Chapter 5

Inflammatory Mediators in Abdominal Aortic Aneurysms

Ismail Cassimjee, Regent Lee and Jyoti Patel

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Abstract

Aortic wall dilatation in abdominal aortic aneurysms is characterized by extracellular matrix degradation together with a loss of smooth muscle cells from the aortic media. This occurs in conjunction with a marked inflammatory cell infiltration. The inflammatory cell is characteristic of the second phase of aneurysmal development–progression. It is widely accepted that usually there are three phases involved in the development of abdominal aortic aneurysms: initiation, progression and rupture. In this chapter, we present an overview of the inflammatory mediators in abdominal aortic aneurysms and intraluminal thrombus, highlighting evidence from experimental models and human disease.

Keywords: inflammation, vascular, thrombus, macrophage, T cell

1. Introduction

An abdominal aortic aneurysm (AAA) is an abnormal dilatation of the infrarenal aorta to more than 1.5 times its normal diameter. It poses a risk of rupture which is associated with a significant mortality, and a prophylactic repair is recommended at 5.5 cm in diameter [1–3]. The diameter of an aneurysm is used as a surrogate predictor of rupture risk, and it is at this size that the procedure-related mortality approximates the rupture risk for an overall net benefit in patient survival. There has been much progress in treating aneurysms over the past two decades. The ability to treat aneurysms as minimally invasively, alongside improved perioperative care, has decreased the mortality from elective repair [2—4].

Evidence indicates AAAs as being a disease characterized by an underlying inflammatory cell infiltrate. The inflammatory cell infiltrate consists of differing cell types [macrophages, CD4/CD8 T cells, B cells, natural killer (NK) cells], which interact with each other creating a

microenvironment that produces factors, which result in wall degradation as well as further recruitment of other inflammatory cells.

An imbalance in collagen formation and degradation is thought to be responsible for aortic wall rupture [5]. It is a degenerative disease that shares many of the risk factors that predispose a person to atherosclerosis, but it is thought to be a separate pathological process from atherosclerosis (**Table 1**). Atherosclerosis presents typically as an occlusive disease; however, aneurysmal disease is characterized by elastin degeneration and smooth muscle cell apoptosis together with compensatory collagen deposition in the wall of the aneurysm. This may be a result of differing cytokine responses to the underlying inflammatory cell infiltrate [6].

The process of aneurysm formation is complex, and the progression is typically slow. It is multifactorial and requires a combination of anatomical predisposition and common risk factors to trigger its development. The natural history encompasses stages: initiation, formation, growth and rupture [7].

Atherosclerosis	Abdominal aortic aneurysm
Infiltrate through intima	Adventitial inflammation
TH1 predominately early on	TH2 response in the late stages
Diabetes is a significant risk factor	Diabetes may be protective
Stenosing with plaque burden	Dilating with wall rupture
Genetic associations with familial hypercholesterolaemia	Genetic associations with soft tissue degeneration (Col3A1, FBN-1)
Affects both genders equally	Predominantly affects males

TH1: T-helper cell type 1, TH2: T-helper cell type 2.

Table 1. Key differences between atherosclerosis and abdominal aortic aneurysm pathology.

2. Risk factors for AAA development

The development of degenerative AAAs is significantly related to major risk factors such as smoking, advanced age, hypertension and male gender. Having a first-degree relative with an AAA significantly increases the risk of developing an aneurysm. More especially in young patients, there may be an underlying connective tissue disease, like Ehlers-Danlos (Type IV) or Marfan's syndrome. Rarely, inflammatory conditions such as Takayasu's arteritis and Bechet's disease or infective conditions like HIV may present with an aneurysm [4].

3. The aneurysm prone infrarenal aorta

The combination of altered haemodynamics, a different smooth muscle cell derivation and a decrease in the elastic lamella of the infrarenal aorta predisposes it to aneurysm development. The embryological origin of the smooth muscle cells in the aorta of the infrarenal aorta may

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contribute to aneurysm propensity as they are derived from the splanchnic mesoderm, whereas the arch and thoracic aorta are derived from the neural crest and somite-derived cells, respectively [8]. There is a decrease in the elastin fibre and a decrease in the thickness of the wall of the aorta as it descends from the thorax into the abdominal aorta [9, 10]. In addition, the infrarenal aorta has its maximum number of elastin cells (which produce elastic fibres) at birth [11]. Also, the infrarenal aorta has an increased susceptibility due to reflected pressure waves from the iliac bifurcation leading to a disturbance of the laminar flow and an alteration in the wall shear stress. When compared to the supracoeliac aorta, the infrarenal aorta has, at times, a reversal of flow during diastole, and this can lead to an upregulation of factors that increase the inflammatory infiltrate and proteolytic pathways [12].

4. Mouse models of AAAs

The pathogenesis of AAAs is multifactorial with contributions from a few key risk factors. Aortic tissues received from human subjects reflect a late stage of the disease and may not reflect the early factors involved in initiation. Thus, animal models may provide a better insight into the mechanisms behind aneurysmal degeneration. One of the major advantages of using experimental models of AAA is the ability to knock out or replace endogenous genes, enabling the assessment of the influence of protein expression on the development of disease.

There are several mouse models of chemical-induced AAAs such as elastase infusion into the infrarenal segments of mouse aortas and periaortic administration of calcium chloride between the renal branches and the iliac bifurcation. A more widely used model administers Angiotensin II to induce reproducible AAA. The Angiotensin II-infused mouse model mimics several features of AAAs in humans such as a male gender bias, dilatation of the lumen, degeneration of elastin fibres, inflammatory cell recruitment and thrombus formation [13].

Angiotensin II, a hormone of the renin-angiotensin system, is produced both systemically and locally in the vessel wall [14]. It has diverse actions on signalling pathways that ultimately promote cell growth, proliferation and vascular inflammation [14]. Accordingly, Angiotensin II-induced vascular inflammation can be studied by treating hyperlipidaemic mice with Angiotensin II to investigate long-term chronic inflammatory responses such as plaque formation or short-term acute inflammatory processes such as cellular infiltration. This is thought to occur via activation of the NF-κB cascade, resulting in elevation of cytokines. Furthermore, there is a growing body of evidence that suggests chemokines are involved in the modulation of Angiotensin II-accelerated leucocyte recruitment to the vessel wall [15].

5. Inflammatory cells in AAA

The inflammatory milieu consists of macrophages, monocytes, T cells, NK cells, B cells and other polymorphonuclear cells. They produce various inflammatory factors and mediators, which add to the degradation of collagen, elastin and smooth muscle cells in the aortic wall. The striking histological feature of AAAs is the adventitial and medial inflammatory infiltrate

together with medial elastin destruction and fragmentation, and destruction of structural collagens (type 1 and 3) [16, 17]. This excessive elastolysis and collagen destruction are mediated by proteases, most notably the matrix metalloproteases (MMP) family [18]. Several MMPs have been implicated in aneurysm development (MMP-2, 8, 9, 12), with the most evidence for MMP-9 [19]. The other proteases involved are serine proteases (tpa, U-pa, plasmin, neutrophil elastase) and cysteine proteases (Cathepsin D, K, L and S) [16]. The MMPs and the other proteases can be secreted by most of the cells in the aorta (endothelial cells, vascular smooth muscle cells, fibroblasts and macrophages) [16, 20]. MMPs interact closely with tissue inhibitors of MMPs (TIMPS) and these are largely secreted by macrophages, and the process is regulated by cytokines through a feedback loop.

Inflammatory cells occur with a greater frequency in the aneurysmal aorta when compared to the atherosclerotic or non-diseased aorta. The T-cell pattern is different when compared to that of atherosclerotic tissue [21]. The predominant cell types are CD4 T cells, macrophages and B cells [22], and this has led to the assertion that an aortic aneurysm is an inflammatory-mediated condition. It is still not definitively known if the inflammatory cell infiltrate is a cause of, or a reaction to AAAs. It is the microenvironment created by the cellular infiltrate that mediates the production of the proteases that underlie aneurysm progression and probably rupture. One theory suggests that aortic atherosclerosis diverges into aneurysmal formation through a Th2 cytokine response under environmental or genetic stimulation [23].

It has been proposed that an AAA is a specific antigen-driven T-cell disease, where the antigenic specificity remained to be determined [24]. AAA may be an autoimmune disease, and this theory is supported by the following [25]:

1. The presence of mononuclear inflammatory cell infiltrates consisting mainly of T and B cells, macrophages and NK cells [22].
2. Mononuclear cells infiltrating the aneurysm wall show early (CD69), intermediate (CD25, CD38) and late (CD45RO, HLA Class II) activation antigens, suggesting an ongoing inflammation [24].
3. IgG antibody purified from the wall of AAA is immunoreactive with protein derived from normal aortic tissue [26].
4. AAA is associated with particular alleles such as the HLA DRB1 [27].
5. Molecular mimicry may be responsible for T-cell responses in AAA [25].

The pattern of cytokine production by the inflammatory cells influences matrix degradation by regulating their MMP, serine protease and cathepsin production. In murine models of AAA, an IL-4 upregulation and interferon-γ (IFN- γ) blockade together with a predominance of macrophages are the features of early aneurysm formation [23]. The macrophages produce MMP-12, which are stimulated by IL-4 production from T cells, reinforcing the role of IL-4 in early atherosclerosis development [23]. The downstream effects of murine cytokine expression are not always applicable to humans; thus, mechanistic animal studies are difficult to interpret. Also, studies are carried out on tissues *in vitro*, and the complex interaction of the various cytokines is not entirely reproducible [6].

5.1. Macrophages

Macrophages are recruited early into the aneurysmal wall, and macrophage cytokines play an important role in AAA progression. This response is associated with innate immunity as opposed to adaptive immunity. Macrophages exhibit plasticity with regard to their phenotypic cytokine output. They can either be M1 or M2 and can change between the two depending on the prevailing conditions. Typically, M1 macrophages are pro-inflammatory, whereas M2 macrophages are involved in repairing tissue. A balance between M1 and M2 is thus vital in preventing a chronic inflammatory cell infiltrate, which leads to persistent inflammation and aneurysm progression. IL-6, tumour necrosis factor (TNF)-α, IL-1β and interferon (IFN)-γ have been detected peripherally and are associated with aneurysm formation [28].

In murine models of AAA, M1 macrophages are strongly associated with aneurysm formation and elastin degradation; conversely, an M2 phenotype is protective for AAA development [29]. Investigation of human aneurysm tissue has revealed an M1 phenotype, though this tissue represents an end stage of the disease. Most human studies have focused on circulating monocytes and their link to increased elastases and ECM breakdown [30]. ECM breakdown is a recruiter of monocytes, and the use of a monoclonal antibody has been shown to decrease this infiltration and prevent further ECM degradation [31]. Furthermore, the monocytes have demonstrated CD14 and CD16 cell surface marker positivity, and this pattern is associated with M1 macrophage activation [32].

5.2. T cells

As a broad categorization, T cells can be divided up into CD4+ and CD8+ cells. CD4 cells can be further categorized into Th1, Th2, Th17 or regulatory (T_{reg}) cells. This is dependent on drivers of cellular output as well as their cytokine expression. Similar to M1 and M2 macrophages, it would appear that the balance in the different subsets is important for regulation.

Th1 cells are activated by IL-12 and output INF-γ. Aneurysmal tissue displays features of Th1 upregulation with increased INF-γ in the aneurysm tissue and in the circulating blood [28, 33, 34]. Although Th2 cells are found in some specific inflammatory diseases, they are considered to be anti-inflammatory. IL-4 activity is responsible for Th2 differentiation of CD4 T cells, and results are conflicting in murine and human models as to the role of Th2 cells. This discrepancy may be a result of a similar cytokine profile to NK cells (Th0) [35] or from differences in the measurement of the cytokines. Th17 cells produce IL-17, are related to several inflammatory diseases and play a key role in vascular superoxide production [36]. Their role in AAA has not been fully clarified, but they appear to be related to aneurysmal progression.

The frequency of CD4+CD25+FOXP3+ T cells (T_{reg}) is decreased in the peripheral blood of patients with AAA when compared to occlusive atherosclerotic disease or healthy donors [37]. T_{reg} cells are a unique class of T cells that serve as a counter-inflammatory mechanism. In the normal autoregulation of bodily function, there is a balance between T effector cells, which promote inflammation, and T_{reg} cells which counteract this [38]. In inflammatory

conditions such as rheumatoid arthritis [39], scleroderma [40], inflammatory bowel disease [41] and transplant organ rejection [42], a dysfunction of Treg cells has been implicated. T_{reg} cells express forkhead box P3 (Foxp3) and are also known as Foxp3+CD4 T cells. They make up approximately 5% of the total CD4+ T cells [43]. The majority of T_{reg} cells express CD25. In the human, T_{reg} cells can be identified by a high expression of CD25 and an absence of IL-7Rα [44].

5.3. Other cell types

Mast cells have been found in the adventitia and media of AAAs and are implicated in AAA formation [45]. They have been found in areas of neovascularization and are able to secrete various cytokines and chemokines. Inhibition of mast cells in experimental mouse models decreases the incidence of aneurysmal formation, furthermore implicating mast cells in the pathogenesis of aneurysms [46]. Neutrophils are early responders to injury and are found in the aneurysm wall as well as the intraluminal thrombus [47]. They interact with many cells including platelets resulting in further inflammatory cell recruitment [48]. In human studies, they have been associated with larger aneurysms, and in animals that are neutrophil deficient, there is a decrease in aneurysm formation [49, 50].

6. Micro-RNAs

Micro-RNAs (miRNA) are a class of non-coding RNA, which are regulators of posttranslational gene expression [51]. They have emerged as potential therapeutic targets due to their ability to control multiple downstream processes. Mir-21 is a regulator of smooth muscle homoeostasis and is upregulated in human as well as animal models of AAA [52]. The mir-29 family encodes multiple ECM targets including elastin and collagen isoforms (type 1 and 3) and fibrillin-1 [53]. Thus, it is important in aneurysm formation. Mir-29b has been found to be downregulated in humans and animal models of AAA as well as in animal models of ageing [54].

7. Intraluminal thrombus (ILT)

The majority of AAAs requiring surgery contain ILT. They are thought to develop secondary to an activated endothelium in combination with disturbances of flow within the aneurysm sac. The volume of ILT is related to growth of the aneurysm, and the thrombus-lined segment of the aorta is structurally different to the non-thrombus-lined area of the aneurysm [55, 56].

There are two major theories on the effect of aneurysmal growth on aortic aneurysm formation. The first relates it to hypoxia of the wall due to the layered thrombus, and the second ascribes it to the inflammatory cell constituents of the thrombus acting in a paracrine manner [57]. The inflammatory cell infiltrate contains macrophages, T cells, granulocytes and NK cells as well as activated platelets [58, 59]. These cells are phenotypically different to the cells found in the wall and the peripheral blood [60]. The exact pathway of interaction between

the wall and the ILT has not been fully elucidated, but one theory suggests that microvesicles (ADAM10/ADAM17) shed from the luminal to the abluminal area result in wall breakdown through the formation of elastases in the wall [61].

8. Conclusion

Abdominal aortic aneurysms are regulated by complex and multifactorial processes. At a cellular level, there is a chronic inflammatory cell infiltrate that controls these processes, which lead to growth and rupture. The role of these inflammatory cells has been elegantly demonstrated in experimental models of AAA, and genetic interventions targeting their recruitment and signalling have been known to prevent the development of disease. However, the lack of experimental tools to test the efficacy in human AAA in the preclinical phase and the composition of the thrombus in experimental models has yet to be explored. There has been much work done to understand the inflammatory process, and the hope is that this will lead us to new biomarker discovery and potential therapeutic targets in treating this disease.

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Author details

Ismail Cassimjee[1], Regent Lee[1] and Jyoti Patel[2, 3]*

*Address all correspondence to: jyoti.patel@well.ox.ac.uk

1 Nuffield Department of Surgery, University of Oxford, UK

2 Division of Cardiovascular Medicine, British Heart Foundation Centre of Research Excellence, University of Oxford, John Radcliffe Hospital, Oxford, UK

3 Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK

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