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GUEST EDITORIAL

O Complement, Where Aren't Thou

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The innate immune system represents the oldest arm of mammalian host defense, of which the complement cascade is of paramount importance. Complement serves several roles, including direct cellular killing, tagging of foreign and self-debris for cell-mediated clearance, and modulation of the adaptive immune response. The Human Genome Organization Gene Nomenclature Committee recognizes 56 proteins within the complement pathway. Given this complexity, most medical students and clinicians devote little time to understanding the intricacies of the cascade.

As molecular tools have advanced, so has the ability to dissect the role of complement in multiple kidney diseases. The importance of complement has been easily recognized in diseases such as membranous glomerulopathy, IgA nephropathy, membranoproliferative glomerulonephritis (immune complex-MPGN and C3 glomerulopathy), antibody-mediated rejection, and complement-mediated thrombotic microangiopathy (atypical hemolytic uremic syndrome). Perhaps less evident by light microscopy but confirmed experimentally is the contribution of complement activation to tissue injury in ANCA glomerulonephritis, diabetic nephropathy, monoclonal gammopathies of renal significance, antiphospholipid antibody syndrome, focal segmental glomerulosclerosis, acute kidney injury, and chronic tubulointerstitial disease.

Despite the importance of complement in such significant diseases, this complicated immunologic pathway has received comparatively little clinical attention, which is partly because, until recently, specific inhibitors targeting complement were not available. High-dose glucocorticoids may reduce complement synthesis and impair neutrophil migration in response to complement signaling, but the toxicity is limiting and the effect imprecise. Antibody depleting therapies—such as elimination of phospholipase A2 receptor antibody in membranous nephropathy—may secondarily reduce complement-mediated injury by indirectly removing stimuli for complement activation. Although useful in specific scenarios, this approach lacks broad utility in the spectrum of complement-mediated kidney disease.

The clinical landscape was revolutionized in 2011 with the approval of the anti-C5 humanized monoclonal antibody eculizumab for the management of atypical hemolytic uremic syndrome (aHUS). The recognition of the primacy of ***a d**isintegrin **a**nd **m**etalloproteinase with a **t**hrombo**s**pondin type 1 motif, member **13*** (ADAMTS13) deficiency to the pathogenesis of thrombotic thrombocytopenic purpura (TTP) provided a molecular distinction to thrombotic microangiopathies (TMAs) previously lumped together as TTP/HUS. Similarly, the response to targeted complement therapy allows further pathophysiologic classification of TMA into complement-dependent (aHUS) and complement-independent mechanisms. Understanding pathogenesis is critical, as timely initiation of plasma exchange for TTP or eculizumab for aHUS can be organ and life saving, while potentially sparing patients with other forms of TMA from ineffective and expensive therapy. As our understanding of the genetic and serologic factors influencing complement regulation expands, so do the nuances required for elegant manipulation of complement in complex diseases. While aHUS is largely a disease of the alternative pathway of complement leading to terminal pathway overactivity, the processes initiating and amplifying complement activation in diseases such as IgA nephropathy or hypertension-associated TMA, for example, are considerably more complicated.

In this issue of *Advances in Chronic Kidney Diseases*, leading experts in the field of complement-mediated kidney disease address the state of the science and active areas of controversy in management and diagnosis.

Critical to appreciating the significance of complement in disease states is having working knowledge of the protein cascade and its regulation. Dr. Thurman (pp 86-94) presents an up-to-date overview of the 3 primary pathways of complement activation—classical, alternative, and lectin—and discusses the increasingly recognized importance of nontraditional pathways such as the

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coagulation cascade. It is now accepted that cross-talk between the complement and coagulation cascades can serve as a primary initiator of both, as well as an amplifier.

While the era of complement therapeutics was introduced by eculizumab, we are now on the cusp of the next generation of complement therapies. Technologies from small inhibitory RNAs to humanized antibodies to small oral molecules have been developed to target the 3 major complement-activating pathways. Building on the background set by Dr. Thurman, Drs. Kelleher and Kocinsky (pp 95-103) explore the novel agents currently in clinical trials for complement-mediated kidney diseases. These agents hold the promise of revolutionizing the ability of nephrologists to treat diseases that heretofore have lacked effective therapies beyond renin-aldosterone-angiotensin system (RAAS) antagonism.

One such disease is C3 glomerulopathy (C3G). Through sophisticated molecular analysis, this entity—composed of C3 glomerulonephritis and dense deposit disease—is now known to be a disorder of upstream complement dysregulation. Although pathogenesis is heavily dependent on soluble phase activation of the alternative pathway, conflicting data suggest possible contributions from the classical and/or lectin pathways as well. Both genetic and humoral factors are implicated in the causal pathway, but terminal complement antagonism with eculizumab has not proven to be sufficiently effective. To that end, we await the results of ongoing clinical trials as discussed by Dr. Kelleher. Drs. Ahmad and Bomback (pp 104-110), in their manuscript, review the pathogenesis and data supporting current empirical therapies for this vexing disease process.

Similarly, few stories in nephrology have been as intriguing as the pathogenesis of IgA nephropathy. Considered to be the most common acquired glomerulonephritis worldwide, our understanding of the immunological and genetic underpinnings has grown rapidly over the past decade. Although IgA antibodies—mesangial deposits of which are the sine qua non of the disease—cannot fix and activate complement via the classical pathway, complement activation is a primary feature of the disease. Drs. Medjeral-Thomas and O'Shaughnessy (pp 111-119) explore mechanisms underlying IgA activation of complement via the lectin and alternative pathways. Apart from RAAS inhibition and conservative care, glucocorticoids are the only immunosuppressant demonstrated to produce short-term improvements in IgA nephropathy, albeit at significant risk of toxicity and with uncertain long-term benefit. The possibility that a multimodal approach of combining RAAS antagonism with tailored complement inhibition could positively impact this global disease is exciting.

Undeniably, the topic of complement-mediated TMA or aHUS has been expertly reviewed over the last several years. Although the initial therapy is generally well understood, significant uncertainty surrounds the genetic evaluation of the disease and how best to interpret the frequent variants of uncertain significance that result from multigene panels. Dr. Perkins (pp 120-127) tackles this topic to provide an illuminating discussion of the genetic hotspots in aHUS as well as C3G. This is a timely synopsis of a challenging aspect of TMA management.

In addition to the genetic evaluation of aHUS, clinicians are commonly challenged with decisions regarding optimal medical management of patients in the perioperative and postoperative kidney transplant setting. Given the incredible expense of eculizumab and the recognition that it is not available worldwide, guidance in best practice management of these patients is greatly needed. Dr. Java (pp 128-137) reviews the literature and provides strategies where available for balancing resource utilization with outcomes.

Continuing, Dr. Bhalla and colleagues (pp 138-148) extend the transplant experience to cover the use of complement therapies in the management of antibody-mediated rejection. Although the presence of peritubular capillary deposition of C4d is a histologic hallmark of antibody-mediated rejection (likely predominately via the classical pathway), the use of eculizumab to target the terminal pathway has not been shown to convincingly alter the course of disease. The authors discuss those trials as well as review ongoing studies of C1 esterase inhibitor to block the classical pathway.

Finally, the final 2 manuscripts explore our emerging understanding of complement in 2 complex disease states, pregnancy-associated kidney disorders and hypertension-associated TMA. The last several years have uncovered a clear role of complement in preeclampsia and HELLP. Other kidney conditions are also associated with pregnancy, including TTP, aHUS, lupus, and antiphospholipid antibody syndrome. Dr. Chinchilla and colleagues (pp 155-164) discuss these disorders, the role of eculizumab, and opine on the potential role of complement in peripartum cardiomyopathy. Finally, a persistent chicken-and-egg phenomenon in nephrology is the interplay among malignant hypertension, TMA, and kidney injury. Although malignant hypertension has long been recognized as an etiology of arteriolar microangiopathy, the development of aHUS often leads to malignant hypertension itself. Clinical and histologic studies have yielded conflicting results on the role of complement in mediating hypertension-induced TMA, likely reflecting complex patient phenotypes and inadequate tools for characterization. Drs. Zuckerman and Chang (pp 149-154) specifically examine the role of complement in hypertensive emergency and scleroderma kidney crisis.

In short, the last 10 years have been exciting times for progressively defining the role of complement in kidney diseases. The next several years will produce results from multiple ongoing clinical trials that should fundamentally influence our approach to the management of these diseases. Further improvements in rapid throughput mutational analysis and easier access to genetic databases will allow refined tailoring of therapies to specific steps in the complement cascade. To the chagrin of medical students, the complement system can no longer remain a footnote in immunology coursework.

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