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Pathogenesis of ANCA-Associated Vasculitis

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Abstract Antineutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitides (AAV) are a group of systemic vasculitis syndromes characterized by inflammation and necrosis of blood vessel walls. Genetic, epigenetic, and environmental factors contribute to the etiology and pathogenesis of AAV. On the basis of currently available clinical and experimental evidence, it is reasonable to believe that, in predisposed patients, different triggers can lead to the production of autoantibodies (ANCA) that, in the context of an inflammatory environment, can cause tissue inflammation and vascular injury. Several different pathways and mechanisms in the pathogenesis of AAV are described in this contemporary review.

Keywords ANCA · ANCA-associated vasculitis · Granulomatosis with polyangiitis · Microscopic polyangiitis · Eosinophilic granulomatosis with polyangiitis · Pathogenesis · Etiology

Abbreviations

NG	Necrotizing granuloma
H	Histiocyte
PMN	Polymorphonuclear neutrophil
T	T Lymphocyte
B	B Lymphocyte
DC	Dendritic cell
GC	Giant cell
P	Plasma cell
Mono	Monocyte
PR3	Proteinase 3
LPS	Lipopolysaccharide
ROS	Reactive oxygen species
ANCA	Anti-neutrophil cytoplasmic antibodies
HLE	Human leukocyte elastase
NO	Nitric oxide
MPO	Myeloperoxidase
IL-8	Interleukin 8
MCP-1	Monocyte chemoattractant protein-1
TNFα	Tumor necrosis factor α
IL-1β	Interleukin 1β
IL-1	Interleukin 1
ICAM	Intercellular adhesion molecule
VCAM	Vascular cell adhesion molecule
PGE2	Prostaglandin E2
TxB2	Thromboxane B2
MAC	Membrane attack complex
TLRs	Toll-like receptors

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Introduction

Three systemic autoimmune small-vessel vasculitis syndromes are associated with antineutrophil cytoplasmic autoantibodies (ANCA) and are collectively known as ANCA-associated vasculitides (AAV) [1]. AAV comprises granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg–Strauss syndrome) [1]. These syndromes have distinguishing clinical manifestations and histological findings. GPA and EGPA are characterized by granulomatous inflammation that usually affects the respiratory tract; this is—by definition—absent in MPA. The granulomatous inflammation of GPA is predominantly neutrophilic, whereas that of EGPA is eosinophilic. In contrast, the clinical manifestations caused by necrotizing small-vessel vasculitis and capillaritis, for example diffuse

alveolar hemorrhage, mononeuritis multiplex, or glomerulonephritis, are shared between all three syndromes.

Two different types of ANCA are associated with these syndromes [2]. ANCA directed against the neutrophil serine protease proteinase 3 (PR3) cause a cytoplasmic (C-ANCA) staining pattern on ethanol-fixed neutrophils in indirect immunofluorescence microscopy. PR3-ANCA are the predominant ANCA type in GPA, less common in MPA, and the rare exception in EGPA [2]. In contrast, ANCA directed against myeloperoxidase (MPO) generating a perinuclear (P-ANCA) fluorescence pattern are found in most patients with MPA, but only in approximately 5–10 % of patients with GPA [2]. In EGPA, ANCA are usually of the MPO-ANCA type and can be detected in 30–70 % of patients [3–5].

There is likely to be a contribution of genetic, epigenetic, and environmental factors in the etiology and pathogenesis of AAV. In this review, our objective is to summarize and discuss current views on and insights into the pathogenesis of AAV with particular focus on GPA and MPA.

Epidemiology of AAV

AAV have a reported incidence of 10–20 cases per million per year [6]. The distribution of the specific syndromes varies geographically and with ethnicity [7]. In different populations the annual incidence of GPA is between 4.9 and 10.6 cases per million and the reported point prevalence varies between 24 and 157 cases per million [6, 8–10]. GPA is more common in Northern Europe than in Mediterranean Europe, where MPA is more common [7]. GPA is also exceedingly rare in African Americans and in Japan, where it is almost exclusively encountered on the Northern island of Hokkaido [11, 12]. A similar latitude-dependent incidence gradient has also been documented in New Zealand [13]. Furthermore, in New Zealand and in France the incidence of AAV is higher in the populations of European ethnicity than among Non-Europeans, Asians, or Pacific Islanders [13, 14].

Etiology and Pathogenesis

The etiology of the AAV syndromes is unclear. As for many other polygenic systemic autoimmune diseases, AAV are in all likelihood the result of complex interactions between genetic factors *predisposing* to loss of self-tolerance and autoimmunity and *triggering* environmental exposure. These factors induce and maintain inappropriate lymphocyte activation and autoantibody production which lead to tissue injury and predispose to disease relapses. Table 1 summarizes different mechanisms and pathways that may contribute to the development of AAV.

Genetic Predisposition

There are studies of rare cases in which single gene defects can cause AAV-like phenotypes [15–17]; however, the vast majority of genetic association studies of AAV have been in the context of single nucleotide polymorphisms (SNPs) with small effect size. A familial aggregation study found a relative risk of 1.56 for GPA among first-degree relatives of patients with GPA, which is similar to the risk for rheumatoid arthritis [18]. Familial clustering has also been reported with other AAV syndromes [19, 20]. Several candidate genes have been investigated in different cohorts of patients with AAV, and SNPs have been found in several genes coding for proteins involved in the immune response [21].

Variants most strongly and most reproducibly associated with AAV are found in the human leukocyte antigen (HLA) and *PTPN22* genes [21]. HLA genes, located on the short arm of chromosome 6, have been associated with a variety of autoimmune disorders, for example rheumatoid arthritis, giant cell arteritis, Behçet's disease, and antiglomerular basement membrane disease [22, 23]. Multiple HLA genes have been confirmed to be prevalent in different AAV populations; for example, a group of investigators reported that HLA-DRB1*04 was over-represented in a Caucasian population of German patients with GPA [24] whereas another group located the risk alleles as HLA-DPB1*0401 in a cohort of 282 subjects with GPA [25]. Among Asians, HLA-DRB1*0901 has been found to be associated with MPA and MPO-ANCA-positive vasculitis patients in a Japanese population [26, 27].

Most candidate gene studies in AAV comprise only GPA cohorts. MPA and EGPA are usually underrepresented in many genetic association studies. Nevertheless, interesting genetic differences are emerging between the different syndromes. For instance, the *HLA-DPB1*0401* variant is a strong and reproducible genetic risk factor for GPA, but not for MPA or EGPA [28–30]. Interestingly, African Americans with PR3-ANCA-associated vasculitis had a 36-fold higher likelihood of having the *HLA-DRB1*15* genotype than community-based controls, and the *HLA-DRB*1501* allele, which is of Caucasian rather than African descent, resulted in a 73.3-fold higher risk of PR3-ANCA-associated vasculitis [31].

In contrast, an increase in the *PTPN22* 620 W allele, which has been linked with other autoantibody-associated autoimmune diseases and has thus been implicated in the regulation of B lymphocyte activity, was found to be associated with both GPA and MPA [32–34].

Cytotoxic T lymphocyte antigen 4 (CTLA4), expressed mostly on CD4 positive T lymphocytes, has an inhibitory effect on T lymphocytes by binding to CD80 and CD86 on antigen-presenting cells. CTLA4 competes with the co-

Table 1 Different potential factors in the pathogenesis of ANCA-associated vasculitis

Mechanism	Evidence
Genetic predisposition	Genetic association studies of different SNPs of following genes: HLA, SERPINA1, CTLA 4, *PRTN3* and *PTPN22*
Environmental trigger	Silica as inflammasome complex activator, drugs (propylthiouracil, hydralazine, and penicillamine) which could have polyclonal B lymphocyte stimulatory properties that may induce the production of ANCA
Infectious trigger	*Staphylococcus aureus* eliciting molecular mimicry and T and B cell activation via superantigens
B cells	B cells are precursors of ANCA-forming plasma cells. Increased proportion and total number of B cells have been identified in AAV patients. Elevated B lymphocyte stimulator factors including BAFF have also been identified in AAV patients
T cells	T cells are found within granulomas and in other lesions present in AAV. Elevated levels of markers of T cell activity, for example soluble interleukin-2 (IL-2) receptor, neopterin, and soluble CD30, have been shown to be associated with disease activity Increased T cell number and activity($CD4^+CD25^+$ and $CD4^+CD25^+CD134^+/GITR^+$) have also been found. Functional defect in Tregs ($CD4^+CD25^{high}$ $FoxP3^+CD127^{low}$) have been reported in patients in remission. GPA patients in remission produce increased amounts of Th17 cells($CD4^+IL\text{-}17^+$) reactive to PR3
Autoantibodies (ANCA)	Pathogenic role of ANCA has been supported by several in-vitro and in-vivo animal models. Activation of neutrophils and monocytes by ANCA causes generation of reactive oxygen species, release of proteases, cytokine production and NET formation, which all cause or promote inflammation and tissue damage.
Complement pathway	Increased neutrophil activity via the alternative complement pathway→C5a primes neutrophils and enhances ANCA-induced neutrophil activation. Complement activation and its resulting products promote inflammation and enhance tissue damage.

SNP, single nucleotide polymorphism; HLA, human leukocyte antigen; CTLA4, cytotoxic T-lymphocyte antigen 4; ANCA, anti-neutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; BAFF, B cell activating factor; GPA, granulomatosis with polyangiitis; PR3, proteinase 3

stimulatory molecule CD28, which exerts a stimulatory effect on T lymphocytes, for binding to CD80 and CD86. If T lymphocytes are activated via the T cell receptor and CD28, CTLA4 expression is increased, probably as a regulatory mechanism. Via these mechanisms CTLA4 is thought to maintain peripheral self-tolerance [35]. Elevated levels of CTLA4 have been found in GPA, undoubtedly a reflection of T lymphocyte activation [36]. CTLA4 is coded for by the *CTLA4* gene, and *CTLA4* polymorphisms, which may negatively affect expression or function of CTLA4, have been associated with autoimmune diseases including GPA [33, 37, 38]. Recently, a meta-analysis of seven studies revealed increased susceptibility to AAV associated with CTLA-4 polymorphisms in European patients [39].

Another gene of interest is *PRTN3,* which codes for PR3, the most prominent target antigen for ANCA in GPA. Eight SNPs have been identified in the *PRTN3* promoter region and exons, but their function in PR3 expression is unclear. An increased frequency of one promoter polymorphism (A546G) was found among patients with GPA [40]. PR3 is not only stored in granules and released during neutrophil activation, but it is also expressed on the neutrophil membrane, where it may be engaged by PR3-ANCA. The membrane expression of PR3 varies between individuals, remains constant over time, and seems to be genetically determined [41, 42]. One study found a link between membrane PR3 expression and HLA antigens [43]. Individuals with high membrane PR3 expression are significantly more frequent among patients with GPA than in the normal population, and patients with GPA and high membrane PR3 expression are at higher risk for relapses than those with low membrane PR3 expression [44, 45].

The major natural inhibitor of PR3 is α1-antitrypsin, coded for by the *SERPINA1* gene (*AAT*). Of the many polymorphisms of *AAT,* the Z and S alleles are responsible for most α1-antitrypsin deficiency cases. Increased frequency of heterozygosity for the Z and S alleles in association with GPA, but not MPA, has been reported by several groups in small studies and recently confirmed in larger studies [46, 47]. The clinical significance of this association is not entirely clear, but heterozygosity for the Z allele has been associated with a worse prognosis of the disease [48]. This may be because Z allele carriers, but not S allele carriers, have increased levels of pro-inflammatory polymers circulating in their blood [47]. Deposits of these polymers have been documented in kidney biopsy specimens from patients with active GPA, and these polymers can prime neutrophils and augment the activation of neutrophils by PR3-ANCA in vitro [47].

Unconfirmed or conflicting results have been reported for the association with either GPA or MPA and polymorphisms of other genes, including those coding for the high-affinity soluble interleukin 2 receptor (*IL-2RA*), interleukin 10 (*IL-10*), leukocyte immunoglobulin-like receptor A2 (*LILRA2*), and CD226 (*CD226*), and for the Fc receptors FcRIIa and FcRIIIb [21].

Another, yet unclear, factor to be considered in interpretation of genetic SNP association studies is the issue of copy number variation [49]. Copy number variation as a result of gene duplication, triplication, or exon shuffling may occur at a higher frequency in the genome than SNPs and may be more important for evolution [49]. Study of the effects of copy number variations on the disease phenotype of complex autoimmune diseases including the AAV syndromes is just beginning. Genome-wide association studies (GWAS) have produced valuable insights into the genetic background of several complex immunologic and non-immunologic disorders. Recently, the first GWAS in AAV (GPA and MPA, no EGPA) was performed in the UK in a discovery cohort of 1233 AAV patients and 5884 controls, and was replicated in 1454 northern European case patients and 1666 controls [50••]. This study confirms previous preliminary data revealing heterogenic genetic backgrounds for GPA and MPA, even though the study was relatively underpowered for MPA cases. The strongest associations found in this study were with the antigenic specificity of ANCA (PR3-ANCA versus MPO-ANCA) rather than with the clinical diagnosis (GPA versus MPA). This GWAS confirmed strong associations with the HLA-DP region, the serpin A1 gene (SERPINA1, which encodes α1-antitrypsin), and with the PRTN3 gene (encodes proteinase 3) in patients with PR3 antibodies, and HLA-DQ in patients with MPO antibodies. Other previously reported associations were not confirmed in this study.

In summary, the predisposing genetic factors in AAV are most likely to be heterogeneous and differ between patients. Genetic factors may result in alterations in HLA-mediated antigen presentation, global T and B lymphocyte activation, defective immune regulation, and abnormal target antigen structure and/or function. Whether any of these predisposing genetic factors by itself or in combination is sufficient to cause the disease remains to be determined.

Environmental Exposures and Drugs as Triggers

Environmental triggers of the onset of AAV in susceptible individuals remain unknown for most patients. A significant association between MPA with MPO-ANCA and exposure to silica has been reported [51]. Silica is a potential activator of the inflammasome complex that generates, among other mediators, interleukin 1 (IL-1) [52].

The onset of AAV (predominantly MPA) has also been reported after exposure to a variety of therapeutic agents including propylthiouracil, hydralazine, and penicillamine [53, 54]. These agents have polyclonal B lymphocyte stimulatory properties, which may induce the production of ANCA. However, several features distinguish drug-induced AAV from typical AAV. First, the ANCA response often targets several different antigens at the same time, whereas in typical AAV ANCA target either PR3 or MPO, but not both, and not other additional antigens, for example human neutrophil elastase or lactoferrin. Second, drug-induced AAV usually subsides after discontinuation of the offending agent. Thus, the cases of drug-induced AAV support the hypothesis of the pathogenic role of ANCA in the development of vasculitis, but they do not explain the loss of tolerance to ANCA target antigens characterizing GPA and MPA.

Infectious Triggers

Infectious pathogens, for example mycobacterial and fungal organisms, are the most frequent cause of granulomatous inflammation of the upper respiratory tract. Therefore the presence of granulomatous inflammation in patients with GPA resulted in an initial extensive search for a causative microorganism [55–57]. So far almost all attempts to culture, stain, or treat for infectious pathogens have failed. There are, however, indicators that imply involvement of microorganisms in GPA. Patients with GPA commonly report symptoms of upper respiratory tract infections immediately preceding their initial presentation or a disease relapse [58–61].

Infections have also been implicated as triggers and persistent drivers of a variety of autoimmune diseases including AAV. A variety of different and often interrelated mechanisms by which infections trigger and perpetuate the disease in predisposed patients have been proposed. Many infectious agents have been reported to induce an ANCA response. In most instances these ANCA are directed against target antigens other than MPO or PR3. Furthermore, these infection-associated ANCA usually disappear when the infection resolves [2, 62, 63]. Thus, it seems that two conditions must be met for infections to trigger AAV. First, tolerance to self-antigens must be broken, i.e. host conditions enabling the development of autoimmunity must also enable the ongoing production of antibodies directed against self antigens (ANCA). Second, the persistent specific autoantibodies (ANCA) must have pathogenic potential for the development of tissue injury characteristic of AAV.

One concept by which infections can elicit an autoimmune response in susceptible hosts is molecular mimicry [64]. Subsequent diversification of T and B lymphocyte responses ("epitope spreading") may lead to reactivity with different epitopes on the same target molecule (intramolecular spreading) or even extend to other molecules (intermolecular spreading) [65, 66]. The only example of direct epitope mimicry leading to ANCA in patients with pauci-immune glomerulonephritis has been reported by Kain et al. [67]. They found ANCA targeting lysosomal membrane protein-2 (LAMP-2) in most patients with pauci-immune focal necrotizing glomerulonephritis [67]. These ANCA

recognized an epitope on LAMP-2 and cross-reacted with the homologous bacterial adhesin FimH [67]. Antibodies to LAMP-2 transferred to rats caused pauci-immune glomerulonephritis in the recipients [67]. Rats immunized with FimH developed antibodies to FimH that cross-reacted with human LAMP-2 and also developed pauci-immune glomerulonephritis [67]. The frequency of LAMP-2-specific ANCA has recently been confirmed in different patient cohorts from Europe [68], but not from the US [69]. It also seems that the LAMP-2-specific ANCA disappear quickly after initiation of immunosuppressive therapy, and methods for their detection are not as robust as those used for the detection of PR3-ANCA and MPO-ANCA [68]. Consequently, the clinical relevance of this finding remains controversial.

An indirect mechanism of molecular mimicry leading to typical PR3-ANCA has been proposed by Pendergraft et al. [70]. They demonstrated that in selected patients ANCA may represent anti-idiotype antibodies [71]. Antibodies are formed against complementary peptides (antisense peptide sequence) to PR3 (cPR3) [70]. The cPR3 peptides, which may be mimics of microbial peptide sequences, are the target of the primary immune response. Indeed, several bacterial peptide sequences including *Staphylococcus aureus (S. aureus)* sequences were found to have homologies with cPR3 [70]. True PR3-ANCA are subsequently the result of a secondary immune response mounted against the idiotype of these anti-cPR3 antibodies [70]. Pendergraft et al. were able to show that mice immunized with cPR3 developed antibodies against both cPR3 and PR3, and they found antibodies against cPR3 in seven of 34 PR3-ANCA-positive patients [70]. However, the same group was unable to demonstrate a similar scenario for MPO-ANCA [72]. Furthermore, Tadema et al. were unable to reproduce the increased frequency of anti-cPR3 antibodies in patients with GPA compared with healthy volunteers or with MPO-ANCA positive patients [73]. Interestingly, portions of the cPR3 sequence have homology with portions of the plasminogen sequence, and anti-plasminogen antibodies were detected in some patients with AAV, potentially contributing, among other potential mechanisms, to the well recognized increased risk of thromboembolic events [74, 75].

Whereas direct or indirect epitope mimicry may account for the development of an antibody response, these phenomena do not fully explain the sustained loss of self tolerance observed in most of these patients. A variety of mechanisms by which infections promote the autoimmune response and the propensity for chronic relapses in AAV have recently been studied. Nearly two thirds of patients presenting with GPA are nasal carriers of *S. aureus* [76]. This is much higher than in the general population. *S. aureus* carriers are at higher risk of relapse of GPA than non-carriers, and treatment with trimethoprim-sulfamethoxazole resulted in significant reduction of relapse rate [76–78]. Multiple mechanisms may contribute to the increased risk of relapse conveyed by *S. aureus*. *S. aureus* produces superantigens known to be powerful non-specific (antigen-independent) T and B lymphocyte activators able to induce significant cell proliferation and cytokine release [79, 80]. Patients colonized with superantigen-producing strains of *S. aureus* are at greater risk of disease flares than those colonized with superantigen-negative strains [81]. Compared with healthy controls, patients with GPA were found to have an expansion of T lymphocytes expressing Vbeta segments specific for *S. aureus* superantigen [82]. However, a direct association between the presence of *S. aureus*-producing superantigens and the expansion of T lymphocytes reactive to these superantigens in individual patients could not be confirmed [82].

S. aureus-derived superantigens and peptidoglycans and fungal beta-glucans can induce the expansion of IL-17 producing CD4 positive T cells, so called Th17 cells, in an IL-23 dependent manner [83–85]. Th17 cells, are now recognized as crucial to the development of autoimmunity. They are highly potent inflammatory cells that initiate and maintain tissue inflammation by recruiting other inflammatory cells while generating a milieu that makes them resistant to control by T-regulatory (Treg) cells [86, 87]. Persistent IL-23 production by antigen-presenting cells seems necessary to maintain Th17 cells at the site of inflammation [87]. Both elevated IL-23 and IL-17 levels have been found in patients with active disease and remained elevated despite treatment during clinical remission [88•]. An increased frequency of Th17 cells responding to staphylococcal enterotoxin B was found in GPA patients in remission compared with healthy controls, irrespective of ANCA status, whereas an increased frequency of PR3-responsive Th17 cells was restricted to PR3-ANCA-positive patients [89]. Chronic infections may thus induce chronic ongoing inflammation and the loss of self tolerance.

Necrotizing granulomatous inflammation consisting of monocytes, macrophages, neutrophils, T cells, B cells, and plasma cells, predominantly located in the respiratory tract, sets GPA clinically apart from MPA [1]. Structures resembling germinal centers have been documented within the granulomatous inflammatory tissue of GPA, and the tissue also stained positive for PR3 [90]. The immunoglobulin (VH) gene mutational patterns obtained from granulomatous nasal tissue of patients with GPA suggest that the selection and maturation of PR3-ANCA-producing B lymphocytes may start within the granulomatous lesions [90].

Cytosine–phosphate–guanine (CPG) motifs are pathogen-associated molecular patterns (PAMPs) recognized by the pattern recognition receptor Toll-like receptor 9 (TLR9). Unmethylated CPG oligodeoxynucleotides (CpG-ODN) are potent immune-stimulants. B lymphocytes isolated from patients with AAV with active disease and during remission can be induced to produce ANCA when exposed to CpG-

ODN and IL-2 [91, 92•]. Significantly, more PR3-ANCA patients than MPO-ANCA patients produced ANCA in vitro in response to CpG exposure [92•]. These observations provide another link between *S. aureus* infection, granulomatous inflammation of the respiratory tract, and the greater incidence of relapse among patients with PR3-ANCA or GPA compared with patients with MPO-ANCA or MPA.

Neutrophils are crucially important in the innate immune defense against microorganisms. An additional antimicrobial defense mechanism of neutrophils has recently been described —a unique type of cell death distinct from apoptosis and necrosis that is associated with the formation and release of neutrophil extracellular traps (NETs) [93]. NETs are extracellular structures containing chromatin and granule proteins (including ANCA target antigens) in which invading microbes are trapped and killed. The formation of NETs depends on reactive oxygen species generated by NADPH oxidase [94]. ANCA, which are known to induce a respiratory burst in primed neutrophils, can also induce the formation of NETs, and ANCA antigens bound to NETs are accessible to ANCA [95••]. NETs containing PR3 and MPO are detectable in the kidneys of patients with AAV in the absence of infection. Interestingly, *S. aureus* can rapidly and strongly induce NETs formation even without causing neutrophil death [96••]. Chromatin–immunoglobulin complexes are thought to lead to loss of tolerance and autoantibody (ANCA) production in a TLR9-dependent manner [97]. Taken together, these observations suggest that ANCA may induce a vicious cycle of self-perpetuated NETs formation and more ANCA production, particularly in the presence of *S. aureus* infection. This hypothesis is further supported by observations of increased TLR9 expression by monocytes of patients with GPA who were *S. aureus* nasal carriers [98•].

To summarize, current evidence suggests that infections and/or colonization with infectious organisms for example *S. aureus* contribute to the pathogenesis of AAV, especially GPA. Pathogens may provide the initial antigen sources (molecular mimicry), pro-inflammatory signals (e.g. stimulation of pathogen-associated molecular pattern receptors by CpG, peptidoglycans and fungal beta-glucans), and triggers for innate (NET formation) and adaptive (superantigens) activation of immune cells. In genetically susceptible individuals and/or in the context of other environmental exposures these factors may trigger a break in immune tolerance and the development of sustained or recurrent autoimmunity.

Role of B and T Lymphocytes

The role of B lymphocytes has attracted increased interest after efficacy in AAV of the B-cell-depleting agent rituximab was demonstrated [99]. B lymphocytes have been found in affected tissues including kidneys and, most significantly, in granulomatous lesions of the respiratory tract, where they are located in close proximity to numerous PR3-positive cells and where the selection and maturation into PR3-ANCA-producing B lymphocytes may occur [90]. Antigen-specific B lymphocytes are the progenitor cells of short-lived plasma cells thought to be the source of autoantibodies including ANCA [100, 101]. The proportion of circulating activated B lymphocytes is increased in patients with GPA compared with healthy controls, and it is higher in patients with active disease than in those in remission, and in patients with generalized disease than in those with limited disease [102]. Moreover, elevated serum levels of B lymphocyte stimulator (BLyS, also known as B cell activating factor, BAFF), a cytokine belonging to the TNF superfamily and known to promote B cell survival, differentiation and proliferation, were found in patients with active AAV [103, 104•, 105].

T cells are usually found within granulomas and in other lesions present in AAV. Circulating T cells in AAV have different abnormalities, and disturbed homeostasis that is skewed towards memory and pro-inflammatory T-cell types. ANCA are high-affinity class-switched antibodies [106]. This implies that ANCA production depends on T lymphocyte help, that autoreactive T lymphocytes are present, and that there is insufficient counter-regulation by regulatory T cells (Tregs). Indeed, T lymphocyte abnormalities have long been suspected of being the main reason for the chronic relapsing nature of GPA [102]. Markers of T cell activity, for example soluble IL-2 receptor, neopterin, and soluble CD30, have been shown to be associated with disease activity [107, 108]. Patients with GPA in remission have an increased percentage of circulating CD4-positive effector memory T lymphocytes and a functional defect of circulating CD4-positive CD25 positive Tregs [109, 110, 111••]. Moreover, patients with reduced numbers of Tregs required more prolonged treatment to achieve remission, and the incidence of relapse among these patients was also higher [111••].

As previously discussed, another T cell subset that has recently attracted attention in autoimmunity is the IL-17-producing T cell subset (Th17) [112]. The number of Th17 cells reactive to the autoantigen PR3 was found to be increased in patients with GPA in remission [88•, 113]. Furthermore, Ordonez et al. found that AAV patients have an expanded CD45RC-positive T helper cell population that is a source of IL-17 [114]. IL-17 acts on endothelial cells, epithelial cells, and antigen-presenting cells, causing release of chemokines that will activate neutrophils, for example IL-8 and CXCL-1 [115]. IL-17 can also induce IL1-beta and TNF-alpha production and release by macrophages, and these cytokines, in turn, prime neutrophils and monocytes resulting in the expression of ANCA-target antigens on their surface [116].

Pathogenic Role of ANCA

Clinical observations and a large amount of experimental data suggest pathogenic involvement of ANCA in the

development of small-vessel vasculitis. The small-vessel injury of AAV seems to be caused by activated leukocytes. The pro-inflammatory pathogenic effects of ANCA are all contingent on their interactions with their target antigens expressed on the surface of primed neutrophils and monocytes. When primed with inflammatory cytokines, for example tumor necrosis factor (TNF)-α or microbial products, in vitro, leukocytes express proteinase 3 (PR3) and myeloperoxidase (MPO) on their surface [117, 118]. PR3-ANCA and MPO-ANCA can activate primed neutrophils and monocytes by binding directly to their antigens expressed on the surface or by Fc-receptor engagement; these interactions initiate signal-transduction cascades via multiple pathways that are similar in neutrophils and monocytes [119–123].

Several pro-inflammatory effects derived from the activation of neutrophils and monocytes by ANCA are responsible for the tissue injury in AAV. Fully activated neutrophils degranulate and release toxic proteases and enzymes including elastase, PR3, MPO, and others [117]. ANCA also induce a respiratory burst resulting in the release of oxygen radical species [117, 124]. ANCA also induce expression of cell-adhesion molecules on neutrophils and endothelial cells leading to increased adhesion of neutrophils to endothelial cells [125–129]. Moreover, the binding of ANCA to primed leukocytes induces the production and release of chemotactic cytokines including IL-1, MCP-1 and IL-8 [130–133]. These cytokines attract more neutrophils and monocytes to the site of inflammation. Thus, when the ANCA-induced cytokine release occurs at the endothelial interface, the normal chemotactic gradient that draws neutrophils out of the vasculature into the tissues is lost. This causes further accumulation of fully activated neutrophils in the vessel wall, where they cause more injury. Figure 1 summarizes several complex interactions between ANCA and inflammatory and endothelial cells thought to be instrumental in the formation of granulomatous inflammation and vasculitis.

The ANCA target antigens released from activated or dying neutrophils can also bind directly to endothelial cells [134]. This may result in apoptosis of endothelial cells and in localized immune complex formation with circulating ANCA [135]. Low levels of localized immune-complex deposition, which has been documented in early vasculitic skin lesions and in renal lesions, can, in turn, induce localized complement activation [136, 137].

In-vitro studies have also suggested that ANCA modify the clearance of apoptotic cells. Opsonization of pre-apoptotic cells by ANCA is associated with increased production of inflammatory cytokines by phagocytosing macrophages [138]. Moreover, pre-apoptotic cells have reduced cell-surface expression of phosphatidylserine (the recognition signal for macrophages) in the presence of ANCA [139]. Consequently, in the presence of ANCA the non-inflammatory clearance of apoptotic cells by macrophages may be perturbed in favor of inflammation and necrosis.

Pathogenic involvement of ANCA has also been supported by several in-vivo animal models. These models are based on the transfer of antibodies generated against ANCA target antigens to healthy recipient animals. The transfer of anti-MPO IgG or splenocytes obtained from MPO-knockout mice, which were immunized with murine MPO, into Rag 2 knock-out mice (lacking mature T and B lymphocytes) and into wild-type mice resulted in pauci-immune crescentic necrotizing glomerulonephritis similar to that found in humans [140]. A direct augmenting effect of MPO-ANCA on neutrophil–endothelial interactions causing microvascular injury has been documented in a rat anti-MPO antibody transfer model [141]. Murine anti-PR3 antibodies generated in a similar fashion only caused an increased inflammatory response at the site of tissue injury, but not a vasculitic phenotype, when transferred into wild-type mice [142].

The inflammatory lesions of AAV are referred to as "pauci-immune", implying that only few immune complexes or complement factors can be identified by immunofluorescence microscopy. Furthermore, in contrast with classic immune-complex mediated disease, patients with active AAV have normal serum complement levels. Nevertheless, low-grade localized immune-complex formation and complement activation may be involved, and there is growing evidence suggesting that the complement pathway is involved in the pathogenesis of AAV [137, 143–145]. Moreover, complement activation might also contribute to the increased risk of venous thromboembolism observed in active AAV, because activated complement factors trigger the coagulation cascade [146, 147].

It has recently been recognized that activation of the alternative complement pathway by ANCA may be an important amplification loop of inflammation that contributes to renal (and other tissue) injury in AAV. In the murine anti-MPO antibody transfer model the development of necrotizing glomerulonephritis is dependent on activation of the alternative complement pathway, and the development of lesions can be prevented and treated with an antibody that inhibits complement factor 5 (C5) activation [148, 149]. Mice lacking the receptor for activated C5 on neutrophils also do not develop the renal lesions [150]. In-vitro studies showed that supernatant from ANCA-activated neutrophils can cause the production of C5a in normal serum, C5a receptor dependent priming of normal neutrophils, and increased neutrophil membrane expression of PR3. Although the renal lesions in humans are called "pauci-immune", components of the alternative complement pathway can be detected in patients with AAV, but not in normal controls or in patients with minimum change disease [151].

Despite all this evidence, proof that ANCA alone can cause disease in humans has remained elusive. One case study in which an infant was born to a mother with active

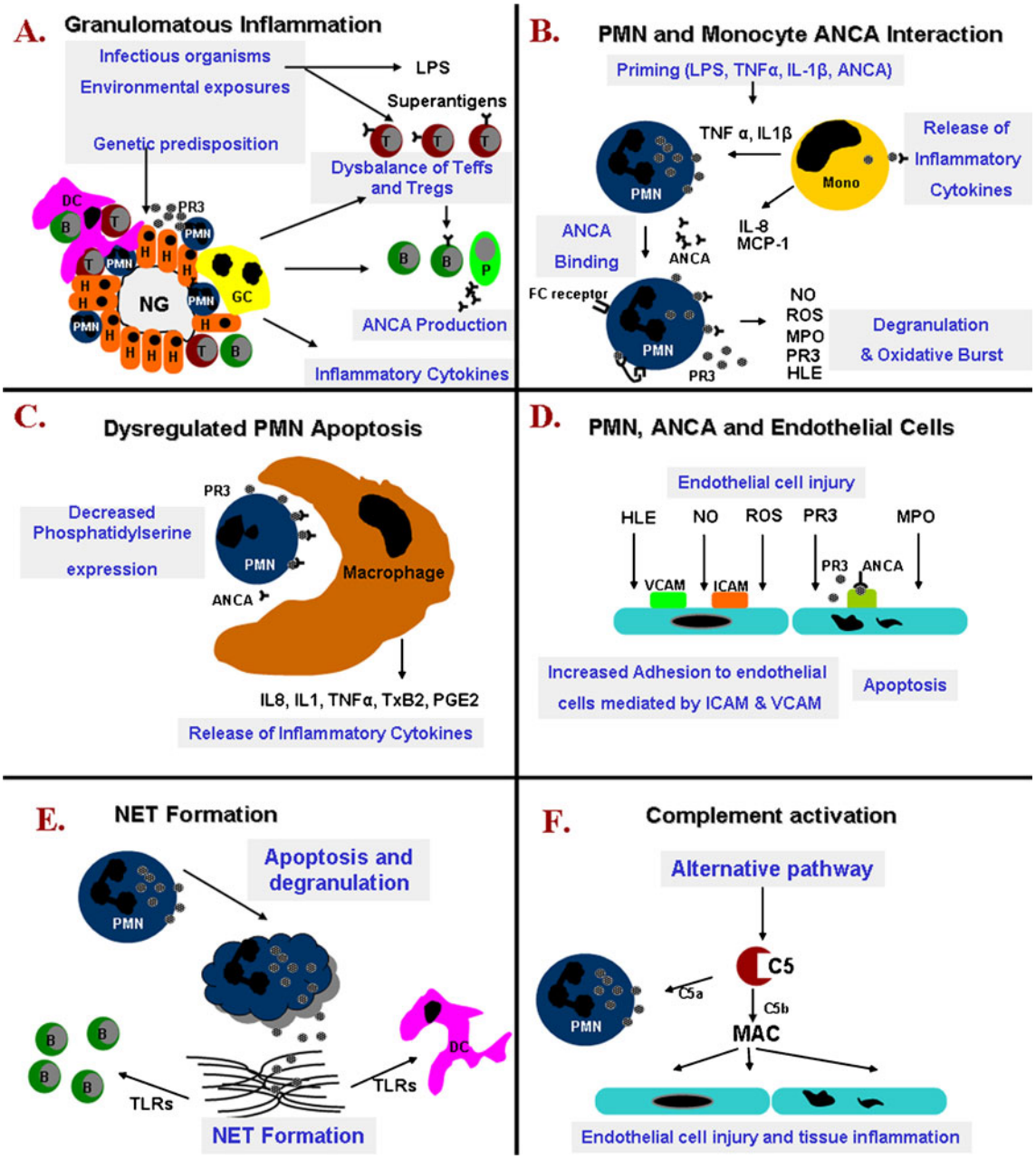

Fig. 1 Pathogenic mechanisms of AAV. (**A**) Necrotizing granulomatous inflammation develops in response to an unknown insult. This inflammatory reaction and the original insult result in release of a variety of cytokines, proteinase 3 (PR3), and, potentially, bacterial superantigens. Granulomatous inflammation in conjunction with the original insult, secreted cytokines, and possibly bacterial superantigen promote the production of ANCA by PR3 specific B lymphocytes and the selection of PR3 specific T cells in predisposed individuals. There is a dysbalance between effector T cells (Teffs) and regulatory T cells (Tregs) with further release of proinflammatory cytokines promoting neutrophil priming. (**B**) ANCA have been shown in vitro to bind to PR3 expressed on the surface of neutrophils and monocytes. ANCA binding results in cellular activation, release of pro-inflammatory cytokines, and neutrophil degranulation. (**C**) In-vitro ANCA also opsonize apoptotic neutrophils by binding to PR3 expressed on their cell surface. In addition in the presence of ANCA, reduced phosphatidylserine expression is observed on the cell surface of apoptotic neutrophils. Neutrophil opsonization and perturbed phosphatidylserine expression result in inappropriate release of pro-inflammatory cytokines by macrophages clearing apoptotic neutrophils. (**D**) Endothelial damage is promoted by a variety of mediators released by neutrophils. In addition, increased expression of cell-adhesion molecules and the presence of ANCA facilitate the binding of neutrophils to endothelial cells. PR3 is internalized by endothelial cells and promotes apoptosis. (**E**) Neutrophil extracellular trap (NET) formation occurs in lesions as a consequence of neutrophil apoptosis and degranulation. NET-derived products activate dendritic cells and B cells by sensing via Toll-like receptors. Interferon (IFN-a) production by dendritic cells might affect local immune regulation and has been shown to impair regulatory T cells function. (**F**) Endothelial damage and tissue inflammation caused by localized complement activation, predominantly by the alternative pathway, resulting in cleavage of C5 into C5b which causes assembly of MAC. C5a is able to prime neutrophils to enhance ANCA-induced neutrophil activation

MPA is often quoted as such evidence [152]. The infant developed a pulmonary-renal syndrome 48 hours after delivery and was found to have serum MPO-ANCA titers similar to the mother [152]. The child was treated with glucocorticoids and plasma exchange and recovered. However, this observation is countered by another report of a case in which MPO-ANCA were also transferred from the mother to the newborn, but the newborn remained perfectly healthy despite persistence of the transferred MPO-ANCA in the newborn for several weeks [153]. The two contrasting case studies are consistent with observations made in large cohort studies. The development of severe vasculitic disease manifestations and severe flares usually do not occur in the absence of ANCA, but not all patients with persistent ANCA inevitably suffer such flares [76, 154–156].

Conclusions

On the basis of currently available clinical and experimental evidence it is reasonable to believe that in predisposed patients different triggers can lead to the production of autoantibodies (ANCA) that in the context of an inflammatory environment can cause tissue inflammation and vascular injury. However, many of the proposed mechanisms behind the pathophysiology of AAV may apply solely to specific clinical subsets of patients. Moreover, despite the several different pathways and mechanisms described in this review, there is not a one-size-fits all cases, or even most of the cases. Despite the substantial advances in our understanding of the pathogenesis of AAV, many open questions remain. As our knowledge regarding the pathogenesis of AAV evolves, new therapeutic targeted strategies are emerging in the continuing quest to control disease activity with the minimum of adverse effects in individual patients.

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- • Of importance
- •• Of major importance

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