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Complement Activation in Pregnancy: Too Much of a Good Thing?

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Preeclampsia and other hypertensive disorders of pregnancy continue to be major contributors to maternal mortality and morbidity worldwide.¹ Currently, primary treatment for preeclampsia centers on the management of symptoms until delivery is indicated; hence, early onset preeclampsia is strongly associated with fetal growth restriction and is one of the leading causes of preterm birth.¹ A wide variety of putative factors and pathways have been implicated in the development of this pregnancy-specific syndrome.¹ Indeed, characterization of biomarkers for the identification of patients at risk for developing preeclampsia continues to be an important endeavor. The complement system is a humoral immune amplification system, and products of complement system activation have been implicated both as biomarkers for the disease and as factors important for the development of preeclampsia. The study by Buurma et al² in this issue of *Hypertension* takes a critical step toward identifying the important pathway of complement activation leading to excessive local complement activation in the preeclamptic placenta, as well as demonstrating key complement regulatory proteins that are increased in preeclampsia presumably to limit activation of the pathophysiologic pathway.

The original discovery of the complement system focused on its ability to complement the actions of antibody in host defense and bacterial killing. As part of innate immunity, the complement system contributes to survival, and components are found in species as ancient as horseshoe crabs. Although basal complement activity is controlled by numerous regulators, excessive activation contributes to autoimmune diseases, including arthritis, systemic lupus erythematosus, and antiphospholipid syndrome. Interestingly, individuals with systemic lupus erythematosus and antiphospholipid syndrome are also at increased risk for adverse fetal outcomes and hypertension during pregnancy.

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A brief overview of the most relevant aspects of the complement system is illustrated in the Figure. Central to all 3 pathways of complement activation (classical, lectin, and alternative) is the enzyme C3 convertase that cleaves C3 to generate C3a with covalent binding of C3b fragment to the invader or neighboring tissue components. The C3b tag marks the surface for attack by phagocytes and also serves as a nucleus for forming C5 convertase for cleavage of C5. After C5 cleavage, C5b inserts in the surrounding membrane, and subsequent protein–protein interactions of C5b with C6, C7, C8, and C9 lead to formation of the membrane attack complex that can lyse cells. The classical pathway is initiated by antigen–antibody interactions with C1q and the lectin pathway by polysaccharide interactions with mannose-binding lectin. In both the cases, C4 is cleaved with covalent binding of C4b to surfaces and C4b participation as part of C3 convertase. Alternative pathway is more promiscuous and is activated by endotoxin and many surfaces, including negatively charged particles. Cleavage product of factor B (Bb) is an alternative pathway marker that does not covalently bind to surfaces but forms a complex with C3b to form an alternative pathway C3 convertase. Properdin stabilizes alternative pathway C3 convertase and thus promotes continued C3 cleavage. Bound C3b and C4b can be further degraded to C3d and C4d, respectively, which still signal phagocytes but do not serve as a nucleus for the formation of C5 convertase.

Components of the complement system are important for normal placentation, and delicate regulation of complement activation is critical for a successful pregnancy. Although some level of placental complement activation is normal in pregnancy, previous studies suggest that excessive activity may contribute to the pathology of preeclampsia.^{3–5} Indeed, animal models show that excessive complement activation is associated with adverse pregnancy outcomes, such as oxidative stress and placental dysfunction⁶ and hypertension,⁷ and inhibiting complement activation ameliorates these features of preeclampsia, respectively, in a mouse and rat model.^{6,7}

In transplantation, tissue-bound C4d indicates classical pathway activation and antibody-dependent allograft rejection. Likening pregnancy to a transplant, studies of Cohen et al⁸ demonstrated more C4d at the maternal–fetal interface in the placenta of patients with systemic lupus erythematosus and antiphospholipid syndrome compared with controls, and C4d was associated with adverse fetal outcomes. Because no differences were seen in mannose-binding lectin and properdin, the pathological complement activation was most likely to occur via classical pathway.⁸ A subset of patients in this recent study had coexisting preeclampsia and set the stage for

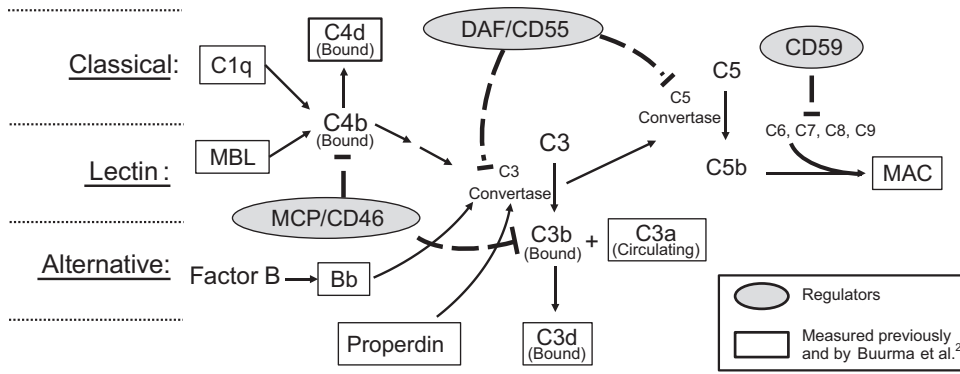


Figure. Simplistic schematic of complement system activation depicting regulators and complement components measured by Buurma et al.² The complement system is activated via 3 pathways, classical, lectin, and alternative. All 3 pathways result in the formation of C3 convertase to cleave C3 into a covalently bound C3b fragment and a fluid phase C3a fragment. C1q is indicative of classical pathway involvement, and mannose-binding lectin (MBL) indicates lectin pathway involvement. With the activation

of either the classical or lectin pathway, C4b covalently binds locally to invader or self surfaces. C4b either participates in the formation of C3 convertase or is degraded to bound C4d. With alternative pathway activation, factor B is cleaved to form Bb, which participates in the formation of the alternative pathway C3 convertase. Properdin stabilizes C3 convertase formed with alternative pathway activation. C3b can either participate as part of the C5 convertase complex to cleave C5 or be degraded to bound C3d. C5b, C6, C7, C8, and C9 assemble in cell membranes to form membrane attack complex (MAC) that deteriorates membrane potential and induces cell lysis. Regulators present on the trophoblast membrane, as well as numerous cells in mother and fetus, include membrane cofactor protein (MCP) (CD46), decay-accelerating factor (DAF) (CD55), and CD59. MCP facilitates degradation of C3b and C4b so that they do not continue as part of the C3 convertase. DAF facilitates decay of convertases assembled from activation of any of the pathways, and CD59 hampers assembly of MAC.

this study in *Hypertension* looking for excessive complement activation in preeclamptic placentas.

In this study by Buurma et al,² the presence of C4d and the lack of mannose-binding lectin and properdin provide evidence of local classical pathway activation at the fetal-maternal interface. An association was noted with the classical complement system activation and the severity of adverse fetal outcome, but no association was seen with increased blood pressure. An upregulation of endogenous complement regulators and no difference in C3 deposition suggested the presence of a fetoprotective feedback mechanism regulating C3 activation. These data suggest that excessive complement activation does not progress beyond C3 in this patient population because of increased mRNA for trophoblastic membrane-bound regulators. The study by Buurma et al² differs from earlier work reporting increased C1q and C3d, as well as C9,^{3,5} in placentas from preeclamptic versus normal pregnancies, indicating that excessive local activation of complement in the preeclamptic placenta went beyond C3 to the membrane attack complex. Investigating complement activation locally in the placenta is an excellent strategy to determine events occurring at the fetal-maternal interface and is clearly limited by heterogeneity of the patient population.

Systemically, increased circulating concentrations of C3a (produced by all pathways) and Bb (alternative pathway) have been documented as early markers of complement activation in the maternal circulation of women who developed preeclampsia compared with normal pregnancies,⁹ with the presence of increased Bb suggesting that alternative pathway activation is important in the pathogenesis. Studies of others⁴ also provide evidence that excessive complement activation is present systemically at the time of delivery of the fetus. Other than the placenta, adipose tissue may also contribute to the complement story. Adipose tissue is a source of acylation-stimulating protein that is identical to C3a without its carboxy terminal arginine (C3a des Arg). Women with prepregnancy obesity and high concentrations of C3a or

Bb early in pregnancy have the highest risk of developing preeclampsia.¹⁰

The idea that complement system and inflammation are involved in cardiovascular disease and associated hypertension is not new. Previously, elevations in C3 have been associated with hypertension. In pregnancy, recent work demonstrates that pregnant C1q-deficient mice develop features of preeclampsia including hypertension, angiogenic imbalance, and fetal distress,¹¹ pointing to the physiological role of C1q in maintaining normal pregnancy. Moreover, recent studies by our group and others demonstrate that the inhibition of complement activation mitigates characteristics of preeclampsia in different animal models.^{6,7} Taken together, there is accumulating evidence that the complement system plays a role in the development and maintenance of hypertension associated with preeclampsia.

The present study by Buurma et al² raises many new questions. Perhaps the foremost question is whether complement activation contributes to preeclampsia in a causal way or is a consequence of one or more aspects of the syndrome. While, it is unclear whether complement is activated by angiotensin II type 1-auto antibodies or whether complement activation plays a role in the development of an angiogenic imbalance, both having been implicated in the pathogenesis of preeclampsia; a recent study by Wang et al provides evidence that autoantibody-mediated C3a generation contributes to preeclamptic symptoms in a mouse model.¹² It is unclear whether complement is activated by angiotensin II type 1-auto antibodies or whether complement activation plays a role in the development of an angiogenic imbalance, both having been implicated in the pathogenesis of preeclampsia. Further studies are also of interest to clarify mechanistic connections between obesity and preeclampsia, given that both are associated with the complement system. Lastly, the question specific to both local and systemic complement activation remains: is it excessive activation, inadequate control, or both? Studies in our laboratories and others are working toward answering these questions with hopes of identifying significant new therapeutic targets to advance

treatment of preeclamptic patients and to minimize the necessity for preterm delivery of the fetus.

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Disclosures

None.

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