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Pathogenesis of abdominal aortic aneurysm – the role of inflammation and proteolysis

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ABSTRACT

Clinical studies show that the morbidity rate for abdominal aortic aneurysms (AAAs) is high, especially among older people. A lack of early diagnosis carries a high risk of fatality. Abdominal aortic aneurysm formation is connected to, among others, inflammatory mediators, proteolytic degradation of the extracellular matrix and genetic predispositions. Additionally, a crucial part of this process is played by the presence of intraluminal thrombus, which participates in the inflammatory reactions and proteolysis contributing to the degradation of the wall's building elements. Intraluminal thrombus and inflammatory cells' which infiltrate the vessel wall characterize the pathogenesis of AAA. The dominant population of cells is lymphocytes T and B, neutrophils, monocytes/macrophages, natural killer (NK) cells, as well as mast cells, which produce different inflammatory factors and mediators which contribute to collagen, elastin and smooth muscle cell degradation in the aortic wall. The intensified inflammatory process may lead to increased proteolytic enzyme activity that is necessary for the progression and rupture of the aneurysm. In the presented paper, we show the participation of inflammatory factors in the pathogenesis of AAA and review chosen mediators of inflammation and proteolysis. A better understanding of the immunological mechanisms in the pathogenesis of AAA may help in modulation, innovation, and improvements in methods of treatment.

Keywords: abdominal aortic aneurysm; inflammation; cytokine; interleukin-1β; interleukin-6; metalloproteinases; neutrophil gelatinase-associated lipocalin.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality and morbidity in high-income countries. A relatively common vascular disorder is abdominal aortic aneurysm (AAA) – a permanent dilatation of the aorta that is formed due to a multifactorial pathological process. Most AAAs are located below the orifices of the renal artery. This segment of the aorta has a unique histological build, containing more collagen fibers and less elastic fibers [1]. The Association of International Vascular Surgeons points out that AAA is a focal dilation 50% greater than the average diameter, and depends on sex, age, and body weight. However, another equally standard definition describes AAA as a local widening of aorta to more than or equal to 30 mm [2].

Abdominal aortic aneurysm morbidity is high. The disease predominates in older men, and the risk of aneurysm occurring increases by about 6% with every decade of life. Certain risk factors are significantly associated with AAA formation including tobacco smoking, hypertension, coronary artery disease, and a family history of AAA [3]. Smoking is the strongest predictor of AAA, along with age and gender. Moreover, some data demonstrate that lifestyle, independently from other risk factors, can influence the formation of AAA, and a BMI higher than 25 kg/m2 increases the risk of AAA. Several studies have demonstrated that elevated plasma homocysteine concentration may be a potentially modifiable risk factor for AAA. However, the role of homocysteine levels in predicting AAA progression is controversial [1, 3, 4]. Moreover, AAA occurrence was linked to infections caused by microorganisms and autoimmune diseases [4]. An AAA is a degenerative disease characterized by adverse remodelling of the aortic wall, including extracellular matrix (ECM) degradation, loss of elastin and collagen fibers, reduction in the thickness of the middle aortic wall, loss of smooth muscle cells (SMC) and neovascularization [1, 4]. As a result, the wall of the aorta becomes weaker, thinner, and less prone to stretching which leads to its deformation under the influence of the pressure of flowing blood. Rupture is a dangerous complication of AAA because it can cause life-threatening bleeding that carries a high risk of fatality [1].

Most AAAs are characterized by the presence of intraluminal thrombus (ILT). It has been shown that its presence might be connected to an increased degradation of elastin, weakening of the SMC, and a high level of inflammatory factors in the aortic wall [5]. It was demonstrated that active processes of coagulation and fibrinolysis take place within the ILT. Additionally, ILT participates in inflammatory reactions and proteolysis processes. Factors released from ILT may be transported to the aortic wall which intensifies the aneurysm's growth. Moreover, it was observed that there are several inflammatory cell types in the ILT, especially neutrophils (probably due to ILTs high affinity with fibronectin) which are located in the ECM. The presence of leukocytes is conducive to the development of a pro-inflammatory environment. Intraluminal thrombus indirectly exposes the aortic wall to the degradative effect of cytokines or reactive oxygen species (ROS) by participating in the activation of platelets, macrophages, and neutrophils circulating in blood [6].

Aneurysms are often asymptomatic and are detected through ultrasonography, computed tomography, or magnetic resonance imaging, usually performed for other purposes [7]. At present, there is a lack of reliable pharmacotherapy. Endovascular aortic repair is becoming the preferred method to treat patients who have an AAA [8]. Surgical intervention is used in the case of aneurysms with a large diameter which is increasing quickly. As this surgery carries a high risk of complications, including fatality, the main emphasis is put on prevention. The risk factors predisposing to AAA development are regularly researched and include inflammatory mediators that could indicate which aneurysms are at risk of rupture. A better understanding and knowledge of the pathogenesis of aneurysms may lead to shaping a pharmacological treatment that could decelerate the growth of aortic diameter and suppress the process of AAA rupture. Additionally, developing optimal and individualized criteria for qualifying for elective surgery would become possible through the identification of aneurysms liable to rupture.

The arterial wall

The arterial wall is composed of 3 distinct layers, which vary depending on the type of artery. The 1st layer of the aortic wall, beginning from the vessel lumen, is composed of a layer of endothelial cells and, lying underneath it, the basement membrane. The tunica media is built of SMC, collagen fibers type I and III, and many elastic fibers. Tunica adventitia is located on the outermost part of the aortic wall. It is composed of fibroblasts, collagen fibers, and blood vessels (vasa vasorum) [9]. In AAA pathogenesis, a significant role is played by deterioration processes which may relate to all layers of the arterial wall, especially in the layer of the endothelium [10]. The endothelium is the 1st physical boundary of the blood vessel wall. Under the influence of sheer stress inside the vessel, including from flowing blood, the cells of the endothelium release humoral factors which then influence the SMC and adventitia. The endothelium may secrete nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor, all of which affect aortic tension [11]. Dysfunction in the endothelium may lead to the activation of blood cells and infiltration of the aortic wall. This is largely because of the increased expression of adhesive particles, vascular cell adhesion molecule 1, intercellular adhesion molecule 1, chemotaxis, inflammatory cytokines, ROS production, and endothelins [12]. Dysfunction of the endothelium may lead to the progression of inflammation within the aortic wall and disturbance of homeostasis; therefore, it is probably key to the occurrence of diseases such as AAA.

Inflammatory and proteolytic processes in the pathogenesis of abdominal aortic aneurysm

The AAA may develop due to injury, severe and chronic infections, inflammatory vascular diseases, or hereditary connective tissue disorder; however, the cause is mostly a result of nonspecific processes which we do not fully understand. Pathogenic processes that have been connected to the formation of AAAs are, among other things, proteolytic degradation of the ECM of the medial layer of the aortic wall, the gradual appearance of inflammatory cells, biochemical tension of the wall, presence of ILT and genetic predispositions. These mechanisms are connected and participate in the process of aortic wall degradation. The consequence of these processes is a reduction of aortic wall thickness, which finally leads to the widening of its diameter and eventually rupture [10].

The presence of a chronic inflammatory process in the AAA wall was indicated [13, 14]. However, the factors that initiate this process are not fully known. In the histological preparation of tissues collected from AAA patients, the infiltration of inflammatory cells into all layers of the aorta can be observed [7, 15]. The presence of B and T-lymphocytes (mainly Th2), neutrophils, monocytes/macrophages, plasma cells, natural killer cells (NK), mast cells, and antigen of tissue compatibility human leukocyte antigens (DR+) have been reported in these tissues. These cells may penetrate through a thrombus and into all layers of the aneurysm wall [16]. Cumulating inflammatory cells release many factors of growth such as cytokines, chemokines, leukotrienes, prostaglandins, and immunoglobulins, and also lead to the migration and proliferation of myofibroblasts and SMC, and as such, maintain the processes of the rebuild. It is suggested that many cytokines – interleukin-1 beta (IL-1β), IL-6, IL-8, interferon-gamma (IFN-γ) as well as tumor necrosis factor-alpha (TNF-α) may participate in AAA formation or correlate with AAA size [14].

Eliason et al. have shown that the recruitment of inflammatory cells is an essential factor in the early stages of AAA pathogenesis [17]. The inflammatory process may lead to an increased activity of proteolytic enzymes, which then destroy the ECM structure and, as a consequence, lead to the widening of the aorta [10]. The matrix metalloproteinase (MMP) and the tissue inhibitor of matrix metalloproteinase (TIMP) are chiefly responsible for this [18]. The proteinases with an increased concentration in the course of AAA are cysteine proteases (cathepsins D, K, L, S), serine proteases, i.e., tissue plasminogen activator, urokinase plasminogen activator and neutrophil elastase [14, 19]. Among the proteolytic enzymes with a documented function in the pathogenesis of AAA, the most crucial role is attributed to MMP which can be secreted by most cells in the aorta (endothelium cells, SMC, fibroblasts, and macrophages). An excessive activity of MMP leads to the destruction of elastin and collagen fibers (type I and II). Moreover, products of elastin degradation show chemotactic features that lead to the inflow of other inflammatory cells. This situation causes a peculiar effect of a vicious circle, contributing to maintaining inflammation in the altered aorta. Additionally, cytokines that are secreted by inflammatory cells present in the aorta wall cause mobilization of other leukocytes that penetrate the adventitia and adjacent tissues. Cytokines can destroy vessel walls directly or activate latent proteases which can regulate the expression of MMP, serine protease, and cathepsins [18, 20].

The neovascularization process that takes place in the adventitia may enhance inflammation. The number of new vessels, both blood and lymphatic, correlates with the degree

of severity of inflammation because they enable the influx of cells secreting additional enzymes and cytokines. Reeps et al. have proven that the vessels created due to neovascularization are the primary source of MMP and may considerably influence the instability of the walls in an aneurysm [21].

Oxidative stress is one of the most critical factors in AAA pathogenesis. During the inflammatory reaction, a disequilibrium between generating and removing ROS occurs. During AAA formation, ROS boost inflammation (thanks to the induction of cytokine synthesis and the infiltration of monocytes into the vessel wall), activate MMP and cause SMC apoptosis. Interestingly, a high level of superoxide anion was shown in aneurysmal tissue in comparison to a normal aorta. It was observed that ROS initiate type Th2 as an autoimmune response; however, antioxidants inhibit vessel inflammation [22, 23].

Factors that activate immunological response and promote the development of inflammatory reactions are still being researched. There are many views on the autoimmune reaction of AAA. One theory is that this is mainly connected to the presence of T-lymphocytes in the vessel wall and that the presence of antigens, such as cytomegalovirus or the oxidized particle of low density lipoprotein, may cause the inflammatory response in the aortic wall [24]. Lymphocyte activation may be mediated by autoantigens generated from vascular structural proteins, possibly through molecular mimicry. Another feature is the presence of immunoglobulin deposits in the pathologically changed aortic wall. It was shown that, when isolated from the tissues of the aneurysm, immunoglobulin G (IgG) behave in an immunoreactive way to regular vessel walls. There is also a hypothesis in which the participation of exogenous pathogens or autoantigen is listed as a factor. In some studies, the occurrence of AAAs was observed alongside *Treponema pallidum* infection. However, one of the most popular theories is that the development of AAAs is influenced by microorganisms, specifically, *Chlamydia pneumoniae*. It was shown that all the classes of antibodies that were examined were more common in AAA patients when compared to the healthy control group [25, 26].

Inflammatory cells present in abdominal aortic aneurysm tissues

As mentioned, inflammatory cell infiltration was observed in AAA tissues extracted intraoperatively, which is not seen in the normal aorta. Dominant cell populations in the walls and AAA thrombus are T-lymphocytes CD4+, T-lymphocytes CD8+, macrophages, and NK cells [27]. The presence of mast cells was mainly shown in the aneurysm wall with visible neovascularisation. However, neutrophils are observed above all in AAA ILT. Among all of the cells infiltrating aneurysm adventitia, the most common group is the sub-polarisation of T-lymphocytes helper (Th) [13].

T cells

The most common group of lymphocytes in AAA tissues are small T-lymphocytes CD4+, among which T helper cells (Th) subclass dominates. Because of the ability to produce different cytokines, we can divide the Th lymphocytes to lymphocytes Th1, Th2, Th17, and T-regulator cells (Treg). The direction of Th cell action depends on their differentiation into type Th1 or Th2, which occurs under the influence of IL-12 or IL-4. Similarly to macrophages M1 and M2, the equilibrium between particular types of Th lymphocytes is essential for proper regulation of the processes that occur in the vessel wall. Th1 lymphocytes are responsible for mediation in cell immunological response and mainly secrete IL-2, IFN-γ, TNF-α, and human granulocyte-macrophage colony-stimulating factor [27]. Releasing these cytokines is conducive to the activation of macrophages, whose presence was frequently observed in the tissues of the aneurysm [14]. Lymphocytes Th2 mediate in hormone type response, activating B-lymphocytes by secretion of IL-4 and IL-10. They also produce IL-5, IL-13, IL-21, and IL-25, which inhibit Th1 lymphocyte growth and, in consequence, cell response which simultaneously activates type M2 macrophages. Both types of cells can become pathogenic in the case of autoimmunization, and Th1 lymphocytes are considered to be one of the factors participating in autoimmune diseases [28, 29].

In the wall of the AAA, in comparison to a normal aorta, a high level of both IFN-γ (secreted by Th1 cells) and mRNA T-bet (the main transcription factor that promotes Th1 response) was shown [30]. Moreover, it was observed that both T CD4+ cells and INF-γ, derived from these cells, promoted the formation of AAAs in mice after induction with calcium chloride [31]. On the other hand, it is suggested that Th2 cells, and the cytokines produced by them, dominate in the aneurysm's tissues. The presence of Th2 and the cytokines secreted by them: IL-4, IL-5, and IL-10, was shown in the AAA wall but not in healthy aortic tissue. Apart from Th2 lymphocytes, there are also other types of cells, including B cells, NK cells, mast cells, basophils (IL-4, and IL-13), and endothelium cells or macrophages (IL-10) that produce Th2 type cytokines [32]. Cytokines produced by both Th1 and Th2 cells (e.g., IFN-γ or IL-4) can induce or inhibit the expression of MMP depending on the specific environment. For example, cytokines secreted by Th2 (e.g., IL-4 or IL-10) may inhibit the production of MMP-1, -2, and -9 by human macrophages, while IL-4 induces the expression of MMP-12 in mice macrophages. In patients with an AAA, a lower frequency in the appearance of Treg CD4+CD25+FOXP3+ lymphocytes in peripheral blood was observed in comparison to healthy people. However, Th17 influence on the pathogenesis of this disease is still unknown [33].

Macrophages

Early stages of AAA are associated with a predominant infiltration of macrophages. Macrophages accumulate in the 3 layers of the aneurysmal aorta; however, max. accumulation occurs in the adventitia and ILT. The influence of macrophages on the development of AAA seems to be significant because of their tendency to secrete numerous proteases, mainly MMP, cysteine proteases, e.g., cathepsins and serine proteases, plasmins, urokinases and neutrophil elastase [14]. Moreover, they are capable of generating large quantities of ROS which makes the aortic wall prone to damage [34]. Elastin-degradation products are

a chemotactic factor for macrophages. Several phenotypes of macrophages have been described in inflamed tissues, with a particular focus on "classically activated" M1 and "alternatively activated" M2 macrophages. Macrophages (M1 phenotype) have pro-inflammatory properties; they release significant amounts of cytokines, i.e., TNF-α, IL-1β, IL-6, IL-12, IL-23, chemokines, and ROS, promoting immunological response type Th1, whereas M2 type macrophages release anti-inflammatory cytokines (IL-10) stimulating type Th2 immune response [35, 36]. Equilibrium between macrophages type M1 and M2 is, therefore, indispensable for preventing intensified infiltration of inflammatory cells. The presence of M1 phenotype and IL-6, TNF-α, IL-1β, and IFN-γ was shown in aneurysm tissues and peripherally [37]. It was observed that M1 macrophages are considerably connected to AAA formation and ECM degradation, which then intensifies the infiltration of monocytes to the aortic wall. In contrast, the presence of the M2 phenotype protects against the development of AAA [38]. Furthermore, on the surface of monocytes present in the tissues of the AAA, the presence of surface markers, CD14, and CD16 was observed, which indicates the activation of M1 macrophages [39].

Neutrophils

the presence of neutrophils was found in ILT and in the adventitia walls of the AAA [13, 40]. Neutrophils contribute to AAA development by participating in oxidative stress and ILT formation. They also mediate in proteolytic destruction of the inner layer of the aorta and inflammatory process [41]. By interacting with many other cells, including platelets, they contribute to further recruitment of inflammatory cells [40]. Factors produced by neutrophils, such as MMP-9 or neutrophil gelatinase-associated lipocalin (NGAL) and myeloperoxidase (MPO), are presumed to be significant for the pathogenesis of AAA [42, 43]. In mice, in which neutropenia was induced, the occurrence of aneurysms decreased [17].

Selected mediators of inflammation in abdominal aortic aneurysm pathogenesis

Interleukin 1β

Interleukin 1β is an inflammatory cytokine produced by different types of cells, including monocytes and macrophages [44]. It was shown that it has a significant influence on the differentiation of Th17 lymphocytes, which can be connected to its inflammatory role in CVD [42]. It is also suggested that the presence of IL-1β promotes aneurysm progression, and an increased level of this cytokine was observed in the blood of patients with an AAA [33]. Interleukin 1β may stimulate MMP secretion, but it can also decrease the production of their inhibitors, which enhances further aortic wall degeneration. It is also suggested that IL-1β may influence NGAL expression and its capability to create a complex with MMP-9. It was shown that genetic and pharmacological attempts to inhibit IL-1β production protects mice from the development of aneurysm [45].

Interleukin 6

Interleukin 6 is mainly produced by monocytes and macrophages but can also be released by several other cells: T and B lymphocytes, eosinophils, fibroblasts, and endothelium cells. The main factor stimulating the secretion of this cytokine is IL-1. For years, an increased level of IL-6 has been observed in both the blood and aneurysm tissues of patients with an AAA [46, 47]. It was also found that the serum concentration of IL-1β and IL-6 might correlate with the size and growth rate of the AAA [48]. Interleukin 6 contributes to, among other things, activation and differentiation of lymphocytes, promotes inflammation, and influences the growth of proteolytic enzyme expression, which contributes to aortic wall degradation. A higher concentration of IL-1, IL-6, TNF-α, and IFN-γ was shown in patients with AAA compared to the control group and patients with atherosclerosis. Moreover, aneurysm itself can be a source of IL-6 in plasma, contributing to the exacerbation of inflammation in AAA patients [49, 50].

Interleukin 8

Interleukin 8, also known as CXCL 8, is an inflammatory chemokine whose sources are monocytes, macrophages, T-lymphocytes, fibroblasts, and endothelium cells [51]. An increased concentration of IL-8 and its receptors was reported in AAA tissue [52]. The concentration of CXCL8 in aneurysm tissue was higher than that in the aortas collected from arteriosclerosis patients [53]. Additionally, it was shown that the level of IL-8 in conditioned media, after incubating with human AAA tissue, was one of the highest among approx. 50 tested cytokines [54].

Moreover, the concentration of IL-8 may correlate with an aneurysm's diameter and progression of the disease. Interleukin 8 is an essential chemotactic factor for neutrophils and lymphocytes and favors their accumulation in the aneurysm wall. Furthermore, it influences the production of MMP by activating macrophages. It also has proangiogenic properties because it supports cell chemotaxis and proliferation of endothelium cells [53]. Progressive angiogenesis, observed in the inner layer of the aorta and accompanying lymphogenesis in the internal layer, may contribute to destructive processes in this part of the aneurysm. It was proved that large macrophages localized in both layers of the aortic wall demonstrated IL-8 expression and other cytokines that contribute to further cell recruitment and increase inflammation [55].

Tumor necrosis factor alpha

Tumor necrosis factor alpha is mainly produced by monocytes and macrophages and participates in the activation of B and T lymphocytes, NK cells and lymphokine-activated killer cells. Moreover, it performs an activating and chemotactic function for monocytes and neutrophils, and also increases the cytotoxicity of phagocytes. It is suggested that TNF-α influences the formation of the AAA [47]. It was shown that TNF-α concentration is higher in AAA patients compared to those who are healthy and correlates with the progression of the disease. Additionally, it is reported that TNF-α probably participates in the early stages of aneurysm development, and as the disease

progresses, its concentration in the aortic wall decreases [56]. Furthermore, it was demonstrated that TNF-α might stimulate MMP-2 and MMP-9 secretion and that blocking TNF-α expression slows the process of the AAA forming in mice [57].

Metalloproteinases

Metalloproteinases are a group of zinc-dependent endopeptidases that include elastase and callogenesis which, in the natural environment, participate in aorta remodelling. They are produced as zymogens and, in this form, are secreted or remain connected to cell membranes. The results of many studies show that MMP, derived from macrophages and smooth cell muscles, play a crucial role in the process of AAA formation [18]. It was observed that IL-1β, IL-6, IL-8, and TNF-α increase MMP expression and accelerate the process of ECM exchange. On the other hand, degradation of aortic wall fibers, developed under the influence of MMP performance, show chemotactic properties by attracting inflammatory cells. It is suggested that the most important role in the pathogenesis of AAA is not only played by MMP-2 and MMP-9 but also MMP-1 and MMP-12 (macrophage elastase) [58]. It was proved that MMP-2, MMP-9, and MMP-12 concentration/activity are higher in the aneurysm wall in comparison to that in a regular aortic wall, and may also correlate with the diameter and growth rate of the AAA [7, 14]. The activity of MMP in the aorta wall depends on the balance between activators and inhibitors. An incorrect ratio of MMP/TIMP may result in uncontrolled changes in the ECM, which may lead to the widening of the vessel and formation of AAA. This may lead to rupture in the future. It is suggested that MMP-2 is connected to the initial stages of the disease and influences the speed of growth in the diameter of the aneurysm. The high concentration/activity of MMP-9 is positively related to aneurysm rupture. Furthermore, it was shown that MMP-9 concentration in plasma is lowered after surgical removal of the AAA [59].

Myeloperoxidase

Several studies have shown a positive association between plasma myeloperoxidase (MPO) and CVD [43, 60]. An elevated concentration of MPO was also observed in the plasma and aneurysm tissue of patients with AAA, however, the influence of MPO on the pathogenesis of AAA is still not clear. Myeloperoxidase released by activated polymorphonuclear leukocytes produce hypochlorous acid (HOCl) that reacts with a variety of biomolecules and is also a precursor of ROS. Myeloperoxidase-derived HOCl inactivates α1-antiprotease, and the tissue inhibitor of metalloproteinase-1, which may indirectly induce proteolytic activity and matrix degradation [40]. A lack of balance between oxidative substances and antioxidants may lead to a weakening of the aortic wall by activating inflammation and SMC apoptosis [23]. Myeloperoxidase-derived HOCl can also increase endothelial tissue factor, which may, in turn, promote thrombosis and promotes the formation of ILT. It is also suggested that MPO contributes to the dysfunction of endothelium by limiting the bioavailability of NO. Deficiency of NO limits the blood vessels ability to widen and favors migration and adhesion of inflammatory cells to the endothelium as well as enhancing aggregation of platelets. Moreover, MPO may increase apoptosis of endothelium cells and influence the activation of metalloproteinases which are responsible for ECM remodelling [43].

Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin is a protein that was detected in activated neutrophils and seemed to be a hopeful marker for AAA pathogenesis. However, it may originate from other sources including, among other things, macrophages, atherosclerotic plaques, and endothelium cells with an inflammatory phenotype. Neutrophil gelatinase-associated lipocalin expression is induced by numerous cytokines such as IL-1α, IL-1β, IL-2, IL-17, transforming growth factor-alpha or TNF-α, which had an increased concentration in AAA patients [61]. It was shown that the concentration of plasma NGAL is correlated to cardiovascular risk factors in patients with atherosclerosis. Moreover, it was reported that NGAL plasma concentration in AAA patients is increased and correlates with AAA growth. Neutrophil gelatinase-associated lipocalin may be released by the resident and circulating leucocytes of AAA patients. Besides, cells within ILT may produce neutrophil activators like MPO or plasmin-antiplasmin complexes, and D-dimers. These activators provoke the chemotaxis of neutrophils, which are the primary source of NGAL [61].

At present, most studies concentrate on showing the connection between NGAL and MMP-9. Forming the NGAL/MMP-9 complex protects metalloproteinase from proteolytic degradation and enhances its enzymatic activities [20]. The intensified activity of MMP leads to the destruction of the vessel wall, which is a characteristic picture of histopathological changes in the course of AAA. Additionally, it was shown that NGAL and MMP-9 concentration was significantly higher in the plasma of patients who had an interruption to the continuity of the aneurysm wall [61].

SUMMARY

An AAA is a disease with a complex multifactorial pathogenesis. A number of studies suggest the potential role of inflammatory cells in the formation of AAAs. The precise cause of inflammatory cell mobilization in the AAA pathogenesis is not yet fully known. It is also still not known whether the infiltration of inflammatory cells is the cause of, or only a reaction, to the AAA. A microenvironment created by infiltrating inflammatory cells that mediate the production of proteases may underlie aneurysm progression and, consequently, rupture. Using anti-inflammatory medicines and antibiotics succeeded in slowing down the growth of the aneurysm both in animal models and in humans which proves the considerable participation of immune response to the AAA pathogenesis. Moreover, the development of new anti-inflammatory therapies, as well as additional technological improvements, may improve the stratification and management of patients with AAA.

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