Autoantibodies in ANCA-associated Vasculitis

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• Necrotizing vasculitis • ANCA • Autoantibodies
• Pathophysiology

Antineutrophil cytoplasmic autoantibodies (ANCAs) are frequently associated with diseases characterized by the presence of vasculitis, affecting small and medium-sized vessels (eg, arterioles, capillaries, and venules).[1,2] Although this association was realized already in the mid-1980s, ANCAs were not immediately included in the classification criteria for this type of vasculitis, and no agreed diagnostic criteria for the diagnosis of these conditions exist as yet. Presence of autoantibodies such as ANCAs most likely reflects pathobiologic events in the affected tissue, in this case neutrophils and monocytes attacking the vascular endothelium of small vessels, causing autoantigen release from these cells and presentation to the immune system.

Because endothelial cells (ECs) become activated and damaged by the attack, autoantibodies to EC constituents (anti–endothelial cell antibodies [AECAs]) are also commonly produced in ANCA-associated vasculitis (AAV).[3] During this inflammatory attack on the vessel walls, the basal membrane of some vessels can also be damaged and autoantibodies to the basement membrane α_3 domain of type IV collagen of glomeruli and pulmonary vessels are produced.[3]

The primary events leading to the onset of these necrotizing vasculitides are not known. However, several hypotheses have proposed that infectious agents can trigger and perhaps perpetuate events[4–6] that, if left untreated, will lead to irreversible tissue damage and organ function failure.[7,8]

Patients suffering from ANCA-associated small vessel necrotizing vasculitides, such as Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS), may produce autoantibodies to several different autoantigens and structures that are involved in the pathology of these diseases.[3]

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Although ANCAs have thus lent name to the group of diseases collectively called AAV, they may not be the only interesting autoantibodies in terms of pathophysiology or classification.

NEUTROPHIL-SPECIFIC AUTOANTIBODIES

Neutrophil-specific autoantibodies (NSAs) have been known to exist since 1959, when their presence was first described in patients with leukopenia[9] and later in those with ulcerative colitis.[10]

Using indirect immunofluorescence (IIF) technique, the autoantibodies found in leukopenia and ulcerative colitis decorated the nuclei of neutrophils, and therefore later work on NSAs in patients with rheumatoid arthritis and Felty syndrome called them granulocyte-specific antinuclear antibodies.[11] Similar NSAs have been described in chronic active hepatitis, sclerosing cholangitis, Sweet syndrome, and other conditions in which chronic recruitment of neutrophils is an essential part of the inflammatory process.[2,12] However, most of the NSAs are not directed to the classic cytoplasmic ANCA antigens proteinase 3 (PR3), myeloperoxidase (MPO), or human leukocyte elastase (HLE) but rather to components found in all compartments of neutrophils and monocytes,[13] probably just showing an immune response caused by chronic neutrophil cell death.

When autoantibodies to neutrophils were described in patients with WG, they were termed anticytoplasmic antibodies because of their preferential staining of granular material in the cytoplasm,[14] but this indistinct term was changed to ANCA during the Second International Workshop on ANCA in Noordwijkerhout, The Netherlands.[15] The main reason for this change was the identification of the 2 most important neutrophil granule antigens, PR3 and MPO, as the dominant targets in patients not only with WG but also in patients with MPA and CSS and their limited forms.[16]

ANCA

In 1982, Davies and colleagues[17] first recognized autoantibodies that were specific for neutrophils in small vessel necrotizing glomerulonephritis. It was initially proposed that the antibodies were produced in response to an arbovirus (Ross River virus) infection, although this was never substantiated. Morphologically similar antibodies giving rise to a coarse granular staining of neutrophil cytoplasm (**Fig. 1**) were subsequently reported in patients with WG,[14] preferentially in those having active disease. This particular pattern of reactivity with neutrophils was then called the classic cytoplasmic ANCA (C-ANCA).[15] In 1988, soon after the first International Workshop on ANCA in Copenhagen, Denmark, the C-ANCA antigen was reported to be directed to the proteolytic enzyme PR3 in azurophilic granules of neutrophils.[18–20]

ANCAs that caused staining of neutrophil nuclei and their close vicinity were called perinuclear ANCAs (P-ANCAs) (**Fig. 2**)[15]; this reactivity is caused by cationic granule antigens, for example, MPO and HLE, that have migrated to the oppositely charged nuclei and was first described for ANCAs directed to MPO.[21] P-ANCAs with specificity for MPO are commonly produced in AAV with kidney or lung manifestations.

Proteinase 3

The conformation of PR3 is essential for its reactivity with PR3-ANCA.[22] PR3 is a linear polypeptide containing 228 amino acids. In 1994, linear epitopes of PR3 were found, and these seemed to occur in regions close to the active site of the enzyme[23] where 4 of 5 epitopes are assumed to be located.[24] The crystal structure of PR3 was resolved in 1996.[25] PR3 is progressively more strongly expressed from the stage of early