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Abdominal Aortic Aneurysm: Novel Mechanisms and Therapies

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Abstract

Purpose of review—Abdominal aortic aneurysm (AAA) is a pathological condition of permanent dilation that portends the potentially fatal consequence of aortic rupture. This review emphasizes recent advances in mechanistic insight into aneurysm pathogenesis and potential pharmacologic therapies that are on the horizon for AAAs.

Recent Findings—An increasing body of evidence demonstrates that genetic factors, including 3p12.3, DAB2IP, LDLr, LRP1, MMP3, TGFβR2 and SORT1 loci, are associated with AAA development. Current human studies and animal models have shown that many leukocytes and inflammatory mediators, such as IL-1, IL-17, TGF-β and angiotensin II, are involved in the pathogenesis of AAAs. Leukocytic infiltration into aortic media leads to smooth muscle cell depletion, generation of reactive oxygen species, and extracellular matrix fragmentation. Recent preclinical investigations into pharmacological therapies for AAAs have provided intriguing insight for roles of microRNAs to regulate many pathological pathways in AAA development. Several large clinical trials are ongoing seeking to translate preclinical findings into therapeutic options.

Summary—Recent studies have identified many potential mechanisms involved in AAA pathogenesis that provide insight for the development of a medical treatment for this disease.

Keywords

Abdominal aortic aneurysm; mechanism genetics; therapy; extracellular matrix fragmentation; microRNA inflammation

INTRODUCTION

Abdominal aortic aneurysm (AAA) is a pathological dilation that predisposes to the potentially fatal consequence of aortic rupture. Strong risk factors for AAA development are

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CONFLICTS OF INTEREST

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smoking, advanced age, and male gender [1]. Population screening studies have determined that the prevalence of AAAs in individuals over the age of 55 is 4–7% in males and 1–2% in females [2]. Although, several studies indicate that AAA incidence may be declining, [3] AAA mortality has not declined globally [4]. The current clinical approach to individuals diagnosed with AAAs is to monitor aortic dimensions, and perform open or endovascular surgical repair when the aortic diameter has attained sufficient expansion predisposing it to a high likelihood of rupture. Presently, no pharmacological therapy has been validated through double blinded randomized clinical trials to limit human AAA progression or rupture [5*]. It is becoming increasingly apparent that an in-depth understanding of the mechanisms involved in initiation and progression of AAAs is needed to facilitate development of effective therapies. The purpose of this brief review is to focus on recent preclinical and clinical advances that provide novel mechanistic insight into this potentially devastating disease.

GENETICS OF AAAs: Population Studies, Gene Variants and Biomarkers

Through population screening and gene-associated studies there is increasing evidence of genetic influences on AAA development. For example, a large crosssectional study of an ultrasound screened population in Denmark found family history to be one of the strongest risk factors for AAA presence [6*]. Several studies have investigated the association of specific genetic markers with AAAs using either candidate gene association or genome wide association analyses. Overall, only a few candidate gene-association studies published have been sufficiently powered to draw firm conclusions. Few associations have been replicated across sample sets. Meta analysis of case-control or candidate gene association studies have identified positive associations with the following polymorphisms: MMP-3 rs3025058 [7], SORT1 rs599839[8], TGFBR2 rs764522 and rs1036095 (Table I) [9].

Beyond candidate gene studies, genome wide association studies (GWAS) have been conducted to perform a nonbiased screen. GWAS studies have identified associations of several additional SNPs with AAAs including: DAB2IP rs7025486 [10], chromosome 3p12.3 rs7635818 [11], LRP1 rs1466535 [12,13], and low density lipoprotein receptor rs6511720 (Table I) [14]. Most of these polymorphisms do not have a readily apparent mechanism in AAA formation and the genetic approaches need to be combined with a mode of determining whether these associations are causal. Finally, recent novel studies suggest that epigenetic modification and DNA methylation may also contribute to a genetic influence on AAA pathobiology [15,16**].

Another expanding avenue of investigation in AAAs is the field of biomarkers. While contemporary imaging can readily determine the dimensions of AAAs, one of the hopes of biomarkers is their ability to discriminate propensity to rupture. Recently, two large meta-analysis studies assessed a wide array of molecular markers for application as AAA biomarkers [17,18]. Sidloff *et al* [17] demonstrated significant increase plasma concentrations of fibrinogen, D-dimer, and thrombin-antithrombin III complex in people with AAA; and also a significant correlation between aortic diameter and D-dimer In addition to these hemostasis markers. Stather *et al* [18*] demonstrated a significant difference in a number of biomakers in patients with AAAs including: matrix

metalloproteinase (MMP) 9, tissue inhibitor of matrix metalloproteinase 1, interleukin (IL) 6, Creactive protein (CRP), α1-antitrypsin, apolipoprotein A and high-density lipoprotein. Despite a wide variety of biomarkers identified in patients with AAA, their prognostic value has yet to be established.

PATHOLOGICAL MECHANISMS OF AAA DEVELOPMENT

The characteristic pathology of AAA is progressive luminal dilation accompanied by aortic wall inflammation, decreased medial smooth muscle cells, and disruption of the extracellular matrix. Many of the mechanisms contributing to this aortic pathology have been reviewed previously [19]. In this section we will focus on recent findings regarding novel mechanisms underlying AAA formation.

Cellular-Related Mechanisms

Inflammatory Cells—Several inflammatory cell types have been identified in human AAAs with the macrophage being the most common cell type present in the aneurysmal media and adventitia. C-X-C motif receptor 4 (CXCR4) and stromal cell-derived factor (SDF)-1 are important in macrophage recruitment. Antagonism of CXCR4 with a selective antagonist, AMD3100, decreased inflammation and suppressed formation and progression of AAAs in both mouse and rat models [20]. Further investigation for a role of macrophages in AngII-induced AAAs demonstrated recently that these cells are derived from monocytes released from the spleen and not from proliferation of resident progenitors [21]. Despite the prevalence of macrophages in AAAs, the specific function of these cells in this disease has not been determined.

Lymphocytes, primarily the T lymphocytes subset, are also present in experimental and human AAA tissues. Enhanced CD4+ cell infiltration augmented AAAs in both AngII-infused and elastase perfused syndecan-1-deficient mice [22]. However, T lymphocyte infiltration is not necessarily always detrimental to AAAs. Recently, a protective role for regulatory T lymphocytes (Tregs) has been demonstrated within AAA formation. Notably, a clinical report of a decreased quantity of $CD4^+CD25^+$ $Foxp3^+$ (Treg) cells in peripheral blood of patients with AAAs. This was interpreted as an impaired immunoregulation by Tregs being involved in its pathogenesis [23]. In animal models, selective depletion of Tregs promoted development and rupture of AngII-induced AAA using multiple approaches including, CD25 specific monoclonal antibody, deficiency of $CD4^+CD25^+$ Tregs by genetic disruption of CD80/CD86, or CD28 costimulatory molecules [24]. Furthermore, expansion of endogenous CD4+CD25+ Foxp3+ Tregs by an interleukin-2 complex (consisting of recombinant IL-2 and an antiIL-2 monoclonal antibody) or adoptive transfer of Tregs prevented AngII–induced AAAs in mice [25,26]. These recent data demonstrates that lymphocytes have a role on AAA formation, although the many subclasses may be complex interactions

Inflammatory Mediators—A number of pro-inflammatory and anti-inflammatory cytokines controlling leukocyte recruitment have been implicated recently in AAAs, including epidermal growth factor, IL-1β, and IL-17. Genetic depletion and selective antagonism of these specific cytokines prevented AAA formation in AngII-induced or

elastase infusion mouse models [27–29]. The importance of IL-1β to AAA pathology was demonstrated further through prevention of AngII-induced AAA formation following genetic depletion of inflammasome enzymes responsible for the proteolytic cleavage of pro-IL-1β into its mature form [30].

Another cytokine that plays a critical role in inflammatory processes is transforming growth factor (TGF)-β. Although it has been most extensively studied in thoracic aortic aneurysms, TGF-β may also have a mechanistic role in AAAs [31]. Systemic blockade of TGF-β activity or genetic deletion of SMAD3, a downstream signal of TGF-β, augmented AngII and calcium chloride-induced AAAs [32,33]. Separately, attenuation of thrombosponsin-1-directed activation of TGF-β1 promoted AngII-induced AAAs in ApoE−/− mice [34*].

Many intracellular signaling pathways have also been inferred as inflammatory mediators in development of aneurysms including Notch1 signaling and diverse pathways regulated by reactive oxygen species. Recently, increased Notch1 signaling has been demonstrated in both human aortic tissue samples as well as AngII-induced AAAs [35,36]. Haploinsufficiency in the Notch1 pathway or pharmacological inhibition prevented formation of AngII-induced AAAs in mice [35–37].

Regarding reactive oxygen species, hypoxic conditions and hydrogen peroxide induce a number of genes, including hydrogen peroxide–inducible clone 5 (Hic-5). Lei *et al*. [38] demonstrated that Hic-5 activated the mitogen-activated protein 4/p54 c-Jun N-terminal kinase pathway leading to AAA formation. Furthermore, deletion of Hic-5 in ApoE−/− mice attenuated AngII-induced AAA development [38]. However, not all enzymes involved in production of reactive oxygen species are deleterious to the integrity of the vascular wall. One enzyme known to be important in the generation of reactive oxygen species in vascular SMCs is nicotinamide adenine dinucleotide phosphate oxidase (Nox) isozyme 2. Surprisingly, deletion of Nox2 was found to augment AngII-induced AAA formation by increasing vascular inflammation in LDL receptor −/− mice fed a saturated fat-enriched diet [39].

Leukotrienes mediate inflammatory responses in various cardiovascular diseases such as atherosclerosis and aortic valve disease. 5-Lipoxygenase (5-LO) is a key enzyme in leukotrienes biosynthesis [40]. To date, studies investigating a role of 5-LO in AAA have been equivocal [41–43]. Recently, additional studies have investigated the relation of 5-LO with AAA pathogenesis demonstrating that genetic depletion or pharmacological inhibition of 5-LO inhibited formation of AAAs in the elastase and AngII-induced animal models [44*].

Finally, a number of animal studies have demonstrated a relationship between the renin-angiotensin-aldosterone system (RAAS) and AAA development. The most direct implication of the RAAS is the demonstration of AAA formation during subcutaneous infusion of AngII into normo-and hypercholesterolemic mice [45]. In rodent models of AAA, including those relying on AngII or employing chemical agents, AT1 receptor blockers (ARBs) inhibited aneurysm development [46,47]. Recently, aliskiren, a direct renin inhibitor, limited progression and inflammation of established AAAs in ApoE−/− mice [48].

Furthermore, Liu *et al*. [49] demonstrated that aldosterone can provoke aneurysm formation independently of AngII related mechanisms [49,50].

Smooth Muscle Cells—Aneurysms are characterized by depletion of medial smooth muscle cells (SMCs) in the aortic wall. Although the paucity of SMCs in AAA tissue has been documented extensively, it is not entirely clear whether cell death is an active pathological event or a consequence of tissue deterioration. Historically, apoptosis and necrosis have been considered two distinct forms of cell death. However, accumulating experimental evidence asserts that certain forms of necrosis are regulated by orchestrated signaling networks, and should be considered as programmed necrosis or necroptosis [51]. Receptor-interacting serine/threonin-protein kinase 3 (RIPK3) has been identified as a critical mediator of the necroptosis process. Wang *et al*. [52] demonstrated that deletion of RIPK3 reduced vascular SMC cell necroptosis and inhibited development of elastaseinduced AAAs in C57BL/6 mice [52].

In recent investigations, low density lipoprotein receptor related protein 1 (LRP1), a protein highly expressed in vascular SMCs, has been linked to the presence of human AAAs [12,13]. In mouse studies, SMC–specific deletion of LRP1 increased tissue content of high temperature requirement factor A1t, a molecule that regulates extracellular matrix integrity [53]. However, a role of LRP1 in aneurysmal disease development remains to be defined as SMC deletion of LRP1 exacerbated ascending, but not abdominal aortic aneurysm, formation during AngII infusion [54].

Extracellular Matrix Fragmentation

Permanent luminal dilation is a defining characteristic of AAAs. Dilation in any region of the aorta is typically accompanied by proteolytic degradation of extracellular matrix. Two commonly considered classes of proteases that are assumed to be responsible for extracellular matrix degradation are cathepsins and matrix metalloproteinases (MMPs) [55–57]. Evidence for involvement of cathepsins was provided by the recent demonstration that deficiency of cathepsin K or cathepsin G attenuated elastase or calcium chloride-induced AAAs, respectively [58,59]. A major regulator of protease activity and MMPs is osteoprotegerin that is positively associated with human AAA growth [60]. Genetic deficiency of osteoprotegerin inhibited AngIIinduced aortic dilatation and reduced aortic concentrations of MMP-2 and MMP-9 in ApoE−/− mice [61].

Post-transcriptional Regulators

Given that AAA formation involves a complex interaction of cellular-related mechanisms, inflammatory mediators, and extracellular matrix degradation, a novel therapeutic approach for AAAs would modulate these extensive functional networks. This has been demonstrated recently through use of microRNAs. MicroRNAs, are small, noncoding RNAs, that have emerged as key post-transcriptional regulators for a large number of genes and physiological processes occurring during AAA development. Five microRNAs have been implicated recently in AAA development including: miR-21, miR-24, miR-29b, miR-712, and miR-205. Inhibition of miR-29b reduced aortic dilation in elastase-perfused and AngII-infused mice [62]. In contrast, overexpression of miR-21 or miR-24 inhibited AAA

development induced by either elastase or AngII infusions [63,64]. The varying effects of overexpression or inhibition of microRNAs on AAA formation relate to the downstream gene targets of each specific microRNA. This is highlighted further in miR-712, which contributes to AAA formation by targeting and preventing translation of endogenous inhibitors of MMPs. This action subsequently produces overactivation of proteases. Silencing of miR-712 or human homolog miR205 in AngII-infused mice decreased leukocyte accumulation and aneurysm formation [65*]. Alterations in microRNA profiles have also been reported in human aortic aneurysmal tissue samples [66].

An intriguing role for microRNAs is as an AAA biomarker as they are stable and measurable with high sensitivity in human blood. Recently, both miR-24 and miR-195 were shown to inversely correlate with aneurysm size [63,67]. While concentrations of miR-15a-3p and miR-30a-5p were increased in plasma of AAA patients [68]. Currently, it is unclear if manipulation of microRNAs represents a viable therapeutic strategy for AAAs in humans. Challenges remain in microRNA manipulation, such as potential offtarget effects and a need for local or cell type specific delivery mechanisms prior to deployment of a clinically feasible therapy [69].

POTENTIAL MEDICAL THERAPY FOR HUMAN AAAs

Current clinical management of AAAs is determined by aortic size or percent luminal dilation. Once risk of rupture exceeds risk of surgery, patients may undergo surgical repair. Although surgical procedures have become increasingly sophisticated and less invasive, there remains no pharmacological therapy validated through control trials that limits AAA progression or the risk of rupture [5*]. In this section, we will focus on ongoing clinical trials that are determining whether preclinical findings translate to effective clinical approaches (Table II).

Given the predominance of inflammatory cells in AAAs, several large clinical trials are ongoing to analyze the effects of immunosuppresion via cyclosporine (NCT02225756) or IL-1β specific inhibition (NCT02007252) on AAA progression. Additionally, permanent aortic dilation via degradation of the extracellular matrix is another defining characteristic of aortic aneurysms. In humans, MMPs have been most extensively studied [70,71]. Doxycycline, a broad spectrum MMP inhibitor, has been investigated as a potential medical approach for preventing AAA progression in animal models [72]. Recently, a randomized trial of 286 patients unexpectedly found that doxycycline administration significantly increased AAA expansion [73**]. Although further examination of doxycycline as a treatment for AAAs is ongoing in an additional randomized control trial (Non-Invasive Treatment of Abdominal Aortic Aneurysm Clinical Trial - NCT01756833), the most recently completed trial firmly challenges its therapeutic benefit.

Clinical studies have also investigated the importance of the renin-angiotensin system to aortic aneurysm. A small clinical study demonstrated that treatment with an angiotensin converting enzyme (ACE) inhibitor 4 weeks prior to surgery reduced inflammation in AAA tissues compared to placebo controls [74]. Recently, a nationwide retrospective cohort study demonstrated that patients treated with ACE inhibitors or ARBs had reduced AAA

mortality[75**]. Currently, there are several large randomized control trials ongoing that are designed to investigate effects of ACE inhibition (AARDVARK - NCT01118520), ARBs (TEDY - NCT01683084; and NCT01904981), or aldosterone antagonism (NCT02345590) on AAA growth rate.

CONCLUSION

AAA is an asymptomatic and potentially lethal disease. Recently, there has been expansion in research on genetic and molecular mechanisms of AAA formation. These studies provide insight into cellular pathways, extracellular matrix fragmentation, inflammatory mediators, and microRNAs. Despite these advances, many uncertainties remain regarding mechanisms of aneurysm development. This lack of understanding hinders development of effective therapies to prevent AAA progression and rupture. Currently, there are several clinical trials ongoing. Continued cooperation between preclinical and clinical investigators is necessary to further unravel mechanisms of AAA and validate medical approaches.

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Abbreviations

AAA	Abdominal aortic aneurysm
AngII	Angiotensin II
MMP	Matrix metalloprotease
RAAS	Renin-angiotensin-aldosterone system
SMC	Smooth muscle cell

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KEY POINTS

- Several genetic loci and alterations in DNA methylation have been associated with AAAs.
- Human studies and animal models have shown that several classes of leukocytes and inflammatory mediators, such as IL-1, IL-17, TGF-β and angiotensin II, are important in AAA pathogenesis.
- Novel investigations have demonstrated that microRNAs regulate many pathological pathways in AAA development.
- Ongoing randomized clinical trials are investigating if pharmacological inhibition of protease activity, inflammation, platelet activation, or the renin-angiotensionaldosterone system may be used as effective therapeutic options for AAAs.

Table I

Genetic loci implicated with candidate gene association meta-analysis					
		Population			
Genetic Locus	SNP	Cases	Controls	OR (95% CI)	P*
MMP3	rs3025058	1258	1406	1.48 (1.23–1.78)	3.95×10^{-5}
SORT1	rs599839	7048	75976	0.81 (0.76–0.85)	7.20×10^{-14}
TGFBR2	rs764522	1904	2616	1.69 (1.28–2.25)	2.70×10^{-4}
TGFBR2	rs1036095	1904	2616	1.59 (1.23–2.07)	4.80×10^{-4}
Genetic loci implicated with genome-wide association studies					
		Population			
Genetic Locus	SNP	Cases	Controls	OR (95% CI)	P*
3p12.3	rs7635818	502	736	1.33 (1.01–1.21)	0.0028
DAB2IP#	rs7025486	1292	30503	1.21 (1.11–1.32)	4.6×10^{-10}
LDLR#	rs6511720	1830	5435	0.76 (0.70–0.83)	2.08×10^{-10}
LRP1#	rs1466535	1866	5435	1.15 (1.10–1.21)	4.5×10^{-10}

95% CI, 95% confidence interval; SNP, single nucleotide polymorphism

*P values are taken from the original report

#Replicated across multiple populations

Table II

Ongoing Randomized Clinical Trials for Medical Management of AAAs

Target	Intervention	Primary Outcome	Estimated Completion	Trial Registration
Extracellular Matrix				
MMP inhibition	Doxycycline (100 mg twice daily) vs placebo	AAA growth by CT	2017	NCT01756833
Cellular-Related				
Platelet inhibition	Ticagrelor (90 mg twice daily) vs placebo	AAA volume growth by MRI	2015	NCT02070653
Renin angiotensin aldosterone system				
Angiotensin receptor antagonism	Telmisartan (40 mg daily) vs placebo	AAA diameter change by CT	2016	NCT01683084
Angiotensin receptor antagonism	Valsartan (80 mg daily) vs atenolol (50 mg daily)	AAA growth by CT	2016	NCT01904981
ACE inhibition	Perindopril (10 mg daily) vs amlodipine (5 mg daily) vs placebo	AAA growth by U/S	2015	NCT01118520
Aldosterone antagonism	Eplerenone (25 mg daily) vs placebo	Maximum AAA orthogonal diameter	2019	NCT02345590
Anti-inflammatory				
Calceneurin inhibition	Cyclosporine A (two different doses daily) vs placebo	AAA diameter change by CT	2018	NCT02225756
IL-1β Antibody	Subcutaneous ACZ885 (monthly) vs placebo	AAA growth rate by U/S	2015	NCT02007252

MMP, Matrix metalloproteinase; CT, Computerized tomography; MRI, Magnetic resonance imaging; ACE, Angiotensin converting enzyme; U/S, ultrasound.