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Pathogenesis of anti-neutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) encompasses a group of potentially life-threatening disorders characterized by necrotizing small vessel vasculitis with positive serum ANCA. To date, the pathogenesis of AAV has not been fully elucidated, but remarkable progress has been achieved in the past few decades. In this review, we summarize the mechanism of AAV. The pathogenesis of AAV involves various factors. ANCA, neutrophils, and the complement system play key roles in disease initiation and progression, forming a feedback amplification loop leading to vasculitic injury. Neutrophils activated by ANCA undergo respiratory burst and degranulation, as well as releasing neutrophils extracellular traps (NETs), thus causing damage to vascular endothelial cells. Activated neutrophils could further activate the alternative complement pathway, leading to the generation of complement 5a (C5a), which amplifies the inflammatory response by priming neutrophils for ANCA-mediated overactivation. Neutrophils stimulated with C5a and ANCA could also activate the coagulation system, generate thrombin, and subsequently cause platelet activation. These events in turn augment complement alternative pathway activation. Moreover, disturbed B-cell and T-cell immune homeostasis is also involved in disease development. In-depth investigation in pathogenesis of AAV might help to offer more effective targeted therapies.

Keywords

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) encompasses a group of potentially life-threatening autoimmune disorders characterized by inappropriate recruitment of activated neutrophils with subsequent necrotizing small-vessel vasculitis (involving small intraparenchymal arteries, arterioles, capillaries, and venules) with little or no immune deposits.[1] AAV comprises granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).[1] ANCAs against neutrophil cytoplasmic constituents, in particular proteinase 3 (PR3) and myeloperoxidase (MPO), are serological biomarkers of AAV. In most cases, MPO-ANCA is more frequent in patients with MPA, and PR3-ANCA is more frequent in patients with GPA.[2] EGPA is less commonly associated with ANCAs, notably MPO-ANCA.

AAV could manifest as multisystem disease or single-organ vasculitis. MPA and GPA can involve small vessels in almost any organ, but the most commonly involved ones are the kidneys and lungs.[1] EGPA has less overlap with MPA and GPA and is increasingly recognized as a distinct entity regarding its genetic, pathogenetic, clinical, and pathological features.

The etiology of AAV is multifaceted, including genetic and environmental predisposing factors. ANCA, neutrophils and complements are key components in the pathogenesis. In this review, we present the current understanding and recent advances in the etiology and pathogenesis of AAV.

Etiology

Although the precise etiology of AAV has yet to be fully elucidated, studies have revealed that genetic, environmental and infectious factors as well as drugs are involved in the

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occurrence of AAV.

Genetic Factors

Epidemiological differences have been observed in AAV, for example, the predominance of MPA with MPO-ANCA in Asian populations and the predominance of GPA with PR3-ANCA in Caucasians,[3,4] suggesting that genetic factors might be one of the causes of AAV. The strongest genetic associations with human AAV are displayed by class II major histocompatibility complex (MHC) (also known as human leukocyte antigen, HLA) genes. A genome-wide association study (GWAS) from Europe demonstrated that MPA and GPA were genetically distinct, and the strongest genetic associations were with the antigenic specificity (MPO or PR3) of ANCA instead of with the clinical manifestation (MPA or GPA).[5] PR3-ANCA-positive AAV is most strongly associated with the *HLA-DP* region, in particular the HLA-DPB1*0401 allele, whereas MPO-ANCA-positive AAV is highly associated with the *HLA-DQ* region.[5-7] Moreover, the *HLA-DPB1*0401* genotype is associated with an increased risk of relapse in PR3-ANCA-positive disease.[8] Studies from Japan and China have shown that *HLA-DRB1*0901*, *DQB1*0303*, and *DRB1*1101* are associated with MPA.[9,10] Further research revealed that MPO-HLA class II complexes could be detected both in neutrophils from patients with MPA and healthy donor-derived neutrophils stimulated with cytokines, indicating that MPO-HLA-DR complexes may be involved in the pathogenesis of MPA.[11]

In the non-MHC genes, the *PTPN22* variant is associated with disease susceptibility to AAV because this gain-of-function variant results in suppression of interleukin-10 (IL-10, an immunosuppressive cytokine).[12] Variants of *PRTN3* (encoding PR3), *SERPINA1* (encoding α1-antitrypsin, a main inhibitor of PR3) and *SEMA6A* (encoding semaphorin 6a) are associated with GPA- or PR3-ANCA-positive AAV.[5-7] In the *BACH2* gene, a rare variant which could reduce luciferase gene expression in endothelial cells is associated with MPO-ANCA-positive AAV.[7]

Epigenetic factors, such as DNA methylation, are also linked with AAV by implicating in the regulation of *PRTN3* and *MPO* gene expression.[13,14] Patients with active disease have hypomethylation of *PRTN3* and *MPO* and upregulated gene expression, whereas DNA methylation increases during remission with downregulated gene expression.[14]

Environmental Factors

Accumulating evidence suggests that environmental factors participate in the development of AAV. A group of geoepidemiological triggers have been identified, including latitude-dependent and seasonality factors such as UV radiation. In the 1990s, an increasing positive rate of ANCA was observed among practitioners in the mining and construction industries.

One of the most commonly reported substances associated with the occurrence of AAV is silica.[15] The role of silica is further supported by the increasing frequency of AAV observed following 3 large earthquakes in Asia.[16-18] Silica-induced apoptosis of macrophages and polymorphonuclear leukocytes might act as a trigger of AAV, notably MPO-ANCA-positive MPA.[15,19]

Infectious Factors

Bacterial infections have been implicated in the initiation and relapse of AAV, especially GPA. Among these bacteria, *S. aureus* seems to have the strongest association with GPA.[20,21] Particular virulence genes (presence or absence) of *S. aureus* isolates from AAV patients contribute to disease progression and/or relapse.[22] *S. aureus* can also produce toxic shock syndrome toxin 1, which supplies homologous peptides of complementary PR3 (cPR3) and leads to the generation of both anti-PR3 and anti-cPR3 antibodies, exacerbating GPA.[23] Moreover, proinflammatory stimuli of infectious origin, such as bacterial lipopolysaccharide (LPS), could act synergistically with ANCA to cause vasculitis.[24]

Kain *et al*. first reported that ANCA targeting human lysosomal membrane protein-2 (LAMP-2) could be detected in most active ANCA-associated necrotizing crescentic glomerulonephritis (NCGN).[25] As a lesser known ANCA antigen, LAMP-2 is homologous to the bacterial adhesion protein FimH. FimH is found in gram-negative bacteria, so fimbriated bacteria might induce autoantibodies to human LAMP-2 through molecular mimicry and contribute to the development of NCGN.[26] In contrast, Roth *et al*. reported a lower prevalence of anti-LAMP-2 antibodies in AAV. Furthermore, these antibodies failed to induce glomerulonephritis in WKY rats.[27] Therefore, the relevance of anti-LAMP-2 antibodies in AAV is still controversial.

Drugs

Certain drugs can induce ANCAs or even AAV, such as propylthiouracil (PTU), minocycline, D-penicillamine, hydralazine, sulfasalazine and anti-TNF agents.[28,29] Among these agents, the most often implicated drug is PTU.[29] ANCA expression ranges from 4% to 46% in patients treated with PTU, and multiple target antigens including MPO, PR3, cathepsin G, lactoferrin, neutrophil elastase and azurocidin have been detected. Gao *et al*. reported that only 27.3% (6/22) of these ANCA-positive patients had clinical vasculitis (All four patients with MPO-ANCA and two of the three patients with PR3-ANCA).[30,31] The interaction between PTU and MPO has been suggested to contribute to the development of vasculitis. After repeated exposure to PTU, MPO might undergo structural changes and make itself a neoantigen.[32] In addition, PTU can be transformed into cytotoxic metabolites by neutrophil-derived MPO in the presence of hydrogen peroxidase.[33] The converted drug and its cytotoxic metabolites
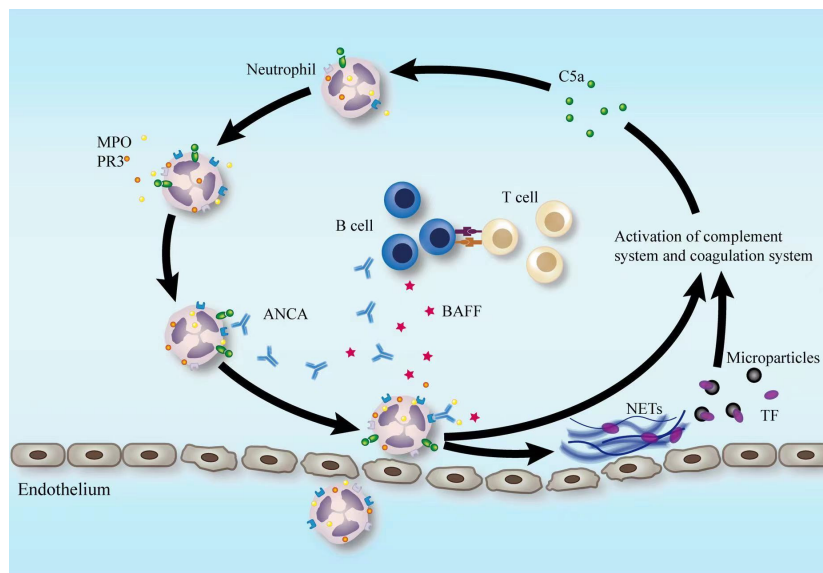
Figure 1: Common pathogenetic events in AAV. Priming of neutrophils by cytokines, such as C5a, leads to upregulation of the expression of ANCA target antigen on the cell surface. The primed neutrophils are further activated by ANCA, resulting in respiratory burst and degranulation, as well as the release of NETs, thus causing damage to vascular endothelial cells. Activated neutrophils could further activate the complement alternative pathway, resulting in the generation of C5a, which amplifies the inflammatory response by priming neutrophils for ANCA-mediated activation. TF-bearing microparticles are released by activated neutrophils as well, activating the coagulation system and producing thrombin. Thrombin causes activation of platelets, which in turn can further amplify the alternative complement pathway. Disturbed B-cell and T-cell immune homeostasis is also critically involved in disease development. ANCA, anti-neutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; C5a, complement 5a; TF, tissue factor; NETs, neutrophil extracellular traps; MPO, myeloperoxidase; PR3, particular proteinase 3; BAFF, B-cell activating factor.

are immunogenic and then stimulate T cells to participate in B-cell production of ANCA.[34] In a rat model of MPO-ANCA-mediated AAV, PTU treatment induces the generation of neutrophil extracellular traps (NETs),[35] which could enhance inflammation in AAV.

Pathogenesis

To date, the pathogenesis of AAV has not been fully elucidated, but increasing evidence shows that the interaction among neutrophils, ANCA, the complement system and the coagulation system is of vital importance in the development of AAV. (Figure 1)

ANCA

Pathogenicity of ANCA

ANCAs were first reported in pauci-immune NCGN patients in 1982[36] and are the most important serological biomarkers of AAV. IgG-ANCA is the most common isotype, but IgA-ANCA and IgM-ANCA have also been reported.[37,38] Clinical and experimental data evidence that ANCAs are crucial in the pathogenesis of AAV.

In 2004, Bansal and colleagues first reported that transplacental transfer of MPO-ANCA IgG from the mother to the neonate resulted in pulmonary hemorrhage and glomerulonephritis, providing direct evidence for the pathogenicity of ANCA.[39] The *in vivo* pathogenicity of ANCA was also demonstrated indirectly by the efficacy of plasma exchange for severe renal vasculitis.[40] Rituximab is a chimeric murine/human monoclonal antibody against CD20 (targeting B cells), and randomized controlled clinical trials have shown rituximab efficacy and safety in inducing remission of AAV,[41,42] suggesting a pathogenic effect of ANCA produced by mature B cells.

The strongest supporting evidence for ANCA pathogenicity comes from compelling animal models. In 2002, Xiao *et al*. developed a passive immune model.[43] MPO knockout (Mpo-/-) mice were immunized with mouse MPO. Transfer of anti-MPO IgG or MPO-reacting splenocytes from these mice to Rag2-/- mice (lacking functioning T lymphocytes and B lymphocytes) or wild-type mice successfully induced pauci-immune NCGN and, in some recipient mice, vasculitis in the lung and other organs. This animal model clearly demonstrates the pathogenicity of ANCA. Proinflammatory stimuli and ANCA act synergistically to induce vasculitic disease. Huugen *et al*. revealed that the disease severity of MPO-ANCA-induced NCGN could be enhanced in the presence of bacterial LPS.[24] Kuligowski *et al*. further demonstrated that low-dose anti-MPO antibody could bind to neutrophils in mice

and mediate their adhesion to glomerular endothelial cells (GEnCs) in the presence of LPS, whereas high-dose anti-MPO antibody can directly mediate the adhesion between neutrophils and GEnCs independent of LPS.[44] In 2005, Little *et al*. established a novel rat model by immunizing WKY rats with human MPO.[45] These rats developed small vessel vasculitis with MPO-ANCA directed against leukocytes. These antibodies enhanced leukocyte adhesion and transmigration in response to the chemokine Groalpha (CXCL1). Passive transfer of immunoglobulin from these rats to naive rats conferred enhanced adhesion and transmigration responses in the recipients. Furthermore, MPO-immunized rats and recipients of ANCA-positive immunoglobulin developed extensive microvascular lesions in response to CXCL1, thus providing *in vivo* evidence for the capacity of ANCA to enhance leukocyte-endothelial interactions and cause microvascular damage.

In contrast, well-designed PR3-ANCA-induced AAV animal models are still lacking. The lower homology of human and mouse PR3 may contribute to the difficulty in developing GPA animal models.[46] A model of PR3-ANCA-induced lesions developed in PR3-neutrophil elastase-deficient mice. In this model, the passive transfer of murine anti-mouse PR3 resulted in stronger localized cutaneous inflammation, and perivascular infiltrates were observed around small vessels at intradermal injection sites of TNF-α.[47] In 2012, Little *et al*.[48] injected human hematopoietic stem cells into irradiated NOD-scid-IL2Rγ-/- mice and then treated the chimeric mice with human PR3-ANCA-IgG. Finally, mild pauci-immune proliferative glomerulonephritis developed, with infiltration of mouse and human leukocytes. In aggregate, these animal studies have documented that both MPO-ANCA and PR3-ANCA are capable of causing vasculitis.

The mechanism by which ANCAs cause vasculitis has been explained as follows. Small amounts of proinflammatory cytokines (e.g., IL-1β and TNF-α generated during infection) at low concentrations unable to cause full neutrophil activation are capable of inducing the translocation of ANCA target antigens (namely, PR3 and MPO) to the cell surface (priming of neutrophils).[49] ANCAs bind to their autoantigens by the F(ab')2 portion, while the Fc portion binds to Fcγ receptors (FcγR) on neutrophils.[50] Fc–FcγR engagement results in activation of neutrophils, including respiratory bursts with the release of reactive oxygen species (ROS), degranulation, phagocytosis, upregulation of adhesion molecules, and abnormal inflammatory cytokine production accompanied by lytic enzymes, which initiate vascular endothelial injury.[44,51] ANCA antigens (PR3 and MPO) released from activated neutrophils and monocytes also cause cell damage.[52-55] Excessive neutrophil activation results in the subsequent generation of NETs, which are lattice-like structures containing extruded DNA, histones, and neutrophil granule proteins such as PR3 and MPO. NETs can augment the autoimmune response, activate the alternative complement pathway and directly enhance tissue injury.[51,56-58] In addition to the FcγR–mediated mechanism, the ANCA F(ab')2 portion plays a role in ROS production and transcription of cytokine genes in normal human monocytes and neutrophils.[59] Microarray gene chip analysis has shown that the ANCA F(ab')2 portion and ANCA IgG stimulate the transcription of a distinct subset of genes,[60] suggesting that ANCA F(ab')2 portions are capable of low-level monocyte and neutrophil activation.

ANCA Production

As mentioned above, the pathogenicity of ANCA has been well demonstrated by clinical, animal model, and *in vitro* experimental evidence. However, there is less understanding of the inciting events in the breakdown of tolerance and the production of ANCA. Jennette *et al*. proposed the hypothetical theory of autoantigen complementarity.[23,51] This theory is based on evidence that proteins transcribed and translated from the sense strand of DNA bind to proteins that are transcribed and translated from the complementary (antisense) strand of DNA. Initiating ANCA formation entails an initial reaction to complementary peptides and results in production of antibodies not only to complementary(antisense) peptide, but also to the immunogen's sense peptide.[23,51] For example, S. aureus can supply homologous peptides of cPR3, leading to the generation of PR3- and cPR3-ANCAs.[25,26]

The overactivation of neutrophils induced by ANCAs results in NETs formation. NETs will, in turn, augment the production of ANCA by presenting PR3 and MPO antigens to dendritic cells and activating autoreactive B cells.[61]

Neutrophils

Neutrophils are of great importance in the pathogenesis of AAV. The *in vitro* evidence for pathogenic roles of overactivated neutrophils and NETs has been discussed in the above section of "Pathogenicity of ANCA". As for evidence from *in vivo* studies, Xiao *et al*. reported that depletion of neutrophils in mice can prevent MPO-ANCA-induced necrotizing crescentic nephritis.[62] Later, Schreiber *et al*.[63] immunized *Mpo*-/- mice with mouse MPO and exposed them to irradiation. Then, a transplant of *Mpo*+/+ bone marrow (BM) was performed. Engraftment of *Mpo*+/+ BM cells in MPO-ANCA-positive *Mpo*-/- mice led to pauci-immune NCGN. In contrast, transfer of *Mpo*-/- BM cells into irradiated *Mpo*+/+ mice did not result in vasculitis. Anti-MPO IgG was applied intravenously to irradiated *Mpo*-/- mice with *Mpo*+/+ BM transplantation or irradiated *Mpo*+/+ mice with *Mpo*-/- BM transplantation. Only chimeric *Mpo*-/- mice with circulating MPO-positive neutrophils (with *Mpo*+/+ BM transplantation) developed NCGN, thereby indicating that BM-derived cells, in particular neutrophils, are crucial for the induction of AAV.

Complements

In the past decade, the complement system has emerged to play an important role in the development of AAV, and C5a is considered to be a key neutrophil-activating chemokine.[64] Activation of neutrophils could further activate the complement system, in particular *via* the alternative pathway,[65] forming an amplification loop.

Evidence from Animal Studies

The pathogenetic role of complement activation was first verified by Xiao *et al*. in a mouse model of MPO-ANCA vasculitis.[65] In this model, wild-type mice with complement 3 (C3) depletion failed to develop vasculitis. Further investigation showed that factor-B-deficient and C5-deficient mice were completely protected from AAV, while disease development was comparable in C4-deficient and wild-type mice, suggesting that activation of the complement alternative pathway plays an important role in the pathogenesis of vasculitis.[65] In subsequent studies, C5a and C5a receptor (C5aR, also known as CD88) were proven to be the key players. Using the same mouse model, NCGN was markedly ameliorated or completely abolished by treating the mice with anti-C5 antibodies or C5aR-deficient BM transplants.[66,67] Knockout of C5aR ameliorated the disease in mice, whereas knockout of C5a-like receptor 2 (C5L2) exerted the opposite effect, suggesting that C5aR/CD88 enhances and C5L2 suppresses inflammation in AAV.[68] In contrast, C6 is not required for disease development in mice.[68] In summary, among the end-products of complement activation, C5a, but not C5b−9, has a crucial role in the pathogenesis of AAV.

Evidence from Human Studies

The results of human studies are consistent with those of animal studies. Chen *et al*. reported that patients with renal C3c deposition had more severe renal involvement.[69] C3d and factor B (marker of the alternative complement pathway) colocalized with C5b−9 in active glomerular lesions,[70] suggesting that alternative complement pathway activation is involved in human AAV. In AAV patients with renal involvement, low serum C3 levels are also associated with unfavorable outcomes.[71] Moreover, the levels of various complement activation products, in particular, Bb in urine or plasma, were higher in patients with active AAV than in patients in remission.[72]

Complement factor H (CFH) is a key regulator of the alternative complement pathway. Chen *et al*. found that circulating CFH levels in active AAV patients were lower than those in patients in remission and were associated with disease activity and renal outcome of AAV patients.[73] More importantly, biofunction of CFH was impaired in AAV patients.[74] One possible mechanism is that MPO binds to CFH, and the MPO-CFH interaction influences the regulatory activity of CFH.[75] In addition, modifications of CFH tyrosine residues could be detected in active AAV patients and might be relevant to the deficient activity of CFH in inhibiting neutrophil activation.[76] These findings indicate that regulators of the alternative complement pathway potentially contribute to the development of AAV.

Although all evidence for the role of the alternative complement pathway emanates from MPO-ANCA-mediated disease, notably in animal models, clinical trials suggest that this also applies to PR3-ANCA-mediated disease. In the phase III study (ADVOCATE trial)[77] involving patients with AAV, 331 patients were included, and 166 of them were assigned to receive avacopan (a small molecule inhibitor of C5aR). The first primary end point was remission at week 26 and no glucocorticoid use in the previous 4 weeks. The second primary end point was sustained remission at both weeks 26 and 52. Remission at week 26 (the first primary end point) was observed in 120 of 166 patients (72.3%) receiving avacopan and in 115 of 164 patients (70.1%) receiving prednisone (P < 0.001 for noninferiority, P = 0.24 for superiority). Sustained remission at week 52 (the second primary end point) was observed in 109 of 166 patients (65.7%) receiving avacopan and in 90 of 164 patients (54.9%) receiving prednisone (P < 0.001 for noninferiority, P = 0.007 for superiority). Among the 166 patients treated with avacopan, 94 (56.6%) were MPO-ANCA positive, and 72 (43.4%) were PR3-ANCA positive.

Evidence from in Vitro Studies

In vitro studies have demonstrated that C5a contributes to the process of neutrophil priming, which is crucial for ANCA-induced neutrophil activation.[64] Blocking C5aR could significantly downregulate neutrophil activation. In animal studies, C5L2 suppresses inflammation in AAV.[68] In contrast, Chen *et al*. found that the inflammatory response of C5a-primed neutrophils *in vitro* could be mitigated by blocking human C5L2.[78] Conclusions about the pathogenesis of AAV from animal models or *in vitro* studies must be tempered because they may not accurately replicate human disease. The role of C5L2 in AAV development needs further investigation.

Two key molecules, namely, high mobility group box 1 (HMGB1) and sphingosine-1-phosphate (S1P), are important downstream effector molecules in the C5a-neutrophil interaction. HMGB1 locates in the nucleus and acts as a proinflammatory mediator when released extracellularly.[79] HMGB1 increases the translocation of ANCA antigens, including MPO and PR3. During the C5a priming process, HMGB1 is released from the cytoplasm into the extracellular space and further enhances the effects of ANCA-induced neutrophil activation. In addition, HMGB1 can potentiate ANCA-induced NETs formation when interacting with RAGE, TLR2 and TLR4

in an NADPH oxidase-dependent manner.[80] The serum HMGB1 level correlates with the disease activity of AAV.[81,82] S1P is a bioactive sphingolipid metabolite released from neutrophils and can upregulate the expression of C5aR on the surface of neutrophils. S1P triggered by C5a-primed neutrophils could further activate neutrophils, forming a vicious cycle.[83] Blocking the S1P receptor will attenuate C5a-induced neutrophil activation by ANCA.[83]

Coagulation System

Patients with AAV are in a hypercoagulable state, with an increased risk of developing venous thromboembolic events.[84] In recent years, increasing evidence has suggested that coagulation system activation may also take part in AAV development. Certain serine proteases from the coagulation cascade, plasmin and thrombin in particular, can directly activate C3 and C5 independent of the traditional C3/C5 convertase.[85] C5a, in turn, can induce the expression of tissue factor (TF) in endothelial cells and neutrophils, thus triggering the extrinsic coagulation system.[86-88] This interaction between the coagulation and complement systems may contribute to the pathogenesis of glomerular capillary tuft infarction as well as the increase in thromboembolic events in AAV.

In addition, the role of complement and platelet interactions in the pathogenesis of AAV was evidenced by Chen's group.[89] In patients with active AAV, platelet counts and platelet-derived microparticles are usually elevated and correlate with disease activity.[90,91] Plasma from active AAV patients could activate platelets, and this could be inhibited by thrombin or protease-activated receptor (PAR) antagonists, indicating that this activation is mediated by the thrombin-PARs pathway.[89] These activated platelets could further amplify complement alternative pathway activation.[89]

B Cells and T Cells

B Cells

ANCA is a major participator in AAV development, and B cells contribute to damaging autoantibody production. B cells can also act as antigen-presenting cells and interact with T cells. Abnormal activation of B cells was observed in AAV patients and was associated with disease severity or poor outcomes.[92-94] Clinical trials have shown that depletion of B cells with rituximab is a useful treatment for AAV.[41,42] All evidence suggests that B cells have a vital role in the pathogenesis of AAV.

Loss of B-cell tolerance results in the emergence of autoreactive B cells and plasma cells. The cause of the loss of immune tolerance is not known. One possible explanation is the hypothetical theory of autoantigen complementarity.[23,51] ANCA formation entails an initial response to complementary

peptides produced by the host or by the invading microorganism and induces anti-idiotypic antibodies of autoantigen epitopes. In addition, B-cell activating factor (BAFF, also known as BLyS) is of vital importance in B-cell homeostasis and interaction with activated T cells. Elevated BAFF concentrations correlate with ANCA titers and disease activity.[95,96] In AAV patients, activated neutrophils could release BAFF and improve the survival of B cells.[97] Overproduction of BAFF may be one of the causes for the presence of autoreactive B cells.

T Cells

T cells have been evidenced to be implicated in the pathogenic process. Such a role is suggested by the presence of CD4+ T cells in AAV lesions[98-100] and by some correlation of the levels of soluble markers of T-cell activation with disease activity.[100,101] Depletion of CD4+ T cells could significantly attenuate the disease severity of AAV in mice.[102] CD4+ T helper (T_H) cells can be classified as T_H1 or T_H2 cells. T_H1 cells exert cellular immune responses and phagocyte-dependent inflammation, while T_H2 cells participate according to their cytokine profile and function. Different cytokine patterns are associated with different functions. In general, T_H2 cells evoke B-cell antibody production (particularly of the IgE class) and eosinophil accumulation, but inhibit functions of phagocytic cells. It is suggested that a shift from the T_H1 to T_H2 response has a crucial role in the development and progression from localized to generalized GPA.[103] Regulatory T (T_{reg}) cells in AAV patients seem defective in their ability to suppress the proliferation of effector cells in cytokine production.[104] The percentage of T cells secreting IL-17 (T_H17) increases in the periphery in active AAV.[105] Moreover, the transcriptional characteristics of CD8+ T cells are associated with the frequency of recurrence in AAV patients.[106]

The cause of the loss of T-cell tolerance and disturbance of T-cell immune homeostasis is not well known. B cells can act as antigen-presenting cells to T cells; thus, the state of T cells in AAV might partially depend on B-cell function.[107] In addition, T cells responsive to cPR3 have been detected in PR3-ANCA vasculitis,[108] suggesting the role of complementary peptides in T-cell autoimmunity. T_H1 cells, T_H17 cells and CD8+ T cells could recognize ANCA antigens released by activated neutrophils and provide help to B cells for the production ANCA or granulomatous formation.[2,19]

In summary, priming of neutrophils by cytokines, including C5a, leads to upregulation of the expression of ANCA target antigen on the cell surface. The primed neutrophils are further activated by ANCA, resulting in respiratory burst and degranulation, as well as releasing of NETs, thus causing damage to vascular endothelial cells. Activated neutrophils could further activate the complement alternative pathway, resulting in the generation of C5a, which amplifies the

inflammatory response by priming neutrophils for ANCA-mediated activation. TF-bearing microparticles are released by activated neutrophils as well, activating the coagulation system and producing thrombin. Thrombin causes activation of platelets, which in turn can further amplify the alternative complement pathway. Disturbed B-cell and T-cell immune homeostasis is also critically involved in disease development.

Conclusion

The development of AAV involves various factors. ANCA, neutrophils, and the complement system are key players that form a positive feedback loop and lead to the pathogenesis of AAV. In-depth exploration of the pathogenesis of AAV might help to offer more effective targeted therapies in the future.

Author contributions

Sun XJ and Li ZY contributed the central idea. Sun XJ drafted the manuscript. Li ZY and Chen M contributed to the revisions.

Informed Consent

Not applicable.

Ethical Statement

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

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