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REVIEW ARTICLE

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Complement in antineutrophil cytoplasmic antibody-associated vasculitis

Jun Yuan · Min Chen · Ming-Hui Zhao

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Abstract Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a group of autoimmune disorders. It was previously assumed that the complement system is not involved in the development of ANCA-associated vasculitis due to its "pauci-immune" feature in renal histology. However, increasing evidence indicates that activation of the complement system, especially via the alternative complement pathway, plays a crucial role in the pathogenesis of ANCA-associated vasculitis. In this brief review, we discuss the evidence, including in vivo, in vitro, and clinical studies, for complement system activation in ANCA-associated vasculitis.

Keywords ANCA · Vasculitis · Complement

J. Yuan · M. Chen (✉) · M.-H. Zhao
Renal Division, Department of Medicine,
Peking University First Hospital, 100034 Beijing, China
e-mail: chenmin74@sina.com

J. Yuan · M. Chen · M.-H. Zhao
Institute of Nephrology, Peking University,
100034 Beijing, China

J. Yuan · M. Chen · M.-H. Zhao
Key Laboratory of Renal Disease, Ministry of Health of China,
100034 Beijing, China

J. Yuan · M. Chen · M.-H. Zhao
Key Laboratory of CKD Prevention and Treatment,
Ministry of Education of China,
100034 Beijing, China

J. Yuan · M. Chen · M.-H. Zhao
Peking-Tsinghua Center for Life Sciences,
100034 Beijing, China

J. Yuan
Hubei University of Traditional Chinese Medicine,
Wuchang, 430061 Wuhan, China

J. Yuan
Hubei Hospital of Traditional Chinese Medicine,
Wuchang, 430061 Wuhan, China

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises a group of autoimmune disorders, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and Churg–Strauss syndrome (CSS) [1]. These diseases are characterized by necrotizing small-vessel vasculitis. ANCA are the serological hallmarks for the above-mentioned vasculitides. ANCA are predominantly IgG autoantibodies directed against neutrophil cytoplasmic constituents, in particular proteinase 3 (PR3) and myeloperoxidase (MPO).

The pathogenesis of AAV has not been fully elucidated. ANCA and neutrophils play a central role [2, 3]. The histopathological hallmark of ANCA-associated glomerulonephritis is "pauci-immune" necrotizing crescentic glomerulonephritis (NCGN), characterized by little or no glomerular staining for immunoglobulins and complements on renal histology by immunofluorescence microscopy examination. Therefore, it was previously assumed that the complement system is not involved in the pathogenesis of AAV. However, increasing studies suggest that complement plays a crucial role in the development of AAV.

The complement system can be activated through the classical, alternative, or mannose-binding lectin (MBL) pathway [4]. The classical pathway is activated by immune complex. The alternative pathway is spontaneously activated through hydrolysis of C3. Binding of MBL to terminal carbohydrate groups on certain microbes leads to

activation of the MBL pathway [4]. This brief review focuses on the evidence, including in vivo, in vitro, and clinical studies, for complement system activation in AAV.

Evidence from animal studies

In the mouse model of AAV [3], complement depletion can completely block disease development [6]. In this model, C5- or factor B-deficient mice were completely protected from the disease, while C4-deficient mice developed disease comparable to wild-type mice [5]. These results suggest that complement activation via the alternative pathway is critical in the pathogenesis of AAV. Further study by Huugen et al. [6] found that C5-inhibiting antibody could prevent or alleviate ANCA-associated glomerulonephritis. Schreiber et al. [7] further tested the role of C5a receptor (C5aR) in a model of ANCA-induced NCGN, finding that C5aR-deficient mice were protected from the disease.

Evidence from in vitro studies

Activation of neutrophils by ANCA can release factors including reactive oxygen, MPO, and proteases which are capable of stimulating complement amplification [8–10]. Neutrophils can release properdin on activation [11]. Moreover, neutrophils store and secrete C3 and factor B [11]. The elevated complement component of the alternative pathway would contribute to alternative pathway activation. In turn, activation of the alternative pathway led to further activation of neutrophils [12]. Therefore, the complement alternative pathway acts as positive feedback amplification of neutrophil activation. Likewise, generation of C5a could lead to infiltration and degranulation of more neutrophils at sites of complement activation, which result in development of inflammation.

Schreiber et al. [7] found that supernatants from ANCA-stimulated neutrophils activated the complement cascade in normal serum, resulting in production of C5a; recombinant C5a dose-dependently primed neutrophils for the ANCA-induced respiratory burst. This supports an interaction between ANCA, neutrophils, and complement.

Our recent study further investigated the intracellular events that control ANCA-mediated activation of C5a-primed neutrophils [13]. It was found that activation of p38 mitogen-activated protein kinase (p38MAPK), extracellular signal-regulated kinase (ERK), and phosphoinositol 3-kinase (PI3K) are important steps in translocation of ANCA antigens and C5a-induced activation of neutrophils by ANCA [13]. These are different from tumor necrosis factor-alpha (TNFα)-stimulated neutrophil activation, which is mediated by p38MAPK, not ERK and PI3K [14].

Evidence from clinical studies

Our previous study investigated the relationship between complement deposition and clinicopathological characteristics. C3c deposition was found in 37 out of 112 patients with ANCA-associated pauci-immune glomerulonephritis. Patients with C3c deposition are associated with more severe renal injury [15].

Our further studies investigated the various components of complement, including membrane attack complex (MAC), C3d, C4d, MBL, factor B, and factor P, in renal biopsy specimens of patients with NCGN by using immunohistochemistry and immunofluorescence. MAC, C3d, factor B, and factor P could be detected in glomeruli and small blood vessels with active vasculitis of patients with NCGN. C3d co-localized with MAC, and factor B co-localized with MAC in diseased glomeruli. In contrast, C4d was not detected in renal specimens of NCGN. The results indicated the alternative pathway of complement system activation in human AAV [16].

To reveal evidence for circulating activation of the complement system in AAV, our recent study further measured various circulating complement components. It was found that plasma levels of C3a, C5a, soluble C5b-9, and Bb level were significantly higher in active stage than in remission of AAV, while plasma levels of properdin were significantly lower in active stage than in remission of AAV [17]. These results provide evidence of ongoing alternative complement activation in active stage of AAV. Moreover, the plasma level of Bb in patients with active AAV correlated with the proportion of total crescents and cellular crescents in the renal specimen, the level of erythrocyte sedimentation rate, and the Birmingham Vasculitis Activity Scores. These results indicated that circulating Bb might be a useful biomarker in assessing disease activity of AAV [17].

There are two C5a receptors, C5aR (CD88) and C5L2 [18]. CD88 appears to contribute to the initiation of acute inflammatory responses, such as chemotaxis, enzyme release, the respiratory burst, etc. [18, 19]. However, C5L2 was assumed not to play an active, positive role in inflammatory responses, therefore being called a "default" or "scavenger" receptor [18, 19]. As described above, study by Schreiber et al. [7] found that the interaction between C5a and C5aR (CD88) may play a central role in ANCA-mediated neutrophil recruitment and activation. We further investigated expression of renal C5a receptors (CD88 and C5L2) in kidneys of patients with AAV. In renal specimens of AAV patients, expression of CD88 was downregulated, while expression of C5L2 was upregulated, mainly in neutrophils, monocytes, and macrophages. Interestingly, the extent of CD88 expression was inversely associated with initial renal function and renal interstitial fibrosis [20].

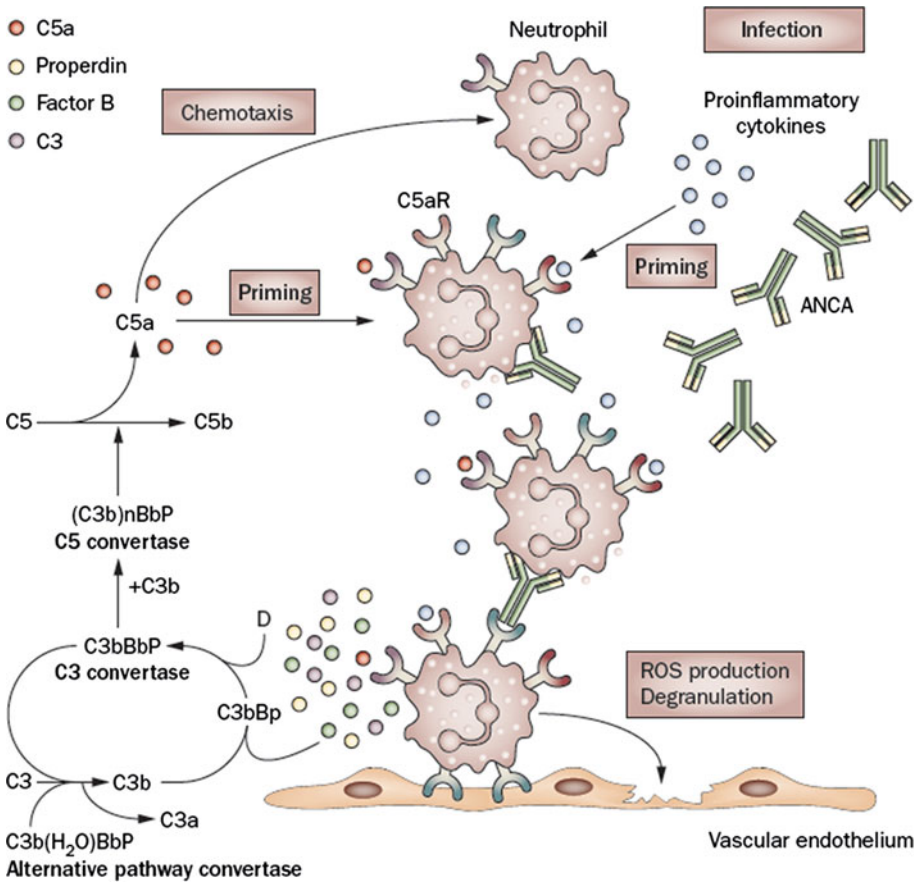

Fig. 1 Working model of the contribution of alternative complement activation to AAV. Neutrophils are primed by proinflammatory cytokines, resulting in expression of target antigens (MPO or PR3) at the cell surface, where they are available to interact with ANCA. Antigen–antibody complex is able to activate neutrophils to produce reactive oxygen and release lytic enzymes, which activate the alternative complement pathway with release of C5a. C5a in turn mediates chemotaxis and degranulation of neutrophils. A proinflammatory amplification loop is formed between neutrophil activation and complement activation, resulting in the aggressive necrotizing inflammation of ANCA disease. *AAV* ANCA-associated vasculitis, *ANCA* antineutrophil cytoplasmic antibody, *C* complement, *C5aR* C5a receptor, *ROS* reactive oxygen species. Reproduced with permission from Nature Publishing Group [21]

In conclusion, complement activation via the alternative pathway participates in the development of AAV. Among various components of the complement system, the interaction between C5a and its receptors plays a central role in the pathogenesis of AAV. Inhibition of complement, especially C5a, is a potential therapeutic approach to AAV. A proposed working model for ANCA-mediated vascular inflammation through alternative pathway complement activation is shown in Fig. 1 [21].

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Conflict of interest None.

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