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ATVB In Focus
Abdominal Aortic Aneurysms: Pathophysiological Mechanisms and Clinical Implications

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Inflammation and Cellular Immune Responses in Abdominal Aortic Aneurysms

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Abstract—Expansion and rupture of abdominal aortic aneurysms (AAA) result in high morbidity and mortality rates. Like stenotic atherosclerotic lesions, AAA accumulate inflammatory cells, but usually exhibit much more extensive medial damage. Leukocyte recruitment and expression of pro-inflammatory Th1 cytokines typically characterize early atherogenesis of any kind, and modulation of inflammatory mediators mutes atheroma formation in mice.[1] However, the mechanistic differences between stenotic and aneurysmal manifestations of atherosclerosis remain unexplained. We recently showed that aortic allografts deficient in interferon-γ (IFN-γ) signaling developed AAA correlating with skewed Th2 cytokine environments, suggesting important regulatory roles for Th1/Th2 cytokine balance in modulating matrix remodeling and important implications for the pathophysiology of aortic aneurysm and atherosclerosis. Further probing of their distinct aspects of immune and inflammatory responses in vascular diseases should continue to shed new light on the pathophysiologic mechanisms that give rise to aneurysmal versus occlusive manifestations and atherosclerosis. **(*Arterioscler Thromb Vasc Biol*. 2006;26:987-994.)**

Key Words: aortic aneurysm ■ atherosclerosis ■ cytokine ■ pathogenesis ■ T-lymphocytes ■ transplantation

Aortic aneurysms are permanent and localized aortic dilations defined as having diameters 1.5-times greater than normal (ie, >3 cm diameter for abdominal aortic aneurysms [AAA]). In comparison, the term aortic ectasia describes localized aortic enlargement <1.5-times normal diameter.[2] Although most aneurysms remain asymptomatic and undiagnosed, risk of rupture increases dramatically when diameters exceed 5.5 cm. Despite surgical advances, the prognosis of ruptured AAA remains poor, and the overall mortality remains high (80% to 90%).[3] Although surgical or endovascular repair constitutes the major therapeutic options for AAA >5.5 cm, such invasive procedures provide no therapeutic advantage for AAA <5.5 cm diameter.

Most AAA develop below the renal arteries and end above the bifurcation of the iliac arteries; they typically exhibit a fusiform morphology, with symmetrical circumferential enlargement involving all layers of the aortic wall. Less frequently, aneurysms have a saccular form, with aneurysmal degeneration affecting only part of the aortic circumference. The AAA wall usually becomes laminated with thrombus and its intraluminal diameter often appears relatively normal by angiography. Important histological features of aneurysms include chronic adventitial and medial inflammatory cell infiltration, elastin fragmentation and degeneration, and medial attenuation. Collagen (especially types I and III) in the media and adventitia provides tensile strength to the aortic

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wall. Collagen synthesis increases during the early stages of aneurysm formation, suggesting a repair process.[4] However, in later stages, collagen degradation exceeds its synthesis (accompanied by excessive degradation of other extracellular matrix macromolecules, notably elastin), ultimately favoring AAA rupture. Indeed, AAA exhibit increased local production of enzymes capable of degrading collagen and elastin extracellular matrix proteins.[5–7]

In AAA, inflammatory cells (polymorphonuclear neutrophils, T cells, B cells, macrophages, mast cells, NK cells, etc) percolate through the luminal thrombus and all layers of the wall.[8,9] These infiltrating cells secrete various humoral inflammatory factors, including cytokines, chemokines, leukotrienes, reactive oxygen species, and immunoglobulins. The vessels of the vasa vasorum form the pathways by which inflammatory cells access the aortic intima and media.[10] Medial neovascularization and decreased vascular smooth muscle cells also characterize AAA lesions. The intraluminal thrombus may contribute to the process by causing a functional hypoxia at the luminal intima and inner media, thus inducing subsequent neovascularization and inflammation.[11] Inflammatory cells in the thrombus also release active proteases such as matrix metalloproteinase (MMP)-9 and urokinase-type plasminogen activator (u-PA).[12]

Recent human studies indicate that human AAAs comprise an inflammatory disease characterized by the predominance of T helper cell type 2 (Th2) cytokine expression and the paucity of Th1 cytokines, especially interferon-γ (IFN-γ).[13] This review focuses on the role of specific cytokines produced by inflammatory cells within AAA as well as the downstream pathways they induce to form aneurysmal lesions.

Risk Factors of AAA

The risk factors for AAA include family history, smoking, advanced age, male gender, atherosclerosis, and hypertension.[14] Approximately 25% of cases occur in patients with first-degree relatives with AAA. In AAA with hereditable elements, elastin and collagen degradation may correlate with genetically unstable proteins or locally increased protease production in aneurysmal lesions. In some cases, autoimmune responses involving the DRB1 major histocompatibility locus may contribute to AAA formation.[15] Connective tissue disorders such as type III procollagen mutation, Ehlers-Danlos syndrome type IV, or Marfan syndrome, and inflammatory diseases such as Takayasu arteritis and Behçet disease[16–19] may also have familial predilections, although few such patients develop AAA. Familial clustering of AAA not only may result from a particular genetic background but also may associate with shared environmental factors such as smoking. Smoking is the most important environmental risk factor for AAA formation and progression.[14,20,21] Smoking associates with AAA in men 2.5-times more frequently compared with coronary artery disease.[22]

Inflammatory Aneurysm and Atherosclerotic Aneurysm

Walker et al first used the term "inflammatory aneurysm" in 1972,[23] defining it as a triad of thickened aneurysm wall, extensive perianeurysmal and retroperitoneal fibrosis, and dense adhesions of adjacent abdominal organs. Patients with such inflammatory aortic aneurysms more commonly present with a triad of abdominal or back pain, weight loss, and an elevated erythrocyte sedimentation rate (65% to 90% versus 8% to 18% in noninflammatory AAA).[24–27] Further, viral and *Chlamydia pneumoniae* infection may contribute to inflammatory aneurysm development. Polymerase chain reaction showed that herpes simplex viruses or cytomegaloviruses were more prevalent in the wall of aneurysms in inflammatory versus ordinary atherosclerotic ("noninflammatory") AAA.[28] Interestingly, polymerase chain reaction also detected *Chlamydia pneumoniae* DNA in the wall of AAA in 14 (35%) of 40 noninflammatory AAA >5 cm in diameter.[29] Consequently, some investigators concluded that these entities (inflammatory versus noninflammatory AAA) are the same disease, differing only in the degree of inflammation.[24,26] A case control study demonstrated elevated plasma levels of C-reactive protein in AAA patients, further supporting the contention that inflammation contributes importantly to all AAA development.[30–32]

Leukocyte recruitment and expression of pro-inflammatory cytokines characterize early atherogenesis.[1] AAA typically arise in the setting of severe atherosclerosis,[33] and several studies suggest that the aneurysmal disease may progress from occlusive disease.[34] Because AAA frequently coexist with generalized atherosclerosis, they are frequently termed "atherosclerotic aneurysms."[35,36] Nevertheless, the majority of patients with advanced atherosclerosis do not develop AAA; conversely, some patients lacking substantial atherosclerosis develop AAA.

The prevalence of abdominal aortic atherosclerosis greatly exceeds that of AAA. AAA occurs in 48% of men older than 60 years,[37] whereas only 4.3% to 7.7% of men aged 65 to 80 years have AAA.[38] Thus, only 9% to 16% of patients with atherosclerotic abdominal aortas develop AAA. Consequently, atherosclerosis per se probably does not directly cause AAA but may provide the first inflammatory triggers to recruit inflammatory cells and direct their subsequent heightened elaboration of further mediators (eg, proteases, reactive oxygen species). Although aneurysmal and occlusive diseases demonstrate common pathologic features and share common risk factors, the specific pathogenesis of aortic aneurysm versus aortic occlusive disease remains ill- defined.

Collagenases and Elastases Associate With Aortic Aneurysm Development

Medial elastin fibers and interstitial collagens (types I and III) in the media and adventitia determine much of the structural integrity and stability of arteries. The dominant histological features of AAA include chronic medial and adventitial inflammation with medial degeneration including smooth muscle cell (SMC) apoptosis and excessive loss of extracellular matrix (ECM), especially extensive elastin fragmentation.[7,39,40] Increased turnover and loss of types I and III fibrillar collagens[4] as well as excessive elastolysis caused by increased collagenase, elastase, and especially MMP expression[7] probably underlie aortic dilation and rupture. Similarly, genetic fragility of these structures in humans (Marfan and

Erhlers-Danlos syndrome) and experimental exposure of proteinases to the aortic wall also culminate in aortic aneurysm formation. Because of the extremely long half-life of elastin (≈50 years), loss of elastin in adults almost certainly results from increased elastolysis rather than insufficient synthesis.[7,41] Nevertheless, elastogenesis in atherosclerosis may also be defective, producing poorly cross-linked immature elastin.[42,43] Elastic fibers can degenerate and alter their structure through aging;[44] elastolysis could also expose neoantigens that might provoke an autoimmune response. Tropoelastin and various elastin-derived peptides may also mediate neutrophil, fibroblast, and monocyte/macrophage chemotaxis.[45–47]

MMP (MMP-1, -2, -3, -9, -12, and -13),[6,41,48–51] serine proteases (tissue-type plasminogen activator [t-PA]; u-PA; plasmin; and neutrophil elastase),[35,52–55] as well as cysteine proteases (cathepsin D, K, L, and S)[56–59] all localize in aneurysm walls at concentrations higher than occur in normal or stenotic atherosclerotic arteries. Endothelial cells (ECs), SMCs, fibroblasts, or macrophages can all produce these proteinases.[35,57,59,60] CD40 ligation on inflammatory and vessel wall cells induces MMPs as well as neutrophil elastase from human vascular EC and monocyte/macrophages.[54]

MMPs are initially secreted as inactive zymogens (pro-MMP), requiring activation in the extracellular compartment. Similarly, 2 plasminogen activators (t-PA and u-PA) generate plasmin from the inactive precursor plasminogen. Plasmin, a serine proteinase with little direct elastolytic or collagenolytic activity, can indirectly induce ECM degradation by activating MMPs.[61] Cathepsins S and K have potent elastolytic activity, and cathepsin L can degrade type IV and V collagen, laminin, elastin, and proteoglycans.[59,62] Notably, levels of cystatin C (a major inhibitor of the cysteinyl elastases, cathepsins S and K) decrease in human AAA[57]; mice lacking cystatin C show increased elastic fragmentation with resulting ectasia in atherosclerotic aortas.[63]

Immunologic Aspects of AAA

The cellular immune response in AAA may contribute importantly to regulation of the underlying pathobiology. Inflammatory cells accumulate in AAA lesions with a predominance of CD4+ T cells (3- to 20-fold greater than CD8+ T cells), B cells, and macrophages.[34] Inflammatory cells occur more abundantly in AAA lesions than in occlusive aortic atherosclerosis.[34] B cells rarely exist in occlusive atherosclerotic aortas,[34,64] whereas AAA often display local deposition of immunoglobulin,[40] potentially reflecting humoral immune responses. Additionally, B cells can serve as antigen presenting cells (APC). A similar pattern of leukocyte accumulation in inflammatory aneurysms provides additional evidence that AAA and inflammatory aneurysms represent variants along a spectrum of aneurysmal disease rather than distinct pathologic entities.[34] The numerous lesional monocytes and macrophages may function in either innate or adaptive immune roles, not only as APC but also contributing to AAA pathogenesis by secreting collagenases and elastases.[65] Despite the impressive collection of inflammatory cells, it remains unclear whether a specific immune response by lymphocytes and immunoglobulin incite lesion formation, or whether they simply accumulate in response to some other injury. Despite this uncertainty, cytokine environments driven by local inflammatory cells likely direct the nature of tissue response.

T cell recruitment with expression of pro-inflammatory Th1 cytokines typically characterizes early atherogenesis and stenotic atherosclerotic plaque.[1,66] CD4+ T cells secrete IL-2, causing activation and proliferation of T and B cells.[67] However, potential mechanistic differences in immune and inflammatory pathways in stenotic versus aneurysmal manifestations of atherosclerosis remain unexplained. Recent studies showed a shift toward Th2 responses in human AAA compared with stenotic atheromas.[13]

Pattern of Cytokine Expression in Aortic Occlusive and Aneurysmal Disease

Most AAA occur in the context of atherosclerosis, and all stages of atheromata contain T lymphocytes, with a predominance of CD4+ helper T cells.[34,64,68] T cells and macrophages may affect atherogenesis by producing various cytokines that induce either matrix synthesis or degradation. In particular, different T-cell subsets secrete IFN-γ or IL-4 that drive opposing effects on a variety of biological processes. CD4+ Th1 cells and CD8+ T-cytotoxic type-1 (Tc1) cells characteristically produce IFN-γ, IL-2, and tumor necrosis factor, whereas Th2 and Tc2 cells secrete IL-4, IL-5, IL-10, and IL-13. Th1 cytokines tend to drive cellular inflammatory responses including macrophage activation. The Th2 cytokines play important roles in distinct inflammatory processes, particularly in the pathogenesis of allergy, asthma, and atopic dermatitis; they also inhibit certain forms of autoimmunity.[69] T cell responses polarize toward a Th1/Tc1 phenotype in the presence of IFNγ, whereas IL-4 predisposes to Th2/Tc2 T cell responses.[70] Because IL-4 and IL-13 have a similar 3-dimensional structure and share receptor complexes, they have overlapping but pleiotropic functions, including enhanced B cell proliferation and isotype-switching as well as antagonism of the effects of IFN-γ, induction of dendritic cell differentiation, T cell proliferation and differentiation, and enhanced production of certain chemokines (eg, IL-8/CXCL8, MCP1/CCL2, and RANTES/CCL5) from ECs and SMCs.[71] In addition to Th2 and Tc2 lymphocytes, various other cell types including B cells, NK cells, mast cells, basophils (IL-4 and IL-13), and endothelial cells as well as macrophages (IL-10) produce Th2-type cytokines.[72,73]

Besides the cytokine mediators already described, pluripotent eicosanoid lipid mediators including prostaglandins (PG) and leukotrienes may contribute to AAA. These mediators derive from arachidonic acid by action of cyclooxygenase and 5-lipoxygenase (5-LO) respectively and associate with a variety of inflammatory processes, including allergic reactions and atherosclerosis.[74–76] Interestingly, deficiency of 5-lipoxygenase attenuates aneurysm formation of atherosclerotic apolipoprotein E-deficient mice,[77] suggesting a role for the 5-LO pathway in AAA formation. Significantly, the PG mediators can also modulate Th2 cytokine production; for example, a murine asthma model showed that PGD_2 augments Th2 type inflammation by inducing macrophage-derived chemokine.[78] Two receptors for PGD_2 exist, namely the D prostanoid (DP) receptor (DP_1 and DP_2) and the chemoattractant receptor-homologous molecules that are expressed on

Th2 cells ($CRTH_2$). In humans, DP_2 preferentially localizes on Th2 cells, eosinophils, and basophils and mediates chemotaxis in vitro, suggesting that DP_2 promotes Th2-related inflammation.[79–81]

Reactive oxygen species may also contribute to the pathogenesis of AAA. In humans, levels of superoxide anion (O_2^-) significantly increased in AAA lesions compared with tissue from adjacent nonaneurysm or normal control aortas.[82] In animal models, reactive oxygen species initiate Th2 type autoimmune responses; antioxidant treatment suppressed vasculitis and IgE production in this model.[83]

Th1 and/or Th2 cytokines produced by inflammatory cells conceivably could influence the outcome of arterial inflammation. Several studies demonstrated elevated circulating levels of IL-1, IL-6, tumor necrosis factor-α, or IFN-γ in patients with AAA, and also specifically implicated these cytokines in AAA pathogenesis.[84,85] Another human study demonstrated increased expression of IFN-γ and undetectable Th2 cytokines in tissue extracted from ascending thoracic aortic aneurysms (TAA).[86] DNA array analysis using human tissue showed that the altered pattern of gene expression observed in TAA is distinguishable from that observed in AAA, suggesting that TAA and AAA are fundamentally different pathophysiologic entities at a molecular level.[87] Conversely, other human studies showed that Th2 type cytokines (IL-4, IL-5, or IL-10) predominate in human AAA lesions, whereas stenotic atherosclerotic lesions preferentially express Th1 cytokines (IL-2 and IFN-γ).[13,88] These apparently discordant findings may result from specimen sources (ethnic groups, postmortem material), sampling differences (eg, neck or center of aneurysm), stage of aneurysm formation (early stage $<$5.5 cm or late stage $>$5.5 cm in diameter), or tissue preservation conditions.

Such descriptive clinical observations make it difficult to interpret whether increased Th1 cytokines actually cause aneurysm development or simply associate with a precursor atherosclerotic injury. Indeed, Th1 responses might drive occlusive atherosclerosis, whereas a Th2 environment could favor aneurysm formation. Th1 cytokines might even protect against aneurysm development, because IFN-γ–depleted mice demonstrate markedly augmented inflammatory responses.[89]

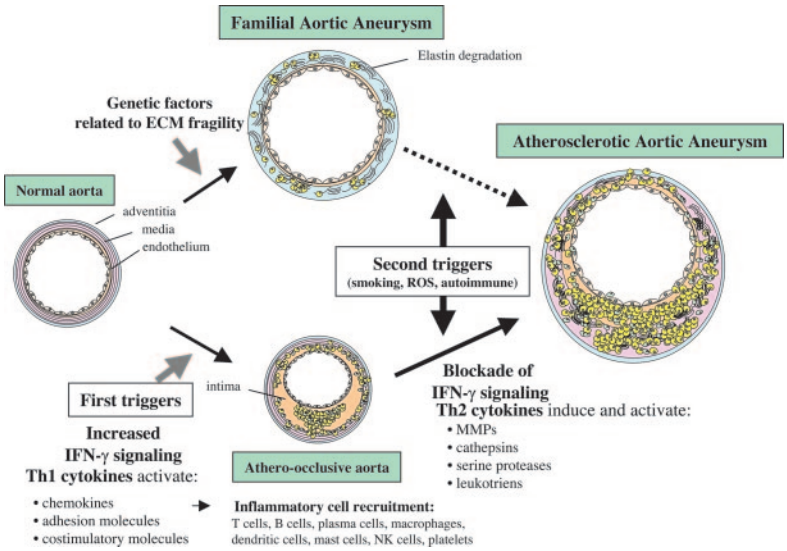
Cytokines Modulate MMP, Serine Protease, and Cathepsin Expression, and Correlate With AAA Development

Cytokines regulate MMP, serine protease, and cathepsin expression. Indeed, both Th1 and Th2 cytokines (eg, IFN-γ or IL-4) can induce or inhibit expression of specific MMPs,[60] depending on the particular experimental conditions. Such variability requires consideration in determining the applicability of animal models to human AAA disease. For example, IFN-γ induces MMP-9 from human melanoma cells,[90] but inhibits MMP-9[91,92] and MMP-12[93–95] production by murine and human macrophages. Th2 cytokines (eg, IL-4 or IL-10) inhibit MMP-1, -2, and -9 production by human macrophages,[60,96] whereas IL-4 induces MMP-12 expression by murine macrophages.[93] Others report that IL-13 potently induces MMP-2, -9, -12, -13, and -14, and cathepsins B, L, S, H, and K.[97,98] IFN-γ induces cathepsin S from vascular SMCs,[57] whereas IL-4 and IL-13 augment cathepsin L secretion from glomerular visceral epithelial cells.[99] IL-4 and/or IL-13 augment u-PA and t-PA expression from vascular ECs,[100] SMCs,[101,102] and monocyte/macrophages.[103,104] With regard to extracellular matrix synthesis, IFN-γ inhibits collagen production by SMCs, the principal source of collagen in the arterial wall.[105] In all these cases, the isolated cytokine effects are measured in vitro, whereas the integration of effects in a given cytokine milieu in vivo may be distinctively different. Nevertheless, these results also demonstrated that blockade of IFN-γ signaling associated with Th2 cytokine skewing alters local MMP and protease activity so as to result in aneurysm formation.

Aortic Aneurysm Formation Correlates With IFN-γ Signaling Blockade and Increased IL-4

Studies based on surgical specimens of human aneurysms inevitably deal with a late phase of disease and do not necessarily reflect the conditions that initiated aortic dilation. Consequently, an in vivo animal preparation can better help to clarify the functional role of cellular subsets of innate or adaptive immunity in the initiation of aortic aneurysm formation. However, the lack of a universally accepted animal model hinders our ability to identify a discrete trigger of AAA formation. Although elastase perfusion,[106] angiotensin II infusion,[107] or local treatment with $CaCl_2$[108] result in aneurysm formation in animals, each of these models uses high nonphysiological doses of inflammatory agents (eg, elastase, angiotensin II, or calcium chloride) to induce artificial aortic expansion and may not adequately mimic the inflammatory triggers that initiate aortic aneurysm during human atherogenesis. Moreover, few studies have used animals with specific chemokine or cytokine deficiencies to define the function of physiological mediator proteins (eg, cytokines) in aneurysm formation.

We hypothesized that the cytokine milieu created by specific inflammatory cells (Th1 or Th2 type cytokine-secreting cells) would affect whether an atherosclerotic lesion would become an aneurysmal lesion. To test this hypothesis, we used an immunologically driven model, ie, murine aortic transplantation, to focus local inflammation in allograft aortic segments. Transplantation into wild-type hosts specifically elicits IFN-γ predominant responses in the allograft segment[93]; conversely, transplantation into hosts lacking the IFN-γ receptor (GRKO) led to IL-4-dominated responses. Notably, death of medial SMCs caused by rejection does not itself suffice to cause aneurysm formation.[109] Thus, although acute rejection causes virtually complete medial SMC death in aortic allografts of wild-type recipient, the transplanted aortas develop not aneurysms but rather intimal hyperplasia.[109] In comparison, allografts in GRKO recipients developed profound aneurysmal dilation with medial elastin loss similar to that seen in human AAA. Moreover, in GRKO hosts, IL4 blockade using anti-IL4 antibodies or hosts concurrently lacking IL-4 reduced AAA formation in aortic allografts with associated decreases in elastic tissue fragmentation and in MMP-9 and MMP-12 expression.[93] These results suggested important regulatory roles for Th1 and Th2



Hypothetical scheme of a Th1/Th2 paradigm for aortic disease. In early atherogenesis, recruitment of inflammatory cells and the accumulation of lipids leads to the expansion of the intima. If inflammatory conditions persist (first trigger), Th1 cytokines such as IFN-γ secreted by the activated leukocytes act on endothelial cells (ECs), smooth muscle cells (SMCs), and macrophages. The activated aortic wall cells and infiltrating cells secrete inflammatory mediators such as chemokines, adhesion molecules, and costimulatory molecules, as well as platelet-derived growth factor (PDGF), leading to further recruitment of inflammatory cells and SMCs as well as interstitial collagen production. These secreted mediators increase migration, proliferation and ECM synthesis by SMCs and cause further expansion of the intima, yielding lumenal obstruction. Incompletely characterized second triggers, eg, smoking, reactive oxygen species (ROS), autoimmune factors, or genetic predilection, induce expression of Th2 cytokines from T cells, B cells, macrophages, mast cells, NK cells, or ECs, and/or block IFN-γ signaling, and cause macrophages and/or SMCs to secrete leukotrienes and elastolytic MMPs, eg, MMPs-9 and -12, cathepsins, or serine proteinases. These proteinases favor degradation of elastic lamellae, leading to aortic expansion and subsequent aneurysm development. Development of aortic aneurysms in familial settings often involves certain genetic factors related to ECM structure (eg, Marfan syndrome, Erhlers-Danlos syndrome) or autoimmune factors. However, these aneurysms may also interact synergistically with environmental factors (second triggers).

cytokines in modulating matrix remodeling, and have important implications for the pathophysiology of AAA and atherosclerosis.

The majority of inflammatory cells at early stages of AAA consist of macrophages that express the metalloelastase MMP-12. Macrophages cultured in vitro showed augmented expression of elastolytic MMP-12 in the presence of IL-4; IFN-γ co-administration inhibited that effect. These findings and our immunologically driven model further support a central role for IL-4 in AAA formation and suggest that IFN-γ attenuates collagenolytic and elastolytic activity. Such results provide new insights into the mechanisms of aneurysmal disease and suggest that IL-4 antagonism could attenuate the formation and/or expansion of arterial aneurysms.

Triggers for a Cascade of Events Leading to Atherosclerosis and Aortic Aneurysm

The presence of inflammatory infiltrates in AAA raises the possibility that immune responses contribute to aneurysmal degeneration. Certainly, Th1 cytokines (eg, IFN-γ) potentiate early atherosclerotic development.[66] Conversely, Th2 type cytokines and chemokines localize in late stages of the human AAA disease.[110] Although our recent study appears to contradict previous results suggesting that IFN-γ participates critically in AAA development,[111] we emphasize that Th1 cytokines may critically initiate the early accumulation of inflammatory cells. Attenuated production of IFN-γ (or other Th1 cytokines) may diminish the early stages of atherosclerotic inflammatory cell recruitment, thus modulating subsequent protease activity and attenuating aneurysm formation.

To integrate the current data regarding Th1 versus Th2 effects, we propose the model for AAA development depicted in the Figure. In familial AAA, patients with abnormal ECM components can develop AAA early without concomitant atherosclerosis. In sporadic AAA, however, aneurysmal lesions require initial inflammatory cell recruitment, particularly involving macrophages that will contribute to subsequent ECM degradation. In most cases, the default pathway will be a Th1-dominated obstructive lesion; however, when the local environment is skewed toward Th2 predominance, aneurysms will develop.

The factors initiating Th2 predominance may associate with the known risk factors for aneurysm development. Aging is one of risk factors for AAA. Innate immune cells produce greater IL-4 with aging.[112] Smoking is a potent risk factor of AAA,[113] and chronic smoke exposure accelerates enlargement of experimental AAA.[114] Interestingly, human peripheral blood mononuclear cells isolated from smokers have elevated IL-4 levels compared with those isolated from nonsmokers.[115] Moreover, cigarette smoke induces IL-4 expression from human aortic ECs,[116] and cigarette smoke extract inhibits IL-2 and IFN-γ production by peripheral blood mononuclear cells.[117] Other studies demonstrated that cigarette smoke induces MMP-1,[116] MMP-9,[118] and MMP-12[119] from human endothelial cells, monocytes/macrophages, or epithelial cells. In patients with acute Kawasaki disease, another setting where inflammation potentially drives coronary arterial aneurysm formation, clinical studies report elevated IL-4 and IL-10 levels in the serum and peripheral blood mononuclear cells of these patients.[120,121] Interestingly, genetic variation in IL-4 expression may help explain why aneurysm formation occurs in only ≈25% of Kawasaki disease patients.[122,123]

Based on these studies, we propose that secondary triggers, eg, smoking and/or genetic predilection, inhibit local IFN-γ signaling and/or elicit Th2-dominant cytokine environments (inducing macrophage elastolytic activity) in a subset of patients with aortic atherosclerosis and ultimately result in AAA formation. We foresee elucidating and targeting the secondary triggers or blocking relevant Th2 cytokines, eg, IL-4, as promising strategies for prevention and therapy of AAA.

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