Discoveries

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Involvement of Myeloid Cells and Noncoding RNA in Abdominal Aortic Aneurysm Disease

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Abstract

Significance: Abdominal aortic aneurysm (AAA) is a potentially fatal condition, featuring the possibility of high-mortality rupture. To date, prophylactic surgery by means of open surgical repair or endovascular aortic repair at specific thresholds is considered standard therapy. Both surgical options hold different risk profiles of short- and long-term morbidity and mortality. Targeting early stages of AAA development to decelerate disease progression is desirable.

Recent Advances: Understanding the pathomechanisms that initiate formation, maintain growth, and promote rupture of AAA is crucial to developing new medical therapeutic options. Inflammatory cells, in particular macrophages, have been investigated for their contribution to AAA disease for decades, whereas evidence on lymphocytes, mast cells, and neutrophils is sparse. Recently, there has been increasing interest in noncoding RNAs (ncRNAs) and their involvement in disease development, including AAA.

Critical Issues: The current evidence on myeloid cells and ncRNAs in AAA largely originates from small animal models, making clinical extrapolation difficult. Although it is feasible to collect surgical human AAA samples, these tissues reflect end-stage disease, preventing examination of critical mechanisms behind early AAA formation.

Future Directions: Gaining more insight into how myeloid cells and ncRNAs contribute to AAA disease, particularly in early stages, might suggest nonsurgical AAA treatment options. The utilization of large animal models might be helpful in this context to help bridge translational results to humans. *Antioxid. Redox Signal.* 33, 602–620.

Introduction

THE PREVALENCE OF UNHEALTHY DIETS, smoking, and inactive lifestyles in conjunction with an aging society has laid the cornerstones for cardiovascular diseases being a major public health burden in the developed world. Whereas atherosclerotic changes in arterial walls cause plaque formation and narrowing of the lumen, associated mechanisms may promote dilation at susceptible sites of the arterial tree. Arterial enlargement over 150% of the norm is defined an aneu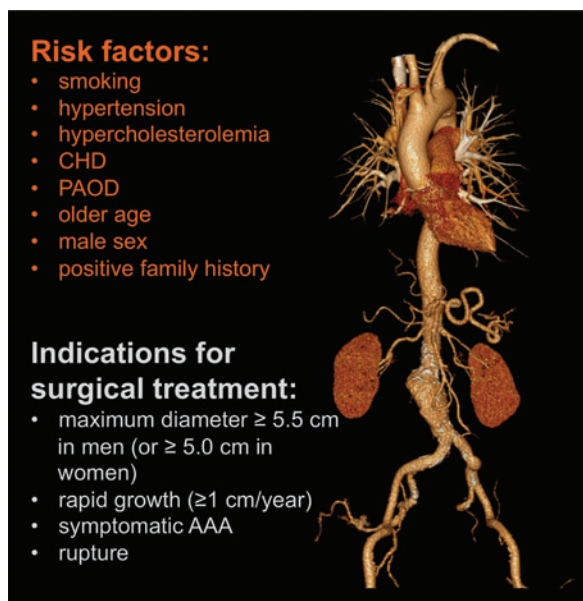rysm, with abdominal aortic aneurysm (AAA) being typically defined as an infrarenal portion of the aorta wider than 3.0 cm.

Although not considered to be merely a variant of atherosclerosis, AAA risk factors are similar, and include modifiable risks (smoking, hypertension, hypercholesterolemia, coronary heart disease, and peripheral arterial occlusive disease [PAOD]), and nonmodifiable risks (older age, male sex, and a positive family history) (Fig. 1) (55). Lower risks are seen in African American, Asian, and Hispanic patients as opposed to Caucasians, and with an active lifestyle combined with a healthy diet containing fruits, vegetables,

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FIG. 1. **AAA in spotlight.** Computed tomography angiogram of the thoracoabdominal arterial tree presenting with an infrarenal AAA. Presence of concomitant atherosclerotic calcifications predominantly in the regions of the aortic neck and the iliac arteries is frequent and attributable to similar risk factors. AAA, abdominal aortic aneurysm; CHD, coronary heart disease; PAOD, peripheral arterial occlusive disease. Color images are available online.

and nuts. Counterintuitively, patients with diabetes mellitus are also at lower risk (55).

Possibly due to a decline in smoking, the prevalence of AAA has been decreasing in recent years to $\sim 2.2\%$ in a cohort of 65-year old men (64, 129). Nevertheless, the natural course of disease is progressive with a risk of potentially lethal rupture. Mortality of ruptured AAA was described as high as 97.2% if untreated, decreased to 37.3% and 24.7% when treated by open surgical repair (OSR) or endovascular aortic repair (EVAR), respectively (50).

To date, available therapy is aimed at rupture prevention. Although recommended to reduce cardiovascular events (4), antiplatelet medications and antihypertensive agents have not been shown to influence AAA growth or rupture risk. Although a large systematic review found a possible association of statins with a reduction in AAA growth and rupture (114), similar effects have not been shown for other medication classes including angiotensin converting enzyme inhibitors, beta blockers, and doxycycline (41, 58). Accordingly, screening for AAA in populations at risk (23), surveillance of small AAAs, and pre-emptive surgical repair at the point when risk of rupture outweighs the surgical risks are crucial.

The maximum diameter of the aorta has been the most commonly employed reliable predictor for rupture. Whereas AAAs sized smaller than 5.5 cm in male patients were found to possess an annual rupture rate $\sim 1\%$ (102), the rupture risk increases significantly beyond this threshold (66).

Based on these data, current guidelines recommend surgical treatment of AAAs if the maximum diameter is at least 5.5 cm in men (or 5.0 cm in women). Surgery is also recommended for rapidly progressing AAAs (≥ 1 cm/year), symptomatic AAAs, ruptured AAAs, and those with an excentric or saccular configuration (16, 142).

Two surgical techniques coexist today (Fig. 2). OSR involves clamping of the infrarenal aorta and replacement by an alloplastic aorto-aortal tube graft or aorto-bi-iliac bifurcated graft. Since the early 1990s, EVAR has represented a minimally invasive option using a stent graft, which is inserted through the groin arteries. In EVAR, sealing is uniquely accomplished by the radial force and additional mechanisms (*i.e.*, hooks and barbs) of the device. Insufficient sealing at the proximal or distal sealing zone, or inverse blood flow in branches emerging from the aorta, will lead to endoleaks,
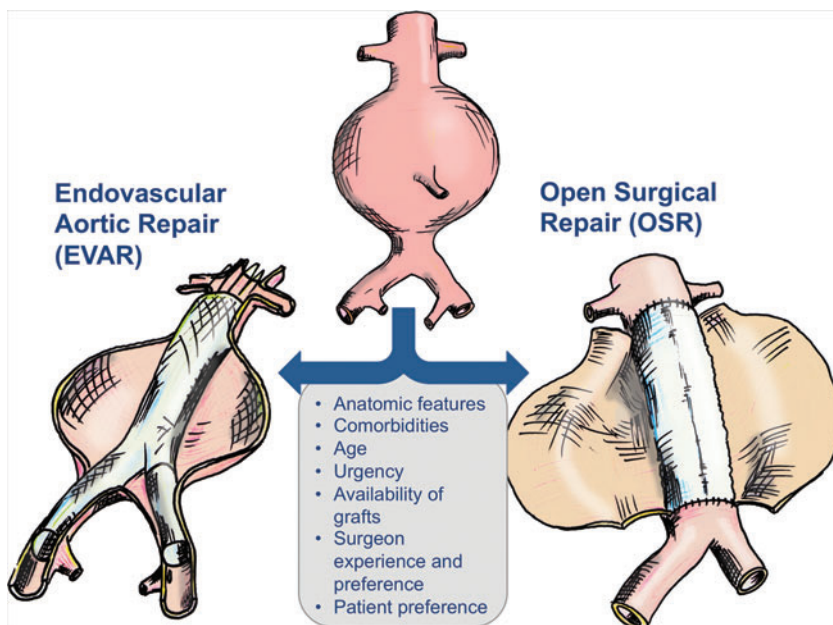
FIG. 2. **Decision-making and therapeutic options for AAA**. Color images are available online.

defined as persistent perfusion of the aneurysm sac. Delayed endoleaks may also occur, requiring life-long surveillance. Depending on the type of endoleak, reinterventions may become necessary.

Whereas initial results from randomized controlled trials found lower perioperative mortality rates after EVAR (0.5%–1.7%) compared with OSR (3%–4.7%) (43, 65, 103), long-term follow-up revealed a loss of the survival benefit over the first 2 years (98, 138). Furthermore, the reintervention rate and aneurysm-related mortality were found to be higher after EVAR than after OSR (98).

In light of the perioperative mortality and morbidity inherent to OSR and the long-term risks linked to EVAR (including the associated exposure to radiation during the procedure and follow-up), alternative options to treat or to prevent the occurrence of AAAs are desirable. A prerequisite for the evolution of treatment options targeting early stages of the disease, thereby preventing AAA development, is to understand the underlying pathomechanisms. This review aims to give an overview on the role of myeloid cells and noncoding RNAs (ncRNAs) as potential targets for future therapeutic approaches to cure AAA disease. With respect to ncRNAs, emphasis is placed on those species involved in inflammatory processes.

The Role of Myeloid Cells in AAA

Various immune cells including monocytes, macrophages, T and B cells, mast cells, neutrophils, and dendritic cells have been demonstrated to be involved in AAA formation (26).

Circulating blood monocytes

Hematopoiesis in the bone marrow involves differentiation of monocytes from multipotent hematopoietic stem cells. Monocytes are the largest leukocytes circulating in the blood stream and can differentiate into macrophages.

Various subsets of monocytes with different morphology, surface markers, gene expression profiles, and functions have been described. Based on the expression of CD14 and CD16 as cell surface markers, they can be classified into three main subsets (Table 1). The major population of monocytes ($\sim 90\%$) is defined as classical monocytes, which are characterized by high surface level expression of CD14 ($CD14^{++}CD16^-$). The minor population of cells with low expression of CD14 and high expression of CD16 ($CD14^+CD16^{++}$) is defined as nonclassical monocytes. Monocytes in between these two subsets are defined as intermediate monocytes ($CD14^{++}CD16^+$) (160).

Different expression of surface antigens determines the various functions of the three monocyte populations. Classical monocytes express a broad range of sensing receptors and proteins involved in tissue repair and immune responses. Furthermore, high-level expression of proinflammatory genes (e.g., S100A12 and S100A8/9) suggests their ability to support inflammation (146). The nonclassical subset of monocytes expresses high levels of proteins involved in cytoskeleton rearrangement, which might contribute to their patrolling behavior (24) and FcR-mediated phagocytosis (146). Beyond this, nonclassical monocytes produce high levels of tumor necrosis factor alpha (TNF-α) and IL-1β in response to lipopolysaccharide (LPS) (146) or after activation with Toll-like receptor ligands (7).

Intermediate monocytes seem to possess superior T cell stimulatory functions, which might originate from their high MHC class II expression (146).

The involvement of monocytes in AAA disease has been suggested by a number of studies. AAA patients have higher proportions of intermediate blood monocytes than healthy individuals. However, the proportion of circulating classical monocytes is lower in these patients (40).

Monocyte-derived macrophages in AAA patients differ from those in PAOD patients in terms of protein and gene expression, suggesting specific involvement in AAA disease. Those derived from AAA patients showed differences in expression of proteins related to extracellular matrix (ECM; e.g., beta-actin and fibronectin) and inflammation (e.g., tissue inhibitor of metalloproteinases [TIMP]-3) (61).

Alterations to monocytes have also been shown in murine AAA models. After infusion of angiotensin II (AngII) for 2 weeks, ApoE$^{-/-}$ (apolipoprotein E) mice reacted with an increase in circulating classical CCR2$^+$ monocytes, which seem to play a role in the inflammatory reaction contributing to AAA formation (90). Similar results showed elevated monocyte levels [lymphocyte antigen (LY)6C^{high} and lymphocyte antigen LY6C^{low} monocytes] after AngII infusion in mice that later developed AAA. These monocyte subsets were shown to have been mobilized from the spleen rather than the bone marrow. Splenectomy led to a reduction of aortic macrophages. Mice with unchanged monocyte levels did not present with later AAA formation (86). When ApoE$^{-/-}$ mice were studied as an atherosclerosis model, LY6C^{high} monocytes were shown to dominate the population in the blood stream (130). In contrast, within the arterial wall, LY6C^{low} (corresponding to nonclassical monocytes in humans) monocytes are more frequently seen to develop into plaque cells, and express the dendritic cell-associated marker CD11c (132).

Although LY6C^{high} monocytes require C-C motif chemokine receptor 2 (CCR2), CCR5, and C-X$_3$-C motif chemokine receptor 1 (CX$_3$CR1) to enter the arterial wall, recruitment of LY6C^{low} monocytes seems to partially rely on CCR5, but not on CX$_3$CR1 (132). Notably, combined inhibition of CCL2, CX$_3$CR1, and CCR5 using ApoE$^{-/-}$/CCL2$^{-/-}$/CX$_3$CR1$^{-/-}$ triple knockout mice together with Met-CCL5 (an antagonist of CCR5 signaling) resulted in significantly reduced atherosclerotic lesion size and near-complete abrogation of macrophage accumulation (19).

Furthermore, monocyte binding to the AngII-infused aorta was dependent on CD14 (8). Despite contradictory findings on subset predominance between human data and animal models, it is widely agreed that circulating blood monocytes may contribute to the pathogenesis of AAA. Although human studies found an increase of intermediate nonclassical monocytes to the expense of classical monocytes in AAA patients (40, 112), mouse models also revealed an increase of classical monocytes (86, 90). Leaving out the fact that animal models are prone to confounders, this difference might be due to different phases of AAA disease. Although mouse models regularly display the early stages of AAA development, studying humans with fully evolved AAAs depicts the end stage of a chronic disease. Conversion of monocyte subsets from the classical toward nonclassical subsets over the time course of disease was demonstrated for other conditions (e.g., myocardial infarction and rheumatoid arthritis) (59).

TABLE 1. MYELOID CELL SUBSETS AND THEIR INVOLVEMENT IN ABDOMINAL AORTIC ANEURYSM DISEASE

Cell subset	Surface markers	Stimulating factors	Pathway	Secreted products	Function	References
Monocytes						
Classical	CD14^{++}CD16^{-}	CCL2/CCR2		IL-1	Proinflammatory	(160)
Nonclassical	CD14^{+}CD16^{++}	NR4A1, CX$_3$CL1/CX$_3$CR1		IL-10, TGF-β	Tissue repair, patrolling	(131)
Intermediate	CD14^{++}CD16^{+}	CCL2/CCR2, CCL5/CCR5		IL-1, TNF-α	Proinflammatory	(146, 160)
Macrophages						
M1	CD80, CD86, CD16, CD14, CD68	TNF-α, IFN-γ, LPS, NF-κB	STAT1, AP-1, NF-κB	TNF-α, IL-6, IL-1β, iNOS, MCP-1	Proinflammatory, cytotoxicity	(131)
M2	CD206, CD163, CD68	IL-4, IL-13, IL-10, TGF-β	STAT6, PPAR-γ, CREB	Arg1, Ym1	Anti-inflammatory, tissue remodeling, tissue repair	(131)
Lymphocytes						
Th1	CD4	IL-12, IFN-γ	STAT4, T-bet	IFN-γ, TNF-α, IL-2	Activation of macrophages, recruitment of proinflammatory cells	(159)
Th2	CD4	IL-2, IL-4	STAT6, GATA-3	IL-4, IL-5, IL-10, IL-13, IL-25	Limitation of macrophage cytotoxicity, regulation of MMPs	(26, 116, 159)
Th17	CD4	IL-1, IL-6, IL-21, IL-23, TGF-β	STAT3, RORγt	IL-17A, IL-17F, IL-21, IL-22	Promotion of macrophage recruitment	(26, 159)
Th$_{reg}$	CD4	IL-2, TGF-β	STAT5, Foxp3	IL-10, IL-35, TGF-β	Limitation of T$_{eff}$ proliferation, reducing TNF-α and IFN-γ secretion from T$_{eff}$; removing of autoreactive T cells	(26, 159)
B	CD19, CD20, CD21, CD22, CD24, CD72	Non-nucleic acid components of microbes, bacterial LPS/flagellin, dsRNA, ssRNA	MyD88, IRAK	IL-2, IL-4, IL-6, IL-10, IFN-γ, TNF-α	Activation of complement cascade, promoting MMP expression, recruitment of proinflammatory cells	(63, 84, 134)

CCR2, C-C motif chemokine receptor 2; CX$_3$CR1, C-X$_3$-C motif chemokine receptor 1; dsRNA, double-stranded RNA; Foxp3, forkhead box P3; IFN-γ, interferon gamma; LPS, lipopolysaccharide; MMPs, matrix metalloproteinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; RORγt, receptor-related orphan receptor γt; ssRNA, single-stranded RNA; STAT, signal transducer and activator of transcription; T$_{eff}$, T effector; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.

A similar polarization toward a more mature monocyte phenotype during AAA development is possible.

Macrophages

Previous dogma stated that tissue macrophages originated exclusively from bone marrow-derived ''passenger'' monocytes, and extravasated from the blood stream into the aortic wall. More recent studies suggest that, in parallel, a pool of ''resident'' tissue macrophages exists (Fig. 3). These originate from the yolk sac, migrate into tissues during embryonic development, and can persist throughout adult life by local proliferation (100). Fate-mapping experiments have shown that arterial macrophages can arise embryonically from CX_3CR1^+ precursors and from bone marrow-derived monocytes that colonize the tissue immediately after birth (34). An additional source of macrophages might be phenotypic switching of smooth muscle cells (SMCs). In a mouse model it was demonstrated that some lineage-traced SMCs in advanced atherosclerotic lesions lacked expression of typical SMC markers like ACTA2 (140) and instead expressed macrophage markers (*e.g.*, LGALS3) (118). Furthermore, cholesterol loading of mouse aortic SMCs resulted in a decrease of SMC-related genes (*e.g.*, SM alpha-actin, alpha-tropomyosin, myosin heavy chain), whereas expression of macrophage-related genes (CD68, Mac-2, adenosine triphosphate-binding cassette transporter A1

[ABCA1]) was increased (111). However, despite their immunohistochemical resemblance, the functional properties of cholesterol-loaded SMCs and macrophages seem to differ. After incubation with 1 μm latex beads, cholesterol-loaded SMCs showed significantly less phagocytic activity compared with macrophages. Furthermore, SMC-derived macrophage-like cells were shown to possess less efferocytotic activity compared with macrophages (139).

Although a transdifferentiation of SMCs toward a macrophage-like phenotype was demonstrated in atherosclerotic disease (42) rather than in AAA, similar mechanisms are likely to be present.

In AAA specimens, accumulation of macrophages is found predominantly in the adventitia (30) and the intraluminal thrombus (108). Which population primarily fuels this increase of macrophages in AAA needs further investigation (106). Figure 4 shows immunohistochemical staining of human AAA tissue using anti-CD68 antibodies. As already outlined, macrophages and other CD68$^+$ cells (*i.e.*, SMC-derived macrophage-like cells) cannot be distinguished with this technique.

Macrophages are typically classified into M1 and M2 phenotypes (Table 1) (91, 131). *In vitro*, M1 macrophages are usually induced by two substances: interferon gamma (IFN-γ), which originates from natural killer cells *in vivo*, and LPS, which is a component of Gram-negative bacteria cell walls (131). Triggering macrophages with the mentioned stimuli
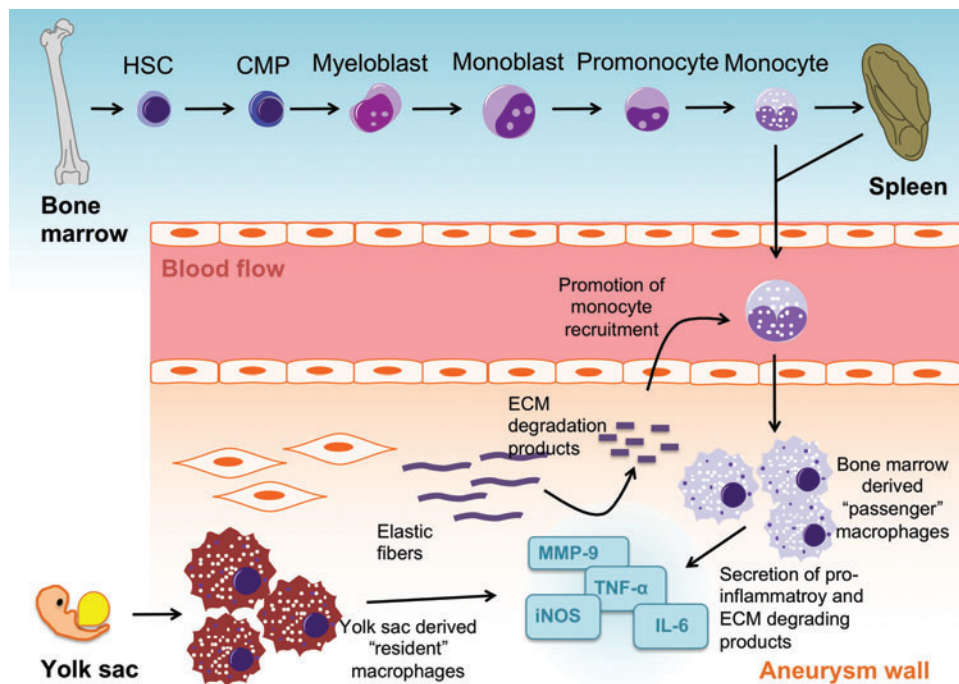

FIG. 3.   Different origins and modes of action of tissue macrophages in AAA. Myelopoiesis in the bone marrow is the source of circulating blood monocytes with the spleen acting as a reservoir. Extravasation of ''passenger'' monocytes into the aneurysm wall is a CD14-dependent mechanism. In parallel, a pool of ''resident'' tissue macrophages exists, which originate from the yolk sac and migrate into aortic tissue during embryonic development. During the early phase of AAA development, a shift toward M1 macrophages entails increased secretion of proinflammatory cytokines, including TNF-α, IL-6, IL-1β, iNOS, MCP-1, and ECM degrading products such as MMP-9. The inflammatory response within the aneurysm wall is a self-perpetuating system, as degradation products act as chemokines to attract further monocytes to extravasate. CMP, common myeloid progenitor; ECM, extracellular matrix; HSC, hematopoietic stem cell; MMP, matrix metalloproteinase; TNF-α, tumor necrosis factor alpha. Color images are available online.
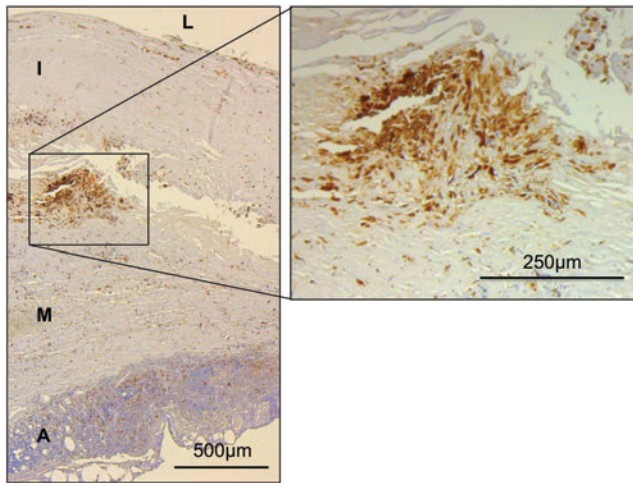
FIG. 4. Immunohistochemical staining of macrophages in human AAA tissue. Macrophages and other CD68$^+$ cells (*i.e.*, SMC-derived macrophage-like cells) stained with anti-CD68 antibodies. Note CD68$^+$ cells are accumulating mainly in the border region between tunica intima and tunica media, whereas lymphocytes are predominantly located in the adventitia forming the VALT. A, adventitia; I, tunica intima; L, vessel lumen; M, tunica media; SMC, smooth muscle cell; VALT, vascular-associated lymphoid tissue. Color images are available online.

causes production of proinflammatory cytokines and chemokines (*e.g.*, IL-1β, IL-12, TNF-α, MCP-1, CCL2, and iNOS), all of which play a role in accelerating inflammation and killing pathogens (131). Alternatively activated macrophages (*e.g.*, those formed after incubation with IL-4 and IL-13) are classified as M2. This phenotype produces molecules thought to play anti-inflammatory roles in tissue remodeling and repair (*e.g.*, IL-10 and transforming growth factor beta [TGF-β]) (131).

Notably, macrophages *in vivo* are exposed to a multitude of different stimuli, making them difficult to distinctly classify into M1 or M2. Studies quantifying M1 and M2 macrophages in AAA have not been entirely conclusive, with one study showing a higher proportion of M2 macrophages in the adventitia (30), and another demonstrating predominantly M1 macrophages in the adventitia with a higher proportion of M2 macrophages in the intraluminal thrombus (11). Therefore, most likely due to the complexity of human AAA wall tissue and the human organism, the current evidence suggests no clear polarization toward either macrophage phenotype.

Various proinflammatory cytokines secreted by M1 macrophages (*e.g.*, TNF-α, IL-6, IL-1β, and IFN-γ) were found to be elevated in the serum of AAA patients (53). Murine animal models confirmed central roles for these cytokines in aortic disease, as deletion of TNF-α (150), IL-1β (52), and IFN-γ (151) resulted in reduced aneurysm formation, and deletion of IL-6 led to fewer aortic dissections (136).

Animal models have suggested a predominance of M1 macrophages in the AAA wall during early stage disease, whereas later-stage AAA seems to be associated with a shift toward M2 polarization. Infusion of male ApoE$^{-/-}$ mice with AngII induces AAA formation and an increase in the M1/M2 ratio. This increase was detected as early as 7–10 days after

starting the infusion and persisted until day 28 (105). A shift favoring the healing M2 rather than proinflammatory M1 phenotype in advanced AAA disease might counteract aneurysm growth and rupture. However, AngII infusion of ApoE$^{-/-}$ mice for an additional 56 days both increased luminal diameters and aneurysmal rupture-associated deaths, and was associated with accumulation of macrophages that were consistent with an M2 phenotype (109).

Macrophages are involved in ECM degeneration, inflammation, and tissue healing and repair processes within the AAA wall. ECM degeneration is promoted by an increase of proteases such as cathepsins and matrix metalloproteinases (MMPs), and a decrease of their inhibitors (*e.g.*, TIMP). Elastase-induced aneurysm formation in mice was suppressed by treatment with doxycycline as a nonselective MMP inhibitor (104). MMP-9-deficient mice were shown to be resistant to elastase-induced aneurysm formation, and they lost this resistance after bone marrow transplantation from wild-type animals (104). In support of this, TIMP-1 knockout mice showed a significant increase in elastase-induced aneurysm formation compared with wild-type animals (35).

The proinflammatory M1 macrophage phenotype seems to be more involved in ECM degeneration, expressing higher messenger RNA (mRNA) and protein levels of MMP-9 than M2 macrophages (11). ECM degeneration is thought to promote a self-sustaining inflammatory response, as certain breakdown products act as chemokines to further recruit monocytes (26). A repetitive peptide (Val-Gly-Val-Arg-Pro-Gly) found in human elastin is able to bind to cellular elastin receptors, promote monocyte chemotaxis to the AAA wall, and promote the inflammatory response that accompanies aneurysmal degeneration (Fig. 3) (45). Although ECM degeneration and inflammation are predominantly induced by M1 macrophages and M2 macrophages contain anti-inflammatory and tissue healing properties, recent studies suggest that the latter's nature is not entirely protective. For instance, it was demonstrated that CD163$^+$ macrophages were associated with plaque progression, microvascularity, and expression of hypoxia-induced factor 1α (HIF1α) and vascular endothelial growth factor (VEGF)-A in human atherosclerotic lesions (44).

Lymphocytes

Lymphocytes represent the majority of inflammatory cells within the AAA wall. Their mode of action is characterized by secretion of different proinflammatory cytokines, activation of various pathways promoting SMC apoptosis, and promoting synthesis of MMPs (31).

Lymphocytes are divided into B cells and T cells, with the latter are subdivided based on the expression of surface markers. Although modulatory T cells usually express CD4, most cytotoxic T cells express CD8 (26). Most inflammatory cells in AAA tissue are CD4$^+$ T cells. Depending on stimulating factors, secretion products, and their functions, these are further subdivided into T helper (Th) or T effector (T$_{eff}$) cells (*i.e.*, Th1, Th2, Th17), and regulatory T cells (T$_{reg}$) (26, 159).

Th1 cells are usually activated by IFN-γ or IL-12 (159). Activation of the "signal transducer and activator of transcription 4" (STAT4) and T-bet/TBX21 pathways results in secretion of IFN-γ, TNF-α, and IL-2 (159), which activate more Th1 cells, restrict polarization to other T cell subspecies,

and activate macrophages (Table 1). Once activated, the macrophages produce IL-12, activating more Th1 cells (116). Thus, Th1 cells and macrophages show positive feedback stimulation, leading to ongoing augmentation of inflammation and ECM degeneration. Human AAA tissue expressed high mRNA levels of IFN-γ (in contrast to IL-4), suggesting a predominance of Th1 cells rather than Th2 cells. This hypothesis was fortified by an overexpression of the transcription factor T-bet, in the absence of GATA-3 expression (39).

Th1 cells and their secretion products seem to be associated with aneurysm growth, as increased IFN-γ serum levels correlated with AAA growth rate (53). Furthermore, deficiency of CD4$^+$ T cells in a calcium chloride (CaCl$_2$)-induced murine aneurysm model was shown to be related to lower expression of MMP and inhibition of aneurysm development. Replacement of IFN-γ by reinfusion of competent splenocytes from wild-type mice promoted aneurysm formation in these CD4$^{-/-}$ animals (151), underlining the crucial role of IFN-γ in AAA disease.

Polarization toward the Th2 phenotype is promoted by IL-2 and IL-4. STAT6 and GATA-3 pathways lead to secretion of IL-4, IL-5, IL-10, IL-13, and IL-25 (Table 1) (159). Notably, IL-13 is an activator of anti-inflammatory M2 macrophages. The effects of these pathways on MMPs seem to be variable, as IL-4 suppressed collagenase expression in human monocytes (21), whereas IL-13 induced MMP-2, -9, -12, -13, and -14 (62).

At variance with the data suggesting predominance of Th1-specific cytokines (IFN-γ) and pathways (T-bet) in human AAA tissue (39), another study indicated a predominance of Th2-associated cytokines (IL-4, -5, -10), with Th1-characteristic cytokines (IL-2, -15) showing only low-level expression (116). The same research group showed that in allografted mouse aortas, IFN-γ deficiency promoted AAA development and increased levels of MMP-9 and -12. However, IL-4 deficiency seemed to protect against AAA formation (120), suggesting an imbalance toward the Th2 phenotype in AAA disease. The conflicting results regarding Th1/Th2 phenotype predominance might be explained by interspecies (murine AAA model vs. human AAA) differences, or changes at different stages of AAA disease (earlier phases in mouse model vs. advanced phases in human AAA).

Th17 lymphocytes are mainly stimulated by IL-1, IL-6, and IL-23, which activate the retinoic acid receptor-related orphan receptor γt (RORγt) and STAT3 pathways, resulting in secretion of IL-17 isoforms A and F, IL-21, and IL-22 (Table 1) (159). In a mouse model (AngII infusion in ApoE$^{-/-}$ animals on high-fat diet), IL-17A was found to promote aortic superoxide production as well as aortic leukocyte and dendritic cell infiltration, but did not seem to affect aneurysm formation (79). However, in a different mouse model (elastase perfusion), knockout of IL-17 and IL-23 resulted in reductions in aneurysm diameter and cytokine levels (MCP-1, RANTES, KC, TNF-α, MIP-1α, and IFN-γ) (119). Furthermore, it has been demonstrated that human AAA tissue expresses significantly increased levels of IL-17 and IL-23 (119), suggesting that Th17 cells contribute to AAA disease.

The main role of T$_{reg}$ cells seems to be to antagonize the aforementioned mainly proinflammatory T$_{eff}$ cells. They are stimulated by IL-2 and TGF-β, activating STAT5 and forkhead box P3 (Foxp3) pathways, resulting in IL-10 and TGF-β secretion (Table 1) (159). T$_{reg}$ cells have antiproliferative effects on T$_{eff}$ cells (117). A loss of T$_{reg}$ cells (relative to T$_{eff}$ cells) may increase the proinflammatory milieu within the AAA wall. A relative reduction of T$_{reg}$ cells compared with T$_{eff}$ cells has been found in AAA tissue, with reduced levels of Foxp3 expression in peripheral CD4$^+$CD25$^+$ T$_{reg}$ cells of AAA patients (152).

In summary, with respect to T lymphocyte involvement in AAA disease, the mechanism is thought to involve an imbalance within T$_{eff}$ cells, which (despite conflicting data) seems to be in favor of the Th1 phenotype in humans, with minimization of T$_{reg}$ cells. This disequilibrium promotes a proinflammatory environment with ECM degeneration leading to AAA progression.

Compared with T cells, the evidence on B lymphocytes and their involvement in AAA disease is sparse (156). B cells are categorized into B1 and B2 cells. After activation by T cells, B1 cells produce IgM antibodies. Activation of B2 cells can cause them to undergo isotype switching to become plasma cells, secreting large amounts of highly specific IgG antibodies. These, in turn, can activate the complement system, resulting in the activation of anaphylatoxins and the formation of the membrane attack complex (MAC) (156).

B lymphocytes have also been shown to be increased in the AAA wall, mainly in the adventitia (Fig. 4) (57). Indeed research suggests that, within the adventitia, the majority of lymphocytes are B cells (CD19$^+$CD22$^+$) (37). Atherosclerosis models have given rise to the concept of vascular-associated lymphoid tissue (VALT), consisting of disseminated accumulations of immunocompetent and antigen presenting cells (145). Whereas inflammatory cells in atherosclerosis typically accumulate within the arterial intima, VALT in AAA disease seems to accumulate in the adventitia, where it can organize into lymphoid follicles, aggregated in lymph node-like structures (9). Within these lymphoid follicles, B cells were found to form germinative centers (9, 156). The nodular centers also contained follicular dendritic cells, T lymphocytes, and macrophages (49).

The evidence regarding the effects of B cells on aneurysm growth is somewhat conflicting. One study showed that deficiency of B cells protected mice from developing elastase-induced AAAs, which was attributed to the absence of IgG-mediated complement activation (158). However, another study found that B cell-deficient mice were equally prone to AAA formation compared with wild-type mice. Adoptive transfer of B2 cells was even shown to suppress AAA formation, presumably due to an increase in splenic T$_{reg}$-cells (84).

Autoantigens, such as aneurysm-associated protein-40 (AAAP-40) (149) or carbonic anhydrase 1 (CA1) (2), have been proposed to activate B cells. Owing to a cross reaction between antibodies against outer membrane proteins of Chlamydia pneumoniae and the heavy chain of immunoglobulins within the AAA wall, molecular mimicry has been proposed as an initiator of AAA formation after previous infection (77).

Activation of B2 lymphocytes leads to the secretion of IgG antibodies, of which IgG1, IgG2, and IgG3 were found to be increased in the AAA wall, as was the complement component C3. This observation was interpreted to suggest that IgG1, IgG2, and IgG3 may activate the complement system by the classical pathway, thereby promoting matrix

proteolysis in AAA (14). This was supported by another study demonstrating upregulation of C1q and C4 in all AAA wall layers (3).

In the elastase-induced AAA mouse model, it was shown that IgG antibodies activate C3 convertase, which is a central enzyme of all three complement pathways. Deficiency in B cells was associated with abrogated C3 deposition in the elastase-perfused aortic wall and with protection from AAA formation (158).

Activation of C3 convertase leads to formation of MAC, and an important regulator of MAC (CD59) was shown to be downregulated in human AAA tissue (47). In the AngII-induced AAA mouse model, CD59 was shown to protect from AAA formation. Furthermore, it was demonstrated that MAC activates c-Jun and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways, which promote upregulation of MMP-2 and MMP-9 (148), presumably leading to degradation of ECM proteins.

The alternative complement pathway leads *via* C3 convertase to generation of C3a and C5a. In the elastase AAA mouse model, these were shown to recruit neutrophil leukocytes to the aortic wall promoting AAA formation (96).

B cells in the aortic wall produce pro- (IFN-γ, IL-6, and TNF-α) and anti-inflammatory cytokines (IL-2, IL-4, and IL-10) (84, 134). Results from a murine aneurysm model suggested that TNF-α promotes MMP-2 and MMP-9 expression, increasing macrophage infiltration into the aortic tissue, thereby leading to aneurysm formation (150).

In summary, despite a relative paucity of evidence, B lymphocytes appear to play an important role in the pathogenesis of AAA disease, especially by activating the complement cascade and by recruitment of other inflammatory cells, converging in inflammation and degradation of the ECM.

Mast cells

Mast cells have also been found to be involved in AAA development. The number of mast cells is increased in the outer media and the adventitia of human AAA walls. Furthermore, mast cell-deficient mutant rats were resistant to $CaCl_2$-induced aortic aneurysm. In a cell culture experiment, it was shown that mast cells directly augmented the activity of MMP-9 produced by monocytes or macrophages (137). In addition, chymases (serine proteases exclusively secreted by mast cells) were found to induce SMC apoptosis (69) and to be involved in activation of promatrix metalloprotease 9 (pro-MMP-9) and pro-MMP-2 (135). However, inhibition of mast cells in humans did not alter AAA growth in a randomized controlled trial during 12-month follow-up (121). Although mast cell inhibition does not seem to affect the growth rate of a fully evolved AAA, a possibly beneficial effect in the early stages of AAA formation needs further investigation.

Neutrophil leukocytes

Neutrophils produce a variety of proteases and collagenases (1), which supposedly are involved in ECM degradation and ultimately in aneurysm rupture (29). Neutrophils are also thought to promote AAA formation *via* mechanisms independent of MMPs (33). In the elastase-induced AAA mouse model, neutrophil infiltration was observed in the AAA wall. If treated with antineutrophil antibody (resulting in neutropenia before elastase perfusion), mice were protected from AAA formation, but without alteration in MMPs (33).

Formation of neutrophil extracellular traps (NETs), mainly to entrap pathogens, is a defense mechanism enacted by neutrophils. NETosis, which was demonstrated to be promoted by IL-1β, seems to play a role in AAA formation, and inhibition of NETosis significantly attenuated AAA formation in a mouse model (85).

Neutrophils are also known to possess pro-oxidant activities *via* nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and myeloperoxidase, producing reactive oxygen species and reactive nitrogen species. Circulating polymorphonuclear neutrophils from AAA patients were found to contain higher H_2O_2 and myeloperoxidase levels, and diminished catalase levels compared with control patients, underlining a relevant role for oxidative stress in AAA disease (107).

IL-8, which is an important chemoattractant cytokine for neutrophils, was upregulated 11-fold in the AAA wall compared with controls (88), Another study found that neutrophil-derived leukotriene B (4), which is a major neutrophil chemotactic factor, is released from the intraluminal thrombus (48), supporting the finding that most leukocytes are found at the luminal layer of the intraluminal thrombus (101).

Taken together, the available evidence suggests that neutrophils participate in AAA development through the promotion of oxidative stress, secretion of proteolytic agents, and NET formation.

The Role of ncRNA in AAA

Sequencing of the human genome has shown that only $\sim$1.5% contains protein-coding sequences. Together with introns within protein-coding genes and 5′- and 3′-untranslated regions, the combination occupies $\sim$28% of the human genome (38).

However, $\sim$80% of the genome potentially participates to some extent in biochemical activities. Despite not being translated into proteins, $\sim$70% of the genome (at least) is transcribed into mRNA (20). These elements are referred to as ncRNA.

There exist constitutive types of housekeeping ncRNAs, which are expressed in all cells and possess well-defined functions within the cell. This class includes transfer RNAs (tRNAs), ribosomal RNAs (rRNA), small nucleolus RNAs (snoRNAs), small nuclear RNAs (snRNAs), and possibly also telomere complex-associated guide RNAs (38).

Beyond this, there are regulatory ncRNAs, which can be expressed in a highly regulated manner in different cell types and/or during different developmental periods. Owing to their various functions in different physiologic and pathologic processes, these have attracted substantial attention within the past decade. ncRNAs are usually classified based on their size, with short noncoding RNAs (miRNAs) and long noncoding RNAs (lncRNAs) being defined as smaller or larger than 200 nucleotides, respectively.

Short noncoding RNA

miRNAs are short ($\sim$18 to 23 nucleotides) single-stranded RNAs (6, 60). They are transcribed as long primary transcripts (pri-miRNAs), which are processed in the nucleus into

stem-loop precursors of ~ 70 nucleotides (pre-miRNAs). This step is mediated by an RNase III called Drosha. After active transportation into the cytoplasm, pre-miRNA is processed into mature miRNAs, mediated by another member of the RNase III family named Dicer (67). Please refer to Figure 5 for a schematic illustration of miRNA processing and mode of action. Mature miRNAs are involved in post-transcriptional processes, and commonly repress the expression of target genes by incorporating together with argonaute into a protein complex called the RNA-induced silencing complex (RISC) and binding to the 3' untranslated region of mRNA (6). Accordingly, one miRNA can bind to and potentially suppress multiple mRNAs (60).

Contributions from miRNAs to inflammatory processes have been demonstrated for a multitude of diseases (123), including rheumatoid arthritis (126), psoriasis (124), asthma (78), ulcerative colitis (147), systemic lupus erythematosus (133), different forms of glomerulonephritis (93), and also atherosclerosis (51, 127).

Furthermore, various miRNAs have been established to be involved in the cell fates of vascular SMCs and in AAA (Table 2) (60, 68, 74). However, the evidence on miRNA species involvement in the inflammatory processes driving AAA disease is limited.

An association with those inflammatory processes was demonstrated for miR-24, seemingly pertaining to its regulation of chitinase 3-like 1 (Chi3l1). By reducing the expression of Chi3l1, miR-24 inhibits cytokine synthesis (*e.g.*, IL-8 and CCL2) in macrophages and their survival, and thereby limits inflammation and ECM degeneration (Fig. 6) (82). Accordingly, overexpression of miR-24 inhibited AAA growth in a mouse model (82). In human macrophages, overexpression of miR-24 attenuated phagocytosis and secretion of inflammatory cytokines (*e.g.*, TNF-α, IL-6, and IL-12p40) (94). Similar effects were demonstrated for miR-30b and miR-142-3p (94), although for these, a relation with AAA disease has not been established yet.

Another miRNA, miR-33, affected AAA formation through monocyte and macrophage regulation. Knockout of miR-33 was associated with less accumulation of macrophages, and lower expression of monocyte chemotactic protein-1 within the aortic wall. In addition, peritoneal macrophages from miR-33$^{-/-}$ mice were found to express lesser levels of MMP-9 (92). MiR-33 knockout mice showed decreased AAA formation after either AngII or CaCl$_2$ treatment (92). Apart from these proinflammatory functions, miR-33 is also involved in cholesterol homeostasis. In human and murine cells, miR-33 inhibits the expression of the ABCA1, limiting cholesterol efflux to apolipoprotein A1 and reducing circulating high-density lipoprotein levels (Table 2) (110).

Furthermore, miR-155 has been found to enhance vascular inflammation by suppressing BCL6 expression, which itself attenuates proinflammatory NF-κB signaling (95). The proinflammatory properties of miR-155 may be attributable to its effects on macrophage activation and polarization (25), with increased miR-155 levels in M1 macrophages and decreased levels in the M2 phenotype (12). Notably, apart from elevated expression in M1 macrophages, miR-155 also supports macrophage polarization toward the proinflammatory M1 phenotype. Similar effects were demonstrated for miR-125b (17) and miR-127 (153), which equally have not been implicated in AAA disease yet.

This also applies to miR-342-5p, which alongside miR-155 was found to be upregulated in early atherosclerotic lesions in ApoE$^{-/-}$ mice. By suppression of Akt1, miR-342-5p causes an upregulation of miR-155, which again induces proinflammatory mediators such as Nos2 and IL6 in macrophages (143). Therefore, a synergy of miR-342-5p and miR-155 is supposed to drive macrophages toward a proinflammatory and proatherogenic state (144).

Although a possible involvement in AAA disease still is to be demonstrated, miR-103 was shown to play a role in atherosclerosis by promoting inflammation and endoplasmatic reticulum stress in endothelial cells derived from a mouse
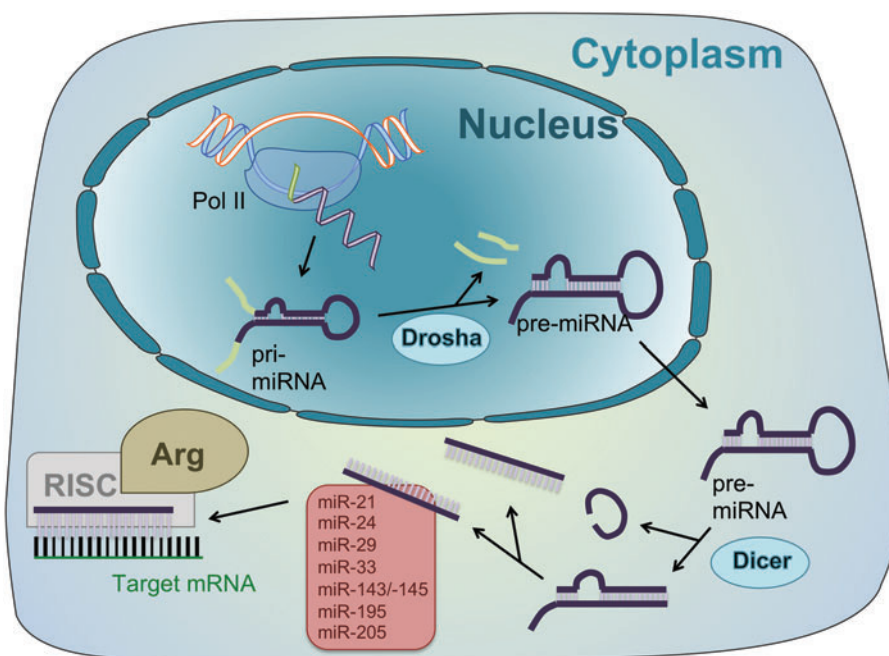

FIG. 5. Processing and mode of action of miRNAs. Once transcribed by Pol II, an RNase named Drosha processes pri-miRNA into pre-miRNA. The latter is transported into the cytoplasm, where processing mediated by another RNase called Dicer leads to formation of mature miRNA. Together with argonaute, the different miRNAs incorporate into RISCs, which bind to distinct mRNAs and thereby suppress translation into various proteins. Arg, argonaute; miRNA, short noncoding ribonucleic acid; mRNA, messenger RNA; Pol II, RNA polymerase II; RISC, RNA-induced silencing complex. Color images are available online.

TABLE 2. INVOLVEMENT OF SHORT NONCODING RNAs IN ABDOMINAL AORTIC ANEURYSM DISEASE
AND UNDERLYING INFLAMMATORY PROCESSES

miRNA	Cell types	Regulation	Target genes	Function in AAA	References
miR-21	SMC, EC, FB	↑	PTEN	Overexpression reduces AAA	(80)
miR-24	SMC, EC, MPh	↓	Chi3l1	Limits inflammation and ECM degeneration; overexpression reduces AAA	(82)
miR-29	SMC, EC, FB	↓ ↑	COL1A1, COL3A1, COL5A1, ELN MMP-9	Inhibition reduces AAA	(10, 81)
miR-33	SMC, MPh, HC	↓	ABCA1	Monocyte chemotaxis, MPh accumulation; inhibition reduces AAA	(92, 110)
miR-103	EC	↑	PTEN, MAPK	No direct effect on AAA demonstrated; promotion of inflammation and atherosclerosis	(51)
miR-143/-145	SMC, FB, EC	↓ ↑	KLF4, Elk-1, CamkII-δ Myocd	Promotion of SMC differentiation counteracting AAA formation; repression of SMC proliferation	(22, 32)
miR-146a	SMC	↕	KLF4	Promotion of SMC proliferation	(128)
miR-155	SMC, FB	↓	AT$_1$R, BCL6	Inhibition of SMC maturation; enhancing vascular inflammation; MPh polarization toward M1 phenotype	(12, 27, 95, 157)
miR-181a	MPh	↓	TAB2, NEMO, MEK1, NF-κB	No direct effect on AAA demonstrated; inhibition of inflammation	(122, 127)
miR-195	SMC	↓	ELN, MMP-2, MMP-9	Regulation of ECM	(154)
miR-205	EC	↓	TIMP-3, RECK	Promotion of AAA development	(56)
miR-206	EC	↑	α-SMA, smoothelin and calponin	Maintaining contractile SMC phenotype	(76)
miR-221/-222	SMC	↓	c-Kit, p27-Kip1	Promotion of SMC proliferation	(28)
miR-342-5p	MPh	↓	Akt1	No direct effect on AAA demonstrated; MPh polarization toward M1 phenotype	(143)
miR-663	SMC	↑ ↓	SM22α, SMA, calponin, MYH11 JunB, Myl9, MMP-9	Promotion of SMC differentiation; inhibition of SMC proliferation and migration	(72)
miR-712	EC	↓	TIMP3, RECK	Promotion of AAA development	(56)

Shading indicates involvement in inflammatory processes.

AAA, abdominal aortic aneurysm; ABCA1, adenosine triphosphate-binding cassette transporter A1; Chi3l1, chitinase 3-like 1; EC, endothelial cell; ECM, extracellular matrix; FB, fibroblast; MAPK, mitogen-activated protein kinase; miRNA, short noncoding RNA; MPh, macrophage; PTEN, phosphatase and tensin homolog; SMC, smooth muscle cell; TIMP, tissue inhibitor of metalloproteinases.

model (51). Depletion of miR-103 was shown to counteract atherosclerosis through blocking phosphatase and tensin homolog (PTEN)-mediated mitogen-activated protein kinase (MAPK) signaling (51).

In contrast, miR-181a seems to suppress inflammation by decreasing proinflammatory gene expression (*e.g.*, VCAM-1, ICAM-1, and E-selectin) and infiltration of macrophages, leukocytes, and T cells into atherosclerotic plaques (127). Again, no direct association with AAA disease was shown so far.

Notably, the predominating mechanisms of action of most miRNAs that are known to be involved in AAA disease are not directly related to myeloid cells and inflammation. Overexpression of miR-21 was seen in human AAA samples as well as mouse models of AAA (80). Lentiviral overexpression of miR-21 decreased the expression of the PTEN protein, and promoting downstream activation of the serine–

threonine kinase AKT, which itself has proproliferative and antiapoptotic properties (Table 2). Overexpression of miR-21 inhibited AAA growth, whereas inhibition of miR-21 promoted AAA expansion (80). miR-21 has further been evaluated for its role in vascular inflammation and myeloid cell activation in the context of atherosclerosis. Canfran-Duque *et al.* found that lowering miR-21 in macrophages accelerates atherosclerosis and plaque necrosis by increasing the expression of MKK3, an upstream mediator of p38-CHOP and JNK signaling (13).

In contrast, miR-29 promotes AAA formation by inhibition of expression of ECM proteins, including collagens (COL1A1, COL3A1, and COL5A1) and elastin (Table 2) (81). In murine animal models, overexpression of miR-29b resulted in augmented AAA growth and a significantly higher aortic rupture rate. Conversely, inhibition of miR-29b by administration of locked nucleic acid anti-miR-29b reduced
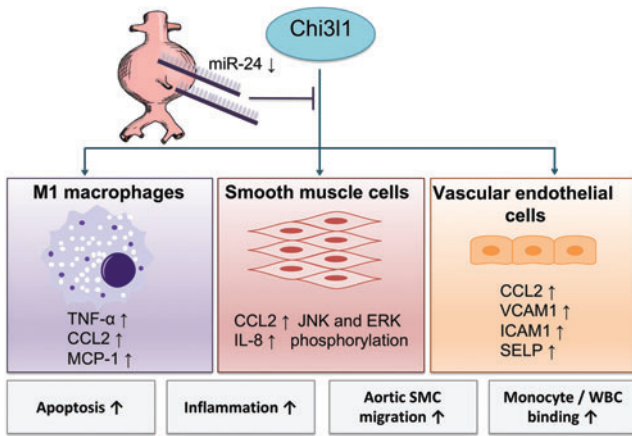
FIG. 6.   Different effects of miR-24 in AAA disease. The expression of miR-24 is decreased in AAA, leading to an increased expression of Chi3l1. This again promotes the synthesis of various cytokines in M1 macrophages, SMCs, and vascular endothelial cells, converging toward proapoptotic and proinflammatory processes (82). Chi3l1, chitinase 3-like 1; WBC, white blood cell. Color images are available online.

AAA progression by increasing collagen expression, which seemed to stabilize the aortic wall (81). Also, inhibition of miR-29 was found to decrease the expression of MMP-9 in the aorta (10).

Upregulation of miR-29b with advanced age was shown in mice, suggesting involvement in older patients' susceptibility to AAAs (10). Furthermore, elevated miR-29b levels were found in human thoracic aortic aneurysms (10) and in the aortic roots of Marfan (Fbn1$^{C1039G/+}$) mice (87). In the latter, increased miR-29b expression was shown to result from a decreased activation of NF-κB, which seemed to act as a repressor (87).

Another miRNA that affects aortic ECM remodeling is miR-195, which targets collagens, elastin, and MMPs (154). Plasma levels of miR-195 showed an inverse correlation with human AAA diameter.

The miR-143/145 cluster is involved in SMC differentiation, inducing a contractile, quiescent, and mature phenotype (32), potentially stabilizing the AAA wall (60). This is achieved by inhibition of multiple factors, including Elk-1, Klf4, and CamkII-δ, and activation of Myocd (22). The expression of miR-143 and -145 is decreased in human AAA tissue compared with undiseased aortas. A loss of miR-143 and miR-145 expression seems to be associated with incomplete differentiation of SMCs and alteration of the aortic wall, promoting AAA formation (32).

In summary, despite growing evidence on the involvement of miRNAs in AAA disease, their effect on myeloid cell function and inflammation is still understudied.

Long noncoding RNA

As noted, ncRNA fragments exceeding a length of 200 nucleotides are referred to as lncRNAs. Acting as signaling cues, decoys, scaffolds, or miRNA sponges, their modes of action are manifold and generally different from those described for miRNAs (*i.e.*, complementary binding) (60).

In relation to miRNAs, involvement in various inflammatory conditions including rheumatoid arthritis (125), osteoarthritis (99), celiac disease (15), multiple sclerosis (155), and Kawasaki disease (75) was demonstrated (18, 83). However, their role in AAA disease and particularly in the inflammatory processes underlying AAA disease is much less investigated.

So far, H19 is the only lncRNA found to be involved in AAA formation (71). Although involvement in vascular disease has been demonstrated for a number of other lncRNAs (5, 70, 73), distinctive functional roles in AAA formation have not been proven. Knockdown of H19 using antisense oligonucleotides led to a significant reduction of aneurysm formation in two different murine AAA models. Upregulation of H19 promoted SMC apoptosis in the aneurysm wall (Fig. 7). Cultured human SMCs showed decreased apoptotic rates after knockdown of H19, and in this context apoptosis of SMCs seems to be mediated by the transcription factor HIF1α (71).
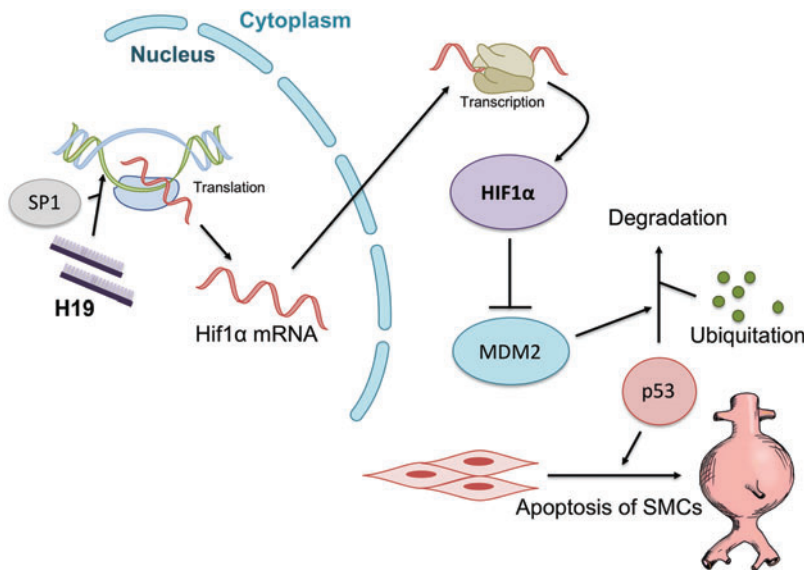

FIG. 7.   Schematic effect of H19 on vascular SMC apoptosis in AAA disease. H19 induces AAA progression by promoting Hif1α translation in the nucleus under the influence of SP1 recruitment. In the cytoplasm, HIF1α protein is transcribed and inhibits MDM2. This results in reduced degradation of p53, leading to SMC apoptosis and AAA formation (71). HIF1α, hypoxia-induced factor 1α; MDM2, murine double minute 2; SP1, specificity protein 1. Color images are available online.

To date, there is no evidence on the contribution of lncRNAs to inflammatory processes underlying AAA disease.

Conclusions and Future Directions

Myeloid cells are involved in AAA development and growth. Over the past decades, a large body of evidence has accumulated on monocytes, macrophages, and lymphocytes and their contribution to AAA. In contrast, knowledge on the role of neutrophils and mast cells with respect to AAA disease is still minimal. In summary, the early phase of AAA development seems to be characterized by an imbalance of myeloid cells toward proinflammatory cell types and phenotypes (39, 53, 105). M1 macrophages from different origins accumulate within the aortic wall (34), whereas lymphocytes (especially B cells) predominantly aggregate within the adventitia (57). Interaction of M1 macrophages and Th1 lymphocytes induces secretion of different proinflammatory and ECM-degrading cytokines (*e.g.*, TNF-α, IFN-γ, IL-6, MMPs, and iNOS) (131, 159), which in conjunction with activation of the complement cascade by B cells (3, 14) sustains a cytotoxic and ECM-degrading environment. ECM degradation products themselves contribute to this milieu by recruiting additional monocytes (26). Evidence is growing that mechanisms involving ncRNAs contribute by altering this milieu (82, 92, 95, 110).

Understanding the distinct mechanisms of AAA disease is considered a prerequisite to reach two high-priority targets. First, factors shown to be involved in the development of AAA might eventually serve as biomarkers to identify patients at risk for later AAA formation and to predict the course of disease. Regarding myeloid cells, changes in circulating monocyte subsets (40) or variations in gene or protein expression (115) potentially might serve as predictors for AAA growth. Diminished catalase levels in circulating polymorphonuclear neutrophils and plasma were found to be associated with the presence of AAA (107). Markers of ECM degeneration including elastin peptides and MMP-9, and inflammatory markers such as IFN-γ (53) and MIF (97) have been proposed as biomarkers for AAA disease (46). With respect to ncRNAs, miR-24 may represent a biomarker for AAA development (60), and miR-195 might be of prognostic value to predict the growth of AAAs (141).

The second aim of understanding the mechanisms of AAA disease is to discover possible targets for medical intervention at earlystage. Such medical intervention might counteract AAA development or stabilize the aortic wall, and thereby prevent future AAA growth and rupture. Inhibition of MCP-1 (specifically in bone marrow-derived cells), to reduce monocyte recruitment into the aortic wall, has been proposed as a potential therapeutic option (89). Inducing a shift of macrophages from a proinflammatory M1 phenotype toward an anti-inflammatory M2 phenotype might also be effective. A promising approach to attenuate AAA formation is the inhibition of AAA enhancing miRNAs. For instance, the inhibition of miR-29b (using anti-miRs) reduced AAA progression in a mouse model (81).

An alternative therapeutic option might be the overexpression or local delivery of AAA-attenuating miRNAs. Possible targets could include miR-21 or miR-24. Owing to pharmacological challenges (*e.g.*, degradation in serum by nucleases or endocytic escape) and difficulties with local delivery, systemic or local administration of naked miRNA mimics or miRNA mimics encoded in viral vectors has proven ineffective in other contexts (113). Chemical modifications (*e.g.*, methylation or locked nucleic acids) or the use of delivery systems (*e.g.*, lipid nanoparticles) are possible options to overcome these issues (113). Another problem to be solved is potential toxicity related to off-target effects.

Although there is a decent body of evidence to investigate potential effects of anti-inflammatory substances on AAA evolvement in animal models, the literature on AAA attenuating drugs in humans is limited (41, 58). Interestingly, one singular study assessed the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on AAA development. Only published as a conference abstract, the authors report a reduction in AAA growth rate (1.8 *vs.* 3.2 mm/year) in patients taking NSAIDs ($n = 19$) compared with a matched control group ($n = 59$) (36). To date, only one randomized controlled trial to assess a potential effect of an anti-inflammatory substance in human was performed. In the AORTA trial, AAA patients were allocated to different doses of the mast cell inhibitor pemirolast or placebo. After a follow-up of 12 months, no significant difference was seen in AAA growth rates in between all study arms (121). However, as the study was performed on patients who already had fully evolved AAAs, these results cannot preclude a potential effect of mast cell inhibition on early stage disease.

A potential beneficial effect of anti-inflammatory substances on AAA formation in the early stages of disease is underpinned by a recent study to investigate the impact of anti-inflammatory diet on AAA incidence. In 81,705 patients, the anti-inflammatory diet index (AIDI) was inversely associated with both ruptured and nonruptured AAA incidences (54).

One major issue in the field of AAA basic research is that most current evidence on myeloid cells and ncRNAs originates from small animal models, which makes extrapolation of results difficult. Although it is feasible to collect human AAA samples from OSR patients, acquiring samples is becoming more challenging as a growing proportion of AAA patients are treated with endovascular techniques. In addition, human AAA tissue samples nearly always reflect end-stage disease, leaving the critical mechanisms behind AAA initiation undetected.

The use of large animal models might play an important role to reduce interspecies variations and to make results more applicable to humans. Earlier studies have already been performed, showing the contribution of the lncRNA H19 during AAA formation in a porcine pancreatic elastase-induced Yucatan Ldlr$^{-/-}$ (low-density lipoprotein receptor) mini-pig aneurysm model (71). Further research using this model will potentially pave the way for novel therapeutics that inhibit aneurysm growth and limit the risk of fatal acute ruptures.

Funding Information

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Abbreviations Used

AAA = abdominal aortic aneurysm
ABCA1 = adenosine triphosphate-binding cassette transporter A1
AngII = angiotensin II
ApoE = apolipoprotein E
$CaCl_2$ = calcium chloride
Chi3l1 = chitinase 3-like 1
CX_3CR1 = C-X$_3$-C motif chemokine receptor 1
ECM = extracellular matrix
EVAR = endovascular aortic repair
Foxp3 = forkhead box P3
HIF1α = hypoxia-induced factor 1α
IFN-γ = interferon gamma
lncRNAs = long noncoding RNA
LPS = lipopolysaccharide
MAC = membrane attack complex
miRNA = short noncoding RNA
MMPs = matrix metalloproteinases
mRNA = messenger RNA
ncRNA = noncoding RNA
NET = neutrophil extracellular trap
NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells
NSAID = nonsteroidal anti-inflammatory drug
OSR = open surgical repair
PAOD = peripheral arterial occlusive disease
PTEN = phosphatase and tensin homolog
SMC = smooth muscle cell
STAT = signal transducer and activator of transcription
T_{eff} = T effector
TGF-β = transforming growth factor beta
TIMP = tissue inhibitor of metalloproteinases
TNF-α = tumor necrosis factor alpha
T_{reg} = regulatory T
VALT = vascular-associated lymphoid tissue