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The Role of Complement in the
Pathogenesis of Artery Aneurysms

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1. Introduction

Aneurysm is an abnormal widening or ballooning of a portion of an artery due to weakness in the wall of the blood vessel. Although venous aneurysms do occur, arterial aneurysms are much more common and severe than venous aneurysms. Aneurysmal degeneration of the abdominal aortic and iliac arteries is a common and frequently lethal age-related disease process (Baxter et al., 2008; Weintraub, 2009). Arterial aneurysm is a potentially lethal vascular disorder, much more common in older men with estimates of prevalence ranging up to 10 percent (Thompson et al., 2002). Death from a ruptured aneurysm accounts for about 1 percent of all the deaths in the Western world (Collin et al., 1988). Extensive evidence indicates that mediators of immunity and inflammation participate in the development of aneurysm formation (Duftner et al., 2006; Shimizu et al., 2006). However, the pathogenesis of the aneurysm formation and rupture remains unclear. Recent results obtained from clinical and experimental studies suggest that complement, an important mediator for immune and inflammatory responses may contribute to the pathogenesis of artery aneurysms. Here, we will extensively review the potential roles of complement in artery aneurysm formation and rupture.

2. Artery aneurysms

Artery aneurysms such as aortic, cerebral and ventricular aneurysms develop as a result of weakening of the vascular wall in response to the initiation of a complex extracellular matrix remodeling process that culminates in alterations in artery compliance and resilience (Powell and Greenhalgh, 1989; Schneiderman et al., 1995). Aortic aneurysm is located within the wall of the aorta. Typically, the widened part of the aorta is considered to be an aneurysm when it is more than 1.5 times its normal size. Cerebral aneurysm, also known as a berry aneurysm, occurs in the wall of a blood vessel in the brain. Ventricular aneurysm is a ballooning out of part of the wall of the heart. Most aneurysms are asymptomatic and undiagnosed and the rupture of aneurysms is associated with a systemic inflammatory

response and multiple organ dysfunctions, which remain a primary cause of death in patients who survive the initial surgery (Harkin et al., 2004). Aneurysm rupture has an overall mortality rate of 80–90 percent, and an operative mortality rate of 50 percent. Other than relatively high risk and costly open surgical repair, few interventional modalities are available to treat patients with AAA (Baxter et al., 2008; Krishna et al., 2010). This mainly stems from little understanding of the underlying mechanism of aortic aneurysms. Therefore, better understanding of the pathogenesis of artery aneurysms and developing more effective therapies for the treatment and prevention of artery aneurysms is imperative. Extensive evidence indicates that the mediators of immunity and inflammation participate in the development of aneurysm formation (Duftner et al., 2006; Shimizu et al., 2006). The aneurysm is characterized by chronic adventitial and medial inflammatory cell infiltration, extracellular matrix degeneration, and apoptosis of smooth muscle cells, which lead to vessel wall weakening, aortic dilatation and aneurysm formation (Jagadesham et al., 2008). Inflammatory cells accumulate in aortic aneurysm lesions with a predominance of CD4+ T ,B cells and macrophage, which secrete various inflammatory factors, including cytokines, chemokines, leukotrienes, reactive oxygen species, and immunoglobulins, contributing to the immune response in aneurysm lesions (Shimizu et al., 2006). Macrophages promote aneurysm development by secreting collagenases and elastases, which could degrade elastic lamellae and extracellular matrix (ECM) proteins, constituting the underlying characteristics of the aneurysm (Kadoglou and Liapis, 2004). Consistently, extensive evidence indicates that MMP2 and MMP9 play critical roles in the pathogenesis of artery aneurysms, and macrophages are the primary source of MMP-9 production in human and mouse aneurysm tissues (Longo et al., 2002; Thompson et al., 1995). The excessive local production of the matrix metalloproteinases (MMPs), which are mainly secreted from macrophages, results in the damaging of smooth muscle cells (SMC) and thinning of the artery wall (Allaire et al., 1998; Caird et al., 2006; Eliason et al., 2005; Hannawa et al., 2009; Newman et al., 1994; Palombo et al., 1999; Tanaka et al., 1995). Moreover, the development of aneurysms is suppressed by pharmacologic inhibition of MMPs, such as the use of tetracycline derivatives, or genetic alterations that eliminate the expression of either MMP 9 or MMP 2 (Curci et al., 2000; Mosorin et al., 2001; Pyo et al., 2000). Elastolytic cysteine proteases, including cathepsin, also play a critical role in the development of aneurysms (Shi et al., 1999). In addition, endothelial and smooth muscle cells in aneurysm lesions may release an array of growth factors and cytokoines to attract inflammatory cells recruitment, which contributes to aneurysm development (Nicholson-Weller and Halperin, 1993). Nevertheless, the exact underlying mechanism and cause of aneurysms are unclear. The risk factors for aneurysms include advanced age, male gender, smoking, hypertension, diabetes, obesity, high cholesterol, genetic predisposition, and atherosclerosis (Wassef et al., 2007). Among these factors, the most common culprits are atherosclerosis and high blood pressure (Daugherty and Cassis, 2004; Wassef et al., 2007). Most of the abdominal aortic aneurysms (AAA) in humans are associated with atherosclerosis (Daugherty and Cassis, 2004; Wassef et al., 2007).

Although both atherosclerosis and aneurysm are immune and inflammatory diseases, they have different pathogeneses. The hallmark pathologic feature of atherosclerosis is foam-cell formation, whereas aneurysms are typified by intense oxidative stress, inflammation, matrix degradation, and apoptosis of smooth-muscle cells (Miller et al., 2002; Weintraub, 2009). In aneurysm development, first, inflammatory leukocytes play an important role in the degradation of elastin and collagen in the vessel wall. Subsequent dilation of the vessel will trigger the vascular cells to remodel and repair to prevent vessel rupture (de Waard et al.,

2010). Most aortic aneurysms occur in association with advanced atherosclerosis (Nordon et al., 2009). Atherosclerosis may induce AAA formation by causing mechanical weakening of the aortic wall with loss of elastic recoil, along with degenerative ischemic changes, through obstruction of the vasa vasorum. Many patients with advanced atherosclerosis do not develop artery aneurysms, while some patients for which there is having no evidence of atherosclerosis do develop artery aneurysms. The observed association between atherosclerosis and aneurysm is probably not causative; however, atherosclerosis may represent a nonspecific secondary response to vessel wall injury that is induced by multiple factors. These facts clearly indicate that aneurysm has a different pathogenesis and consequences for aortic walls vs. atherosclerosis. Although increasing emerging evidence obtained from clinical and experimental studies indicates that complement system plays a critical pathogenic role in the development of atherosclerosis (An et al., 2009; Halas et al., 2005; Hansson et al., 1984; Lewis et al., 2009; Meuwissen et al., 2006; Niculescu et al., 1999b; Nijmeijer et al., 2003; Ross, 1999; Seifert and Kazatchkine, 1988; Vlaicu et al., 1985; Wu et al., 2009; Yun et al., 2008), the role of complement system in the pathogenesis of aneurysm remains unclear.

3. Complement activation and regulation

3.1 Complement activation

The complement system consists of about 30 soluble and membrane-bound proteins, and is activated by three distinct pathways: classical, mannose-binding lectin (MBL) and alternative pathways, either on pathogen surfaces or in plasma (Yu et al., 2010; Zhou et al., 2008). Activation of these pathways depends on different molecules for their initiation (Qin and Gao, 2006; Zhou et al., 2008). All three activation pathways converge at the level of C3 to form C5 convertase such as the C4bC2bC3b from classical and MBL pathways and (C3b)2Fbb from alternative pathway. The C5 convertase then cleaves C5 to form C5b and C5a. The terminal complement activation pathway is induced initially by C5b, followed by the sequential condensation of C6 form to C5b6, and then C7, C8, and C9. Polymerization of C9 bound to the C5b-8 complex forms the MAC, an end-product of the complement activation pathway. The MAC forms a lytic pore in the lipid bilayer membrane that allows the free passage of solutes and water across the membrane and destroys membrane integrity, followed by killing of foreign pathogens and cells (Mayer, 1984).

The liver (mainly hepatocytes) is the main source of complement proteins, accounting for 80%~90% of plasma complement components and their soluble regulators (Qin and Gao, 2006). Many other non-hepatic cells including macrophage, endothelial, neutrophil and lymphocytes could produce complement proteins. This local synthesis of complement occurs in the brain, heart, lung, joints, intestine, skeletal muscle and bone marrow (Morgan and Gasque, 1997). It has been demonstrated that the absence of locally synthesized complement component C3 is capable of modulating the rejection of renal allografts in vivo and regulating T-cell responses in vivo and in vitro (Pratt et al., 2002). The result indicates that the local complement production also plays a critical role in the pathogenesis of human diseases such as organ rejection.

3.2 Biological functions of complement activation byproducts

The byproducts produced in complement activation, such as C1q, C3b, iC3b, and C4b, are critical opsonins for host defense against pathogen and for disposal of immune complexes

and dead cell debris by the phagocytosis/lysis effect of the immune cells (macrophages, neutrophils, natural killer [NK] cells, etc.) through their surface receptor binding to these byproducts. On the other hand, the small fragment byproducts such as C3a, C4a, and C5a, termed anaphylatoxins, also play an important role in inflammation and especially in host defense against parasites. These anaphylatoxins can cause mast cell and basophil degranulation, with the release of histamine and other substances that increase vascular permeability and stimulate smooth muscle constriction. C3a and C5a are potent leukocyte chemoattractants, and can also activate these immune effector cells by binding to cell surface receptors (Haas and van Strijp, 2007). Among these anaphylatoxins, C5a has the most potent biological activity (Guo and Ward, 2005).

3.3 MAC function

The cellular response to MAC formation can be classified into two groups along a response continuum: lytic and sublytic. Lytic MAC formation results in colloidoosmotic swelling and lysis of the target (Mayer, 1984; Yu et al., 2010). Normally, MAC attacks homologous nucleated cells mainly through sublytic MAC because nucleated cells possess several protective mechanisms against the cytolytic effect of the MAC, including CD59, anti-apoptotic genes and endocytosis/shedding of MAC (Haskard et al., 2008; Zhou et al., 2008). The sublytic MAC can mediate non-lethal physiological and/or pathological responses in autologous cells (Nicholson-Weller and Halperin, 1993).

Biological functions of sublytic MAC include insertion into the membrane of endothelial cells resulting in the release of: a) bFGF and PDGF (Benzaquen et al., 1994; Halperin et al., 1993; Shankland et al., 1999); b) interleukin-1, which stimulates the expression of pro-inflammatory adhesion molecules such as VCAM-1 and E-selectin, and of prothrombotic tissue factor (Acosta et al., 1996); and c) MCP-1, which attracts monocytes and macrophages that contribute to the pathogenesis of the atherosclerotic plaque (Fosbrink et al., 2006; Torzewski et al., 1996). Consistently, we have demonstrated that sublytic MAC up-regulated the transcripts of these growth factors and cytokines in the plaques of the deficient CD59 mice as well as of targeted macrophages and endothelial cells. However, the role of MAC-induced growth factors and cytokines in the aneurysms is unclear.

In vitro studies have shown that sublytic MAC induces following cellular signaling pathways (Niculescu et al., 1999a; Niculescu and Rus, 1999, 2004), which may contribute to the increase of the release of these growth factors and cytokines. These cellular signaling pathways include 1) elevated Ca^{2+} via Ca^{2+} influx through transient pore in cells, which partially activates PKC and other cellular signaling pathways (Carney et al., 1990; Papadimitriou et al., 1991); 2) G protein coupled-activation of Ras, Raf-1, MEK, ERK-1 pathway and increased activities of ERK-1, c-jun NH2-terminal kinase JNK1 and p38 MAPK in many cells including endothelial cells and smooth muscle cells (Niculescu et al., 1999a; Niculescu and Rus, 1999; Niculescu et al., 1997); 3) activation of the PI3/Akt kinase pathway (Fosbrink et al., 2006; Hila et al., 2001; Niculescu et al., 1999a; Soane et al., 2001); 4) activation of the nuclear factors NF-κB and activator protein-1 (AP-1), which may be responsible for MAC-induced release of IL-6 in smooth muscle cells and IL-8 and MCP-1 in endothelial cells (Viedt et al., 2000) (Kilgore et al., 1996; Kilgore et al., 1997); and 5) activation of the JAK1/STAT3 pathway (Niculescu and Rus, 1999). These in vitro experimental results strongly suggest that MAC is an important mediator of cellular signals that may trigger cell mitogenic effects, which could explain MAC-mediated growth factor and cytokine release. Their activations may result from the secondary effects from the released inflammatory

mediators by transiently sublytic MAC and/or the direct effect from sublytic MAC, which have not been addressed so far.

3.4 Complement regulation

To prevent the potentially harmful effect of complement activation on autologous cells, about 10 plasma- and membrane-bound inhibitory proteins have evolved to restrict complement activation at different stages of activation pathways (Yu et al., 2010; Zhou et al., 2008). The soluble plasma complement regulatory proteins include C1 inhibitor, which regulates C1; factor H and factor I, which regulate the cleavage of C3b and C3/C5 convertases; C4 binding protein, which splits C4 convertase and assists factor I in the cleavage of C4b; and S-protein, clusterin, and serum lipids, which compete with membrane lipids to react with nascent C5b67 (Yu et al., 2010; Zhou et al., 2008). Moreover, three membrane proteins that are expressed on the surface of almost all cell types inhibit autologous complement activation, thereby protecting self cells from complement-mediated injury (Morgan, 1999). These regulators include decay-accelerating factor (DAF or CD55), membrane cofactor protein (MCP or CD46), and membrane inhibitor of reactive lysis (CD59). DAF inactivates the C3 (C4b2a and C3bBb) and C5 (C4b2a3b and C3bBb3b) convertases by accelerating the decay of these enzymes (Davitz et al., 1986; Medof et al., 1987; Nicholson-Weller et al., 1985). MCP acts as a cofactor for the cleavage of cell-bound C4b and C3b by the serum protease factor (Brodbeck et al., 2000). CD59 restricts MAC formation by preventing C9 incorporation and polymerization (Sugita et al., 1989).

3.4.1 Anti-MAC regulator CD59

Several lines of evidence indicate that CD59 is much more relevant than DAF, MCP and other complement regulators in protecting cells from MAC formation and MAC-induced phenomena (reviewed in (Acosta et al., 2004; Fisicaro et al., 2000)): 1) an isolated deficiency of DAF has been described in four families that had an unusual blood group phenotype termed Inab (Lin et al., 1988; Telen and Green, 1989). Although DAF was completely absent from all circulating cells (Reid et al., 1991), none of the propositi had symptoms suggestive of paroxysmal nocturnal hemoglobinuria (PNH), a complement-mediated hemolytic disease due to the deficiency of complement regulators such as CD59 and DAF; 2) a mDAF knockout mouse did not show any evidence of intravascular hemolysis (Sun et al., 1999); and 3) an index case report from Japan described a man who had a global deficiency of hCD59 due to single nucleotide deletions in the CD59 gene, which placed the gene product out of frame and introduced a premature stop codon. This subject expressed a severe PNH phenotype from the unusually young age of thirteen and also had a stroke that left him with permanent neurological damage (Yamashina et al., 1990). Not only does the Cd59 knockout out mouse exhibit a full PNH-like anemia as well as platelet activation, but it also exhibits progressive loss of fertility (Holt et al., 2001; Qin et al., 2009; Qin et al., 2003). Also, although the role of S-protein as an inhibitor of MAC formation in tissues has been suggested, the S-protein knockout mouse did not show any detectable phenotype and instead developed normally and was fully fertile (Zheng et al., 1995). This indicates that, at least in mice, the S-protein is not essential for survival nor does it play a major role in restricting complement activation or MAC formation. In addition to the anti-MAC role, CD59 has a complement-independent function in regulating NK, B, and T cell activities (Longhi et al., 2007; Sivasankar et al., 2007).

3.4.2 The delicate balance between complement activation and regulation

There is a delicate balance between complement activation and regulation on autologous cells, which is subject to perturbation by either increased complement activation or decreased regulation. The perturbation may cause a variety of immune diseases and chronic diseases (Yu et al., 2010). It is very likely that this delicate balance between complement activity and regulation differs in the different tissues because of differential expression of complement regulatory proteins and focal activation of complement proteins (Acosta et al., 2004). Indeed, extensive study has shown an offset balance between complement activation and complement regulation, which contributes to the pathogenesis of inflammatory or immune diseases, such as systemic lupus erythematosus (Abe et al., 1998), rheumatoid arthritis (Breitner et al., 1995), Alzheimer's disease (Gasque et al., 1995), and acute renal transplant rejection (Pratt et al., 2002). In the case of the development of aneurysms, there may be an offset balance between complement activation and regulation in the vascular walls, thereby leading to the development of aneurysm formation and rupture, which will be discussed below.

4. Clinical evidence indicates that complement may contribute to the development of aneurysms

There are a few clinical studies examining the role of complement and MAC in the pathogenesis of aneurysms. The results obtained from human studies only provide indirect evidence supporting the role of complement and highlighting the possible involvement of each complement activation pathway in the development and rupture of artery aneurysms like cerebral and aortic aneurysms.

4.1 Complement activation and complement deposition in autoimmune disease-associated aneurysms

The potential role of complement in the artery aneurysms was first recognized by the study of autoimmune disease-associated aneurysms. Early demonstration that there is a negative correlation between serum immunoglobin level and complement activity in the Kawasaki disease patients with aneurysm provides the clinical evidence to link the potential role of complement to the formation of artery aneurysms (Miyata et al., 1984). Kawasaki disease (KD), is an autoimmune disease that manifests as a systemic necrotizing medium-sized vessel vasculitis and is largely seen in children under five years of age (Ozkan et al., 2007). It affects many organ systems, mainly those including the blood vessels, skin, mucous membranes and lymph nodes; however, its most serious effect is on the heart, where it can cause severe coronary artery aneurysms in untreated children. In 1984, Miyata et al (Miyata et al., 1984) conducted a study to measure the serum immunoglobin level and complement activity in 32 Kawasaki disease patients with or without coronary aneurysm. They (Miyata et al., 1984) demonstrated that the group of patients with coronary aneurysm showed relatively higher levels of IgG. Regardless of the presence of coronary aneurysm, the level of IgE in the acute phase was higher than that in the convalescent phase. In addition, the level of immune complexes was higher in the group of patients with coronary aneurysm. There was a low negative correlation between immune complexes and CH50, a clinical measurement for total complement activity.

Another clinical study demonstrates that there is an extensive complement deposition in Behcet's disease-related aneurysm (Yamana et al., 1988). Behçet's disease is a multisystem

disorder of probable autoinflammatory etiology with manifestations that can affect many organ systems (Gul, 2005). Its classical presentation includes recurrent oral and genital ulcers and skin inflammatory reactivity. Neurologic involvement is rare, as is the development of peripheral arterial aneurysms (1990). In 1988, Yamana et al (Yamana et al., 1988) reported two patients with vasculo-Behçet's disease who had femoral and popliteal aneurysms. They found that the most interesting histological features in these patients were prominent fibrosis of the adventitia, including the surrounding tissue, venous occlusion, perivasculitis and deposits of C3, C4 and immunoglobulins (IgA, IgG and IgM) in the arterial wall and surrounding tissue. These findings indicate that the formation of aneurysm in vasculo-Behçet's disease is caused by destruction of the intimal and outer side of the arterial wall. Complement may participate in this destruction. Therefore, the complement activation/consumption from increased immune complexes in the circulation of autoimmune diseases may be involved in the development of aneurysms associated with autoimmune diseases.

Extensive clinical and experimental evidence indicates that inflammatory aortic aneurysm is associated with increased incidence of autoimmune disease (Haug et al., 2003; Jagadesham et al., 2008). Complement plays a critical role in the pathogenesis of a variety of autoimmune diseases. However, the role of complement in the autoimmune-associated aneurysms remains unclear and requires further investigation.

4.2 Immunoglobins and C3 deposition in aneurysms

Gregory et al used immunoblotting techniques to compare the reactivity of IgG (detected with secondary goat antihuman antibody) from fourteen patients with abdominal aortic aneurysm (AAA) with soluble proteins extracted from normal and aneurysmal aortas (Gregory et al., 1996). Immunoglobulins G purified from extracts obtained from nine patients with no AAA were used for control experiments. They demonstrated that a unique band at approximately 80 kd was visualized when the filters were probed with IgG from eleven (79 percent) of fourteen patients with AAA compared with only one (11 percent) of nine control subjects. Immunoglobulins G from patients with AAA co-distributed with matrix fibers in normal aortic sections, particularly in the adventitia (suggestive of a microfibrillar component). These findings suggest that these IgGs may participate in the development and progression of AAA because these IgGs binding to the matrix fibers in artery may initiate local classical pathway activation and mediate complement attack on the artery wall, leading to initiation of the formation of artery aneurysms associated with autoimmune disease.

This prediction was further confirmed by increased C3 deposition, along with IgG content in the AAA (Capella et al., 1996). In 1996, Capella et al further demonstrated that compared to the amounts of IgG by subclass in normal aorta, AAA had increases of 193-fold in IgG1, 160-fold in IgG2, 389-fold in IgG3, and 627-fold in IgG4. There was a 125-fold increase in immunoreactive C3 by ELISA in AAA vs normal aorta. Western immunoblotting techniques revealed the presence of multiple C3 degradation products in AAA. Increases in IgG1, 2, and 3 may be responsible for activation of complement in AAA by the classical pathway (Capella et al., 1996). Consistent with this finding, Stella et al (Stella et al., 1991) demonstrated that the interstitial matrix contained deposits of IgG, IgM and C3c together with an increase in type III collagen and a reduction in elastin which appeared fragmented and swollen. The degree of activation shown by these cell elements and the activation of complement suggest that the relevant antigen may have been localized in the aneurysm wall

at the time of observation. Taken together, the presence of complement-fixing IgG subclasses along with increased C3 in the aneurysm wall may be an important mechanism promoting matrix proteolysis in AAA.

Moreover, in addition to C3 and IgG deposits in aneurysm, C9 were also found to deposit in aneurysm (Chyatte et al., 1999). Chyatte et al. conducted immunohistochemistry studies with aneurysm tissue collected at the time of microsurgical repair from 23 unruptured and two ruptured aneurysms (25 patients) and compared with 11 control basilar arteries harvested at autopsy. Immunohistochemistry revealed the localization of complement (C3c, C9) and immunoglobulins (IgG, IgM) with inflammatory cells such as macrophages and monocytes (CD68), T lymphocytes (CD3), and B lymphocytes (CD20). Complement (C3c), immunoglobulin (IgG), macrophages (CD68), and T lymphocytes (CD3) were all frequently present in the wall of aneurysm tissue but were rarely identified in control basilar arteries. A few B lymphocytes (CD20) were found in aneurysm tissue, but none were found in the basilar arteries. Extensive inflammatory and immunological reactions are common in unruptured intracranial aneurysms and may be related to aneurysm formation and rupture. These results strongly suggest that the IgM and/or C3 and MAC deposits located in the endothelium of intracranial arteries may play a role in aneurysm-associated neurological complications.

4.3 Complement activation in ruptured aneurysm associated with hemorrhage

The roles of complement and complement activation in ruptured aneurysms were further investigated by several independent groups. In 1987, Ostergaard et al, (Ostergaard et al., 1987) monitored circulating immune complexes and complement activation (plasma C3d levels) during a two week period in patients with ruptured cerebral aneurysms and also in patients with cerebral hematoma unrelated to saccular aneurysms. They found that thirteen of eighteen aneurysm patients were found to have immune complexes on admission as compared to three of 21 healthy blood donors. The presence of immune complexes in aneurysm patients was associated with a poor prognosis. Patients with vasospasm showed a twofold increase in plasma C3d levels at the time when the spasm occurred, whereas no significant changes in the C3d concentration could be demonstrated in aneurysm patients without spasm or in patients with hematoma unrelated to aneurysm rupture. These findings suggest that complement-activation mediated by immune complex are involved in the pathogenesis of cerebral vasospasm following rupture of saccular aneurysms (Ostergaard, 1989).

Kawano et al. investigated serum complements (CH50, C3, C4) after aneurysmal subarachnoid hemorrhage in 21 patients over a two to three week period (Kawano and Yonekawa, 1990). Preoperative grading was well correlated with the C4 level but not the C3 level. C4 levels in patients without symptomatic vasospasm did not change markedly after subarachnoid hemorrhage over investigation. There were no remarkable changes of serum complements in the control patients. C3 and C4 levels of the patients without symptomatic vasospasm did not change markedly after subarachnoid hemorrhage, while they decreased severely in patients with severe vasospasm and majorneurological deficit. The patients with mild symptomatic vasospasm without major neurological deficit showed transient decrease of C3 and C4 levels within a period of five to ten days after subarachnoid hemorrhage. These results show that sequential determinations of serum complement (C3 and C4) levels after subarachnoid hemorrhage is a useful method for the choice of therapy and for the prognosis of aneurysmal patients after subarachnoid hemorrhage. The reduction of plasma C3 and C4 in patients with aneurysmal vasospasm indicates that complement have been

activated before rupture of the aneurysm. These results further support the role of complement activation in the pathogenesis of aneurysmal hemorrhage (Kawano and Yonekawa, 1990).

4.4 Complement including MAC deposits in ruptured aneurysm associated with hemorrhage

Complement including MAC deposition in ruptured intracranial aneurysm has been extensively investigated in clinical samples. An intracranial aneurysm is an important acquired cerebrovascular disease that can cause a catastrophic subarachnoid hemorrhage. Despite modern therapy, most patients die or are left disabled as a direct result of a severe initial hemorrhage. The development of more effective treatment strategies depends on understanding the fundamental biology of cerebral aneurysms. The presence of IgM and/or C3 in the endothelium of intracranial aneurysms was demonstrated in five out of six patients with subarachnoid hemorrhage (SAH) (Ryba et al., 1992). In none of them were the immune deposits found in the gyrus rectus. Cortical tissue of four epileptic patients which served as a control gave negative results.

Complement activation associated with the rupture and subarachnoid hemorrhage of sacculare cerebral artery aneurysm (SCAA) was also examined by electromicroscopy and immunoelectron microscopy. Tulamo et al recently demonstrated that MAC localized consistently in a decellularized layer in the outer SCAA wall, and was found in all SCAA samples (Tulamo et al., 2006). The percentage of MAC-positive area relative to the total SCAA wall surface area was greater in ruptured than in unruptured SCAAs. It was also associated significantly with SCAA wall degeneration, de-endothelialization, and CD163+ macrophage and T-lymphocyte infiltrations. Apoptotic terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling-positive nuclei and MAC were located at the same wall areas in four out of 14 double-stained samples, but no double-positive cells were found. Electromicroscopy and immunoelectron microscopy of an unruptured SCAA showed cell death in the MAC-positive layers in the outer SCAA wall. These results suggest that complement activation and MAC formation are involved in SCAA wall degeneration and rupture (Tulamo et al., 2006).

4.5 Local classical complement activation may be involved in aneurysm formation and rupture

Tulamo et al further investigated initiators and the pathway of complement activation in unruptured and ruptured intracranial aneurysms (Tulamo et al., 2010a). Unruptured and ruptured intracranial aneurysm wall samples were studied in parallel sections by immunohistochemical and immunofluorescence stainings. Classical pathway components such as C1q, C3b/iC3b, C3d, C4b/iC4b and MAC were seen in all intracranial aneurysms, and they were located mostly in the extracellular matrix. The early pathway complement components co-localized with each other, but were present in larger areas than C5b-9. The areas positive for complement component accumulation were significantly broader in ruptured than in unruptured intracranial aneurysms. The potential complement activators IgG, IgM, CRP and OxLDL were found mostly in the extracellular matrix and in partial overlap with MAC. These results indicate that immunoglobulins, CRP, and OxLDL may locally activate classical complement pathway, thereby leading to complement and MAC deposits in the intracranial aneurysms wall, which participates in the formation and rupture of aneurysms (Tulamo et al., 2010a).

Furthermore, Tulamo et al also reported that the complement regulatory capacity of the complement system thus appears disturbed in the outer part of the intracranial aneurysms (IA) wall (Tulamo et al., 2010b). The outer part of the IA walls, where MAC is mainly localized in, lacked CD59 and cellular parts in comparison to normal controls. In contrast, complement inhibitors factor H, C4b binding protein, and CD59 as well as glycosaminoglycans were sufficient in the luminal part of the IA wall where MAC was lacking from (Tulamo et al., 2010b). Thus, these human studies indicate that dysregulation of the complement system, such as loss of CD59 in the outer intracranial aneurysm walls leads to an increased susceptibility to complement activation and MAC formation which may associate with inflammation and aneurysm formation. The insufficiency of complement regulation may be due to matrix remodeling and cell loss by mechanical hemodynamics and/or inflammatory stress (Tulamo et al., 2010b). Therefore, there is an imbalance between complement activation and regulation in the outer part of the intracranial aneurysms wall, which results from more complement activation and less complement regulation. This imbalance may allow full pro-inflammatory complement activation to occur before aneurysm rupture.

In contrast, whether alternative and lectin pathways are involved in the aneurysm formation and rupture remains unclear. Recently, Bradley et al (Bradley et al., 2010) demonstrated that there was no evidence for significant association between presence or size of aneurysm with 49 single nucleotide polymorphisms, including common putatively functional polymorphisms, in the genes of the alternative complement cascade (CFH, CFB, CFD, CFI, properdin, CR1, CR1L, CR2, CD46, vitronectin, C3, C5, C6, C7, C8A, C8B, C8G and C9). This study suggests that variation in the genes of the alternative pathway is not an important cause of AAA development. However, the relative role of each of the complement activation pathways in the pathogenesis of artery aneurysms still warrants further investigation. This is because 1) complement system is a critical mediator of the inflammatory process; and 2) the complement-mediated inflammatory process results from imbalance between complement activation and regulation, which highly depends on the sites and tissues of complement activation.

4.6 Complement participates in the ischemia-reperfusion injury of the patients undergoing the surgery for aneurysm repair

Although open surgical repair is highly costly and has high mortality rate, it still is a common approach for the treatment of aortic aneurysm because few interventional modalities are available to treat patients with aortic aneurysm (Baxter et al., 2008; Krishna et al., 2010). Since complement activation contributes to ischemia-reperfusion injury, it is conceivable that patients undergoing thoracoabdominal aortic aneurysm repair suffer extensive ischemia-reperfusion and considerable systemic inflammation. Consistent with this prediction, Odegard et al (Odegard et al., 2007) reported that preoperatively, the thoracic aortic aneurysms patients had significantly elevated concentrations of myeloperoxidase, neopterin and complement activation products compared to controls. Myeloperoxidase and lactoferrin increased after the first contrast dose and peaked at 8 h postoperatively. Platelet counts decreased, while soluble MAC increased from 8 h postoperatively. This result indicates that stent graft treatment induces further activation, and markers of endothelial, platelet, and complement activation were increased for several days after the procedure.

4.6.1 Lectin pathway activation participates in the ischemia-reperfusion injury of patients undergoing surgery for aneurysm repair

Norwood et al reported that there is the consumption of MBL during AAA repair (Norwood et al., 2006). They demonstrated that 23 patients undergoing AAA repair experienced a mean decrease in plasma MBL levels of 41 percent representing significant lectin pathway activation (p = 0.003). In contrast, no lectin pathway activation could be demonstrated in eight control patients. The consumption of MBL occurs during AAA repair and is indicative of an important role for the lectin pathway in the ischemia-reperfusion injury associated with aortic aneurysm repair.

The degree and mechanism of complement activation and its role in inflammation were further investigated in the patients undergoing thoracoabdominal aortic aneurysm (TAAA) repair by Fiane et al (Fiane et al., 2003). Substantial complement activation was seen in TAAA patients but not in controls. C1rs-C1-inhibitor complexes increased moderately, whereas C4bc, C3bBbP, C3bc, and the soluble C5b9 (MAC) increased markedly after reperfusion, reaching a maximum at eight hours after reperfusion. Interleukin (IL)-1, tumor necrosis factor α (TNF-α), and IL-8 increased significantly in TAAA patients but not in controls, peaking at 24 hours postoperatively and correlating closely with the degree of complement activation. IL-6 and IL-10 increased to a maximum 8 hours after reperfusion in the TAAA patients, were not correlated with complement activation, and increased moderately in the control subjects. Furthermore, no increase was observed in complement activation products, IL-1, TNF-α, or IL-8 in a MBL–deficient TAAA patient, whereas IL-6 and IL-10 increased as in the controls. Two other MBL-deficient TAAA patients receiving plasma attained significant MBL levels and showed complement and cytokine patterns identical to the MBL-sufficient TAAA patients. These results strongly suggest that complement activation during TAAA repair is MBL mediated, amplified through the alternative pathway, and responsible in part for the inflammatory response (Fiane et al., 2003).

Altogether, these clinical results suggest that complement contributes to the formation and rupture of artery aneurysm and plays a critical role in ischemia-reperfusion injuries associated with aortic aneurysm repair. However, the underlying molecular and cellular mechanisms, through which complement participates in the pathogenesis of artery aneurysm still remains unclear. Therefore, there is a strong need to experimentally dissect the mechanisms in animal models.

5. Animal studies

5.1 Current animal model of aneurysms

Experimental models of artery aneurysms played an important role in understanding the underlying mechanism of artery aneurysms. A number of chemically induced AAA mouse models have been used extensively for the study of aneurysm pathogenesis (Daugherty and Cassis, 2004). These chemical approaches include intraluminal infusion of elastase, periaortic incubations of calcium chloride, and subcutaneous infusion of angiotensin II (Ang II) in Apoe$^{-/-}$ background (Daugherty and Cassis, 2004). These mouse models can recapitulate some pathological features of human aneurysms, including medial degeneration, inflammation, thrombus formation, and rupture (Daugherty and Cassis, 2004).

5.2 Complement-dependent neutrophil recruitment is critical for the development of elastase-induced AAA in mice

Transient perfusion of the abdominal aorta with a porcine elastase solution reproducibly leads to the formation of AAA in all C57BL/6 WT mice. In this elastase-induced model of AAA, Pagano, M.B et al reported that mice that were treated with cobra venom factor(CVF, a potent complement inhibitor with the ability to deplete serum C3), before or 24 hours after elastase perfusion, were resistant to elastase-induced AAA, characterized by smaller aortic dilatation, well-preserved elastic fibers, significantly less smooth muscle cell depletion, reduced numbers of macrophages, and activity of mast cells (Pagano et al., 2009). These results indicate that complement activation was involved in elastase-induced AAA development. Examination of mice deficient in factor B further indicated that the alternative pathway of complement played a major role in this process. Activation of the alternative pathway led to generation of the anaphylatoxins C3a and C5a, which recruited neutrophils to the aortic wall. Moreover, antagonism of both C3a and C5a activity was required to block AAA, which suggests that each can independently promote the aneurysmal phenotype. In addition, Pagano, M.B et al demonstrated that complement alternative-pathway involvement was not restricted to this experimental model, but was instead also evident in human AAA (Pagano et al., 2009). These results indicate that complement dependent neutrophile recruitment is critical for the development of AAA.

5.3 Complement may play a role in canine subarachnoid hemorrhage models

Gao et al (Gao et al., 2009) investigated the correlation between sympathetic nerve activation and inflammatory response in the acute stage of subarachnoid hemorrhage (SAH) in a canine perforating model. SAH was induced by perforation of the basilar artery with the use of a microcatheter via the femoral artery in twenty mongrel dogs. They demonstrated that the peak values of C3a and soluble MAC in plasma correlated positively with the peak value of noradrenaline. The peak values of IL-6 and IL-8 also correlated positively with the peak values of noradrenaline. These results suggest that a pronounced activation of the sympathetic nervous system and the inflammatory response occur in the acute stage of SAH and highlight that sympathetic activation and immune responses such as complement activation are quantitatively linked in the early stage after SAH (Gao et al., 2009). These results further support the potential role of complement activation in the aneurysm rupture.

5.4 C5a receptor antagonist attenuates multiple organ injury in a model of ruptured AAA in rats

The C5a-C5a receptor pathway may also play a critical role in multiple organ injuries after aneurysm rupture. Harkin et al (Harkin et al., 2004) examined the role of a novel complement factor 5a (C5aR) receptor antagonist, the cyclic peptide AcF-(OpdChaWR), in attenuation of pathologic complement activation and tissue injury in a model of AAA rupture. They demonstrated that C5aR antagonist AcF treatment significantly reduced lung and intestinal permeability index and myeloperoxidase activity and down-regulated lung TNF-alpha levels. These results indicate that a potent antagonist of C5a receptor protects the rat intestine and lung from neutrophil-associated injury in a model of AAA rupture. These data suggest that complement-mediated inflammation can be modulated at the C5a receptor level, independent of pro-inflammatory TNF-alpha production, and can prevent acute local and remote organ injury (Harkin et al., 2004).

5.5 Protective role of CD59 and potential pathogenic role of MAC in the AAA model

Extensive evidence from human and animal studies indicates a protective role of CD59 and an atherogenic role of MAC in the pathogenesis of atherosclerosis (Wu et al., 2009). In a well-accepted rabbit model of atherosclerosis induced by a 3 percent cholesterol diet, the deficiency of C6, a necessary complement for formation of MAC, protected against the development of atherosclerosis (Schmiedt et al., 1998; Seifert et al., 1989; Seifert and Kazatchkine, 1988). Recently, four independent groups defined the anti-atherogenic role of CD59 using mCd59 deficient mice (An et al., 2009; Lewis et al., 2009; Wu et al., 2009; Yun et al., 2008). Furthermore, we (Wu et al., 2009)* and Lewis et al (Lewis et al., 2009) have recently documented the in vivo atherogenic roles of MAC using anti-mouse C5 antibody (Ab) to block the formation of MAC in mCd59 deficient mice and using mC6 deficient mice to block the formation of MAC respectively. Moreover, MAC mediated endothelial damage and promoted foam cell formation (Wu et al., 2009). These combined results highlight the atherogenic role of MAC (Wu et al., 2009). Although atherosclerosis and AAA have different pathogeneses, they are all immune and inflammatory diseases. Atherosclerosis is considered to be a main cause of AAA, thus the atherogenic role of MAC shed light on its possible role in aortic aneurysm.

Moreover, human studies have suggested that MAC may play a role in the formation and rupture of aorta aneurysms as we discussed above. Taken together, this evidence prompted us to explore the role of MAC in the pathogenesis of AAA with our recent generation of both anti-MAC inhibitor CD59 deficient and overexpressing mice (Qin et al., 2009; Wu et al., 2010). In an angiotensin (Ang) II-induced AAA model, deficiency of both mouse Cd59a and Cd59b (mCd59ab$^{-/-}$) in ApoE-null mice accelerated the disease development, while transgenic over-expression of human CD59 in the endothelial and circulating cells(macrophages and platelets) (hCD59$^{ICAM-2+/-}$) attenuated AAA progression (Wu et al., 2010), these results suggest a protective role of CD59 in AAA development. Staining of the aneurysm sections with anti–C9-specific antibodies revealed that mCd59ab$^{-/-}$/ApoE$^{-/-}$ mice had significantly more extensive deposits of C9 than ApoE$^{-/-}$ mice and that ApoE$^{-/-}$ mice have significantly more deposits of C9 than hCD59$^{ICAM-2+/-}$/ApoE$^{-/-}$mice. The fact that deposition of MAC in the AAA Lesions correlated with the severity of AAA strongly supports a pathogenic role of MAC in the development of AAA (Wu et al., 2010).

Macrophage plays a critical role in the development of aorta aneurysms. Macrophages are the primary source of MMP-9 production in human and mouse AAA (Longo et al., 2002; Thompson et al., 1995). Consistent with the pathogenic role of MMPs, AAA aortic extracts from mCd59ab$^{-/-}$/ApoE$^{-/-}$ mice exhibited significantly higher MMP2 and MMP9 activities, whereas extracts from hCD59$^{ICAM-2+/-}$/ApoE$^{-/-}$ mice showed lower activities than ApoE$^{-/-}$ mice. Meanwhile, in the AAA lesions of mCd59ab$^{-/-}$/ApoE$^{-/-}$ mice, the macrophage content is significantly increased, which is consistent with higher levels of MMP2 and MMP9 and the severity of AAA in this model (Wu et al., 2010). Furthermore, in vitro study demonstrated that sublytic MAC treatment in mouse endothelial, macrophage, and smooth muscle cells (SMC) increased MMP2 and MMP9 activities (Wu et al., 2010). Twelve hours after MAC treatment on these cells, activities of MMP2 or MMP9 from the cell extracts significantly increased. Further studies demonstrate that MAC upregulates MMP2 and MMP9 activities through AP-1 and NF-κB signaling pathways. Western blot assay revealed significantly increased phosphorylation of c-Jun, c-Fos, IKK-a/b and p65 in lesions of mCd59ab$^{-/-}$/ApoE$^{-/-}$ mice, whereas decreased phosphorylation in hCD59$^{ICAM-2-/-}$/ApoE$^{-/-}$. Firefly luciferase reporter gene assay and RNA interference assay confirmed that MAC-activated c-Jun and NF-κB signaling pathways participate in the upregulation of MMP2 and MMP9, which may in turn contribute to the pathogenesis of AAA in Ang-II-induced AAA model.

It was previously demonstrated that MAC induced more severe endothelial dysfunction in mCd59ab$^{-/-}$/ApoE$^{-/-}$ mice than in ApoE$^{-/-}$, which contributes to atherogenesis (Wu et al., 2009). MAC also mediates endothelial cell apoptosis in vitro. MAC insertion into endothelial and other cell membranes releases an array of growth factors and cytokoines, which may participate in the development of aneurysms.
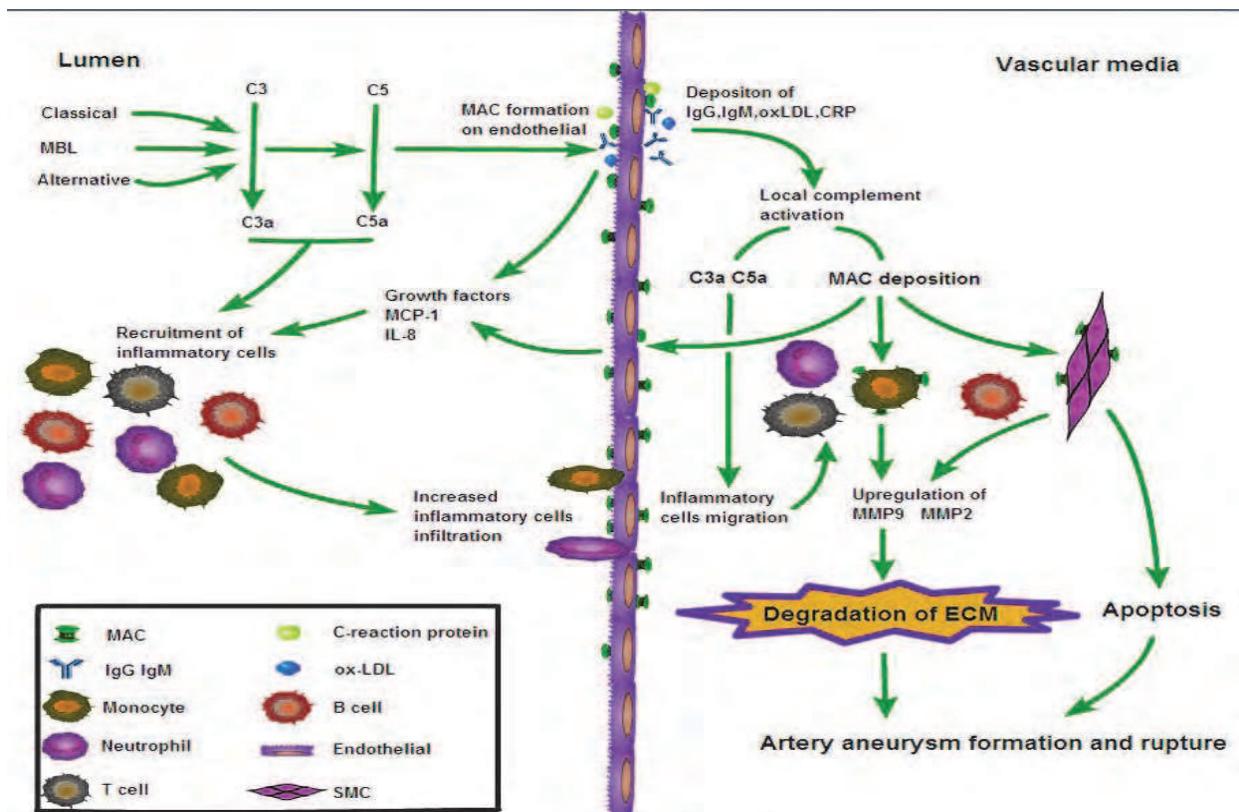

Fig. 1. Potential roles of complement in the pathogenesis of artery aneurysms
MBL: Mannose Binding lection pathway, oxLDL: Oxidized low density lipoprotein, CRP:
ECM: extracellular matrix and MAC: Membrane attack complex.

Furthermore, the supernatant obtained from MAC-treated endothelial cells triggers the migration of both MAC-treated and non–MAC-treated macrophage in vitro. The increase in macrophage migration may result from the release of growth factors and cytokines induced by sublytic MAC assembly in endothelial cells. These findings suggest that MAC may promote AAA development through different target cells or signal pathways. In Ang-II induced AAA model, increased MMP expression in the aorta in AAA could be caused by increased macrophage infiltration, upregulation by increased MAC tissue levels, or some combination of these two mechanisms.

Our study strongly supports the hypothesis that MAC may accelerate the initiation and development of AAA through mediation of endothelial dysfunction, attraction and activation of macrophages, which lead to the secretion of MMP2 and MMP9 that destroy the wall of blood vessels and thereby form aneurysm (Fig. 1). Taken together, these results shed light on the important pathogenic role of MAC in aneurysms, point towards the molecular mechanism of MAC-activated signaling pathways in aneurysm, and suggest inhibition of MAC may provide a novel approach for the treatment/prevention of aneurysms.

6. Conclusion

In this review we summarized an increase in clinical and experimental evidence on the potential role of complement system in aortic aneurysms. The role of complement and MAC in artery aneurysms has only been suggested in human studies and has not been extensively studied in experimental models. Complement activation in the circulation has been identified in the course of the formation and rupture of artery aneurysms. Complement and MAC extensively deposit in aneurysm walls and more in rupture aneurysms than unruptured aneursyms. Complement also plays a critical role in the pathogenesis of reperfusion-ischemic injury after aneurysm repair. Experimental evidence indicates that C3a and C5a play a critical role in the development of elastase-induced AAA, CD59 plays a critical protective role, and MAC plays a critical pathogenic role in the development of AAA. Together, these finding lead us to postulate the following hypothesis that 1) after complement is activated by one or three complement activation pathways in the circulation, the MAC, a terminal complement activation product, mediates endothelial dysfunction in the artery wall. This process will lead to the migration of inflammatory cells such as macrophage, the promotion of the interaction with the damaged endothelial cells, and deposition of activated complement bioproducts such as C3a and C5a and MAC, and complement activators such as immunoglobins, CRP and OxLDL in the artery wall; 2) the deposition of immuneglobin and CRP, OxLDL locally activates the classical complement activation pathways; 3) complement activation byproducts such as C3a and C5a and MAC amplify the inflammatory process in the artery wall through the release of inflammatory mediators and the attraction of more inflammatory cells to the artery wall; 4) these inflammatory process mediate the release of MMP2 and MMP9, which will degrade the elastic lamellae and extracellular matrix and damage the smooth muscle cells, finally leading to artery wall weakening and the formation of aneurysm or even aneurysm rupture (Fig. 1).

Although the emerging evidence supports the role of complement in the pathogenesis of artery, there are still a number of questions that remain to be further studied. For example, the molecular and cellular mechanisms of C3a, C5a, and MAC, and the relative role of complement activation pathways in the pathogenesis of artery aneurysms still require further investigation with these different animal models. Whether the early complement components play a role in the pathogenesis of aneurysms has not been studied so far. Whether the restriction of complement activation and MAC formation serves as a novel approach for the treatment/prevention of aneurysm also warrants future studies.

7. Acknowledgment

8. References

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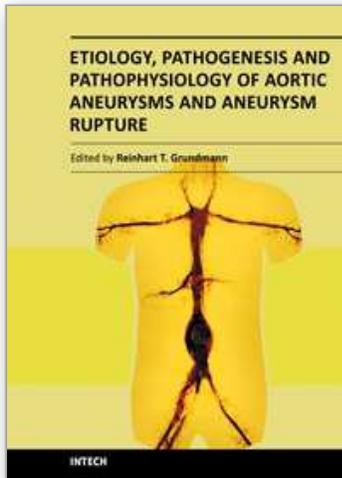
Etiology, Pathogenesis and Pathophysiology of Aortic Aneurysms and Aneurysm Rupture

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This book considers mainly etiology, pathogenesis, and pathophysiology of aortic aneurysms (AA) and aneurysm rupture and addresses anyone engaged in treatment and prevention of AA. Multiple factors are implicated in AA pathogenesis, and are outlined here in detail by a team of specialist researchers. Initial pathological events in AA involve recruitment and infiltration of leukocytes into the aortic adventitia and media, which are associated with the production of inflammatory cytokines, chemokine, and reactive oxygen species. AA development is characterized by elastin fragmentation. As the aorta dilates due to loss of elastin and attenuation of the media, the arterial wall thickens as a result of remodeling. Collagen synthesis increases during the early stages of aneurysm formation, suggesting a repair process, but resulting in a less distensible vessel. Proteases identified in excess in AA and other aortic diseases include matrix metalloproteinases (MMPs), cathepsins, chymase and others. The elucidation of these issues will identify new targets for prophylactic and therapeutic intervention.

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