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INVITED COMMENTARY

The complement system, an integral component of innate immunity, is the first line of immunological defense against foreign pathogens. Although it is designed to target pathogens and is tightly regulated by a series of complement inhibitors, excessive activation and failure in the intrinsic regulation of the complement system result in tissue injury [1]. This injury is directly mediated by the membrane attack complex and indirectly by the anaphylatoxins (C3a, C4a, and C5a) through their effects on neutrophils, eosinophils, and mast cells.

Association of complement activation with inflammatory diseases has been recognized since the 1960s. However, it was not clear until recently whether complement activation in various pathologic conditions is coincidental or is truly responsible for the inflammation and tissue damage that are observed. Recent data from animal models of diseases produced using complement-deficient, knockout, and transgenic animals clearly indicate that complement activation is indeed a major source of tissue damage in many pathologic conditions [2]. These include various autoimmune diseases, neurodegenerative diseases, and immune complex diseases, and bioincompatibility situations such as dialysis, cardiopulmonary bypass (CPB), and xenotransplantation, to name a few. Thus, there is a clear need for developing complement inhibitors.

A central question in complement-targeted therapies is which protein(s) should be targeted. This question remained unanswered in many pathologic conditions because of a lack of information regarding the pathway(s) or anaphylatoxin(s) responsible for complement-related tissue damage. Under these circumstances, blocking all three pathways of complement by blocking the activation at the C3 level would be advisable. However, discerning the role of individual pathway(s) or anaphylatoxin(s) would allow the design of inhibitors that would permit partial functioning of the system, a desirable feature [2]. Undar and colleagues, in their article, used anti-factor D monoclonal antibodies (Mabs) to determine the role of the alternative pathway (AP) of complement activation in systemic inflammation and tissue injury during CPB. Their data, produced using a baboon model of CPB, clearly indicate that the AP is a major player in inducing systemic inflammation and tissue injury in this setting. Thus, anti-factor D Mabs could be developed for treating the systemic inflammatory response, which in turn could reduce organ failure subsequent to CPB.

At present, complement inhibitors, and specifically anti-human C5 Mabs (5G1.1 and 5G1.1-scFv; www.alex-

ioninc.com), are being evaluated in phase I and phase II clinical trials in various clinical conditions, including CPB. The data obtained thus far are very encouraging. Although these Mabs have shown promise and will be useful in reducing the clinical morbidity in several diseases, recombinant protein therapies are not cost-effective. Thus, current emphasis is being placed on the development of small-molecule inhibitors of complement. Promising small-molecule inhibitors, which are currently under development, include a C3-specific peptide inhibitor, Compstatin [3-5], and newly designed C5aR antagonists [6, 7].

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