coding RNAs ^[23]. Non-coding RNAs regulate gene expression at the post-transcriptional level ^[24]. miRNAs are a class of non-coding RNAs, which act as epigenetic regulators without affecting the chromatin architecture ^[25]. In the human genome, miRNAs are encoded by introns of "host genes" and also enriched within unique miRNA clusters ^[25]. miRNA biogenesis starts with RNA polymerases II/III, which transcribe a primary miRNA (pri-miRNA) molecule from the intergenic or intragenic region ^[24]. Successively, pri-miRNAs are processed by a multi-component microprocessor complex (Drosha/DGCR8) to precursor miRNAs (pre-miRNAs) with specific hairpin structures ^[24]. Pre-miRNAs are exported from the nucleus to the cytoplasm via the transport factor exportin-5 using GTP as a cofactor ^[24]. Within the cytoplasm, pre-miRNAs are released from exportin-5 following GTP hydrolysis and are further processed by an RNase III, called "Dicer", generating double-stranded miRNAs of approximately 22 nucleotides ^[24]. This product is incorporated into the RNA-induced silencing complex multiprotein complex (RISC) in which a helicase ensures that only one of the miRNA duplex strands remains in the complex to control the post-transcriptional expression of target genes ^[26]. miRNAs are known as negative regulators of gene expression ^[26]. Precisely, miRNAs induce the cleavage and degradation of target mRNAs or the inhibition of the translation process ^[26]. miRNAs have been demonstrated to play a critical role in several physiological processes, such as cell proliferation, apoptosis, fat metabolism, neuronal development, cell differentiation, hormone secretion and the development of multiple diseases ^[27]. In the last few years, many studies have reported an aberrant miRNA expression in different cardiovascular diseases such as atherosclerosis, cardiac remodeling, myocardial infarction and aneurysms ^[28].

5. The Regulatory Role of miRNAs in AAAs

Different studies have reported that inflammation, endothelial dysfunction, ECM remodeling and SMC proliferation/apoptosis, which characterize the AAA aortic wall, are associated with specific miRNA deregulations ^[29]. ECM proteins such as collagen and elastin are mainly produced by SMCs, and the apoptosis of those cells has been demonstrated to be implicated in the development of AAA ^[30]. It has been reported that SMAD3, a key intracellular mediator of the fibrotic process ^[31], is down-regulated in AAA ^{[32][33]}. It was also found that miR-195, an important regulator of ECM proteins, was up-regulated in AAA patients ^[34]. Bioinformatics analysis revealed that miR-195 has a binding site in the 3'-UTR for SMAD3, and their interaction was confirmed by in vitro studies ^[35]. miR-195 overexpression in vitro inhibited SMC proliferation, inducing apoptosis, whereas SMAD3 overexpression blocked those effects ^[35]. Therefore, miR-195 displays a crucial role in AAA pathogenesis and represents a potential therapeutic target ^[35].

As mentioned above, AAA is characterized by an increased degree of calcification, which can lead to rupture ^[36]. During AAA progression, SMCs switch from the contractile to the synthetic phenotype and synthesize osteogenic factors, such as

the osteogenic transcription factor Runt-related gene (RUNX). The latter is functionally associated with SMAD2/3, which, in turn, are activated by angiotensin II (AngII) signaling [37]. The activation of the SMAD-RUNX2 signaling pathway induces osteogenic differentiation of SMCs [37]. It has been demonstrated that miR-424 has a key role in cardiovascular pathologies. miR-424 is also called “osteomir” as it regulates vascular calcification [38]. Bioinformatics analysis revealed that AAA patients express high levels of *RUNX2* and exhibit down-regulation of miR-424 compared with control subjects [37].

Another miRNA, reported to be involved in the chronic inflammation that characterizes the AAA aortic wall, is miR-33-5p [39]. Some studies reported that this miRNA regulates the innate immune response by the adenosine triphosphate-binding cassette transporter A1 (ABCA1) [40][41]. ABCA1 is a protein that transports free cholesterol and phospholipids from intracellular compartments to the cell membrane by using ATP as a source of energy, so this protein is fundamental in macrophage cholesterol efflux and reverse cholesterol transport [42][43]. It has been reported that ABCA1 acts as an anti-inflammatory receptor, and the enhancement of its function could be a beneficial therapeutic approach [44].

Another study correlated miR-21 expression to inflammatory response and aortic remodeling in AAA. Precisely, Yu et al. investigated the effects of dexmedetomidine (Dex) on miR-21 expression [45]. It has been reported that Dex suppresses the activities of inflammatory mediators and maintains a balanced myocardial function and coronary blood flow [46]. miR-21 is reported to control the inflammatory responses, ECM remodeling and lipid accumulation in cerebral aneurysms [47][48]. Moreover, it has been demonstrated that miR-21 inhibition blocks AAA development. Programmed cell death 4 (*PDCD4*), an inflammation- and apoptosis-related gene, has been proven to be a gene target of miR-21 [49][50]. In order to evaluate the effects of Dex on miR-21 expression and consequently on AAA progression, rat models of AAA were injected with Dex. The authors discovered that Dex administration in AAA rat models down-regulated the expression of inflammatory factors and MMPs as well as up-regulating miR-21 expression [45].

6. The Regulatory Role of miRNAs in Sporadic TAAs

As previously reported, TAA formation is associated with progressive pathological remodeling of the aortic wall that leads to structural parietal degeneration, with rearrangement of hemodynamic loads, and finally rupture [51][52]. During this remodeling, both endothelial cells and SMCs undergo phenotypic changes in response to pathogenetic stimuli [16][53][54]. Recently, miRNA deregulation has been reported to be associated with vascular cell phenotypical changes. The phenotypic switching of SMCs from a contractile to a synthetic phenotype has been suggested to be involved in the development of aortic aneurysm and its dissection [53][54]. As already mentioned, aortic SMCs of sporadic TAA generally switch into a myofibroblast phenotype with the increased collagen synthesis and consequent aortic fibrosis [55][56]. During this process, SMCs reduced the expression of functional markers such as smooth muscle 22 α (SM22 α), smooth muscle cell-specific myosin heavy chain (MYH11) and α -smooth muscle actin (α -SMA) [53]. However, the molecular mechanisms underlying the SMC phenotypic switch is not completely understood. The analysis of aortic tissues derived from patients with severe TAA evidenced a strong miR-335-5p down-regulation and Specificity Protein 1 (*SP1*) up-regulation; the latter is involved in SMC proliferation and phenotype switching [57]. However, cultured human SMCs overexpressing miR-335-5p showed *SP1* down-regulation with reduced proliferation and migration as well as increased expression of contractile markers, such as SM22 α , α -SMA and CNN1 [57]. In addition, the authors documented *SP1* as a gene target of miR-335-5p. In a mouse model of aortic dissection, the administration of miR-335-5p clearly suppressed aorta dilatation and vascular media degeneration [57]. Aberrant down-regulation of miR-134-5p has been evidenced in aortic tissues derived from sporadic TAA patients [58]. In vitro studies, on aortic SMCs, revealed that miR-134-5p overexpression promoted differentiation and expression of contractile markers, suggesting a crucial role of miRNA in aortic SMC homeostasis [58]. PDGF and TGF β are involved in SMC differentiation, vascular remodeling and aortic aneurysms [59][60].

Endothelial cells play a fundamental role during pathological aortic aneurysmatic remodeling [16]. Several studies identified the aberrant expression of different miRNAs in TAA and their role in the regulation of endothelial cell phenotyping and functions [61]. The activation of endoplasmic reticulum stress (ERS) contributes to the pathogenesis of cardiovascular diseases, in particular endothelial dysfunction [62][63][64]. The mechanism through which ERS mediates vascular cell dysfunction is not completely understood. miRNAs regulate the ERS response by targeting specific genes [65]. In particular, miR-204 seems to be associated with ERS by targeting sirtuin1 lysine deacetylase (*SIRT1*) [66][67]. Kassin et al. investigated the role of miR-204 in ERS and endothelial dysfunction by targeting *SIRT1* [68]. Overexpression of miR-204 in HUVECs induced ERS by up-regulation of specific stress markers, such as glucose-regulated protein, C/EBP homologous protein and Activating Transcription Factor 6, as well as phosphorylation of PKR-like ER kinase and eukaryotic initiation factor 2.

7. miRNA Regulation of Vascular Cell Phenotype in Genetic TAAs

As reported above, TAAs are, in some cases, associated with genetic mutations [69]. BAV (bicuspid aortic valve) is a congenital cardiovascular malformation leading to an increased risk for severe cardiovascular events, such as TAA [70][71][72]. The BAV condition is associated with different genetic mutations including the *NOTCH1*, *TGFBR2*, *FBN1*, *SMAD6*, *GATA5* and *GATA6* genes [70][71][72]. Several studies described the differential expression of miRNAs between BAV and TAV (tricuspid aortic valve) patients [73]. Some studies reported that BAV aortopathy is also characterized by a lower expression of End-Mt markers compared with sporadic TAAs [8][74]. However, some studies demonstrated that, before dilation, BAV aortas showed an activation of the End-Mt process [75]. Using a systemic biological approach, a strong association between the miR-200 family, which targets the End-Mt transcription factors zinc-finger E homeobox-binding transcription factors 1 and 2 (*ZEB1* and *ZEB2*) [76][77], with the BAV signaling network was highlighted [75].

The differential expression of ERG and its transcription factor miR-126-5p has also been demonstrated, in the vascular phenotypic changes occurring in BAV and TAV aortas [8]. The expression levels of the protein ERG and miR-126-5p were up-regulated in TAA samples derived from BAV compared to TAV patients. Moreover, this up-regulation in BAV TAA was shown to be associated with a down-regulation of SMAD2/3 proteins [8], whose activation induces End-MT [78]. Therefore, the down-regulation of SMAD2/3 could explain the different phenotypic changes observed in the endothelium of BAV TAA. Similarly, the tunica media of BAV TAA showed an up-regulation of ERG and miR-126-5p in association with an evident aortic calcification compared with TAV tunica media; the latter were mainly characterized by a marked fibrosis [8].

8. Conclusions

Aortic aneurysms remain a serious health concern with many clinical complications as the associated ruptures can cause significant morbidity and mortality. The onset and development of AAA and TAA are associated with different risk factors. AAA is generally associated with atherosclerosis, hypertension and aging, whereas TAA frequently occurs in patients with genetic diseases. Both types of aortic aneurysms are characterized by pathological aortic remodeling. In that light, AAA shows a more marked inflammatory parietal response compared with TAA. miRNAs have been identified to be involved in the regulation of vascular cell phenotypic transformation, inflammation and SMC apoptosis. In AAA, miR-195 and miR-21 deregulation are associated with SMC apoptosis; miR-424 down-regulation is associated with calcification of the aortic wall; miR-33b and miR-33-5p deregulation is involved in the parietal inflammatory response. In TAA, miRNA deregulation induces a vascular cell phenotype switch. In sporadic TAA, miR-335-5p, miR-134, miR-155b-5p, miR-122-3p and miR-23b-5p down-regulation lead to a reduction in SMC cytoplasmic contractile cytoskeletal filaments with a switch into a synthetic phenotype promoting medial fibrosis. In TAA, endothelial cells characteristically lose physiological endothelial markers, with an End-Mt phenotypic switch and consequent endothelial dysfunction. For genetic TAA, MFS TAA shares histopathological features with sporadic TAA such as End-Mt and fibrosis, but in a more accentuated manner. Deregulation of specific miRNAs such as miR-29, miR-122 and miR-632 plays a key role in the regulation of the phenotypical cell changes and parietal remodeling observed in MFS TAA. Aortic remodeling in BAV TAA differs from sporadic and MFS TAAs, and miRNAs appear crucial in the regulation of aortic remodeling. Deregulation of miR-126, miR-200 and miR-423-5p seems to inhibit the End-Mt process and favor the calcification of the tunica media observed in BAV TAA. Schematic representations of the phenotypic alterations and aortic remodeling of AAA and TAA regulated by miRNAs are shown in **Figure 1** and **Figure 2**.

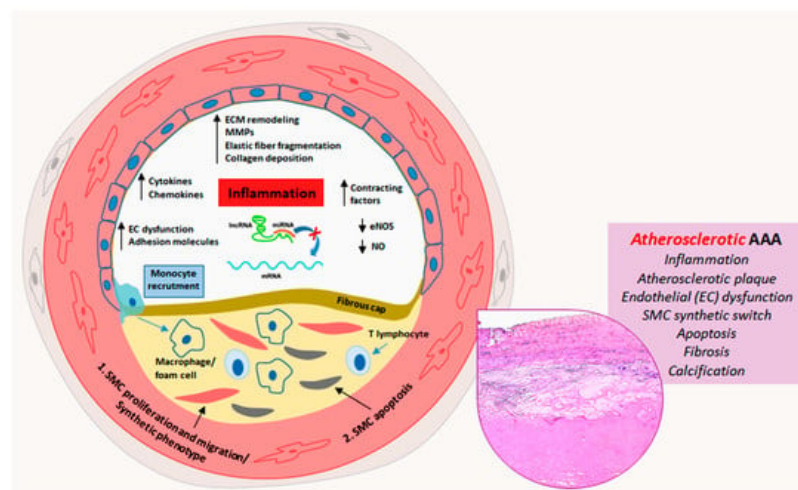


Figure 1. Schematic representation of miRNA deregulation-related pathogenic mechanisms in atherosclerotic abdominal aortic aneurysms. Atherosclerotic process prevails in the progression of abdominal aortic aneurysm (AAA) and is

characterized at least in part by miRNA deregulation-driven endothelial dysfunction, inflammation, smooth muscle cell (SMC) proliferation, migration and apoptosis, fibroatheromatous plaque formation and thrombosis, with medial fibrosis and calcification (insert, Hematoxylin and Eosin staining).

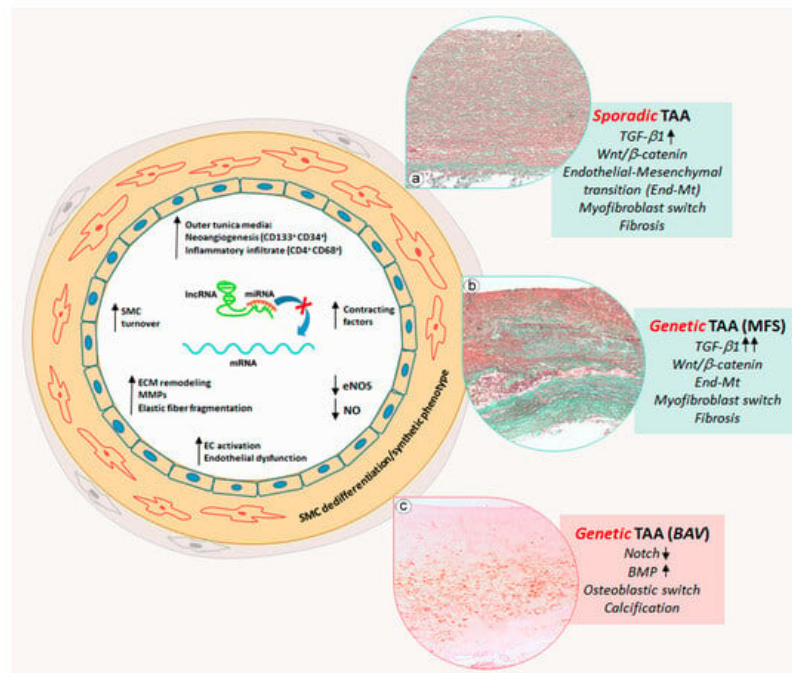


Figure 2. Schematic representation of miRNA deregulation-related pathogenic mechanisms in thoracic aortic aneurysms. Thoracic aortic aneurysms (TAAs) are sporadic or frequently related to genetic diseases. Sporadic and Marfan syndrome disease (MFS) TAAs show an aortic cell differentiative process, in which endothelial cells switch into a mesenchymal phenotype, whereas medial SMCs switch into a myofibroblastic phenotype and synthesize collagen and glycosaminoglycan with consequent aortic degeneration and fibrosis (inserts (a,b), Masson's Trichrome Goldner staining). Those processes are precocious, much more marked and strongly accentuated in MFS TAAs, in which $TGF-\beta$ signaling is hyperactivated. Genetic bicuspid aortic valve (BAV) TAA displays a specific degenerative process, in which SMCs dedifferentiate into osteoblast-like cells promoting medial calcification (insert (c), Alizarin Red staining) by miRNA deregulation-mediated activation of NOTCH and BMP signaling.

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