Aortic Aneurysms

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Aortic aneurysms are manifested as progressive dilation with high risk for death caused by rupture. The most common locations are the infrarenal abdominal and ascending aortic regions in humans. This article highlights some recent publications in *ATVB* that have provided insights into understanding mechanisms and potential therapeutic strategies for aortic aneurysms.

Abdominal Aortic Aneurysms

Human Studies

The incidence of abdominal aortic aneurysms (AAA) is increasing in the elder population.[1] Independent risk factors for AAA include not only aging but also male and smoking,[2–6] whereas some risk factors such as hypertension and hypercholesterolemia have not been consistently demonstrated to be independent risk factors.[3,7,8] There are several recent population studies that have enhanced or extended insights into risk factors for AAA or associations with AAA.

The ARIC study (Atherosclerosis Risk in Communities) is a 24-year prospective study recruited 15 792 participants. Tang et al[9] evaluated lifetime risk and risk factors for AAA in this large cohort. Smoking is not only the most prevalent risk factor but also a lifetime risk for AAA in men. Higher plasma low-density lipoprotein or total cholesterol is also associated with increased risk for AAA.

Inflammation is apparent during the initiation and development of AAA in animal models. Inflammatory cell types and markers have also been detected in human AAA.[10–12] Psoriasis and asthma have profound inflammatory responses. A previous systematic review and meta-analysis has shown an association between psoriasis and AAA.[13] Recently, retrospective cohort studies using Danish populations reported that psoriasis[14] and asthma[15] were associated with higher risk for AAA.

Animal studies have provided consistent evidence that the renin–angiotensin system plays a critical role in development of AAA.[16–18] There is also evidence from a retrospective human study that inhibition of angiotensin-converting enzyme in the renin–angiotensin system prevents progression of AAA.[19] In Danish nation-wide registries (1995–2011), Kristensen et al[20] found that administration of either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was associated with reduction of mortality in patients with AAA.

Human studies have demonstrated that diabetes mellitus is associated with lower risk for AAA.[21–23] Experimentally, hyperglycemia attenuates development of AAA in elastase or angiotensin II (AngII)–induced AAA.[24] Hemoglobin A1c reflects an average of blood glucose concentrations within an extended interval of ≈3 months. Using the participant information collected from the VIVA (Viborg Vascular) randomized screening trials of the Central Denmark Region, Kristensen et al[25] 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.

Animal Studies

Three common AAA mouse models were developed in the early 2000s.[26–28] AAA develops in these mouse models by elastase perfusion into the infrarenal aorta,[26] calcium chloride periaortic application to the infrarenal region,[28] or AngII subcutaneous infusion.[27,29] A spectrum of potential mechanisms of AAA have been studied using these mouse models in their original or modified forms.[11,12,30–34]

Inflammatory Cell-Related Mechanisms

Inflammation is a common characteristic of AAA lesions,[11,16,35,36] which is manifested by inflammatory cell accumulation and a wide range of inflammatory molecular and signaling changes.

Mellak et al[37] studied the trafficking behavior of monocyte subsets in AngII-induced AAA in apolipoprotein E ($Apoe^{-/-}$) mice using multiple approaches including bone marrow transplantation, spleen removal, and lymphocyte-deficient mice ($Rag2^{-/-}$). This study provided evidence that AngII promoted mobilization of monocytes in spleen to the suprarenal aortic region, which was associated with development of AngII-induced AAA. In addition to inflammatory cell accumulation, markers of inflammasomes are present in plasma and AAA.[38–40] Two research groups found that inflammasome activation contributed to AAA in AngII-infused mice.[40,41]

Contributions of lymphocytes to AAA have also been reported in recent studies.[11] Splenic B-cell depletion prevented monocyte mobilization and attenuated AngII-induced AAA formation.[37] Consistent with this finding, Schaheen et al[42] reported that depletion of B cells by anti-CD20 antibody reduced AAA in both AngII-induced and elastase-induced AAA models.

Neutrophils are an essential component of the innate immune system.[43] Previous studies have implicated potentially important roles of neutrophils in AAA development.[44–46] Yan et al[47] reported that neutrophils contributed to elastase-induced AAA in mice associated with release of neutrophil extracellular traps and activation of plasmacytoid dendritic cells.

Several studies have demonstrated the contribution of mast cell activation to AAA development.[48–50] Mast cell activation is

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also one important feature of asthma. A recent study reported an association between active asthma and AAA in humans.[15] This group also studied whether pulmonary inflammation, a distinguishing feature of asthma, contributed to AAA in animal models.[51] The authors reported that lung inflammation augmented AngII and calcium chloride–induced AAA in mice, respectively, accompanied by increases of many inflammatory markers in plasma, lung, and AAA tissues.

Smooth Muscle Cell, Stem Cell, or Platelet-Related Mechanisms

Elastin fragmentation and disruption of aortic integrity are prominent components of AAA.[36] In a mouse model infused with both AngII and β-aminopropionitrile, elastin damage of the aortic wall was severe.[34] Hypoxia-inducible factor 1α is a transcription factor responding to hypoxia, which is abundant in vasculature.[52] Deficiency of this transcription factor in smooth muscle cells augmented AAA in mice infused with both AngII and β-aminopropionitrile, accompanied by disruption of elastin fiber formation.[53]

Mesenchymal stem cells are multipotent cells present in bone marrow that have the potential to differentiate into a spectrum of cell types.[54] Sharma et al[55] studied the effects of mesenchymal stem cells on elastase-induced AAA in mice. They first reported that administration of mesenchymal stem cells attenuated elastase-induced AAA and reduced interleukin-17, a T-lymphocyte-produced proinflammatory cytokine. Their recent study provided insights that mesenchymal stem cell infusion inhibited macrophage-produced high mobility group box 1 production and diminished release of proinflammatory cytokines, thereby preventing elastase-induced AAAs.[56]

Aortic rupture is the fatal consequence of AAA. Platelets contribute to thrombosis.[57] Studies in mouse and rat models have demonstrated that platelets play a critical role in AAA development.[58–60] To extend insights into the contributions of platelets to AAA, Owens et al[61] studied the effects of platelet inhibitors, aspirin and clopidogrel, on established AAA in AngII-infused mice and found that inhibition of platelets profoundly reduced aortic rupture. In addition to effects of platelets in thrombosis and AAA, thrombomodulin, a cofactor of thrombin, has also been reported to contribute to both calcium chloride–induced and AngII-induced AAA in mice.[62] Findings in these study implicate important roles of hemostatic factors in the development and progression of AAA.

Enzymes, Proteins, Peptides, and Other Factors

This section introduces a variety of factors that have been studied for both their unique features and common targets, such as inflammation and oxidative stress, in AAA development. Considering the diversity of their features, we distinguish them in general categories and introduce each molecule in independent paragraphs following the sequences of enzymes, proteins, peptides, and others.

Enzymes

Cysteine proteases are present in human AAA.[63] Subramanian et al[64,65] reported that calpains, calcium-dependent intracellular cysteine proteases, contributed to AngII-induced AAA. Although macrophages are an abundant source of calpains, their effects on AngII-induced AAA were not dependent on their presence in macrophages.[66]

Focal adhesion kinase is a cytoplasmic tyrosine kinase in regulating integrin-mediated signal transduction.[67] A phamacological inhibitor of focal adhesion kinase diminished both the initiation and progression of calcium chloride–induced AAA in mice,[68] which was associated with modulation of macrophage behavior.

p110δ, a member of phosphatidylinositol 3-kinase family, is predominantly expressed in leukocytes. Genetic inactivation of p110δ in mice led to accumulation of macrophages in the aorta and augmented calcium chloride–induced AAA.[69]

Association of AAA with oxidative stress has been studied extensively.[70] The paraoxonase gene cluster reduces oxidative stress. Yan et al[71] reported that AngII-induced AAA was reduced in the paraoxonase gene cluster transgenic mice in an Apoe$^{-/-}$ background, providing new evidence to support association between AAA and oxidative stress.

Proteins

Inhibition of transforming growth factor (TGF)-β leads to augmentation of AngII-induced AAA and aortic rupture rate.[72,73] Thrombospondin-1 exerts an important role in regulating TGF-β1 activity. Krishna et al[74] reported that a peptide antagonist of thrombospondin-1 accelerated the progression of AngII-induced AAA in Apoe$^{-/-}$ mice.

Serum amyloid A is a member of apolipoproteins associated with high-density lipoprotein. Serum amyloid A is also identified as an acute phase inflammatory marker.[75] In Apoe$^{-/-}$ mice infused with AngII, plasma serum amyloid A profoundly increased. Deficiency of serum amyloid A reduced AngII-induced AAA, accompanied by lower matrix metalloproteinase-2 activity in the aortic wall.[76]

Peptides

AngII is an octapeptide-inducing vasoconstriction, whereas bradykinin is a vasodilator peptide, of which its effects are mediated by kinin B2 receptor. Moran et al[77] explored effects of this receptor on AAA development. Pharmacological manipulations provided evidence that kinin B2 receptor contributed to AngII-induced AAA in mice and calcium phosphate–induced AAA in rats.[77]

Intermedin is a calcitonin gene-related peptide. Intermedin 1–53, a product of preprointermedin, reduced AngII or calcium chloride–induced AAA in mice.[78] This preventive effect on AAA was associated with attenuation of oxidative stress in AAA.

Vitamin D3 and Iron

Mineral homeostasis is important for human health. Recent research has also investigated effects of minerals such as calcium and iron on AAA development.

Calcitriol is the active form of vitamin D3, an important vitamin in regulating calcium absorption. Administration of calcitriol reduced AngII-induced AAA in Apoe$^{-/-}$ mice.[79]

Accumulation of iron is detected in AAA of humans and AngII-infused mice.[80] Sawada et al[80] discovered that restriction of dietary iron intake diminished AngII-induced AAA.

Recently Reported AAA models

Hypercholesterolemia augments AngII-induced AAA.[27,81–84] To explore molecular mechanisms using this mouse model usually requires that mice are bred to either low-density lipoprotein receptor$^{-/-}$ or Apoe$^{-/-}$ mice, which is both time and

cost consuming.[85] Several research groups have reported a new approach for mimicking depletion of low-density lipoprotein receptor in C57BL/6 mice to augment atherosclerosis by inducing hypercholesterolemia through persistent expression of a gain-of-function mutation of PCSK9 (proprotein convertase subtilisin/kexin type 9).[86–90] This mode of inducing hypercholesterolemia has also been demonstrated to augment AngII-induced AAA.[90] A caveat to the wide application of this approach is the potential for variable response in different strains of mice.[88,90]

Yamanouchi et al[91] modified the traditional calcium chloride–induced AAA mouse model by adding phosphate buffered saline after the introduction of calcium chloride onto the infrarenal aorta, which led to the formation of calcium phosphate. Their recent study has also provided evidence that calcification is present in human AAA, and pharmacological inhibition of osteoclastogenesis prevents the development of calcium phosphate–induced AAA in mice.[92]

Kawasaki disease is an inflammatory disease, which is manifested by myocarditis and coronary arteritis.[93,94] A Kawasaki disease mouse model induced by stimulation with *Lactobacillus casei* cell wall extract mimics myocarditis and coronary arteritis of the human disease.[95,96] Wakita et al[97] reported that this Kawasaki disease mouse model also developed AAA in the infrarenal aortic region, which was associated with interleukin-1 signaling. This finding provides new insights into understanding inflammation-mediated mechanisms of AAA.

Thoracic Aortic Aneurysms

Genetic disorders are a prevalent cause of thoracic aortic aneurysms (TAA).[98] Recognized representative genetic disruptions include mutations in fibrillin-1 (Fbn1) gene and TGF-β receptor–related genetic changes, which cause progressive aortic dilation in the aortic root and ascending aortic regions.[99–103] Mouse models have been developed based on some of the genetic disruptions identified in humans.

In addition to identified genetic disruptions, bicuspid aortic valves in humans are associated with increased risk for TAA.[104,105] A recent study compared a set of TGF-β–related genes between patients with bicuspid and tricuspid aortic valve diseases. The findings implicate that TGF-β–related genes and classic signaling pathway are lower in TAA patients with bicuspid aortic valves.[106]

Marfan Mouse Models

There are 2 common mouse models representing Marfan syndrome.[107,108] One is called Fbn1C1039G/+ mouse containing a transgene with cysteine to glycine mutation on amino acid 1041 of the Fbn1 gene (Fbn1C1041G/+; equivalent to C1039Y in humans).[107] This transgene leads to modest aortic root and ascending aortic dilation in adult mice.[107,109,110] The other common model is an Fbn1 hypomorphic mouse model, which has profound dilation in the aortic root and ascending aortic regions with high rates of aortic rupture.[108] Recent studies using these 2 mouse models report that multiple potential therapeutic strategies hold promise for the treatment of TAAs. These include AT1 receptor blockade,[109,111,112] caspase inhibition,[113] and administration of resveratrol.[114] Although TGF-β signaling activation has been postulated in the aortic pathologies,[102,115] whether inhibition of TGF-β preventing or augmenting TAA in Marfan mouse models has not been consistently reported in the literature.[109,112,116]

Genetic Disruptions of TGF-β or Its Receptors

TGF-β–related manipulations induce aortic aneurysms in the ascending aortic region in mice that also recapitulate the aortic pathologies in humans such as Loeys–Dietz syndrome.[115] An earlier study reported that haploinsufficient *Tgfb2* (+/-) mice had aortic root dilation.[117] Subsequent studies from several independent laboratories have demonstrated that genetic disruption of TGF-β receptor 2 in smooth muscle cells induced in adult mice exhibits profound aortic root and ascending aortic dilation and disruption of aortic structural integrity.[116,118–121] Wei et al[116] also provided direct evidence that deletion of TGF-β receptor 2 in smooth muscle cells of Fbn1C1041G/+ mice accelerated aortic pathologies. Another recent study reported that TGF-β receptor 1 deficiency in smooth muscle cells caused severe aortopathy in mice.[121]

Angiotensin II or Other Chemical-Induced TAA

Recently, several groups have reported that AngII induces TAA that is restricted to the ascending aortic region.[40,122–124] In contrast to AngII-induced AAA, TAA induced by AngII is independent of hypercholesterolemia.[125] In addition to AngII-induced TAA, coinfusion of AngII and β-aminopropionitrile also induces TAA in mice.[34,126] Ikonomidis et al[127] developed a mouse model of TAA by applying calcium chloride onto the descending thoracic aortic region. Using these mouse models, recent studies discovered that genetic depletion of AT1 receptor reduced AngII-induced TAA[128,129]; nucleotide oligomerization domain-like receptor family, pyrin domain containing 3 caspase-1 inflammasome contributed to AngII-induced TAA[40]; smooth muscle cell–specific deficiency of low-density lipoprotein receptor–related protein 1 augmented AngII-induced TAA[130]; genetic MMP-2 (matrix metalloproteinase) deficiency accelerated AngII-induced TAA, but attenuated calcium chloride–induced TAA[123]; and smooth muscle cell–specific deficiency of hypoxia-inducible factor-1α increased TAA in mice coinfused with AngII and β-aminopropionitrile.[53]

Summary

Aortic aneurysms in both abdominal and thoracic regions have complex pathophysiological features. There are still many unanswered questions and conflicting findings that need to be clarified. We hope that this brief review prompts interest in reading these highlighted articles to understand potential mechanisms of the 2 aortic pathologies from a broad viewpoint. We also hope the introduction of these recent publications helps develop experiments based on current findings to explore new mechanisms and effective therapeutics.

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