along with the discovery of rare variants in age-related macular degeneration have ignited the field of complement therapeutics.

**Learning Objectives**

- Describe the long history of the complement system’s interactions with lupus for the lupologist
- Advances in defining the role of ‘complement’ as a biomarker for lupus
- Discuss recent advances understanding how complement deficiency predisposes to SLE

**REFERENCES**


**THE ROLE OF COMPLEMENT AND COMPLEMENT INHIBITION IN APS PREGNANCY**

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Women with antiphospholipid syndrome (APS) are at increased risk for adverse pregnancy outcomes, including preeclampsia, fetal and neonatal death and fetal growth restriction. Studies in mice implicate inflammation, particularly complement activation, as an essential and causative factor in placental insufficiency, fetal loss and growth restriction. Complement activation is initiated by classical, alternative and lectin pathways. The convergence of the three pathways on C3 results in generation of common effectors: anaphylatoxins, opsonins and the membrane attack complex. Mice deficient in alternative and classical pathway complement components (factor B, C4, C3 and C5) and mice treated with inhibitors of complement activation (anti-C5 mAb, anti-factor B mAb, C5a receptor antagonist peptide) are resistant to fetal injury induced by aPL, indicating that both pathways contribute to damage. Similarly, pregnancies in hypertensive mice prone to preeclampsia are rescued with inhibitors of complement activation. Studies in humans support the role of complement in aPL-associated pregnancy complications and in preeclampsia and growth restriction in non-autoimmune women. Complement fragment C4d, a marker of classical pathway activation, is present in placenta from women with systemic lupus erythematosus (SLE) and/or APS and from women with preeclampsia. Mild hypocomplementemia has also been reported in primary APS. The presence of loss of function variants in complement regulatory proteins in patients with preeclampsia with SLE and/or aPL antibodies or without autoimmunity links complement activation to disease pathogenesis. Furthermore, in prospective studies of SLE and/or APL-positive patients and in non-autoimmune patients, elevated levels of the complement activation products in blood, particularly factor Bb, were associated with adverse pregnancy outcomes. Taken together, these findings suggest a role for complement inhibition for the prevention of APS-triggered placental insufficiency in high risk pregnancies.

**THE INTERFACE OF COMPLEMENT AND COAGULATION PATHWAYS**

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The most menacing challenge to survival faced by organisms throughout the animal kingdom is injury accompanied by invasion of foreign pathogens. To survive these threats, organisms have developed effective means to contain wounds by simultaneously and coordinate limiting bleeding with clot formation, restricting and fighting infections, while facilitating rapid initiation of healing. This finely tuned, synchronized activation of coagulation and complement—the latter, a major component of innate immunity—supports the notion that complement is a key mediator of pregnancy complications in women with systemic lupus erythematosus and/or anti-phospholipid antibodies.
and immune (e.g. systemic lupus erythematosus)\textsuperscript{4} disorders, but underscored by the thrombotic diathesis associated with the rare but devastating genetic complement-mediated disorders, paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS).\textsuperscript{5} Both of these complement-mediated disorders that feature thrombosis, are extraordinarily responsive to treatment with a highly specific inhibitor of complement, highlighting the importance of delineating the relationship between complement and coagulation.

**Learning Objectives**

- Describe the cellular and molecular links between the complement and coagulation systems
- Discuss the role of complement in different diseases
- Explain the importance of delineating the relationship between complement and coagulation

**REFERENCES**


**LESSONS LEARNED FROM COMPLEMENT INHIBITION IN ANCA VASCULITIS**

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In the absence of cures for multi-system inflammatory disease, therapies aim to dampen long-term inflammation, control symptoms and prevent tissue damage. Glucocorticoids (GC) are a key anti-inflammatory agent with a rapid mode of action and broad targeting of multiple pathways. However, GC toxicity causes organ damage affecting organ function and patient quality of life.\textsuperscript{1} Recent advances in anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) treatments, include B-cell targeting therapies that work over the medium to longer term, yet few drugs are in development that aim to replace GCs. Herein lies an opportunity for complement inhibition.

Despite the lack of overt evidence of complement activation in AAV, where circulating C3 and C4 levels are usually normal and immune deposition in tissues is described as ‘pauci-immune’, a rationale for alternative complement pathway inhibition has emerged.\textsuperscript{2} ANCA vasculitis has a neutrophil dependent pathogenesis and C5a (anaphylatoxin) is a potent neutrophil chemotacticant, but also capable of priming resting neutrophils to induce autoantigen translocation to the cell surface and cell activation triggered by ANCA autoantibody binding. Rare patients with low C3 or C4 levels have more aggressive disease, and those with lower C3 levels in the normal range also do worse. Complement split products such as Bb, C3d and the C5b-9 terminal attack complex are found in the glomeruli of kidney biopsies from vasculitis patients, and functional factor H deficiencies occur in ANCA vasculitis. Neutrophil NETs are substrates for complement cleavage and activation and complement both activates platelets and microthrombosis, a key component of pathology. Experimental data has demonstrated that either non-specific depletion of complement by cobra venom factor or specific inhibition of the C5a receptor abrogates experimental vasculitis.\textsuperscript{3} The latter experiment, using a humanised C5aR ‘knock in’ model, was a key step in the development of agents targeting the C5a receptor, which also demonstrated that the alternative C5a receptor (C5L2) may be regulatory in this setting. This is relevant when considering the targeting of anti-C5 agents.

Clinical studies of vasculitis are analogous to lupus, whereby newer agents are added to standard of care to assess efficacy without the opportunity to demonstrate GC sparing or avoidance. A Phase II trial of the oral anti-C5aR inhibitor avacopan was designed to look at stepwise removal of GCs and replacement with avacopan.\textsuperscript{4} The results of the CLEAR trial confirmed non-inferiority when comparing to GCs and superiority in renal response, quality of life and safety seen in secondary endpoints. This along with a second Phase II trial (CLASSIC) assessing safety of avacopan in addition to GCs provided a strong rationale to proceed to a Phase III trial directly comparing avacopan with GC. The ADVOCATE trial randomised 330 ANCA associated vasculitis patients to either avacopan for 12 months or prednisone tapered to zero by 21 weeks.\textsuperscript{5} All patients received either cyclophosphamide or rituximab. Non-inferiority of avacopan was confirmed for disease remission at 6 months and superiority of avacopan over the prednisone taper group was seen at 12 months. All secondary endpoints, relapse, recovery of renal function, quality of life and safety, were superior in the avacopan group. Now avacopan has entered a regulatory pathway, the discussion has turned to whether it has a role in the most severe patients (i.e. those excluded from ADVOCATE), in longer term relapse prevention and whether its use could avoid the need for rituximab or cyclophosphamide in some patients. There are also mechanistic questions about the impact of avacopan on circulating complement components, on autoantibody levels, and B and T cell activity. Avacopan has also been studied in the immune-mediated renal disease C3 nephropathy with reductions in nephritis activity.

Is complement inhibition likely to work in lupus? There has been a small early phase study of eculizumab (anti-C5) in lupus and an anti-MAST 2 therapeutic is being developed for lupus nephritis. The pathogenesis of lupus and potential for complement inhibition is more complex than for ANCA associated vasculitis. Complement deficiencies can promote lupus and complement is required for clearance of apoptotic debris, a major drive of immune dysregulation. Conversely, the classical complement pathway is a component of immunoglobulin mediated tissue injury, neutrophil activation contributes to injury and the alternative complement pathway is implicated in contributing to this activation. Specific pathologies, such as, thrombotic microangiopathy are complement dependent and have responded to anti-C5 therapy.\textsuperscript{6} Complement also plays roles in T- and B-cell, platelet and endothelial-cell activation relevant to lupus pathogenesis. There is strong experimental evidence for complement in the pathogenesis of experimental lupus, but a paucity of studies exploring inhibition or augmentation of specific complement or complement-regulatory elements. Both anti-C5 and anti-factor B approaches have reduced injury in the NZB-NZW model and hyperexpression of complement-regulatory proteins has protected lupus prone