



Abdominal Aortic Aneurysm: Roles of Inflammatory Cells

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Abdominal aortic aneurysms (AAAs) are local dilations of infrarenal segment of aortas. Molecular mechanisms underlying the pathogenesis of AAA remain not fully clear. However, inflammation has been considered as a central player in the development of AAA. In the past few decades, studies demonstrated a host of inflammatory cells, including T cells, macrophages, dendritic cells, neutrophils, B cells, and mast cells, etc. infiltrating into aortic walls, which implicated their crucial roles. In addition to direct cell contacts and cytokine or protease secretions, special structures like inflammasomes and neutrophil extracellular traps have been investigated to explore their functions in aneurysm formation. The above-mentioned inflammatory cells and associated structures may initiate and promote AAA expansion. Understanding their impacts and interaction networks formation is meaningful to develop new strategies of screening and pharmacological interventions for AAA. In this review, we aim to discuss the roles and mechanisms of these inflammatory cells in AAA pathogenesis.

Keywords: abdominal aortic aneurysm, inflammation, T cells, macrophages, inflammasome, neutrophil extracellular traps

INTRODUCTION

Abdominal aortic aneurysm (AAA) is one of the most common types of true aneurysms in the world. AAA is defined when the maximal abdominal aortic diameter reaches 30 mm or 1.5 times of the normal ones. The estimated AAA prevalence in men aged over 60 years is about 4–8%, and the prevalence in women gets 0.5–1.5% or so (1). The major risk factors of AAA include cigarette smoking, aging, male gender and corresponding family history (2, 3). The most common cause of death for AAA patients is aneurysm rupture, which accounts for an approximately 60% of mortality (4).

In the past decades, AAA has been regarded as a result of long-term atherosclerotic lesions, which shares the same pathogenesis with other cardiovascular diseases (CVD), due to similar risk factors such as male sex, tobacco consumption, family history, hyperlipidemia and elder population (5, 6). However, diabetes mellitus (DM), a common comorbidity of atherosclerotic disease, is conversely related to AAA development. Patients with DM have a reduction of morbidity by nearly 30 percent (7). Besides, in contrary to the infrarenal segment of aorta, which is the most commonly involved part of AAA, the external iliac artery is often aneurysm-resistant, but it is strongly

vulnerable to atherosclerotic occlusive disease (8). Another phenomenon is that the lipid profiles of patients with AAA are not always abnormal like other CVD patients. These findings indicate that the atherosclerotic lesion may be independent of AAA formation.

Recent studies suggest the pathophysiology of AAA is a multifactorial process consisting of inflammation responses, matrix metalloproteinase (MMP) activation, oxidative stress, intraluminal thrombus, smooth muscle apoptosis and extracellular matrix (ECM) degeneration (9–11). The proteases secreted by inflammatory cells can induce degradation of ECM. In the meanwhile, due to destruction of ECM structure and loss of resistance of tunica media, soluble blood components like inflammatory cells are transferred and accumulated in tunica media through the highly vascularized adventitia, resulting in infiltration of inflammatory cells into the vascular media. These processes together with platelet accumulation and coagulation system activation promote intraluminal thrombosis, and subsequently causes aortic dilation and increased vulnerability to AAA rupture (12). Intraluminal thrombosis is capable to create an inflammatory microenvironment containing neutrophils, cytokines, proteases, and reactive oxygen species, and thereby decrease aortic wall strength. These phenomena indicate that inflammatory cells are in the central position of the whole process. This review is an update of recent advances of inflammatory cell-related mechanisms during AAA development.

INFLAMMATORY MICROENVIRONMENT

The aortic wall can be generally divided into three layers: tunica adventitia, tunica media and tunica intima, of which tunica adventitia is fully vascularized and permit leukocyte diapedesis. The aortic wall inflammation is characterized as a multicellular-participating process including mononuclear cell infiltration, immunoglobulin (Ig) secretion and cytokine production, suggesting that both innate and adaptive immune responses are involved (13). The histological specimen of human aortic aneurysm tissue reveals that there were a variety of inflammatory cells gathering in the aortic wall. Recent studies showed that perivascular adipose tissue (PVAT) played an essential role in the process of leukocyte infiltration. When the vascular damage initiates, PVAT increases its volume and then upregulates the expression of inflammatory factors such as resistin, leptin, cytokines and chemokines (14), which induce infiltration of inflammatory cells, including neutrophils, macrophages, natural killer cells (NK cells), dendritic cells (DCs), T and B lymphocytes and mast cells. All these inflammatory cells are implicated in the formation of AAA (13), and the interactions among them formed the inflammatory microenvironment of aortic walls. For example, cytokines secreted by T cells are essential for macrophage activation, while DCs and macrophages can present antigens to T cells to stimulating primary T cell responses (15). Decreasing the activity of inflammatory cells may be a therapeutic strategy to treat non-ruptured AAAs. Daphnetin was recently proved to be eligible to

suppress AAA generated with elastase by reducing the infiltration and accumulation of inflammatory cells such as macrophages, T cells and B cells (16). In addition, suppressing the infiltration of CD11b⁺ macrophage and CD4⁺ T cell with antagonism of toll-like receptor 2 significantly ameliorated CaCl₂-induced aneurysms (17). The fact that animals can benefit from inhibitors of inflammatory cells independent of models proved the central role of these cells in pathogenesis of AAA.

INNATE IMMUNE CELLS

Macrophages

There are generally two origins of macrophages involved in the pathogenesis of AAA: tissue-resident macrophages arising from embryonic precursors, and monocyte-differentiated macrophages from peripheral blood (18). Single-cell RNA sequencing has revealed markedly expansion and activation of aortic resident macrophages, blood-derived monocytes and inflammatory macrophages in the samples of elastase-induced AAA models (19). Tissue-resident macrophages are self-renewed independently of bone marrow activity and can continuously migrate to peripheral tissues. However, the circulating monocytes are the major origin of macrophages gathering in aortic walls (20).

Circulating monocytes originating from the bone marrow play a critical role in encoding antimicrobial and phagocytosis-related proteins (21). When the local environment undergoes inflammatory changes, blood monocytes can be recruited to the tissue and differentiated into macrophages. In response to different inflammatory stimuli, blood monocytes migrate to the tissue and differentiate into distinct macrophage subgroups, including classically activated macrophages (M1 macrophages) and alternatively activated macrophages (M2 macrophages) (22). This process is termed as macrophage polarization. Interestingly, these two subgroups of macrophages serve almost opposite roles in the pathogenesis of AAA.

M1 macrophages are preferentially located in the tunica adventitia of the aortic wall (20). They can be activated by the stimuli like lipopolysaccharide (LPS) and IFN- γ (23). By upregulating massive inflammatory cytokines including TNF- α , IL6, IL12, IL1 β , chemokine (C-C motif) ligand 2, and nitric oxide (NO) (24), M1 macrophages aggravate local inflammation and promote the aortic dilation as well as vascular remodeling. On the other hand, M2 macrophage polarization is typically induced by Th2 cytokines like IL-4 and IL-13 (23, 25). By mobilizing together with mast cells and NK cells, M2 macrophages can regulate angiogenesis, cell recruitment, and collagen deposition (26). With the progression of AAA, the aortic walls undergo a switch from M1 macrophage dominance to M2 macrophage dominance, which reflects a compensatory mechanism of the anti-inflammatory and tissue-repair effect of M2 macrophages (20). The counteracting effects of M1 and M2 macrophages in AAA make them eligible for therapeutic applications to control inflammation and destruction of aortic

walls. Cheng et al. introduced Notch receptor inhibitors which upregulated M2 macrophages and downregulated M1 macrophages to *ApoE*^{-/-} mice with AAA, and identified this intervention remarkably ameliorated progression of AAA (27).

Neutrophils

Neutrophils are a kind of polymorphonuclear leukocytes, which are consistently generated in the bone marrow from myeloid precursors (28). Neutrophils are one of the most abundant immune effector cells of the human immune system, whose main functions include phagocytosis, degranulation, and formation of neutrophil extracellular traps (NETs) (29, 30). Some studies suggest circulating neutrophils may be an important contributor to AAA formation in the early phase. Eliason et al. found AAA of wild-type animals (WTs) grew faster than mice with neutropenia 4 days after elastase perfusion to induce AAA, although there was not a significant difference in the 7th day (31). A cohort study showed that there were strong associations between elevated neutrophil counts and AAA (32). Li et al. that identified FAM3D, a novel chemokine, was strikingly upregulated in human AAA tissues, and *Fam3d*^{-/-} mice had decreased levels of neutrophil infiltration than WTs. Besides, administration of FAM3D neutralizing antibody markedly suppressed AAA expansion (33).

The effective integrant of neutrophils is composed with granules and secretory vesicles consisting of various enzymes (28). There are three kinds of granules within neutrophils in total. The azurophilic granules contain myeloperoxidase (MPO),

an enzyme essential for the oxidative burst, and other components including defensins, lysozyme and some proteases such as neutrophil elastase and proteinase 3 (34). The specific (secondary) granules are peroxidase-negative and storage lactoferrin, hCAP18, NGAL, lysozyme, and NRAMP-1 (35). The last type is called gelatinase (tertiary) granules. Although there are very few antimicrobials in gelatinase granules, they contain a host of MMPs (34).

NETs are net-like structures protruding from cell membranes of neutrophils or released from ruptured neutrophils (36). When neutrophils are activated, a process named NETosis (**Figure 1**) initiates. The first way of NETosis starts with nuclear delobulation and decondense of chromatin, followed by cellular depolarization and membrane rupture to release NETs. Another kind of NETosis, which is termed as non-lytic form of NETosis, proceeds with expulsion of chromatin and degranulation (37). NETs may have several impacts on aortic wall. To begin with, the proteases hanging on NETs like MMPs can cause direct damage to aortic walls after chromatin are cleaved by DNases (38). Besides, NETs can increase the transcription of IL-6 and pro-IL-1 β in macrophages, induce Th17 cell differentiation and recruit more inflammatory cells (30). Another possible effect of NETs on AAA pathogenesis is promoting vascular occlusion. The net-like structure of NETs can render blood cell gathering within the aorta and finally cause thrombosis (36). NETs also help establish the bridge between neutrophils and other immune cells. Cathelicidin-related antimicrobial peptide exposed by NETs can bind to self-DNA

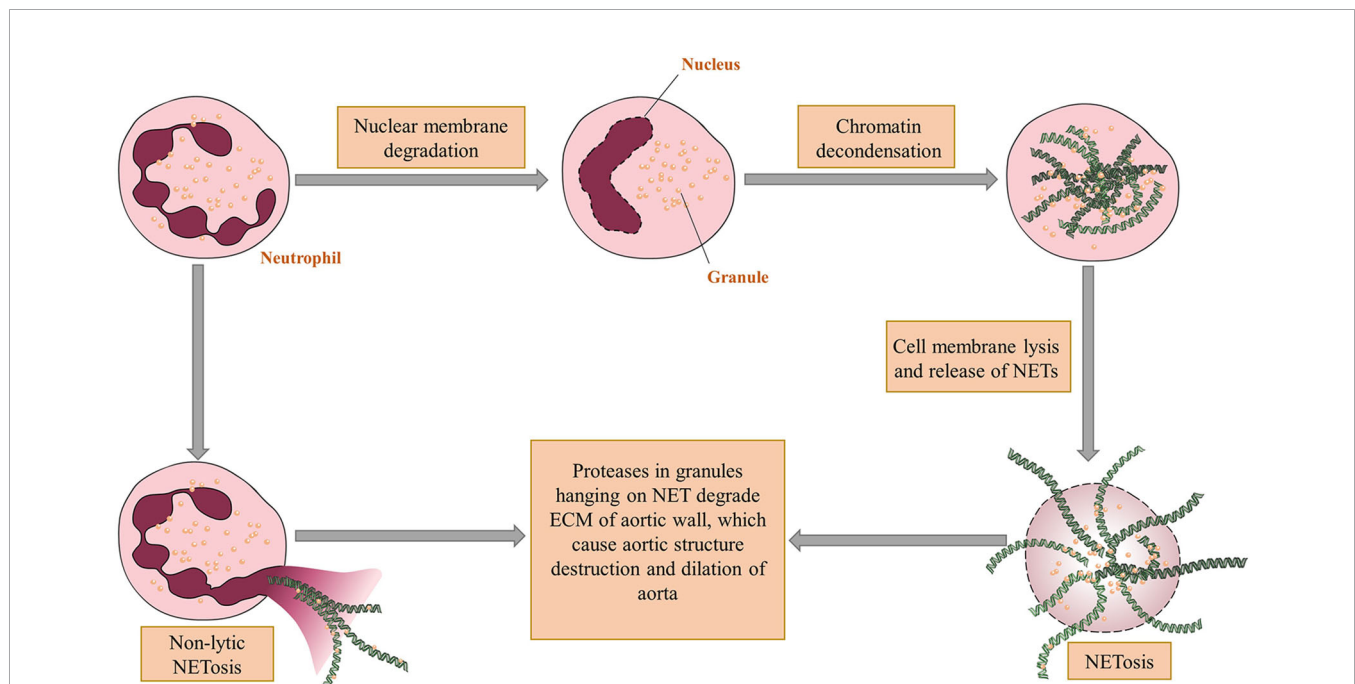


FIGURE 1 | The mechanism of NET formation and acting on aortic walls. There are two ways for neutrophil extracellular traps (NET) come into being. The first one is called NETosis in which nuclei of neutrophils undergo delobulation, chromatin decondensation and nuclear membrane lysis. After that neutrophil granules adhering to released chromatin enter extracellular spaces through ruptured cell membranes. The other way, which is a non-lytic form of NETosis, occurs after partial depolarization of nuclei and render granules hanging on chromatin out of plasma without cell deaths. The proteases within granules can thereby directly degrade the vascular structure and cause aortic dilation. Figures were produced using Servier Medical Art (www.servier.com).

and subsequently recruit plasmacytoid DCs (pDCs) that induce type I interferon synthesis (39).

Dendritic Cells

Dendritic cells (DCs) are a kind of antigen presenting cells (APC) which are able to process and expose antigen components to T lymphocytes, play a key role in the induction of innate immune responses and are implicated in the immune tolerance to self-antigens (40, 41). Krishna et al. indicated that depletion of CD11c⁺ cells can significantly decrease the maximum diameter of AAAs 28 days after angiotensin II infusion (40), which suggests that DCs may also have important impact on the development of AAA.

DCs generally express CD11c and major histocompatibility (MHC) class II molecules. The four subsets of DCs are conventional DCs (cDCs), Langerhans cells, monocyte-derived DCs and pDCs (42). In that the main resident site of Langerhans cells are the epidermis and mucosa, the effective types of DCs on AAAs are cDCs, monocyte derived DCs and pDCs. All kinds of DCs derive from macrophage and DC precursors (MDP), which give rise to monocytes and the common DC precursors (CDP) (43). CDP could further differentiate into pDCs and pre-cDCs. pDCs are a special DC subset which can promote antiviral responses and are also involved in pathophysiology of autoimmune diseases (44). pDCs are able to produce type I interferons, such as IFN- α and IFN- β , to promote proinflammatory responses through activating effector T cell, cytotoxic T cells, and NK cells (39, 45). These inflammatory cells can further facilitate AAA development. cDC1s and cDC2s are two subsets differentiated from pre-cDCs. cDC1s are well known for their cross-presenting functions, and are involved in immune responses to bacterial and viral infections. cDC2s are specialized for sensing danger signals and producing high levels of IL-6 and IL-8 (46). These two phenotypes of cDCs are both characterized as regulatory mediators of immune responses. cDC1 can activate CD8⁺ T cells, promote T helper type 1 (Th1) activation by MHC class I, and activate natural killer responses with by IL-12 (47, 48). cDC2 can cross-present antigens to induce the proliferation of Th1 cells through MHC class II molecules (49). Their effects enrich the communications in the inflammatory microenvironment of AAA tissues. The process that monocytes differentiate into DCs under the induction of GM-CSF plus IL-4 has been observed *in vitro* culture. Monocyte-derived DCs have the potential to transform into cDCs, and *in vivo* experiments showed they can induce Th1 and Th17 cell polarizations (50). However, the detailed roles of DC subsets in AAA need to be explored.

Mast Cells

Mast cells are widely distributed in the tunica adventitia and media of aortic wall. The mast cell count is positively correlated with the maximum of AAA diameter (51). The roles of mast cells in AAA have been intensively discussed in Shi et al.'s review, that elevated proteases of mast cells like chymase and tryptase in patients with AAA, and these proteases contribute to leukocyte adhesion and migration, vascular smooth muscle cells (VSMC)

apoptosis, foam cell formation, and expression of MMP and cathepsins (52). Cathepsin is a kind of enzyme containing in mast cells. Cathepsin C (*Ctsc*) acts as an upstream activator of tryptases, chymases and other cathepsins by cleaving the N-terminal pro-peptide of the zymogen forms of these proteases (53). Cathepsin G has similar function with chymases, which can generate angiotensin II from angiotensin I. Mice deficient of *Ctsc* were resistant to elastase perfusion-induced AAA compared with WT mice, and suffered from less transmural inflammatory cell infiltration (54). However, controlling mast cells solely are not efficient enough as a medical treatment option for aortic aneurysms. A randomized clinical trial showed that pemirolast, a potential mast cell stabilizer, could not inhibit the development of AAA at several different doses, which may be due to the limited influences of pemirolast on plasma tryptase concentration (55, 56). In addition to directly suppress the activity of mast cells, diminishing their impact like inducing VSMC apoptosis might be an alternative way to treat AAAs. A master regulator of autophagy and lysosome biogenesis named transcription factor EB, for example, was shown to prevent VSMC apoptosis and attenuate AAA development (57).

Natural Killer Cells

NK cells are lymphocytes which have important effects on innate immune responses to tumors and infections (58). Although the fraction of NK cells is not that high as T cells in AAA tissues, they have an impact on aneurysm development both through causing aortic wall damage and through accelerating atherosclerotic changes (59–61). NKT cells, a special subtype of immune cells that express both T cell receptor and markers characteristic of NK cells, are amplified both *in vivo* and *in vitro* after injected with Ang II. NKT cells exacerbate aneurysm progression by increasing matrix degrading enzymes in VSMC and macrophages, and by secreting cytokine downregulating VSMC viability (62, 63). Forester et al. reveal peripheral level and cytotoxicity of NK cells are increased in AAA patients than control groups, and these NK cells retained amount and cytotoxicity to destruct VSMC even after aneurysm repair (64).

ADAPTIVE IMMUNE CELLS

CD4⁺ T Cells

The most predominant infiltrated inflammatory cells in AAA specimens are T lymphocytes (65), and the majority are CD4⁺ T cells (mainly helper T cells). The distinct phenotypes and functions of CD4⁺ T cells are summarized in **Table 1**. Depending on surface markers and functions, CD4⁺ T cells can be differentiated into diverse subsets in response to various microenvironment stimuli, including Th1 cells, Th2 cells, Th17 cells, regulatory T cells and follicular helper T (T_{fh}) cells (66). Specifically, these CD4⁺ T cells express various immune molecules, including $\alpha\beta$ T cell receptors, T cell activation markers, memory cell phenotypes (CD45RO⁺CD45R A⁻CD62L⁻), and distinct patterns of cell surface molecules

TABLE 1 | Differentiation, function, and role of various phenotypes of CD4⁺ T cells in AAA.

	Th1	Th2	Th17	Treg	Tfh
Activators	IFN- γ , IL-12	IL-2, IL-4	IL-1, IL-6, TGF- β	TGF- β , IL-2	IL-21, Bcl-6
Affiliated cell	Macrophage, CD8 ⁺ T cell	B cell, eosinophil, mast cell	Neutrophil		B cell
Products	IFN- γ , IL-2 and TNF- β	IL-4, IL-5, IL-6 and IL-10, FasL	IL-17, IL-21, GM-CSF	TGF- β , IL-10, IL-35	CXCR5, IL-21
Role in AAA	Activate macrophage, inhibit collagen synthesis	↓Macrophage cytotoxicity and MMP secretion, ↑VSMC apoptosis	↑Macrophage and neutrophil recruitment	↓T cell proliferation and IFN- γ production, ↓Inflammatory cell chemotaxis, arterial wall remodeling, and angiogenesis	May upregulate autoantibody secretion through assisting B cell proliferation

(including CD54, CD31, CD11a, CD29, CD44, CD95, and CD27) (67).

Th1 and Th2 Cells

The most significant effect of CD4⁺ T cells on AAAs rely on cytokine secretions, such as Th1 cytokines (IFN- γ , IL-2 and TNF- β) and Th2 cytokines (IL-4, IL-5, IL-6 and IL-10) (13, 67). Some of these cytokines are associated with macrophage activation, regulation of VSMC apoptosis and direct destruction of aortic walls (68). Deletion of *Il12b* can inhibit macrophage expansion, decrease production of cytokines like IL-6 and TNF- α in the early stage of AAA, and suppress aneurysm development (69). Another research determined a strikingly higher level of circulating IL-4 in patients with AAA than healthy individuals (70). Wanfen et al. showed that aneurysm dilation and MMP secretion were prevented in *Ifng* deficient mice (71).

Th1 cells, Th2 cells also have effects on aortic wall degradation. There are profound interactions between various types of helper T cells and vascular smooth muscle cells (VSMCs) through autoimmunity. Fas ligand (FasL) expressed by Th2 cells are indicated to promote VSMC death (72). Besides, TNF and IFN- γ released by Th1 cells can further inhibit collagen synthesis (73, 74). A study aiming to investigate the interactions among immune cells in AAAs reveals that CD4⁺ T cells could promote VSMC proliferation through direct cell-to-cell contact (60). VSMC, the main cellular constituent of the aortic wall (75), subsequently induce NK cells aggregation and finally result in VSMC apoptosis. Extracellular matrix (ECM) enables artery wall to obtain the blood containing function, and the main component of ECM, especially collagen and elastin, are synthesized and processed by VSMC. Collagen defects can lead to aneurysm rupture, while elastin depletions are associated with continuous dilation (11). All these results demonstrate the essential position of Th1 and Th2 in aneurysmal diseases.

Th17 Cells

Th17 cells, the main origin of IL-17, are elevated in AAA tissues (76). IL-17 secreted by Th17 cells mediates a quantity of immune responses like neutrophil recruitments and plays a central part in vascular superoxide production (77). This can sharpen oxidative stress in aortic walls. Oxidative stress is one of the major pathogenic factors of AAA, and a study proved riboflavin (vitamin B2), a kind of antioxidant, could prevent aneurysm

formation in rat models (78), which suggests inhibiting oxidative stress by controlling IL-17 synthesis and activity of Th17 cells may be a potential therapeutic target for AAA patients.

Owing to their various cytokines in addition to IL-17, such as IL-17F, IL-21 and granulocyte-macrophage colony-stimulating factor (GM-CSF), Th17 cells have been implicated in several autoimmune diseases, including inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis (79). Therefore, it is rational to anticipate that Th17 cells is also probably of great relevance to AAA. Ashish et al. showed that there is an evidently higher expression of IL-17 in AAAs. Besides, *Il17a*^{-/-} mice are relatively resistant to AAA, and plasma concentration of inflammatory cytokines are also decreased, which proved the proinflammatory and atherosclerotic properties of IL-17 (76). Wei et al. introduced digoxin to antagonize retinoic acid-related orphan receptor gamma thymus, a master transcription of Th17 cell differentiation, and found out that this can attenuate aneurysm expansion in two different kinds of models with AAA (80). These findings indicate the role of Th17 cells in AAA development.

Tfh Cells

Tfh cells express CXCR5, a chemokine receptor that helps guide cells into B cell follicles (81). Tfh cells could provide assistant to B cells activation through autocrine or interactions with B cells, and are essential for formation and maintenance of germinal centers (82). Tfh cells have a role in atherosclerosis. Gaddis et al. found that deletion of *Bcl6*, a transcription factor of Tfh cells, prevented plaque formation in *Ldlr*^{-/-} murine models (83). This finding suggests decreasing Tfh cells activity may slow down the exacerbation of aneurysms. However, the roles of Tfh cells in AAA need to be established.

Regulatory T Cells

Regulatory T (Treg) cells are a specific kind of CD4⁺ T cells which express forkhead box protein 3 (FOXP3) and regulate the effects of other T cell subsets (84). Treg cells have an impact on suppressing local inflammation, and compromised Treg functions may promote AAA growth (85). The suppressive effect is determined by acetylation levels of FOXP3, which is lower in human aneurysm tissue. SIRT1 can specifically regulate the acetylation of FOXP3 (86). Studies have shown that EX-527, an inhibitor of SIRT1, can recover the acetylation levels of FOXP3, increase the number of active Treg cells and bring

back their suppressive functions on AAA (86). Zhou et al. found that Treg cells could release IL-10 and thereby suppress inflammatory cell chemotaxis, arterial wall remodeling, and angiogenesis (87). Another study showed that the proportion of Treg cells in peripheral mononuclear cells were markedly decreased in AAA patients than controls (88). The average aortic diameters of *Foxp3*^{-/-} mice were larger than WT after CaCl₂ induction, while infusion of normal Treg cells to *Foxp3*^{-/-} mice can render their similar aortic size with WT after CaCl₂ induction (88). Administration of IL-2 to expand FOXP3⁺ Treg cells also reduced the incidence and mortality of AAA in *ApoE*^{-/-} mice with angiotensin II infusion (89). Besides, Treg cells are an essential source of TGF- β , which is a matrix-protecting and anti-inflammatory cytokine in human. Wang et al. concluded that systemic neutralization of TGF- β would increase the activity of MMP-12 and subsequently contributed to aneurysm progression and rupture (90). This growing body of evidence suggests an important role of Treg cells in enhancing inflammation and inducing AAA enlargement.

CD8⁺ T Cells

CD8⁺ T cells represent a considerable part of adaptive immunity. According to the immune state, CD8⁺ T cells can be generally divided into effector cells and memory cells, which can provide both immediate clearance and long-term protective effect on killing tumor cells and virally infected cells (91). CD8⁺ T cells are found to be elevated in AAA wall and perivascular tissues (92). Zhou et al. indicated that IFN- γ released by CD8⁺ T cells could promote cellular apoptosis *in vivo* and MMP-producing macrophage recruitment (93). CD8⁺ T cells exert versatile impacts on atherosclerosis. Chemokines like MCP-1 and CCL-2, which can induce monocytes infiltration in atherosclerotic lesions, were observed to be decreased in mice depleted of CD8⁺ T cell (94). However, CD8⁺ T cells can promote apoptosis of antigen presenting cells and suppress functions of CD4⁺ T cells, which can resist progression of atherosclerosis (95). This discrepancy may result from production of inflammatory cytokines and lysis of endothelial cells by CD8⁺ T cells. The pro-atherogenic and protective effects of CD8⁺ T cells may also regulate the enlargement of AAA, but need to be further explored.

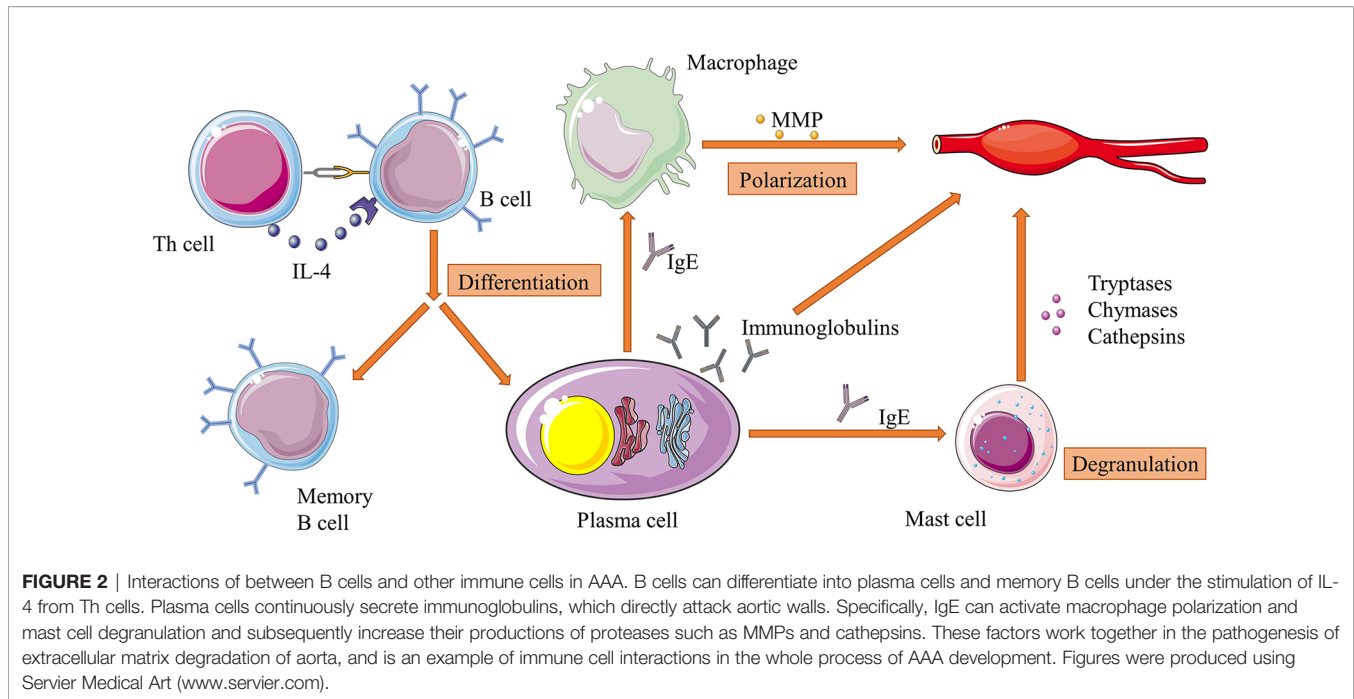
$\gamma\delta$ T Cells

In contrast to $\alpha\beta$ T cells, $\gamma\delta$ T cells are independent of MHC class II or β 2 microglobulin for development and activation (96), suggesting that they are eligible to generate rapid immune responses in blood. $\gamma\delta$ T cells can produce various cytokines including TNF- α , IL-17, IL-22, and IFN- γ (97). Besides, $\gamma\delta$ T cells also secrete chemokines, which influence recruitment of other immune cells at the site of inflammation and modulate the function of other innate and adaptive immune cells (97). These features establish distinct role of $\gamma\delta$ T cells in sterile and non-sterile inflammation. $\gamma\delta$ T cells were found to be present in samples of AAA patients (98), so the special immune properties of $\gamma\delta$ T cells may play of role in early stage of aneurysm formation.

B Cells

B cells serve as essential functional parts in humoral immunity of the adaptive immune system through secreting antibodies. B cell can be divided into three subpopulations, including B1, B2 and regulatory B cells (99). Schaheen et al. discovered that depletion of B1 and B2 cells with anti-CD20 antibody significantly limit AAA growth in animals treated with elastase perfusion or angiotensin II-infusion (45). However, B2 cell refusion was exhibited to ameliorate AAA exacerbation in B cell-deficiency murine models (100). This anomalous phenomenon might be due to upregulation of Treg cells and TGF- β despite of the atherogenic effects of B2 cells (101), and also serves as another proof that AAA is an inflammation-driven disease rather than simple atherosclerotic lesions. The complex impact of B cells on AAA development may need more studies to verify, such as purely B1 cell deficiency murine models.

In addition to producing cytokines like TGF- β , the main function of B cells is to secrete immunoglobulins. After contacting with antigens, the activation-induced cytidine deaminase (AID)-driven somatic hypermutation (SHM) of the variable regions of immunoglobulin genes generate a number of mutated B cells that can differentiate into immunoglobulin-secreting plasma cells and memory B cells, which provide both immediate and persistent effects on the same antigens (102). Some of these B cells are overactive and produce autoantibodies after stimulated by autologous components of human tissues, and result in a variety autoimmune diseases including AAA (103, 104). Immunoglobulins were found widely deposited in mouse AAA tissues, and these autoantibodies can not only induce secretions of IL-6 and MMP-9 from T cells and macrophages, but directly cause local destruction of aortic walls (105). For example, B cell-derived anti-beta 2 glycoprotein I antibody was shown to exacerbate HHcy-aggravated vascular inflammation and AAA expansion (106). In addition, a study isolated antiphospholipid (aPL) antibody (a kind of autoantibody able to cause blood clots) from human AAA tissue, and found that more aPL-positive patients underwent AAA progression than aPL-negative patients (107). Another study purified antibodies against *Chlamydia pneumoniae* outer membrane proteins (OMPs) from serum of AAA patients, and used these antibodies to analyze the aortic walls of AAA patients with western blot and found positive reactions in all of the tested samples, which could be an evidence of the association between the *Chlamydia pneumoniae* OMP antigens and AAA (108). Besides, some of the immunoglobulin subtypes can interact with other immune cells. For instance, IgE can affect macrophage polarization and induce mast cell activated to synthesize various elastases (109, 110). These dramatically increasing evidences indicate that B cell may be an ideal target to treat AAA patients, and subsequent experiments confirmed this hypothesis. Zhang et al. reported that vinpocetine could alleviate AAA development by suppressing TNF- α -induced B cell activation and proinflammatory mediator expression in primary cultured macrophages both *in vitro*, and *in vivo* (111). The interactions of between B cells and other immune cells are illustrated in **Figure 2**.



OTHER INFLAMMATORY-INVOLVED MECHANISMS

Matrix Metalloproteinases

MMPs have been implicated in the pathologic origin of AAAs. MMPs have significant destructive effects on elastin fiber integrity, and thereby cause elastin to lose its mechanical properties (112). Several types of MMPs can be secreted by AAA tissue, such as MMP-2, MMP-3, MMP-8, MMP-9, MMP-12 and MMP-13 (113, 114). MMP-9 is the most abundant elastolytic proteinase found in AAA tissue and is predominantly expressed by macrophages infiltrated in AAA (115). Several studies showed that *Mmp9* and *Mmp2* knockout mice are protected from CaCl_2 challenging, indicating the important role of MMPs in AAA developments (116). Besides, targeted delivery of MMP inhibitors with nanoparticles was shown to inhibit aneurysmal progression (113). Robert et al. found that the relative resistant to AAA formation in *Mmp9* deficient mice was related to the preservative structure of elastic lamellae despite the presence of infiltrating mononuclear phagocytes and neutrophils (115). It has also been found that MMP-9 can hardly cause local tissue injury without the presence of MMP-2, because MMP-2 can initiate cleavage of the triple-helix-structured collagen into one-quarter and three-quarter lengths, which complement the effects of MMP-9 (116). Netrin-1, a neuronal guidance signal that can specifically regulate the activity of MMP-3, was found to be elevated in murine and human AAA tissues, and targeted depletion of *Ntn1* in macrophages evidently decreased the risk of developing murine AAA (117).

All of above mechanisms give MMP the potential to be a target of screening and therapy for AAA patients. As a specific

history hallmark of aneurysm formation, fragmentation of ECM by MMPs has been frequently studied to investigate particular biomarkers in AAA patients (118). A meta-analysis including eight case-control studies revealed strikingly increase of circulating MMP-9 levels in AAA patients (119). Hovsepian et al. found that the elevated MMP-9 had a sensitivity of 48% and a specificity of 95% to establish AAA diagnosis (120). Several other types, such as MMP-1, -2, -3, -7, -12 and -13 have been shown to have an increased level accompanied with reduction of their inhibitors by some researchers (121–123). Doxycycline is a kind of tetracycline antibiotic which is capable to suppress a cast of MMPs, and has been shown to be effective in reducing elastin degradation and aneurysm development in murine AAA models (1). Small randomized clinical trials showed doxycycline suppressed the expansion of AAA (124). A meta-analysis, however, concluded that patients with doxycycline prescription had no significant growth rate reduction of aneurysm diameter than control groups (125).

Inflammasomes

Inflammasomes are large multimolecular complexes that are able to induce inflammation reactions and control the activation of caspase-1, which regulates the proteolytic maturation of IL-1 β and IL-18 (126, 127). These intracellular molecular protein scaffolds work through inducing pyroptosis (an inflammatory form of cell death) and necroptosis (a lytic form of inflammatory cell death) by cleaving the N-terminal of pro-IL-1 β and pro-IL-18 with caspase-1 (128). Five kinds of receptor proteins have been identified so far to assemble inflammasomes, including nucleotide-binding oligomerization domain (NOD), leucine-rich repeat (LRR)-containing protein (NLR) family members NLRP1, NLRP3 and NLRC4, as well as the proteins absent in melanoma 2

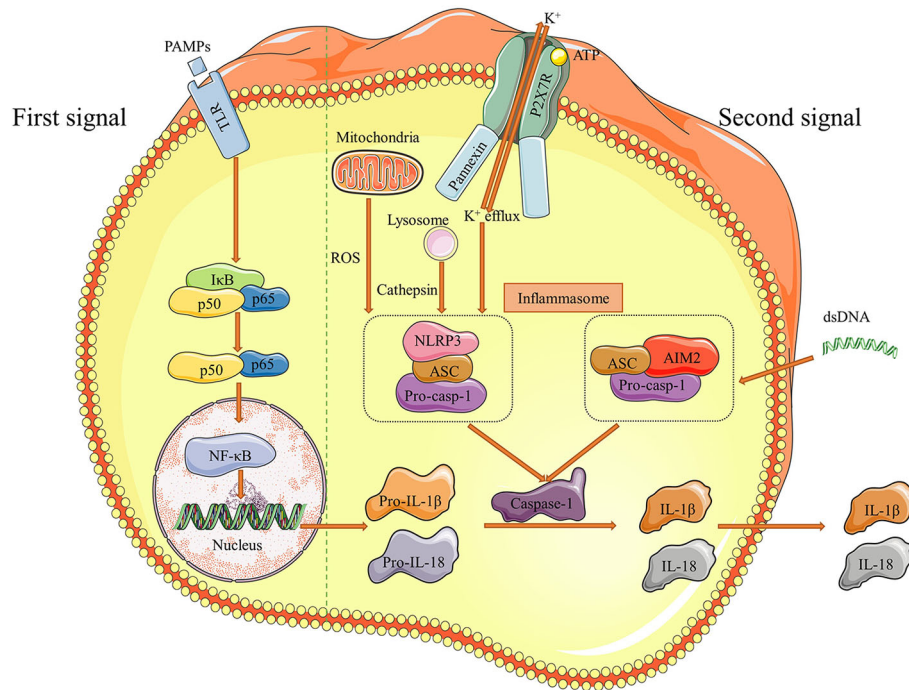


FIGURE 3 | Pathways of NLRP3 and AIM2 inflammasome activation. There are two distinct signals needed for inflammasome to be effective. Initially, pathogen-associated molecular patterns (PAMPs) as the first signal binds to Toll like receptors (TLRs) and stimulate NF- κ B, which increases downstream pro-IL-1 β and pro-IL-18 production. Then, efflux of K⁺ and dsDNA are the second signals correspondingly to induce NLRP3 and AIM2 inflammasome formation. The pathway of NLRP3 inflammasome activation usually proceed under the assistant of cathepsin released by lysosome and ROS mtDNA from mitochondria. The final result of inflammasome activation is cleaving pro-casp-1 into caspase-1, which transforms pro-IL-1 β and pro-IL-18 to IL-1 β and IL-18. These two effective cytokines are secreted out and participate the inflammatory responses in aortic walls. Figures were produced using Servier Medical Art (www.servier.com).

(AIM2) and pyrin (126). It has been shown that inflammasomes are involved in a cast of inflammatory disorders (126). Recent works suggest that NLRP3 and AIM2 inflammasomes are implicated in the pathogenesis of AAA, and we summarized the process of these inflammasome activations in **Figure 3**.

A pilot study demonstrated an upregulation of the inflammasome core components ASC (apoptosis associated speck-like protein containing a caspase activation and recruitment domain), caspase-1 and IL-1 β in AAA tissue compared to normal aortas and claimed AAA-associated lymphoid cells could carry on inflammasome signaling (129). Some subsets of inflammasomes like AIM2 were significantly increased in circulating granulocytes, monocytes, B lymphocytes of AAA patients, and IL-1 β released by peripheral blood mononuclear cells of AAA patients was significantly higher than controls (130). Another study found expression of NLRP3 and AIM2 were notably lower in control samples than AAA. However, with the AAA lesion progression, inflammasome expressions decreased (131), which suggests the inflammasome-induced signaling plays a more important role in early AAA pathogenesis. Markus et al. found that necrotic cell debris from autologous cells promotes AIM2 and NLRP3 inflammasomes in VSMC of late stage AAA tissues, and thereby activates downstream inflammatory attacks (132). Ren, et al. found that NLRP3 inflammasomes directly activate MMP-9 by cleaving its

N-terminal inhibitory domain, so blocking the inflammasome pathway with MCC950, a potent selective small-molecule NLRP3-inflammasome inhibitor, could prevent aortic aneurysm formation (133). Similarly, silencing of NLRP3 in macrophages remarkably ameliorated AAA formation (134). In the meanwhile, NLRP3, caspase 1, and IL-1 β levels were elevated in hyperhomocysteinemia (HHcy) models compared with WTs, and administration of folic acid to reverse the HHcy-accelerated AAA could alleviate activation of inflammasomes in the tunica adventitia (134). These studies demonstrate inflammasomes may be a promising target for medical intervention of AAA.

PERSPECTIVES

AAA still remains to be a life-threatening disease. In the current review, we summarized the updated pathogenic roles of inflammatory cells in AAA development. The roles of T cells and macrophages in AAA have been predominantly studied, including inflammatory cytokines, MMPs, inflammasomes, etc. However, how the other types of inflammatory cells influence AAA are still not fully verified. Despite of the advances of endovascular aneurysm repair and open surgery for large or ruptured AAA, there is still lacking efficient medical therapy

choices for asymptomatic patients. This review lists a considerable number of pathways of inflammatory cell effects, and provides evidences from studies that suppressing corresponding pathways may influence the development of AAA in murine models or patient samples *in vitro*. These evidences not only prove the irreplaceable roles of inflammatory cells in AAA, but provide new methods to develop ideal drugs for researchers and physicians. Specific targets, such as inflammatory cytokines and MMPs, have been investigated for biomarker screening and possible medical therapies for asymptomatic AAA. These novel applications may serve as advanced strategies for early identification and therapeutic intervention for AAA.

It should be noted that most studies on detailed cellular mechanisms were conducted in animal models or *in vitro* experiments, which could not entirely mimic the pathogenesis of AAA in humans. Studies bridging pre-clinical mechanisms and clinical data are needed. Furthermore, most of the animal studies were only focused on the initiation of diseases, while how to prevent AAA rupture in real-world patients are more

challenging. Further studies on different stages of AAA will be helpful.

AUTHOR CONTRIBUTIONS

YZ, YL, JW, JQW, JY, and ZX drafted, edited, and approved the manuscript and figures. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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