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

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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.¹ 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,¹ indicating that both pathways contribute to damage. Similarly, pregnancies in hypertensive mice prone to preeclampsia are rescued with inhibitors of complement activation.² Studies in humans support the role of complement in aPL-associated pregnancy complications and in preeclampsia and growth restriction in non-autoimmune women.³ Complement fragment C4d, a marker of classical pathway activation, is present in placentae 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 autoimmune links complement activation to disease pathogenesis.⁴ 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.⁵ Taken together, these findings suggest a role for complement inhibition for the

prevention of APS-triggered placental insufficiency in high risk pregnancies.

Learning Objectives

- Explain the risk factors for adverse pregnancy outcomes in APS
- Describe the mediators and mechanism of pregnancy complications in patients in APS
- Describe potential targets to treat and prevent pregnancy complications in patients with APS

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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 coordinately 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 common molecular mechanisms regulate these multi-protein, blood-borne cascade systems, and that dysregulation of either, may negatively impact on both, causing disease.

The last couple of decades has seen major progress in identifying cellular and molecular links between the complement and coagulation systems, yielding diagnostic insights and strategies for the design of innovative therapies. We and others have delineated mechanisms by which complement activation promotes coagulation.¹ For example, the complement-mediated anaphylatoxin C5a, triggers activation of endothelial cells, platelets and monocytes, and upregulates the coagulation initiator, tissue factor (TF). The lytic membrane attack complex (C5b-9), generated terminally by activation of complement, also induces TF expression, while the complement lectin pathway serine proteases (MASPs) directly activate clotting factors. Notably, the key coagulation-induced clotting protease, thrombin,² feeds back and amplifies complement activation, thereby sustaining a vicious, escalating cycle, that may result in profound damage to the host.

The physiologic relevance of the interplay between coagulation and complement is evident in many metabolic, malignant, inflammatory, infectious (e.g. COVID-19),³ thrombotic