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Review

Non-coding RNAs in aneurysmal aortopathy

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A B S T R A C T

Aortic aneurysms represent a major public health burden, and currently have no medical treatment options. The pathophysiology behind these aneurysms is complex and variable, depending on location and underlying cause, and generally involves progressive dysfunction of all elements of the aortic wall. Changes in smooth muscle behavior, endothelial signaling, extracellular matrix remodeling, and to a variable extent inflammatory signaling and cells, all contribute to the dilation of the aorta, ultimately resulting in high mortality and morbidity events including dissection and rupture. A large number of researchers have identified non-coding RNAs as crucial regulators of aortic aneurysm development, both in humans and in animal models. While most work to-date has focused on microRNAs, intriguing information has also begun to emerge regarding the role of long-non-coding RNAs. This review summarizes the currently available data regarding the involvement of non-coding RNAs in aneurysmal aortopathies. Going forward, these represent key potential therapeutic targets that might be leveraged in the future to slow or prevent aortic aneurysm formation, progression and rupture.

1. Introduction – the impact of aortic aneurysm

Aortic aneurysms are typically defined as a focal dilation of > 50% above normal diameter, and can occur in the thorax, but have their highest incidence in the infrarenal abdominal aorta. Abdominal aortic aneurysms (AAA) have a set of well-defined risk factors, including age, male sex, tobacco use, family history, obesity and hypertension [1, 2]. AAA are common in Western populations, particularly in men over age 65. A meta-analysis by Li et al. yielded a pooled prevalence of 4.8% (6% male, 1.6% female) [3]. In contrast, thoracic aortic aneurysm disease (TAAD) origin is more dependent on age group. While most cases are sporadic, numerous heritable sources of TAAD exist, including several syndromic forms (e.g. Marfan, Loeys-Dietz and vascular Ehlers-Danlos). Notably, at least 20% of non-syndromic TAAD cases appear to be familial [4].

The most feared complications of aortic aneurysm are dissection and rupture, particularly given that aneurysms are nearly always asymptomatic [5]. Although rare, AAA rupture mortality is approximately 80% [6]. TAA dissection has an incidence of 6/100,000 persons per year [7]. Further, complications of aortic aneurysms are collectively responsible for as many as ~50,000 U.S. deaths each year [4, 8], and the Global Burden Disease 2010 project suggested an overall global death rate of 2.78 deaths/100,000 inhabitants [7].

To date, no effective medical therapy is known to prevent progression or rupture in aneurysm patients, leaving only surgical options including open and endovascular repair [9]. These procedures carry significant risk, even when performed electively. As an example, elective ascending/root replacement carries a surgical mortality of ~1.6–4.8% [10]. While endovascular stent grafts for AAA have fewer up-front complications, these devices fail to limit progressive wall expansion and are associated with high morbidity [11]. Stent grafts experience endoleak complications in 10–30% of patients [12, 13], resulting in secondary interventions (20%) or explantation (8%). Furthermore, endovascular stent grafting insufficiently halts aneurysm growth in nearly 40% of patients [14]. Accordingly, numerous investigators have sought to identify effective treatments for aneurysm prevention and mitigation [9, 15, 16].

Considerable work to-date has focused on the important and defining roles played by non-coding RNAs in aneurysm pathogenesis, both to improve understanding of the underlying biological processes involved, and to explore their potential as therapeutic agents and targets.

2. MicroRNAs and long non-coding RNAs

Non-coding RNAs are transcribed but not translated into protein. While there are several subclasses, this review will focus on two primary groups: the comparatively well-explored microRNAs (miRs), and the less-understood long-non-coding RNAs (lncRNAs). MiRs are small and single stranded, usually ~22 nucleotides in length, and generally repress the expression of messenger RNAs (mRNAs) by binding to

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Table 1
Non-coding RNAs involved in aortic aneurysms.

Non-coding RNAs	Related disease	Cell types	Targets & signaling	Change in disease	Proposed Action flow	Therapeutic indication	References
miR-15	AAA	VSMC	CDKN2B, Bcl-2, p53 and TGF-β signaling	↑	miR-15↑–CDKN2B/Bcl-2↓–TGF-β signaling?, p53-dependent apoptosis?	Unclear, not yet tested.	[66–67]
miR-21	AAA	VSMC	PTEN, BCL2, SPRY1, PDCD4, AKT and NFκB signaling	↑	miR-21↑–PTEN↓–AKT↑, apoptosis↓, proliferation↑	Overexpression of miR-21 limits growth of AAA	[22, 74–79]
miR-26a	AAA	VSMC	SMAD1, SMAD4, TGF-β signaling	↓	miR-26a↓–SMAD1, SMAD4↑–TGF-β signaling↑, apoptosis↓, proliferation↑	Inhibition of miR-26 may be beneficial for AAA, not yet tested.	[80]
miR-129-5p	AAA	VSMC	Wnt5a, SOX4, Wnt/β-catenin pathway	↓	miR-129-5p↓–Wnt5a↑–proliferation↑, apoptosis↓	Inhibition of miR-129-5p may be beneficial for AAA, not yet tested.	[81–85]
miR-143/145	TAA, TAD, AAA	VSMC	Klf4/5, myocardin, MRTFA, Elk-1, SRF, p38/MAPK signaling	↓	miR-143/145↓–p38/MAPK signaling↓–proliferation↓, apoptosis↑	Overexpression of miR-145 inhibits AAA incidence and maximum diameter.	[65, 86–93]
miR-504	AAA	VSMC	p53, p53 signaling	↓	miR-504↓–p53↑–proliferation↓, apoptosis↑	Overexpression of miR-504 may prevent AAA, not yet tested.	[95]
miR-516a	AAA	VSMC	MTHFR, MMP2, TIMP1	↑	miR-516↑–MTHFR↓–medial arterial elastin↓, homocysteine↑	Inhibition of miR-516 may be beneficial for AAA, not yet tested.	[96–98]
miR-126	AAA, TAA	EC	VCAM-1, RGS16	↑	miR-126↑–VCAM-1↓, RGS16↓–leukocyte adhesion↓, vascular integrity↑	Overexpression of miR-126 may be beneficial for TAA/AAA, not yet tested.	[61, 99–103]
miR-24	AAA	VSMC, macrophage	CHI3L1, NFκB signaling, MAPK pathway	↓	miR-24↓–CHI3L1↑–SMC proliferation↓, apoptosis↑, inflammation↑	Overexpression of miR-24 is beneficial for AAA.	[24, 104–113]
miR-33	AAA	VSMC, macrophage	ABAC1, p38/MAPK signaling	↑	miR-33↑–ABCA1↓–p38/MAPK↑, inflammation↑	Inhibition of miR-33 may be beneficial for AAA, not yet tested.	[114–117]
miR-155	AAA	EC, VSMC, macrophage, leukocyte	CTLA4, SMAD2, BCL-6, Ets-1, MAP3K10	↑	Depends on target genes and cell types	Unclear	[118–122]
miR-103a	AAA	EC	KLF4, ADAM10	↓	miR-103a↓–KLF4↑, ADAM10↑–monocyte-endothelial adhesion↑, pro-inflammatory substrates↑	Overexpression of miR-103A may be beneficial for AAA, not yet tested.	[123–126]
miR-223	AAA	VSMC, macrophage	MMP12, inflammation signaling	↑ in tissue, ↓ in plama	Pro − /anti-inflammation	Unclear	[103, 127–129]
miR-17-family	TAA-bicuspid AV	VSMC	TIMP1, TIMP2	↑	miR-17-family↑– TIMPs↓–MMP2↑–ECM↓	Inhibition of MIR-17-family may be beneficial for TAA, not yet tested.	[131–132]
miR-29	AAA, TAA	Fibroblast, VSMC	COL1A1, COL3A1, COL5A1, ELN, MMP2, MMP9, TGF-β signaling	↓↑?	miR-29↓–COL1A1, COL3A1, COL5A1, ELN, MMP2, MMP9↑–ECM↓, fibrosis↓	Suppression of miR-29 is beneficial for TAA/AAA.	[23, 133–139]
miR-195	AAA	VSMC	COL1A1, COL1A2, COL3A1, FBN1, ELN, MMP2, MMP9	↑	miR-195↑–COL1A1, COL3A1, COL5A1, ELN, MMP9↑ –ECM↓, fibrosis↓, angiogenesis↓	Unclear	[91, 134, 141]
miR-181b	AAA/?TAA	Macrophage, VSMC	TIMP3, ELN	↑	miR-181b↑–TIMP3, ELN↓–MMP↑, ECM↓	Inhibition of miR-181b is beneficial for AAA.	[64]
miR-205/712	AAA	EC, leukocytes	TIMP3, RECK	↑	miR-205/712↑–TIMP3, RECK↓– ECM↓	Inhibition of miR-205/712 is beneficial for AAA.	[63, 142]
HIF1A-AS1	TAAA	Plasma, VSMC	Regulated by BRG1	↑	HIF1A-AS1↑–VSMC proliferation↓, apoptosis↑	Inhibition of HIF1A-AS1 may be beneficial for TAAA, not yet tested.	[146, 147]
LncRNA AK056155	LDS, TAA	PBCEC, HUVEC	AKT/PI3K/TGF-β signaling	↑	AKT/PI3K/TGF-β signaling↑–AK056155↑–LDS, TAA	Inhibition of AK056155 may be beneficial for LDS-TAA, not yet tested.	[148]
lnc-ARG	AAA	–	ALOX5	↓	lnc-ARG↓–ALOX5, ROS production↑	Unclear	[149]

(*continued on next page*)

Table 1 (*continued*)

Non-coding RNAs	Related disease	Cell types	Targets & signaling	Change in disease	Proposed Action flow	Therapeutic indication	References
HOTAIR	TAA	–	–	↓	HOTAIR↓–proliferation↓, apoptosis↑, collagen↓	Overexpression of HOTAIR may be beneficial for AAA, not yet tested.	[150]
Lnc-HLTF-5	TAA	–	–	↑	Positively correlated with hypertension, expanded ascending aortic diameter and MMP9 level	Unclear	[151]

AAA: abdominal aortic aneurysm; TAA: thoracic aortic aneurysm; TAD: thoracic aortic dissection; TAAA thoraco-abdominal aortic aneurysm; LDS: Loeys-Dietz Syndrome; VSMC: vascular smooth muscle cell, EC: endothelial cell; PBCEC: peripheral blood circulating endothelial cell; HUVEC: human umbilical vascular endothelial cell; CDKN2B: Cyclin-dependent kinase inhibitor 2B; PTEN, phosphatase and tensin homolog; BCL2/6: B cell lymphoma 2/6; COL1A1/2, SPRY1: sprouty homolog 1; PDCD4: programmed cell death 4; AKT: Protein Kinase B; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; SMAD: mothers against decapentaplegic homolog; TGF-β: transforming growth factor-β; Wnt5a: Family Member 5A; KLF4, Kruppel-like factor 4; MRTFA: myocardin-related transcription factor-A; ELK1, ETS domain-containing protein; c-kit/SCFR: Mast/stem cell growth factor receptor; MTHFR: methylenetetrahydrofolate reductase; MMP, matrix metalloproteinase; TIMP: metalloproteinase inhibitor; VCAM-1: vascular cell adhesion molecule 1; RGS16: regulator of G-protein signaling 16; CHI3L1: chitinase 3 Like 1; ABCA1: ATP-binding cassette transporter A1; CTLA4: cytotoxic T-lymphocyte associated protein 4; Ets-1: v-ets erythroblastosis virus E26 oncogene homolog 1; MAP3K10: mitogen-activated protein kinase kinase kinase 10; ADAM10: a disintegrin and metalloproteinase 10; COL1A1/2: collagen type 1 alpha 1/2; COL3A1/2, collagen type 3 alpha 1; FBN: fibrillin; ELN, elastin; RECK, reversion-inducing-cysteine-rich protein with kazal motifs; BRG1: Brahma-related gene 1; PI3K: phosphoinositide 3-kinase; ALOX5: 5-lipoxygenase; ECM: extracellular matrix; ROS: reactive oxygen species.

entirely or partially complementary 3′-untranslated regions. Hundreds of different mRNAs may be regulated by a single miR [17–19]. MiRs are integral to nearly all physiological processes, post-transcriptionally modulating perhaps 60% of human protein-coding genes. Many miRs are ubiquitously expressed, while some others exhibit more tissue-specific patterns of expression, including cells relevant to aneurysm such as endothelial cells (ECs), vascular smooth muscle cells (SMCs), and inflammatory cells. Unsurprisingly, miRs have been shown to regulate numerous pathways known to be relevant to cardiovascular pathophysiology, including aortic aneurysms [20–24].

In contrast, lncRNAs are defined as non-coding transcripts > 200 nucleotides in length, and have been found to function in numerous ways to regulate transcription, directing ribonucleoprotein complexes to specific targets through protein binding, acting as molecular decoys and as molecular scaffolds that assemble effectors three-dimensionally within cells [25, 26]. They are also capable of hosting miR transcription [27]. Notably, some transcripts previously identified as purely long non-coding were later found to also be translated [28]. Much less is known regarding the specific role of most lncRNAs, with fewer than 200 to date with characterized human biological functions [29]. They more closely resemble mRNA in their origin and regulation. However, their expression patterns are comparatively much more tissue-specific (estimated at 78%), and nearly always display alternative splicing [30]. Several lncRNAs have been found to regulate epigenetic control of gene expression, particularly during cellular differentiation and organ development. For example, XIST controls inactivation of human X chromosome, while other lncRNAs may perform organizational functions within the nucleus [31].

LncRNAs have been strongly implicated in cancer and neurological disease in humans [32, 33]. However to-date only a small group of lncRNAs have been connected to cardiovascular disease. Examples include MIAT (myocardial infarction associated transcript) at the 22q12 locus, which contains single nucleotide polymorphisms associated with myocardial infarction [34], and ANRIL/CDKN2B-AS1 (9p21.3 locus), strongly associated with coronary artery disease [35]. ANRIL has also been associated with intracranial aneurysms, with proposed mechanisms including regulation of retinoid metabolism, cell cycling, Krüppel-like factor 2 (KLF2), and caspase recruitment domain family member 8 [36]. These mechanisms may imply a role in aortic aneurysm as well. Table 1

3. Aneurysm pathogenesis

As suggested above, the processes that lead to aortic aneurysm formation are complex, and vary depending on underlying conditions, etiology and locations. Preclinical models and human pathological samples have provided a picture of AAA formation and progression that involves local inflammatory processes with chronic adventitial and medial infiltration of monocyte/macrophages, polymorphonuclear leukocytes (PMNs), and lymphocytes, with macrophages and CD4+ T-cells dominating [37–39]. Numerous locally elaborated cytokines/chemokines, including CCL2, IL-6, IL-1β, and TNFα, contribute to this chronic inflammatory state [39]. Inflammatory cell infiltration is accompanied by elastin fragmentation and degeneration, and loss of medial vascular SMC [40]. Proteolytic destruction of the media and supporting adventitia occurs through the degradation of elastin and collagen by cysteine and serine proteases, and matrix metalloproteinases (MMPs), either elaborated by local SMCs/fibroblasts, or by infiltrating macrophages [9, 40, 41]. In animal models, an initial compensatory increase in collagen synthesis [42] is countered by matrix filament cleavage (collagen turnover). Further, in response to pro-aneurysmal stimuli, aortic SMCs de-differentiate towards the proliferative, migratory, and secretory phenotype. Subsequently, SMC dropout due to apoptosis dominates, leading to AAA expansion, and ultimately rupture [43, 44]. Notably, part of the predisposition to AAA in the infrarenal aorta in humans may relate to the absence of significant medial vaso

vasorum below the renal arteries, leading by necessity to a thinner wall to permit tissue oxygenation [45]. Hypoperfusion of adventitial vaso vasorum in AAA may therefore cause hypoxic damage, exacerbating the condition [46].

Thoracic aortic aneurysms in patients over age 65 are generally degenerative, mimicking AAA in terms of risk factors and character, and a significant percentage of patients with this variety of TAA have been found to also have infra-renal AAA. This age group is also more likely to have TAA in association with auto-immune vasculitis [7, 47]. TAA in patients under 65 are more commonly of heritable origin, arising from many underlying conditions, including disorders which affect microfibrils/extracellular matrix proteins or TGF-β signaling (e.g. Marfan syndrome, Loeys-Dietz syndrome), smooth muscle cell protein aortopathies (e.g. mutations in ACTA2, MYH11 or MYLK), or as a complication of bicuspid aortic valve [4, 48–52]. Accordingly, the underlying pathophysiology of TAAD can be quite variable. In general, heritable forms concatenate abnormal TGF-beta signaling, abnormal smooth muscle cell phenotypic switching, contractility and apoptosis, and pathological matrix remodeling [49], while degenerative forms share similar pathways with AAA. The role of TGF-β is somewhat controversial, as decreased canonical signaling is thought to drive thoracic aneurysm formation, while at the same time the disease has been attributed to TGF-β hyperactivity. Recent work suggests that in heritable disease the underlying structure is defective, and it is the SMC response to hemodynamic load that leads to aneurysm formation, with TGF-β overactivity acting as a secondary, ineffective corrective response. Further, abnormalities in actin and related proteins which contribute to SMC cytoskeletal and contractile functions can contribute to TAAD [52]. Other acquired causes of TAA can range from inflammatory vasculitides (e.g. Takayasu's arteritis, giant cell arteritis), to chronic infections such as tertiary syphilis.

The astute observer will note that all of these underlying pathways in the aorta ultimately lead to dysfunctional endothelium, initial SMC de-differentiation and proliferation followed later by apoptosis, elastin breakdown, and adventitial extracellular matrix protein remodeling with luminal enlargement, which together constitute the core features of aortic aneurysm formation despite etiology or location.

Several animal models have been developed to study aortic aneurysm. For AAA, the most frequently employed rodent models involve locally applying external $CaCl_2$ to the infra-renal aorta, short-term intraluminal infra-renal infusion of porcine pancreatic elastase (PPE), or chronic infusion of angiotensin II (AngII) in atherosclerosis model mice (ApoE−/−, or LDLR−/−). Other models include surgical induction, and mice with pro-aneurysmal gene mutations. Some of these methods have been adapted to larger animals such as pigs or sheep [53]. Each model mimics various elements of human disease. Recent work has suggested that classic AngII-infusion, which typically forms supra-renal AAA, may more accurately model dissection rather than standard dilatory progression [54].

Models for studying TAA tend to reflect their heritable causes, including for example mice with mutations in fibrillin-1 for Marfan, or in TGF-β receptors for Loeys-Dietz [55]. Ikonomidis et al. has applied the $CaCl_2$ approach to descending thoracic aorta in mice [56], and variants of the AngII-infusion approach have also been used to study TAA [57].

4. miRNA and aortic aneurysm

MicroRNAs are now relatively established as having crucial roles in vascular homeostasis and pathobiology, including aortic aneurysm. As one example, SMC-specific Dicer (involved in mature miR production) is required for vessel development and maintenance of post-natal SMC differentiation [58, 59]. MicroRNAs have also been shown to regulate numerous elements known to be related to aneurysm biology, such as EC function, TGF-β signaling, inflammatory signaling, SMC phenotypic switching, matrix production and remodeling, and crosstalk between these elements [20–24, 38, 60]. Many miRs are differentially regulated in aneurysm tissues in humans and animal models. Some studies have attempted to identify unique AAA vs. TAA microRNA signatures from human aneurysmal tissue, suggesting for example that miR-221 is uniquely upregulated in human TAA, while miR-146a is only upregulated in AAA specimens [61]. Intriguingly, some miRs may be sensitive to SMC actin-polymerization state and regulation, which alter with aneurysm development [62]. Further, several miRs have been directly assessed for their potential therapeutic capabilities in aortic aneurysm, such as miR-21, miR-24, miR-29b, miR-145, miR-181b, and miR-205(human)/miR-712(murine) [22–24, 63–65]. While the impact of miR regulation on aneurysm-specific tissues and cell subtypes has been demonstrated, their typically ubiquitous expression (with some exceptions, like miR-126) and multiple targets can make it difficult to exclude potential off-target effects on non-related cells, or additional signaling pathways in vivo.

4.1. miRNA - regulators of aortic SMCs

4.1.1. miR-15

In general, SMC proliferation as an early (and potentially protective) response to aortic aneurysmal stimuli gives way over time to apoptosis and dropout, and tilting this balance could alter disease progression. Members of the miR-15a/16 cluster are generally thought to be pro-apoptotic tumor suppressors in mammals, capable of triggering apoptosis cascades, primarily through inhibition of Bcl-2 and Bcl-xl [66]. CDKN2B, thought to be involved in SMC apoptosis, was also found to be directly targeted by miR-15a-5p [67]. SMCs isolated from human AAA tissue showed upregulation of miR-15a-5p and downregulation of CDKN2B gene expression and protein, with inverse regulation of the two during in vitro transfection studies. Confusingly, in these experiments, miR-15a-5p mimic promoted SMC viability and lowered apoptosis, with the reverse seen for antagomir. However, the study did not appear to directly test whether the observed effects of miR-15a on SMC viability were specifically mediated through CDKN2B, nor were they tested in vivo [67]. Notably, CDKN2B signaling is also complex and controversial, and as mentioned above is associated with elaboration of a lncRNA from the 9p21 locus. Some work suggests that loss of CDKN2B may impair TGF-β signaling, and promote aortic aneurysm formation while stimulating p53-dependent SMC apoptosis [68, 69]. While the role of TGF-β in aortic aneurysm is also complex, recent work suggests that proper functioning of canonical TGF-β signaling is critical for the protection of aortic SMC and tissues from pro-aneurysmal factors and pathways [70–73]. Given the variable effects of miR-15 on these pathways, it is difficult to predict its potential impact if modulated in vivo.

4.1.2. miR-21

Our lab identified miR-21 as a crucial factor in regulating SMC phenotype during AAA pathogenesis [22]. MiR-21 was already known to be highly expressed in SMC, and to target genes related to SMC apoptosis, contractile function and proliferation including phosphatase and tensin homolog (PTEN), B cell lymphoma 2 (BCL-2), and sprouty homolog 1 (SPRY1) [74–76]. Also, TGF-β and BMP signaling had been found to rapidly upregulate mature SMC miR-21, which then downregulated programmed cell death 4 (PDCD4), permitting SMC contractile gene expression [77, 78]. MiR-21 regulates neointimal hyperplasia after vascular injury, promoting proliferation and decreasing apoptosis, and its suppression prevents luminal obliteration in models of carotid injury and in-stent restenosis [74, 79]. We found that miR-21 was significantly upregulated in AAA tissue in both the AngII-ApoE−/− and the PPE model, as well as in human AAA tissue (vs. non-aneurysmal controls) [22]. This correlated with inverse regulation of PTEN in vivo. Systemic locked nucleic acid (LNA)–modified anti-miR-21 markedly increased aortic aneurysm progression in both murine models, accompanied by the expected changes in PTEN, and showing increased SMC apoptosis with decreased proliferation. The reverse was

observed with lentiviral overexpression of miR-21, with substantial reduction in murine AAA in vivo, and increased phosphorylation and activation of AKT in SMC in vitro. Notably, miR-21 was inducible via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in SMC after treatment with nicotine, IL-6 and AngII. Overall, the data obtained indicated that up-regulation of miR-21 is a physiological response to aneurysm development, one that was augmented in the presence of a deleterious stimulus (e.g. nicotine), but in which the endogenous induction was insufficient to prevent AAA. However, overexpression of miR-21 did limit aortic growth, suggesting that it could be a potential therapeutic target.

4.1.3. miR-26a

We profiled microRNA in aortic SMC during differentiation, yielding miR-26a as significantly upregulated, and showed in vitro that anti-miR-26a transfection accelerated the appearance of SMC differentiation markers, reduced proliferation and migration, and increased H_2O_2-induced apoptosis [80]. MiR-26a was significantly and progressively down-regulated in AAA in both the AngII/ApoE−/− and the PPE murine models. Overexpressed mir-26a regulated the TGF-β signaling cascade by directly targeting SMAD1 and SMAD4 in SMC. We therefore posited that miR-26a might be both a key regulator of SMC biology, and a therapeutic target in AAA, although the latter has not yet been tested. Given miR-26a inhibition might increase TGF-β signaling and reverse SMC de-differentiation, but also lower proliferation and increase apoptosis, the impact if modulated in vivo is difficult to predict.

4.1.4. miR-129-5p

Another miR which appears to regulate SMC apoptosis and proliferation is miR-129-5p, which Zhang et al. found by microarray to be the most down-regulated in AAA tissue obtained from an unusual composite model involving PPE infusion of male ApoE−/− mice [81]. Transfection of miR-129-5p into human SMCs inhibited proliferation and induced apoptosis, suggesting that blockade might be beneficial in vivo. A bioinformatic approach yielded a potential target (Wnt5a) which was confirmed by luciferase assay, and overexpression of Wnt5a blunted the impact of miR-129-5p on cellular proliferation. Notably, this miR has also been found to inhibit cellular proliferation in cancer cells by targeting ETS1 [82], as well as the SOX4/Wnt/β-catenin pathway [83]. The cancer literature suggests that at least two lncRNA (MALAT1 and NEAT) may alter tumor cell proliferation by targeting miR-129-5p [84, 85]. The effect of modulating this miR in AAA remains to be investigated.

4.1.5. miR-143/145

Arterial SMC differentiation relies on expression of the miR-143/145 cluster, which is transcribed as a bi-cistronic transcript from a common promoter, and is regulated by serum response factor, myocardin, and myocardin-related transcription factor-A [86]. The cluster targets multiple transcription factors (e.g. KLF4, KLF5, and ELK-1), and cluster downregulation leads to increased levels of PDGF receptor, protein kinase C epsilon, and fascin (an actin bundling protein of podosomes) [87–90]. These last appear necessary for vascular wall matrix remodeling, with potential to affect aneurysm progression. Together, miR-143 and -145 promote differentiation, suppress proliferation, and increase contractile gene expression, and are is strongly down-regulated in the context of vascular injury [86–89]. One of the earliest reports examining miRs in aneurysm found that miR-143/145 are reduced in human TAA (later confirmed by Liao et al. [91]), promoting SMC phenotypic switching/de-differentiation [92]. Also, loss of miR-143 and miR-145 expression in knockout mice led to incomplete aortic SMC differentiation with resultant structural modifications.

Recent work has shown the miR-143/145 cluster is also downregulated in ascending TAA dissection, and that AngII, which is elevated in the serum of ascending TAA dissection patients, downregulates the cluster in SMC, a process mediated by the p38/MAPK signaling pathway [93]. Another study found that lentiviral overexpression of miR-145 in the AngII/ApoE−/− model inhibited AAA incidence and maximum diameter, reduced degradation of elastin, and downregulated MMP2 expression and activation in vivo [65]. That study also found that miR-145 suppressed MMP2 response to AngII in SMC in vitro.

As a side-note, miR-663 (which we found to be the most upregulated miR during in vitro aortic SMC differentiation), has now been found by another group to promote SMC differentiation and inhibit proliferation and migration in a manner similar to miR-143/145 [80, 94]. It targets the transcription factor JunB, and decreased downstream myosin light chain 9 and MMP9. MiR-663 was down-regulated in aortic SMC in vitro by platelet-derived growth factor, and miR-663 mimic also suppressed neointimal formation after murine vascular injury. While not yet studied in aortic aneurysm, miR-663's similarities to miR-143/145 make it attractive for future work.

4.1.6. miR-504

A recent publication utilized a miR PCR array and found that miR-504, which targets the tumor suppressor p53, was downregulated in human AAA SMC compared with control cells [95]. They obtained overexpression in SMC using transfection with a pMSCV-miR-504 vector, and found upregulation of proliferating cell nuclear antigen (PCNA), replication factor C subunit 4 (RFC4), and B-cell lymphoma-2 (Bcl-2) with inhibition of caspase-3/9 and p53, as well as increased SMC proliferation. Downstream molecules in the p53 pathway such as p21 and Bcl-like protein-4 were also suppressed. Taken together, the data suggest that miR-504 may have an anti-apoptotic/pro-proliferative effect on SMC in AAA. Our previous miR-21 results suggest that this would be protective against aneurysm progression.

4.1.7. miR-516a-5p

In similar work, Chan et al. mined microarray profiling of human AAA SMC and identified upregulated miR-516a-5p. They subsequently used SMC explant cultures from human AAA to show that a key regulator of homocysteine metabolism and potential risk gene for AAA (methylenetetrahydrofolate reductase – MTHFR) was directly targeted by miR-516a-5p [96]. Previous work with MTHFR-deficient mice had shown decreased medial arterial elastin, and homocysteine is elevated in AAA patients [97, 98]. Chan et al. found that overexpression of miR-516a-5p in these cells led to increased MMP-2 and decreased TIMP-1 expression, intimating that this miR may increase homocysteine and promote elastin degradation in AAA [96].

4.2. miRNA - aortic inflammation and endothelial regulation

4.2.1. miR-126

Endothelial cells act as a natural barrier between aortic tissues and the bloodstream, maintaining hemostasis and helping to regulate vascular tone, angiogenesis and inflammation. In the aorta, they operate both at the luminal interface and within the vaso vasorum. MiR-126 appears to be unique to the endothelium, mediates developmental angiogenesis and vascular integrity in vivo, and directly targets and suppresses the adhesion molecule VCAM-1 (a known mediator of vascular inflammation), preventing leukocyte adhesion [99–101]. MiR-126 also contributes to atherosclerotic plaque stabilization through its inhibition of “regulator of G-protein signaling 16” (RGS16) [102]. Kin et al. found that miR-126 was upregulated in human AAA tissue, and was negatively correlated with local TNFα protein levels [103]. It has also been found to be upregulated in TAA tissue [61]. Given its protective role as regards endothelial inflammation, overexpression of

miR-126 might be a valid therapeutic approach for aortic aneurysm.

4.2.2. miR-24

Inflammation and immune cell response are crucial aspects of aortic aneurysm development and dissection. These complex pathways are regulated by multiple miRs, including the miR-23b-24-27b cluster, which is also involved in angiogenesis, atherosclerosis, cancer, and cardiomyocyte survival [104–106]. This cluster regulates the NF-κB pathway in macrophages in response to oxidative stress [107]. MiR-24 is also involved in a multi-factor inflammatory feedback loop in tumor cells [108], negatively regulates classical macrophage activation, and promotes alternative activation [109]. MiR-24 overexpression attenuates phagocytosis and cytokine release by myeloid inflammatory cells [110]. Together, miR-24 and miR-27 suppress allergic inflammation by inhibiting Th2 cell differentiation in primary T-cells, targeting a network of genes that together limit IL-4 production [111].

We identified miR-24 as a crucial regulator of inflammation and pathogenesis in AAA [24]. The cluster as a group was down-regulated in two murine AAA models, with miR-24 showing the most widespread inverse expression correlation with predicted gene targets. MiR-24 was also downregulated in human AAA vs. organ donor controls, and inversely correlated with aneurysm size. Examining potential targets we identified CHI3L1/Chil1, an inflammatory mediator secreted by macrophages in early atherosclerosis which modulates SMC migration and proliferation, as a strong potential effector in aneurysm [112]. We showed that inflammatory stimuli downregulate miR-24 in macrophages and aortic SMCs, at least partly via NF-κB, and that loss of miR-24 in turn up-regulates inflammation and other critical aneurysm-related processes in a CHI3L1-dependent fashion in M1-subtype macrophages, aortic SMC and vascular EC. Further, we showed that systemic lentiviral miR-24 mimic attenuated AAA development and inflammation in both murine models, while miR-24 antagomiR accomplished the reverse. Jingjing et al. recently showed miR-24 encourages macrophage polarization towards the anti-inflammatory M2 phenotype and away from the pro-inflammatory M1 phenotype, and that these too are mediated by CHI3L1 and MAPK pathway inhibition [113].

4.2.3. miR-33

MiR-33 regulates adipogenesis, but is also found in vascular SMC and macrophages. Studies suggest that inhibition of miR-33 leads to increased serum high-density lipoprotein cholesterol, M2 rather than M1 macrophage polarization, and less atherosclerosis in model mice [114–116]. MiR-33 targets ATP-binding cassette transporter A1 (ABCA1), which itself down-regulates c-Jun N-terminal kinase and p38 MAPK. Very recently, Nakao et al. found a gradient of miR-33a-5p expression in human AAA, with higher levels in the central region than at the margins [117]. Using murine AAA models (AngII/ApoE−/− and $CaCl_2$), they showed that genetic deletion of miR-33 attenuated AAA development and reduced fatal rupture, with decreased monocyte chemotactic protein-1 (MCP-1) cytokine and macrophages in the aortic wall. In vitro, miR-33-knockout (KO) SMC showed decreased MCP-1 expression, while KO peritoneal macrophages had decreased MMP9 expression. Also seen in vivo was an augmented anti-inflammatory effect of high-density lipoprotein from miR-33-KO mice.

4.2.4. miR-155

The role of miR-155 in vascular inflammation is complicated. MiR-155 regulates the behavior of numerous cells involved in aneurysm formation, including endothelial cells, macrophages, SMCs, and leukocytes [118]. It is broadly expressed in various tissues and cells, but is overexpressed in AAA tissue and AAA patient serum [119], and has been proposed to promote chronic inflammation by targeting cytotoxic T-lymphocyte associated protein 4 (CTLA4), while blocking expression of SMAD2 protein (interrupting TGF-β signaling) – suggesting that it might be pro-aneurysmal. Nazari-Jahantigh et al.'s work with miR-155 in macrophages implied that it is a key inducer of atherosclerosis development, promoting the expression of MCP-1 and directly suppressing Bcl-6 (a transcription factor that inhibits NF-κB) [120]. It has also been reported that miR-155 is induced in vascular cells by the cytokine TNF-α and by AngII.

However miR-155 targets the transcription factor v-ets erythroblastosis virus E26 oncogene homolog 1 (Ets-1) in ECs, leading to down-regulation of downstream VCAM1, MCP1 and FLT1, which are thought to be pro-aneurysmal factors [121]. In that study miR-155 also targeted endothelial AngII type 1 receptor, and inhibited binding of Jurkat T cells to endothelial cells, suggesting that it suppresses vascular inflammation. A separate publication proposed that miR-155 is part of a negative feedback loop which decreases inflammatory cytokines and atherosclerosis progression, targeting mitogen-activated protein kinase kinase kinase 10 (MAP3K10) [122]. Given these apparently contradictory results, it is unclear to-date what specific role miR-155 might play in aortic aneurysm [118].

4.2.5. miR-103a

Like miR-155, miR-103 (a member of the miR-15/107 family) is thought to be involved in several diseases including myocardial infarct, diabetes and cancer, and also vascular inflammation, specifically by mediating endothelial dysregulation in atherosclerosis. It suppresses KLF4, increases monocyte-endothelial adhesion by increasing CXCL1 expression, and inhibiting miR-103 reduces lesion buildup [123]. In a recent manuscript Jiao et al. found that miR-103a directly targets “a disintegrin and metalloproteinase 10” (ADAM10), a tobacco-smoke-responsive protease involved in the shedding of pro-inflammatory substrates (e.g. IL6-Receptor, TNFα, CX3CL1, CD44 and VE-cadherin), and which appears to contribute to both AAA and TAA formation [124–126]. The authors also found that ADAM10 was increased in murine AAA samples, while miR-103a was decreased, and posited that miR-103a might inhibit aneurysm formation by limiting aortic wall inflammation.

4.2.6. miR-223

MiR-223, the most abundant miR in peripheral blood microvesicles and a so-called “oncomiR”, has also been linked to aortic aneurysm formation via inflammation, albeit indirectly [127, 128]. This conserved miR modulates differentiation of the hematopoietic lineage, specifically monocyte/macrophages, and has a role in atherosclerosis and vascular calcification [127]. While it has been proposed to be anti-inflammatory for its role in inhibiting formation of the inflammasome and IL1-β, it also may augment inflammation by increasing IL-17 in lymphocytes, and appears to promote inflammation in forms of arthritis. Overexpression of miR-223 in SMC also increases proliferation and migration [129]. In patients with AAA, miR-223 was significantly upregulated in diseased aortic tissue (negatively correlated with local MCP-1 and TNFα protein levels), but was decreased in plasma samples [103].

4.3. miRNA-aortic extracellular matrix

Modification and remodeling of the aortic extracellular matrix (ECM) is a crucial element in aneurysm development. Matrix metalloproteases (which are produced by macrophages and other cell types and which are elaborated during aneurysm formation) can assist with vascular repair, but also can destabilize and deplete both adventitia and mural matrix, altering local cellular behavior. Signaling pathways and molecules, including JAK/Stat, AMPKα2, osteopontin and JNK can activate MMPs, which then target collagens, elastin, and matrix proteoglycans and glycoproteins. Data also suggest that specific MMPs may dominate in different regions of the aorta [130]. Partially balancing these forces are tissue inhibitors of metalloproteases (TIMPs) and fibroblast/SMC elaboration of new elastin and collagens.

4.3.1. miR-17-family

Bicuspid aortic valve (BAV, the most common congenital heart defect in the developed world) is known to be associated with risk of ascending TAA. The etiology is not well understood, although hemodynamic/flow-related factors may be partly responsible. Some research suggests elements of related connective tissue disease with genetic aspects [131]. Wu et al. found that a cluster of miR-17-related miRs were increased in human BAV-patient ascending aortic regions that were mildly dilated when compared with severely dilated regions from the same patient or from normal regions [132]. These changes were associated with increased MMP2 activity and decreased levels of TIMPs-1, -2 and -3, and they hypothesized that these regions were undergoing ECM breakdown. They found that miR-17 directly suppressed TIMP-1 and -2, and showed that this led to increased MMP2 activity in vitro in SMCs, suggesting a potential role for this cluster in BAV-associated TAA formation, and implying that miR-17-related miRs might be potential targets to prevent TAA development.

4.3.2. miR-29

The miR-29 family members (29a, 29b, and 29c) target dozens of collagen isoforms and ECM structural protein subtypes, including COL1A1, COL1A2, COL3A1, elastin and fibrillin-1. Elaborated primarily by fibroblasts in the aorta, they are also capable of regulating fibrotic processes in various other organs [23, 133]. Suppression of miR-29 typically leads to aggressive fibrosis, which is often pathological in the heart, lungs, kidneys and liver, but because aortic aneurysm development involves ECM breakdown this process can instead lend stabilization. We found that miR-29b in particular has a key role in AAA, showing that it alone of the family was consistently decreased in AAA tissue in two mouse models and in human AAA specimens (vs. non-aneurysmal organ donor controls), presumably as a protective response (albeit endogenously insufficient) to limit aneurysm growth [23]. Systemic antagomiR suppressed aortic miR-29b, increasing expression of collagen and elastin genes, and decreasing AAA growth in the mouse models. Lentiviral miR-29b mimic led to adventitial thinning, rapid aneurysm expansion and increased rupture rates. The antagomiR effect was later confirmed by Zampetaki et al. in the AngII-ApoE−/− model [134]. We also found that repression of miR-29b led to down-regulation of MMP-2 and MMP-9 expression and activity in vitro and in vivo, while the reverse was found with overexpression [23].

MiR-29 has also been studied in the context of TAA. Jones et al. suggested that miR-29a was involved in ascending TAA development, finding it was suppressed in human TAA compared to normal specimens, but was inversely related to MMP-2 levels [135]. Another study examined miR-29 and aortic aneurysm in aging, finding that aged mice (18 months) showed increased aortic expression of miR-29 family members (vs. 6-week old), accompanied by downregulation of ECM structural elements [136]. They further found that human TAA tissues in both bicuspid and tricuspid aortic valve patients showed increased expression of miR-29b (specifically, and not miR-29a or 29c). It is unclear why the two TAA studies showed differing directions for human expression of miR-29 subtypes, although it might in part be related to age differences in control vs. TAA samples between the studies, methodologic variables, or other factors. As in our study, Boon et al. found that systemic LNA-modified anti-miR-29b decreased supra-renal aortic dilatation in aged AngII-treated mice, again accompanied by increased expression of ECM structural proteins [136].

As mentioned above, TGF-β is a key regulator of aortic aneurysm, particularly in heritable forms of TAA. TGF-β also increases fibrosis, in part due to its ability to suppress miR-29b [23, 137]. Merk et al. found that miR-29b is involved in early aneurysm development in a murine model of Marfan syndrome [138], with increased expression in ascending TAA. LNA-anti-miR-29b prevented TAA development, increased ECM protein levels and decreased local cellular apoptosis in the aortic root. In a follow-up study, the same lab showed that miR-29b blockade did not slow aortic growth in $Fbn1^{C1039G/+}$Marfan mice once aneurysms had already developed. However, prenatal miR-29b suppression was effective in decreasing ascending TAA up to 32 weeks of age, while postnatal weekly injections of LNA-anti-miR-29b continued to be protective out to 16 weeks [139].

4.3.3. miR-195

Like miR-29, miR-195 (a member of the miR-15 family) has been found to target elastin and numerous other ECM structural elements – including collagens, proteoglycans, and microfibrillar proteins – albeit not as strongly as miR-29b [134]. It has also been found to be down-regulated in tissue from human thoracic aortic dissections when compared with normal aorta [91]. Interestingly, miR-195 was the only member of its family to be increased in AAA tissue from AngII-ApoE−/− mice [134]. Also, it was inversely correlated in human plasma with the presence of AAA and aortic diameter. Unfortunately, in vivo inhibition of miR-195 in AngII-ApoE−/− mice did not abrogate disease, despite clear suppression of miR-195 in the aorta with correlating increases in expression of elastin and collagens. In those experiments, immunohistochemistry showed increased MMP9 expression in anti-miR-195 transfected aortae. Notably, miR-195 may suppress angiogenesis. As angiogenesis inhibition is believed to limit AAA progression, this might have undermined the treatment's effectiveness [140, 141].

4.3.4. miR-181b

MicroRNA-181b targets and represses macrophage TIMP-3 and elastin. Recent work has shown that miR-181b is upregulated in human AAA, correlating with decreased expression of its targets [64]. Systemic administration of LNA-anti-miR-181b in atherosclerotic mouse models (ApoE−/− and Ldlr−/−) suppressed plaque formation, and attenuated aneurysm growth in multiple locations with AngII infusion, including in the thoracic aorta. This was accompanied by a fibrotic response, with large increases in expression of collagen and elastin and prevention of elastic lamellar fragmentation. The majority of this impact appeared to result from TIMP3 de-repression, as suggested by Timp3−/− validation experiments. However, anti-miR-181b decreased mortality in Timp3−/−/ApoE−/− mice subjected to AngII, possibly via increased elastin expression. Further, miR-181b inhibition appeared to mitigate progression of pre-existing AngII-induced AAAs in the model mice [64]. The authors suggested that the cytokine GM-CSF may play a prominent role in aneurysm formation by augmenting miR-181b.

4.3.5. miR-205/712

Intriguingly, a similar mechanism may be at work for miR-205 and miR-712. These two miRs are potential homologs, and target the same seed sequence. Both miRs are mechanosensitive/flow-induced [142]. Human miR-205 was upregulated in human AAA vs. normal aorta. Murine miR-712 and human miR-205 were induced by AngII in aortic endothelium in vitro and in aortic tissue, and were also found to target TIMP3. Additionally, they directly targeted the MMP inhibitor RECK (reversion-inducing cysteine-rich protein with Kazal motifs). Anti-miR-based suppression of miR-205 and miR-712 limited aortic inflammation, decreased MMP activity, and prevented AAA formation in the AngII-ApoE−/− model [63].

5. lncRNA and aortic aneurysm

As mentioned above, the field of lncRNA is still somewhat nascent, and specific roles for most transcripts have yet to be identified. While several lncRNA have been proposed to have roles in SMC proliferation and apoptosis as well as in inflammatory regulation (e.g. ANRIL, RNCR3, H19, lnc-Ang362, SENCR, lnc-MEG3, MYOSLID, THRIL, PACER), direct links for the majority of these to aneurysm pathophysiology have not yet been made [143, 144].

The first study linking lncRNA to aneurysm formation was

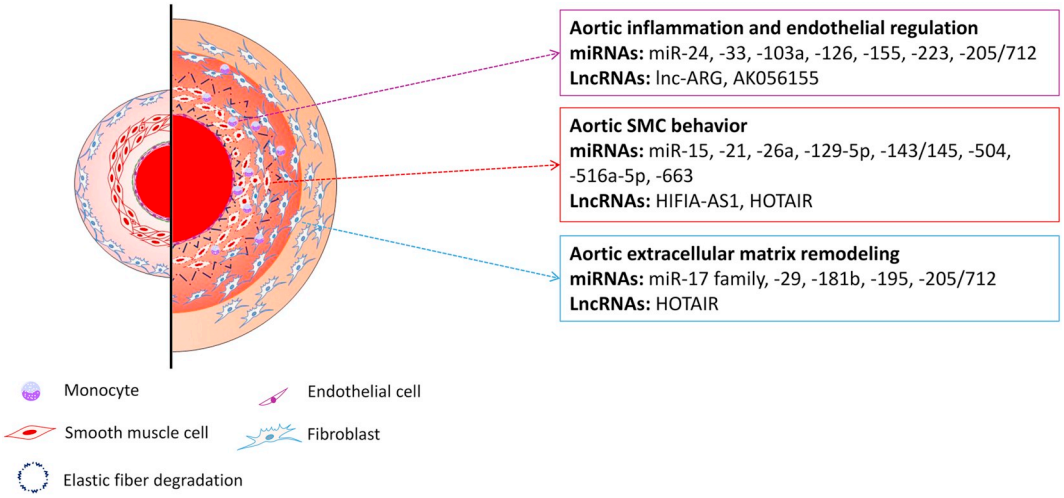

Fig. 1. Non-coding RNAs affect aortic cells and pathways involved in aneurysm pathogenesis.

performed by Falak, et al. in 2014 [145]. They identified protease inhibitor 15 (Pi15) as a candidate gene for the risk of abdominal aortic internal elastic laminal ruptures in rats. Within the linkage region of Pi15 is a putative lncRNA, which has yet to be functionally validated. The lncRNA HIF1 alpha-antisense RNA 1 (HIF1A-AS1) was found to be elevated in serum of thoraco-abdominal aortic aneurysm (TAAA) patients [146]. Its expression seemed to be regulated by Brahma-related gene 1 (BRG1), whose level is significantly increased in TAAAs. Suppression of HIF1A-AS1 by siRNA in vascular SMCs resulted in reduced apoptosis and promoted proliferation [147]. LncRNA AK056155 was increased in Loeys-Dietz syndrome (LDS), an autosomal dominant genetic connective tissue disorder which leads to arterial tortuosity and fragility and typically features ascending TAA. In LDS, this lncRNA correlated with AKT/PI3K/TGF-β signaling [148]. Recent microarray data revealed that lnc-ARG correlates with 5-lipoxygenase (ALOX5) expression in AAA [149]. Another lncRNA termed HOTAIR was found to be significantly decreased in sporadic TAA specimens, where it negatively correlated with aortic diameter [150]. Knockdown of HOTAIR induced cell apoptosis and reduced proliferation, while decreasing collagen type I and III expression. In addition, Li et al. very recently discovered that most differentially expressed lncRNAs in TAA were sense-overlapping, and that expression of lnc-HLTF-5 correlated with hypertension, increased ascending aortic diameter, and MMP9 level [151]. However, none of the studies mentioned above have performed functional in vivo validation, or fully dissected the molecular mechanisms of action for the lncRNAs in question. Future investigations will determine whether lncRNAs are as crucial to aneurysm development and progression as miRs. Fig. 1.

6. Summary and perspective

The lack of pharmacological approaches to limit aneurysm progression and rupture mandates improved understanding of the pathogenesis and cellular mechanisms of aneurysm development. As suggested above, aneurysm formation is a complex process, involving all vascular cell subtypes [37] and numerous non-coding RNA regulatory networks. How to assemble the data and tease out the most effective and feasible therapeutic targets remains challenging. Systematic and integrative analysis [152, 153] will likely be required. Notably, the regulatory effects of miRs are ubiquitous due to their generally wide expression and multiple targets. Thus, the utilization of local delivery tools has been discussed intensively and is under current investigation by our labs and others [154]. Local delivery into the vasculature and diseased aorta may be feasible using drug eluting stents and balloons, enabling miR-based therapies and avoiding off-target effects [79]. Several miRs when modulated (e.g. miR-21, miR-24, miR-29b, miR-33, miR-145, miR-181b, miR-205/712) have already displayed the capability of altering disease progression in pre-clinical animal models, and would therefore likely be the best current candidates for pharmaceutical development. Additionally, pro-aneurysmal miRs found to have particularly high/elevated expression levels in aneurysmal tissue (e.g. miR-33, miR-181b, miR-205/712, miR-516a-5p) might represent more effective targets for suppressive drug therapies. Similar criteria and delivery systems could be applicable to lncRNA-based therapies, although lncRNAs seem more tissue/development/disease-specifically expressed, which makes their modulation enticing for therapeutic purposes.

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