The development of a saccular (nondissecting) aortic aneurysm follows the destruction of the connective tissue in the media, in particular the elastic lamellae. The vessel wall is then unable to withstand the expansile force of each systolic contraction. The current view is that the great majority of aortic aneurysms, >90% of which are below the renal arteries, are associated with atherosclerosis. This view is based on the fact that the lower abdominal aorta is the site at which atherosclerosis first develops and confluent intimal involvement becomes common by middle age. Resected abdominal aortic aneurysms show advanced atherosclerosis with mural thrombus in the wall. This view, however, is a paradox in that atherosclerosis is an intimal disease, whereas in the abdominal aorta, aneurysms are due to major medial damage. There are also other reasons to believe that aortic aneurysms have an additional component to their pathogenesis. Abdominal aortic aneurysms are familial and under genetic influences unrelated to lipid-related risk factors for atherosclerosis. First-degree relatives of index cases with abdominal aortic aneurysms have a significantly higher risk of developing a similar lesion when compared with the general population. Prospective family studies suggest a figure of 14.5% for offspring and 13% to 32% for siblings compared with the general population risk of 2% to 5%. Risk factors such as elevated plasma cholesterol, hypertriacylglyceridemia, hypertension, and smoking are found in many subjects with abdominal aortic aneurysms, yet 60% of cases have plasma cholesterol levels of <240 mg/dL. Smoking is the single largest external contributor to the risk of aortic aneurysm formation. These data suggest that there are additional factors involved in aortic aneurysm formation. Some of the factors are genetic. A very small subgroup of saccular aneurysms are due to genes controlling connective tissue structural proteins. The fibrillin gene is largely responsible for dissection of the aorta, but occasional families with saccular abdominal aneurysms have been identified on chromosome 16 or close to the haptoglobin gene, which might enhance elastic degradation, but the exact mechanism is unclear.

The view has evolved that the medial destruction in aortic aneurysms is due to an inflammatory response within the media and adventitia. Mediastinal and adventitial infiltration by a mixture of chronic inflammatory cells including T and B lymphocytes, mast cells, and macrophages is a very striking feature of human atherosclerosis in the abdominal aorta. These cells probably represent a response to oxidized lipid leaching into the vessel wall from the intima. Antibodies to oxidized LDL are produced locally within the adventitia.

The mode of action by which an inflammatory infiltrate destroys connective tissue matrix is by proteolytic digestion. The best-studied group of such enzymes involved are the metalloproteinases (MMPs). MMPs are Zn2+- and Ca2+- dependent enzymes, and at least 12 with different molecular sizes have been sequenced. Each has different substrate preferences. Those with a particular affinity for elastin are stromelysin 1 (MMP-3, 57 kD) and metalloelastase (MMP-12, 57 kD). In the destruction of a connective tissue matrix under pathologic conditions, however, a mixture of MMPs are probably needed to break down additional components of the connective tissue matrix, including collagen types I and III (interstitial collagenase MMP-1, 55 kD), collagen type IV (gelatinase B, MMP-9, 92 kD), laminin, proteoglycans and fibronectin (stromelysins 1 to 3, MMP-3). A constant feature of the MMPs is that they are released from the inflammatory cells into the tissues as an inactive zymogen, which is then converted into an active form. The major activator of MMPs in tissues is plasmin generated by the action of plasminogen activating factor on plasminogen. Inhibitors of the proteins exist and include α2-macroglobulins, α1-antitrypsin, and specific inhibitors known as TIMPs (tissue inhibitors of metalloproteinases), which carefully regulate connective tissue turnover in physiologic states. Plasminogen activating inhibitors (PAI-1) also occur in tissues. Pathologic destruction of the media would imply a considerable excess of active MMPs over their specific inhibitors. Alternative pathways of MMP activation include a membrane-bound, 66-kD MMP probably concerned in very local dissolution of connective tissue matrix in smooth muscle migration. Mast cells will also activate MMP zymogen.

A wide range of cell types produce MMPs. One form (gelatinase A, MMP-9) is produced by smooth muscle cells and is concerned with both cell migration and proliferation after vascular injury. The main cell capable of producing a
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wide range of MMPs in the aorta is the macrophage. A range of inflammatory cytokines including tissue necrosis factor-α (TNF-α) and interleukin-6 upregulate MMP production by macrophages. Such inflammatory foci also contain high levels of plasminogen activating factor. Neutrophils also secrete MMP-8, which has a powerful collagenolytic function and is important in pulmonary emphysisma. However, neutrophils are relatively sparse in the vessel wall when compared with the numbers of macrophages.

The current hypothesis for aortic aneurysms is that the inflammatory response in the vessel wall produces an overwhelming degree of enzymatic degradation of the connective tissue matrix. Human studies can only provide observational data to support this view. A wide range of MMPs have been shown to be present in human aortic aneurysm walls.6,11-13 Observational studies on human aortic aneurysm do suggest acceleration of connective tissue breakdown. Increased elastolytic activity and collagenolytic activity have been shown by functional assays in aortic aneurysm walls.14 Gelatinase A (MMP-2) and gelatinase B (MMP-9) were both studied in a comparison of samples taken from small compared with large human aortic aneurysms. In the larger expanding aneurysms, gelatinase B was increased and associated with large numbers of macrophages.16 Reduced amounts of TIMPs have been shown within human aneurysm walls.17 However, it is impossible to differentiate between primary reduced amounts of inhibitor and a secondary reduction caused by binding with increased MMP production. Inhibition of proteolytic enzymes by α1-antitrypsin has been suggested to be abnormal in patients with aortic aneurysms, giving an interesting analogy with elastolytic activity in smoking and emphysisma.18 An analysis of the subtypes of α1-antitrypsin in subjects with abdominal aortic aneurysms did not, however, yield conclusive results, but there was a small excess of patients with aneurysms who had the MZ phenotype for α1-antitrypsin in which enzyme levels are reduced. The figures were 3% to 4% frequency in the general population against 11% in the 47 patients with aortic aneurysms.

Experimental models would be a very desirable means of testing the mechanisms involved in aneurysm formation. Some models have been developed. Hyperlipidemia in rabbits will produce extensive aortic atherosclerosis but does not produce aortic aneurysms. The application of irritants such as CaCl₂ or agents such as thioglycollate, which activate macrophages, to the adventitia will, however, enhance aortic wall inflammation, after which aneurysms do develop.19 In another model a segment of guinea pig aorta had the cells removed by treatment with 0.1% SDS, and the resulting tube of extracellular connective tissue matrix was used as a xenograft into a rat. The xenograft became an aneurysm as the result of a progressive loss of elastin over the subsequent few weeks. Rat-to-rat isografts prepared in an identical way do not become aneurysmal. When the arterial xenograft was seeded with synogenic rat smooth muscle cells that overproduce TIMPs-1, aneurysm formation was inhibited. TIMPs-1 will inhibit MMPs 1, 9, 3, and 12 and thus will suppress proteolytic digestion of a wide range of the components of the connective tissue matrix.

Further use of this model is reported in this issue of Circulation by Allaire and colleagues.21 The question being asked is whether more upstream inhibition of MMPs would be effective in preventing aneurysms. In the model, the graft was seeded with syngenic rat smooth muscle cells overproducing PAI-1. In this way local plasmin production would be inhibited, and if this is the main activator of the MMPs, inhibition of aneurysm formation would occur. In the study, unseeded grafts became aneurysmal by 4 weeks. Within this time frame, inflammatory cells infiltrate the media and elastic lamella destruction begins. The zymograms of tissue extracts suggested the presence of MMPs 2, 3, and 9. In contrast, in seeded grafts the elastic pattern seen on histology was preserved and aneurysm formation did not occur. The results are entirely consistent with the view that prevention of activation of MMPs is equally efficient in preventive terms compared with inhibiting the active enzyme itself. Quantitative zymography showed that tissue plasminogen activator and the levels of activated MMPs were decreased in the seeded grafts.

One problem with MMPs causing pathologic destruction within human tissues is whether one type is dominant or whether concordant action between several members of the group is needed. The experimental model described highlighted that stromelysin-1 (MMP-3), which has an initial molecular weight of 57 kD, is present in large amounts and is activated into lower-molecular-weight fragments (45, 28, and 24 kD) with activity against proteoglycans, type IV collagen fibronectin, laminin, and elastin. Other studies on the disruption of human atherosclerotic plaques within the intima have also found stromelysin present in large amounts. The other MMP found in the model was gelatinase B (MMP-9), which also has elastinolytic properties. This MMP is also known to be associated with plaque disruption.22 Therefore, the perception that human aortic aneurysms are due to the overactivity of MMPs in the vessel wall appears to be soundly based.

How does this view fit with the known genetic component of aortic aneurysms? One explanation is that polymorphisms exist in the tissue plasminogen activator/PAI-1 system, allowing the local generation of plasmin to be enhanced. Although in theory active generation of plasmin may remove fibrin rapidly from plaques, reducing smooth muscle proliferation, it might also potentiate activation of MMPs. Polymorphisms in the MMP genes themselves may lead to forms less readily inhibited by TIMPs and therefore more active. Any gene that led to nonfunctional TIMPs would equally potentiate aneurysm formation. Single gene defects in the MMPs or TIMPs are not yet identified as factors in causing aneurysm formation, and polygenic influence seems more likely.6 The role of smoking, which remains the single largest external risk factor for abdominal aortic aneurysms, remains to be elucidated. Good experimental models at a molecular level will provide ways in which such factors can be unraveled and drugs that inhibit MMP activity tested.

References


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