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REVIEW

Chronic Inflammation, Immune Response, and Infection in Abdominal Aortic Aneurysms

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Abdominal aortic aneurysms (AAA) are associated with atherosclerosis, transmural degenerative processes, neovascularization, decrease in content of vascular smooth muscle cells, and a chronic infiltration, mainly located in the outer aortic wall.
The chronic infiltration consists mainly of macrophages, lymphocytes, and plasma cells. The dominant cells are Th2 restricted CD3+ lymphocytes expressing interleukine 4, 5, 8, and 10, and tumor necrosis factor-α for regulation of the local immune response. They also produce interferon-γ and CD40 ligand to stimulate surrounding cells to produce matrix metalloproteases and cysteine proteases for aortic matrix remodeling. The lymphocyte activation may be mediated by microorganisms as well as autoantigens generated from vascular structural proteins, perhaps through molecular mimicry. As in autoimmune diseases, the risk of AAA is increased by certain genotypes concerning human leucocyte antigen class II. These types are also associated with increased aneurysmal inflammation indicating a genetic susceptibility to aortic inflammation.
Chlamydia pneumoniae *is often detected in AAA but the validity of the methods can be questioned, and two small antibiotic trials have been disappointing. However, serum antibodies against* C. pneumoniae *have been associated with AAA growth and cross-react with AAA wall proteins. Thus, immune responses mediated by microorganisms and autoantigens may play a pivotal role in AAA pathogenesis.*

Keywords: Abdominal aortic aneurysm; Pathogenesis; Inflammation; Immunology; Immune response; Infection; Autoimmune; Chlamydia.

Introduction

The natural history of abdominal aortic aneurysms (AAA) is dominated by inflammation,[1] dilatation, and terminal rupture. The pathogenesis has been a mystery through decades—and still is. Even the treatment remains controversial, and many believe a pharmacological treatment of AAA is possible to avoid surgery. If true, screening for AAA would certainly become very cost effective.

Consequently, the present scientific interest in AAA is probably at the highest level ever. However, the combination of a high-pressured vessel located deep in the body makes repeated biopsies impossible in prospective cohorts, and progress difficult. Nevertheless, our knowledge about the fascinating pathogenesis of AAA has increased rapidly the last few years, especially concerning the key roles played by the immune response.

Human AAAs are characterized by inflammation with induction of intracellular and extracellular inflammatory cytokines, expression of cell adhesion molecules, increase of protease expression, and release of reactive oxygen species. The most important pathologic feature of human AAA is probably the infiltration of inflammatory cells including monocytes, lymphocytes, and plasma cells, mainly in the outer part of the aorta, but also often beyond the aortic wall into surrounding tissues.[1] In addition to secrete matrix-degrading proteases for vascular wall remodelling, these infiltrates are the main sources of inflammatory cytokines, which are significantly

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increased in AAAs and play multiple roles in regulating mesenchymal cell matrix metabolism, endothelial cell growth and proliferation, lymphocyte activation, antigen presenting cell (APC), major histocompatibility (MHC) class II molecule expression, vascular adhesion molecule expression, and even matrix degrading protease expression of surrounding cells.[2] Logically, inhibition of such infiltrate recruitment has been demonstrated to reduce substantially the expansion rate of experimental AAAs,[3] and treatment with anti-inflammatory drugs as steroid and cyclosporine reduce AAA-size in animals,[4] while macrolides and non-steroid anti-inflammatory drugs reduce the aneurysmal growth rate in human AAA.[5,6]

Thus, the understanding of the inflammatory process in AAA may hold the solution for a low risk pharmocological treatment, so a review was conducted. This review is only based on AAA, and thus it cannot be taken for sure that the features are common for all aneurysms.

Searching Strategy

Medline was searched for publications with the keywords abdominal aortic aneurysms and immunity or infection or autoimmune or autoimminty or chronic inflammation including human as well as animal studies. Reviews, non-English publications, and papers without abstracts were omitted. In all, 401 papers were identified. More than half were irrelevant clinical papers without hypothesized investigation of the topics including a substantial number of case reports. They were all omitted. Nevertheless, it seemed irrational to cite all the rest, so representative citations were selected, leaving mostly repetitive studies and papers based on a small number of participants uncited. A more complete list can be achieved at the website 'EJVESextra'.

Histiological Findings

Lymphocytes

The main cell population found in these inflammatory infiltrates in AAAs is lymphocytes.

Using AAA tissue immunocytology analysis and immunoblot analysis strategies, Schonbeck *et al.* identified the majority of the lymphocytes as T-helper(Th)-2-restricted $CD3^+$ T lymphocytes. Other lymphocytes such as B cells and Th1 cells were relatively fewer.[7]

It is intriguing to understand why these cells are the predominant population in AAAs and what these cells contribute to the pathogenesis and how these cells are regulated during the AAA development.

Th2-type lymphocytes in AAA lesions produce interleukines (IL) such as IL-4, 5, 8, and 10.[7] These cytokines modulate the immune response by attraction of other inflammatory cells, stimulate further T cell cytokine production, and neovascularization—all factors amplifying the immune response (Fig. 1). In addition to secrete cytokines, Th2 cells release Fas ligand and Fas associated phosphotase-1 (FAP-1) to regulate the apoptosis of vascular smooth muscle cells (SMC) and Th1-restricted T lymphocytes.[7,8] Other non-lymphocytic cells can also be sensitized to Fas-mediated cell death by this cytokine.[9] This is probably one of the mechanisms causing the reduced numbers of Th1-type T lymphocytes and SMC, typically detected in AAA lesions. Alternatively, Th2 cytokines such as IL-4 also rescue Th2 lymphocytes, but not Th1 lymphocytes, from apoptosis in AAA.[10]

In addition to regulating the immune response and cell apoptosis, these Th2-cells also produce interferon (IFN)-γ as well as CD40 ligand, especially when the vascular wall is injured with microorganisms, surgery, or even cigarette smoking.[11–14] These cytokines stimulate macrophages and monocytes to produce matrix metalloproteinases (MMPs), such as MMP-3 and MMP-9, which are central proteases acquired for vascular wall matrix remodelling.[14]

On the other hand, the most dominant Th2 cytokines are IL-4, 5 and 10, which suppress human macrophage expression of MMP-9.[15] While, the most dominant Th1 cytokines are IFN-γ, IL-2, IL-12, IL-15, and IL-18. These cytokines are reported elevated in the blood and aortic tissue of patients with AAAs,[16] and serum-IFN-γ correlates with aneurysm progression rate.[17] It could suggest that Th2 immune responses might serve to diminish aneurysmal degeneration.[18] This is supported by animal studies showing that mice lacking IL-4, IL-10 or CD4 develops larger elastase induced aneurysms compared to common mice, whereas no significant effect on AAAs has been observed in mice with IFN-γ deficiency. Others have found that CD4-deficient mice do not develop experimental aneurysms, unless IFN-γ is administrated. It could indicate that Th1-type immune responses are essential in aneurysmal disease, and shifting the cellular immune response from domination of Th1 cytokines to one favouring Th2 cytokines could then in theory suppress aneurysmal degeneration.[19]

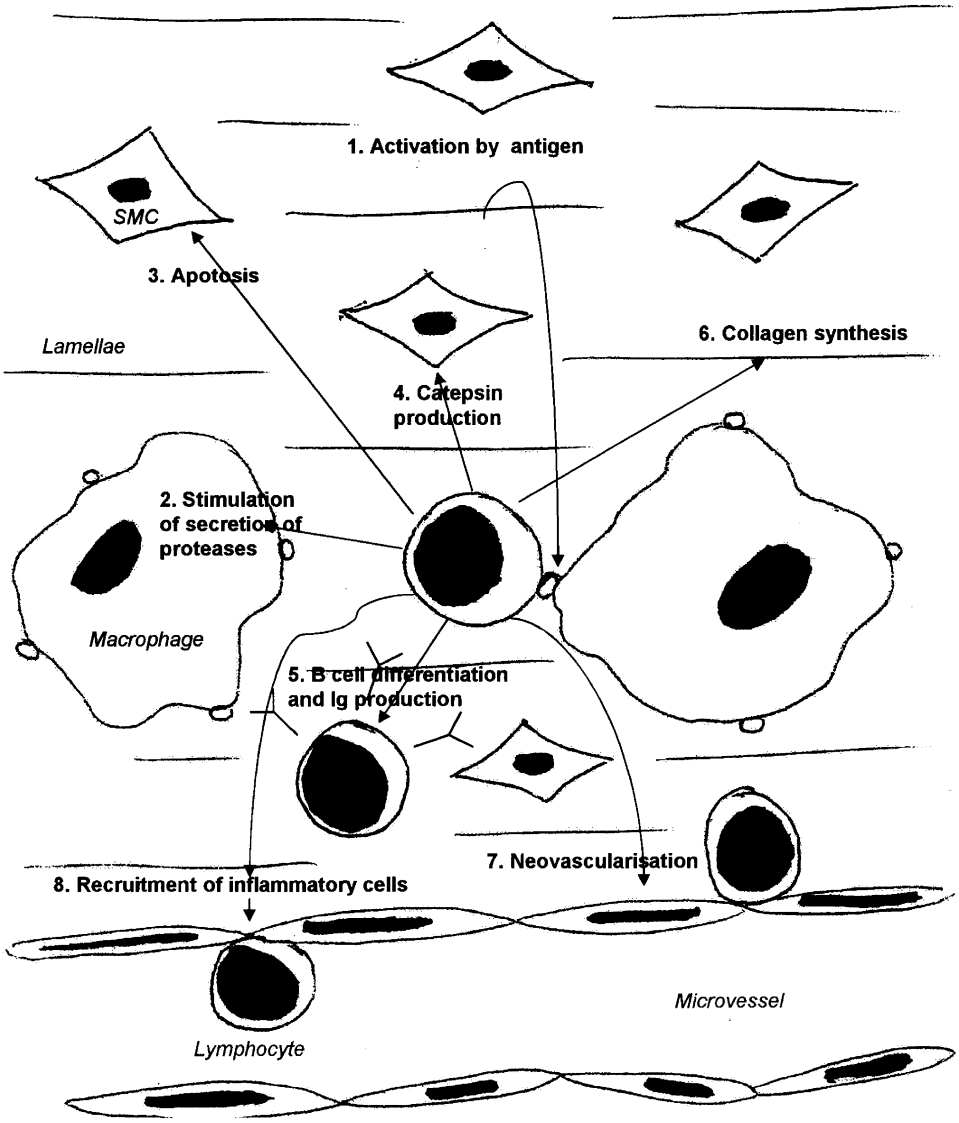

Fig. 1. Major roles of Th2-lymphocytes in the chronic inflammation of the aneurysmal wall. Th2 lymphocyte activation by antigen presenting cells such as macrophages, smooth muscle cells (SMC), and endothelial cells may depend on the function of cathepsins. The activation causes secretion of cytokines. TNF-α and INF-γ stimulates among others macrophages to produce and secrete MMPs for matrix remodeling. Secretion of FAS-ligand and FAP-1 causes apoptosis of SMC and Th1 cells. Further, inflammatory cells are recruited by TNF-α and IL-8, which also take part in stimulating neoangiogenesis. INF-γ stimulates cathepsin production for further Th2 activation, B-cell differentiation and Ig secretion.

Furthermore, histocompatibility-mismatched aortas transplanted into IFN-γ receptor-deficient recipients causes an immune response dominated by IL-4 and development of large aortic aneurysms—this development could be prevented by administration of anti-IL-4 blocking antibodies. Consequently, IL-4 specifically mediates an inflammatory process leading to aneurysmal degeneration in this allograft model.[20]

In all, Th1 and Th2-restricted T lymphocyte proliferation and activation seems very central in regulating the immune response in AAA. It seems that elevated local production of Th1 cytokines likely serves to enhance macrophage expression of matrix-degrading proteinases and thereby accelerate aneurysmal degeneration, whereas Th2 cytokines appear to exert responses that would tend to suppress macrophage MMP production and limit disease progression.

Macrophages

Animal studies suggest macrophages are some of the first inflammatory cells migrating to the developing

AAA—most likely attracted by elastin degradation products.[15] They may play a major role in the immune response and matrix destruction due to their capacity to secrete cytokines, elastase, and collagenases (Fig. 2). The macrophage secretion of cytokines, as IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α, recruits inflammatory cells and stimulates cytokine production, protease production, B-cell differentiation and Ig secretion, cytotoxic T-cell differentiation, and neovascularization. Besides their capacity to secrete cytokines, their secretion of various proteases must be considered very important in the natural history of AAA, in particular MMP9, since it has been associated with aneurysmal expansion and rupture (Fig. 2).[21–23]

The importance of the macrophages in the pathogenesis of AAA is illustrated by animal studies showing that the application of macrophages and plasmin to the aorta is sufficient to cause human-like aortic aneurysmal degradation without further manipulation.[24] Serum-plasmin has also been reported to be one the most predictive factors for aneurysmal growth.[25]

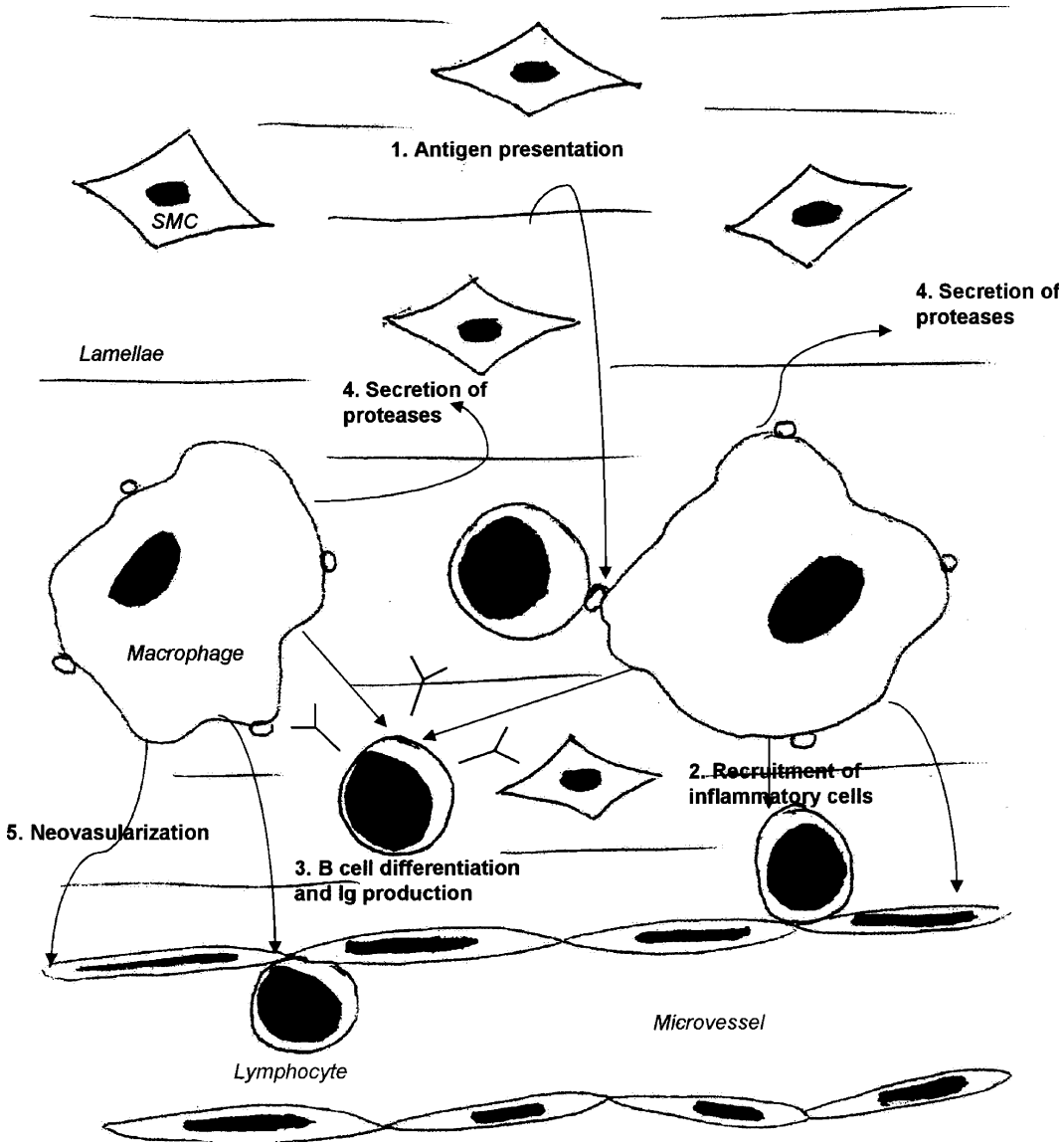

Fig. 2. Major roles of macrophages in the chronic inflammation of the aneurysmal wall. Acting as antigen presenting cell, Th2 lymphocytes are activated possibly depending on cathepsins. Cytokines from the activated Th2 cells stimulates MMP secretion, secretion of IL-1β stimulates ICAM-1 presentation for recruitment of inflammatory cells, and B-cell growth, differentiation and Ig secretion together with IL-6 secretion. Inflammatory cells are attracted by IL-8. Neoangiogenesis are stimulated by secretion of TNF-α.

Endothelial cells

Apart from the luminal layer, endothelial cells are present in AAA in large numbers due to the neoangiogenesis observed throughout the media. Their role may be even larger because inflammatory cells expressing MMP as macrophages are mostly localized in the surrounding areas of the microvessels, where lymphocytes are also seen in large numbers. It could be due to the capacity of the endothelium cell to secrete IL-1β and IL-8, which stimulate ICAM-1 presentation for recruitment of additional inflammatory cells, attract lymphocytes, stimulate endothelial proliferation, and stimulate B-cell differentiation and Ig secretion.

The proliferating endothelium also produces various matrix proteinases such as MMPs, as well as their inhibitors—such as some of the tissue-inhibitors of metalloproteinases (TIMP). Thus, the endothelium has the capacity to break down the aortic matrix, but also to control this degradation. Consequently, it has been suggested that the magnitude of the neoangiogenesis is associated with the severity of the aortic degradation, and a histological study has demonstrated that the degree of neovascularization correlates positively with the degree of inflammation.[26]

Fibroblasts

Fibroblasts are very frequent in the outer part of AAA, and produce IL-6 which stimulates B-cell and cytotoxic T-cell differentiation together with several MMPs in considerable amounts.[27] In spite their capacity to participate with a large pathogenic potential, very little is known about their role.

Immune Responses and T Cell Activation in AAA

Analysis of lymphoid areas in the adventitia from AAA patients indicates the existence of T lymphocytes and APCs, including B cells, dendritic cells, and macrophages. These areas may locally serve as sites for both cellular and humoral immune responses in human AAAs.[28] These interactions probably trigger T cell activation to release the mentioned spectrum of inflammatory cytokines, which participate in the cellular and humoral immune response taking place in AAAs (Fig. 2). Therefore, the mechanism of how the T lymphocytes are activated during AAA development becomes a key event in the AAA development and essential to investigate.

Several mechanisms have been implicated in the regulation of the T lymphocyte activation in AAA. By analyzing the serum components from AAA patients, several laboratories have isolated AAA-specific antigens that are most likely generated from vascular wall matrix as well as microorganisms.[29–33] Several microorganisms have been linked to aneurysm development. *Treponema pallidum* infection, for example, may lead to aortic aneurysm.[34] Cytomegalovirus (CMV) infection is common in inflammatory AAA although this infection is asymptomatic.[35] CMV virus is largely co-localized with human leukocyte antigen (HLA)-DR positive macrophages, fibroblasts, endothelial cells, and lymphocytes.[33]

Other microbiological findings are reported in very limited frequencies, and must probably be interpreted as false positive findings due to contamination, superinfections or coincidental findings.

Data from our laboratories indicate that *Chlamydia pneumoniae* infection is associated with human AAA progression. We have found a significant positive correlation between IgA antibodies against *C. pneumoniae* and the aneurysmal expansion rate ($r=0.29$, $P=0.006$)[36] suggesting a possible immunologic role for this microorganism in AAA. Further, Ozsvath *et al.* at Tilsons laboratories have demonstrated that, in serum components from AAA patients, there are several antigens derived from microorganisms which are closely related to normal vascular structural proteins.[37] IgG purified from AAA patients are immunoreactive to these autoantigens. The circulating self-reactive autoantibodies are correlated with AAA size, indicating an involvement of autoantigen in AAA pathogenesis, possibly via T lymphocyte proliferation and activation, although a clear mechanism and consequence is missing and needs further investigations.[38]

Clearly, more activated T cells are detected in AAA lesions than control vessels. T cell activation has been associated not only with AAA lesion levels but also AAA lesion repairs. In patients undergoing AAA repairs, different repair mechanisms lead to different levels of T cell activation. By measuring peripheral blood circulating T cell, aortic aneurysm-wall T cell, and even perianeurysmal T cell phenotypes, several groups have demonstrated that AAA endovascular repair, which produces less tissue trauma, has much less post-operative T cell activation than those of conventional open surgery AAA repair.[39,40] Flow cytometry analysis indicates that the numbers of activated T lymphocytes are associated with the degree of vascular wall operative injury.[40,41] A recent study also demonstrated that different surgical traumas altered the Th1/Th2 cell balance differently.

Significantly more Th2 cells were detected when patients underwent conventional infrarenal aortic aneurysm repair than those who underwent endovascular repair,[42] correlating with the levels of active T cells.

It can, therefore, be speculated that T lymphocyte activation plays a key role in the AAA pathogenesis and, consequently, that inhibition of T cell activation may reduce AAA formation and progression.

Chronic Infection in Aortic Aneurysms?

As mentioned, several microorganisms have been linked to human AAA etiology. At present, *C. pneumoniae* seems to be the major target for intensive research. Although we currently do not have direct evidence to support an etiologic role for *C. pneumoniae* in AAA, presence of antibodies against *C. pneumoniae* (Ig–Cp) has been associated with the expansion of AAA.[43–45] Further, *C. pneumoniae* has been demonstrated in AAA by a variety of tests, including immunohistochemical staining, enzyme-linked immunosorbent assay, polymerase chain reaction (PCR), electron microscopy, and culture (Table 1).[45–50]

The PCR tests were believed to be more sensitive than the other methods for direct detection. However, for validation, Apfalter *et al.* showed that the results of attempts to detect intravascular *C. pneumoniae* DNA varied in accordance between 0 and 100% among the different laboratories. Further, several of the participating laboratories reported positive findings in the negative controls.[51] This may explain, in part, the reported poor correlation between demonstrating present *C. pneumoniae* DNA/antigen in AAA or atherosclerotic plaques and serum Ig–Cp.[32,52,53]

Regardless of the more sensitive PCR-test, immunohistochemical staining apparently demonstrates more positive results for *C. pneumoniae* than DNA-based PCR techniques, and the results have a very poor accordance with PCR-findings.[45] An explanation could be that the staining is too unspecific; we have earlier demonstrated that Ig–Cp used for immunohistochemical staining does not react on present chlamydial protein in AAA-walls but cross-reacts with other vascular contents of AAA.[54]

Finally, intervention trials with macrolides seem only to have transient benefit, if any, but the trials concerning AAA are few and small (Table 1).[5,53,55] Nevertheless, similar but much larger intervention studies concerning ischemic heart disease show the same tendency for a short transient benefit, if any.[45] This transient benefit could easily be caused by the well-known anti-inflammatory effect of macrolides.[56]

Finally, it must be questioned whether *C. pneumoniae* is present in AAA at all. However, Tambiah *et al.* showed in an animal model that *C. pneumoniae* stimulates the influx of macrophages and dilatation of the abdominal aorta.[57] Ig–Cp are associated with AAA, and we have demonstrated that such antibodies correlate positively with aneurymal growth rates in Danish as well as British populations of patients with small AAA.[45]

Table 1. Studies concerning *Chlamydia pneumoniae* and abdominal aortic aneurysms

Reference	Method	Patients/controls	Results
Lindholt[43]	Serological cohort study	112	Increased expansion rate in AAA-patients with CP–IgA >20, and the level of IgG were predictive for cases expanding to operation recommendable sizes
Lindholt[44]	Serological cohort study	99	Positive correlation between CP-IgG and the aneurysmal growth rate
Petersen[46]	PCR	40/40	35% positive AAA patients, 5% positive controls
Lindholt[47]	PCR	20/0	0% positive
Juvonen[48]	IHC, PCR, EM, culture	12/3	100% positive, no positive controls. No cultured
Blasi[49]	PCR	51/0	51% positive
Ong[50]	IHC	25/6	56% positive in AAA patients, none in controls
Cheuck[17]	PCR	16+30/19	16/16 (100%) positive in ruptured cases, 22/33 (73%) in asymptomatic cases, and 2/19 (11%) in controls
Vammen[5]	RCT: 300 mg roxithromycin for 28 days *versus* placebo	45/47	44% reduced expansion rate the 1st year in the group treated with macrolide compared with placebo. No effect during the 2nd year
Mosorin[53]	RCT: doxycycline 150 mg daily for 3 months *versus* placebo	17/15	0–6 months: no significant difference in expansion rate 6–12 months: significant difference in expansion rate 12–18 months: significant difference in expansion rate
Scott (Chichester)	RCT: 300 mg azithromycin for 28 days *versus* placebo	50/50	Ongoing

CP, antibodies against *Chlamydia pneumoniae*; IHC, immunohistochemistry; PCR, polymerase chain reaction; EM, electron microscopy; RCT, randomized clinical controlled trial.

Recently, we purified such antibodies from AAA patients, applied them to homogenized AAA-walls and performed 2D-gel electrophoreses of materials. No sign of *C. pneumoniae* outer membrane protein was observed, but the purified antibodies constantly cross-reacted with components of the AAA wall components, especially the heavy chain of human immunoglobulin. The only known human antibodies binding to the heavy chain of human immunoglobulin are rheumafactors, which are strongly associated with autoimmune diseases. This finding combined with the reported positive correlation between antibodies against *C. pneumoniae* with aneurysmal expansion rate could indicate an important involvement of autoantigens in progression of AAA.[58]

An Autoimmune Disease?

The specificity of the immune response in AAAs remains unclear, as B lymphocytes derived from AAAs exhibit an unrestricted repertoire of immunoglobulin,[59] and a similar T cell polyclonal response,[60] as well as presence of activated memory cells.[61] These results suggest an autoimmune disease and existence of a cellular immune response in AAA. The possibility that AAA is an autoimmune disease is further supported by histological examinations of AAA-walls, which show chronic inflammation, Russells bodies (as in the autoimmune disease—Hasimoto's thyroiditis[62–64]), elevated cytokines that activate proteolysis,[65] and substantially increased amounts of autoantibodies compared with aortic occlusive diseases and normal aortae.[63] Furthermore, the prevalence of autoimmune diseases has been described increased cases with inflammatory aneurysms.[67]

Like other autoimmune diseases, AAA susceptibility is associated with particular human leukocyte antigens (HLA) molecules. For instance, specific alleles of HLA-DR2, but not HLA-DQ3 are frequently observed in AAA, similar to what is reported in rheumatoid arthritis and multiple sclerosis.[60–70] Rasmussen *et al.* showed that the B1(*)02 and B1(*)04 alleles in HLA were associated with more than a doubled risk of AAA, and that the degree of inflammation quantified histologically was associated with these tissue types. These results suggest the HLA class II immune response genes possess both disease-modulation and disease-risk properties, and thus that some kind of a genetic susceptibility to aortic inflammation exists.[71] These findings could have an important clinical impact because if these genotypes affect aneurysmal expansion rates and risk of rupture, they could provide us with a valuable predictive tool for the use of surveillance *versus* surgery.

AAA tissues also contain large amounts of immunoglobulin protein, and IgG extracted from human AAAs exhibits immunoreactivity with aortic wall matrix proteins.[72] This suggests that a humoral (auto)immune response is a frequent occurrence in AAAs. Recent work has led to identification of several putative antigens that may be novel extracellular matrix proteins associated with large arteries.[31]

What still remains mysterious is the finding of autoantibodies, which recognize human proteins as well as epitopes on frequent invading microorganisms.[72] Although the presentation of autoantigen and the production of autoantibodies are acquired for T cell proliferation and activation, the actual resource of autoantigens is still under investigation. For instance, the aortic aneurysm antigenic protein-40 (AAAP40) is a microfibril-associated glycoprotein and is artery-specific antigenic protein. Protein-sequence homology search indicates its similarity to all three fibrinogen chains and a short sequence similarity to vitronectin.[30]

A puzzle waiting to be solved is how the individual immune system recognizes both exogenous microorganisms and its own human aortic-wall proteins. It has been hypothesized that microorganisms and normal aortic wall may share the same or similar epitopes, which can be recognized and presented by B cells, dendritic cells, macrophages, activated endothelium, and even HLA-DR$^+$ SMC in AAA via a process known as 'molecule mimicry'.[73] The presence of *C. pneumoniae* in the AAA walls is questioned at the moment, but recurrent respiratory tract infections due to *C. pneumoniae* are common and the following systemic immune response could trigger or amplify a local aortic immune response due to molecule mimicry when age-related degenerative changes of the aorta occur. Alternatively, immune responses against aortic wall structural components may arise secondary to long-standing inflammation and connective tissue destruction, through proteolytic exposure of neoepitopes within matrix proteins.

Nevertheless, in conclusion, several autoantigens including elastin fragment, interstitial collagen, and oxidized LDL have been identified in patients with AAA. Immunoglobulins recognizing such autoantigens have been purified from patient serum samples.[37,38,72–76] All in all, the findings indicate that autoimmunity plays a role in AAA progression and perhaps development. The magnitude and exact role is still unknown, however, the combination of the correlation between aneurysmal progression rate and antibodies against *C. pneumoniae* that also are

immunoreactive against AAA wall proteins suggests a major role.

Potential Immunomodulating Autoantigen-specific T-cell Response Therapy

One alternative to regulate T cell activation is controlling the APCs to present aneurysm-specific antigens. Although, currently, we do not have any evidence to prove this concept, several possibilities exist. In AAA, macrophages, activated endothelium, and HLA-DR$^+$ SMCs are the main APCs. A classic mechanism of activating T helper cells involves interaction of T helper cells and HLA DR$^+$ APCs mediated by T cell surface CD4 molecules and APC surface antigen associated MHC class II molecules. During the process of antigen presentation, exogenous antigens have to be processed into antigenic peptide and presented by the MHC class II molecule via a chaperon molecule known as invariant chain (Ii) to the cell surface.[77,78] Recent findings indicate a role for cysteine proteases in regulating Ii chain processing. In mice with deficient cathepsin L expression, CD4$^+$ T helper cell maturation within the thymus is decreased by up to 50%.[79] Such down-regulated CD4$^+$ T cells may impact the pathophysiology of vascular diseases including atherosclerosis and AAA as both lesions contain CD4$^+$ T cells as the predominant lymphocytes.[2,7]

Cathepsin S, another mammalian elastase highly expressed in both atherosclerosis and AAA, has also been demonstrated to be essential for APCs to properly present exogenous and autoantigens. In mice and in cell cultures, inhibition or deficiency of cathepsin S impairs Ii processing and leads to the accumulation of incompletely processed Ii (Ii p10) bound MHC class II molecules at the cell surfaces.[80,81] Phenotypically, these mice show impaired immunoglobulin isotype switching and decreased antibody production, although T lymphocyte maturation is unaffected. However, todate, no data have been provided to show if such altered T cell maturation or impaired APC antigen presentation have any impact on AAA.

A few lines of indirect evidence may suggest a potential role for these immune response-related proteases in AAA pathogenesis. First, using AAA tissue extracts in Western blot analyses, we detected significantly higher amount of both cathepsins S[82] and L compared with normal aortae (Shi, unpublished data). In contrast, the normal vessel walls contained negligible levels of these enzymes. In addition, to cause vascular extracellular matrix degradation, these enzymes may be required for AAA immune responses. Inhibition of cysteine proteases by high doses of LHVS (morpholinurea leucine-homophenylalanine-vinylsulfone-phenyl, a small molecule cysteine-protease inhibitor) leads to accumulation of macrophage cell surface Ii p10/MHC class II complexes in culture, and impaired pulmonary eosinophilic responses and IgE production in a mouse pulmonary hypersensitivity model.[83] Given the fact that macrophages are among APCs in AAA, inhibition of cysteine proteases may affect macrophage antigen presentation, impair immune responses and T cell activations, and further reduce AAA lesion growth. This is supported by clinical prospective data showing a negative correlation between aneurysmal growth rate and the systemic level of its major inhibitor, cystatin C.[84]

Second, activated endothelium and HLA-DR$^+$ SMCs are another two main APC populations. Both endothelium and SMCs express MHC class II molecules when cells are stimulated with IFN-γ, an inflammatory cytokine released in AAA from either infiltrated T cells or monocytes.[2] Consistently, this cytokine has been shown to regulate cysteine protease expression in both human endothelium and SMCs *in vitro*.[85,86] In human atherosclerotic lesions, both endothelium and SMCs show strong staining for immunoreactive cathepsin S expression with colocalized MHC class II positive SMC.[82] Therefore, it is plausible that cathepsin S may regulate MHC class II$^+$ EC and SMC antigen or autoantigen presentation in AAA. Further, inhibition of cathepsin S activity has been proven to be effective to regulate autoantigen presentation in a mouse model of Sjogren syndrome, a clinicopathologic entity resulting from lacrimal and salivary gland immunologic destruction.[87] Similar to AAA, in addition to lymphocyte infiltration, organ-specific autoantigen and autoantigen-specific T cell responses play an essential role in Sjogrens Syndrome. Inhibition of cathepsin S prevents such T cell responses and associated autoimmunity,[87] suggesting a possibility of regulating AAA by controlling cathepsin S activity in modulating autoantigen-specific T cell responses.

Clinical Aspects

So far the clinical aspects of our knowledge of the immune response in AAA are limited. The potentials are prediction of the natural history of AAA concerning expansion and rupture, and pharmacological treatment to prevent need for AAA repair. However, so far little is known.

Stimulated by the possibility of an infectious pathogenesis, small intervention trials with macrolides have been performed but they only to have transient benefit, if any (Table 1).[5,53,55]

However, this transient benefit could be due to the known anti-inflammatory effect of macrolides. Consequently, a long term trial with doxycycline treatment is ongoing.[88] Another indication of the potential of anti-inflammatory effect was noticed by Franklin *et al.* in a case–control study; the expansion rate of AAA in 15 patients taking non-steroidal anti-inflammatory drugs were 1.5 mm annually compared to 3.2 mm/year in 63 patients not taking non-steroidal anti-inflammatory drugs, $P=0.001$.[89] This comparison was done after the observation that indomethacin abolished PGE2 secretion and significantly reduced IL-1β and IL-6 secretion in aneurysm explant cultures. However, as IL-1β, IL-6, and IFN-γ failed to show any correlation with aneurysmal expansion rate in 50 cases of small AAA, whereas TNF-α did with a correlation similar to the best serological markers known at present ($r=0.37$).[11]

Summary and Future Topics

Abdominal aortic aneurysms (AAA) are associated with a chronic infiltration, mainly located in the outer aortic wall. The dominant cells are Th2 restricted CD3+ lymphocytes that express different cytokines essential for the regulation of the local immune response and the secretion of matrix metalloproteases (MMP) and cysteine proteases, all essential for vascular wall matrix remodelling.

The presence of *C. pneumoniae* in AAA walls is questioned, and two small antibiotic trials have been disappointing. However, serum antibodies against *C. pneumoniae* have been associated with AAA growth and cross-react with AAA wall proteins. Thus, the lymphocyte activation may be mediated by microorganisms as well as autoantigens generated from vascular structural proteins through molecule mimicry. HLA studies have shown that some HLA DR2 B1 alleles are associated with increased risk of AAA and, when an AAA is present, with increased aneurysmal inflammation. Recent studies suggest the key enzyme in this antigen presentation could be cathepsin C.

Investigations are in progress analyzing the relationship between various known autoantibodies and cases with AAA by comparison with controls, and the correlation of these antibodies with aneurysmal progression rates. Studies analyzing the association between the predisposing HLA DR2 B1 alleles and expansion rates and risk of rupture would be welcome, since that information could provide us with a immediate valuable predictive tool for the selection between surveillance or surgery. Additionally, investigations are now in progress to try to confirm the role of cathepsin S by clinical data, but intervention trials inhibiting cathepsin S in mouse models of AAA would be relevant.

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