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MiRNAs in aortic aneurysm and dissection: a narrative review

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Abstract: Background and Objective: Aortic aneurysm and dissection are serious life-threatening cardiovascular emergencies, and their pathogenesis includes vascular inflammation, extracellular matrix remodeling and matrix metalloproteinases, phenotype switch of vascular smooth muscle cells and apoptosis, but the specific mechanisms have not been fully elucidated. As gene expression regulators, microRNAs are also key molecules in vascular function. This article not only describes the role of microRNAs in the pathogenesis and progression of aortic aneurysm and dissection, but also further illustrates the molecular mechanism of aortic aneurysm and dissection, which is of great significance for their prevention and treatment. In addition, we discuss miRNAs as clinical biomarkers for the diagnosis and monitoring of aortic aneurysms and dissection, as well as the possibility of developing new effective therapeutic targets. Methods: As of October 8, 2023, relevant publications containing miRNAs involvement in aortic aneurysms and dissection were systematically searched in the PubMed database. Key Content and Findings: Many miRNAs are involved in the pathogenesis of aortic aneurysm and dissection, including vascular inflammation, extracellular matrix remodeling, and homeostasis regulation of vascular smooth muscle cells. Among these miRNAs, some candidates have become potential biomarkers for the early diagnosis and long-term prognosis of aortic aneurysm and dissection due to their high sensitivity, specificity and stability. In addition, miRNAs are also becoming important targets for drug discovery. We have summarized miRNAs with clinical application prospects in aortic aneurysm and dissection. Conclusions: MiRNAs play a vital part in the pathogenesis of aortic aneurysm and dissection. The research on miRNAs is moving from

the laboratory to the clinical, and miRNAs are expected to be used for the diagnosis and treatment of aortic aneurysm and dissection in the future.

Keywords: miRNAs; aortic aneurysm; aortic dissection

1. Introduction

The aorta as a whole organ may be subject to acute or chronic effects involving thoracic and/or abdominal components [1]. Aortic diseases can be roughly divided into congenital and acquired diseases, among which acquired diseases mainly include aortic aneurysm and dissection (AAD) [2].

AAD is the focus of clinical attention and is characterized by structural changes to the aortic wall that can lead to aortic rupture and other life-threatening complications. When the progressive weakening of the aortic wall leads to local dilation of the aorta to 150% of its normal diameter, it is considered an aortic aneurysm (AA) [3]. In addition to aortic dilation, patients may also experience aortic dissection (AD). AD is a tear in the lining of the aorta that causes blood to enter the middle layer of the artery wall through the opening of the lining, forming a false lumen [4].

AAD is a serious cardiovascular disease, and since most patients present as asymptomatic for many years until acute presentation after rupture, approximately 24% of patients die within 24 hours and 50% within 48 hours [5–7] and the mortality rate due to rupture is approximately 90% [8]. At present, the only treatment option for AAD is surgical repair, there is no effective drugs available to prevent, delay or reverse AAD [9]. These results suggest that early diagnosis is more important than treatment for patients with AAD.

MicroRNAs (miRNAs) are emerging as new fundamental regulators of gene expression. This article reviews the role of miRNAs in AAD, focuses on the latest research on the involvement of miRNAs in the pathogenesis of AAD, and discusses the potential role of miRNAs as novel intracellular therapeutic intervention targets and extracellular clinical biomarkers. We present this article in conformity to the Narrative Review reporting checklist.

2. Methods

As of October 8, 2023, relevant publications were systematically searched in the PubMed database. The search terms included “non-coding RNA”, “miRNA”, “aortic aneurysm”, “aortic dissection”. The publications were selected as these were original articles and reviews in English to involve the current knowledge of miRNAs in aortic aneurysm and dissection. We use a table (Table 1) to present detailed search methods.

Table 1. Summary of the search methods.

Items	Specification
Date of search	October 8, 2023
Databases and other sources of searched	PubMed
Search items	(non-coding RNA OR ncRNA OR microRNA OR miRNA OR miR) AND (aortic aneurysm OR AA) (non-coding RNA OR ncRNA OR microRNA OR miRNA OR miR) AND (aortic dissection OR AD)
Time framed	Papers published before October 8, 2023
Inclusion and exclusion criteria	Inclusion criteria: Focus on original articles and reviews in English about miRNAs involved in aortic aneurysm and dissection. Exclusion criteria: Published in a language other than English.
Selection process	Authors independently chose original articles and reviews based on the search methods provided. Original articles and reviews identified using the search methods were further retrieved to obtain supplemental references. Original articles and reviews were chosen based on the robustness of their research. The final choice of original articles and reviews was agreed between authors.

3. MiRNAs in the pathogenesis of aortic aneurysms and dissections

MicroRNA (miRNA, miR) is a non-coding small ribonucleic acid that negatively regulates gene expression. More and more studies have shown that miRNAs are key regulators of vascular cell functions, including cell proliferation, migration, contraction, differentiation, apoptosis, and play a crucial role in the progression of many cardiovascular diseases, including aortic aneurysm and dissection [10,11]. Specifically, miRNAs are involved in the development of AAD through various mechanisms. This study aims to elucidate the pathogenesis of miRNAs in promoting AAD by focusing on key aspects, including vascular inflammation, extracellular matrix remodeling, phenotype switching of vascular smooth muscle cells (VSMCs), and apoptosis (Figure 1).

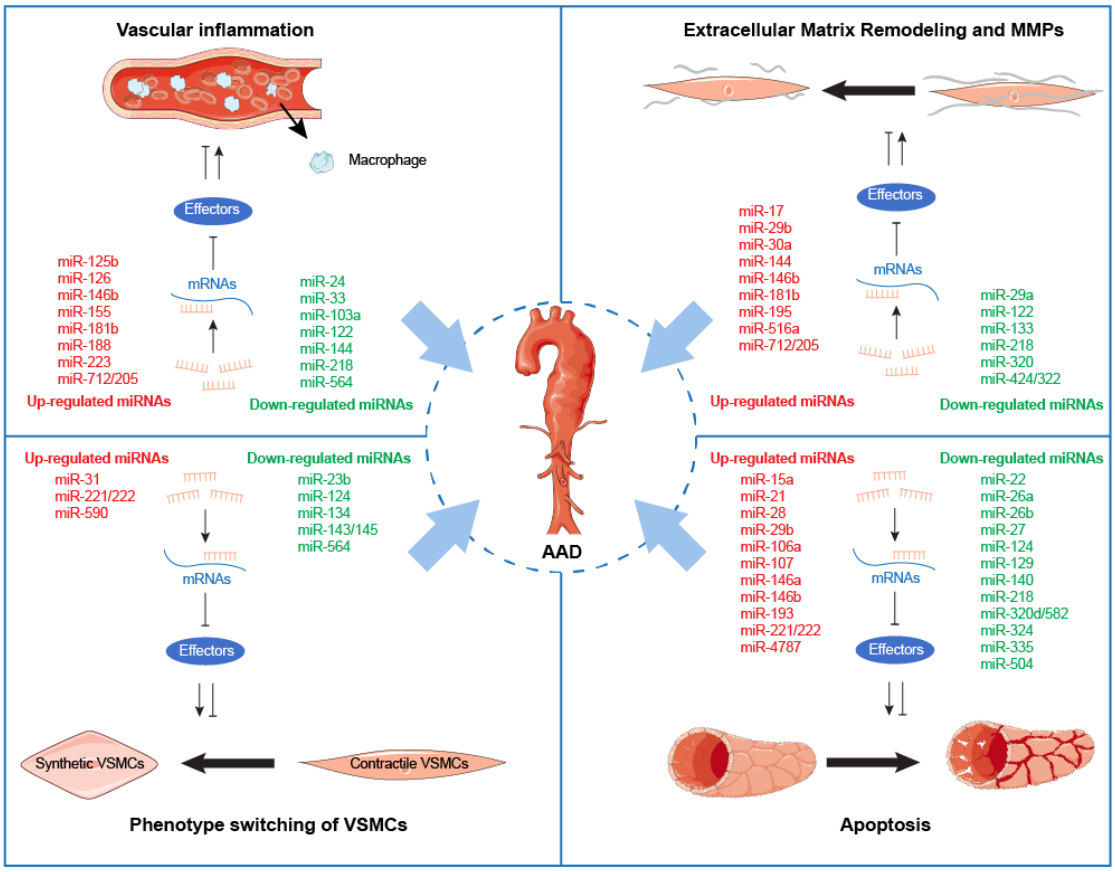

Figure 1. MiRNAs in the pathogenesis of aortic aneurysms and dissections.

3.1. Vascular inflammation

Vascular inflammation caused by endothelial cell (ECs) injury is a key factor in the formation and development of AAD [12]. Inflammatory cells including neutrophils, macrophages and dendritic cells, infiltrate the pathological aortic wall and then involve in tissue injury, repair and remodeling [13,14]. Among the miRNAs associated AAD aortic tissue or cell samples, eight miRNAs (miR-125b, miR-155, miR-146b, miR-181b, miR-126, miR-188, miR-223 and miR-712/205) are upregulated and seven miRNAs (miR-24, miR-103a, miR-33 miR-144, miR-218, miR-122) are downregulated (Table 2). MiR-155 target cytotoxic T-lymphocyte-associated protein (CTLA4) and SMAD2 to Promote chronic inflammation, contributing to AAA pathology [15]. MiR-24 target chitinase 3-like 1 (CHI3L1), regulating cytokine synthesis in macrophages as well as their survival, promoting aortic smooth muscle cell migration and cytokine production, and stimulating adhesion molecule expression in vascular endothelial cells [16]. MiR-103a targeting a disintegrin and metalloproteinase 10 (ADAM10) to Attenuate inflammation, inhibiting AAA growth [17]. Studies have indicated that some miRNAs participate in the regulation of vascular inflammatory response and play a significant part in the occurrence and development of AAD.

Table 2. Summary of tissue miRNAs associated with vascular inflammation.

Disease	miRNA	Regulation	Target(s)	Function	Ref
AD	miR-564	↓	SKI, NRGN	Inhibit inflammation and VSMCs proliferation, migration and phenotypic transformation	[18]
TAAD	miR-146b	↑	NF-κB1, TRAF6, MMP-16, ACTA2	Promote inflammation, apoptosis, ECM degradation	[19,20]
AA	miR-181b	↑	TIMP-3, ELN	Endow macrophages with more invasive and proliferative capabilities	[21]
AAA	miR-24	↓	CHI3L1	Regulate cytokine synthesis and survival in macrophages	[16]
AAA	miR-33	↓	ABCA1	Attenuate inflammation	[22]
AAA	miR-103a	↓	ADAM10	Macrophage infiltration	[17]
AAA	miR-125b	↑	Suv39h1, TNFAIP3	Regulate proinflammatory gene expression	[23]
AAA	miR-126	↑	-	Modulate VCAM-1 expression, inhibit leukocyte adhesion and inflammation	[24]
AAA	miR-144	↓	TLR2, OLR1	Mitigate M1 macrophage-associated inflammation	[25]
AAA	miR-155	↑	CTLA4, SMAD2	Promote chronic inflammation	[15]
AAA	miR-188	↑	-	Inflammatory cell recruitment	[26]
AAA	miR-218	↓	ADAMTS5	Regulate the proliferation, migration, and apoptosis of VSMCs, inflammatory molecules expression and ECM molecules	[27]
AAA	miR-223	↑	TIMP-1 TIMP-2, MMP-2, MMP-9	Inhibits vascular inflammation	[24,28]
AAA	miR-712/205	↑	TIMP3, RECK	Affect the adhesion of circulating leukocytes, and induces inflammation	[29]
TAA	miR-122	↓	CCL2, IL-1β, MMP-12	Increase inflammatory cytokines and MMP-12 to elastic lamina fragmentation	[30]

Abbreviations: AD, aortic dissection; TAAD, Stanford type A aortic dissection; AA, aortic aneurysm; TAA, thoracic aortic aneurysms; AAA, abdominal aortic aneurysm; NRGN, neurogranin; NF-κB1, Nuclear factor kappa B1; TRAF6, tumor necrosis factor receptor-associated factor 6; MMP, Matrix metalloproteinase; ACTA2, actin alpha 2; TIMP, tissue inhibitor of metalloproteinase; ELN, Elastin; CCL2, C-C motif ligand 2; IL-1β, interleukin-1β; CHI3L1, chitinase 3-like 1; ABCA1, ATP-binding cassette transporter A1; ADAM10, a disintegrin and metalloproteinase 10; ATP7A, Copper-transporting P-type ATPase/Menkes ATPase; TLR2, Toll Like Receptor 2; OLR1, ox-LDL Receptor 1; CTLA4, cytotoxic T-lymphocyte-associated protein 4; ADAMTS5, A Disintegrin And Metalloproteinase With Thrombospondin 5; RECK, reversion-inducing cysteine-rich protein with kazal motifs; VSMC, vascular smooth muscle cell; ECM, extracellular matrix; VCAM-1, vascular cell adhesion molecule-1; Ref, Reference.

3.2. Extracellular matrix remodeling and MMPs

Vascular inflammation is regulated by immune response mechanisms that subsequently activate matrix metalloproteinases (MMPs), enzymes that degrade the extracellular matrix (ECM) and ECM structural proteins (collagen and elastin) that are essential for the maintenance of the structure and function of the aorta. The pro-inflammatory miRNAs (miR-181b, miR-712/205) and the anti-inflammatory miRNAs (miR-122, miR-44, miR-218) cause damage to the aortic wall by exacerbating vascular inflammation and thereby degrading ECM (Table 3). Tissue inhibitor of metalloproteinases (TIMPs) are the most specific endogenous inhibitors of MMPs. The balance of MMPs and TIMPs is crucial for the stability of ECM physiological function, and the imbalance between MMPs and TIMPs will lead to the excessive degradation of ECM [31]. The up-regulation of miR-17/29b/106a/30a/195/516a and the down-regulation of miR-29a/320 target MMPs or TIMPs, degrading the extracellular matrix to compromising the structural integrity and elasticity of the aortic wall (Table 3). Specifically, miRNAs are involved in the expression of MMPs that alter inflammatory factors, degrading ECM through different mechanisms. The increase in MMPs ultimately leads to damage to protein structural integrity, rupture of elastic fibers, and thinning of the aortic wall, thereby promoting AAD [32].

Table 3. Summary of tissue miRNAs associated with ECM remodeling and MMPs in AAD.

Disease	miRNA	Regulation	Target(s)	Function	Ref
AD	miR-30a	↑	LOX	Inhibit cross□link collagen and elastin	[33]
AD	miR-144	↑	TE	Reduce elastin	[34]
AD	miR-320	↓	MMPs	Regulate MMPs expression by macrophages	[35]
TAD	miR-17	↑	TIMP-1, TIMP-2	Increase MMP-2 activity and ECM degradation	[36]
TAAD	miR-146b	↑	NF-κB1, TRAF6, MMP-16, ACTA2	Promote inflammation, apoptosis, ECM degradation	[19,20]
AA	miR-181b	↑	TIMP-3, ELN	Regulate elastin production	[21]
TAA	miR-29a	↓	MMP-2	Downregulate ECM	[37]
TAA	miR-29b	↑	ELN, MMP-2	Repress elastin mRNA and increase MMP-2 expression and activity	[38]
TAA	miR-122	↓	CCL2, IL-1β, MMP-12	Increase inflammatory cytokines and MMP-12 to elastic lamina fragmentation	[30]
TAA	miR-133a	↓	Furin	Regulate aortic fibroblast phenotype	[39]

Table 3. *Cont.*

Disease	miRNA	Regulation	Target(s)	Function	Ref
AAA	miR-106a	↑	TIMP-2	Induce apoptosis and ECM degradation	[40]
AAA	miR-195	↑	ELN	Increase MMP-2 and MMP-9 activity and ECM degradation	[41]
AAA	miR-218	↓	ADAMTS5	Regulate the proliferation, migration, and apoptosis of VSMCs, inflammatory molecules expression and ECM molecules	[27]
AAA	miR-424/322	↓	MMP-2, MMP-9, VEGF, Smad2/3, RUNX2	Elastinolysis	[42]
AAA	miR-516a	↑	MTHFR, MMP-2, TIMP-1	Promote the disruption of Hcy metabolism and proteolytic degradation of elastin	[43]
AAA	miR-712/205	↑	TIMP-3, RECK	Regulate ECM and stimulate aortic MMP activity and inflammation	[29]

Abbreviations: AD, aortic dissection; TAD, progressive aortic dilation; TAAD, Stanford type A aortic dissection; AA, aortic aneurysm; TAA, thoracic aortic aneurysms; AAA, abdominal aortic aneurysm; LOX, lysyl oxidase; TE, tropoelastin; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinases; NF-κB1, nuclear factor kappa B1; TRAF6, tumor necrosis factor receptor-associated factor 6; ACTA2, actin alpha 2; ELN, elastin; CCL2, CC chemokine ligand 2; IL-1β, cytokine interleukin-1β; VEGF, vascular endothelial growth factor; RUNX2, Runt-related gene; MTHFR, methylenetetrahydrofolate reductase; RECK, reversion-inducing cysteine-rich protein with kazal motifs; ECM, extracellular matrix; VSMC, vascular smooth muscle cell; Regulation; Ref, Reference.

3.3. Phenotype switching of VSMCs and apoptosis

VSMCs are the main cells that make up the aortic wall and play a crucial part in maintaining the structure and function of the aorta. Therefore, dysfunctional VSMCs, including phenotypic transformation and apoptosis, are considered to be one of the main factors in the pathogenesis of AAD. VSMCs have two phenotypes: contraction and synthesis. The characteristics of contraction type VSMCs are high expression levels of contraction genes, low rates of proliferation, migration, and ECM synthesis, and their main function is to maintain vascular wall tension and compliance; synthetic VSMCs, on the other hand, mainly produce various extracellular matrix proteins. The phenotype of VSMCs can transition between contractile (differentiated) and synthetic (dedifferentiated) states to adapt to constantly changing environmental conditions. The contraction phenotype present in healthy vascular walls is transformed into a synthetic phenotype [44] when the vascular walls are stimulated by trauma, hypertensive shock, and atherosclerosis, were found in many cardiovascular diseases including atherosclerosis [45], hypertension [46], aortic aneurysm and dissection [47,48]. The function of VSMCs is regulated by a large number of miRNAs. Three miRNAs (miR-590, miR-31, and miR-221/222) have been identified that promote

phenotypic switching, while four miRNAs (miR-124, miR-236, miR-134, and miR-143/145) have been found to inhibit phenotypic switching in dysfunctional VSMCs associated with AAD. In addition, the upregulation of miR-15a/21/28/29b/106a/107/146a/146b/4787 and the downregulation of miR-22/26a/26b/27/129/140/218/324/504 induce apoptosis. (Table 4). The function of VSMCs is also regulated by the deletion of Dicer in VSMCs, an enzyme that regulates miRNA biogenesis, leads to embryonic death and vascular dysplasia [49] further indicating the important role of miRNAs in VSMCs homeostasis.

Table 4. Summary of tissue or VSMCs miRNAs associated with dysfunctional VSMCs in AAD.

Disease	miRNA	Regulation	Target(s)	Function	Ref
AD	miR-22	↓	p38MAPKα	Regulate the apoptosis of VSMCs through the MAPK signaling pathway	[50]
AD	miR-27	↓	FADD	Regulate vascular remodeling by targeting ECs' apoptosis and interaction with VSMCs	[51]
AD	miR-107	↑	ITM2C	Promote proliferation and inhibit apoptosis	[52]
AD	miR-124	↓	Sp1	Repress proliferation, migration and phenotypic switching	[53]
AD	miR-140	↓	NCKAP1	Repress proliferation, migration and invasion of VSMCs	[54]
AD	miR-320d/582	↓	TRIAP1/NET1, COL1A1/SPP1	Inhibit apoptosis	[55]
AD	miR-335	↓	SP1	Represses proliferation, migration and phenotypic switching	[56]
AD	miR-564	↓	SKI, NRGN	Inhibit inflammation and VSMCs proliferation, migration and phenotypic transformation	[18]
AD	miR-590	↑	LOX	Promote the phenotypic switching of VSMCs	[57]
AD	miR-4787	↑	PKD1	Inhibit the PI3K/Akt/FKHR pathway	[58]
TAD	miR-134	↓	STAT5B, ITGB1	Inhibit VSMC phenotypic switch and migration	[59]
TAD	miR-143/145	↓	Klf4, myocardin, Elk-1	Promote differentiation and repress proliferation of VSMC	[60]
TAD	miR-146a	↑	SMAD4	Induce VSMC proliferation and migration	[61]
TAAD	miR-26b	↓	HMGA2	Regulate TGF-β/Smad3 signaling pathway	[62]
TAAD	miR-146b	↑	NF-κB1, TRAF6 MMP-16, ACTA2	Promote inflammation, apoptosis, ECM degradation	[19,20]
AA	miR-193a	↑	CCNE1, CCND1, CXCR4	Promote the phenotypic transformation	[63]

Table 4. *Cont.*

Disease	miRNA	Regulation	Target(s)	Function	Ref
TAA	miR-29b	↑	ELN, MMP-2	Increase cleaved caspase-3 and caspase-9, enhance caspase-3 activity, and decrease levels of the antiapoptotic proteins, Mcl-1 and Bcl-2	[38]
TAA	miR-221/222	↑	kip1, kip2, c-kit	Pro-proliferative, pro-migration, and anti-apoptotic effects, promote a synthetic phenotype in VSMCs	[64–66]
TAA	miR-324	↓	RAN	Promote apoptosis	[67]
AAA	miR-15a	↑	CDKN2B	Promote proliferation and decrease apoptosis of VSMC	[68]
AAA	miR-21	↑	PTEN, SPRY1, PDCD4, BCL2	Promote proliferation and decrease apoptosis of VSMC	[69,70]
AAA	miR-23b	↓	FoxO4	Inhibit phenotypic switching	[71]
AAA	miR-26a	↓	SMAD1, SMAD4	Promote proliferation and inhibit differentiation, apoptosis, alters TGF-β signaling	[72]
AAA	miR-28	↑	LYPD3, GRIA4	Regulate the apoptosis of VSMCs	[73]
AAA	miR-98	-	-	Induce VSMC apoptosis	[74]
AAA	miR-106a	↑	TIMP-2	Induce apoptosis and ECM degradation	[40]
AAA	miR-129	↓	Wnt5a	Inhibit proliferation and induce apoptosis of VSMC	[75]
AAA	miR-218	↓	ADAMTS5	Regulate the proliferation, migration, and apoptosis of VSMCs, inflammatory molecules expression and ECM molecules	[27]
AAA	miR-504	↓	p53	Anti-apoptotic	[76]
AAD	miR-31	↑	ALDH2	Downregulate myocardin	[77]

Abbreviations: AD, aortic dissection; TAD, thoracic aortic dissection; TAAD, Stanford type A aortic dissection; AA, aortic aneurysm; TAA, thoracic aortic aneurysms; AAA, abdominal aortic aneurysm; AAD, Aortic aneurysm/dissection; p38MAPKα, p38 mitogen-activated protein kinase α; FADD, fas-associated protein with death domain; ITM2C, Integral Membrane Protein 2C; Sp1, specificity protein 1; NCKAP1, NCK Associated Protein 1; SKI, proto-oncogene; NRGN, neurogranin; LOX, lysyl oxidase; PKD1, Polycystic kidney disease 1; STAT5B,Signal transducer and activator of transcription 5B; Klf4, Kruppel-like factor 4; HMGA2, High-mobility group AT-hook 2; NF-κB1, Nuclear factor kappa B1; TRAF6, tumor necrosis factor receptor-associated factor 6; ACTA2,actin alpha 2; CCNE1, CyclinE1; CCND1, CyclinD1; ELN, elastin; MMP, matrix metalloproteinase; CDKN2B, Cyclin-Dependent Kinase Inhibitor 2B; PTEN, phosphatase and tensin homolog deleted on chromosome ten; SPRY1, sprouty-1; PDCD4,programmed cell death 4; BCL2, B cell lymphoma 2; FoxO4, forkhead box O4; LYPD3,LY6/PLAUR domain containing 3; GRIA4, glutamate ionotropic receptor AMPA type subunit 4; TIMP, tissue inhibitor of matrix metalloproteinases; ADAMTS5, A Disintegrin and Metalloproteinase with Thrombospondin motifs 5; ALDH2, accompanied with overtly lowered aldehyde dehydrogenase 2; VSMC, vascular smooth muscle cell; MAPK, mitogen-activated protein kinase; TGF, transforming growth factor beta; EC, endothelial cell; ECM, extracellular matrix; Ref, Reference.

4. MiRNAs in the prediction and treatment of aortic aneurysms and dissections

4.1. Extracellular: potential prediction and diagnostic biomarkers

Because the non-specific symptoms of AAD, which often overlap with other cardiovascular diseases, making early clinical diagnosis particularly difficult, and due to its very high mortality rate at the time of onset, undetected asymptomatic AAD is regarded as a non-time bomb. Some proteins have been reported as potential candidates for AAD, such as D-dimer, calponin, elastin, CD40L, MPO, MMP-1, and TIMP-1 *etc* [78,79], but these biomarkers have not been adopted in routine clinical practice due to their low sensitivity and specificity. D-dimer is probably currently the most clinically useful, with the best diagnostic results within the first 6 hours, but its specificity is low (46.6%) and it overlaps with other clinical conditions [80]. MiRNA has higher sensitivity and specificity compared with them.

With the increasing maturity of miRNA research, circulating miRNAs have also played a part in the early diagnosis, risk classification, prognosis and treatment of many cardiovascular diseases, especially in some acute cardiovascular diseases. For example, plasma miR-1, miR-133a, and miR-208a are up-regulated in a time-dependent manner in patients with acute myocardial infarction (MI), and their sustained increases during the first 4 hours after MI are detected before other conventional biomarkers detectable [81,82].

As mentioned above, given the important role of miRNAs in the pathogenesis of AAD, their differential expression patterns in AAD make miRNAs a promising biomarker for prediction and diagnosis. The research significance of biomarkers based on extracellular miRNAs (mainly circulating) is mainly as follows: on the one hand, establishing predictive markers can help identify patients more prone to AAD in the context of hypertension, acute chest pain, and other conditions; on the other hand, the establishment of diagnostic markers may indicate the classification and prognosis of the disease, which can be treated timely before acute symptoms occur. There have been many studies that encompass these different aspects, Table 5 details extracellular miRNAs that are valuable in predicting and diagnosing AAD (AUC $\geq$ 0.8). We summarized several miRNAs that may have the most clinical application value in the detection and diagnosis of AAD, including miR-26b, miR-1281 and miR-191.

MiR-26b was significantly down-regulated in the plasma of AAAD patients [7,62]. The study by *Yang et al.* indicated that miR-26b impeded AAAD development by regulating HMGA2 and TGF-β/Smad3 signaling pathway [62].

MiR-1281 was significantly down-regulated in the plasma of AAA patients [83,84]. miR-1281 mainly targeted genes that were associated with cell-cell adhesion, extracellular matrix metabolism, cytoskeleton organization, inflammation, and multiple signaling pathways related to cellular cycles [84].

MiR-191 was significantly down-regulated in the plasma of AAA patients [83,85], promoting the progression of AAA by promoting apoptosis, ECM degradation, and inflammation [86].

In addition, miR-15a [24,87–89] and miR-155 [15,24] also have great potential as biomarkers for AAA, however the diagnostic utility of these particular miRNA was not assessed with ROC curve analysis, and further studies are needed to verify it.

Table 5. Circulating miRNAs as prediction and diagnostic biomarkers in AAD.

Disease	miRNA	Sample	Reg	Sen (%)	Spe (%)	AUC	FC	P-value	No. case	No. ctrl	Ref
AD	hcmv-miR-US-33-5p	Plasma	↑	73.50	85.70	0.815	>20	<0.05	8	14	[90,91]
AD	let-7b	Plasma	↑	79.40	92.90	0.887	>5	<0.001	8	14	[90]
AD	miR-23a	Plasma	↑	91.90	85.70	0.925	>15	<0.05	8	14	[90]
AD	miR-143	Serum-EV	↓	96.50	84.00	0.957	>2	<0.001	75	86	[92]
AD	miR-202	Serum-EV	↑	97.30	88.40	0.973	>2	<0.001	75	86	[92]
AD	miR-499	Serum-EV	↑	96.00	95.30	0.990	>2	<0.001	75	86	[92]
AD	miR-4306	Plasma	↑	-	-	0.874	>2	<0.01	98	56	[93]
AD	miR-4787	Plasma	↑	-	-	0.898	>5	<0.01	98	56	[93]
AD	miR-15a	Plasma	↑	75.70	100.0	0.855	>5	<0.001	8	14	[90]
AAAD	miR-26b	Serum	↓	88.00	90.00	0.911	>2	<0.001	25	30	[7,62]
AAAD	miR-25	Serum	↑	92.00	76.67	0.881	>2	<0.001	25	30	[7]
AAAD	miR-29a	Serum	↑	80.00	93.33	0.899	>2	<0.001	25	30	[7]
AAAD	miR-155	Serum	↑	84.00	83.33	0.863	>2	<0.001	25	30	[7]
AAA	miR-155	Serum	↓	-	-	-	>2	<0.05	10	10	[15,24]
AAA	miR-1281	Plasma	↑	76.70	98.30	0.921	>5	<0.001	10	10	[83,84]
AAA	miR-191	Plasma	↑	93.30	96.70	0.970	>5	<0.001	10	10	[83,85]
AAA	miR-15a	Plasma	↓	-	-	-	>2	<0.05	15	10	[24,87–89]
AAA	miR-455	Plasma	↑	95.00	100.0	0.983	>5	<0.001	10	10	[83]
TAA	miR-22	Serum	↑	-	-	0.800	>5	<0.05	9	10	[94]
TAA	miR-574	Serum	↑	78.60	85.00	0.870	>2	<0.001	28	20	[95]

Abbreviations: AD, aortic dissection; AA, aortic aneurysms; AAA, abdominal aortic aneurysm; TAA, thoracic aortic aneurysms; AAAD, Acute Stanford type A aortic dissection; Reg, regulation; Sen, sensitivity; Spe, specificity; AUC, area under curves.; FC, Fold change; Ref, reference.

4.2. Intracellular: possible therapeutic targets

At present, there is no perfect treatment for AAD, and the main treatment methods include drug control, interventional therapy and open surgery. With the continuous deepening of research on the molecular basis of AAD, people hope to find more effective treatment methods. Many previous studies have demonstrated the therapeutic potential of miRNAs in cardiovascular diseases, and the abnormal expression of multiple miRNAs in AAD is accompanied by changes in their target genes and protein expression, which also provides

possibilities for miRNA-based AAD treatment methods. Based on extensive animal research, several candidate miRNAs, miR-21 and miR-29b, may be the most promising miRNAs for clinical application.

The study by *Megadiverse et al.* [69] identified miR-21, one of the commonly upregulated miRNAs in cardiovascular disease, as a key molecule in the proliferation and apoptosis of VSMCs during AAA development. They found that overexpression of miR-21 in different AAA mouse models can promote VSMCs proliferation and reduce apoptosis, inhibit aneurysm expansion, and protect AAA. In contrast, systemic injection of LNA-modified antagomir targeted miR-21 resulted in a significant increase in aneurysms. The same phenomenon was also observed in human aortic tissue samples, and these findings support the strategy of increasing miR-21 expression to limit AAA progression.

In addition, some studies have focused on the abundant expression of miR-29 (a, b, c) in smooth muscle cells [96], especially miR-29b [97]. They found that the development of AAA was accompanied by a decrease in miR-29b expression in the aorta. *In vivo* injection of miR-29b antagomir significantly increased collagen expression, and delayed the progression of aortic aneurysm. Overexpression of miR-29b was significantly associated with increased risk of AAA amplification and aortic rupture. Therefore, there is also promising for future treatment of AAA by changing the level of miR-29b.

In general, miRNAs have broad therapeutic prospects for AAD. The therapeutic procedures for miR-21 and miR-29b candidates are also easy to implement, but there are still many problems when developing miRNA-based AAD therapies. Systemic injections are often used in animals, and studies have been limited to target tissues of interest without conducting systematic evaluations of other organs. The effectiveness of precise delivery, and the security of delivery tools (commonly viruses) need to be considered.

5. Conclusion

Up to now, the clinical management of severely life-threatening AAD remains unsatisfactory, and surgical intervention is the only valuable option. Therefore, there is an urgent need to seek new means to fill the gap in clinical demand for AAD.

MiRNAs, which are molecular switches that function by regulating post-transcriptional levels of target mRNA, play a key role in the pathogenesis of AAD. With the rapid development of sequencing technology, research on the role of miRNAs in AAD is gradually deepening, and their potential mechanisms are being elucidated: miRNAs play a crucial part in the pathological process of AAD by participating in the regulation of vascular inflammation, ECM degradation and VSMCs homeostasis. For example, the up-regulation of pro-inflammatory miR-125b/146b/181b, and the down-regulation of anti-inflammatory miR-24/33/122, promote the ECs injury and vascular inflammatory response in AAD, further activate MMPs and ECM degradation induced by miR-17/30a/195. Moreover, through the pro-apoptotic effect of miR-15a/21/107 and the promotion of phenotypic transformation of VSMCs by miR-31/221/222/590, VSMCs homeostasis is disrupted, and ultimately leading to a decrease in aortic wall elasticity and susceptibility to rupture, resulting in the occurrence

of AAD. Despite there are still many uncertainties regarding miRNAs and their regulation of the pathogenesis of AAD, the different expression levels of miRNAs at different stages and progression of AAD suggest that miRNAs may be a novel and effective diagnostic and therapeutic strategy.

Cell or tissue specificity and circulating stability make extracellular miRNAs valuable biomarkers for early diagnosis and long-term prognosis of AAD. We summarized several miRNAs with significant changes, high sensitivity, and specificity in the circulation of AAD patients. This non-invasive examination method may help to identify patients who are more prone to AAD in the context of hypertension, acute chest pain and other diseases, and provide timely treatment before the occurrence of acute symptoms, which has great prospects for future clinical application.

Previous studies have demonstrated that miRNA has broad therapeutic prospects for AAD. Due to the importance and operability of intracellular miRNAs, miRNAs are also becoming important targets for drug development. There are currently two main research strategies for the development of cardiovascular drugs for miRNAs: using miRNA mimics to supplement therapeutic miRNAs and enhance their effects on target genes; alternatively, miRNA inhibitors by forming complementary sequences with target miRNAs to inhibit miRNAs that promote disease occurrence [98]. Many companies have already laid out the development of miRNA related therapies, and research on miRNA is gradually moving from the laboratory to the clinical stage. Previously, the world's first human clinical trial of miRNA demonstrated the safety and effectiveness of miRNA drugs with stunning data. In this study, researchers used a drug called CDR132L, which specifically inhibits miR-132 expression, normalizes cardiomyocytes, prevents, and reverses the pathological remodeling process of the myocardium to treat heart failure [99].

This milestone research result makes the development of cardiovascular miRNA drugs possible, and also brings hope for the development of miRNA drugs targeting AAD, such as miR-21, miR-29b. However, there are also some challenges and limitations to the analysis of miRNA therapy for AAD: The standardization of miRNA detection methods still needs to be further improved. MiRNA is mainly detected by quantitative real-time pcr(qPCR) and RNA sequencing (RNA-seq). qPCR method has high sensitivity, but its presence of false positives and difficult primer design limit its application. Moreover, RNA-Seq has the characteristics of more accurate quantification and wider detection range, but it is expensive, with huge data and complicated data analysis. Although certain research results of miRNA therapy have been achieved in the laboratory, but systemic injections are often used in animals, and studies have been limited to target tissues of interest without conducting systematic evaluations of other organs. The translation of miRNA therapy into clinical practice is hindered by problems related to specificity, delivery and tolerability. The regulation of miRNAs often lies in the regulation of the overall gene network function, means a single miRNA may regulate multiple targets, and may have off-target effects [100]. Therefore, it is necessary to thoroughly understand their regulatory pathways and functions before drug development. ‘Naked’, chemically unmodified miRNAs are structurally unstable, their inefficiency in delivery in the body, lack of suitable targeted organs and delivery vehicles, and are often

terminated in clinical trials for lack of efficacy. Tolerance problems are caused by the recognition of RNA structures by pathogen-associated molecular pattern (PAMP) receptors, resulting in undesirable immune effects [101].

This article mainly discusses the mechanism of miRNAs involved in the pathogenesis of AAD, and demonstrates the potential clinical value of miRNAs in the early diagnosis, risk reduction and disease treatment of AAD. We believe miRNA therapy will become a key factor in the clinical management of AAD in the future.

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Conflicts of interests

The authors have no other conflicts of interest to declare.

Ethical statement

The authors are 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.

Authors' contribution

Conceptualization, X.J., H.Z., X.C., S.K. and J.X.; methodology, X.J., H.Z., X.C., S.K. and J.X.; data curation, X.J., H.Z., X.C., S.K. and J.X; formal analysis, X.J., H.Z., X.C., S.K. and J.X.; Writing–original draft, X.J., H.Z., X.C., S.K. and J.X.; Writing–review & editing, All Authors. All authors have read and agreed to the published version of the manuscript.

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