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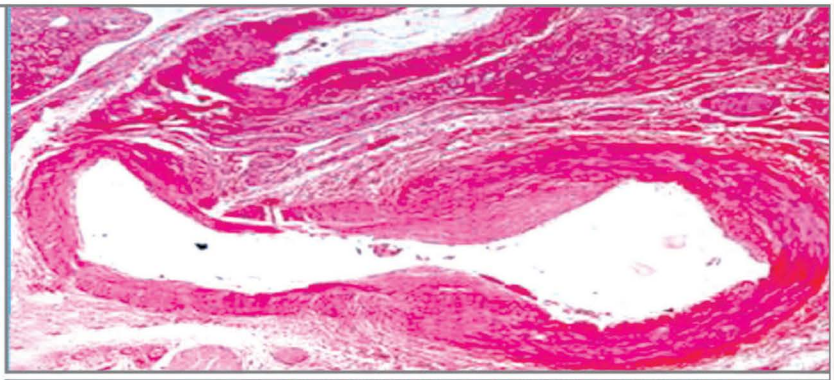
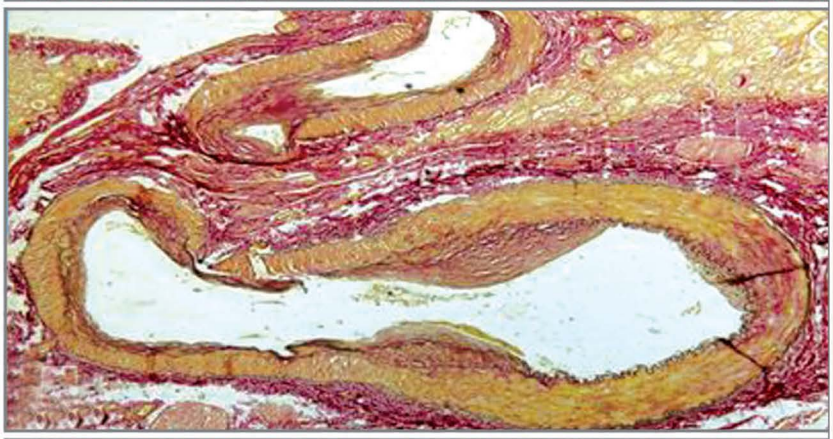
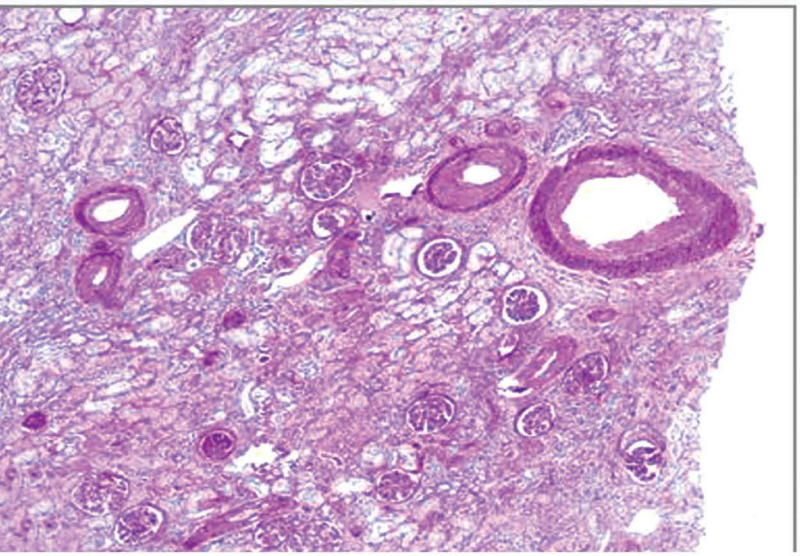
Aman Sharma

Textbook of Systemic Vasculitis











2nd Edition

Foreword
Loïc Guillevin

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CHAPTER

4

Neutrophils in ANCA-associated Vasculitis

Jennifer Amsler, Véronique Witko-Sarsat

INTRODUCTION

The pathogenesis of antineutrophil cytoplasmic antibodies (ANCAs)-associated vasculitides (AAVs) is poorly understood, but consistent with a primary role of neutrophils in the acute injury. Neutrophils are the key players in the pathophysiological process in AAV, since they are both targets of autoimmunity and effector cells responsible for endothelial damage. The two main target antigens of ANCA are the neutrophil granule proteins, proteinase 3 (PR3) and myeloperoxidase (MPO).[1] Anti-PR3 ANCAs are found in sera from patients with granulomatosis with polyangiitis (GPA) (Wegener), which is characterized by granulomatous inflammation of the upper or lower respiratory tract as well as pauci-immune glomerulonephritis. Anti-MPO ANCAs are present in sera from patients with microscopic polyangiitis (MPA) and less frequently in eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg–Strauss syndrome), which associates late-onset asthma, hypereosinophilia, and small-vessel vasculitis. The selectivity of ANCA target antigens is surprising regarding the wide range of proteins stored within cytosolic granules of neutrophils **(Fig. 1)**. It has been proposed that the formation of neutrophil extracellular traps (NETs) that are composed of DNA extruded from dying neutrophils, which bear all the cationic granule proteins including PR3 and MPO, could be involved in the pathophysiology of AAV.[2]

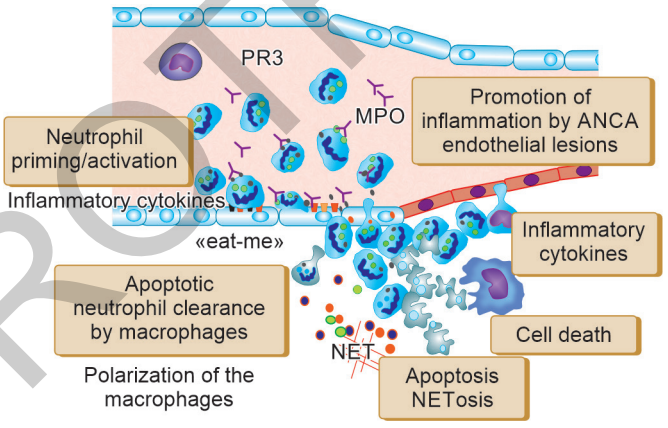

Fig. 1: Originally a trigger such as an infection primes the neutrophils on one hand, and on the other hand, an upregulation of endothelial adhesion molecules through proinflammatory cytokines occurs. This priming causes upregulation of neutrophil adhesion molecules and translocation of the ANCA antigens from granules to the cell surface. The interaction between the ANCAs and their antibodies on the cell surface activates the neutrophil, causing increased neutrophil-vessel wall adherence and transmigration. ANCA-mediated neutrophil activation also triggers reactive oxygen radical production and causes neutrophil degranulation leading to release proteolytic enzymes, injuring the vessel wall. Apoptotic neutrophils showing an "eat-me" signal maintain an inflammatory polarization of macrophages after being cleared. During inflammation, neutrophils are able to release NETs, which are responsible for the release of PR3 and MPO.

(ANCAs: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase; NETs: neutrophil extracellular traps; PR3: proteinase 3)

THE ANCA ANTIGENS PR3 AND MPO: KEYS IN THE PATHOPHYSIOLOGY OF ANCA-ASSOCIATED VASCULITIDES

Proteinase 3 and MPO are localized in the neutrophil azurophil granules and are both involved in the microbicidal activity of neutrophils. However, their structure and function differ dramatically. Thus, PR3 and MPO share proinflammatory properties and are also able to modulate the inflammatory process during which they can have synergistic activities.[3] However, it is striking to note that, among the multiple proteins contained in neutrophils azurophil granules, these two biochemically very different proteins are preferred targets for the ANCA in AAV. Interestingly, the clinical presentation of patients with AAV differs, depending on the specificity of ANCA. Thus, in systemic GPA, characterized by glomerulonephritis and typically granulomatous involvement of lungs and upper airways, 85% of the patients have anti-PR3 ANCA and slightly less than 10% have anti-MPO ANCA. Interestingly,

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anti-MPO ANCAs are detected in 60–70% of patients with MPA, a systemic vasculitis typically characterized by pneumorenal syndrome, as well as in 30–38% of patients with EGPA. Importantly, these two types of antibodies are mutually exclusive and very rarely detected in the same patient. It is of interest to mention that the distinct biochemical properties of MPO and PR3 were exploited empirically in the indirect immunofluorescence test of ANCA; thus, a perinuclear fluorescence is observed with anti-MPO ANCA, whereas a cytoplasmic fluorescence is noted with anti-PR3 ANCA.

Myeloperoxidase: An Oxidant-generating Protein

Myeloperoxidase is very abundant (up to 5% of dry weight) and exclusively found in the azurophilic granules of neutrophils. It is a key element of the intracellular microbicide oxygen-dependent system,[4] synthesizing hypochlorous acid ($HOCl^-$) from superoxide anion that exerts its toxic effect not only on microorganisms (bacteria, fungi, and parasites) but also on the host cells by oxidizing a wide variety of molecules. In addition, $HOCl^-$ can react with endogenous amines (R-NH2) to generate chloramines (SHR-Cl) that were baptized long-lived oxidants compared to free oxygen radicals whose life is extremely short, much less than 1 second. $HOCl^-$ can also oxidize plasma proteins and generate advanced oxidized protein products (AOPPs) that have proinflammatory properties.[5] Finally, several teams focused their work on the characterization of the role of MPO in the mechanisms of inflammation in the absence of an infection. In this setting, the detection of MPO in atherosclerotic plaques unraveled the pathogenesis of atherosclerosis and marked the starting point of many efforts to demonstrate its involvement in atherogenesis, contributing to consider this condition at least in part as an inflammatory disease.[6] Indeed, MPO can oxidize low-density lipoproteins and proteins of the extracellular matrix in the blood vessel wall.[7]

Proteinase 3: A Pathogenic Membrane-associated Serine Protease

Proteinase 3 differs from MPO in many aspects. Thus, if biological activity of MPO is unique, since it is the only enzyme to generate chlorinated oxidants, PR3 has homologous proteins called serprocidins, which means antibiotic serine proteinases, namely elastase, azurocidin, and cathepsin G, which are also stored in azurophilic granules. Generally, the serine proteinases have a rather proinflammatory activity,[8,9] as demonstrated in several animal models using mice genetically deficient in elastase or cathepsin G or double deficient in elastase and PR3. Mice deficient in dipeptidyl peptidase enzyme required for cleavage of the prosequence of these serine proteases have been widely used to show the proinflammatory role of these enzymes. For example, it has been shown that neutrophil serine proteases (NSPs) have a deleterious role in a model of vasculitis associated with anti-MPO antibodies.[10]

Interestingly, elastase, which shares 56% of homology with PR3, is not a specific target of ANCA. PR3 was cloned, named myeloblastine, and described as a protein involved in the granulocytic differentiation. In fact, inhibition of its expression at the promyelocytic stage triggers the differentiation of these cells.[11] The PR3 has structural features that distinguish it from its counterparts, in particular its capacity to anchor to the plasmic membrane,[12,13] and therefore to be expressed at the membrane of neutrophils in the absence of activation, which can have many implications on its biological functions. Furthermore, patients with a significant proportion of their neutrophils expressing membrane PR3 are at risk for developing vasculitis.[14] PR3 expression at the membrane of neutrophils is genetically determined. Thus, we had hypothesized studying two representative families that the percentage of neutrophils expressing PR3 could be a genetically transmitted character[14] and this hypothesis has not been refuted after a study of twins.[15] As it has been shown that ANCA can activate neutrophils, amplifying the inflammatory process, the accessibility of the autoantigen (PR3 and MPO) to the ANCA, is therefore a mechanistic prerequisite for cell activation by the ANCA. Moreover, the oxidative activity in response to ANCA is increased in neutrophils expressing membrane PR3 as compared to neutrophils not expressing PR3.[15] In addition, we have shown that PR3 was localized in the secretory vesicles, an easily mobilizable neutrophil compartment arising at the end of the differentiation of neutrophils, to increase its membrane expression on the surface of the neutrophil, demonstrating that the PR3 did not follow the rules of compartmentalization “in use” in the neutrophil.[16] This observation opened new fields of investigation on membrane PR3, in particular its protein partners and its functions.

Interestingly, the CD177, also called NB1,[17,18] is a membrane protein of neutrophils with a glycosylphosphatidylinositol (GPI) anchorage that has a similar bimodal expression on human neutrophils and is involved in the migration process of neutrophils. NB1 was suggested to be a receptor of PR3 but the mechanisms by which the PR3 would be released, then caught by a neutrophil, in the absence of activation are not clear. Several groups demonstrated that PR3 can localize in membrane microdomains called lipid rafts and join CD11b/CD18 and CD16,[19] contributing to explain its binding to the membrane. Interestingly and unlike its counterparts, PR3 is able to fit into lipid vesicles. Furthermore, molecular modeling studies using dynamics simulations allowed to demonstrate that, from a structural point of view, PR3 is able to bind to neutral or anionic membranes via a hydrophobic patch consisting of four hydrophobic amino acids,[12,13] which is not the case for the elastase. These four hydrophobic amino acids are crucial for the association of PR3 to the membrane[20] and might bind to CD177.[21] The importance of the complex consisting of PR3

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and CD177 has been demonstrated in a recent work.[22] An association of PR3 and phospholipid scramblase I has also been identified. Phospholipid scramblase I is an enzyme responsible for the lipids scrambling during apoptosis.[23] The coexpression of PR3 and phospholipid scramblase was shown to be closely associated with the externalization of phosphatidylserine during apoptosis.[24] Thus, PR3 can be associated with various proteins, depending on the principle leading to its membrane expression: constitutive, initiated by degranulation or apoptosis.[25]

Importantly, membrane expression of PR3 increases during neutrophil apoptosis, thus interfering with phagocytosis by macrophages and inhibiting the resolution of inflammation. In this setting, an association between PR3 and calreticulin has been reported. Calreticulin, a chaperone protein described as an "eat-me" signal, promotes phagocytosis of apoptotic cells by macrophages.[26] In patients with GPA, when macrophages phagocytose PR3-expressing apoptotic neutrophils, they release massive amounts of proinflammatory mediators, notably interleukin-1 (IL-1), thereby generating a proinflammatory microenvironment conducive to autoimmunity.[27,28] Indeed, enzymatically active membrane-associated PR3 on apoptotic cells also triggered secretion of inflammatory cytokines, including granulocyte colony-stimulating factor (G-CSF) and chemokines. This response required the IL-1R1/MyD88 signaling pathway as macrophages from animals lacking these pathways did not exhibit a PR3-associated proinflammatory response. This deregulation of immune processes is accompanied with activation of plasmacytoid dendritic cells and with polarization of T-helper-2 (Th2), Th9, and Th17 cells. These data highlight the dual role of PR3, both autoantigenic and autoinflammatory, showing that PR3 disrupts immune silencing associated with clearance of apoptotic neutrophils and providing insight into how PR3 promote GPA pathophysiology.

A human PR3 transgenic mouse (hPR3Tg) has reinforced the evidence that PR3 can affect the resolution of inflammation and exacerbate systemic inflammation.[29] During zymosan-induced peritonitis, hPR3Tg displayed an increased accumulation of neutrophils within the peritoneal cavity compared with wild-type control mice, with no difference in the recruitment of macrophages or B or T lymphocytes. Mice were also subjected to cecum ligation and puncture, a model used to induce peritoneal inflammation through infection. hPR3Tg displayed decreased survival rates in acute sepsis, associated with increased neutrophil extravasation. The decreased survival and increased neutrophil accumulation were associated with the cleavage of Annexin A1, a powerful anti-inflammatory protein known to facilitate the resolution of inflammation. Additionally, neutrophils from hPR3Tg displayed enhanced survival during apoptosis compared with controls, and this may also contribute to the increased accumulation observed during the later stages of inflammation. Taken together, this human PR3 transgenic mouse strain seems to be a suitable model to examine the PR3-dependent proinflammatory mechanisms and might be used to tailor a murine model of GPA.

NEUTROPHIL FUNCTIONS IN ANCA-ASSOCIATED VASCULITIS

Neutrophils play a major role in the pathophysiology of AAV, particularly in the mechanisms of endothelial injury and immune dysregulation associated with these conditions. The number of activated neutrophils in renal biopsies from patients with PR3-ANCA glomerulonephritis correlates with the ANCA titer and renal damage[30,31] and MPO deposition correlates with the extent of renal dysfunction.[32]

Thus, neutrophils are not simple terminal effector cells but are also capable of immunomodulation with the secretion of a variety of cytokines and chemokines[33] as a consequence of an active crosstalk with monocytes, dendritic cells, T lymphocytes, and B lymphocytes. For instance, neutrophils secrete high amounts of B-cell-activating factor (BAFF) and a proliferation-inducing ligand, which are both members of the tumor necrosis factor (TNF) superfamily and involved in the B lymphocyte homeostasis.[34] In particular, serum BAFF levels are higher in patients with GPA as compared to controls.[35] Interestingly, there is a subpopulation of granulocytes in peripheral blood that are not sufficiently studied yet in AAV: the low-density granulocytes (LDGs). They are reported to be expanded in patients with acute AAV, but hyporesponsive to MPO antibodies compared with neutrophils.[36] Their importance and functions in the disease pathogenesis have yet to be determined.

Neutrophil Extracellular Trap as Mediators of Glomerulonephritis

It was also suggested that the formation of NETs, composed of DNA expelled by dying neutrophils, which contain granules-derived cationic proteins including PR3 and MPO, might be involved in the pathophysiology of AAV.[2] One of the possible mechanisms of presentation of target antigens, PR3 and MPO, is the formation of NETs.[37] NETs components, PR3 and MPO, have been reported in ANCA vasculitides renal lesions[2] and PR3-ANCA patients have demonstrated higher free MPO levels in circulation during active disease than in remission.[32] It was shown that NETs from ANCA-stimulated neutrophils can cause endothelial damage in vitro[38] and can activate the alternative complement pathway, which plays a role in amplifying the inflammatory process in AAV as described below.[39-41] However, the relevance and the exact mechanisms of NET formation in ANCA vasculitides is still subject of discussion and it is unclear how this mechanism might explain the selectivity of ANCA toward PR3 and MPO in AAV.

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Enhanced Granular Protein Synthesis

Neutrophils from patients with AAV might have intrinsic defects that would contribute to amplify the pathogenetical process. Most of the studies performed in this setting focused on the interaction between neutrophils and ANCA, and relatively few studies were dedicated to the potential alteration of these cells during disease flare or in remission. Interestingly, at the time of disease flare, neutrophils of patients with GPA strongly re-express *PR3* and *MPO* genes, while these genes are usually expressed only during the promyelocytic phase of the granulocytic differentiation, according to the "targeting by timing" theory.[42] Gene expression profiling studies on peripheral blood leukocytes identified more than 200 genes overexpressed in neutrophils of patients with ANCA-positive vasculitis.[43] The *PRTN3* (the *PR3* gene) was correlated not only with the ANCA-type but also with clinically defined syndromes as shown in a genome-wide association study.[44,45]

Increased Neutrophil Survival and Dysregulation of Death Pathways

Upon activation by ANCA, neutrophils from patients with AAV are characterized by increased apoptosis in vitro as compared to healthy controls.[46] On the other hand, it has been documented that the spontaneous apoptosis of neutrophils was delayed in patients with AAV.[47] Also, we reported that neutrophils from patients with GPA express increased expression of cytosolic proliferating cell nuclear antigen, a molecule known to be associated with increased neutrophil survival.[48] Interestingly, proteomic results from the cytosol of GPA neutrophils do not resemble the one from healthy controls and even in remission they do not fully reconstitute to a healthy control proteome suggesting that treatment cannot resolve all the intrinsic defects that could contribute to the pathogenesis of the disease.[49] These differences are most remarkable when cells enter apoptosis compared to a basal state and many of the proteins identified are involved in cell survival/death such as Annexin A1, a phospholipid binding protein, which plays a role in apoptotic cell clearance and has shown to be associated with PR3. The correlation is more significant in patients with more severe disease such as renal involvement. This different expression of Annexin A1 is also correlated with phospholipid scramblase I at an apoptotic state. Thus, a delay in the phagocytosis of apoptotic cells, in the setting of inflammation, might play a crucial role in the emergence of autoimmune manifestations, as observed in systemic lupus erythematosus (SLE). Altogether, the potential consequences of these disturbances in the survival/apoptosis balance and the clearance of apoptotic neutrophils are the actual focus of ongoing research.

ROLE OF ANCA IN NEUTROPHIL ACTIVATION

During the pathological course of AAV, accumulation of neutrophils at the inflammatory site is initiated by the so-called "priming" of these cells. Priming of neutrophils can be induced by adhesion, bacterial products (lipopolysaccharide), inflammatory cytokines, or lipid mediators. Primed neutrophils are in a "ready to go" state, which results in a faster and amplified response upon exposure to a second stimulus. Priming is responsible for the induction of membrane expression of PR3 and MPO that can be targeted by ANCA, triggering neutrophil activation. When incubated in vitro with immunoglobulin G (IgG) purified from the serum of patients with anti-PR3 ANCA or anti-MPO ANCA, primed neutrophils produce superoxide anion and release lytic granular proteins.[50] Interestingly, to exert their biological effect, ANCAs must be intact since both antigen binding through the variable regions and Fcγ receptor (FcγRIIa or FcγRIIIb) binding through the Fc portion are required and β2-integrin must be engaged.[51] It has been suggested that ANCA-activated neutrophils release oxygen radicals, destructive enzymes through degranulation and extrude NETs that have proinflammatory properties. However, recent work has shown that neutrophils and monocytes from AAV patients have an impaired function and are not particularly activated. There is a negative association between reactive oxygen species (ROSs) and disease severity consistent with findings in other autoimmune diseases such as SLE.[52] Further, it has been demonstrated in an anti-MPO murine model that the transplantation of phagocyte NADPH oxidase (Phox) protein deficient bone marrow (gp91phox- and gp47phox-) shows accelerated disease.[53] In vitro challenge with anti-MPO antibody of gp91phox- and gp47phox-deficient monocytes enhance caspase-1 activity and IL-1β generation, thus suggesting that the NADPH oxidase restrains the inflammasome by downregulation of caspase-1. However, further investigations are needed to identify the molecular mechanisms regulating the interactions between ANCA, neutrophils, and endothelial cells, and their potential perturbations in AAV.

Although ANCA detection represents a valuable diagnostic tool, the use of ANCA as a biomarker to predict relapses is questionable. Thus, the detection of ANCA in the serum of patients reflects disease activity in some, but not all patients with AAV. In addition, a significant proportion of patients with biopsy-proven MPA or GPA have no detectable ANCA. Taken together, these observations raise again the question of the pathogenicity of anti-PR3 ANCA in vivo. One study has shown that there are more than 20 epitopes of MPO recognized by MPO ANCAs in patients with AAV.[54] Interestingly, in this study, anti-MPO IgG ANCA from patients with active AAV recognized a large number

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of epitopes, including epitopes that were never recognized by anti-MPO IgG ANCA from patients with inactive disease and from healthy controls. Some patients with clinical and pathologic features of AAV who were negative for ANCAs using conventional clinical assays reacted with a specific MPO epitope. IgG ANCA binding to this MPO epitope was blocked by a fragment of ceruloplasmin, which is a natural inhibitor of MPO and binds to the portion of the MPO molecule that contains this epitope. This result suggests that the epitope specificity of ANCAs might influence their biological activity independently of the ANCA titers. In keeping with this concept, it has been shown that anti-PR3 antibodies can exert a dual biological effect according to their epitope specificity, thus raising the possibility of "good" and "bad" anti-PR3 ANCA, the first of which could contribute to limit, whereas other could potentiate inflammation. A similar concept has been proposed by the existence of altered Fc N-glycosylation patterns of IgG, where agalactosylation is proposed to be proinflammatory and galactosylation and sialylation of IgG antibodies is proposed to be anti-inflammatory.[55] Agalactosylation of total IgG has been associated with AAV and the sialylation level of anti-PR3 antibodies inversely correlated with disease activity.[56,57] Another group investigated the value of galactosylation and sialylation levels of IgG as a prognostic marker for relapse in AAV and showed an inverse correlation only with total IgG1.[58] Interestingly, the occurrence of anti-PR3 antibodies in healthy individuals reinforces the need to clarify factors influencing the potential involvement of anti-PR3 ANCA in the pathogenesis of AAV.

Animal Models to Study the Pathogenicity of ANCA In Vivo

Twenty years after the description of the ANCA, the pathogenic role of anti-MPO in vivo has been demonstrated, which is not so obvious for the anti-PR3. In a mouse model invalidated for the *MPO* gene and immunized by murine MPO, an immune response against MPO was documented.[59] The transfer of purified serum IgG containing anti-MPO antibodies or spleen cells from these animals into *recombinase-associated gene* type-2 deficient mice that have no B-cell, T-cell, or antibodies, resulted in the occurrence of extracapillary glomerulonephritis,[59] thus demonstrating the pathogenic role of anti-MPO ANCA in vivo.[60] In human pathology the occurrence of a pneumorenal syndrome in a newborn of a mother who had developed vasculitis with anti-MPO ANCA confirmed the in vivo pathogenetic role of these antibodies in humans.[61] Alternatively, as discussed above, one study points to the fact that there are dominant pathogenic epitopes for anti-MPO ANCA and that the absence of detection of ANCA in patients with MPA might result from the fact that anti-MPO ANCAs were associated with a fragment of ceruloplasmin and were eliminated during the purification of IgG from serum.[54] On the other hand, the demonstration of the pathogenicity of anti-PR3 ANCAs in vivo is still missing. The detection of circulating anti-PR3 ANCA reflects the activity of the disease among some patients suffering from vasculitides, but not all. In vivo, the immunization of mice invalidated for the *HNE-PR3* gene with recombinant PR3 did not result in the appearance of vasculitis-compatible manifestations. Thus, the passive transfer of anti-PR3 ANCA in the presence of lipopolysaccharide gave similar results.[62] Another group used human PR3, murine recombinant PR3, and a chimeric human/mouse PR3, and demonstrated the presence of antibodies against these chimeric proteins in the absence of pathological manifestation, especially in the kidneys or lungs.[63] Further, one group generated double-transgenic mice that expressed human PR3 and CD177. Even though the murine neutrophils bound human anti-PR3 antibodies, they were not activated properly and the mice did not develop glomerulonephritis.[64] However, a recent model of a severe combined immunodeficiency (SCID) humanized mouse seems to reproduce pauci-immune glomerulonephritis induced by human anti-PR3 ANCA.[65] Chimeric mice were generated by the injection of human hematopoietic stem cells into irradiated NOD-SCID mice invalidated for the IL2 receptor encoding gene (NOD-SCID-IL2R). Paired chimeric mice were treated with serum IgG obtained from patients suffering from renal and pulmonary vasculitis with anti-PR3 antibodies, renal disease other than vasculitis or healthy controls. Mice receiving injections of anti-PR3 antibodies developed a moderate form of pauci-immune proliferative glomerulonephritis with infiltration of human and murine leukocytes. In contrast, there were no glomerular changes in controls. Even if this result is a major step toward the demonstration of the pathogenetic role of anti-PR3 ANCA in vivo, it must be confirmed by other groups.

NEUTROPHILS AS TARGETS FOR NEW THERAPEUTIC APPROACHES

Treatment of AAV is challenging and can have many side effects. Neutrophils could be a suitable target in order to control the disease. When neutrophils are stimulated by ligation of neutrophil receptors, several kinases are activated to initiate neutrophil degranulation, ROS generation, and NET formation. Some of these pathways have been used to develop new therapeutic targets.[30]

Harnessing Signal Transduction Pathways

The cytoplasmic spleen tyrosine kinase (SYK) has shown increased phosphorylation in renal biopsies of patients with AAV and SYK inhibition evoked reduced glomerular inflammation in a MPO-ANCA rat model.[66] Similarly, phosphorylation of p38 mitogen-activated protein kinase (MAPK) and the extracellular signal-regulated kinase (ERK) induce ROS generation.[67] This has been shown to be associated with the formation of NET, which was promoted by MPO and protein-arginine deiminase type 4 (PAD4).[68] Thus, inhibition of MAPK,[69,70] MPO,[32] or PAD4[71] can attenuate neutrophil activation and crescentic glomerulonephritis in animal models.

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Targeting Serine Protease by Cathepsin C Inhibitions

Neutrophil serine proteases have been implicated to be involved in glomerular injury. They have to be proteolytically activated by cathepsin C in the bone marrow. Inhibition of cathepsin C has been shown to reduce NSP expression and proteolytic activity in mice[72,73] and to reduce glomerular microvascular endothelial cell damage in vitro.[74]

Modulating the Alternative Complement Pathway

Myeloperoxidase- and PR3-ANCA-activated neutrophils release C5 fragments such as C5a, which interact in turn with the C5a receptor 1 (C5aR1) and amplify the neutrophil proinflammatory responses.[75,76] C5a has been reported to be elevated in plasma of active AAV.[77] Blocking of C5aR1 with the small molecule avacopan was successful in two phase 2 trials[78,79] and recently a phase 3 randomized controlled trial showed a superiority of avacopan compared to the standard care with corticosteroids.[80]

CONCLUSION

Pauci-immune necrotizing small-vessel vasculitides and extravascular granulomatosis are associated with ANCAs. The distinctive extremely destructive necrotizing vascular inflammation appears to be fueled by an amplification loop comprising ANCA-activated neutrophils that release factors that activate the alternative complement pathway that in turn attracts and activates more neutrophils. Promising therapies that can target multiple components of this vicious cycle are under studies and novel biomarkers of disease activity, disease severity, and organ involvement are being evaluated.[81]

New perspectives in the research on neutrophils in AAV should include studies to determine whether some intrinsic dysregulation could favor a failure in the resolution of inflammation. A specific investigation of the functions and the immunomodulatory roles of the target antigens, either MPO or PR3, should be carried out in order to confirm their specific and presumably differential involvement in MPA and GPA.

KEY POINTS

- The ANCA antigens PR3 and MPO are key elements in the pathophysiology of AAVs.
- Neutrophil activation by ANCA promotes inflammation.
- Neutrophils in AAV appear to have specific and probably intrinsic functional dysregulation.
- Membrane-associated PR3 disrupts immune silencing.

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The second edition of *Textbook of Systemic Vasculitis* expands the scope and strengths of popular first edition of this book. This edition includes some newer topics like deficiency of adenosine deaminase 2 (DADA2), VEXAS syndrome, and other autoinflammatory vasculitides. The histopathology section has a new addition in the form of gastrointestinal (GI) vasculitis.

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- Newer and future treatment modalities.

Aman Sharma MD FAMS FIACM FICP FACR FRCP (London) is a Professor in the Clinical Immunology and Rheumatology wing of Department of Internal Medicine at PGIMER, Chandigarh, India. He has a special interest in rare rheumatic diseases such as systemic vasculitides and relapsing polychondritis. He was the local principal investigator and expert reviewer of the American College of Rheumatology and European League against Rheumatic disease multicentric study for development of diagnostic and classification criteria for systemic vasculitis (DCVAS). He was the invited expert from India to an international research group which developed and validated Relapsing Polychondritis Disease Activity Index (RPDAI) and Relapsing Polychondritis Damage Index (RPDAM). He is also one of the members of GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis). He has been awarded with the "Young Investigator Award" in 2007, "Zydus Oration" in 2011, and prestigious "Annual IRA Oration" in 2015 by Indian Rheumatology Association; "Shurvir Trust Visiting Professorship" in 2014; "R Subramanian Oration" and "Rabindranath Tagore oration" in 2016 by Association of Physicians in India (API); and "CMC Vellore Eminent Mid Carrier Oration" in 2018. He was awarded CME Dronacharya Award by Integrated Health and Wellbeing Council. He has been awarded the Fellowship of Royal College of Physicians (FRCP, London), American College of Rheumatology (FACR), and Academy of Medical Sciences (FAMS). He founded the Indian Vasculitis registry and Indian relapsing polychondritis registry. He was a member of the ACR Annual Meeting Planning Committee (2015–2018). He was invited by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Health (NIH), USA to deliver the NIAMS grand rounds on "Exciting World of Systemic Vasculitis and Relapsing Polychondritis" in 2022.

He is the Honorary Secretary of Indian Rheumatology Association and Program Director of Center of Excellence in HIV care at PGIMER, Chandigarh, India. He is the Incoming Editor-in-Chief of Indian Journal of Rheumatology and Associate Editor of IJRD and Frontiers in Medicine (Rheumatology). He has published more than 440 research papers in various peer reviewed international and national journals and has written 60 book chapters. He has edited seven books and monographs. He has been instrumental in starting DM program in Clinical Immunology and Rheumatology at PGIMER, Chandigarh, India.

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