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REVIEW ARTICLE

Pathogenesis of Abdominal Aortic Aneurysms — Cellular and Biochemical Mechanisms

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Introduction

Despite advances in the treatment of abdominal aortic aneurysms (AAAs), the pathogenesis of aneurysmal disease remains obscure. Aneurysm screening programmes have successfully identified a proportion of patients with early or small aortic aneurysms,[1–3] who do not fulfil the current criteria for elective aneurysm repair on the basis of aortic diameter.[4] At present these patients are managed conservatively, with regular ultrasonographic follow-up, but with increased knowledge of aneurysm pathophysiology, it is possible that aneurysm growth may be retarded with medical or gene therapy.[5] This review presents the current theories of aneurysm pathogenesis, with emphasis on the cellular and biochemical events within this disease process.

Histology of Abdominal Aortic Aneurysms

The ability of the aorta to counter the force exerted by the blood is dependent on the structural proteins of the arterial wall.[6] Collagen and elastin are the predominant proteins within the aorta, which act to uniformly distribute stresses within the tissue, and maintain an appropriate viscoelastic response to pulsatile oscillation. Smooth muscle cells (SMCs) are the major cell type,[7] and together with adventitial fibroblasts, have the capacity to synthesis all components of the extracellular matrix (ECM).

In the normal infrarenal aorta, the media is arranged in a series of well-defined concentric elastic lamellae. Each layer, bounded by relatively thick elastin bands, contains circumferentially oriented collagen fibres, along with a network of fine elastin fibres, and a layer of SMCs compacted between adjacent elastic lamellae. The close association of elastin, collagen, and SMCs in the aortic media is responsible for the viscoelastic properties of the adult aorta.[8]

Abdominal aortic aneurysms are characterised by degeneration, destruction, and remodelling of the aortic wall. Aneurysmal dilatation is accompanied by an overall thickening of the aortic intima and adventitia, with a marked loss of elastin from the tunica media,[6] and a ubiquitous chronic inflammatory infiltrate.[9]

Composition of the Extracellular Matrix

The expansion of infrarenal AAAs is accompanied by an increase in total protein, microfibrillar protein, and collagen content, together with a marked reduction in elastin concentration, and medial smooth muscle cell number.[6,9–12] Sumner *et al.*[13] were the first to document depletion of elastin in aneurysmal tissue, and numerous subsequent biochemical studies have confirmed this finding.[11,14–16] The total elastin concentration of infrarenal AAAs has been reported to be only 5–8%,[14,17] when compared to the 15–35% of age-matched aortas. However, relative changes in elastin concentration may be misleading. Due to the concomitant increase in wall thickness with increasing aneurysm circumference,[12] elastin content, as opposed to concentration, has been shown to increase in AAA tissue. Nevertheless due to the increased total protein content in the aneurysmal aorta, the elastin concentration actually decreases.[10,12,13]

The fibrillar collagen network provides most of the

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tensile strength of the aortic wall. This network contains predominantly type I and III collagen[14] with the tensile characteristics being attributed to type III.[18] Collagen is the principle component of the adventitia of any AAA, regardless of size. The relative collagen concentration, and absolute collagen content of the aneurysmal aorta have been demonstrated to be elevated in several studies. Minion *et al.*[12] and Baxter *et al.*[10] found a five-fold and three-fold increase in collagen content respectively, whilst Menashi *et al.*[18] showed an increase in collagen concentration from 62 to 84% in aneurysmal vs. control aortic tissue.

There appears to be a correlation between increasing aneurysm size and collagen content,[12] which suggests a causal relationship between collagen synthesis and aortic dilatation. This relationship may be a compensatory response to increased wall stress,[19] as stretch is known to be a stimulus for connective tissue synthesis.[20] McGee *et al.*[21] suggested that collagen synthesis and deposition was accelerated in the walls of unruptured aneurysms, as mRNA levels for α 1-procollagen were increased in AAA tissue extracts. Since elastin gene expression is unaltered in the wall of aortic aneurysms,[22] these data suggest that discordant gene expression may contribute to the relative decrease in elastin concentration in aortic aneurysms. Others have argued that since the ratio of type I to type III collagen is unchanged in comparison to normal aorta,[18] selective degradation of elastin in the aneurysmal media would give an apparent dilutional increase in collagen concentration. It seems likely that a combination of increased collagen synthesis, and enhanced elastin degradation are responsible for the changes in matrix composition in the walls of AAAs.

Interestingly, the matrix abnormalities demonstrable in AAAs are not confined solely to the aneurysmal segment, but are also found in aortic tissue proximal to the aneurysmal site.[10] Ward[23] also demonstrated that mean diameters for the carotid, femoral, brachial and popliteal arteries were significantly greater in patients with aortic aneurysms than in controls, suggesting that infrarenal aneurysmal disease may be a localised manifestation of a systemic dilating process.

In addition to elastin, collagen, and SMCs, the medial elastic lamellae are associated with microfibrillar proteins, a family of glycoproteins defined by their proximity to amorphous elastin and their fibre diameter on electron microscopy. Several biochemical studies of aneurysmal tissue have shown an increase in content of approximately 20% of an unknown connective tissue protein, most likely to be a microfibrillar protein such as fibrillin.[16] The reasons for the increase in this unknown microfibrillar protein are currently unclear.

The increased turnover of extracellular matrix components observed in the aneurysmal aorta, results in a relative imbalance in structural proteins. It is not known whether this imbalance is an important aetiological factor in aneurysm formation, or whether it results from changes such as wall tension and chronic inflammation. However, it is probable that the abnormal mechanical properties of AAAs are due to a decrease in the ratio of elastin to collagen, resulting in a functionally compromised aortic wall.

Genetic Susceptibility

Aortic fragility and rupture have been associated with inheritable mutations in two of the connective tissue components of the aortic wall, namely fibrillin in Marfan's syndrome,[24] and type III collagen in Ehlers-Danlos type IV disease.[25] However, these congenital diseases represent distinct clinical entities which do not often manifest as true AAAs.

The first report of familial aggregation of AAAs without any known hereditary connective tissue disorder, was presented by Clifton in 1977.[26] This report described three siblings in a family with ruptured AAAs. Since then many epidemiological reports have been published demonstrating a higher than normal incidence of blood-relatives affected with AAAs. These data demonstrated the existence of a hereditary component predisposing to AAA formation, which provided the impetus for genetic studies into AAA disease.

To address the question of whether a single identifiable locus accounts for the observed familial clustering, several studies have utilised segregation analysis to examine multigenerational pedigrees. Majumber *et al.*[27] suggested that the pattern of inheritance observed in 91 families could be explained by a major autosomal diallelic locus with the aneurysmal allele being recessive. In contrast, Verloes *et al.*[28] examined 313 pedigrees and concluded that the major genetic defect was a dominant trait with age-dependent penetrance. Differences in methodology may account for the discrepancy in the mode of inheritance between these two studies, but both series support the concept of a genetic element in aneurysm pathogenesis.

There are several mechanisms by which genetic variables may predispose to AAA development. Increased enzymatic destruction of matrix components might result in arterial dilatation and studies on α 1-antitrypsin seemed initially to lend weight to this

hypothesis.[29] Serine proteinases are inhibited predominantly by α1-antitrypsin, a deficiency of which is associated with emphysema and accelerated destruction of elastic tissue in the lung. Chronic pulmonary disease has been considered to predispose patients with AAA to rupture.[30] Cohen *et al.*[29] initially described that the poorly inhibitory MZ α1-antitrypsin phenotype was found with increased frequency in patients with AAA. However this association has not been confirmed, and several larger studies have now demonstrated that the MZ and ZZ α1-antitrypsin phenotype are not related to aneurysmal disease.[31,32] Moreover, 85% of patients with AAA have the common MM phenotype.[29]

Alternatively, inherited defects in elastin and collagen might result in an aortic media more prone to enzymatic degradation. Genetic variation in the elastin gene is negligible and has not been demonstrated in patients with AAA.[6] However, indirect evidence implicating the involvement of different collagen genotypes, resulted from the observation that some patients with cerebral aneurysms also appeared to have impaired synthesis of type III collagen.[33] A single base mutation Gly — Arg, at position 619 in the coding gene for type III collagen has subsequently been associated with AAA disease in a single family in the U.S.A.,[34] although as with Ehlers-Danlos syndrome, these patients had aortic dissections rather than true aneurysms. Surprisingly, this anomaly had little effect before the fourth to sixth decade of life, and has not been identified in other patients presenting with abdominal aneurysms.[35]

One recent study by Powell *et al.*[35] found a specific polymorphism in the type III collagen gene, detected with the restriction enzyme Ava II, to be associated with AAA. This result may be significant, since the elastin content of the aortic media decreases in aneurysmal disease, thereby shifting the mechanical load of the pulse pressure from elastin to collagen.[15] In this situation subtle variations in the structure of type III collagen could influence the mechanical properties of the aorta. It was concluded that a genetic influence may determine whether, in the presence of atherosclerotic risk factors, the aorta stenoses or dilates and might also determine how rapidly an aneurysm grows, since the polymorphic variation observed was proportional to aneurysm diameter. However, a recent study using detailed DNA sequencing of the triple helical domain of type III procollagen demonstrated that mutations in type III collagen are the cause of only 2% of aortic aneurysms.[36]

On balance, it seems likely that inheritance of AAA disease is multifactorial,[37] involving a complex interaction between environmental influences and a constitutional genetic susceptibility.[14] Although the familial clustering of AAA indicates a hereditary component and several candidate genes have been investigated, the precise genetic basis of aneurysm formation remains obscure.

Haemodynamic Influences

The tensile strength of the aortic wall results from the concentric arrangement of the medial elastic lamellae. The infrarenal aorta contains fewer elastic lamellae in contrast with the thoracic aorta,[8] which results in a relative deficiency of elastin, and a stiffer less compliant vessel. Superimposed upon this is a natural age-related decrease in the distensibility and elasticity of the aorta, owing to the effects of haemodynamic stress imparted during the cardiac cycle.[38]

Aortic aneurysms appear to have a predilection for the infrarenal aorta, and it has been suggested that this may be due to the unique haemodynamic conditions that characterise this region.[39] As the aorta descends from thorax to abdomen, it tapers and becomes less compliant. This has the effect of increasing the pulse pressure which becomes maximal in the infrarenal aorta.[40] In addition, pressure waves are reflected from the aortic bifurcation, which may contribute to localised regions of increased pressure in the infrarenal aorta. An interesting example of this haemodynamic effect was noted in a study of amputees which resulted in an asymmetric flow pattern at the aortic bifurcation and an increased risk of aortic aneurysms.[41] Recent improvements in magnetic resonance imaging have also allowed blood velocity profiles to be calculated in the normal aorta. Oyre *et al.*[42] reported that peak wall shear stress is lower in the infrarenal than suprarenal aorta and that the magnitude and duration of negative shear stress is higher at the posterior than anterior wall in the infrarenal segment.

Although the infrarenal aorta is associated with high pulse pressure and low shear stress, the haemodynamic conditions become increasingly deranged with aortic dilatation. Bluth *et al.*[43] validated early experimental studies[44,45] by demonstrating that abdominal aneurysms may exhibit both laminar and turbulent flow *in vivo*. At low flow rates, the flow is laminar with a core of swiftly moving fluid being surrounded by an annulus of slower moving fluid circulating as a rotating vortex.[46,47] Low *et al.*[48] confirmed these observations and showed that intra-aneurysmal flow is slow compared with the non-dilated vessel and that stagnation of flow may occur in

the dome of the aneurysm. In contrast, at higher flow rates the flow becomes turbulent,[49] and the threshold Reynolds number determining turbulence is reduced as the aneurysm expands.[50] These observations have important implications for shear stress within aortic aneurysms. In small aneurysms, laminar flow may predominate, and the resulting shear stress is lower than recorded in the normal calibre vessel, and may even become negative. However, in larger aneurysms, the likelihood of turbulent flow is greater, and in turbulence, the peak shear stress will be much greater than in the non-dilated vessel.[50]

Systemic and Localised Proteolysis

The normal vascular ECM is a complex network of proteins and proteoglycans which exist in a state of constant flux. Homeostasis within the ECM is achieved by an intricate balance between synthesis and degradation of the matrix proteins, orchestrated by the resident mesenchymal cells. The physiological maintenance of tissue integrity involves the interaction of numerous degradative enzymes and their inhibitors. The family of enzymes that selectively digest the components of the ECM are collectively called the matrix metalloproteinases (MMPs), since their catalytic mechanism depends on the presence of zinc at the active site.[51] The MMPs belong to three main groups according to their substrate specificity: the collagenases, the gelatinases, and the stromelysins (Table 1). The proteinase activity of MMPs is inhibited under physiological conditions by the endogenous family of tissue inhibitors of metalloproteinases (TIMP-1,2, and 3).[51]

The enzymatic activity of the MMPs is tightly regulated at several levels. Many growth factors, cytokines, hormones, or tumour promoters regulate MMP expression at the transcriptional level. All these enzymes are secreted as inactive zymogens, which require proteolytic cleavage by other proteinases (such as plasmin, trypsin and even other MMPs) to exert their matrix-degrading potential. The balance between MMPs and their natural inhibitors, further modulates the enzymatic activity of the matrix degrading proteins.[51]

Pathological changes in tissue integrity resulting from proteolytic processes are of central importance during the arterial degradation that accompanies aneurysm formation. Many studies employing sophisticated enzymatic assays have reported increased elastase, collagenase, and gelatinase activities within the aneurysmal aortic wall.[52–58]

Table 1. Names and molecular weights (secreted and active form) of several well-characterised matrix metalloproteinases (MMPs) and their inhibitors (TIMPs).

Metalloproteinase	Other names	Molecular weight (kDa)	
MMP-1	Interstitial collagenase	52	secreted
		42	active
MMP-2	72 kDa Gelatinase, Gelatinase-A	72	secreted
		66	active
MMP-3	Stromelysin-1	57	secreted
		48	active
MMP-7	Uterine metalloproteinase, PUMP-1, Matrilysin	28	secreted
		19	active
MMP-8	Neutrophil collagenase	85	secreted
		65	active
MMP-9	92 kDa Gelatinase, Gelatinase-B	92	secreted
		84	active
MMP-10	Stromelysin-2	53	secreted
		47	active
MMP-11	Stromelysin-3	51	secreted
		44	active
MMP-14	MT-MMP-1	60	membrane bound
MMP-15	MT-MMP-2		
TIMP-1	TIMP-1	29	secreted/ active
TIMP-2	TIMP-2	20	secreted/ active

In separate studies, Busuttil *et al.*,[54] and Cannon and Read[59] reported increased elastase activity in aneurysmal disease. Subsequent reports,[52,53,60] speculated that this elastase activity was attributable to a serine proteinase, possibly circulating pancreatic elastase,[53] or leucocyte elastase.[59] Indeed, the activity of serine proteinases have been extensively utilised in experimental animal models, with the direct infusion of elastase into cross-clamped segments of rat aorta resulting in aneurysm-like dilatation.[61,62]

However, subsequent data,[63] suggested that the increased elastase activity was due to a non-serine proteinase. In 1987, Campa *et al.*[15] described a 90 kDa proteinase that discriminated between aneurysmal and atherosclerotic tissue. This elastase belonged to the metalloproteinase rather than the serine proteinase family, as it did not cross-react with antibody to circulating leucocyte elastase, and it possessed an inhibitory profile consistent with an MMP.[15] In 1991, Brophy *et al.*[64] identified an elastolytic proteinase in AAA tissue using substrate gel enzymography which had a molecular weight of approximately 80 kDa, in contrast to neutrophil and pancreatic elastases, which have a MW of 30 kDa.[64]

Recent work[56–58] has proven overwhelmingly that the elastases involved in aneurysmal tissue are members of the metalloproteinase family. Vine and Powell[56] found the elastolytic activity of AAA tissue

specimens to be significantly increased when compared with homogenates from either atherosclerotic or normal aorta, with the principal enzyme observed being an MMP with a molecular mass of 92 kDa.[56] They concluded that this enzyme was consistent with the latent form of MMP-9.[56] In 1994, two major studies by Newman *et al.*[57,58] used substrate gel electrophoresis to compare AAA tissue extracts with age-matched controls. Both studies observed a band of activity at 80 kDa which was demonstrated to be the active isoform of MMP-9 by immunoblotting. On the basis of these observations and the known elastolytic properties of MMP 9,[65] this proteinase is believed to play a central role in aneurysm pathogenesis.

Interest in the role of interstitial collagenase (MMP-1) in AAAs was initiated by Busuttil *et al.*[55] Vine and Powell[56] found considerable MMP-1 activity in aneurysmal aortas, whilst Irizarry *et al.*[66] demonstrated that AAA extracts contained increased amounts of material immunoreactive to MMP-1. However, Herron *et al.*[52] were unable to immunoprecipitate MMP-1 from either aneurysmal or normal aortic extracts, and Webster *et al.*[67] likewise found it impossible to extract active interstitial collagenase under non-reducing conditions. It has been suggested[68] that these conflicting results were due to the binding of MMP-1 to its natural inhibitor, TIMP-1, which may mask its detection in activity assays. Irizarry *et al.*[66] resolved this problem by running immunoblots after polyacrylamide gel electrophoresis under reduced conditions. Immunoreactive bands of AAA extracts to the MMP-1 antibody were subsequently detected, whereas control extracts had little or no levels of immunoreactive material.

Stromelysin-1 (MMP-3) has also been implicated in the destruction of the aortic matrix during aneurysm formation, both directly[51,69] and through indirect activation of MMPs-1 and 9.[70] In examining homogenates from aneurysmal aortic media, Vine and Powell[56] reported increased levels of MMP-3, a finding which has been confirmed by other investigators.[57,58] The results of investigations into enzymatic activity within the aortic wall suggest that MMPs-1,3, and 9 are significantly elevated in aneurysmal tissue when compared to atherosclerotic controls. Recently, Freestone *et al.*[71] demonstrated that MMP-2 was the dominant proteolytic enzyme in small aortic aneurysms, whereas in larger vessels with a pronounced inflammatory infiltrate, MMP-9 was the principle gelatinase.

Whilst an over activity of MMPs may explain the proteolytic degradation observed in AAAs, a contributory role of a deficiency in the natural anti-proteolytic system has also been postulated. Recent investigations by Brophy *et al.*[72] have shown that TIMP-1 is decreased in AAA tissue, although this does not appear to be a result of a primary genetic defect.[73]

Although Newman *et al.*[57,58] were able to conclusively prove that the ~80 kDa proteinase isolated from AAA homogenates contained active MMP-9, they also observed that a portion of the 80 kDa activity could not be bound to a recombinant-TIMP-1 affinity column. This activity was inhibited by a serine proteinase inhibitor, suggesting that some of the activity demonstrated in the tissue extracts was not MMP-9, but serine proteinase. Studies by Jean-Claude *et al.*[74] conclusively demonstrated the presence of plasmin in AAA extracts, whilst Reilly *et al.*[75] found levels of tissue-type plasminogen activator to be abundant in AAA tissue by comparison with normal or atherosclerotic aorta. These results appear to be important, as plasmin itself can degrade the ECM, but has also been shown to activate latent pro-MMP-1, pro-MMP-3, and pro-MMP-9.[76] The presence of plasmin in the aneurysm wall suggests that it may play an important role in the overall cascade of enzyme activation.

The synergistic actions of the MMPs present in elevated levels in AAA tissue could both initiate and maintain the ECM degradation observed in the aneurysmal aortic media. The 92 kDa gelatinase is not only capable of degrading elastin[65,77] but can also degrade denatured collagen, thus facilitating the action of interstitial collagenase on native type I and type III collagens, which are major constituents of the vascular wall.[14] In addition, Okada *et al.*[69] have reported that MMP-9 may degrade native fibrillar collagens, which are also reduced in the aneurysm wall. The presence of active forms of MMP-3, and plasmin, suggest a cascade of events leading to activated forms of both MMP-1 and MMP-9 that could then result in the concerted degradation of elastin, fibrillar collagens, and other ECM components in the vascular wall, during aneurysm developmental and progression.[57]

The Role of Inflammation

Abdominal aortic aneurysms are typically characterised by a marked chronic inflammatory infiltrate of varying intensity throughout the aortic wall.[9,58,78,79] These cells have been purported to play a significant role in the destruction of the extracellular matrix, both directly, and through cytokinetic paracrine control of the native aortic mesenchymal cells.

Koch *et al.*[9] demonstrated that the majority of inflammatory cells in the aneurysmal aorta were $CD3^+$

T-lymphocytes, which were found predominately in the adventitia. A $CD19^+$ B-lymphocyte component was also prominent, with the remainder of the inflammatory cells being $CD11c^+$ macrophages. The aggregating lymphocytes were often found in clusters, with B-cells surrounded by $CD3^+$ T-cells, often located around the adventitial vasa vasorum. Macrophages were also found scattered within these lymphoid aggregates.

Components of the inflammatory infiltrate have the potential to secrete all the MMPs responsible for ECM degradation, and the participation of inflammatory cells in the genesis of AAAs was suggested by Vine and Powell,[56] who demonstrated a positive correlation between elastolytic activity and the presence of white cell infiltration. Macrophages are known to produce an array of degradative proteinases. Shapiro *et al.*[80] have shown that as monocytes migrate into tissue and differentiate into macrophages, their potential to secrete serine proteinases ceases, while gene expression for a variety of MMPs, including MMP-1, MMP-3 and MMP-9 increases dramatically.

A recent immunohistochemical study attempted to delineate the *in situ* source of the enzymes present in AAA tissue using specific monoclonal antibodies.[81] This study identified the infiltrating inflammatory cells, specifically the $CD14^+$ macrophage, to be responsible for the delivery of two of the MMPs present, namely MMP-3 and MMP-9.

In addition to the direct destruction of the ECM by MMP secretion, the infiltrating macrophages and lymphocytes may be important in activating resident mesenchymal cells[7] through cytokinetic control mechanisms. A number of cytokines have been shown to be significantly increased in homogenates and explants from the aneurysmal aortic wall, e.g. tumour necrosis factor-α (TNF-α),[82] interleukin-1β (IL-1β),[82] interleukin-6 (IL-6),[83] interferon-gamma (IFN-γ),[83] monocyte chemoattractant protein-1 (MCP-1)[84] and interleukin-8 (IL-8).[84]

Interleukin-1β is secreted by B cells, endothelial cells, and fibroblasts,[85] although the principle source is from stimulated macrophages. Positive-feedback involving the resident vascular cells may act locally to amplify and propagate the inflammatory reaction,[86] as IL-1β is a versatile cytokine which exerts biological effects on resident endothelial and smooth muscle cells.[87] Elias *et al.*[88] demonstrated IL-1β to induce collagen synthesis in mesenchymal cells, which may partly explain the increase in collagen content reported by numerous biochemical studies on the aneurysmal aortic wall.

Tumour necrosis factor-α is a 17 kDa protein secreted primarily by activated macrophages,[85] although other cells, including lymphocytes and vascular smooth muscle cells, may produce it.[89,90] TNF-α induces its own gene expression in vascular smooth muscle cells[90] and significant levels of TNF-α have also been detected in homogenates of aneurysmal aortas.[82] In addition to its other inflammatory actions, TNF-α has been shown to be angiogenic, stimulating endothelial cell growth and proliferation.[91] Recently, Holmes *et al.*[92] demonstrated that abdominal aneurysms exhibited a marked angiogenic response in comparison to normal or atherosclerotic aortic tissue. This has significant implications, as neovascularisation is associated with an elevated production of MMPs and a marked inflammatory response,[93] which may exacerbate matrix degradation.

Interleukin-1β and TNF-α can induce the expression of endothelial cell adhesion molecules.[94] Davis *et al.*[95] localised a significant increase in intercellular adhesion molecule-1 (ICAM-1), to the endothelial cells of the vasa vasorum in aneurysmal tissue, suggesting recruitment of monocytes and other inflammatory cells by means of the adventitial vasa. This induction of ICAM-1 expression on the endothelial cells of the vasa vasorum may induce a permissive state in which mononuclear cells enter the adventitial matrix. Once in place, aortic tissue macrophages may further stimulate the expression of ICAM-1 via IL-1β and TNF-α, which then enhance the attraction of additional inflammatory cells to the arterial wall. While *et al.*[19] have suggested that destruction of adventitial elastin may play a primary role in the pathogenesis of AAA formation, and may result from the recruitment of inflammatory cells by ICAM-1 expression and neovascularisation.

Szekanecz *et al.*[83] revealed a significant increase in IL-6 and IFN-γ production by AAA tissue. Interleukin-6 is mainly produced by macrophages[96] and is predominately involved with T- and B-lymphocyte activation during inflammation.[83] The accumulation of immunoglobulin in aneurysmal walls may be the result of increased local levels of IL-6.[78] Interferon-γ has the ability to both stimulate lymphocytes and induce MHC class II antigen expression in smooth muscle and endothelial cells. The enhanced levels of IL-6 and IFN-γ in AAA tissue strongly suggest that they play an important regulatory role in the ongoing active immune response seen within aneurysmal tissue.

While it seems possible that aneurysmal dilatation partially represents an immune-mediated disease, the signals that initially attract leucocytes into the tissue remain obscure. Analogies have been drawn between the processes involved in aneurysm formation and

those involved in other pathologies.[9] Cid *et al.*[97] have postulated that the putative antigenic substance responsible for temporal arteritis might be an inert substance, such as elastin derived peptides. In the aneurysm wall, elastin could potentially degenerate and have its structure altered by the ageing process, or its degradation could be initiated by some proteolytic imbalance defined by a genetic predisposition. The generation of elastin derived peptides may then initiate aneurysm genesis through attraction of white cells and induction of MMP production from mesenchymal cells in the arterial wall.[98,99]

Several studies have demonstrated that cytokines derived from the inflammatory infiltrate may influence the expression of MMPs at the transcriptional level.[100] Keen *et al.*[101] cultured smooth muscle cell explants from human aneurysmal tissue with IL-1β, and demonstrated a dose-dependent increase in interstitial collagenase gene expression. More importantly, Newman *et al.*[81] observed that MMP-1 could be localised to mesenchymal cells in the aneurysm wall, suggesting that both white cells and mesenchymal cells may act as sources of MMPs *in vivo*. In addition, Galis *et al.*[7] showed that smooth muscle cell secretion of MMPs –1, –2, –3 and –9 followed stimulation with IL-1β or TNF-α, and that whilst SMCs stimulated with cytokines expressed several MMPs, mRNA and protein levels of TIMPs 1 and 2 appeared unaffected. These data further support the concept that cytokines may alter the balance between matrix degradation and synthesis.

Although SMCs, fibroblasts, and macrophages can all potentially produce interstitial collagenase *in vitro*, the capacity for mesenchymal cells to produce MMP-1 appears to be much greater than that found in macrophages.[101] Welgus *et al.*[102] observed that stimulated fibroblasts produced sixfold greater amounts of collagenase than an equal number of stimulated macrophages. The observation by Vine and Powell[56] that collagenase activity in aneurysms is greatest in the outer aspect of the media is consistent with the results obtained by Keen *et al.*[101] and Newman *et al.*,[81] suggesting that the SMC is the source of the elevated collagenase found in AAAs.

It appears likely that the cascade of events resulting in the destruction of the extracellular matrix is highly complex, with both cell-matrix and cell-cell interactions contributing to the processes *in vivo*.[82] The importance of the inflammatory cellular infiltrate found in aortic aneurysmal disease lies in both the potential paracrine modulation of adventitial endothelial and vascular smooth muscle cell function, and autocrine activation and recruitment of migrating leucocytes through the cytokine network.[86]

Atherosclerosis and Aneurysm Pathogenesis

Abdominal aortic aneurysms have historically been classified as atherosclerotic in origin because of the almost universal finding of calcified atherosclerotic degeneration in the walls of aneurysms.[15] This assumed "causative" relationship is based on common risk factors,[14,103] other regional manifestations of atherosclerosis, and localisation of aneurysms to the atherosclerosis prone infrarenal aorta.

Zarins *et al.*[104] were able to induce AAA formation in monkeys fed on a lipid-rich atherogenic diet. They found that five of 443 monkeys who experienced prolonged exposure to an atherogenic diet, and who were then transferred to a low cholesterol regimen developed aneurysms. They hypothesised that the development of fibrous tissue within atherosclerotic plaques provided structural support to the aortic wall, and that during the period of regression of the atherogenic diet, the plaques receded, removing the support that these lesions provided which resulted in AAA formation.

In contrast to the thoracic aorta, the infrarenal abdominal aorta contains relatively few vasa vasorum, with appropriate levels of oxygenation and nutrition being provided by pressure filtration from the lumen.[105] This paucity of vasa has been suggested as a factor that may explain the particular propensity of the infrarenal segment of the human aorta to develop early and severe atherosclerosis.[103] Consequently, advanced thickening of the intima by atherosclerotic lesions and thrombus could further impede the only source of nutrients to a faltering media, and theoretically exacerbate deterioration of the elastic and collagen architecture of the aortic wall, initiating aneurysm formation.

However, it has also been argued that, aneurysms may become atherosclerotic as a secondary phenomenon, since atheromatous plaques are preferentially formed in regions of turbulence and low shear stress.[106–109] Tilson[107] has also proposed that the effects of smoking and hypertension, risk factors in both atherosclerotic occlusive, and aneurysmal disease, may mediate the promotion of either disease through unique disease-specific mechanisms, dependent on the constitutional susceptibilities to both diseases.

Reports of familial clustering of aneurysmal disease[26,110,111] has left little doubt that there must be an important genetic susceptibility to AAA formation. In addition, Ward[23] observed that AAA patients demonstrated systemic arterial dilatation in peripheral arteries which are seldom, if ever, involved in atherosclerosis. These findings add further support to the

view that aneurysmal disease has specific determinants that may be unrelated to the atherosclerotic process and distinguish it from occlusive disease as a unique pathogenic entity.

The controversy surrounding the aetiological role that atherosclerosis plays in AAA formation necessitates further detailed studies on a molecular level to reveal precisely which disease is the prerequisite for the other.

Summary and Future Prospects

Abdominal aortic aneurysms are characterised by degradation and remodelling of the extracellular matrix. These changes derive from excessive proteinase activity within the arterial wall which may result from, or cause a widespread inflammatory response. Despite the success in characterising the pathological characteristics of established abdominal aortic aneurysms, relatively little progress has been made in determining the initiating aetiological factors in this disease. Genetic components certainly play a role, but do not appear to be causative in all cases. Most studies investigating aneurysm pathogenesis have utilised tissue from established abdominal aneurysms. By definition, this tissue represents the end-stage of a pathological process, and it may be difficult to differentiate causative factors from secondary degenerative changes.

Further progress in elucidating the pathogenesis of abdominal aortic aneurysms is likely to result from studies attempting to identify abnormalities in gene expression. To separate cause from secondary effects, it may be necessary to culture individual cell lines from the aortic wall, whilst the use of animal models may allow specific cellular interactions to be studied. Knowledge of pathogenesis may allow therapeutic options for small aneurysms to be explored, and evidence has already begun to emerge that metalloproteinase inhibitors may reduce the growth of experimental aneurysms.

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