Updates of Recent Aortic Aneurysm Research

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Aortic aneurysms are defined as a pathological condition characterized by permanent dilation of the aorta that most commonly occurs in the infrarenal and proximal thoracic regions. While generally asymptomatic, progressive aneurysmal dilation is associated with the devastating consequence of aortic rupture. Current therapeutic options to prevent aortic rupture are restricted to surgical repair, with an absence of proven pharmaceutical treatments to prevent progressive growth or rupture. Although surgical treatments have become increasingly sophisticated and less invasive over the previous decade,[1] there remains an urgent need to identify pathways that predispose to aneurysmal formation and to divert treatment from surgical to medical approaches.[2] An improved understanding of the subcellular mechanisms and regulatory networks triggering aneurysm development and subsequent expansion is essential for discovery of novel therapeutic targets. This article highlights recent publications in the journal of *Arteriosclerosis, Thrombosis, and Vascular Biology* that provide insights into understanding mechanisms and potential therapeutic strategies for aortic aneurysms.

Abdominal Aortic Aneurysms

Human Studies

Abdominal aortic aneurysms (AAA) are the most common form of aneurysmal disease with dilation typically presenting in the infrarenal region. The incidence of AAA increases with age and is positively associated with smoking.[3,4] Population ultrasound screening studies have reported that the prevalence of AAA is 4% to 7% in males over the age of 65, and 1% to 2% in females, with some studies indicating decreased AAA incidence.[5,6] The falling prevalence of AAA in the developed countries has largely been credited to falling rates of tobacco use.[7]

Recently, several population studies have provided enhanced insights into pathological risk factors for AAA. Human AAA surgical samples are characterized by the presence of cholesterol crystals and macrophage infiltration.[8] Two recent meta-analyses have demonstrated a potential role of lipoproteins in the pathogenesis of AAA.[9,10] In addition, HDL (high-density lipoprotein) cholesterol concentrations have been shown to predict aneurysmal growth rate in a population-based prospective cohort study.[11] To understand how HDL particles influence aneurysmal disease, Martínez-López et al[12] analyzed the composition of HDL in AAA patients and the impact of HDL particles on macrophage cholesterol efflux. Patients with AAA exhibited lower apoA-I and plasma HDL cholesterol concentrations in comparison to control subjects. Further, ApoB-depleted plasma from AAA patients displayed an impaired ability to promote macrophage cholesterol efflux, implicating impaired HDL function as a mechanistic association with AAA.

Within regions of AAA expansion, aneurysms commonly develop an intraluminal thrombus adjacent to regions of maximal aortic diameter.[8,13] Finite element analyses using computed tomography angiography from AAA patients demonstrated that cracks and fissures in the intraluminal thrombus increased wall stress on the underlying AAA wall.[14] It also implicates that differences in intraluminal thrombus composition may result in different quantities and compositions of biologically active proteins accumulating near and within AAA tissue. To further investigate the effects of intraluminal thrombus on aortic aneurysm progression, one study[15] performed a single-center proteomic analysis of human tissue samples collected from the AAA wall and thrombus at the time of operative repair. These analyses demonstrated a negative association between AAA growth rates and ECM (extracellular matrix) proteins and a large number of proteins related to cellular functions, but a positive correlation between AAA growth and increased abundance of multiple plasma proteins within the intraluminal thrombus and arterial wall. These findings implicate that increased porosity of the intraluminal thrombus may have led to plasma proteins diffusing to the aortic wall.

Diabetes mellitus is associated with lower risk for AAA.[16,17] There is also experimental evidence that hyperglycemia attenuates AAA development in elastase or Ang II (angiotensin II)–induced AAA.[18] Hemoglobin A1c reflects an average of blood glucose concentrations within an extended interval of ≈3 months in humans. Using the participant information collected from the VIVA (Viborg Vascular) randomized screening trials of the Central Denmark Region, Kristensen et al[19] reported that growth rates of AAA were inversely associated with concentrations of hemoglobin A1c. This study provides insights that long-lasting elevated blood glucose concentrations impair progression of AAA in humans. However, molecular mechanisms by which hyperglycemia reduces the progression of AAA expansion remain unclear.

Animal Studies

Given the difficulty in defining mechanisms of AAA in humans, research has been relying heavily on the use of

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animal models. A review by Sénémaud et al[20] diligently discussed the similarities and differences among these models as well as their translational relevances.

Recently Reported AAA Models

A variety of animal models have been developed to better understand the pathophysiology of AAA. The 3 most commonly used mouse AAA models are adventitial exposure to calcium chloride, transient perfusion of elastase into the infrarenal aorta, and chronic subcutaneous infusion of Ang II.[21–25] A spectrum of potential mechanisms of AAA development have been studied using these mouse models in their original or modified forms. Unfortunately, none of these established models fully recapitulate the human pathophysiology of aortic aneurysmal disease.[20] To address deficiencies of the present animal AAA models, several modifications have been described including coadministration of Ang II and a TGF (transforming growth factor)-β neutralizing antibody, as reported by several laboratories.[26–28] Recently, Lareyre et al[29] combined topical application of elastase with systemic inhibition of TGF-β, accomplished by intraperitoneal injection of a TGF-β neutralizing antibody. Elastase stimulation with inhibition of TGF-β led to progressive dilation of the infrarenal aorta and aortic rupture. Synchron-based high-resolution imaging detected elastin degradation, adventitial thickness, intraluminal thrombus, medial dissection, or rupture. Depletion of monocyte or genetic depletion of IL (interleukin)-1β in mice prevented aortic dilation and rupture in this mouse model. However, administration of an IL-1β neutralizing antibody did not improve aortic rupture when initiated 7 days after elastase application, implicating that inhibition of IL-1β would have no beneficial effects on preexisting AAA. We hope that future research would gain pathophysiologic insights into the human disease with extensive application of this mouse model.[30]

Sex Differences in AAA Pathology

Male sex is the most potent nonmodifiable risk factor for AAA, with estimates ranging from a 4- to 10-fold higher incidence in men than in women.[31] Studies have shown that both gonadal sex hormones and sex chromosomes contribute to the increased risk for Ang II–induced AAA in hypercholesterolemic mice.[32,33] To evaluate the separate effects of gonadal sex hormones and sex chromosomes, Alsiraj et al[34,35] used an inbred mouse strain with a natural mutation in the sex-determining *Sry* gene, which was substituted with an autosomal wild-type Sry transgene. Breedings generated phenotypic males with either XX or XY sex chromosomes. XY male mice primarily developed diffuse adventitial thickening throughout the thoracic and abdominal aorta, whereas XX male mice developed aneurysms that were predominantly in the suprarenal abdominal aorta. These striking differences in regional aortic pathology were abolished by castration. These findings implicate that genes on the Y chromosome or X chromosome genes that escape X inactivation contribute to significant sex differences in regional aortic remodeling in response to Ang II infusion. Given the sexual disparities in aneurysm pathology demonstrated in this and multiple other publications, the ATVB Council has recently established guidelines for designing and reporting sex as a biological variable in animal models of aneurysmal disease.[36]

Inflammatory Cell-Related Mechanisms

Histological analyses of human AAA surgical samples have revealed leukocytic infiltration, degradation of ECM, and disruption of vascular smooth muscle cell plasticity and functions as 3 pathological hallmarks of AAA.[37] The transmural inflammation observed in AAA involves a variety of inflammatory cell types, where macrophages and lymphocytes are the most prominent with mast cells and neutrophils migrating to a lesser extent.[24,38]

Within AAA, macrophages accumulate in the aortic media and adventitia.[39] One signaling pathway shown to be involved in macrophage inflammation is FAK (focal adhesion kinase). Using human tissue specimens, Harada et al[40] demonstrated that both FAK expression and activity were enhanced in AAA lesions. In vitro experiments revealed that FAK stimulated secretion of MCP-1 (monocyte chemotactic protein-1) and MMP (matrix metalloproteinase)-9 and positively regulated MCP-1–mediated chemotaxis. Pharmacological inhibition of FAK reduced macrophage accumulation and blocked $CaCl_2$-induced AAA progression.[40] Overall, macrophages exist in either a proinflammatory (M1) or anti-inflammatory (M2) state as revealed by the effects of cytokines, including IL-1β and TNF (tumor necrosis factor)-α. Previous investigations have demonstrated that M1 macrophage polarization promotes aneurysm formation in the $CaCl_2$ model.[41] *Tnfα*$^{-/-}$ macrophages expressed higher concentrations of M2 cytokines in contrast to *Il1β*$^{-/-}$ macrophages. Further, infusion of *Tnfα*$^{-/-}$ macrophages, but not *Il1β*$^{-/-}$ macrophages, inhibited AAA formation.[42] IL-10 is an anti-inflammatory cytokine. Plasma concentrations of IL-10 have been shown to be lower in patients with AAA, compared with patients having coronary artery disease.[43,44] Increased IL-10 by systemic transfection of an IL-10 expressing nonimmunogenic minicircle vector resulted in decreased AAA formation in Ang II–infused mice. These beneficial effects on aneurysm development were accompanied by a significant increase in regulatory T cells, and local macrophages were more likely to differentiate into the anti-inflammatory M2-phenotype.[45]

Beyond macrophage phenotype, macrophage function can also be regulated by epigenetic modification including microRNAs (miRs). The investigation by Nakao et al[46] demonstrated that miR-33 was an important regulator of inflammatory cell function in AAA formation as mice with genetic deficiency of miR-33 displayed decreased AAA formation in response to Ang II infusion or calcium chloride application. Further, in vitro experiments revealed that peritoneal macrophages from miR-33$^{-/-}$ mice showed reduced MMP-9 expression via c-Jun N-terminal kinase inactivation. HDL cholesterol derived from miR-33$^{-/-}$ mice reduced expression of MMP-9 in macrophages and MCP-1 in vascular smooth muscle cells. In addition to inflammatory cell accumulation, markers of inflammasomes are present in plasma and AAA tissues.[47,48] Wu et al[48] demonstrated that activation of the NLRP3 (NACHT, LRR [leucine-rich repeat] and PYD [pyrin domain] domains-containing protein 3)-caspase-1 inflammasome cascade was associated with degradation of contractile proteins of the arterial wall.

Inhibition of the inflammasome pathway, by either genetic depletion of *Nlrp3* or *caspase-1* in mice or administration of glyburide inhibited Ang II–induced AAA formation.

CD4+ T cells have been found to be a highly prevalent cell type in end-stage aneurysmal human tissue. Through its profile of secreted cytokines, CD4+ T cells indirectly control matrix metabolism by recruitment of macrophages and regulation of ECM and protease synthesis.[38] One important signaling pathway for the communication of antigen-presenting cells, macrophages, and T Cells is the CD40-CD40 ligand interaction. Kusters et al[49] demonstrated that genetic deficiency of CD40 ligand resulted in decreased Ang II–induced AAA formation, accompanied by decreased macrophage and T-cell infiltration as well as reduced expression of MMPs.

Neutrophils are an essential component of the innate immune system.[50] Previous studies have implicated potentially important roles of neutrophils in AAA development.[51] Neutrophils are the first cell population recruited to the site of inflammation through the actions of chemokines in inflammatory vascular diseases. Investigation by He et al[52] identified FAM3D (Family With Sequence Similarity 3, Member D) as a novel chemokine involved in AAA pathogenesis. FAM3D was markedly upregulated in both human and mouse AAA tissues. FAM3D deficiency or application of FAM3D-neutralizing antibody 6D7 attenuated the development of elastase or CaPO4-induced AAA in mice. The authors demonstrated that FAM3D exhibited its effects as a dual agonist of FPR (formyl peptide receptor) 1 and FPR2, inducing macrophage-1 antigen-mediated neutrophil recruitment and aggravated AAA development. An additional investigation into the effects of neutrophil recruit on AAA formation detailed the impact of neutrophil extracellular traps. Neutrophils contributed to elastase-induced AAA in mice associated with release of neutrophil extracellular traps. Moreover, genetic depletion of IL-1β or administration of Cl-amidine, an inhibitor of neutrophil extracellular trap formation, significantly attenuated AAA formation.[53]

Mechanisms Related to Disruption of the Aortic Wall Integrity

Permanent aortic dilation is a defining characteristic of aortic aneurysm formation. During initiation and development of AAA, the integrity of the aortic wall, particularly the smooth muscle cells, fibroblasts, and ECM, is compromised, as evident by altered smooth muscle cell phenotype, apoptosis, and increased activity of extracellular proteases present in the aneurysmal vascular wall.[54–56] Reactive oxygen species and oxidative stress play a vital role in AAA pathogenesis with the induction of inflammation, smooth muscle cell apoptosis, and ECM degradation.[57] A recent study[58] determined the ability to limit oxidative stress in the prevention of AAA formation by overexpressing human paraoxonase gene cluster, which reduced intracellular oxidative stress and caspase activation. This transgenic approach in mice demonstrated that increased paraoxonase gene cluster expression suppressed Ang II–induced AAA formation. Further, vascular smooth muscle cells from paraoxonase gene cluster transgenic mice showed decreased reactive oxidative species and MMP-2 and MMP-9 activities.[58]

Recently, multiple studies have conducted in-depth analysis of mechanisms that compromise the integrity of the aortic wall. LRP1 (low-density lipoprotein receptor-related protein-1), a member of the LDL superfamily, has multiple functions including lipoprotein metabolisms as well as maintaining cardiovascular functions and the integrity of the aorta.[59–66] Smooth muscle cell-specific deletion of LRP1 promotes aortic dilation and fragmented elastin fibers in mice.[64,67] Au et al[65] found that LRP1 was critical for regulating vascular smooth muscle cell contractile phenotype by controlling Ca^{2+} signaling events important for actin polymerization and cytoskeletal dynamics, which may be associated with mechanisms of AAA development.

Circadian disruption in aortic dissection and rupture has been reported previously,[68,69] implicating a potential involvement of circadian rhythmicity in pathophysiology of AAA development. Lutshumba et al[70] investigated the impact of BMAL1 (brain and muscle ARNT-like protein-1) on AAA development, as global deletion of BMAL1 has been demonstrated previously to cause complete loss of circadian rhythmicity. Within this study, smooth muscle cell-specific deletion of BMAL1 prevented AAA formation in mice administered aldosterone with high-salt intake and in mice infused with Ang II. This aortic protection was shown to be regulated by increased expression of Timp4, which led to inhibition of MMPs and prevention of elastin fragmentation.[70,71]

Although ECM degradation is a hallmark of aortic aneurysm formation, the underlying mechanisms behind this remodeling process remain unknown. Recently, several studies analyzed certain factors contributing to alteration of aortic ECM architecture. Fava et al[72,73] used a proteomics approach for evaluating the effect of a metalloproteinase, ADAMTS-5, on AAA formation. Using mice lacking the catalytic subunit of ADAMTS-5 ($Adamts5^{\Delta cat}$), the authors demonstrated that $Adamts5^{\Delta cat}$ exacerbated aortic aneurysm formation. This process was driven by accumulation of versican, a large ECM proteoglycan, which has been linked to loss of ECM organization and smooth muscle cell apoptosis.[74]

Another protein frequently shown to affect aortic aneurysm formation is TGF-β.[75] The impact of TGF-β on AAA formation remains controversial, with data supporting both pathogenic and protective roles.[26,27,76,77] To gain insights into this controversy, a well-designed experiment was performed using mice with smooth muscle cell-specific deletion of TGF-β signaling, as well as systemic neutralization of TGF-β activity with an antibody, to evaluate their impact on aneurysmal disease.[78] Systemic neutralization of TGF-β worsened abdominal but not thoracic aortic pathology, whereas conditional deletion of TGF-β signaling in smooth muscle cells exacerbated thoracic but not AAA. It has been shown previously that TGF-β protects the abdominal aorta from Ang II–mediated disease through effects on cell types other than smooth muscle cells[26] and that TGF-β signaling in smooth muscle cells protects the thoracic aorta from spontaneous or genetic aortic disease.[28,79] The advance of this recent study is that the effects of systemic or conditional inhibition of TGF-β signaling in both the thoracic and abdominal aortic regions were compared in the same murine model of Ang II–mediated aortic diseases.[80]

Adventitial fibrosis predominately mediated by adventitial mesenchymal cells including fibroblasts and myofibroblasts also plays a crucial role in ECM remodeling. Yu et

al[81] found that CYLD (cylindromatosis) was critical for the transdifferentiation of fibroblasts to myofibroblasts via the regulation of NOX (NADPH Oxidase) 4, which mediates homocysteinemia-aggravated AAA formation. Deletion of CYLD prevented CaPO4-induced AAA formation and ECM remodeling. IL-6 secretion mediated by RelA from adventitial fibroblasts promotes macrophage recruitment and AAA formation.[82] Ijaz et al[83] expanded these previous findings using a $RelA^{f/f}$; Col1α2-CreERT mouse model, which had RelA depletion in aortic fibroblasts and myofibroblasts, but not in endothelial cells. Infusion of Ang II into the $RelA^{f/f}$; Col1α2-CreERT mice decreased AAA formation and monocyte infiltration, in comparison to wild-type animals.[83] This study provides evidence that mesenchymal RelA plays a causal role in Ang II–induced AAA.

Potential Novel Pathway

Proteins that relate to bone homeostasis may contribute to AAA formation and development.[84,85] SOST (sclerostin) is a secreted cysteine-knot protein in bone, where it has been shown to control bone mineralization with limited studies investigating its role in vascular disease.[86] One of the major regulatory roles of SOST is inhibition of the canonical Wnt (wingless-type mouse mammary virus integration site) signaling pathway, which has been shown to play an important role in vascular remodeling.[87] The publication by Krishna et al[88] exhibited that the SOST protein was downregulated in mouse AAA samples. Further, overexpression of SOST via either transgenic introduction of human SOST in apolipoprotein E deficient mice or administration of recombinant mouse SOST inhibited Ang II–induced AAA formation. As a translational corollary, the authors also demonstrated that SOST was downregulated in human AAA samples with a reciprocal upregulation of the Wnt signaling pathway. In human samples, the downregulation of SOST is likely driven by increased DNA methylation of cytosine-phosphate-guanine islands in the SOST gene promoter. These findings support the concept that SOST upregulation could be a potential means to inhibit AAA in patients.

Potential Medical Therapies

There is no proven medical therapy to prevent AAA growth and rupture.[89–91] Over the years, several therapeutic strategies have been investigated in murine models. However, few have been translated into clinical trials.[55] In an attempt to expedite the translation of preclinical findings, several recent studies have examined effects of clinically approved pharmaceuticals in murine models. One study evaluated the effect of cilostazol on Ang II–induced AAA formation. Cilostazol is a selective inhibitor of phosphodiesterase III that is used commonly in patients with peripheral artery disease. Administration of cilostazol (0.1% wt/wt) mixed in rodent diet, which approximated plasma cilostazol concentrations of patients who take 100 mg daily, reduced Ang II–induced AAA formation.[92] Another study determined the effect of resveratrol, a common dietary supplement, on AAA formation. Administration of resveratrol decreased AAA progression in mice.[93] The authors also found that reduced suprarenal aortic dilation by resveratrol was associated with elevated serum angiotensin-converting enzyme 2, the enzyme that cleaves Ang II to form Ang (1–7). Although further studies are needed to validate the above findings and their translational impact on clinical treatment, the fact that these pharmaceuticals are already available clinically for the treatment of other conditions may expedite this process.

Thoracic Aortic Aneurysms

The natural history of thoracic aortic aneurysms (TAA) is progressive enlargement of the thoracic aorta, which increases the risk for acute aortic dissection and rupture. The causes underlying TAA are diverse and range from degenerative or hypertensive associated aortic enlargement to less common genetic disorders, such as Marfan syndrome, Ehlers-Danlos syndrome, and other syndromic connective tissue diseases. National registries, such as Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions, have provided important resources for identifying many of the pathways that contribute to TAA formation. Over the past decade, there has also been rapid progress in identifying additional genes vital for the function and signaling pathways that predispose to TAA formation. A review by Milewicz et al[94] provides a detailed summary of the genetic mutations that predispose to TAA in humans. This review summarizes how genes encoding proteins critical for smooth muscle contractile function or mechanotransduction are vital for the maintenance of the structure of the ascending aorta throughout a lifetime.

The role of the TGF-β signaling pathway in TAA is controversial. Early analyses of Marfan syndrome mice with nondissecting TAA ($Fbn1^{C1041G/+}$ mice) concluded that aneurysm formation is largely accounted for by AT1a receptor-induced TGF-β hyperactivity.[95] However, subsequent characterization of Marfan syndrome mice with a more severe phenotype ($Fbn1^{mgR/mgR}$ mice) demonstrated protective effects of AT1a receptor inhibition but deleterious effects of TGF-β inhibition on TAA.[96] The authors also investigated the impact of endothelial cell- or smooth muscle cell-specific deletion of AT1a receptor on TAA development in this $Fbn1^{mgR/mgR}$ Marfan mouse model. Deletion of AT1a receptor in endothelial cells reduced aortic rupture rate and mitigated aneurysm growth and media degeneration, whereas smooth muscle cell-specific AT1a receptor deletion did not reduce aneurysm growth or overall survival.[97]

MiR-21 is an important modulator for proliferation and apoptosis of vascular smooth muscle cells during AAA development.[98] This miR had an increased abundance in TAA isolated from human samples, which was associated with activation of the mitogen-activated protein kinase.[99,100] TGF-β signaling is mediated through phosphorylation of the canonical pathway, including Smad (mothers against decapentaplegic homolog) 2/3 proteins, as well as the noncanonical pathway with activation of the mitogen-activated protein kinase cascades. Ang II infusion augmented ascending aortic dilation in $Smad3^{+/-}$ mice. Opposite to the protective effects of miR-21 inhibition in AAA formation, deficiency of miR-21 exacerbated aortic dilation with high mortality rate at early time points following Ang II infusion in $Smad3^{+/-}$ mice.[101] The authors further found that Smad7, a regulatory molecule involved in TGF-β signaling, was upregulated in $Smad3^{+/-}$; $miR\text{-}21^{-/-}$ mice resulting in suppression of canonical TGF-β signaling. Silencing of Smad7 in vivo prevented TAA formation and rupture in $Smad3^{+/-}$;$miR\text{-}21^{-/-}$ mice. These results

implicate that TGF-β signaling plays a complex role in maintaining the integrity of the aortic wall.

Summary

Aortic aneurysms in both abdominal and thoracic aortic regions have complex pathophysiological features. In recent years, a considerable increase in research on aneurysm pathogenesis has resulted in the discovery of novel mechanisms and implementation of clinical trials that seek to assess strategies for preventing aneurysm expansion. Despite progress on our understanding of aortic aneurysms, there are still many unanswered questions and conflicting findings requiring clarification. This uncertainty highlights the importance of continual cooperation between preclinical and clinical researchers in validating findings from preclinical studies to the human disease, to discover medical treatments that prevent or halt the progression of aortic aneurysmal disease. We hope that this brief review prompts interest in reading these highlighted articles and spurs further investigation into this complex and devastating disease.

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Disclosures

None.

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