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Complement in ANCA vasculitis, insights on pathophysiology and targeted therapies

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ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a debilitating disease with the potential to cause significant morbidity and mortality if not treated. The pathogenesis of this disease is not understood, though emerging evidence suggests that alternative complement pathway system is involved. C5a, mediates several pro-inflammatory effects through its receptor C5aR. Avacopan, targets C5a by preventing it from binding to its receptor C5aR. Complement dysregulation, imbalance between regulatory activity of Factor H and stimulation by Factor H related proteins, has been identified as a new mechanism of disease.

Introduction

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), is a devastating disease affecting multiple organs.[1,3,4,7] Disease limited to the kidneys is called renal limited vasculitis.[1,3,4,7,13,22,24] An autoinflammatory disease, untreated, missed or delayed diagnosis has critical implications, with patients with renal limited disease experience significant morbidity. Therefore, prompt diagnosis and treatment are required. ANCA vasculitis refers to distinct diseases that typically affect small vessels. Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA), Eosinophilic Granulomatosis with Polyangiitis (EGPA).[22] The pathogenesis of this disease is complex and is not fully understood.[1,3,4,7,13]

The complement system was previously thought to exhibit limited activity in patients with ANCA vasculitis.[22] Histopathology of renal tissue has been described as pauci-immune with minimal immunoglobulin and complement deposition.[22] Recent evidence suggests that the complement system plays a role in the development of ANCA vasculitis.[3] Priming of Neutrophils with cytokines and ANCA activates the complement cascade.[3] Moreover, renal tissue analysis revealed C3 deposition in the glomerulus.[1-57] Recently, it has been shown that C5a produced by the alternative complement pathway primes neutrophils, which in turn activate the alternative pathway, leading to a positive feedback loop. [7,13,18,24,26] Avacopan, a C5a receptor antagonist, is a novel therapeutic agent that has been shown to be effective in the treatment of patients with AAV.[21] In this narrative review, the pathophysiological mechanisms of the complement system, and new targeted therapies for ANCA vasculitis are discussed.

The Complement System; Physiology and Regulation

The complement system has multiple components comprising plasma proteins, cell membrane receptors, and regulatory factors that interact with each other in a complex cascade of reactions linking the innate and adaptive immune systems.[1,3,4,5,6,13] It begins with small inactive protein precursors that are synthesised by the liver and released into circulation. These protein precursors transform into complement proteins in their active forms, which function as serine proteases that cleave specific proteins to produce cytokines that amplify further downstream reactions.[1,3,4,5,6,13]

The net result is the stimulation of phagocytes to clear foreign antigens and promotion of further inflammation to attract more phagocytes, culminating in the formation of the membrane attack complex (MAC) which can kill cells.[1,3,4,5,6,13,18,23]

Complement activation can occur through three different pathways: classical, lectin, and alternative.[1,2,13,14,17,24,25-29] (Figure 1)

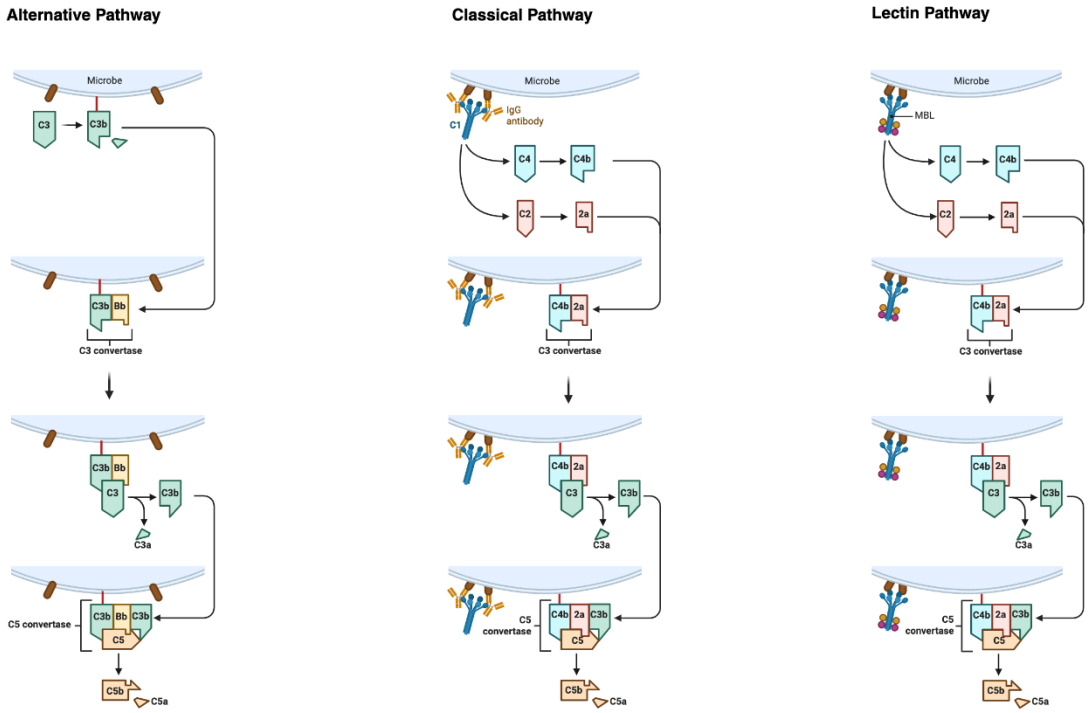

Figure 1:
Complement activation by Alternative, Classical and Lectin Pathway. Alternative pathway activated by bacterial endotoxin, lipopolysaccharide present on gram negative bacteria. Spontaneous hydrolysis to C3b which combines with other factors to form C3 convertase. C3 convertase combines with C3b and C5 to form C5 convertase complex. Classical pathway activated by C1q binding to antigen or antigen-antibody complex, forming C3 convertase. Lectin Pathway stimulated by Mannose binding Ligand (MBL) on pathogen activating MASP to form C3 convertase.

The activation of each pathway produces C3 convertase, an enzyme which is degraded into C3a and C3b fragments.[1,3,4,13,17,22,23,27]

The classical pathway is activated when IgG and IgM bind to target antigens, resulting in the formation of immune complexes.[1-57] The lectin pathway is activated by pattern recognition proteins, such as mannose binding lectin, which binds to sugar ligands present on the outer surface of bacteria and damaged host cells.[1,3,4,13,17,22,23,27]

C3a and C5a act as anaphylatoxins that are released into circulation following the degradation of C3 and C5. The effects of C3a and C5a occur through their interactions with their receptor, a seven G-coupled transmembrane protein expressed on parenchymal and leucocyte cells. [37] (Figure 2)

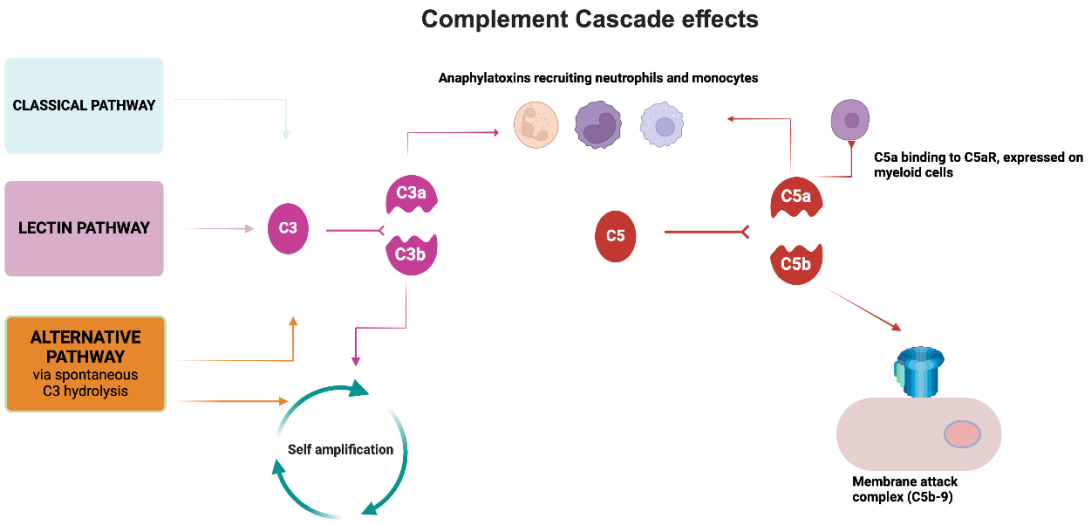

Figure 2:
C3 cleaved to C3a and C3b. C3b involved in phagocytosis and opsonisation. C3b also involved in amplification loop of the alternative pathway. C3a and C5a as chemotactic factors recruiting inflammatory cells. C5a binding to C5aR expressed on myeloid cells to mediate effects. C5b involved in formation of Membrane attack complex (C5b-9) leading to cell lysis and death.

C3a and C5a have pro-inflammatory effects, but are also said to have anti-inflammatory effects, aiding in tissue recovery.[46]

C5a has several key functions, including acting as a powerful chemotactic factor for neutrophils, monocytes, and macrophages, thus enabling for the migration of these inflammatory cells to areas where complement activation occurs.[30]

Moreover, C5a delays apoptosis of neutrophils thereby prolonging its survival and promoting the expression of adhesion molecules on the surface of neutrophils.[25] It also causes neutrophils to release Properdin, a positive stimulant of the alternative pathway, by stabilising C3 convertase (C3bBb).[54]
Counteracting these proinflammatory responses can also produce reactive oxygen species (ROS) in phagocytes which can cause degranulation of neutrophils.[36]

C5aR is a target for Avacopan, preventing C5a interacting with C5aR. Supporting evidence for the use of Avacopan in clinical studies will be discussed later.

The complement system is regulated by plasma and cell surface proteins that prevent complement activation. These regulatory proteins act at various levels in the complement cascade. C3 and C5 convertases which play central roles in complement activation, serve as the targets of these regulatory proteins.[2,31,57]

Factor H, a key regulator of the alternative pathway, is a soluble glycoprotein produced by the liver. It binds to C3 activation fragments causing accelerated decay and reduced cofactor activity.[29] Factor H dysfunction has been suggested to have a pathogenic role in the development of C3 glomerulopathy and atypical haemolytic uraemic syndrome. Moreover, it has been suggested that it is a prognostic marker of worsening disease in these patients [31,44]

The regulatory activity of Factor H can be countered by Factor H related proteins (FHR1-5), another member of the Factor H family.[29]

Structurally, FHRs share surface recognition domains like those of Factor H. They differ in that FHRs lack the complementary regulatory domains of Factor H.[29] Factor H functions in an alternative pathway by inactivating the surface bound C3b. This action prevents further generation and deposition of C3b, which has a negative effect on downstream complement reactions.[5,6,9,12] It has been postulated that an imbalance between Factor H and FHRs can lead to the development of complement mediated diseases. This pathogenic mechanism has been proposed in glomerular diseases such as Ig A Nephropathy and C3 Glomerulopathy.[32]

This mechanism has been supported by Lucientes-Continente et al. who speculated a potential genetic association.[29] They showed that genetic variants in components of the alternative complement pathway correlated with disease susceptibility (CFB32Q/W) or the severity of kidney damage (CFH-H1, CFH-H2 Delta

CFHR3/1) in a Spanish cohort of 100 patients with AAV.[29] High basal FHR-1 levels and low FH/FHR-1 ratios were determinants of kidney disease severity.[29] Moreover, the plasma levels of complement components were different in active disease compared to those in remission.[29] In patients with active disease, the plasma levels of C3, Factor H, Factor B and Properdin were lower than those in patients in remission.[29] Conversely, soluble C5b-9 (sC5b-9) levels were high in patients with active diseases.[29] This study reported that a high degree of alternative complement activation is associated with worse disease outcomes, although the underlying molecular mechanisms are not understood.[29] It has been proposed that FHR-1 can induce inflammation, by activating the inflammasome, Nucleotide binding, oligomerisation domain, leucine rich receptor and pyrin-domain containing 3 (NLRP3) expressed on monocytes and cause tissue damage by releasing interleukin 1 b (IL-1B).[17,45] The NLRP3 inflammasome is a multiprotein complex expressed on a variety of immune cells, such as neutrophils and macrophages, that regulates the innate immune system and inflammatory signalling.[17,45]
High FHR-1 levels are linked with increased IL-1B levels in patients with AAV.[17,45] Similarly, as described earlier surface-bound FHR-1 promotes alternative complement pathway activity which can compromise the regulatory activity of Factor H.[29] Whether the deleterious effects of FHR-1 are due to its direct action on the NLRP3 inflammasome, activation of the alternative pathway, or both is yet to be determined.[29]

The Alternative Complement pathway in ANCA vasculitis

Murine mouse models were the first to suggest the involvement of an alternate pathway.[15,55] Xiao et al. injected cobra venom factor into mice with experimental anti-MPO glomerulonephritis. This causes the depletion of C3, resulting in reduced neutrophil and macrophage infiltration within the glomeruli.[15] Furthermore, in mice with anti-MPO glomerulonephritis with knockout of C5 and factor B, no necrosis and no crescents were evident within the glomeruli.[15] However, this was not observed in mice with knockout of C4.[15]

Huugen et al. observed similar findings in mice with anti-MPO glomerulonephritis treated with a monoclonal antibody targeting C5a; reduced neutrophil glomerular infiltration and absence of necrotic and crescentic changes were observed.[55]

In the 1980s, C3 glomerular deposits were reported in patients with AAV.[35] Importantly, patients diagnosed with AAV who have C3d and immunoglobulin deposits on renal biopsy have been observed to have higher urine proteinuria and a higher percentage of crescents than AAV patients without C3 and immunoglobulin deposition, indicating a worse prognosis.[10,13] Similarly, low serum C3 levels have been reported to correlate with low survival rates as opposed to serum C4 levels.[1,4,8]

In their meta-analysis of AAV patient studies, Moiseev et al. demonstrated high levels of C3a, C5a, Factor B and C5b-9.[35] Notably, patients who achieved clinical remission had lower C3a, C5a and Factor B levels. The C5b-9 levels did not change.[35]

However, the pathogenic mechanisms involved in this alternative pathway are not fully understood. It has been proposed that priming of neutrophils is the first step, triggered by respiratory infection and C5a, causing the translocation of PR-3 and MPO antigens to be expressed on the cell surface of neutrophils. This is followed by binding of ANCA to these antigens, causing activation of the neutrophils.[24,25]

Adhesion molecules bound to the endothelial surface bind to activated neutrophils, causing the release of ROS, degradative enzymes, and neutrophil extracellular traps which can activate complement and create an amplification loop.[24,25]

Clinical Studies of Complement Inhibition: Avacopan

The CLEAR trial was a phase 2 clinical trial involving 67 patients with newly diagnosed or relapsing ANCA vasculitis (MPA and GPA) who received Avacopan, an oral C5aR inhibitor.[20] Key inclusion criteria included patients with a glomerular filtration rate (GFR) of greater than 20 mls/min/1.73 m2, treated with either Rituximab or Cyclophosphamide as induction therapy.[20] The exclusion criteria were patients with rapidly progressive glomerulonephritis or diffuse alveolar haemorrhage; patients recently treated with cyclophosphamide; patients treated with a high dose of corticosteroids, cumulative dose of intravenous methylprednisolone of more than 3 g in the last 3 months; or patients treated with oral prednisolone at a dose of more than 10 mg or its equivalent for more than 6 weeks.[20]

The patients were randomised into three groups: a placebo group receiving 60 mg prednisolone, patients receiving 30 mg bd of Avacopan, 20 mg of prednisolone, and patients receiving 30 mg bd of Avacopan. Notably, the median GFR of patients in the study was 50 mls/min/1.73 m2, indicative of mild to moderate kidney disease. The patients involved in the study were followed-up for 12 weeks.[20]

Results showed that patients who received Avacopan had decreased disease activity, as assessed by the Birmingham vasculitis activity score (BVAS), and lower albuminuria.[20] Importantly, patients who received Avacopan without steroids did not experience any adverse effects related to corticosteroid therapy.[20]

The CLASSIC trial was another phase 2 clinical trial that evaluated the safety of Avacopan.[33] In this study, 42 patients newly diagnosed with AAV were treated with therapy comprising of steroids with either Cyclophosphamide or Rituximab as standard care of therapy (SOC), plus Avacopan with SOC.[33] These patients were randomised to receive SOC or Avacopan, 10 mg or 30 mg bd with SOC.[33] The study revealed no difference in the rate of serious adverse events between patients who received SOC and those who received Avacopan plus SOC. Patients who received a higher dose of Avacopan (30 mg bd) had better outcomes, including earlier time to remission, improved GFR, and better quality of life.[33]

The phase 3 study, ADVOCATE, involved 331 patients

with new or relapsing AAV (GPA and MPA; PR3 and MPO positive).[21] Patients in this trial had a GFR greater than 15 mls/min/1.73 m2 and received induction therapy with steroids plus either cyclophosphamide or rituximab.[21] In this study, patients were randomised to receive high dose steroids, as in the CLEAR trial, with tapering and discontinuation by week 21 or Avacopan 30 mg twice daily. The primary outcome of the study was remission, defined as a BVAS score of 0 at week 26, and sustained remission at week 52.[21] Secondary outcomes included the adverse effects of therapy, glucocorticoid toxicity, timing of glucocorticoid toxicity, and quality of life.[21] The study revealed that 72.3% of patients in the Avacopan cohort achieved remission at week 26, as opposed to 70.1% in the Prednisolone arm, suggesting the non-inferiority of Avacopan to Prednisolone.[21] Furthermore, sustained remission at week 52 was achieved in 65.7% of the patients in the Avacopan arm compared with 54.9% in the Prednisolone cohort. Avacopan was superior to Prednisolone and increased GFR.[21] Statistically, no significant difference was observed when comparing the adverse effects between the two groups.[21] Lower rate of glucocorticoid toxicity was observed in the Avacopan group.[21] The positive findings of this study led the US food and drug administration to approve Avacopan as an adjunctive therapy in October 2021.[50] Subsequently, it received approval from The European Medicines Agency in 2022.[50]

Conclusion

The Complement pathway, particularly the alternative pathway, plays a critical role in the development of ANCA vasculitis. Clinical trial data have shown improved clinical outcomes and reduced adverse drug effects with Avacopan, an oral C5aR inhibitor, compared to glucocorticoids, thus increasing the therapeutic armamentarium. New complement targets are awaited, and further research using these drugs in ANCA vasculitis is needed.

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