Exploring autoimmunity in the pathogenesis of abdominal aortic aneurysms

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Chang TW, Gracon AS, Murphy MP, Wilkes DS. Exploring autoimmunity in the pathogenesis of abdominal aortic aneurysms. Am J Physiol Heart Circ Physiol 309: H719–H727, 2015. First published June 26, 2015; doi:10.1152/ajpheart.00273.2015.—The abdominal aortic aneurysm (AAA) is a disease process that carries significant morbidity and mortality in the absence of early identification and treatment. While current management includes surveillance and surgical treatment of low- and high-risk aneurysms, respectively, our narrow understanding of the pathophysiology of AAAs limits our ability to more effectively manage and perhaps even prevent the occurrence of this highly morbid disease. Over the past couple of decades, there has been considerable interest in exploring the role of autoimmunity as an etiological component of AAA. This review covers the current literature pertaining to this immunological process, focusing on research that highlights the local and systemic immune components found in both human patients and murine models. A better understanding of the autoimmune mechanisms in the pathogenesis of AAAs can pave the way to novel and improved treatment strategies in this patient population.

abdominal aortic aneurysm; autoimmunity; antigens

ABDOMINAL AORTIC ANEURYSM (AAA) is a pathological expansion of the aorta by more than 50% of the normal diameter and represents the 13th leading cause of death in the United States (34, 36). Current management involves observation and periodic monitoring of the aneurysm until the risk of rupture outweighs that of surgery, which is a threshold diameter of 55 mm in transverse diameter (34). The most recent United States Preventive Services Task Force recommendations indicate a one-time ultrasound for male smokers 65–75 yr of age, but otherwise selective screening for nonsmoking men in the same age range (41). Despite these recommendations, a significant number remain undiagnosed, with 15,000 patients experiencing rupture yearly, with an overall mortality rate of 80–90% (75). Management of AAA < 55 mm consists of risk factor modification, smoking cessation, statin, and aspirin therapies (44, 71, 89).

While some risk factors linked to AAA are known, the pathogenesis is multifactorial and not well understood. The disease predominates in elderly Caucasian men and is closely associated with smoking, hypertension, and chlamydial infection (34). There is also an increasing body of evidence pointing to a genetic component related to the various human leukocyte antigen-DR alleles present across ethnicities (32, 46). While atherosclerosis is a common feature of many patients with AAAs, it is not necessarily causative and is not found in all patients. Interestingly, evidence in angiotensin II (ANG II) infusion mouse models indicates that aneurysmal development occurs before atherosclerotic lesions (68). What little we do understand about this disease comes largely from studies of human aneurysmal tissue obtained from open surgical repair. The histology from these specimens shows that AAAs are characterized by inflammatory changes in the adventitia and media, with infiltration of neutrophils (8, 22, 52), macrophages, natural killer (NK) and natural killer T (NKT) cells, T and B cells, as well as mast cells (11, 39, 82). There is also protease degradation of the extracellular matrix, especially of collagen and elastin, medial smooth muscle depletion, and neovascularization, all of which contribute to loss of tensile strength of the aortic wall (15).

The exact pathogenic mechanisms that initiate this mural inflammatory cascade remain unclear. Recently, there has been an intense focus on the role of autoimmune mechanisms in AAA formation. Characterization of inflammatory infiltrates (39), identification of immunoglobulins (9), cytokines (11, 25, 72, 84), and proteases (23, 55) in the aneurysmal aortic wall implicate activation of host innate and adaptive immune responses. Although putative autoantigens have been identified that may “pull the trigger” that initiates this process (27, 56, 81, 90), the exact causative antigen(s) remain to be identified.

Putative Autoantigens in AAA Tissue

One proposed mechanism of pathological humoral immunity in AAA concerns autoantigenic components of the aortic wall. The CD4+ T cells found in AAA are memory cells likely activated in response to presently unidentified antigens (55). The oligoclonal expression of T-cell receptor β-chain variable region in 8 of 10 AAA patients in one study indicates that these antigens are driving the clonal expansion of T cells (46). However, there is another study of five patients that found polyclonal T-cell receptor β-chain variable region gene expression (92).
In a study by Bobryshev and Lord (8), lymphoid follicular aggregates with germinal centers, referred to as vascular-associated lymphoid tissue, were prominent in the adventitia of the AAA wall of 17 out of 30 patients. Eight of these patients also had lymph node-like clustering of these follicles. Dendritic cells are scattered along the periphery of these lymphoid follicles, in contact with the T cells and sometimes also B cells, suggesting presentation of an unknown antigen to these cells (8).

Gregory et al. (27) isolated IgG from the wall of AAAs and found they were immunoreactive to an ~80-kDa protein extracted from the aortic tissue. Chew et al. (12) later confirmed the finding that IgG found in the wall of AAAs is immunoreactive to an 80-kDa microfibrillar aortic wall protein. However, it was shown that this same protein did not result in immunoreactivity of serum IgG from AAA patients. It was also shown that IgG in the AAA wall bound to collagen components of normal aortic wall, and goat anti-human IgG bound to collagen components of the AAA wall (12). Not only did the IgG bind to the 80-kDa protein, it also bound to tenasin, an extracellular matrix molecule. As Tilson (81) described, the 80-kDa protein could potentially be a human homologue of the bovine aorta-specific microfibrill-associated glycoprotein-36, which is 36 kDa and occurs in dimers and has tenascin-like domains. In fact, in further experiments, the 80-kDa protein was processed to produce an ~40-kDa protein (aortic aneurysm associated protein–40) that had homologies to fibrinogen, vitronectin, and bovine microfibril-associated glycoprotein-36 (90). Hirose et al. (31) then showed that anti-vitronectin and anti-fibrinogen β-antibodies localize to the adventitial fibrillar areas of aortic wall and were immunoreactive to a 40-kDa protein within the wall. Interestingly, in response to these findings, a separate study by Zhou et al. (96) reported findings of a natural IgG that binds fibrinogen found in aortic wall of elastase perfusion-induced AAA mice. They identified a specific B-cell clone, named G10, that produced monoclonal IgG antibodies that were specific for fibrinogen, and, when transferred to B-cell-deficient mice, led to AAA development. They also determined that reduced Fc region galactosylation of that antibody was deficient mice, led to AAA development. They also determined that reduced Fc region galactosylation of that antibody was responsible for pathogenicity by activating the lectin complement pathway (96).

Carbonic anhydrase, an enzyme that regulates ectopic calcification (64), as occurs in many AAA patients, may also serve as an autoantigen. In a proteomic survey of AAA walls by Ando et al. (3), carbonic anhydrase 1 (CA1) was identified as a candidate autoantigen. Furthermore, autoantibodies to CA1 were found more frequently in AAA patients compared with healthy individuals. Their findings also suggested that CA1 in AAA walls appears to have neoeptopes compared with CA1 of healthy controls, suggesting a role in the pathogenesis of AAA (3).

Besides identifying antigens, others have identified potentially important antibodies. Antiphospholipid (aPL) antibodies are associated with some autoimmune diseases (24). Duftner et al. (17) showed that peripheral aPL antibodies in AAA patients were associated with disease progression. Increased levels of inflammation were seen, as evidenced by higher serum levels of neopterin and circulating CD4+CD28− T cells. Neopterin is released by monocytes and macrophages in response to IFN-γ (35), and CD4+CD28− T cells correlated to a loss of regulatory T cells (Tregs), promoting AAA (2). While their group emphasized aPL antibodies as more of a marker for disease progression rather than playing an autoimmune role, it does not preclude this from being a possibility.

### Cells and Immunomodulatory Cytokines in AAA

As previously discussed, human aneurysm tissue collected from surgical specimens is characterized by inflammatory infiltrates that are largely absent in normal aorta (23). The dominant cell populations are T and B lymphocytes, with smaller numbers of macrophages and NK cells (23, 55). The majority of lymphocytes are CD4+ T cells (55), but B cells are also found to be prominent and form lymphoid follicular aggregates with germinal centers in some specimens (8). Mast cells can be found in the neovascularized media of the aneurysmal wall (53), and neutrophils have been found in atherosclerotic plaques and mural thrombi of these aneurysms (22, 52). Table 1 lists cells, their targets, and the type of inflammatory response in AAA pathology. Figure 1 is a pictorial representation of the hypothetical sequence of cellular events and cytokine expression.

### T cells

CD4+ T cells, the most abundant cell type, have the ability to give rise to helper T cells or Tregs. Helper T cells consist of the Th1, Th2, and Th17 lineages. Th1 and Th2 responses can be seen as a promoter of cellular- and humoral-mediated immunity, respectively (21). Both cell types can become pathogenic in the setting of autoimmunity (74).

The inflammatory milieu of the AAA wall gives rise to a host of cytokines that play a role in its destruction. One of the most studied Th1 cytokines in AAA disease is IFN-γ, although there are others, such as IL-2, IL-12, IL-18, and TNF-β (74). T-bet is a major transcription factor that promotes a Th1 response (21). High levels of both IFN-γ and T-bet mRNA have been found in AAA walls compared with normal aorta. In fact, infiltrating CD4+ T cells preferentially express IFN-γ when stimulated in vitro (25). In a study using the calcium chloride model of aneurysm induction, both CD4+ T cells and the IFN-γ derived from these cells promoted AAA formation. IFN-γ induced production of matrix metalloproteinase-9 (MMP-9) in macrophages and MMP-2 in smooth muscle cells (SMCs), both of which are gelatinsases thought to contribute to the enzymatic degradation of the aortic wall (91). While these studies show a deleterious effect of IFN-γ, another study by King et al. (38) revealed a protective effect of IFN-γ. Specifically, infusions of ANG II in apolipoprotein E-deficient (ApoE−/−) mice genetically deficient in IFN-γ exacerbated AAA formation compared with IFN-γ-sufficient mice (38). Similarly, genetic deletion of chemokine (C-X-C motif) ligand (CXCL) 10, an effector cytokine that is induced in response to IFN-γ, also caused increased AAA formation (38).

Th2 cytokines, including IL-4, IL-5, and IL-10, have also been found in the wall of human AAAs, while they are not present in stenotic atherosclerotic and normal tissue. Schonbeck et al. (70) have shown that these cytokines are in fact dominant in AAA, and that, while the classic Th1 cytokine IFN-γ was found in both AAA and atherosclerotic tissue, its receptor IFN-γRα was found only on atherosclerotic tissue (70).

Yet another set of helper T cells implicated in AAAs is the Th17 lineage. Its major cytokine, IL-17A, is proinflammatory and has been implicated in autoimmune disease (87). Another
related cytokine, IL-23, is produced by antigen presenting cells and functions to sustain the Th17 response (21). Both IL-17 and IL-23 levels were found to be increased in the aortic walls of AAA patients, and IL-17 and IL-23 knockout mice were found to have significantly attenuated AAA formation with the elastase perfusion model (72). Using this Th17 pathway in an effort to develop preventive medical therapy, digoxin has been recently studied to eliminate the deleterious Th17 response. Administration of this drug to mice induced with both the ANG II ApoE−/− and the elastase perfusion models consistently resulted in decreased incidence and severity of AAA, inflammation within the aortic wall, as well as inflammatory cytokine levels (88). However, the literature regarding the role of IL-17 in AAA is inconsistent. Another study using an ANG II, anti-transforming growth factor (TGF)−β mouse model developed by Wang et al. (86) that has shown that Tregs inhibit the proinflammatory effects of monocytes (77), one might postulate that TGF-β was suppressed, and monocyte deple- tion resulted in decreased levels of gelatinolytic activity via gelatin zymography, presumably for both MMP-2 and MMP-9, and decreased severity of AAA (86). In light of a recent study that has shown that Tregs inhibit the proinflammatory effects of monocytes (77), one might postulate that TGF-β suppression inhibits Treg development, which results in uninhibited proliferation and proinflammatory cytokine production by monocytes. In contrast, the previously mentioned study by King et al. (38) that demonstrated increased AAA formation with CXCL10 depletion also showed that blockade of TGF-β1 resulted in decreased AAA size, implying a destructive role for this cytokine.

Another subset of Tregs is the naturally occurring, thymus-derived Tregs that are both FOXP3 and CD25 positive (21). There are the inducible Tregs that come from a distinct lineage of CD4+ T cells that express the transcription factor forkhead box P3 (FOXP3), but not CD25. Inducible Tregs are promoted, in part, when TGF-β is expressed in combination with IL-2 (6). Interestingly, neutralization of TGF-β was found to result in AAA formation in a mouse model without the need for hyperlipidemia, as mentioned earlier. Monocyte infiltration of the aortic wall was also observed when TGF-β was suppressed, and monocyte deple- tion resulted in decreased levels of gelatinolytic activity via gelatin zymography, presumably for both MMP-2 and MMP-9, and decreased severity of AAA (86). In light of a recent study that has shown that Tregs inhibit the proinflammatory effects of monocytes (77), one might postulate that TGF-β suppression inhibits Treg development, which results in uninhibited proliferation and proinflammatory cytokine production by monocytes. In contrast, the previously mentioned study by King et al. (38) that demonstrated increased AAA formation with CXCL10 depletion also showed that blockade of TGF-β1 resulted in decreased AAA size, implying a destructive role for this cytokine.

A variety of autoimmune conditions (40). There are the inducible Tregs that come from a distinct lineage of CD4+ T cells that express the transcription factor forkhead box P3 (FOXP3), but not CD25. Inducible Tregs are promoted, in part, when TGF-β is expressed in combination with IL-2 (6). Interestingly, neutralization of TGF-β was found to result in AAA formation in a mouse model without the need for hyperlipidemia, as mentioned earlier. Monocyte infiltration of the aortic wall was also observed when TGF-β was suppressed, and monocyte deple- tion resulted in decreased levels of gelatinolytic activity via gelatin zymography, presumably for both MMP-2 and MMP-9, and decreased severity of AAA (86). In light of a recent study that has shown that Tregs inhibit the proinflammatory effects of monocytes (77), one might postulate that TGF-β suppression inhibits Treg development, which results in uninhibited proliferation and proinflammatory cytokine production by monocytes. In contrast, the previously mentioned study by King et al. (38) that demonstrated increased AAA formation with CXCL10 depletion also showed that blockade of TGF-β1 resulted in decreased AAA size, implying a destructive role for this cytokine.
ANG II infusion into Treg-depleted mice produced severe AAAs to the point of rupture without the usual requirement of hyperlipidemia (e.g., ApoE−/− mice). With Treg depletion, levels of IL-10, involved in the protective effect of Tregs, were decreased, and levels of proinflammatory IL-12 and IFN-γ, involved in the Th1 response, were increased (2). In a study of 22 AAA patients, decreased levels of peripheral CD4+CD25+FOXP3+ T cells in AAA patients correlated with decreased expression of FOXP3 from Tregs as well as decreased Treg suppressive function (93). In another study of 101 AAA patients, higher levels of CD4+CD28+ T cells were found in the peripheral circulation of patients with small AAAs (18). CD28 is necessary for development of Tregs, so T-cell deficiency of CD28 results in loss of Tregs (2). These CD4+CD28− T cells had increased IFN-γ and perforin production. These findings suggest that a spectrum of T-cell-mediated responses is critical early in the pathogenesis of AAA (18).

CD4+CD31+ T cells are another group of cells that have immune regulatory capabilities. CD31 is a receptor expressed in leukocytes that promotes peripheral tolerance and, therefore, is integral in preventing autoimmunity (50). In the setting of AAA, CD4+CD31+ T cells are protective against CD8+ T-cell-mediated SMC destruction. They are also involved in regulating macrophage-mediated MMP-9 activity. Interestingly, CD31+ T-cell levels are reduced in patients with AAA (10), suggesting that the loss of these regulatory capabilities promotes AAA pathogenesis.

While CD4+ T cells are the most abundant inflammatory cells in the AAA wall (25), CD8+ T cells are also present and have been implicated in the pathogenesis via IFN-γ production. In a study using an elastase perfusion model, the presence of lymphocytic surface protein CD43 on T cells was found to be necessary for AAA development (98). The interaction between CD43 and ezrin-radixin-moesin proteins of CD8+ T cells involved in cytoskeletal remodeling (59) promoted IFN-γ production. Macrophages were thus recruited, increasing the expression of MMPs and invoking cellular apoptosis (98).

Other evidence compiled by Zhang et al. (94) points to impaired regulation of peripheral T cells in AAA patients that makes them less responsive to Fas-induced apoptosis compared with those with aortoocclusive disease and normal controls. As a result, these cells may have an increased ability to promote inflammation and destruction in the aorta, leading to aneurysm development. This study also found a single nucleotide polymorphism 988C→T that was significantly unique to the Fas gene of AAA patients, although it was a silent single nucleotide polymorphism (94).

B cells. Compared with T cells, there is a relative paucity of literature regarding the role of B cells in aneurysm formation. B cell clusters have been shown to be present in lymphoid follicular-like aggregates in aneurysmal walls (8). One may postulate that their antibody producing ability would confer a destructive role in an autoimmune mechanism of pathogenesis, and the removal of these antibodies would be protective. Indeed, one group has shown that B-cell-deficient mice were

Fig. 1. Hypothetical sequence of cellular events and cytokine expression in the pathogenesis of abdominal aortic aneurysms relating to an autoimmune etiology. NK cell, natural killer cell; NKT cell, natural killer T cell; MMP-9, matrix metalloproteinase-9; T help, helper T cell; Treg, regulatory T cell; MCP-1, monocyte chemoattractant protein-1; CXCL2, chemokine (C-X-C motif) ligand 2.
protected from elastase perfusion-induced AAA (97). In contrast, Meher et al. (54) showed that reconstituting B2 cells (a murine B-cell subset) in B-cell-deficient mice actually protected them from AAA formation, potentially via increased production of protective Tregs.

While there is no direct evidence of B-cell involvement in AAA pathogenesis, there is a great deal of literature regarding the role of antibodies and their respective antigens. B-cell antibody production and T-cell clonal expansion in response to antigens in the aortic wall are proposed mechanisms of autoimmunity. Putative antigens that may elicit these lymphocytic responses include infectious sources such as Chlamydia pneumoniae and Treponema pallidum (37, 56), as well as autoantigens (3, 12, 27, 31, 81, 85, 90).

Neutrophils. CD15+ granulocytes, presumably including neutrophils, have been observed in the adventitia (8), and neutrophils have been identified in the intraluminal thrombus (22, 52) of human AAA specimens. Neutrophils are also present in murine models of AAA (58). This finding may be due to the fact that late-stage aneurysms have chronic inflammation, while the acutely induced aneurysms of mouse models produce only the early stages of inflammation, which is when neutrophil presence is predominant. The proteases that neutrophils can produce, such as MMPs, are usually thought to be relevant to AAA pathogenesis via wall protein degradation (79). However, in a study using the elastase perfusion model, reduced neutrophil activity resulted in AAA inhibition, but did not affect MMP-2 and MMP-9 levels, suggesting that neutrophil involvement in AAA formation may not be via these MMPs (19). Also with the elastase perfusion model, dipetidyl peptidase I (DPP1) induced granule-associated serine proteases, which are proinflammatory and recruit neutrophils. DPP1 was also necessary for neutrophil-dependent production of CXCL2, involved with the development of AAA. The DPP1−/− mice had decreased severity of aortic dilation and reduced inflammatory cell infiltration and preservation of the elastin in the aortic wall (57).

Macrophages/mast cells. Macrophages and mast cells, while less prominent than T and B cells, are also present in the AAA wall (23, 53). In experimental AAAs using the ANG II ApoE−/− model, IgE has been found to activate macrophages, mast cells, as well as CD4+ T cells, to produce proinflammatory cytokines such as IL-6. Inhibiting IgE actions decreased AAA severity (84). In fact, peripheral IL-6 levels are higher in patients with AAA (78). IL-6 has also been shown to increase monocyte expression of CD14, involved in the innate immune system via binding of lipopolysaccharide and display to toll-like receptor 4 to activate macrophages, contributing to AAA formation and macrophage infiltration in both the elastase and ANG II ApoE−/− models. In human AAA tissue, increased CD14 levels also correlated with areas of macrophage infiltration (7).

Monocytes and macrophages also produce monocyte chemoattractant protein-1 (MCP-1), a chemokine that directs the flow of immune cells such as memory T cells, NK cells, as well as the monocytes themselves (16). It has been implicated in many disease processes, including atherosclerosis (16). One school of thought is that atherosclerosis, mediated largely by macrophages that secrete inflammatory factors, is intimately associated with AAA pathology (47). It is well accepted that atherosclerotic lesions begin with the formation of lipid-laden macrophages and T cells in the intima, which then progress to fibrous plaques that also include SMCs (66). While the opposing proinflammatory M1 and anti-inflammatory M2 subpopulations of macrophages have been described, it is thought that the M1 subset prevails in the athrogenic environment (47). It should be noted, however, that M1 and M2 macrophages are not necessarily mutually exclusive; it has been suggested that they can have a mixed phenotype where the dominant phenotype results from the cytokines to which they are exposed (51). Similar to Th1 cells, the M1 phenotype is activated by IFN-γ and produces proinflammatory mediators such as IL-6, TNF-α, and IL-1 (33). As previously mentioned, depletion of monocytes resulted in decreased severity of AAA in mice (86); this result can potentially be attributed to the lack of the monocyte-derived macrophages necessary in the formation of atherosclerosis.

Vascular cells. While monocytes and macrophages are the largest producers of MCP-1, many other cells can produce this chemokine, including vascular cells, such as endothelial cells, fibroblasts, and SMCs (16). SMCs are found in the medial layer of the aortic wall. SMC apoptosis is characteristic of aneurysmal wall (29). When mouse AAA wall cells from the elastase model were studied in vitro, apoptotic SMCs released MCP-1, which induced macrophages to kill SMCs via the Fas ligand/Fas-caspase-8 receptor interacting protein-1-mediated mechanism (85). In response to MCP-1, SMCs also release the proinflammatory IL-6 and proliferate via activation of NF-κB and activator protein-1 (83).

Interestingly, there is some evidence that SMCs can differentiate to macrophages in the setting of atherogenesis. Feil et al. (20) showed that SMCs in the aortas of atherosclerosis-prone hyperlipidemic mice developed macrophage-like characteristics. This population of smooth muscle-derived macrophages is thought to be distinct from the better known monocyte-derived macrophages.

NK and NKT cells along with Th1 cells found in atherosclerotic AAA tissue also affect SMCs. These cells produce IFN-γ, which induces the SMCs to produce IL-15, a cytokine that promotes proliferation of NKT cells. The NKT cells in turn promote SMC apoptosis via the Fas pathway (11).

Other vascular cells such as the endothelial cells have also been implicated in AAA formation. In an ANG II ApoE−/− model, interfering with NF-κB signaling in the endothelium resulted in decreased levels of inflammatory mediators, such as MCP-1 and VCAM-1, decreased macrophage infiltration of the aortic wall, and overall suppression of AAA formation (67). Of note, endothelial cell NF-κB activity is also thought to be increased with aging, promoting atherogenesis, and subsequently cardiovascular diseases such as AAA (13). In addition to endothelial cells, adventitial fibroblasts secreting MCP-1 have also been shown to recruit monocytes to the aortic wall, which then promote the proliferation of more fibroblasts that amplify the inflammatory response (80).

Complement Pathways

The three complement pathways, classical, alternative, and lectin pathways, have all been implicated in AAA. The presence of complement components has been detected in aneu-
Atherosclerotic plaques. In fact, studies had noted the presence of the bacteria in 70% of the setting of atherosclerosis. In a review published in 2002 by Infection Associated with AAA: Molecular Mimicry?

The significance of complement regulatory proteins in AAAs. Further studies would be warranted to determine CD46 were decreased in lung tissue, both supporting complement levels of complement regulatory proteins such as CD55 and complement pathway activation via factor B caused neutrophil infiltration of the aortic wall, resulting in AAA development, while factor B depletion inhibited AAA development. The same study also investigated human AAA walls and revealed the presence of many components of the classical and alternative complement pathway (58). The alternative complement pathway has also been shown to be triggered by IgG deposited in the wall of AAAs, a process that is dependent on properdin stabilizing the C3 convertase (97). The fibrinogen-specific IgG in the study by Zhou et al. (96) was shown to activate the complement pathway, with the alternative complement pathway occurring downstream of the lectin pathway. There is also evidence of lectin pathway activation in human AAA; mannose binding lectin in the AAA wall is closely associated with inflammatory cells as well as areas with deposition of G10 antibody, which cross-reacts with human fibrinogen (96). Otherwise, in a genomewide microarray expression profiling study, AAA patients were found to differentially express 13 genes mostly related to the lectin and classical complement pathways. Immunohistochemistry results showing higher C2 levels in the adventitia of AAA tissue compared with controls provided further evidence of lectin and classical complement activation (30).

While there are many studies showing the role of the complement pathway in AAA formation, there are no studies to date that might explain how this process might be modulated. Obliterative bronchiolitis (OB) developing in patients after lung transplantation has been shown to have an autoimmune component to its pathogenesis, with complement activation as an additional pathogenic factor (76). In OB patients, levels of complement regulatory proteins such as CD55 and CD46 were decreased in lung tissue, both supporting complement activation in OB, as well as its presence as a modulatory factor (76). Further studies would be warranted to determine the significance of complement regulatory proteins in AAAs.

Infection Associated with AAA: Molecular Mimicry?

Chlamydia pneumoniae has been studied extensively in the setting of atherosclerosis. In a review published in 2002 by Leinonen and Saikku (42), they reported that 55 different studies had noted the presence of the bacteria in 70% of atherosclerotic plaques. In fact, C. pneumoniae antigens and antibodies have also been found in human AAA tissue (37). This evidence raises the question of whether molecular mimicry could be a cause of autoimmunity, where antibodies against C. pneumoniae cross-react with epitopes in the aortic wall? In a study of AAA, 33 patients that were shown to have the presence of the bacterial DNA in their aortic tissue exhibited no significant serological response to C. pneumoniae (61). Another study demonstrated that patients with AAA (n = 17) possessed serum antibodies against the outer membrane protein of C. pneumoniae and cross-reacted with the heavy chain of immunoglobulins in AAA walls (45). T lymphocytes isolated from AAA wall have also been shown to have positive responses in 8 of 22 patient samples used in C. pneumoniae proliferation assays (28).

Treponema pallidum is another infectious agent that has been implicated in AAA pathogenesis. Antibodies against T. pallidum were found to bind to AAA wall matrix components. Additionally, IgG from the aneurysmal wall was found to bind T. pallidum proteins (56).

Conclusion

AAA is a fatal disease that remains without a clear understanding of the exact mechanisms of pathogenesis. Consequently, the discovery of therapeutic agents that may prevent or halt disease progression is restricted. It is becoming more evident that the innate and adaptive immune responses have autoimmune features. These responding cells produce toxic mediators that appear to contribute to wall degeneration, including proinflammatory cytokines, extracellular matrix-degrading proteases, and induction of Fas-mediated cell apoptosis. Additionally, there is evidence of autoimmune action on as-yet unidentified antigens, as well as complement-dependent mechanisms of AAA formation. Dysfunction of regulatory mechanisms also contributes to progression of disease. To date, while there is no direct evidence of autoimmunity, the current body of literature certainly alludes to the existence of inciting autoactive immune cells in response to an antigen.

One line of investigation for future consideration is the effect of aging on the pathogenesis of AAAs. It is known that immune cells lose their ability to function with age. Immunosenescence can give rise to the loss of tolerogenic mechanisms and, therefore, to the development of autoimmunity (62). Furthermore, the prevalence of AAA increases with age (69). As autoimmune diseases are more common in the elderly population, we might speculate that aging might occur with loss of the presence or function of Tregs, leading to loss of tolerance and increased sensitivity to autoantigens. In fact, mouse studies have shown that, while there is an increase in the percentages of CD4+CD25+ Tregs in the periphery of aged mice, the function of these regulatory cells was impaired (95). However, other studies have shown that the elevated Treg population in aged mice was responsible for immune deficiency, at least in an antitumor capacity (73). Therefore, future investigation is warranted to clarify how immunosenescence impacts the development of this highly morbid geriatric disease.

GRANTS

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AUTOIMMUNITY IN ABDOMINAL AORTIC ANEURYSMS


