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Pathogenesis of ANCA-Associated Pulmonary Vasculitis

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Abstract

Antineutrophil cytoplasmic antibodies (ANCAs) are autoantibodies specific for antigens located in the cytoplasmic granules of neutrophils and lysosomes of monocytes. ANCAs are associated with a spectrum of necrotizing vasculitis that includes granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis. Pulmonary vasculitis and related extravascular inflammation and fibrosis are frequent components of ANCA vasculitis. In this review, we detail the factors that have been associated with the origin of the ANCA autoimmune response and summarize the most relevant clinical observations, in vitro evidence, and animal studies strongly indicating the pathogenic potential of ANCA. In addition, we describe the putative sequence of pathogenic mechanisms driven by ANCA-induced activation of neutrophils that result in small vessel necrotizing vasculitis and extravascular granulomatous necrotizing inflammation.

Keywords

ANCA; granulomatosis with polyangiitis; microscopic polyangiitis; pulmonary vasculitis

Antineutrophil cytoplasmic antibodies (ANCAs) are autoantibodies specific for antigens located in the cytoplasmic granules of neutrophils and lysosomes of monocytes.[1] The two major autoantigen targets of ANCA are myeloperoxidase (MPO) and proteinase 3 (PR3).[1] The term ANCA vasculitis refers to a particular group of autoimmune disorders characterized by necrotizing vasculitis, absence or paucity of immune deposits, and predominant involvement of small vessels, that is, capillaries, venules, arterioles, and small arteries.[2] Granulomatosis with polyangiitis (GPA, formerly called Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss' syndrome) are the major clinicopathologic forms of small vessel vasculitis associated with ANCA. Some patients with ANCAvasculitis have no evidence for lungdisease, for example, patient with renal limited vasculitis (RLV). Optimum clinical classification of ANCA vasculitis includes both the serotype (PR3-ANCA,

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MPO-ANCA, or ANCA negative) and the clinico-pathologic phenotype (MPA, GPA, EGPA, RLV).[2]

ANCA vasculitides are the major cause of vasculitis affecting the lung. Pulmonary involvement has been reported to occur in almost half of GPA patients at diagnosis. Characteristic acute pulmonary pathologic lesions include hemorrhagic capillaritis, necrotizing arteritis, and necrotizing granulomatous inflammation (►Fig. 1). Approximately 70 to 90% of GPA patients will eventually develop evidence of lung disease during the course of their disease, for example, pulmonary hemorrhage, nodules, masses, cavities, or airway inflammatory lesions.[3,4] In MPA, the overall prevalence of pulmonary vasculitis, typically presented as diffuse alveolar hemorrhage caused by pulmonary capillaritis, is around 35 to 50%.[5,6] Pulmonary vasculitis is less frequently associated with other primary vasculitides, systemic autoimmune disorders, infections, and drugs (►Table 1). This article reviews the current understanding of the origin and pathogenesis of ANCA vasculitis, with a special focus on GPA and MPA. EGPA is reviewed by Guillevin et al on page 471–481.

Genesis of the ANCA Response

The precise cause of ANCA immune genesis remains unclear, but probably involves a complex process where multiple elements converge, that is, infections, genetic influences, environmental exposures, and abnormalities of the innate and acquired immune system.[7] The role that each of these factors plays in the induction of the autoantibodies and the persistence of the ANCA pathogenic response varies among individuals.

Infections

As the lungs are affected in most patients with ANCA vasculitis, respiratory pathogens have been largely implicated in the pathogenesis of these diseases, particularly in GPA. One proposed mechanism for the development of ANCA suggests the initiation of the autoimmune response by peptides that are complementary to peptides in the target antigens, such as PR3. Putatively, the adaptive immune response against a complimentary peptide of PR3 (cPR3) elicits its cognate antibody, which in turn evokes an antiidiotype of this antibody with specificity for PR3.[8] Findings that support this theory included the detection of antibodies directed against antisense peptides that are complementary to autoantigen epitopes on PR3 in patients with PR3-ANCA vasculitis, the presence of circulating anti-cPR3 specific memory T cells, and the production of anti-PR3 antibodies after immunization of mice with cPR3.[8,9]

Of particular interest for lung vasculitis is the fact that *Staphylococcus aureus* has peptides that mimic cPR3, and thus, in theory, infection by this microorganism might initiate or augment an immune response to the peptide mimic of antisense PR3, which in turn would result in anti-idiotypic antibodies that react with PR3.[8] It is important to realize that *S. aureus* has long been known to be associated with GPA. Previous studies have shown that 60 to 70% of PR3-ANCA GPA patients are chronic nasal carriers of *S. aureus,* a state that has been associated with an increased risk of relapses, including pulmonary flares.[10,11] Furthermore, the risk for reactivation in these patients is highest in the presence of *S. aureus*

strains producing the toxic shock syndrome toxin-1, superantigen with a strong immunostimulatory capacity.[12] Of relevance, the addition of trimethoprim/sulfamethoxazole to standard remission maintenance reduced the risk of nonsevere relapses in GPA patients, probably by preventing respiratory tract infections.[13,14]

Entamoeba histolytica and Ross River virus are other pathogens with known peptides that mimic cPR3.[8] In addition, ANCA has also been detected in patients with bacterial endocarditis. In these rare cases, ANCA are usually directed to both MPO and PR3 and are associated with other autoantibodies, such as antiphospholipid and antinuclear antibodies.[15,16]

Drugs

Certain drugs such as propylthiouracil, minocycline, allopurinol, levamisole-adulterated cocaine, D-penicillamine, and diphenylhydantoin have been associated with the induction of ANCA and the development of pulmonary capillaritis, diffuse alveolar hemorrhage, and glomerulonephritis.[17,18] In contrast with primary ANCA disease, drugs usually induce a heterogeneous ANCA response with antibodies that are not only directed to MPO and PR3 but also to other neutrophil granule proteins, for example, azurocidin, cathepsin G, elastase, or lactoferrin.[19,20]

Environmental Factors

As for pulmonary vasculitis, the inhalation of an external agent seems to be an interesting, although still unproven possible trigger event.[21,22] In this sense, previous epidemiological studies have shown a significant association between ANCA vasculitis and high exposure to dust and heavy metals, that is, silica, mercury, and lead.[21,23–25] Extensive exposure to silica might result in its accumulation in antigen-presenting cells and macrophages of the reticuloendothelial system, where it can act as an effective adjuvant enhancing the autoimmune ANCA response. Strong occupational exposures to inhaled fumes, pesticides, and hydrocarbons have also been reported in GPA patients.[26,27] Further, as the incidence of GPA correlates inversely with ambient ultraviolet (UV) radiation, some authors have suggested a causative role for low UV radiation exposure (possibly acting via vitamin D status) in the development of ANCA vasculitis.[28,29]

Genetic Factors

Genetic predisposition influences the onset and development of ANCA vasculitis. Results of two large-scale genomewide association studies (GWASs) have implicated a genetic role on the pathogenesis of ANCA disease, that is, PR3-ANCA vasculitis was associated with single nucleotide polymorphisms (SNP) in the HLA-DP1 area and genes encoding PR3 (PRTN3) and α1-antitrypsin (SERPINA1), the predominant inhibitor of PR3; for patients with MPO-ANCA serotype, a significant association was identified with SNP in HLA-DQ.[30,31] The strong association of ANCA disease with distinct HLA molecules suggests a central role of autoimmunity in ANCA implicating that HLA-determined immune response against PR3, MPO, and cPR3 influences the initiation of the ANCA autoimmune response.[31,32]

In these GWASs, the genetic associations were stronger for ANCA specificity than for clinical phenotype, consistent with two distinct immune responses initiated by recognition by HLA receptors of two different types of initiating antigens. Some of the marked clinical heterogeneity observed in ANCA patients may be influenced at least in part by genetic factors. In this sense, it is interesting to note that certain pulmonary manifestations, that is, lung nodules and cavities, predominate in PR3-ANCA cases, whereas alveolar capillaritis with pulmonary hemorrhage, bronchiectasis, and lung fibrosis are much more associated to MPO-ANCA.[33–37]

Other relevant associations that support the importance of genetics in ANCA vasculitis include an increased prevalence of MHC class II allele HLA-DRB1–15 in PR3-ANCA disease among African American patients as well as polymorphism variants of *PTPN22* and *CTLA4* genes.[32,38] A genetic influence has also been suggested by a greater frequency in first-degree relatives and sporadic reports of familial occurrence.[39]

Finally, epigenetic factors also seem to influence the pathogenesis of ANCA vasculitis. ANCA patients have an abnormal epigenetic regulation of *PR3* and *MPO* genes that results in the continued overexpression of both autoantigens in circulating neutrophils.[40] Theoretically, the increased availability of PR3 and MPO could facilitate the loss of tolerance to these proteins or facilitate pathogenic events.[41]

Abnormalities in the Regulation of the ANCA Autoimmune Response

The ability of the immune system to distinguish between self- and non-self-antigens is known as self-tolerance, an important process finely regulated by regulatory B cells and regulatory T cells (Treg). In the context of ANCA vasculitis, the autoimmune response leading to the development of ANCA appears to be facilitated on one hand by impaired T cell and B cell suppression, and on the other hand by enhanced B cell stimulation by ANCA-activated neutrophils.

Clinical and experimental studies have identified several abnormalities in the number and function of specific T cell subsets in ANCA vasculitis patients.[42–52] Former studies have reported a persistent increase of CD4+ effector memory T cells (T_{EM}) in the peripheral blood of GPA patients.[51] CD4+ T_{EM} cells are probably involved in tissue damage and kidney injury, as suggested by the detection of an elevated number of these cells in urine sediments of active patients and their disappearance during remission.[49–52] Analysis of the CD4+ T cell compartment has also disclosed an increased frequency of a distinct proinflammatory CD4+ effector T cell ($CD25^{int}$) subset that is resistant to Treg suppression.[44] An expanded population of CD4+T cells lacking the costimulatory molecule CD28 has been reported in GPA granulomatous lesions.[46,53] In addition to T_{EM}, the suppressive capacity of regulatory T cells is markedly decreased in these patients, thus probably contributing to loss of tolerance and emergence of a pathogenic ANCA response.[42,44] Aberrant T-helper cell polarization has also been described in ANCA disease, that is, patients have a significant elevation of serum levels of interleukin (IL)-17, IL-21, and IL-23, in addition to increased autoantigen-specific Th17 cells.[47,48,54] Overall, these data indicate that T cells participate in the genesis of autoantibody production and development of ANCA

disease by providing active B cell help, through ineffective suppression of the ANCA autoimmune response, by directly participating in the damage of tissue organs, and by sustaining the autoimmune reaction through interactions with dendritic cells and B cells within the granulomatous lesions of the respiratory tract.[55]

B cells are the precursors for plasma cells that produce ANCA, and undoubtedly are involved in the pathogenesis of ANCA vasculitis. However, several abnormalities in the phenotype of circulating B cells have also been reported, for example, quantitative and qualitative defects of B-regulatory lymphocytes,[56,57] or the overexpression of CD19+, possibly leading to B cell hyperactivation.[58] In addition, activated neutrophils release mediators that enhance the proliferation and inhibit apoptosis of B lymphocytes.[59]

It is important to realize that a certain proportion of mature B cells in healthy individuals are actually autoreactive and able to secrete “natural autoantibodies” against MPO and PR3.[60] In this regard, some authors have suggested that endogenous and exogenous influences (as those previously described in this section) might modify intrinsic characteristics, for example, epitope specificity, of nonpathogenic natural autoantibodies to render them pathogenic.[61,62]

Clinical and In Vitro Evidence for the Pathogenicity of ANCA

Several clinical observations support the participation of ANCA in the pathogenesis of ANCA-associated systemic vasculitis.[62] A frequently cited example is the report of a prematurely born infant who developed pulmonary hemorrhage and renal disease within days after birth following transplacental passage of MPO-ANCA from his mother affected with MPA. Although this report provides direct evidence for the pathogenic role of MPO-ANCA in humans, no other similar cases have been published.[63]

Also consistent with an important role for ANCA in the pathogenesis of human disease is the finding of high levels of these autoantibodies in the vast majority of patients with active generalized GPA and MPA, the fall of ANCA titers during therapy, and the correlation of disease activity with higher levels of PR3 or MPO on the surface of circulating neutrophils.[64–66] Although the correlation is not absolute, several studies have reported that ANCA titers correlate with disease activity and recurrences in specific subsets of patients, for example, an increase of PR3-ANCA level has been associated with the development of severe relapses in patients with previous alveolar hemorrhage or renal involvement and in those treated with rituximab.[67]

The efficacy of rituximab and plasma exchange, targeted therapies that reduce B-lymphocytes and deplete circulating autoantibodies, also argues in favor of the participation of ANCA in the pathogenesis of systemic vasculitis.[68–70] In fact, severe reactivations of ANCA vasculitis following complete remission with rituximab are rare exceptions in the absence of detectable ANCA.[71] In this line, a recent clinical trial showed that the pre-emptive use of rituximab based on rising ANCA levels (or repopulation of CD19+ B lymphocytes) was an effective therapeutic strategy for remission maintenance.[72]

The close association of the development of ANCA vasculitis following specific drug exposures and more importantly, the resolution of clinical manifestations and clearance of the autoantibodies after discontinuation of the offending medication is another observation that adds circumstantial evidence for the pathogenicity of ANCA.[73–76]

Extensive in vitro evidence demonstrates mechanisms by which ANCA could cause vascular inflammation.[77–79] For example, incubation of ANCA immunoglobulin G (IgG) with primed neutrophils and monocytes induces the release of mediators of inflammation such as toxic reactive oxygen species and lytic granule enzymes.[78,80,81] Also, several studies have demonstrated that surface expression of ANCA autoantigens is low or absent in resting neutrophils, but it is rapidly up-regulated after inflammatory stimuli such as tumor necrosis factor (TNF)-α, bacterial lipopolysaccharide (LPS), or the complement anaphylatoxin C5a.[80,82,83] In this regard, a reasonable hypothesis is that in ANCA patients, an inflammatory process, for example, a respiratory tract infection, may cause increased levels of circulating cytokines, which in turn prime neutrophils to interact with circulating ANCA to induce vasculitis.[79] The identification of a "*flu-like syndrome*" (clinical evidence for elevated circulating cytokines) occurring in most ANCA patients shortly before the onset ofovert clinical manifestations is in line with this hypothetical scenario.[79,84] Experimental evidence also supports this hypothesis, as injection of bacterial LPS into mice prior to induction of glomerulonephritis with anti-MPO IgG causes more severe injury.[85]

In vitro experiments have also been used to demonstrate that ANCA-activated neutrophils cause the death of endothelial cells; that ANCA IgG stimulates the adherence and rolling of neutrophils to endothelial monolayers through integrin-mediated mechanisms; that ANCA antigen targets and ANCA-containing immune complexes may become planted in vessel walls, where they might become toxic or contribute to further targeting of endothelial cells by activated neutrophils and monocytes; and that ANCA stimulates the release of neutrophil extracellular traps (NETs), which can cause damage to endothelial cells.[86–91] The effect of ANCA on stimulation of leukocyte adhesion and migration across the endothelium has been confirmed in vivo by intravital microscopy of mice cremasteric vessels.[92]

Although the major pathogenic effects of ANCA are induced by neutrophil activation after the engagement of Fcγ receptors (FcγR), or cross-linking of F(ab′)2 fragments,[93,94] recent studies have suggested that MPO-ANCA antibodies may also cause damage of endothelial cells acting directly through the activation of MPO.[95,96]

Animal Models of ANCA Vasculitis

Although clinical and in vitro observations support the participation of ANCA in the pathogenesis of systemic vasculitis, the most definite evidence that ANCA are pathogenic comes from animal models. The first convincing animal model for ANCA vasculitis was produced in mice through the intravenous injection of high-affinity anti-MPO IgG.[97] In this model, mice with a knockout (KO) of the *MPO* gene ($MPO^{-/-}$) are immunized with purified murine MPO and in consequence develop a robust immune response with high titers of circulating antibodies directed against MPO. Once isolated, the intravenous injection of anti-MPO IgG into wild-type (WT) B6 mice induces over the course of 6 days, necrotizing and

crescentic glomerulonephritis (NCGN) that is pathologically identical to that observed in ANCA patients. In addition, the passive transfer of anti-MPO antibodies into immunodeficient recombinase-activating gene-2-deficient ($Rag2^{-/-}$) mice (lacking both functional T and B cells) produces NCGN with similar characteristics to that found in WT B6 animals, indicating that functioning T lymphocytes are not required for the pathogenesis of vasculitis in this model.[97] Similar lesions are induced in $Rag2^{-/-}$ mice by transplantation of splenocytes from MPO knockout mice that had been immunized with murine MPO. In the initial experiments with these models, NCGN was the most common vasculitic lesion; however, some animals developed pulmonary lesions including hemorrhagic capillaritis, necrotizing arteritis, and granulomatous inflammation (►Fig. 2).

Studies using the model described earlier, or its variants,[85,97–101] have proven to be a valuable tool to demonstrate that (1) MPO-ANCA antibodies alone, in the absence of functional T cells, are sufficient to cause acute disease; (2) depletion of circulating neutrophils protects against the development of NCGN, indicating that these cells are the mainstay effectors of anti-MPO-induced vasculitis; (3) bone marrow–derived cells, that is, MPO-expressing hematopoietic cells, are not only sufficient but also necessary to induce ANCA glomerulonephritis; (4) the synergistic effect of neutrophil priming with proinflammatory stimuli results in an exacerbation of ANCA disease severity; (5) Fc receptors are involved in pathogenesis and disease modulation; (6) genetic background plays a profound effect in the susceptibility and severity of disease; and (7) activation of the alternative complement pathway is a critical mediator of injury in ANCA-associated NCGN, with activation of C5 and engagement of C5a to its receptor playing an essential role in this process.[85,97–101] Several observations made in patients have also confirmed the relevance of the complement system in the pathogenesis of ANCA disease, for example, elevated plasma and urinary levels of C5a in active vasculitis; the detection of complement factors in inflamed glomeruli and small blood vessels; and recently, the successful use of avacopan (selective inhibitor of C5a receptor) for remission induction of patients with ANCA glomerulonephritis.[102–105]

A rat model based on the immunization of animals with human recombinant MPO (hMPO) has confirmed the observations made in mice.[106,107] In this model, injection of purified hMPO into Wistar–Kyoto rats lead to the induction of antihuman MPO antibodies that cross-react with rat MPO, resulting in the development of pauci-immune NCGN.[106] The role of T cells in ANCA pathogenesis has been studied in a mouse model of autoimmune glomerulonephritis that results from the synergy between anti-MPO and antiglomerular basement antibodies.[108]

The discussion so far focused on the pathogenic properties of MPO-ANCA as unfortunately, a clear-cut animal model for PR3-ANCA disease is still lacking. Although several putative models have been proposed,[109] the most promising method for modeling ANCA-PR3 disease involves the development of mice with a humanized immune system.[110] In a recently described model, NOD-SCID IL-2 receptor KO mice (lacking native T, B, and NK cells and the IL-2 receptor), which received human hematopoietic stem cells thus developing a chimeric human–mouse immune system developed mild glomerulonephritis following the administration of human PR3-ANCA IgG.[110] Although the observed lesions identified in the

latter model do not closely resemble those in human disease, the use of chimeric mice engineered with human immune machinery is an exciting future approach to investigate the pathogenesis of ANCA vasculitis.

The aforementioned animal models are centered on the induction of glomerular inflammatory lesions; however, the development of pulmonary vasculitis has been reported only sporadically in these experimental rodents. In the passive transfer model, less than 30% of mice developed mild pulmonary alveolar capillaritis usually affecting less than 5% of the lung parenchyma.[97] In addition, hemorrhagic pulmonary capillaritis was reported only in small proportion of the chimeric NOD-SCID mice and in rats after immunization with human MPO.[106,110]

Until recently, previous attempts to reproduce the pulmonary manifestations of ANCA vasculitis in animal models have been unsuccessful.[111,112] For example, infusion of monoclonal anti-PR3 antibodies and TNF-α-primed human neutrophils into isolated rat lungs resulted in marked edema, but not overt vasculitis.[112] In a different approach, the immunization of BALB/c mice with human IgG C-ANCA generated an anti-idiotypic reaction that resulted in the development of nonspecific foci of inflammation in the lungs of some animals.[111] These pulmonary lesions, however, did not present histologic evidence of vasculitis or granulomatous inflammation and importantly, were mediated by immune complex deposits, clearly contrasting with the pauci-immune nature of ANCA inflammatory injury.

In unpublished studies, our group has observed that MPO-ANCA can cause severe pulmonary vasculitis in mice if they have adequate predisposing characteristics of the innate immune system and synergistic lung inflammation, for example, concurrent influenza infection.[113,114] Furthermore, on the basis of these observations, we recently developed a reproducible method to induce extravascular lung granulomatous inflammatory lesions and necrotizing vasculitis in WT B6 mice.[115] This new GPA model is detailed in the Pathogenesis of Granulomatosis section.

Pathogenesis of Vascular Inflammation

The hypothetical sequence of pathogenic events leading to the development of ANCA-associated vasculitis is illustrated in ►Fig. 3. Once pathogenic ANCA are in the circulation, they activate neutrophils by reacting with ANCA antigens. As previously mentioned, priming of neutrophils by an inflammatory stimuli facilitates the interaction of MPO-ANCA and PR3-ANCA with their target antigens.[62] Binding of ANCA to ANCA antigens on the surface of neutrophils results in neutrophil activation through Fcγ receptor engagement and through cross-linking of F(ab′)2 fragments.[93,94] Then, activated neutrophils adhere and penetrate vessel walls, releasing toxic oxygen radicals; destructive enzymes that cause apoptosis and necrosis of adjacent cells; and granule proteins, which might become planted in vessel walls by a charge-dependent mechanism, allowing their further interaction with additional ANCA.[62,65,80,89,116] Neutrophils also secrete factors that activate the alternative complement pathway leading to the generation of C5a, which recruits and activates more neutrophils to the site of inflammation, establishing an inflammatory amplification loop that

increases destructive necrotizing inflammation.[98] The activation of the complement system by neutrophils is probably mediated by the inhibitory effect of MPO on factor H, a key regulator of the alternative pathway.[117] ANCA-induced NETs probably also play a role in complement activation.[118]

As neutrophils, monocytes are also activated by ANCA, resulting in the production of proinflammatory cytokines, for example, IL-8, and chemokines, for example, monocyte chemoattractant protein 1 (MCP-1).[119–121] On one hand, IL-8 can attract and activate neutrophils thus amplifying neutrophil-mediated injury, and on the other hand, MCP-1 attracts monocytes and macrophages, probably participating in the transition from neutrophil-rich inflammation to predominant monocyte-rich inflammation and in the development of granulomatous lesions.[119] Macrophages are also able to produce inflammatory chemokines in response to phagocytosis of PR3-expressing apoptotic cells.[122]

As a result of the intense necrotizing injury induced by activated neutrophils, blood vessel walls are disrupted producing local hemorrhage and releasing plasma proteins into vascular and perivascular tissues, where activation of coagulation cascade results in the formation of typical fibrinoid necrosis.[62,87] Within days, the severe acute injury elicits an innate inflammatory response and the initial acute neutrophil-rich inflammation and necrosis is replaced by inflammation with a predominance of monocytes, macrophages, and later Tcells.[97] When tissue injury is mild, it resolves with remodeling of the vessel to normal structure. In contrast, severe damage turns into fibroblast activation with collagen deposit, resulting in fibrosis and sclerosis of injured vessels and adjacent tissue.

The pathogenic features of necrotizing vasculitis described here seem to be the same in the skin, kidney, nerve, and every other organ. In the particular case of the lungs, the intense neutrophilic infiltration of the alveolar septa (alveolar capillaritis) produces necrosis, leukocytoclasia, and loss of the capillary integrity with spilling of red blood cells into the alveolar space and interstitium. The clinical expression of this pathogenic injury, that is, diffuse alveolar hemorrhage, is a prominent and life-threatening manifestation of ANCA vasculitis.

Pathogenesis of Granulomatosis

In addition to vasculitis, GPA is characterized by multiple foci of extravascular necrotizing granulomatous inflammation most often affecting the upper and lower respiratory tracts. In the lung, these granulomatous lesions are clinically presented as multiple bilateral parenchymal nodules and masses that may become cavitated.

The pathogenic mechanisms involved in the development of ANCA necrotizing granulomatous inflammation are not completely understood. Based on detailed pathology descriptions[123,124] and a recently described animal model,[115] the leading hypothesis is that in a process analogous to vascular inflammation, granulomatous lesions start with the activation of extravascular primed neutrophils—that have been positioned in the airway mucosa by a respiratory infection or other inflammatory condition—by ANCA located in the interstitial compartment (►Fig. 4). Once activated, neutrophils liberate reactive oxygen

species and destructive enzymes that result in an intense localized tissue necrosis with abundant fibrin formation, initially resembling microabscesses. In these early granulomatous pulmonary lesions, acute parenchymal damage would elicit a high influx of mononuclear cells. Over time, the neutrophil-rich acute necrotizing lesions would accrue large numbers of mononuclear leukocytes evolving into more typical granulomatous appearance, that is, the center of the lesion contains necrotic debris that is walled off by a well-defined band of numerous epithelioid macrophages. In addition to macrophages, granulomatous inflammation is typically composed by a mixed inflammatory infiltrate of dendritic cells, B and T lymphocytes, eosinophils, and plasma cells.[62,116,125] Weeks after the initial insult, necrotic debris and macrophage-rich lesions are replaced by deposition of collagen, fibrous tissue, and organized lymphoid follicles.[62]

In a recent mouse model of anti-MPO-ANCA-induced pulmonary granulomatosis, early granulomatous lesions initiate as neutrophil-rich microabscesses containing neutrophils in varying stages of necrosis and apoptosis;[115] these lesions were identical to those described as an early form of parenchymal necrosis in lung specimens obtained from GPA patients.[123] The time course of this model showed that later, by the end of the first week, the extensive tissue necrosis and fibrinoid material were totally replaced by monocytes, macrophages, and scattered giant cells.[115] Although the participation of functional T cells were not required for induction of granulomatous lesions in this animal model, it is probably that lymphocytes may indeed play a role in human disease as organized lymphoid follicles with clusters of PR3 cells surrounded by mature B lymphocytes and effector memory T cells have been described in lung specimens from GPA patients.[46,126]

An alternative proposal for the pathogenesis of ANCA granulomatous inflammation suggests that in contrast to the exaggerated antigen-independent innate response described earlier, GPA granulomas are indeed a consequence of an antigen-specific T cell immune response.[127] In this theory, PR3 and MPO released from activated neutrophils are processed and presented by antigen-presenting cells to autoreactive T-lymphocytes. As Treg fails to inhibit this autoimmune response, a T cell effector memory response eventually lead to the development of granulomatous lesions, some of which displaying features of ectopic lymphoid-like tissue.[46,127,128] According to some authors, the lymphocyte clusters in these granulomatous lesions may provide a place to sustain the autoimmunity response to ANCA autoantigens.[127]

Pathogenesis of Interstitial Lung Disease

Pulmonary fibrosis is an uncommon although severe complication of ANCA vasculitis. The disease is strongly associated with ANCA specific to MPO and therefore has been reported more frequently in MPA patients. The etiology of ANCA-associated lung fibrosis remains obscure, although recurrent episodes of subclinical alveolar hemorrhage have been incriminated as the leading factor in the pathogenesis of this condition.[129–131] In addition, MPO-ANCA seems to play a direct role in the development of interstitial lung disease (ILD), as suggested by the presence of positive MPO-ANCA autoantibodies in the vast majority of patients who develop this pulmonary manifestation. Further, recent evidence has demonstrated that anti-MPO-ANCA, acting through the activation of MPO, are able to

trigger fibroblast proliferation.[95] Local release proteolytic enzymes by ANCA-activated neutrophils and chronic pulmonary parenchymal ischemia are other putative contributors of ANCA-associated ILD.[34]

Conclusion

Clinical, in vitro and experimental animal model evidence supports the pathogenic role for ANCA in the pathogenesis of ANCA-associated systemic necrotizing vasculitis. In the future, a better understanding of the pathogenic mechanisms leading to the development and progression of pulmonary vasculitis and lung necrotizing granulomatous lesions will enable more targeted and effective therapies, and hopefully, to the cure of these diseases.

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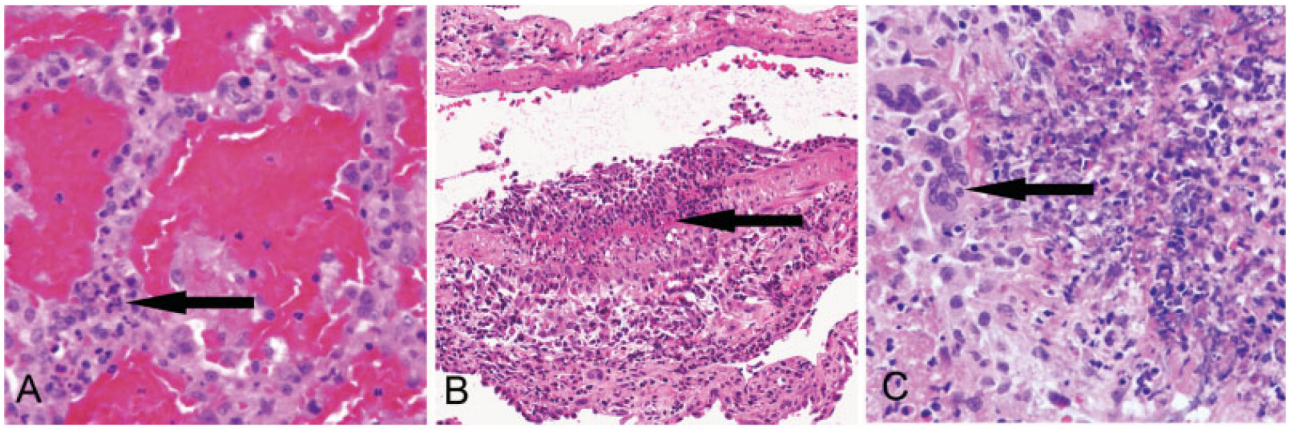

Fig. 1.

ANCA vasculitis lung lesions (H&E stain). (A) Pulmonary hemorrhagic capillaritis showing numerous neutrophils within alveolar septal capillaries (arrow) and red blood cells in air spaces (H&E stain). (B) Intense segmental acute arteritis in lung with transmural inflammation (arrow). (C) Granulomatous inflammation with multinucleated giant cells (arrow) (H&E stain). ANCA, antineutrophil cytoplasmic antibody.

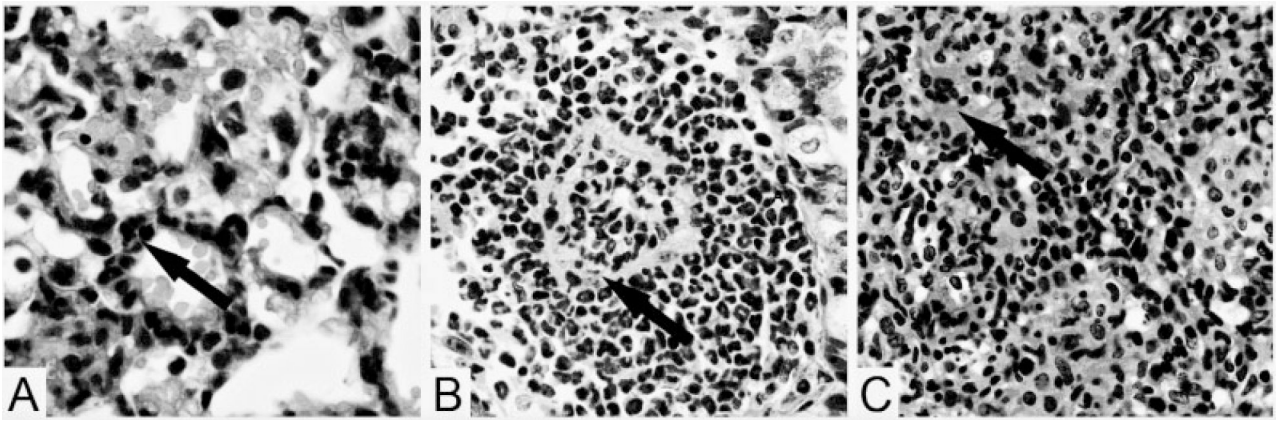

Fig. 2.

Systemic vasculitis and granulomatous inflammation in $Rag2^{-/-}$ mice 13 days after receiving anti-MPO splenocytes. (Reproduced from Xiao et al.[97]) (A) Pulmonary hemorrhagic capillaritis showing numerous neutrophils within alveolar septal capillaries (arrow) and red blood cells in air spaces (H&E stain). (B) Intense acute arteritis in lung with transmural (arrow) and perivascular infiltration of predominantly neutrophils (Masson's trichrome stain). (C) Granulomatous inflammation with multinucleated giant cells (arrow) (H&E stain). MPO, myeloperoxidase.

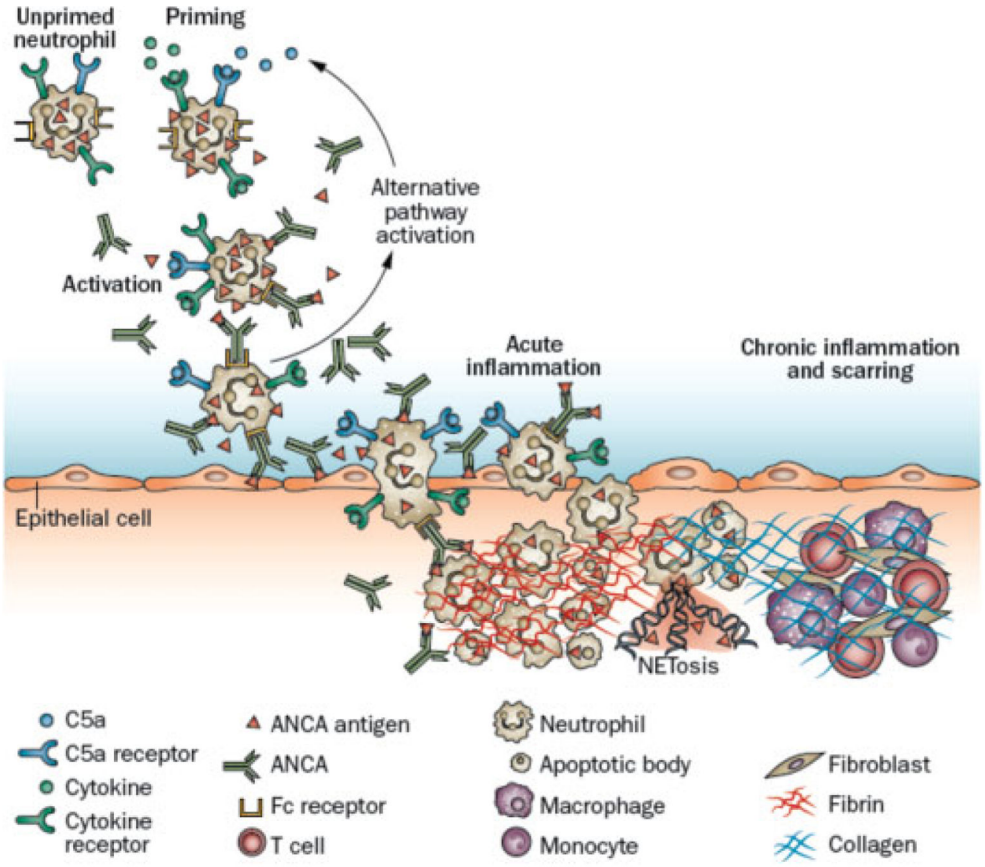

Fig. 3.

Putative sequence of pathogenic events in ANCA-mediated vasculitis. (Reproduced from Jennette and Falk.[62]) Circulating neutrophils are primed for activation by ANCA by inflammatory cytokines or C5a derived from complement activation (note that monocytes can be similarly primed and activated but are not illustrated). Primed neutrophils release ANCA antigens at the cell surface and into the microenvironment, where they interact with ANCA. Fc receptor engagement by ANCA bound to ANCA antigens as well as F(ab′)2 binding to ANCA antigens on neutrophil surfaces cause neutrophil activation. ANCA-activated neutrophils release factors that activate the alternative complement pathway, generating C5a. C5a and ANCA create an inflammatory amplification loop, with C5a attracting and priming more neutrophils for activation by ANCA, which causes, in turn, further activation of the alternative complement pathway and production of more C5a. ANCA-activated neutrophils marginate and penetrate vessel walls and undergo respiratory burst, degranulation, NETosis, apoptosis, and necrosis. Disruption of endothelium allows plasma to spill into vascular and perivascular tissue where activation of the coagulation cascade produces the fibrin strands of fibroid necrosis. The innate inflammatory response orchestrates the conversion of the initial acute neutrophil-rich inflammation into mononuclear leukocyte-rich inflammation and subsequent collagen deposition and fibrosis. ANCA, antineutrophil cytoplasmic antibody.

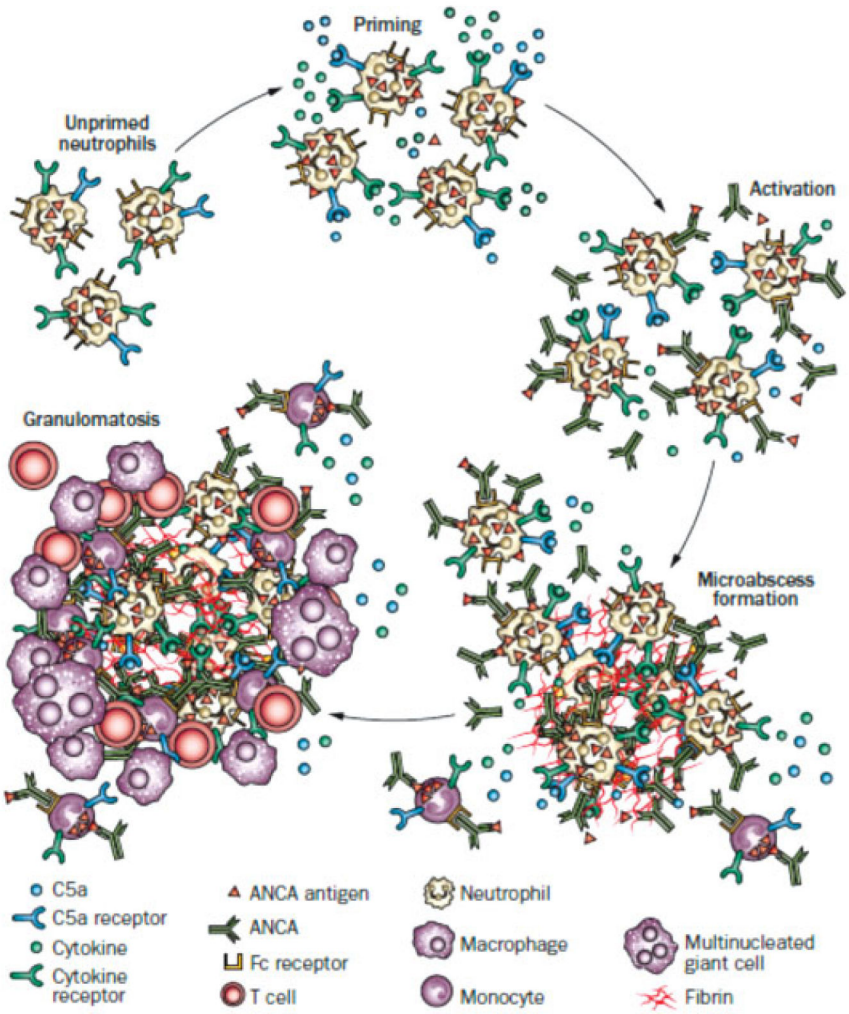

Fig. 4.

Putative sequence of pathogenic events in ANCA-mediated necrotizing granulomatosis. (Reproduced from Jennette and Falk.[62]) An inflammatory prodrome, such as an infectious or allergic inflammatory respiratory tract disease, positions increased numbers of primed neutrophils in extravascular interstitial tissue. ANCA immunoglobulin in the interstitial fluid would activate primed neutrophils and initiate an inflammatory amplification loop that wouldattract and activate more neutrophils, resulting in the formation of a necrotizing microabscess. This acute inflammation and necrosis would initiate an innate inflammatory response that would wall off the necrotic zone with granulomatous inflammation containing a predominance of monocytes and macrophages with admixed lymphocytes. ANCA, antineutrophil cytoplasmic antibody.

Table 1

Etiology of pulmonary vasculitis

Most frequent cause
ANCA vasculitis and granulomatosis
Granulomatosis with polyangiitis
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis
Less frequent causes
Other systemic vasculitis
Antiglomerular basement membrane disease
IgA vasculitis
Behcet's disease
Cryoglobulinemic vasculitis
Takayasu arteritis
Autoimmune diseases
Systemic lupus erythematosus
Antiphospholipid syndrome
Sarcoidosis
Rheumatoid arthritis
Infections
Bacteria, e.g., mycobacteria, syphilis, rickettsias
Fungus, e.g., aspergillosis, histoplasmosis
Virus, e.g., herpes zoster
Malignancy
Drugs-induced ANCA vasculitis
Propylthiouracil, diphenylhydantoin, levamisole-adulterated cocaine

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; IgA, immunoglobulin A.

Source: Modified from Franks and Koss[132] and Heeringa.[133]