

The Pathogenesis of Abdominal Aortic Aneurysms

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The pathogenesis of abdominal aortic aneurysm (AAA) formation is not well understood. AAAs are characterized by destruction of elastin and collagen in the media and adventitia, loss of medial smooth muscle cells with thinning of the vessel wall, and transmural infiltration of lymphocytes and macrophages. Atherosclerosis is a common underlying feature of aneurysms. However, it is naive to suggest that atherosclerosis causes aneurysms as the former is primarily a disease of the intima while aneurysm formation primarily affects the media and adventitia. A National Heart, Lung, and Blood Institute Request for Applications (HL-99-007) entitled "Pathogenesis of Abdominal Aortic Aneurysms" identified four mechanisms relevant to AAA formation including: 1) [proteolytic degradation of aortic wall connective tissue](#), 2) [inflammation and immune responses](#), 3) [biochemical wall stress](#), and 4) [molecular genetics](#).

Proteolytic Degradation of Aortic Wall Connective Tissue

Aneurysm formation involves a complex process of destruction of the aortic media and supporting lamina through degradation of elastin and collagen. *In vivo* models of AAA formation, including periadventitial application of calcium chloride and intraluminal aortic perfusion of elastase, have been used to elucidate the role of various proteases during aneurysm formation. These models, as well as studies on human aortic tissue, suggest that various **matrix metalloproteinase proteinases** (MMPs), derived from macrophages and aortic smooth muscle cells, play an integral role in aneurysm formation. Interstitial collagen dissolution accompanies increased expression of collagenases MMP-1 and MMP-13 in human AAAs. Elastases MMP-2 (gelatinase A), MMP-7 (matrilysin), MMP-9 (gelatinase B), and MMP-12 (macrophage elastase) are also increased in aneurysmal aortic tissue. MMP-12, in particular, is highly expressed along the proximal leading edge of human AAAs and may be important in aneurysm initiation. In addition, high levels of MMP-2, a constitutive enzyme, are found in small aneurysmal aortas, suggesting a role for MMP-2 in early aneurysm formation. Lastly, the inducible elastase MMP-9 is elevated in aortic tissue, as well as in serum from patients with AAAs. Experimental aneurysm models also support a critical role for this elastase as MMP-9 knockout mice do not form aneurysms. Importantly, when these knockout mice undergo wild type bone marrow transplantation, the aneurysm phenotype is restored, adding credence to a central role for MMP-9. During AAA formation, the balance of vessel wall remodeling between **MMPs** and their inhibitors, **Tissue Inhibitors of Metalloproteinases (TIMPs)**, favors elastin and collagen degradation. Yet, the biologic mechanisms for initiating these proteolytic enzymes in the aorta is unknown.

Inflammation and Immune Responses

A prominent histologic feature of AAAs is an extensive transmural infiltration by macrophages and lymphocytes. It is hypothesized that these cells subsequently release a cascade of cytokines resulting in activation of many proteases. The trigger for influx and migration of leukocytes is unknown, but exposed elastin degradation products in the aortic wall may serve as the primary chemotactic attractant for infiltrating macrophages. The concept that AAA formation is an autoimmune response is supported by the extensive lymphocytic and monocytic infiltrate, as well as the deposition of immunoglobulin G reactive to extracellular matrix proteins in the aortic wall. The

adventitia appears to be the primary site of leukocyte infiltration and initial **MMP** activation. Macrophage and lymphocyte-generated cytokines are elevated in the aneurysmal aortic wall, including IL-1 β , TNF- α , IL-6, IL-8, MCP-1, IFN- γ , and GM-CSF. These inflammatory cytokines, as well as plasmin and urokinase-type plasminogen activator, induce expression and activation of **MMPs** and **TIMPs**. A lack of bioavailable nitric oxide (NO), a ubiquitous molecule known to alter vessel wall remodeling, induces MMP-9 expression and may be important in initiating vessel wall degradation leading to aneurysm formation.

Biochemical Wall Stress

The preferential infrarenal site for AAA formation suggests potential differences in aortic structure, biology, and **stress** along the length of the aorta. Increased **shear** and **tension** on the aortic wall result in collagen remodeling. Further, a decrease in the elastin to collagen ratio from the proximal to the distal aorta may be clinically relevant since diminished elastin is associated with aortic dilation, while collagen degradation predisposes to aortic rupture. Once an AAA has developed, it is likely that increased wall stress is an important in accelerating dilation and increasing the risk of rupture. β -blockers serve to reduce wall stress and have been suggested to be protective of continued aneurysm dilation and rupture in animal models.

Molecular Genetics

Familial clustering and a common HLA subtype suggest both a genetic and an immunologic role in the pathogenesis of AAAs. Currently, no single genetic polymorphism or defect has been identified as a common denominator for AAAs. Patients with affected siblings, however, are at substantially increased risk to develop AAAs. Some phenotypes have been found to be associated with AAAs. For example, the Hp-2-1 haptoglobin phenotype and deficiencies in α 1-antitrypsin are associated with aneurysm formation. In addition, there is a decreased frequency of AAAs in patients with Rh-negative blood group and an increased frequency in patients with MN or Kell-positive blood groups.

Proposed Mechanism

A combination of multiple factors including localized hemodynamic **stress**, **medial fragmentation**, and **genetic predisposition**, through an unknown immunologic mechanism is likely to attract inflammatory cells into the aortic wall. Inflammatory cells then release chemokines and cytokines resulting in further influx of leukocytes with subsequent expression and activation of inducible and constitutive proteases, notably the **MMPs**. These proteases result in medial degradation and aneurysmal dilation with ongoing remodeling. Increased **wall stress** then causes continued proteolysis and progressive aneurysm dilation with eventual aortic rupture if untreated.

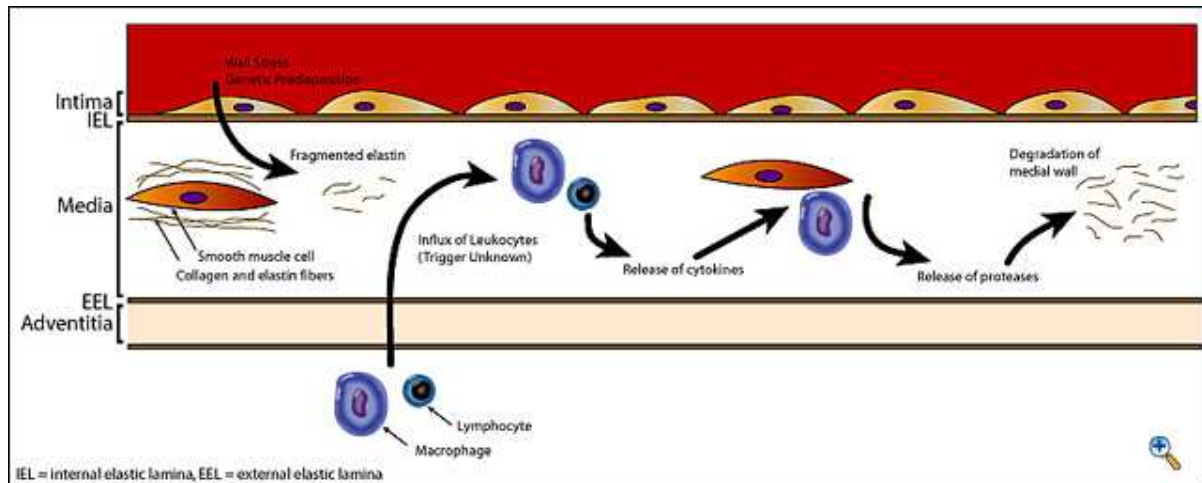


Figure 1.
Schematic depiction of proposed mechanism of aortic aneurysm formation. (Courtesy of BS Knipp, MS, University of Michigan Medical School)

References:

1. Wassef M, Baxter BT, Chisholm RL, Dalman RL, Fillinger MF, Heinecke J, Humphrey JD, et al. Pathogenesis of abdominal aortic aneurysms: A multidisciplinary research program supported by the National Heart, Lung, and Blood Institute. *J of Vasc Surg* 2001; 34: 730-8.
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