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Review

Complement system activation in ANCA vasculitis: A translational success story?

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ABSTRACT

The ANCA-associated vasculitides (AAV) are characterized by pauci-immune necrotizing small to medium size vessel vasculitis frequently including necrotizing crescentric glomerulonephritis. Neutrophil activation by ANCA appears a primary pathogenic event. More recently, the complement system has been shown to be involved as well. Activation of the alternative pathway of complement, at least in part via activated neutrophils, results, amongst others, in the generation of C5a, a strong chemoattractant for neutrophils. C5a is also effective in neutrophil priming, a process leading to surface expression of the ANCA antigens so enabling neutrophils to be further activated by ANCA. Both in vitro and in vivo experimental data and histopathological studies from AAV patients underscore the role of complement, and particularly of C5a, in the pathophysiology of AAV. Preliminary data show that blocking of the C5a-receptor is a promising approach in the treatment of AAV.

1. Introduction

The ANCA-associated vasculitides comprise granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and its renal limited form, and eosinophilic granulomatosis with polyangiitis (EGPA) (Jennette et al., 2013). Anti-neutrophil cytoplasmic autoantibodies (ANCA) are present in almost all patients and are directed against proteinase 3 (PR3), particularly in GPA, or myeloperoxidase (MPO), particularly in MPA and in about 50% of patients with EGPA in whom the clinical presentation is dominated by small vessel vasculitis (Table 1) (Kallenberg, 2014). Renal involvement occurs frequently in ANCA-associated vasculitis (AAV) and is histopathologically characterized by necrotizing glomerulonephritis with crescent formation. Despite the presence of ANCA in serum, direct immunofluorescence of the renal biopsy shows absence or paucity of immunoglobulins (pauci-immune). So, in contrast to anti-GBM disease or immune complex mediated glomerulonephritis, a direct pathogenic role for ANCA was not immediately clear. In vitro studies, however, showed that ANCA are able to stimulate primed neutrophils to the production of reactive oxygen species and the release of lytic enzymes (Falk et al., 1990). In the context of endothelial cells, ANCA-induced neutrophil activation resulted in conversion of rolling of neutrophils to firm integrin-mediated adhesion followed by detachment of endothelial cells and their lysis (Radford et al., 2000). This led to the concept that ANCA are pathogenic by activating (primed) neutrophils at the endothelial surface resulting in necrotizing vasculitis (Kallenberg et al., 2013). This concept was supported by a mouse model in which transfer of anti-mouse MPO IgG-antibodies resulted in the development of pauci-immune focal necrotizing glomerulonephritis and pulmonary capillaritis in the recipients (Xiao et al., 2002). Further exploration of the components involved in lesion development in this model resulted in the elucidation of the importance of complement components in this process.

2. Animal models of AAV: a crucial role for alternative pathway complement system activation

Over the past 20 years a number of animal models of MPO-ANCA vasculitis have been developed and these models have proven instrumental in dissecting the various effector pathways involved in ANCA induced vasculitic injury (van Timmeren and Heeringa, 2012). Although these studies showed that many effector pathways contribute, a surprisingly crucial role has been identified for complement system activation. In a mouse model induced by the transfer of anti-MPO IgG, ablation of C5 and depletion of C3 completely inhibited disease development (Xiao et al., 2007). Additional

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Table 1
Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitis.

Large vessel vasculitis
Takayasu arteritis
Giant cell arteritis
Medium vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Small vessel vasculitis
ANCA-associated vasculitis
Microscopic polyangiitis (MPA)
Granulomatosis with polyangiitis (Wegener's) (GPA)
Eosinophilic granulomatosis with polyangiitis (Churg Strauss) (EGPA)
Immune complex small vessel vasculitis
Anti-GBM disease
Cryoglobulinemic vasculitis
IgA vasculitis (Henoch-Schönlein)
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
Variable vessel vasculitis
Behçet's disease
Cogan's syndrome
Single organ vasculitis
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary CNS vasculitis
Isolated aortitis
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
Vasculitis associated with probable etiology
Hepatitis C virus-associated cryoglobulinemic vasculitis
Hepatitis B virus-associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated ANCA-associated vasculitis
Cancer-associated vasculitis
Others

experiments in this model demonstrated that whereas C4 deficient mice developed glomerulonephritis similar to wild type mice, factor B deficient mice were completely protected indicating complement system activation via the alternative pathway (Xiao et al., 2007). Subsequent studies demonstrated an important role for C5aR activation on inflammatory cells in amplifying the anti-MPO IgG induced inflammatory response and showed that pretreatment or treatment with a C5 inhibiting monoclonal antibody prevented or strongly attenuated glomerulonephritis development, respectively (Schreiber et al., 2009; Huugen et al., 2007).

Collectively, these experimental data indicate that the development of MPO-ANCA mediated glomerulonephritis is a multistep process which is initiated by the recruitment and priming of neutrophils to glomeruli possibly mediated by infectious agents. Once recruited, ANCA initiate injury via activation of primed and adherent neutrophils causing direct endothelial injury. At the same time, ANCA mediated neutrophil activation causes an inflammatory amplification loop by inducing the release of complement factors into the microenvironment leading to alternative pathway complement activation and generation of C5a that in turn causes attraction and activation of additional neutrophils to the inflammatory site (van Timmeren et al., 2009). Importantly, these studies also indicate that interventions aimed to inhibit complement activation could be an attractive strategy to prevent disease progression in AAV. One approach that has been tested in the mouse model of anti-MPO IgG mediated glomerulonephritis is pharmacological blockade of the C5aR (Xiao et al., 2014). In this study, daily oral administration of a small compound antagonist of the human C5aR, CCX168, markedly ameliorated anti-MPO IgG mediated glomerulonephritis development in human C5aR knockin mice in a dose dependent manner (Xiao et al., 2014).

3. Does complement activation play a role in human ANCA mediated vasculitis?

Indeed, a study in 7 patients with MPO-ANCA associated glomerulonephritis showed deposition of factor B and properdin as well as C3d and the membrane attack complex (MAC) in glomeruli and small blood vessels (Xing et al., 2009). Studying plasma from patients with active AAV, Gou et al. (2013a,b) observed increased levels of C3a, C5a, soluble C5b-9 and Bb compared to controls as well as to remission samples whereas levels of properdin were decreased. Levels of C4d did not differ between active disease and remission. Plasma levels of Bb correlated with the proportion of crescents in the renal biopsy (Gou et al., 2013a,b). Those data support the role of the alternative pathway of complement activation in AAV. The same group of investigators also showed that urinary levels of C3a, C5a and soluble C5b-9 were higher during active disease than during remission (Gou et al., 2013a,b). They, furthermore, found a correlation between urinary levels of Bb and serum creatinine. The relevance of the alternative pathway of complement in this process was demonstrated by the deposition of Bb in glomeruli, the extent of which correlated with the proportion of total crescents in the renal biopsy (Gou et al., 2013a,b). These observations arise the question how the complement system is activated in AAV. Xiao et al. (2007) showed that incubation of human neutrophils with IgG from patients with MPO-ANCA and PR3-ANCA leads to release of factors that activate complement via the alternative pathway. In addition, C5a was shown to induce priming of neutrophils with an increase of membrane expression of PR3. Activation of p38 mitogen-activated protein kinase (p38MAPK), extracellular signal-regulated kinase (ERK) and phosphoinositol 3-kinase (PI3K) are involved in signal transduction in this process (Hao et al., 2012). As such, the alternative pathway of complement is activated following neutrophil activation. The generation of C5a plays a major role as this substance is a very strong chemoattractant for neutrophils and is able to prime those cells so enabling their full activation by ANCA. The amplifying role of the complement system in the pathophysiology of AAV is depicted in Fig. 1 (Chen and Kallenberg, 2010).

4. Is the complement system a target for treatment in AAV?

As discussed in the preceding paragraphs the alternative pathway of complement activation and particularly C5a is directly involved in the pathophysiology of an animal model of MPO-ANCA glomerulonephritis. The data from histopathological, serological and in vitro studies on human material strongly support a role for complement in AAV. Targeting C5a seems a logical step in the treatment of AAV. Indeed, in the animal model discussed before, lesions did not develop in C5-deficient mice (Xiao et al., 2007) and treatment with an oral blocker of the C5a-receptor strongly ameliorated the development of (renal) lesions (Xiao et al., 2014). Targeting the C5a-receptor and not C5 itself has the advantage that the final common pathway of complement activation is still intact which is important in relation to the innate immune response toward microbial agents. The oral blocker of the C5a-receptor, CCX168, is currently being evaluated in a phase II multicenter clinical trial in AAV patients (EU Clinical Trial Register ID: EUCTR 2011-001222-15-GB). The primary objective of this trial is to evaluate safety and tolerability of CCX168 in AAV patients with renal involvement with the intent to reduce toxicity of induction therapy and to reduce or even eliminate the use of systemic corticosteroids. The results of this trial are eagerly awaited but first reports are encouraging.