Acta Cardiol Sin 2023;39:675–686
Review Article
doi: 10.6515/ACS.202309_39(5).20230531A

The Role of Immune Mechanisms in Abdominal Aortic Aneurysm: Could It be a Promising Therapeutic Strategy?

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Abdominal aortic aneurysm (AAA) is an enlargement of the aorta greater than 50% in diameter. Although up to 80% of cases result in mortality if the aneurysm ruptures, patients are often diagnosed too late, as most cases are asymptomatic. The current treatment for AAA is still surgery as there are currently no effective drug treatments. Knowledge of the pathophysiological mechanisms is essential for the development of new preventive and therapeutic approaches. However, the molecular mechanisms are complex and remain unclear. Apoptosis of vascular smooth muscle cells, the major cellular component of the aorta, and degeneration of the extracellular matrix, the skeleton of the aortic wall, are hallmarks of AAA pathology. Inflammation, mainly through macrophage cells, has been recognized as a central factor in the development of AAA. Macrophage cells also orchestrate other pathways and immune cells involved in this process. Macrophages do not exist as pure populations at aneurysm sites. M1 macrophages are pro-inflammatory and weaken the aortic wall during AAA development. M2 macrophages, in contrast, are involved in anti-inflammatory reactions and aorta tissue repair. The balancing effect on AAA progression makes M1/M2 macrophages therapeutic targets to control inflammation and destruction of the aortic wall. An early diagnosis is also important to allow for early interventions.
This review article, based on the available data, aims to evaluate the role of an immunotherapeutic approach in controlling AAA development by briefly discussing the immunological mechanisms.

Key Words: Abdominal aortic aneurysm (AAA) • Immune mechanisms • Immunotherapy • Macrophage polarization • M1/M2 macrophages

INTRODUCTION

Abdominal aortic aneurysms (AAA) are persistent focal dilatation ≥ 3.0 cm in the infrarenal region resulting from weakening of the abdominal aortic wall.[1] While most patients with AAA usually do not have symptoms, the aneurysm is fatal in up to 80% of cases once the aneurysm ruptures. Risk factor modeling has shown that there may be more than one million people with AAA, and about 25,000 deaths due to aneurysm rupture are reported each year in the United States.[2] Although potential agents such as nanoparticles loaded with antihypertensive drugs and statins have been proposed, so far no pharmacological treatment has been used to prevent the formation of AAA or cure the disease.[3] For over 40 years, the main modalities of aortic aneurysm treatment have been open surgical repair and replacement of the aneurysmal aortic segment with a synthetic graft. In the last decade, endovascular aneurysm repair (EVAR) has rapidly become the main treatment option due to a significant reduction in mortality and length of hospital stay compared to open surgical repair.[4] However, it remains a major challenge in longer

Received: January 12, 2023 Accepted: May 31, 2023
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Abbreviations

AAA	Abdominal aortic aneurysms
Ang II	Angiotensin II
CSTB	Cystatin-B
DC	Dendritic cells
ECM	Extracellular matrix
EVAR	Endovascular aneurysm repair
GDF-15	Growth/differentiation factor-15
ICAM-1	Intercellular adhesion molecule-1
IFN-δ	Interferon-δ
IL	Interleukin
ILC	Innate lymphoid cells
INKT	Invariant natural killer T cell
M1 macrophage	Classically activated macrophage
M2 macrophage	Alternatively activated macrophages
MMP	Matrix metalloproteinase
mPGES-1	Microsomal prostaglandin E synthase-1
MPO	Myeloperoxidase
NADPH	Nicotinamide adenine dinucleotide phosphate
NET	Neutrophil extracellular trap
NK	Natural killer cell
NO	Nitric oxide
PD-1/PDL-1	Programmed cell death protein-1/death protein ligand-1
PECAM-1	Platelet endothelial cell adhesion molecule-1
PGE2	Prostaglandin E2
PVAT	Perivascular adipose tissue
ROS	Reactive oxygen substances
SMC	Smooth muscle cells
TGF-β1	Transforming growth factor beta 1
TNF-α	Tumor necrosing factor-α
VCAM-1	Vascular cell adhesion molecule-1
VSMC	Vascular smooth muscle cell

follow-up due to the need for additional interventions associated with the risk of late rupture and some new complications.[5]

In the case of an aneurysm without collaterals, blood flow through the aneurysm sac creates vortices. As this variation in blood flow progresses, the vortices within the sac become stronger and reach the aneurysm outlet, resulting in induced stress on the arterial wall; eventually, aortic rupture and hemorrhage occur, which is usually sudden and fatal.[6] The etiology of AAA is multifactorial. Smoking, male sex, advanced age (> 60 years) and family history are among the most important risk factors.[3] It is important to understand the mechanisms associated with aneurysm formation and progression to select the best treatment to prevent progression and AAA rupture. The pathophysiological mechanisms underlying the formation and progression of AAA are multifaceted and include a large number of signal cascades and risk factors.[2] Therefore, despite significant advances, it is not possible to identify a single mechanism contributing to this pathology.[7] However, there is general consensus that inflammation of the aortic wall, reduction of medial smooth muscle cells (SMCs), and degradation of the extracellular matrix (ECM) are the main molecular processes.[3,7] It has recently become clear that chronic inflammation caused by the infiltration and activation of various immune cells is the main driver of AAA.[7] The fundamental components involved in the pathophysiology of AAA are presented in Table 1.

One of the potential therapeutic approaches is to address risk factors, such as the use of antihypertensive and antiplatelet therapeutics. As the roles of pathways, molecules, and mechanisms that contribute to the formation and progression of AAA are understood, the uncertainties in identifying potentially successful drugs will quickly be resolved. Considering the three main mechanisms thought to be involved in AAA formation and progression, potential therapeutic agents can be roughly classified into three overarching groups: regulation of inflammation, regulation of SMCs, and remodeling of the ECM (Figure 1).[1]

In addition to its use as an antibiotic, doxycycline is an MMP inhibitor and shows this effect at doses below its antimicrobial activity. Consequently, it alters AAA growth by reducing ECM degradation.[8] Cyclosporine A is an immunomodulator which acts through transforming growth factor beta 1 (TGF-β1) and calcineurin. Studies have shown that cyclosporine A treatment plays a role in ECM remodeling and cell apoptosis, and decreases matrix metallopeptidase 9 (MMP-9) secretion.[9] Microsomal prostaglandin E synthase-1 (mPGES-1) plays a role in the synthesis of prostaglandin E2 (PGE2) and contributes to the formation of AngII-induced AAAs. It has been suggested that inhibiting PGE2 formation with an mPGES-1 inhibitor would be a good drug target for the treatment of AAA.[10]

Inflammation is one of the main targets in AAA treat-

Table 1. Fundamental components involved in the pathophysiology of abdominal aortic aneurysm[2,3]

Cellular components	Molecular components	Risk factors
SMCs, endothelial cells, neutrophils, monocytes, macrophages, lymphocytes, adipocytes, mast cells, platelets	ECM (mainly collagen, elastin), MMPs (especially MMP-2 and 9), Ang II, cytokines (inflammatory: IFN-δ, IL-2, IL-6 and TNF-α; anti-inflammatory: IL-4, IL-5, TGF-β and IL-10), chemokines, ROS	Smoking, male gender, advanced age (> 60 years), family history

Ang II, angiotensin II; ECM, extracellular matrix; IFN-δ, interferon-δ; IL, interleukin; MMPs, matrix metalloproteinase; ROS, reactive oxygen substances; SMCs, smooth muscle cells; TGF, transforming growth factor; TNF, tumor necrosing factor.

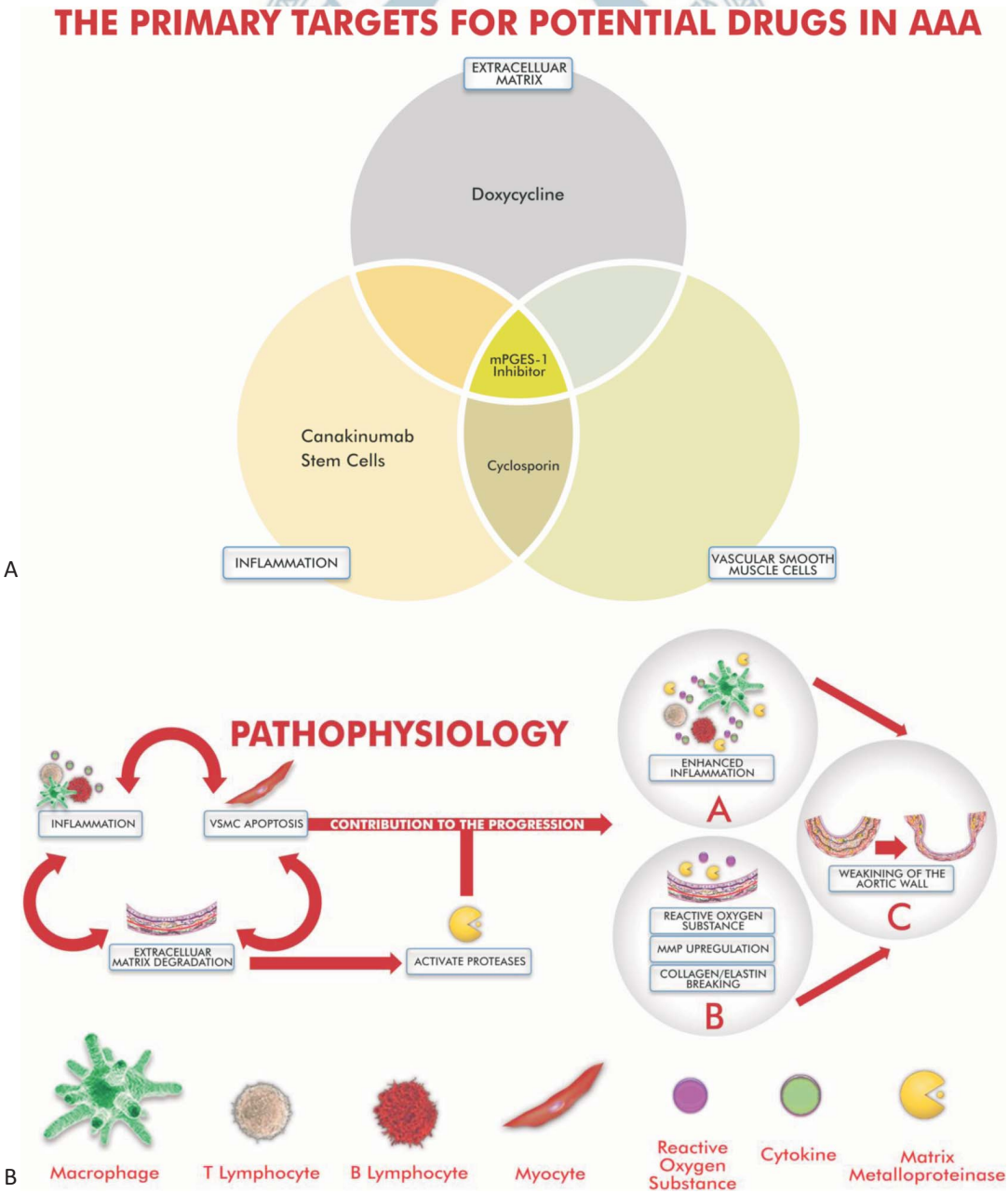


Figure 1. *General categorization of potential drugs under investigation for the treatment of abdominal aortic aneurysms (AAA). (A) In the etiology of AAA, pro-inflammatory factors are the main drivers of vascular smooth muscle cell (VSMC) apoptosis and extracellular matrix (ECM) degradation, two other hallmarks. Subsequently, these factors affect downstream signalers such as upregulation of matrix metalloproteinase (MMP) and infiltration of immune cells in the abdominal aortic wall. (B) The primary targets of these potential drugs are through one or more of these mechanisms of action. (Adapted from ref. 1, with permission of Weaver et al.). mPGES-1, microsomal prostaglandin E synthase-1.*

ment, and corticosteroids or immunosuppressive therapies may play a role. Canakinumab (human anti-IL-1β monoclonal antibody) and stem cell therapy (mesenchymal stem cells) arrest the progression of AAA by modulating inflammation, and are promising future medical treatments of AAA in humans.[11,12] In a study on C57/ BL6 mice, quercetin, a natural flavonoid with anti-inflammatory properties, was shown to inhibit AAA development by blocking the inflammatory response and inhibiting proteases involved in the pathogenesis of the disease.[13]

Family history is an important risk factor for AAA. Genome-wide association studies investigating AAA pathogenesis have identified nine genetic risk alleles for AAA, including single nucleotide polymorphisms in the genes for the low-density lipoprotein receptor and interleukin 6 (IL-6) receptor.[14] Lipid-lowering therapy has been suggested to reduce the risk of AAA rupture,[15] and IL-6 receptor blocking agents are already used in clinical practice.[14]

This review article aims to evaluate the role of an immunotherapeutic approach to control AAA development in light of recent data by briefly discussing the immunological mechanisms.

SMOOTH MUSCLE CELLS AND EXTRACELLULAR MATRIX IN AAA

It is important to consider potential differences and multifactorial mechanisms in the initiation, progression and rupture stages of aneurysm, since the pathogenesis of AAA is a multifactorial and multistage process.[3] SMCs are the main cellular component of the aorta. Apoptosis of vascular smooth muscle cells and ECM degeneration have long been identified as the hallmark of AAA pathology.[2] The ECM is the skeleton of the aortic wall, and it is also responsible for its maintenance and repair.[3] Deterioration of the ECM negatively affects the functioning of the aorta, and it predisposes to the formation and eventual rupture of AAA.[16] Matrix metalloproteinases (MMPs), mainly MMP-2 and 9, play an important role in the breakdown of proteins such as collagen and elastin, which form the basic framework of ECM.[17] MMP-2 is predominantly derived from SMCs and fibroblasts, while MMP-9 is predominantly derived from macrophages.[18]

INFLAMMATORY MICROENVIRONMENT IN AAA

The inflammatory process that occurs in the AAA wall is a key factor in the formation of aneurysms.[3] A variety of immune cells are found in the AAA aorta, of which macrophages and lymphocytes are the most prominent.[19] However, the composition and activation state of the immune cells that infiltrate the aortic wall during the development of AAA is dynamic and changes throughout the development of the disease. Early infiltration of myeloid cells (neutrophils, monocytes, macrophages, and dendritic cells) in the aortic wall suggests that these cells may contribute to the initial steps. The inflammatory process associated with any inducing event plays a diverse and important role in the progression of AAA.[20] This process is triggered by a number of factors such as angiotensin II (Ang II) and the microbiota. Ang II stimulates the mobilization of immune cells from the bone marrow and spleen through growth factor signaling pathways and cytokine-dependent mechanisms, while the microbiota can stimulate various metabolites and bacterial-derived products such as lipopolysaccharide and short-chain fatty acids.[21,22]

Perivascular adipose tissue (PVAT) can also contribute to inflammation in the aortic wall. When vascular damage begins, it can cause the appearance of adipocytes on the vessel wall due to hypoperfusion in the aortic wall, mainly due to arteriosclerosis of the adventitial vasa vasorum. These cells regulate immune cell accumulation in PVAT through the production of adipokines, cytokines, and chemokines. The recruitment of immune cells, particularly macrophages, around PVAT increases the levels of MMP-2 and MMP-9 and degrades the collagen fibers surrounding them. The resulting weakened vascular wall increases the susceptibility to AAA rupture.[23] Intraluminal thrombosis that is triggered in this process can increase the inflammatory process and further reduce the strength of the aortic wall.[19,23]

IMMUNE CELLS IN AAA

Neutrophils

Neutrophils are one of the most abundant immune effector cells and the first to respond to injury. Some studies have suggested that circulating neutrophils make

a significant contribution to the formation of AAA in the early stages.[24] Neutrophils release different types of granules containing various bioactive molecules such as myeloperoxidase (MPO), elastase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and MMPs. MMPs have been found to be highly abundant in AAA tissues.[25] Activated neutrophils also produce growth factors, cytokines, and proteases, as well as extracellular traps (NETs), which are network-like defense structures to trap foreign cells. NETs can have a variety of effects on the aortic wall. They promote inflammation by facilitating the activation of Th17 cells and macrophages that regulate the release of IL-1β, IL-18 and other proinflammatory cytokines.[26] Furthermore, NETs induce apoptosis of vascular smooth muscle cells (VSMCs), leading to fibrous cap thinning and eventual plaque rupture.[27]

Neutrophils play an important role in the inflammatory regulation of AAA, and interact with other cell types in AAA lesions. NETs also help build this interaction.[20,26]

Monocytes/macrophages

In animal models, inflammatory monocytes ($Ly6C^{high}$) have been shown to be highly associated with AAA, while anti-inflammatory monocytes ($Ly6C^{low}$) have been shown to have a potentially protective role.[28] These findings imply that circulating monocytes play an important role in AAA.

If the local environment undergoes inflammatory changes, circulating monocytes accumulate in aortic tissue by increasing the expression of cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), platelet endothelial cell adhesion molecule-1 (PECAM-1), and vascular cell adhesion molecule-1 (VCAM-1).[29,30] They differentiate into macrophages or dendritic cells. Macrophages involved in the pathogenesis of AAA may originate not only from circulating monocytes, but also from tissue-resident macrophages.[20,26] In response to different inflammatory stimuli, these monocytes differentiate into classically activated macrophages (M1 macrophages) or alternatively activated macrophages (M2 macrophages). This process is called macrophage polarization.[30]

M1 macrophages, which are inflammatory, are characterized by high expressions of pro-inflammatory mediators, including tumor necrosing factor (TNF)-α, IL-6, IL-12, IL-1β, chemokine (C-C motif) ligand-2 and nitric oxide (NO).[20,26] M1 macrophages regulate the recruitment and activation of other immune cells, as well as VSMC apoptosis.[3] The expression of these pro-inflammatory molecules is more prominent in the advanced stages of AAA. In addition, Ang II promotes macrophage activation.[31] However, M2 macrophages triggered by IL-4 and IL-13 typically secrete anti-inflammatory cytokines, mainly IL-10 and transforming growth factor (TGF)-β and contribute to tissue repair.[30] M2 phenotype macrophages become more abundant in the late stages of AAA development, and this may represent a compensatory mechanism for the repair of tissue damage.[32]

In the pathogenesis of AAA, there are interactions between monocytes/macrophages and neutrophils. Early monocyte infiltration into the aortic wall and its differentiation into the inflammatory macrophage subset contribute to the destruction of the aortic wall by facilitating neutrophil recruitment. Neutrophils produce IL-6, which contributes to pro-inflammatory macrophage activation.[33]

Dendritic cells

Dendritic cells (DC) contribute not only to innate immunity through the secretion of pro-inflammatory cytokines such as TNF, IL-12 and other chemokines, but also to adaptive immunity that presents antigens to T cells.[33] Activation of the plasmacytoid subtype of DC has been observed in AAA. However, the role of DC in AAA and the mechanisms remain to be clarified.[20]

Lymphocytes

Lymphocytes consist of two main groups, T and B.[34] The number of B and T lymphocytes increases significantly in aneurysm tissues, and their density is negatively correlated with the content of collagen and elastin.[2] The T lymphocyte subset includes CD8+ (cytotoxic T cells) and CD4+ (helper T cells) T cells. CD4+ T cells can differentiate into Th1, Th2, Th17, Th22, and regulatory T (Treg) depending on environmental stimuli.[41] T lymphocytes are predominantly involved in the aneurysm initiation process, with the majority being CD4+ T cells.[2,26]

The effects of CD4+ T cells on AAA are related to the secretion of cytokines such as Th1 cytokines [interferon-δ (IFN-δ), IL-2 and TNF-α] and Th2 cytokines (IL-4, IL-5, IL-6 and IL-10). Some of these cytokines are involved in

macrophage activation, VSMC apoptosis, and direct destruction of aortic walls.[22] In AAA, both Th1 cytokines and Th2 cytokines are believed to have effects on aortic wall disruption, particularly due to their ability to induce VSMC apoptosis.[20] In one study, the Th1 cytokine profile was found to be predominant in patients with large AAA, and the Th2 response was found to be predominant in patients with small aneurysms.[35] CD8+ T cells have been found to be elevated in AAA walls and perivascular tissues, and IFN-δ released by CD8+ T cells has been shown to promote cell apoptosis and the accumulation of macrophages producing MMP.[34]

It should be noted that Treg cells secrete IL-10 and TGF-β. These anti-inflammatory cytokines inhibit or weaken the aneurysm formation process.[2] Treg cells regulate the effects of other subsets of T cells.[26] Furthermore, they suppress the recruitment of other inflammatory cells, mainly macrophages, and the expressions of pro-inflammatory molecules such as CCL2, IL-6, and ICAM-1.[20]

Th17 cells, the main source of IL-17, play a disease-promoting role in many inflammatory pathologies, and they have been implicated in AAA. By secreting IL-17, they mediate responses of immune cells such as neutrophil recruitment, which can increase oxidative stress in the aortic walls through the production of vascular superoxides.[20,26]

Other cells

Various immune cells, such as mast cells, natural killer cells (NK), innate lymphoid cells (ILC), and invariant natural killer T (iNKT) cells, are involved in the AAA process, with different functions such as interacting with each other and secreting or influencing certain molecules.[20,26,35]

Although lymphocyte cells are densely found in the adventitia layer of the aorta in patients with AAA, macrophages and mast cells can be found in both the adventitia and media layers of aortic tissue.[3]

IMMUNOTHERAPY IN AAA

Currently, no effective drug therapies are available to prevent aneurysm progression or rupture.[23] Current care is still mostly limited to surgery, which is usually performed in the late stages of the disease.[20]

Specific targets such as inflammatory cytokines and MMPs have been explored to control inflammation and destruction of the aortic wall for asymptomatic AAA.[26] Experimental studies have demonstrated that the induction of IL-10 reduced inflammation and AAA diameter by promoting SMC proliferation and increasing Treg accumulation in aortic tissue.[36] Similarly, TGF-β has been shown to play a protective role in AAA through various mechanisms, such as reducing macrophage accumulation in the aortic wall and inhibiting degradation of the ECM.[37] MMP-2 and MMP-9 are the two most critical players in AAA, and attempts to block their specific functions are indicated as an appropriate approach.[18] For AAA, these new targeted applications may serve as strategies for detection in the early stages and treatment in the advanced stages.

Unfortunately, cytokines can cause off-target immune-related effects, especially in systemic applications, due to their pleiotropic nature (affecting multiple systems or multiple phenotypes).[38] Due to the multicellular origins of MMP-2 and MMP-9, it may be difficult to specifically block their functions. Furthermore, the available data are derived mostly from animal models or in vitro experiments, and as such they cannot fully mimic the pathogenesis of AAA in humans. Studies that combine preclinical mechanisms and clinical data are still needed.

Immunotherapies are not currently a recommended approach in the clinical treatment of AAA. However, as mentioned above, the mechanism of formation and the results obtained from several therapeutic studies suggest that immunotherapy can be considered as an important alternative to prevent the formation and progression of AAA.

Despite the multifactorial and multistage pathogenesis of AAA, we now know that chronic inflammation plays a central role.[3] Macrophages play a dominant and central role not only in the initiation of AAA, but also in its progression.[20] Macrophages do not exist as pure populations at aneurysm sites, and diversity and plasticity are two hallmarks of macrophages. M1 macrophages are pro-inflammatory, increase the inflammatory side of immunity, and damage the aortic wall. M2 macrophages, in contrast, are associated with anti-inflammatory reactions and tissue repair. Based on available data as sum-

marized in the Central Illustration, the opposing effects of M1 and M2 macrophages on AAA make them suitable for therapeutic applications to control inflammation and destruction of the aortic wall. This goal can be achieved by reducing the increase in the number of M1 macrophages in non-ruptured AAA regions by administering specific agents such as typical inflammatory cytokines (IL-1β, TNF-α, IL-6), chemokines (CCL2 and CCL3) or growth factor inhibitors.[28,32] Another possible approach is to rapidly polarize them towards the M2 phenotype by applying polarizing molecules such as IL-4, IL-10, TGFβ-1 and PGE2 (Table 2).[39]

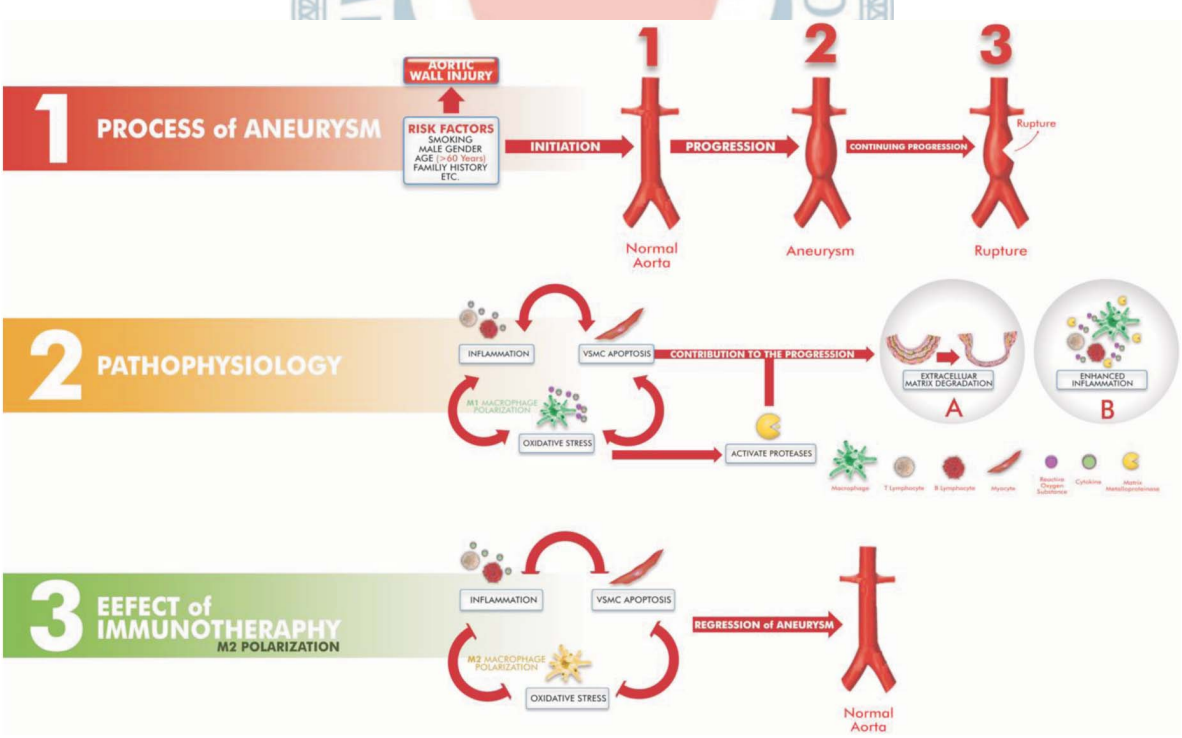
However, undesirable and uncontrollable systemic events may occur due to reducing or polarizing macrophage agents.[46] In this regard, many bioengineered materials, such as nanoparticles decorated with target ligands and loaded with polarizing agents, can make important contributions by enabling controlled and localized delivery of M2 macrophage polarizing agents.[47] A recent study demonstrated that after systemic administration, magnetic nanoparticles loaded with target ligands and M2-polarizing agents could be better localized to the AAA site by applying an external magnetic field (Figure 2A and B).[48]

ROLE OF IMMUNE CHECKPOINT MOLECULES IN AAA

Checkpoint molecules, co-stimulatory and co-inhibitory molecules are crucial in determining the outcome of antigen activation. Of these, co-inhibitory molecules inhibit the antigen presentation process of antigen presenting cells to T cells. The activation of co-inhibitor molecules is associated with a good prognosis in autoimmune diseases. Conversely, cancer patients are treated with antibodies/agents that block inhibitory pathways.[49] Vascular inflammation is known to play a critical role in the pathogenesis of AAA through T cell-mediated immune reactions. In this context, as shown in some experimental studies,[50,51] reducing excessive immune responses by promoting programmed cell death protein 1/death protein ligand 1 (PD-1/PD-L1) or cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4)/CD80-CD86 signaling pathways may be an attractive therapeutic target in preventing AAA.

POTENTIAL BIOMARKERS FOR AAA

AAA is mainly an asymptomatic disease. Current



Central Illustration. *Schematic representation of (1) development process from initiation to rupture, (2) pathophysiology and (3) immunotherapy of abdominal aortic aneurysm.*

Table 2. Some preclinical studies demonstrating the effect of macrophage polarization in the treatment of aortic aneurysm

Reference	Treatment/modality	Model	Inflammatory outcome	Clinical effect
Ashida et al.[40]	M2 macrophage	ApoE$^{-/-}$ mice	– Decreased M1/M2 ratio – Decreased expression levels of IL-1β, IL-6, TNF-α, MCP-1, MMP-9 – Increased IL-4 and IL-10	No difference in AA diameters
Moran et al.[41]	Everolimus	ApoE$^{-/-}$ mice	Reduced circulating CCR2 monocytes (inflammatory)	Protection against aortic dilatation and aneurysm formation
Yoshihara et al.[42]	Omega3 polyunsaturated fatty acids (EPA or DHA)	ApoE$^{-/-}$ mice	– Decreased M1/M2 ratio – Decreased expression levels of TNF-α, MCP-1, MMP-2 and 9, VCAM-1 – Increased Ym1 (anti-inflammatory)	Prevention of AAA development
Pope et al.[43]	D-series resolvins (RvD1 or RvD2)	C57/B6 mice	– Decreased M1/M2 ratio – Decreased expression levels of IL-1β, IL-6, MCP-1, MIF-1α – Increased IL-10	Prevention of AAA formation
Dale et al.[44]	EDPs	C57/B6 mice	– Increased M1/M2 ratio – Increased expression levels of TNF-α and IL-1β – Decreased Ym1	Promotion of aneurysm expansion
Yamawaki-Ogata et al.[45]	BM-MSC	ApoE$^{-/-}$ mice	– Inhibition of M1 infiltration and preservation of elastin construction – Decreased expression levels of IL-6, MCP-1 – Increased IL-10	Prevention of aneurysm expansion

AAA, abdominal aortic aneurysms; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; TNF, tumor necrosing factor; VCAM-1, vascular cell adhesion molecule-1.

guidelines recommend monitoring the diameter of the AAA under ultrasound at regular intervals.[52] Since no effective drug therapy has yet been developed to treat AAA, these patients are treated surgically.[3] AAA diameter is strongly associated with rupture risk and is used as a prognostic indicator for surgery. However, small aneurysms can sometimes rupture, and large aneurysms may not rupture for a long time.[53] Surveillance is also a monetary burden on health systems.[52] Therefore, alternative surveillance markers are of great importance in managing the disease. Unfortunately, there are currently no specific diagnostic, prognostic, or potential therapeutic target biomarkers for AAA. However, recent advances in research have suggested potential biomarkers, including markers associated with underlying risk factors/diseases.[52-54]

Memon et al.[52] evaluated the diagnostic and prognostic potential of 91 proteins associated with cardiovascular disease in plasma samples. They found a significant positive correlation between aortic diameter and levels of 21 proteins associated with proteolysis, oxidative stress, lipid metabolism, and inflammation. Of these proteins, the important were growth/differentiation factor-15 (GDF-15), cystatin-B (CSTB), urokinase plasminogen activator surface receptor, retinoic acid receptor responding protein 2, myeloperoxidase (MPO), fatty acid binding protein adipocyte, and P-selectin. On the other hand, paraoxonase was found to be negatively correlated with aortic diameter. Among these biomarkers, the combination of GDF-15 and CSTB were found to have the best diagnostic potential, while MPO had the best prognostic value.

Amongst clinically applicable biomarkers, D-dimer, low density lipoprotein-cholesterol total cholesterol, apolipoprotein-B, and glycated hemoglobin were found to have the most significant associations with AAA growth rates in a review article by Nana et al.[55] On the other hand, high density lipoprotein-cholesterol has been shown to have a negative association and a protective role against AAA.[53]

A prominent feature of AAA is pathological remodeling of the aortic ECM. In this context, pathological ECM remodeling biomarkers related to MMP-12 activity have been identified.[53]

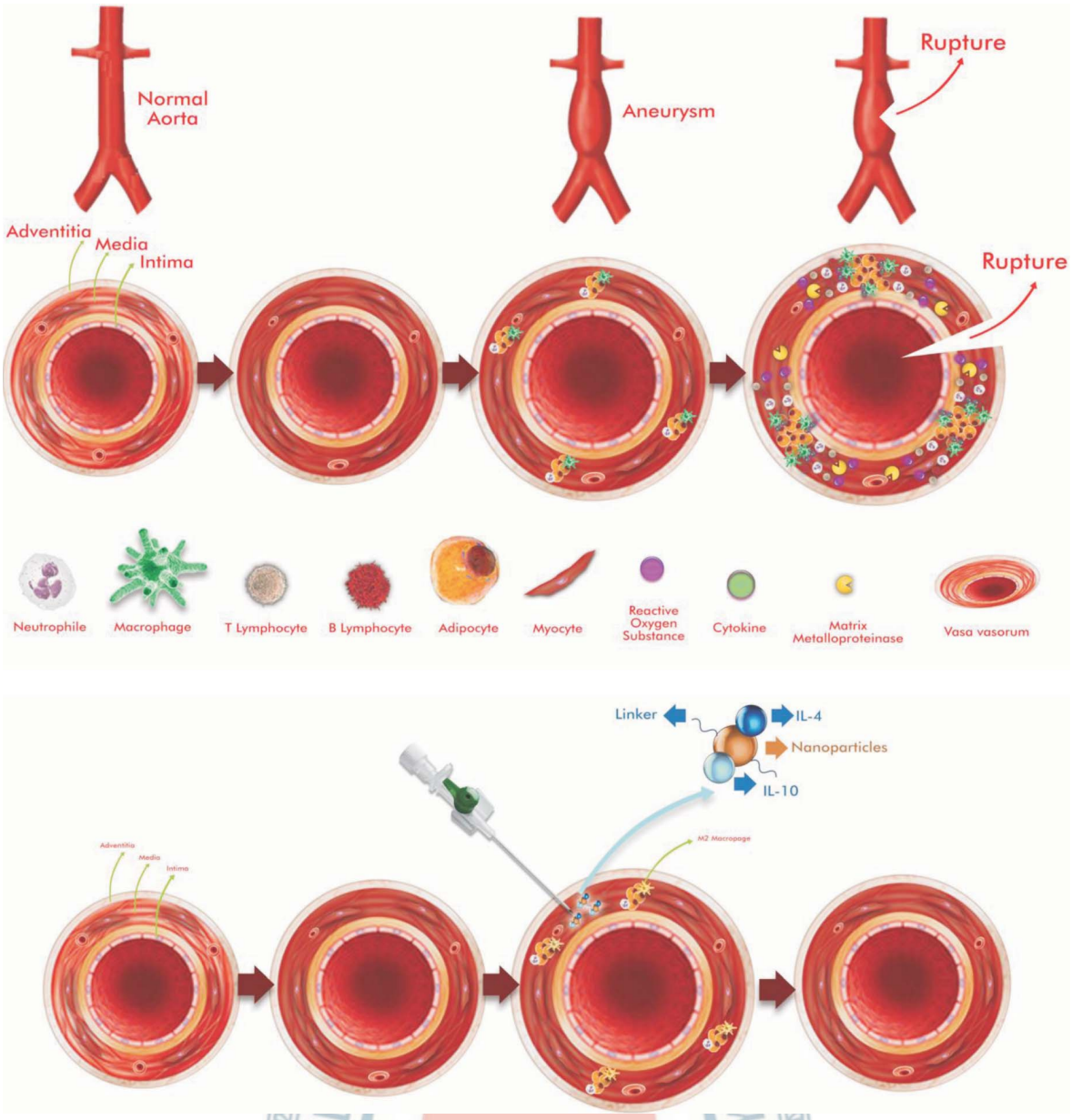


Figure 2. *Schematic illustration of abdominal aortic aneurysms (AAA) pathogenesis and its macrophage polarization therapy. (A) Pathophysiological stages of AAA from initiation to rupture. (B) Macrophage-polarizing immunotherapy. The localization model of cell-polarizing agents by loading them into nanoparticles with targeting ligands was represented. (Adapted from ref. 23, 47, 48; with permission of Kugo et al., Chen et al. and Furlani). ECM, extracellular matrix; MMPs, matrix metalloproteinase; PVAT, perivascular adipose tissue; ROS, reactive oxygen substances; SMCs, smooth muscle cells.*

The relationship between AAA and the underlying disease is an issue that requires further research. For example, smoking and hypertension are important risk factors for AAA. Both smoking and hypertension are associated with high MMP expressions, which can then disrupt the ECM, as in AAA. Similarly, hyperlipidemia, defined as abnormally high levels of any or all blood lipids (such as cholesterol or triglycerides), is also a risk factor for AAA.[56]

Mendelian randomization is a major area of interest in terms of AAA risk. This approach uses genetic alleles as an inherited marker of a risk factor of interest.[14] Early detection of carriers, such as individuals who inherit the gene mutation but do not express the clinical pheno-

type, may allow for individualized aortic surveillance with a recommendation to begin clinical and echocardiographic follow-up in the first decades of life. Genetic testing can also guide family screening by leading to the identification of other family members at risk.[57] Epigenetic factors such as non-coding RNAs and DNA methylation may have a strong contribution to the pathogenesis of AAA. Human epigenetic AAA research has focused specifically on identifying micro-RNAs such as miR-155 and miR-29b that are associated with human AAA.[14] Nana et al.[55] stated that, specifically, genomic DNA analysis of genetic polymorphisms showed an increased risk of aggressive growth relative to slow-growing AAA.

CONCLUSIONS

AAA is a life-threatening disease. The current treatment for AAA is still surgery. The molecular mechanisms of AAA development are complex. Apoptosis of VSMCs and ECM degeneration are hallmarks of AAA, and inflammation plays a central role in its development. The balance between M1 and M2 macrophages modulates the AAA process. This balance may make M1 and M2 macrophages promising therapeutic targets against the development of AAA.

LIMITATIONS OF THIS STUDY

This review article has some other limitations in addition to being a traditional review article. There are currently no immunotherapeutic or other pharmacological drugs in clinical use for the treatment of AAA. Molecular mechanisms are complex, multistage, and multifactorial and remain unclear. Although the immunotherapeutic strategies highlighted are promising, the data are based on early and mostly experimental-based studies.

ACKNOWLEDGEMENT

The authors thank Bilal Coban from Invamed RD Global (Ankara, Turkey) for drawing the figures.

DECLARATION OF CONFLICT OF INTEREST

The author declares that he has no conflicting financial interests or personal relationships that appear to affect the work reported in this article.

ETHICS APPROVAL STATEMENT

This manuscript, which is a review article, does not include studies with human or animal participants.

FUNDING

No funding was received for this study.

AUTHORS' CONTRIBUTIONS

RD designed, conceptualized, searched for data, wrote and finalized.

DATA AVAILABILITY STATEMENT

The authors confirm that data supporting the findings of this study are available in the article.

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