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Novel Mechanisms of Abdominal Aortic Aneurysms

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Abstract

Abdominal aortic aneurysms (AAAs) are a common but asymptomatic disease that has high susceptibility to rupture. Current therapeutic options are limited to surgical procedures because no pharmacological approaches have been proven to decrease either expansion or rupture of human AAAs. The current dearth of effective medical treatment is attributed to insufficient understanding of the mechanisms underlying the initiation, propagation and rupture of AAAs. This review will emphasize recent advances in mechanistic studies that may provide insights into potential pharmacological treatments for this disease. While we primarily focus on recent salient findings, we also discuss mechanisms that continue to be controversial depending on models under studies. Despite the progress on exploring mechanisms of experimental AAAs, ultimate validation of mechanisms will require completion of prospective double-blinded clinical trials. In addition, we advocate increased emphasis of collaborative studies using animal models and human tissues for determination of mechanisms that explore expansion and rupture of existing AAAs.

Keywords

abdominal aortic aneurysms; macrophages; cytokines; proteases; phospholipids

Introduction

Abdominal aortic aneurysms (AAAs) are defined as permanent dilations of the abdominal aorta that predispose to a fatal consequence of aortic rupture. The diagnosis of AAAs is commonly an accidental finding, although there is an increasing number of screening programs, especially targeting high risk populations [1]. A number of screens demonstrate that the disease prevalence is approximately 5% in men and 1% in women over 60 years old [2–4]. The number of deaths attributed to AAA rupture is nearly 15,000 annually in the United States [5]. However, this is likely to be largely underestimated since death from AAA rupture is not readily discernible from other forms of mortality.

While the prevalence of AAAs is greater in men than in women, there is emerging evidence that women succumb to AAA rupture at smaller dimensions than men [6]. Therefore, AAA is a critical disease for both men and women. Currently, the only available treatment is surgical repair [2,4]. The classic surgical approach is insertion of an intraluminal graft

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through open access to AAAs, which has largely been supplanted by an endovascular repair approach. Although both surgical approaches are effective in reducing aortic rupture, both procedures carry a potential operative risk [7]. No pharmacological approach has been proven to effectively prevent expansion or rupture of AAAs. This lack of effective therapies can be partly ascribed to a paucity of defined mechanisms of AAA progression and rupture. The present review focuses on recent advances that have provided mechanistic insights into this devastating disease.

Approaches to Defining AAA Mechanisms

Human AAAs can be detected easily and measured with ultrasound or with a greater accuracy using 3-dimensional images constructed with CT scanning. However, there have been limited mechanistic insights derived from associative physical measurements of AAAs to plasma concentrations of a wide range of bioactive factors that have been putatively linked to the disease [8]. Some landmark studies of the disease etiology have been established from histological and biochemical characterizations of human AAAs, which were obtained from surgically acquired AAA tissues [9]. However, the increased use of endovascular approaches to repair AAAs has markedly diminished acquisition of diseased human aortas. Even before the advent of endovascular approaches, open surgical repairs have only provided AAA samples at advanced stages. Autopsy has the potential to acquire aortic tissues at different stages of human AAAs. While autopsy acquisition has provided mechanistic insight into other vascular diseases such as atherosclerosis [10], this approach to acquiring human AAA tissues is impeded by the low incidence of the disease and the heterogeneous features. Therefore, there are significant barriers to garnering insights into the AAA mechanisms directly from humans.

Given these difficulties in defining mechanisms of human AAAs, research has relied greatly on animal models of the disease. Although there have been AAA models in rats for over 2 decades [11], animal-based research on AAAs has rapidly progressed following the introduction of mouse models [12]. In the three most commonly used mouse models, development of AAAs is initiated by chronic subcutaneous infusion of angiotensin II (AngII) [13], transient intraluminal perfusion of elastase [14], or brief adventitial exposure to a concentrated calcium chloride solution [15]. There are several potential shortcomings in mechanistic studies using these mouse models. One issue is that the vast majority of mouse studies only define mechanistic effects on AAAs within the initial 2 to 4 weeks of development of the disease. Knowledge of this early stage of the disease is scant in human AAAs and is not the phase in which therapy is implemented. Another consideration of these animal models is that no single mouse model fully recapitulates all pathophysiological features observed in human AAAs. Therefore, caution needs to be applied in extrapolating mechanisms from these models to the full spectrum of the human disease. Given these limitations, use of multiple models to define concordance of a mechanism has potential merits. Indeed, there is some advocacy for requiring multiple models to define a mechanism based on the assumption that there are greater chances of extrapolation to the human disease. An implicit assumption of a requirement for multiple models is that each model has known and equivalent predictive value for the human disease. Unfortunately, deficiencies in knowledge regarding the human AAA natural history does not currently enable a determination of the predicative values of mechanisms defined in any mouse model to the human disease. Until greater insight is obtained into the natural history of the human disease and the level of recapitulation in the different mouse models, setting a publication standard of requiring concordance in two mouse models could hinder dissemination of important new mechanistic insight. This current level of uncertainty about the utility of the mouse models highlights the need for continued cooperation of investigators in animal and human AAA research.

The current literature shows similarities and differences among mouse models. Selected examples are provided in Table 1 and Table 2. While cognizance of shortcomings of mouse models needs to be appreciated, they remain the most common approach for defining mechanisms of AAA development and progression.

Cellular and Molecular Mechanisms of AAAs

We have discussed previously multiple potential cellular and molecular mechanisms associated with the contribution of the renin-angiotensin system to AAAs [16–19]. In this section, we focus primarily on more recent findings regarding previously recognized molecular and cellular mechanisms, in addition to some novel mechanisms that have been explored recently in animal models.

The characteristic pathology of AAAs is progressive aortic dilation promoted by an inflammation-related disruption of homeostasis between matrix synthesis and degradation. Therefore, it is not surprising that a wide array of mechanisms have been proposed as potential contributors to development of AAAs.

Inflammatory Cells

Many inflammatory cell types have been identified in AAA tissues. The most common are macrophages. In a rabbit model with AAAs induced by periaortic application of calcium chloride, a striking feature is macrophage accumulation in the adventitia [20]. This feature is also significant in elastase-induced AAAs of rats, while macrophage accumulation within the aortic media becomes pronounced 3 weeks after elastase perfusion [11]. In mice infused with AngII, macrophage infiltration in medial layers of the aorta accompanied by medial rupture is one earliest characteristic [21], and accumulation of macrophages in the adventitia is also profound through the initiative to advanced stages of AAAs [22–24].

Besides evidence of macrophage presence in AAA tissue, there are indications that this cell type actively contributes to AAA formation. CCR2 and monocyte chemoattractant protein-1 (MCP-1) interactions are important for monocyte chemotaxis and many macrophage-mediated inflammatory responses. Deficiency of CCR2 in mice attenuates AngII-induced AAAs [25,26] and calcium chloride-induced AAAs [27]. Myeloid differentiation factor 88 (MyD88) also plays a critical role in macrophage-mediated inflammation. Deficiency of this molecule in macrophages diminishes AngII-induced AAAs in mice [28]. Telomerase reverse transcriptase (TERT), the enzyme to stabilize telomeres, is highly active in macrophages in vascular diseases. Deficiency of this enzyme in macrophages leads to attenuation of AngII-induced AAAs in mice [29]. Although there is compelling evidence that both the presence and function of macrophages are critical in the development of AAAs, it is currently unclear whether specifically targeting macrophage function would improve AAAs in humans.

Both T and B lymphocytes are also frequently detected in AAAs [13,21]. A functional deficiency of CD4+ CD25+ T regulatory cells were reported in patients with AAAs [30]. Disruption of the balance of T helper type 1 and type 2 cell functions induces AAAs in mice with allografted aortas [31]. Nevertheless, total lymphocyte deficiency achieved via genetic deletion of recombination activating gene-1 (Rag-1) did not influence AngII-induced AAAs in ApoE−/− mice [32].

Neutrophils are also present in AAAs of both humans [33] and animal models [34]. An adhesion molecule, L-selectin, is an important mediator for neutrophil recruitment in elastase-induced AAA formation in mice [35]. Neutrophil depletion in mice with aortic perfusion of elastase led to attenuation of AAAs [34].

In addition to leukocyte infiltration, roles for mast cells have also been recognized in AAA tissues from humans [36] and animal models [36–38]. This cell type synthesizes and releases multiple proteases and inflammatory mediators, thereby playing a critical role in inflammation and immunity. There is evidence from both mouse and rat models that deficiency of mast cells reduces AAAs [36,37].

Therefore, the experimental literature has invoked major roles for all the major classes of leukocytes. The ability of this array of cell types to inhibit AAAs infers some level of co-operability in promoting the disease. Indeed, there are some well-known interactions between some leukocyte classes. However, the mechanisms by which deletion of different leukocyte classes can equivalently ablate experimental AAAs need to be further studied.

Cytokines and Chemokines

Roles of many cytokines and chemokines have been determined in the development of AAAs [39]. Tumor necrosis factor (TNF)-α is one of the landmark cytokines in many inflammatory responses. TNF-α is increased in plasma from patients with AAAs [40] and in human AAA tissues [41–43]. TNF-α-converting enzyme (TACE or ADAM17) [42,43] and osteoprotegerin, a secreted glycoprotein member of the TNF receptor superfamily is enhanced in human AAAs [44]. Genetic deficiency or pharmacological inhibition of TNF-α by administration of infliximab attenuates calcium chloride-induced AAAs in mice [45]. Temporal depletion of TACE in mice leads to a reduction of AAAs induced by calcium chloride [43]. While these findings implicate an important role of TNF-α and its related signaling in AAAs, deficiency of the p55 TNF receptor did not show a significant role in AngII-induced AAAs in LDL receptor−/− mice [46]. The availability of thalidomide that inhibits TNF-α synthesis offers a potential approach to validating the role of this cytokine in the human disease.

Transforming growth factor (TGF)-β is another critical cytokine in many inflammatory processes. Although a human investigation did not find an association of genetic polymorphisms in TGF-β receptors and serum TGF-β 1 concentration with human AAAs [47], TGF-β receptor 2 is downregulated in human AAA tissues [48]. Systemic blockade of TGF-β activity augments AngII-induced AAAs in C57BL/6 mice and hypercholesterolemic mice and is associated with smooth muscle cell death, elastin degradation, and enhanced vascular inflammation [49 XX]. Responses of T helper type 1 and type 2 cells are not necessary for blockade of TGF-β to AngII-induced AAAs, whereas depletion of circulating monocytes with clodronate-containing liposomes profoundly reduces AAAs supporting a role of macrophages as the source for this cytokine [49 XX]. In a rat model with chimeric aneurysms located in the infrarenal aorta, TGF-β 1 overexpression via endovascular delivery of an adenoviral construct stabilizes pre-existing aortic aneurysms [50]. Cyclosporine A, an immunosuppressive drug of the calcineurin inhibitor, induces TGF-β 1 transcription and activates latent TGF-β 1. This drug attenuates AAAs in both elastase-induced AAAs in rats and calcium chloride-induced AAAs in mice [51]. In contrast, administration of an anti TGF-β antibody abrogates the beneficial effects of cyclosporine on aneurysmal formation [51]. However, the applicability of positive effects of cyclosporine A in animal models should be considered in the context of a recent case report in which rapid growth of an AAA was noted in a patient receiving an immunosuppressive dose of cyclosporine A [52 XX].

Complement System

Complement activation is critical in immune responses and can be mediated by the classical pathway started with antigen-antibody action, the lectin pathway initiated through its specific carbohydrate recognition complexes, or the alternative pathway activated via C3 hydrolysis. Factor B is an essential component of the alternative pathway, and C4 is

involved in both the classical and lectin pathways. Factor B deficiency, but not C4 deficiency, attenuates elastase-induced AAAs in mice [53], inferring that the alternative pathway, not the classical and lectin pathways, is essential in AAA development. There is further evidence demonstrating the importance of the alternative pathway by showing that properdin, which stabilizes the membrane attack complex, is required for the development of elastase-induced AAAs [54 X]. Conversely, CD59, a key regulator that inhibits the membrane attack complex, protects against AngII-induced AAAs in ApoE−/− mice [55].

Proteases

Multiple matrix metalloproteases (MMPs) have been implicated in human AAAs. MMP-9 is the most frequently studied MMP in human AAAs. A recent meta-analysis included 8 case-control studies that compared serum or plasma MMP-9 concentration between patients with AAAs and subjects without AAAs [56]. While pooled analyses having demonstrated significantly higher circulating MMP-9 concentration in AAA patients than in subjects without AAAs, heterogeneity of circulating MMP-9 concentration was also evident, with value range of 30 – 750 ng/L in patients with AAAs and 9 – 680 ng/L in subjects without AAAs [56]. Roles of MMP-9 on AAA formation have also been studied using MMP-9 deficient mice. MMP-9 deficiency attenuated elastase-induced AAAs [14]. MMP-9 deficiency also reduced calcium chloride-induced AAAs in mice [15]. Infusion of competent macrophages from wild type mice reversed the protection effects of MMP-9 deficiency on AAA formation, indicating macrophage-derived MMP-9 is required in the development of AAAs [15]. The validation of MMP-9 as a critical component of human AAAs is compromised by lack of a specific pharmacological MMP-9 inhibitor. Several studies showed that doxycycline, a broad inhibitor of multiple MMPs, ameliorated elastase-induced AAAs in rats [57,58] and mice [14], and AngII-induced AAAs in mice [59,60]. Additionally, several others MMPs were studied in genetic deficient mice. MMP-8 deficiency in mice did not change elastase-induced AAAs [34]. Deficiency of macrophage-derived MT1-MMP [61 X] or MMP-2 [15] attenuated calcium chloride-induced AAAs in mice. MMP-12 deficiency in mice reduced calcium chloride-induced AAAs [62], but did not change elastase-induced AAAs in mice [14].

Cysteine and serine proteases are also present in AAAs. Dipeptidyl peptidase is a lysosomal cysteine protease critical for activation of neutrophil elastase and some other proteases. Deficiency of dipeptidyl peptidase attenuates elastase-induced AAAs in mice, which is restored by adoptive transfer of neutrophils from wild type mice [63]. Cathepsin K, L, and S are also detected in human AAAs [64,65]. Both cathepsin L deficiency [66] and cathepsin K deficiency [67] markedly reduce elastase-induced AAAs in mice. However, cathepsin K deficiency does not affect AngII-induced AAAs in ApoE−/− mice [68]. Cystatin C, a cysteine protease inhibitor, is diminished in human AAAs [65], and aortic diameters of human AAAs are inversely correlated with serum cystatin C levels [65]. Cystatin C deficiency augments AngII-induced AAAs in ApoE−/− mice [69]. Inhibition of calpain, a calcium-dependent cysteine protease, also reduces AngII-induced AAAs [70].

Among serine proteases, chymase and urokinase-type plasminogen activator (uPA) were studied in AAAs. Deficiency of mast cell chymase prevents elastase-induced AAAs in mice [71], and pharmacological inhibition of chymase reduces AngII-induced AAAs in ApoE −/− mice [72]. Plasminogen degrades multiple extracellular matrix proteins through conversion of plasmin. Deficiency of plasminogen in mice attenuates calcium chloride-induced AAAs in mice, which is reversed by administration of active MMP-9 to plasminogen deficient mice [73]. Plasminogen activator inhibitor-1 (PAI-1) is a natural inhibitor of uPA. Inhibition of PAI-1 via administration of recombinant adenovirus containing the human PAI-1 gene prevents AngII-induced AAAs in ApoE−/− mice only through a local delivery (intra-adventitial injection), but not through systemic delivery (tail vein injection) [74]. Studies

regarding effects of uPA on AAAs have yielded conflicting results. While it was previously reported that uPA deficiency attenuated AngII-induced AAAs in both ApoE−/− mice and C57BL/6 mice [75], our recent study was unable to demonstrate a protective effect of uPA on AngII-induced AAAs in both LDL receptor−/− mice and C57BL/6 mice [76]. In contrast, aortic rupture rate was increased in LDL receptor−/− mice with uPA deficiency [76]. The basis for these conflicting results is unclear.

Overall, many proteases have demonstrated roles in experimental AAAs. An intriguing aspect of this body of work is that although multiple proteases have been implicated, deficiency of a single protease frequently ablates AAA development. As noted above for leukocytes, this may imply a complex cooperation between proteases in some modes that have yet to be determined.

Phospholipid Components

Phospholipids are a class of lipids that not only play critical roles in maintaining cell membrane structure, but also are important inflammatory mediators. Key components in the biosynthesis of cysteinyl-leukotrienes including 5-lipoxygenase (5-LO) and leukotriene C4 synthase are markedly increased in human AAA tissues [77]. While there are no reports for contributions of leukotriene C4 synthase to AAAs in animal models, studies regarding the role of 5-LO yielded conflicting results. Deficiency of 5-LO attenuates hyperlipidemia-induced AAAs [78], but has no effect on AngII-induced AAAs in mice [79]. A pharmacological inhibitor of 5-LO, MK-0591, does not influence AngII-induced AAAs in ApoE−/− mice [79], while another 5-LO inhibitor, LP105, reduces AngII-induced AAAs in ApoE−/− mice [80].

Cyclooxygenase (COX) and a downstream product, prostaglandin E2 (PGE2), have also been implicated in human AAAs [81]. A nonselective COX inhibitor, indomethacin, prevents elastase-induced AAAs in rats [82]. Further studies in a mouse model with AngII-induced AAAs have demonstrated that COX-2 deficiency [83] or its specific pharmacological inhibition [84] reduces AAAs. Microsomal PGE2 synthase-1 (mPGES-1), the enzyme to generate PGE2, contributes to AngII-induced AAAs [85]. Transcripts of PGE2 receptors such as EP2, EP3, and EP-4 are abundant in human AAA tissues [86]. In aortic explants harvested from human AAA tissues or human aortic smooth muscle cells, PGE2 stimulates IL-6 secretion by activation of EP4 in macrophages [86,87]. One research group has shown that pharmacological inhibition (ONO-AE3-208) or genetic disruption (EP4+/−) of EP4 attenuates AAA formation in both AngII-infused ApoE−/− mice and wild type mice with periaortic application of calcium chloride [87]. In contrast, as reported by another group, deletion of EP4 on bone marrow-derived cells augments AngII-induced AAAs [88]. It is unclear why EP4 deficiency in leukocytes yielded opposite effects compared to global inhibition of EP4 in AAA development.

Phospholipase A2 (PLA2) converts phospholipids to lysophospholipids and free fatty acids. Among PLA2 members, group X secretory PLA2 (sPLA2) plays an important role in the development of AAAs, as demonstrated by group X sPLA2 deficient mice infused with AngII [89] or periaortic application of calcium chloride [90]. Neutrophils have been identified as the source of group X sPLA2 that promotes calcium chloride-induced AAAs [90].

Taken together, evidence from animal studies shows that multiple phospholipid components are involved in AAA development. Nevertheless, many of the components exhibit conflicting effects on AAAs in same or different mouse models, implicating complex relationship between phospholipid components and development of AAAs.

Other Mediators

Activation of procarboxypeptidase B (pCPB) inhibits generation of plasmin and inactivates complement C5a and thrombin-cleaved osteopontin. Osteopontin deficiency attenuates formation of AngII-induced AAAs [91]. Deficiency of pCPB augments elastase-induced AAAs, while neither C5a nor osteopontin deficiency affects elastase-induced AAAs [92].

Syndecan-1 is a proteoglycan that regulates proinflammatory molecules and proteases. Whole body deficiency of this proteoglycan enhances AAAs as demonstrated in mice with either AngII infusion or elastase perfusion [93]. The protective effect of macrophage-derived syndecan-1 in AAA formation was determined via bone marrow transplantation using mice with aortic elastase perfusion [93].

Oxidation plays a critical role in many diseases. Diminished catalase in circulating neutrophils and plasma are detected in patients with AAAs [94]. Inducible nitric oxide synthase deficiency or pharmacological inhibition of NADPH oxidase via administration of apocynin attenuates calcium chloride-induced AAAs in mice [95], and vitamin E, a recognized antioxidant, inhibits AngII-induced AAAs in ApoE−/− mice [96].

Peroxisome proliferator-activated receptor (PPAR)(has anti-inflammatory effects and is implicated in protection of AAAs. Administration of pioglitazone did not change diameters of suprarenal aortas in 10-week-old ApoE−/− mice infused with AngII in one study [97], while this PPAR(agonist reduced aortic expansion in the same mouse strain and model at the same age [98]. Rosiglitazone attenuated the development of AAAs and aortic rupture in 12-month-old ApoE−/− mice [99 X]. Smooth muscle cell-specific deletion of PPAR(modestly reduced aortic dilation in calcium chloride-induced AAAs in mice [100]. In contrast, our recent study did not show an effect of either vascular smooth muscle cell-specific deficiency of PPAR(or pioglitazone in AngII-induced AAAs in LDL receptor−/− mice [101].

Despite lack of evidence that hypercholesterolemia is a risk factor for AAA development, effects of statins on AAAs have been studied by many investigators. There is a meta-analysis of 5 observational studies showing statins reduce expansion rate of AAAs in patients with small size AAAs (< 5 cm) [102]. Atorvastatin reduces elastase-induced AAAs in rats [103]. Simvastatin reduces elastase-induced AAAs in Wistar rats [104] and mice [105], and AngII-induced AAAs in ApoE−/− mice [106,107] and LDL receptor−/− mice fed a high fat diet [107] without changing plasma cholesterol concentrations. In contrast, another report failed to show that either rosuvastatin or atorvastatin reduced aortic expansion in AngII-infused ApoE−/− mice [108].

MicroRNAs

MicroRNAs are single-strand small RNA molecules that regulate a large number of genes and orchestrate complex pathophysiological processes in many diseases. Roles of several microRNAs in the development of AAAs have been explored recently.

The miR-29 family is composed of 3 members, miR-29a, miR-29b, and miR-29c. Diminished abundance of miR-29b, but not miR-29a and miR-29c, was detected in human AAA tissues [109 XX]. Comparably, AngII infusion into aged ApoE−/− mice increased miR-29b, but not miR-29a and miR-29c expression [110]. While inhibition of all 3 members of miR-29 via locked nucleic acid-modified antisense oligonucleotides prevented aortic dilation in 6-month-old AngII-infused ApoE−/− mice, it did not change aortic expansion after 28 days of AngII infusion [110], indicating a transient effect or an effect through a miR-29-mediated mechanism in the initiation of AAAs. Over- expression of miR-29b augmented aortic dilation, whereas inhibition of miR-29b reduced aortic dilation in mice perfused with elastase [109 XX]. In contrast to these initial findings [110], Maegdefessel et

al. [109] found reduced, not increased, expression of miR-29b in aortas from AngII-infused ApoE−/− mice (10 weeks old). In AngII-infused ApoE−/− mice, miR-29b manipulation resulted in rather modest changes of aortic diameters [109 XX]. Potential mechanisms of the conflicting findings in these two studies have been discussed in a recent commentary [111].

In both elastase and AngII-induced AAAs, miR-21 was identified as a critical mediator for proliferation and apoptosis of vascular smooth muscle cells in aneurysmal tissues [112 XX]. In contrast to the contribution of miR-29b to AAAs, overexpression of miR-21 prevented AAA formation, whereas inhibition of miR-21 augmented AAA formation [112]. Overall, reported studies have recognized the potential importance of microRNAs in the development of AAAs, which may involve classically defined pathways such as extracellular matrix protein degeneration/regeneration and TGF-β signaling [111].

Gender-related mediators

Gender is a prominent risk factor for human AAAs, with males exhibiting higher prevalence of expansion than females [6]. Similarly, expansion is greater in males than female mice in both elastase-induced and AngII-induced AAAs [113–117]. There are both similarities and differences between the mouse models in mechanisms of sex differences in susceptibility to AAA formation. In elastase-induced AAAs, transplantation of female aortas into male rats abrogated AAA protection, and administration of estradiol to male rats reduced AAA size [113]. While administration of estradiol to AngII-induced male ApoE−/− mice also decreased AAA incidence and size [118], removal of endogenous sex hormones through ovariectomy of female ApoE−/− mice had no effect on AngII-induced AAAs [116]. Rather, male sex hormones mediate gender differences in AngII-induced AAAs, since castration of male ApoE−/− mice reduced AAA incidences to that of age-matched females [116,117]. The developmental window for exposure to sex hormones appears to be critical in AngII-induced AAAs, since that administration of testosterone to 1 day old female neonatal hypercholesterolemic mice resulted in a long-lasting increase in adult AAA susceptibility [119]. Studies on mechanisms of sex differences in AAA formation in mice provide an example where discordant results between models pose difficulties in interpretation to human disease.

Conclusions

Discovery of novel mechanisms of AAAs has resulted in an enhanced understanding of this devastating disease, although there are many undefined perplexities regarding these mechanisms and their potential translational applicability. While we were only able to highlight selected recent advances in novel mechanisms of AAAs, there is evidence of continuing progress towards prevention and therapeutics of this devastating disease. Additionally, the dire need to translate the mechanistic findings into clinical practice requires an ideal animal model that mimics the established/advanced stage of human AAAs [9]. As mentioned at the outset animal models have focused on the mechanisms that prevent AAA formation. There are very limited studies in which mechanisms are studied of established experimental AAA exceptions [120]. However, in a clinical setting, therapies will only be initiated on pateitns with established AAAs. It is unclear whether continued AAA expansion and rupture occur due to the same mechanisms as the disease initiation. Therefore, greater focus should be placed on mechanisms of the expansion and rupture of existing AAAs. Such studies are assisted in rodents by the advent of ultra-high frequency ultrasound that permits sequential imaging of expanded aortic lumen dimensions [121]. These approaches permit noninvasive determinations of the AAA presence at the start of a study, and can be used to define the rate of aortic expansion. Use of genetic approaches to determine mechanisms of expansion in existing AAAs is complicated by the need to use a system that permits inducible gene expression. However, there is a growing number of

whole body and cell-specific inducible systems to facilitate these studies. In addition, well-controlled pharmacological studies remain an approach to drive mechanistic insights into expansion and rupture of existing AAAs. Beyond experimental studies, a major need for the field is completion of prospective double-blinded clinical studies to determine effects of pharmacological interventions on expansion and rupture of AAAs in humans afflicted with the disease [122].

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* Of importance

** Of outstanding importance

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Table 1

Similarities and differences in inflammation-related mechanisms of AAA formation in the three most commonly used mouse models.

Targets	Manipulation	Response to AAA Formation in Mouse Models Promoted by Different Stimuli		
		Calcium Chloride	Elastase	AngII
Macrophages	CCR2 −/−	9 [27]		9 [25,26]
	MyD88 −/−			9 [28]
	TERT −/−			9 [29]
Lymphocytes	Rag-1 −/−			:[32]
Neutrophils	L-selectin −/−		9 [35]	
	anti-neutrophil antibody injection		9 [34]	
Mast cells	$Kit^{W\text{-}sh}/Kit^{W\text{-}sh}$		9 [37]	
TNF and related	TNF-α −/−	9 [45]		
	TNF-α inhibition	9 [45]		
	TACE −/−	9 [43]		
	p55 TNF receptor −/−			:[46]
TGF-β 1	anti-TGF-β antibody injection			8 and rupture [49 XX]
	cyclosporine A	9 [51]		
Complement System	Factor B −/−		9 [53]	
	C4 −/−		:[53]	
	properdin −/−		9 [54 X]	
	CD59 −/−			8 [55]
PPAR(	pioglitazone			:[97,101] 9 [98]
	rosiglitazone			9 [99]
	SMC-specific PPAR(−/−	9 [100]		:[101]

Table 2

Similarities and differences in proteases, phospholipids, and other selected mechanisms of AAA formation in the three most commonly used mouse models.

Target	Manipulation	Response to AAA Formation in Mouse Models Promoted by Different Stimuli		
		Calcium Chloride	Elastase	AngII
	MMP-2 −/−	9 [15]		
	MMP-8 −/−		:[34]	
	MMP-9 −/−	9 [15]	9 [14]	
	MMP-12 −/−	9 [62]	:[14]	
	MT1-MMP −/−	9 [61 X]		
MMPs	doxycycline	9 [123]	9 [14]	9 [59,60]
	dipeptidyl peptidase −/−		9 [63]	
	cathepsin K −/−		9 [67]	:[68]
	cathepsin L −/−		9 [66]	
	cystatin C −/−			8 [69]
Cysteine Proteases	calpain inhibition			9 [70]
	mMCP-4 −/−		9 [71]	
	chymase inhibition			9 [72]
	mMCP-5 −/−		:[71]	
	plasminogen −/−	9 [73]		
	PAI-1 overexpression			9 [74]
Serine Proteases	uPA −/−			9 [75]; 8 rupture [76]
	5-LO −/−			:[79]
	5-LO inhibition			:[79]; 9 [80]
	COX-2 inhibition			9 [84]
	COX-2 −/−			9 [83]
	mPGES-1 −/−			9 [85]
	EP4 inhibition	9 [87]		9 [87]
	EP4 +/−	9 [87]		9 [87]
	EP4 −/− in bone marrow-derived cells			8 [88]
Phospholipid Components	group X sPLA2 −/−	9 [90]		9 [89]
Statins	atorvastatin			:[108]
	rosuvastatin			:[108]
	simvastatin		9 [105]	9 [106,107]