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Recent Advances in Molecular Mechanisms of Abdominal Aortic Aneurysm Formation

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Abstract

Abdominal Aortic Aneurysm (AAA) is an increasingly common clinical condition with fatal implications. It is associated with advanced age, male gender, cigarette smoking, atherosclerosis, hypertension, and genetic predisposition. Although significant evidence has emerged in the last decade, the molecular mechanisms of AAA formation remains poorly understood. Currently, the treatment for AAA remains primarily surgical with the lone innovation of endovascular therapy. With advance in the human genome, understanding precisely which molecules and genes mediate AAA development and blocking their activity at the molecular level could lead to important new discoveries and therapies. This review summarizes recent updates in molecular mechanisms of AAA formation including animal models, autoimmune components, infection, key molecules and cytokines, mechanical forces, genetics and pharmacotherapy. This review will be helpful to those who want to recognize the newest endeavors within the field and identify possible lines of investigation in AAA.

Keywords

Abdominal aortic aneurysm; animal model; autoimmune; infection; cytokines; mechanical force; genetics; pharmacotherapy

Introduction

Aortic pathology, including aneurysms and dissections, is the 13th leading cause of death in the United States (US) with 15,000 deaths per year and greater than 60% mortality when rupture occurs. The infrarenal abdominal aortic aneurysm (AAA) is by far the most common type, comprising greater than 80% of all aortic aneurysms. They are a significant health problem in the US, with approximately 40,000 repair operations and more than 150,000 hospital admissions per year It has been well documented that AAA are associated with advanced age, male gender, cigarette smoking, atherosclerosis, hypertension, and genetic predisposition. The two greatest risk factors, both preventable, are cigarette smoking (85 % of patients) and hypertension (60 % of patients). Other less significant risk factors include chronic obstructive pulmonary disease (COPD), family history, and atherosclerosis of other vascular beds. Interestingly, there is no proven correlation between cholesterol levels and mortality from AAA. Male gender appears to be a significant risk factor, with deaths due to

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aneurysm in the US Caucasian population in a male:female ratio of 3:1. Incidence of AAA in a large autopsy study of men and women was found to be 4.7% and 3%, respectively.[1] AAA prevalence in males increases after age 55 to a peak of 5.9 % at age 80. Female gender appears to be protective in aneurysm development. Sinha *et al.* demonstrated decreased expression of multiple cytokines and chemokines as well as diminished leukocyte trafficking in female rat aortas compared with males.[2]

By definition, an aneurysm is a permanent dilatation of 50% or more compared with the expected normal diameter of the vessel.[3] An arterial dilatation less then 50% of the original diameter is called ectasia. Furthermore, a diffuse enlargement in several arterial segments greater than 50% in diameter is called arteriomegaly. Regarding the infrarenal aorta, multiple studies have shown that AAA become of clinical relevance when their diameter reaches 5 cm or enlarges at a rate greater than 0.5 cm per 6 months. Diagnosis is typically made by non invasive imaging modalities such as ultrasound, computerised tomography (CT) scan or magnetic resonance imaging (MRI) with formal aortic angiography utilized in special clinical scenarios.

In the aorta, there is a gradual reduction of the medial elastin fibers, reducing from 80 layers in the thoracic aorta to 30 in the infrarenal portion. There is also thinning of collagen within the media and thickening of the intima in the distal aorta. These features explicate the tendency of the infrarenal aorta to develop an aneurysm. Histologically, elastin fragmentation and degeneration are observed in the aneurysm wall. The features are characterized by chronic transmural inflammation, destructive remodeling of the elastic media and depletion of medial smooth muscle cells (SMC). Numerous molecular mediators and extracellular matrix-degrading proteinases contribute to the progression of aneurysmal disease. Most recent work has focused on the role of matrix metalloproteinases (MMP) as enzymatic mediators of aneurysmal disease, with special emphasis on MMP-2 and MMP-9. They have elastolytic and collagenolytic properties that are over expressed in both human and experimental AAA. Growth and rupture of AAA have been shown to result from increased collagen turnover as evidenced by increased type I collagen degradation products within the wall of aortic aneurysms. Collagen turnover critically depends on specific collagenases that cleave the triple helical region of fibrillar collagen.[4]

The natural history of aneurysm formation is of progressive aortic wall degeneration occurring over the course of many years culminating in loss of structural integrity and fatal aortic rupture. Although surgical exclusion of an aneurysm can effectively prevent aortic rupture in large aneurysms, small aneurysms are generally asymptomatic and go unnoticed until symptoms or rupture present. The aim of the latest research is to target those small AAA with new pharmacologic and genetic approaches to obtain remission of the disease.[5,6] The purpose of this review is to outline the latest advances in the use of animal models, molecular mechanisms, and genetic approaches in AAA formation as well as therapeutic prevention. This review is aimed at those who want to recognize the newest endeavors within the field and identify possible lines of investigation in AAA.

ANIMAL MODELS

Progress in understanding the pathophysiology of AAA is dependent in part on the development and application of effective animal models that replicate key aspects of the human disease. The basic premise of these animal models is that they share the same biochemical and cellular mechanisms with the human process. Initially, large animal models were used for this purpose, primarily porcine and canine. However, mouse models have recently been utilized more often for genetic studies including applications of transgenic and knockout technologies. In addition, the mouse has advantages such as small size, short

generation time, and relative ease of care. Different approaches have been used to mimic the human disease process in animal studies including: spontaneous aneurysm formation, pharmacologically induced aneurysms, surgically created aneurysms, genetic manipulation, chemical induction, and dietary models.[7] A majority of cellular and biochemicalcharacteristics of human AAA are limited to descriptions ofadvanced disease from tissues acquired at the time of surgicalrepair. The ability to extrapolate the results from animal models would require a logical study of the manner in which human aneurysms initiate and mature.

Various facets of the disease have been replicated utilizing animal models, including medial degeneration, inflammation, thrombus formation, and rupture. The chemical methods include intraluminal infusion of elastase, periaortic incubation of calcium chloride, and subcutaneous infusion of angiotensin II. The genetic approaches consist of spontaneous and engineered mutations employing transgenic and knockout mice to mimic defects in extracellular matrix maturation, increased degradation of elastin and collagen, aberrant cholesterol homeostasis, and enhanced production of angiotensin peptides. Investigations in mice with deletion of targeted genes offer a novel approach to study gene specific aneurysm development.[10]

Based on original experimentation with rats and more recently with mice, many studies have utilized the transient perfusion of the abdominal aorta with porcine pancreatic elastase (Fig. 1). This method has proven to be a reproducible and healthy aortic aneurysm model. The rationale for its development was based on the disrupted nature of elastin in AAA and its requirement for the maintenance of the structuralintegrity of the artery.[8–10] The model is very helpful to identify genes that are essential for the development of aneurysms including MMP9, IL-6, and AT1R. Using this model, Sigala *et al.* examined the expression of inducible nitric oxide synthase (iNOS) in the aortic wall and its relation to cellular proliferation and apoptosis. They showed that iNOS-derived nitric oxide is associated with cellular growth parameters, predominantly smooth muscle cells (SMC), and selective iNOS blockage promotes cellular remodeling seen in AAA.[11] Sho *et al.* employed this model to investigate cell type-specific expression of the aneurysmal wall by isolating SMC and predominantly macrophage-containing mural cell populations. They demonstrated that flow differentially regulates cell-specific gene expression in AAA.[12]

Periaortic application of calcium chloride has also been used to promote arterialwall thickening and aneurysm formation. When calcium chloride combinedwith thioglycollate was applied to arteries of hyperlipidemic rabbits, it promoted the formation of aortic aneurysms.[13] This approach has been applied to mice in a similar fashion either through placement ofa gauze soaked in calcium chloride solution or through direct placement of concentrated solution on the aorta between therenal branches and the iliac bifurcation.[14]

Cassis *et al.* described the effect of angiotensin II (AngII) on induction of arteriosclerosis and aneurysm formation in LDL and apolipoprotein E deficient mice. Delivery of AngII at dosesof 500 to 1000 ng/kg per minute, via subcutaneously implanted osmotic mini-pumps, lead to AAA in the suprarenal region. The precipitating event that occurred within daysof AngII infusion appeared to be medial macrophage accumulation associated with elastin degradation. After approximately 1 week, there were gross dissections of theaortas leading to prominent vascular hematomas and thrombus. At late stagesof the disease evolution, large atherosclerotic lesions and aneurysms wereapparent.[15]

Knockout mice have proven to be a powerful tool for studying the molecules and genes involved in aneurysmal disease. The transgenic technique and gene transfer models have been utilized in studying gene overexpression. Several studies have targeted deletion of

individual genes such as COX-2, [19] MMP-2, MMP-9,[16] IL-6,[10], and Ang I and II.[10] Gatlin *et al.* showed that AAA incidence in COX-2 wild-type mice was 54%, whereas AAAs in COX-2-deficient mice were not detected (0/23) following 28 days of angiotensin II infusion.[19] Godin *et al.* observed that MMP-2 and MMP-9 were upregulated after ligation at different time courses in the vasculature of wild type mice.[20] Shimitzu *et al.* applied an allograft model studying the interferon gamma (IFN-γ) pathway in mice lacking the receptor. They showed wild-type recipients developed intimal hyperplasia, whereas IFN-γ receptor deficient allografts developed severe AAA associated with markedly increased levels of MMP-9 and MMP-12.[21] A common feature of these models is the potential reduction of AAA incidence and severity by the prophylactic administration of inhibitory molecules or alteration of the genes. Table 1 summarizes the most commonly used mouse models of AAA.

AUTOIMMUNE COMPONENTS

Family history and autoimmune reaction relating to aneurysm formation has prompted significant interest. From a clinical perspective, AAA have been linked with various autoimmune diseases including giant cell arteritis, systemic lupus erythematosus (SLE), Takayasu's arteritis, and antiphospholid syndrome. Analogous to autoimmune diseases, the risk of AAA perhaps is increased by certain genotypes concerning human leukocyte antigen class II (HLA-II) molecules. Ultimately, multiple genes with different expressivity and diverse environmental factors may be linked to a multifactorial mode of inheritance.[22]

Monux *et al.* examined HLA-II immune response genes to establish a possible role for autoimmunity in aneurysm formation.[23] They performed HLA-II typing in a series of 72 AAA patients and 380 healthy subjects, and found a higher incidence of the allele subtype HLA-DR B1*0401 in the AAA group (12.5 vs. 5.2%). In contrast, the HLA-DR B1*01 allele tended to behave as a protective factor for AAA (12.5% AAA vs. 21.3% controls). The association observed between HLA-DR B1*0401 and HLA-DR B1*01 in AAA was similar to that reported in several autoimmune diseases. Ogata *et al.* investigated the role of autoimmunity in the etiology of AAA using HLA polymorphisms (HLA-DQA1, -DQB1, -DRB1 and -DRB3-5 alleles) in 387 AAA cases and 426 controls.[24] They observed an association with the HLA-DQA1 locus among male AAA patients. They found a significant difference in the HLA-DQA1*0102 allele frequency, 20.8% vs. 12.4%, respectively between AAA cases and controls suggesting potential evidence that the HLA-DQA1 locus harbors a genetic risk factor. In contrast to the aforementioned evidence, Badger *et al.* utilized PCR and sequence-specific oligonucleotide probes to determine HLA allele distribution within 241 aortic aneurysm specimens. Their study failed to demonstrate the risk association between AAA and HLA alleles.[25] Conflicting evidence regarding an autoimmune component in AAA etiology leaves potential for further investigation.

Other autoimmune factors involved in AAA formation have been theorized including heat shock proteins (Hsp-65), oxidized LDL, and autoimmune vasculitities related to SLE, antiphospholipid syndrome, and Cogan's syndrome. Although rare occurrences have been reported, one study noted that Hsp-65 molecules were not strongly expressed within aortic aneurysm tissue samples.[26] Hobbs *et al.* compared LDL levels in 206 AAA cases vs. 252 controls and found LDL in much higher levels in the AAA group. The connection between LDL and small aneurysms suggests, possibly acting via inflammatory mediated matrix degeneration, that it could be an initiating factor in the development of AAA.[27]

The high association of SLE with vasculitis and hypertension can result in progression of rare cases of AAA. In one retrospective study over ten years, the mean age of the patients with SLE at time of aortic rupture was 55, significantly younger than the general population

mean of 77. This, however, may be influenced by the weakness of elastic lamina and atherosclerosis accelerated by prolonged steroid use rather than primary SLE damage.[28] Rare cases of aortic aneurysms have been demonstrated with antiphospholid syndrome, which may have a more significant relation to peripheral vascular disease and atherosclerosis.[29] Cogan's syndrome is a rare multisystemic disease characterized by vestibuloauditory dysfunction, inflammatory eye disease, and vasculitis. Aortic aneurysms due to aortitis are an under-recognized result of Cogan's syndrome, and warrant further study.

INFECTION

Infected aortic aneurysms are uncommon, and infrequently have their pathological features been described. Panneton and Edwards evaluated clinical and histopathologic features in patients undergoing surgical repair of infected aneurysms of the descending thoracic or abdominal aorta over a 24-year period. The results showed that among cases with an identifiable causative organism, staphylococcus accounted for 30%, streptococcus for 20%, salmonella for 20%, Escherichia coli for 15%, and other organisms for 15%.[30]

During recent years, attention has been paid to the role of atypical bacterial infections, including Chlamydia and Helicobacter pylori, in the process of atherogenesis and arterial disease development. The reported rates of detection within atherosclerotic lesions by PCR vary widely. Regarding Chlamydia, several studies hypothesized this organism as a possible source of vascular disease, including carotid, coronary, and aortic pathology. Its role in the pathogenesis of aortic aneurysms, however, has been controversial. Sodeck *et al.* investigated the presence of C. pneumoniae in 148 tissue samples excised from control and diseased aortas. DNA of C. pneumoniae, C. trachomatis and C. psittaci were assessed by highly sensitive and specific real time polymerase chain reaction (PCR). C. trachomatis-DNA was detected in 1/65 diseased patients and in none of 83 controls (P=0.43).[31] In a similar study, surgical specimens derived from aneurysm or aorta fragments were investigated for C. pneumoniae utilizing PCR. In asymptomatic aneurysms, DNA was found in 9 cases (29%), and in ruptured aneurysms in 14 cases (49%). In the control group, C. pneumoniae DNA was not detected in the aortic wall.32 Conflicting data has failed to show a clear relationship between chlamydia infection and aortic pathology.33 Koullias *et al.*[34] sought to investigate possible H. pylori infection in 54 human specimens of 42 aortic aneurysms and 12 penetrating aortic ulcers. Immunohistochemical staining showed no evidence of H. pylori in these specimens.

Cytomegalovirus (CMV)-induced arterial disease has also been linked to aortic pathology. To further elucidate the mechanism by which CMV may promote atherosclerosis, Westphal *et al.*[35] studied the expression pattern of cellular inflammatory and proliferative signals in the aortic wall of CMV (+) and CMV (−) patients undergoing coronary artery bypass grafting (CABG). CMV-DNA in smooth muscle cells was thought to induce local growth factor expression as well as endothelial activation, both of which can promote the progression of atherosclerosis. Since traditional atherogenic risk factors increase the likelihood of aortic CMV manifestation, CMV may play a crucial role in mediating the progression of atherosclerosis. Yonemistsu *et al.*[36] found that the persistent expression of CMV-gene in the vessel wall plays a role in the vascular cellular response, including progression of atherosclerosis or vasculitis in vivo. Kilic *et al.*[37] performed PCR analysis to demonstrate the relationship between CMV and atheromathosis at the aortic wall. CMV DNA was found in 37.9% atherosclerotic and 32.7% non-atherosclerotic vascular wall specimens.

KEY MOLECULES AND CYTOKINES

Immune-mediated processes involving acute phase reactants, IFN-γ producing T cells, and proinflammatory cytokines play an important role especially in the initiation of aneurysms (Table 2). They have been shown to have an association with aneurysm size and are conceivably produced by the aneurysmal tissue itself. In addition, they perpetuate the cycle of inflammation and proteolysis contributing to the pathogenesis. In vitro studies reveal aneurysms secrete IL-10, IL-6, and C-reactive protein (CRP), proven by higher circulating levels in AAA patients. One study measured inflammatory cytokines in 99 pre-operative and 100 post-operative AAA patients. There was a significant reduction in IL-10 and a marginal reduction in IL-6 and CRP in the post-operative group. Subgroup analysis of the post-operative group revealed significantly lower levels of IL-6 and CRP in the open group compared to endovascular aneurysm repair (EVAR).[38]

The role of matrix metalloproteinases (MMP) in the pathogenesis of AAA has focused on its collagenolytic properties and degradation of the extracellular matrix (ECM). The ECM contains embedded vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGFβ), both responsible for maintenance of the ECM. These factors are downregulated by MMPs. The new frontier of MMP biology involves their role in releasing cryptic fragments and neoepitopes from the ECM and their impact on regulation of the inflammatory response. Both MMP-2 and MMP-9 expose a cryptic epitope that inhibits angiogenesis through the release of endostatin, endorepellin, arresten, canstatin, and tumstatin.[39] MMPs also play an important role in the control of the inflammatory response, through the modification of proinflammatory cytokines, chemokines, and shedding of membrane receptors.

Sukhova *et al*. suggested a role for cysteine proteases, particularly cathepsins S, K, and L in atherosclerosis and AAA formation.[40] Cathepsins express powerful elastolytic and collagenolytic enzyme activity, analogous to MMPs, against triple helical type I collagen. Cystatin C inhibits cathepsin activity both locally, in the wall of AAA, and systemically, in the bloodstream. Two opposite processes coexist in aneurysmal tissue: overexpression of elastolytic cathepsins, and severe suppression of cathepsin inhibition by cystatin C. There was a significant reduction in atherosclerosis and AAA in mouse models lacking different cathepsins. Growth and rupture of aneurysms result from increased collagen turnover confirmed by increased type I collagen degradation products in AAA. Abdul-Hussein *et al*.[4] evaluated the posttranslational regulation of protease activity and showed a threefold increase in MMP-8, a fivefold increase in cathepsins K and L, and a 30-fold increase in cathepsin S activation in diseased aortas. These findings demonstrate the importance of cysteine protease/protease inhibitor balance in dysregulated arterial integrity and remodeling during atherosclerosis and aortic aneurysm formation.

In vitro and animal studies have implicated osteopontin (OPN) in the pathogenesis of aortic aneurysms. OPN is an extracellular structural protein found within many different tissue lines including bone, kidney, endothelium, various malignancies, and atheromatous plaques. Golledge *et al*.[41] studied the relationship between serum concentration of OPN and variants of the OPN gene within human AAA. They found that serum and tissue concentrations of OPN were elevated, but OPN gene variation was not significant. Furthermore, they noted that OPN was found at higher levels in smaller aneurysms (30–49mm) vs. larger ones (50–80mm). This suggests that OPN may have more roles in aneurysm development and progression as an inflammatory mediator and may be a useful biomarker for aneurysm presence and growth.

It is well recognized that a mutation in fibrillin, a glycoprotein essential in the structure of elastin, leads to Marfan's Syndrome. Two fibrillin mutations have been implicated in infrarenal AAA; however, the majority of Marfan's patients have thoracic aortic pathology. This is a result of the increased amount of elastin (80 layers vs. 30) affected in the proximal portion of the aorta. Recent studies show that fibrillin 1 and microfibrils regulate the TGF-β family of growth factors influencing many aspects of cellular performance, including differentiation, proliferation, protein production, and survival. Data in mice demonstrate that a deficiency of fibrillin 1 results in excessive TGF β activation and signaling in the developing lung, aorta, muscle, and many other tissues altered in Marfan's Syndrome.[42] This has led to a novel paradigm suggesting that changes in cytokine (ie. TGF β) equilibrium is critical to their regulated activation and signaling and that perturbation can contribute to proximal and distal aortic injury. Most recently, studies in mouse models have demonstrated that inhibition of TGF-β signaling, through treatment with the angiotensin receptor antagonist losartan, have effectively suppressed aortic pathology.43

MECHANICAL FORCES

The risk of aneurysmal rupture is related to the hemodynamic stress placed on the degenerative aortic wall with tensile distribution largely a function of aneurysm size and geometry.[44] Hypertension is a well known factor in aneurysm development as a result of direct stress on the wall. More importantly, the flow dynamics become more complex when there is a pathological condition that causes changes in the normal structural composition of the vessel wall. Khanafer *et al*. studied the influence of pulsatile, turbulent, non-Newtonian flow in axisymmetric-rigid aortic aneurysm models under rest and exercise.[45] The kinetic energy generated by turbulence impacting the wall of the distal half of the aneurysm increased fluid and wall shear stress resulting in aneurysmal growth and eventual rupture.

Mechanical factors explicate the increased probability of the abdominal aorta to aneurysms. Initially, the pulse wave is transmitted from the aortic root to the inguinal region. As a result, the pulse pressure increases and the rise of pressure becomes steeper, with the largest pulsatile load being localized to the infrarenal aorta. This localization of hemodynamic stress within the abdominal aorta is due to 3 mechanical factors: distal tapering of the aorta, progressive stiffening with age of the aortic wall secondary to changes in the collagen-elastin ratio, and the additive effects of retrograde pressure waves that reflect from the iliac bifurcation combining with the incoming antegrade pressure waves.[46] These features provide insight into how the infrarenal aorta is predisposed to aneurysmal disease.

Asymmetrical flow patterns distal to the aorta are also believed to promote aneurysm enlargement. Ultrasound examination showed AAA in 5.8 % of World War II amputees, compared with 1.1% of non-amputees. Unilateral flow reduction after leg amputation causes an asymmetrical flow pattern at the aortic bifurcation, likely resulting in delayed damage to the aorta.[47] Consequently, the spatial and temporal variations in hemodynamic forces, the formation of regions of stasis, and the transition to turbulence may play an important role in the etiology of the disease by activating intraluminal thrombus formation, lipid deposition, and various inflammatory mechanisms.

GENETICS

Evidence of genetic predisposition to the development of AAA has been noteworthy with 19% of AAA patients reporting one or more first-degree relatives with an aneurysm. There are several approaches used to investigate the ample genetic background of AAA formation. Different genetic risk factors are involved in the development of both dissections and aneurysms,[48] and segregation studies have favored major autosomal genes as the etiology.[49,50] They are thought to be inherited as an autosomal dominant condition with decreased

penetrance and variable condition. Studies have demonstrated a major locus mapped to 5q13-14[51,52] as well as two loci mapped to chromosome 19q13 and 4q31. This shows evidence for genetic heterogeneity indicating additional genetic loci may be identified.[53]

Many cytokine genes contain polymorphic sites, some of which affect cytokine production in vitro. Cytokine gene polymorphisms may therefore influence the pathogenesis of AAA. In order to elucidate the relationship between cytokine gene polymorphisms and AAA, Bown *et al*. studied 100 patients with AAA and 100 age-matched and sex-matched control subjects.[54] The IL-10-1082 A allele was significantly more common in the AAA group than the control group. This association with IL-10-1082 may be that AAA develops in patients who are unable to mount the same anti-inflammatory response.

The “genetic association study” approach has been utilized to identify the genesis of AAA. The rationale for this approach is to select genes for investigation based on deduction of their role in vascular biology. The recent identification of the TGF-β pathway as a key target has opened new avenues for future genetic and therapeutic research. The elastin gene (ELN) has also been chosen given that it is a major protein in the media and provides strength and elasticity to the aortic wall. Polymorphisms of ELN gene were identified in the evolution of AAA development and warrant further investigation. Conflicting evidence exists regarding genetic polymorphisms. Massart *et al*.[55] used 99 AAA patients and 225 controls to study polymorphisms of several genes: TGF-β1, estrogen receptor-alpha (ESR1,2), ELN, and progesterone receptor (PGR). A statistically significant difference was noted between AAA and control polymorphisms only in the ESR2 polymorphism.

The entire genome has been utilized in a statistical technique called DNA linkage study to identify genetic factors contributing to the disease. Kuivaniemi and Ogata[56] describe this approach to find chromosomal regions harboring susceptibility genes in families in which at least two blood relatives were diagnosed with AAA. The affected relative pair linkage analysis approach was employed, with sex and family history as covariates. Strong evidence of linkage to a region on chromosome 19q13 was identified with 36 families when including sex and number of affected first-degree relatives. They then genotyped 83 additional families for the same genetic markers, typed additional genetic markers for all families, and obtained a LOD (logarithm of odds) score of 4.75 (A LOD score of 3 or more is generally taken to indicate two gene loci are linked). They also identified a region on chromosome 4q31 with a LOD score of 3.73 using the same covariate model as for chromosome 19. These findings provide evidence for the presence of susceptibility genes for AAA on chromosomes 19q13 and 4q31.

PHARMACOTHERAPY

The future of AAA therapy may belong to agents which can induce aneurysm regression through delivery methods which specifically target affected arterial tissue. AAA can be easily diagnosed with noninvasive testing; thus, small aneurysms present an excellent opportunity for disease-modifying pharmacological intervention. Currently, diseased aneurysms undergo observation until they reach clinical significance beyond 5 cm. During this interval period, concurrent pharmacotherapy to prevent or even reduce enlargement would be a significant advance.[57]

Inhibition of MMPs or other proteases such as cathepsins offers a tremendous therapeutic strategy. The prevention of AAA enlargement in animal models has been demonstrated using both doxycycline and another MMP inhibitor, BB-94. Doxycycline is perceived to prevent AAA enlargement by two modalities: MMP inhibition and eradication of Chlamydia species within the pathologic aortic wall. Prall *et al*. delivered doxycycline in mouse models and measured the serum levels. They discovered that doxycycline decreased aortic growth

33–66% in mice with increased doxycycline levels corresponding to growth suppression.58 Doxycycline was further studied in a randomized, double-blinded clinical trial evaluating 32 AAA patients over 18 months. They showed a statistically significant decrease in aneurysm expansion rate in the treated group; however a major limitation of the study was a small sample size requiring further investigation.[59] BB-94 (also known as batimastat) was evaluated for its ability to control aneurysmal growth in an experimental AAA rat model. BB-94 appeared to work, not only as a direct pharmacologic inhibitor of MMPs, but also through interference with the inflammatory response seen in AAA.[60]

Inflammation plays an integral role in the development of AAA and expression of the inflammatory molecule, cyclooxygenase (COX)-2, is increased in aneurysmal tissues. King at al.[61] studied nonsteroidal anti-inflammatory drugs (NSAID), which inhibit the activity of COX-1 and COX-2, to evaluate the effect in an angII-induced AAA mouse model. They noted celecoxib decreased the incidence and severity of AAA formation in both hyperlipidemic and nonhyperlipidemic mice. A case-control study showed that AAA patients taking NSAIDs had aneurysms with a lower expansion rate than those in patients who do not take NSAIDs.62

Maintaining the integrity of arterial elastin is vital for the prevention of abdominal aortic aneurysm development. Isemburg at al.[63] hypothesized that in vivo stabilization of aortic elastin with pentagalloyl glucose (PGG), an elastin-binding polyphenol, would interfere with AAA development. Results showed that a one-time periadventitial delivery of noncytotoxic levels of PGG inhibits elastin degeneration, attenuates aneurysmal expansion, and hinders AAA development in rats.

Recent studies indicate that C-Jun N-Terminal Kinase (JNK) is involved in a number of cellular stress responses and also in inflammatory signaling. Moreover, JNK is highly active in human AAA walls and specific inhibition of JNK can significantly suppress the secretion of MMP-9 and prevent collagen degradation.[64] Yoshimura *et al.* utilized a $CaCl_2$ AAA mouse model and treated it with SP600125, a specific JNK inhibitor, for 10 weeks. Treatment completely disrupted the increase in the outer aortic diameter induced by $CaCl_2$. Furthermore, treatment prevented the destruction of the aortic tissue architecture such as thinning of the medial layer and disruption of the elastic lamellae, both hallmarks of human AAA. SP600125 reduced phospho-c-Jun, a marker of JNK activity, and MMP-9 levels as well. In addition, SP600125 reduced macrophage infiltration in the periaortic tissue, suggesting that chronic JNK inhibition reduces proinflammatory signaling in AAA. These findings all indicate that JNK inhibition may play a significant role in impeding the progression of AAA.[64,65]

Other therapeutics with a promising role in treatment of AAA include HMG CoA reductase inhibitors (statins) and ACE inhibitors. A large-scale population based case-control study over 10 years showed that treatment with ACE inhibitors, and not other anithypertensives such as Beta blockers or Ca^{++} channel blockers, was associated with reduced AAA rupture. In contrast, AT1 receptor blockers did not show a beneficial effect with regard to AAA, suggesting that the renin angiotensin system plays a complex role in the pathogenesis of AAA.[66] Statins, in addition to their lipid-lowering effect, are thought to suppress inflammatory signaling possibly by inhibiting the Rho family of small G-proteins. A proposed association between the use of statins and reduction in the levels of MMP-3 and MMP-9 has shown a lower rate of expansion of AAA.[67] Both medications merit additional analysis with potential randomized clinical trials.

SUMMARY

Current AAA research revolves the use of animal models to provide a mode of study for the mechanical, genetic, and molecular mechanisms of the disease. Recent advances in vascular biology have led to a greater understanding of the molecular events and genetic basis leading to aortic aneurysmal expansion and rupture. This is a rapidly evolving field and one in which translation from experimental research to clinical practice could provide a significant reduction in AAA morbidity and mortality. With the advent of the sequenced human genome, new pharmacotherapy trials, and targeted molecules, many new aortic aneurysm therapies are on the forefront of discovery and provide an exciting foundation for innovative study (Fig. 2).

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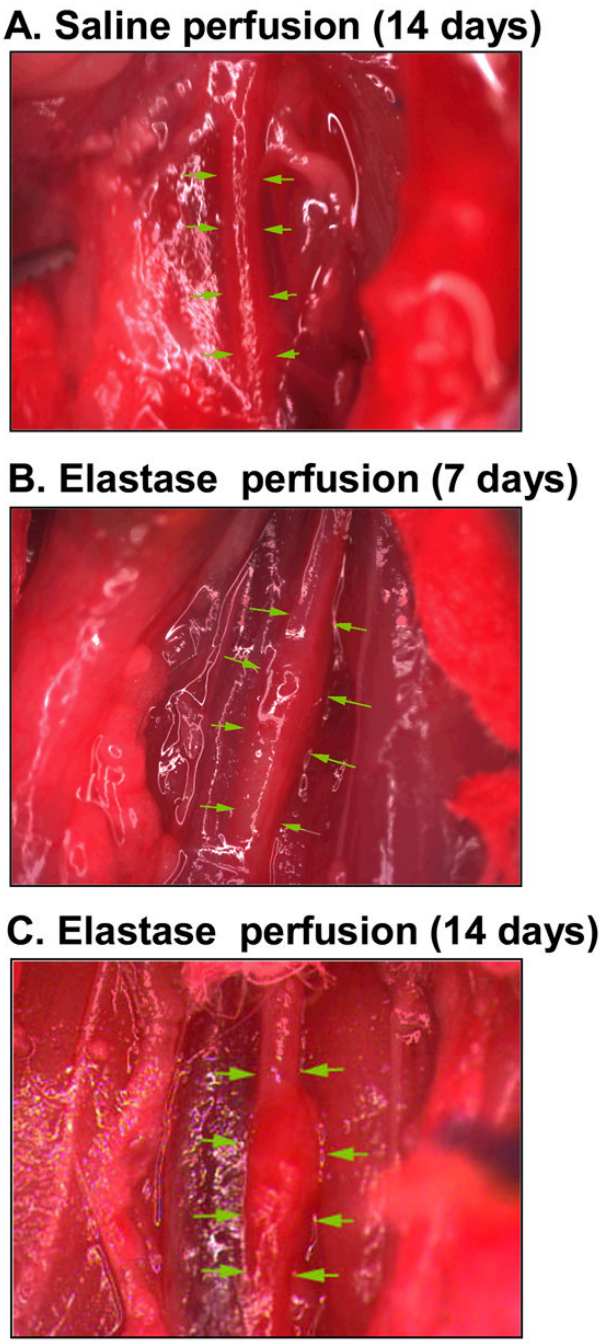

Figure 1.

Mouse model of abdominal aortic aneurysm. Anesthetized mice underwent laparotomy, and the abdominal aorta was isolated from the level of the left renal vein to the bifurcation. Temporary silk ligatures were placed around the proximal and distal portions of the aorta, and an aortotomy was created at the bifurcation with a 30-gauge needle. Heat-tapered polyethylene tubing was introduced through the aortotomy and secured with a silk tie. Using a syringe pump calibrated to 100 mmHg, the aorta was filled with saline containing 0.414 U/mL Type I porcine pancreatic elastase. For controls, the saline solution was used for perfusion. The aorta typically dilated about 50 to 70% during the 5-minute period of elastase or saline perfusion. The perfusion catheter was then removed and the aortotomy closed with

a 10-0 suture to avoid constriction. The aorta was re-exposed by laparotomy, and final aorta diameter measurements were obtained at 7 or 14 days before sacrifice. **A.** Saline perfusion (14 days post perfusion) showing normal size of abdominal aorta. **B.** Elastase perfusion (7 days post perfusion) showing moderate expansion of abdominal aorta. **C.** Elasase perfusion (14 days post perfusion) showing significant expansion of abdominal aorta.

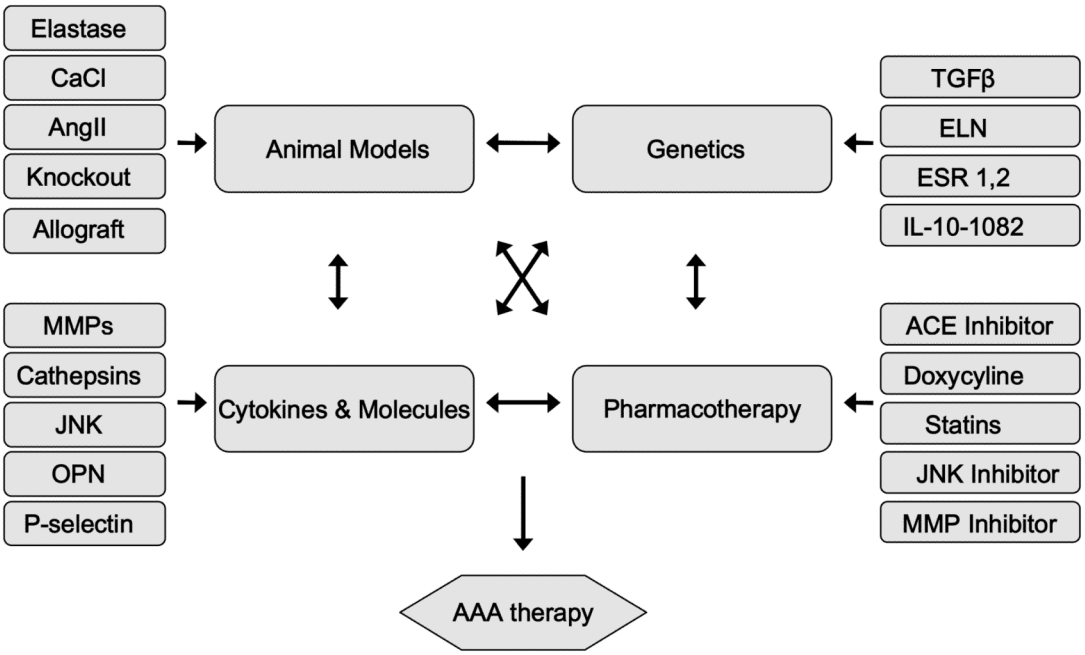

Figure 2.
AAA Research Paradigm. Current AAA research revolves the use of animal models, genetics, cytokines and molecules, and pharmacotherapy.

Table 1

AAA Mouse Models

Mouse Model	Method	Mechanism
Elastase[8–10]	Transient perfusion of the abdominal aorta with porcine pancreatic elastase	Extensive destruction of the elastic lamellae and the adventitial region
Calcium Chloride[13]	Periaortic incubation of calcium chloride combinedwith thioglycollate	Structural disruption of the medial layer and promotion of inflammatory response
Angiotensin II[15]	Delivery of AngII via subcutaneously implanted osmotic mini-pumps	Medial macrophage accumulation associated withelastin degradation
Allografted aorta[21]	Genetic background mismatch (BALB/c (B/c, H-2^d) donor and 129SvEv (129Sv, H-2^b) recipient)	Associated with markedly increased levels of MMP-9 and MMP-12 resulting in severe aneurysm
apoE −/−, LDL receptor −/−[7]	Apolipoprotein E and/or LDL receptor knockout mice	Hyperlipidemic arterial walls develop atherosclerotic and aneurysmal disease

Table 2

Key molecules in AAA development and growth

Molecule/Cytokine	Definition	Role in AAA
Matrix Metalloproteinases (MMP 2,9)[39]	Zinc dependant endopeptidases with role in ECM breakdown and chemokine activation	Elastolytic and collagenolytic properties expressed in vascular smooth muscle
C-Jun N-Terminal Kinase (JNK)[57]	Mitogen activated protein kinases involved in T-cell differentiation and apoptosis	Enhancement of the activity of MMPs and concurrent suppression of the extracellular matrix biosynthesis
P-selectin[68]	Cell adhesion molecule found in endothelial cells and activated platelets	Procoagulant activity and platelet activation marker leading to intramural thrombus formation
Elastase[8–10]	Protease that breaks down elastin	Elastin degredation results in connective tissue breakdown and aneurysm development
Angiotensin II (angII)[15]	Potent vasocontrictor and prothrombotic potential through adhesion and aggregation of platelets; role in renin- angiotensin system	Chronic infusion via subcutaneously placed osmotic pumps reproducibly form AAAs in mice models
Monocyte Chemoattractant protein (MCP)-1[69]	Antisense protein chemotactic for monocytes	Elevated levels in aortic wall of aneurysms suggest role in transmural inflammation
Regulated-on-activation normal T cell expressed and secreted protein (RANTES/CCL5)[69]	Protein chemotactic for T cells, eosinophils and basophils	Elevated levels in aortic wall of aneurysms suggest role in transmural inflammation
Transforming Growth Factor (TGF-β 1,2)[42]	Multifunctional peptide that controls cell proliferation, differentiation, and apoptosis	Mutation in the gene identified as significant role in Marfan's. Dysregulation of TGF-β signaling leads to aneurysm/dissection
Cyclooxygenase (COX-2)[39]	Enzyme responsible for formation of prostaglandins	Promotion of angiogenesis plays a role in AAA development.
Cathepsins S, K, and L[40]	Proteases involved in cellular turnover, connective tissue breakdown, and bone resorption	Collagenolytic activity in vascular smooth muscle against triple helical type I collagen
Osteopontin (OPN)[41]	Extracellular cell adhesion protein involved in nonmineral bone matrix formation; also a key cytokine in mediating type I immune response	May be a useful biomarker for AAA presence and growth
Fibrillin-1[69]	Major component of microfibrils surrounding elastin in connective tissue	Mutation in the gene responsible for Marfan's syndrome