Complement-Mediated Glomerular Diseases

By Andrew Bomback

Why are nephrologists, particularly in the realm of glomerular diseases, talking about complement so much lately?

For years, many of the primary forms of glomerular diseases have been labeled idiopathic without a clear explanation of etiology other than a vague idea of autoimmunity. Focusing on the role of complement activation in the pathogenesis of glomerular lesions has allowed nephrologists to approach an answer to the question so often asked by patients: “Why did this happen to me?”

What should nephrologists know about complement?

The complement system is divided into three initiating pathways—the classical, lectin, and alternative pathways (Figure 1). Proper functioning of each pathway is required for coordinated activity of innate and acquired immunity (1), and each of these pathways has been implicated in the pathogenesis of glomerular disease. The three initiating pathways all converge at C3 to generate an enzyme complex known as C3 convertase that cleaves C3 into C3a and C3b. The association of C3b with C3 convertase results in generation of C5 convertase, which cleaves C5 into C5a and C5b. This cleavage triggers the terminal complement cascade, which is comprised of C5b, C6, C7, C8, C9, and regulators of these terminal complement proteins, such as clusterin and vitronectin. The terminal complement cascade culminates in the assembly of the membrane attack complex (also known as C5b-9) and subsequent cell lysis.

The classical complement pathway, which plays a major role in humoral immunity, is triggered into action by either IgG or IgM antibodies bound to antigen. This immune complex formation of antigen and antibody exposes a binding site on the immunoglobulin (Ig) for the first component of the classical pathway: C1. The lectin pathway is initiated by the binding of mannose binding lectin to the polysaccharide surface of pathogenic bacteria. This binding results in the formation of a tricomplex with two serine proteases and subsequent cleavage of C4 and C2, the next complement proteins in the cascade. The alternative pathway begins at the level of C3. Although microbial antigens can activate this pathway, the alternative pathway is also constitutively active via spontaneous hydrolysis of C3 to C3b, which binds factor B to yield the C3 convertase (C3bBb) of this pathway.

This distinction between the constitutively active alternative pathway and the triggered classical and lectin pathways manifests on immunofluorescence (IF) studies of kidney biopsies. Specifically, the presence of Ig staining (IgG, IgM, and/or IgA) alongside complement on IF microscopy implies that immune complexes of antigen/antibody have triggered consumption of the classical (Figure 2a) and/or lectin pathway proteins, whereas the presence of C3 staining alone without Ig (Figure 2b) suggests that the glomerular lesion is mediated by complement alone in an antibody-independent fashion, implicating the alternative complement pathway (2). For the treating nephrologist, these IF patterns, in turn, focus the workup and treatment of the glomerular disease on 1) the trigger in classical or lectin pathway-mediated injuries, with attention toward infectious, autoimmune, or malignant etiologies, versus 2) the dysregulation of the constitutively active alternative pathway in C3-mediated lesions, with attention toward genetic mutations or autoantibodies targeted at components of the alternative pathway (3).

What is an example of a complement-mediated glomerular disease?

A genetic or acquired (i.e., via autoantibodies or monoclonal gammopathies) defect in either the activation or modulation of the alternative pathway C3 convertase could lead to a transformation from low-grade physiologic activity (“tickover”) to uncontrolled hyperactivity (diseases of complement dysregulation). This loss of alternative pathway control can result in GN that is not only (dominantly) for C3, with complement proteins (and not immune complexes) mediating the glomerular injury. The term C3 glomerulopathy has been proposed as an umbrella classification for any GN with isolated or dominant C3 staining that, in turn, signals an etiology rooted in dysregulation of the alternative complement pathway (4). This term encompasses both dense deposit disease (formerly known as membranoproliferative GN type 2) and C3GN (formerly known as membranoproliferative GN type 1 or type 3 with isolated C3 staining). Carla Nester, MD, will review these disease states in more depth in an upcoming issue of Kidney News.

Are there more common glomerular diseases influenced by complement?

IgA nephropathy, the most common primary GN in the world, seems to be a disease mediated by both the lectin and alternative complement pathways. A multihit pathogenesis model of IgA nephropathy has emerged. Polymeric IgA1 with deficient O-linked glycosylation at the hinge region (galactose-deficient IgA1) forms immune complexes with IgG antibodies directed at the abnormal hinge region (antiglycan antibodies). These immune complexes then deposit in the mesangium (5). On light microscopy, mesangial proliferation and matrix expansion are the typical findings of IgA nephropathy, and diagnosis is established by dominant IgA staining on IF microscopy. The IF microscopy can also show subdominant staining of IgG, C3, C4d, and C5b-9 that colocalizes with IgA: C1q staining, however, is generally absent, suggesting no role of the classical complement pathway in the pathogenesis of disease. Instead, these IF findings suggest a potentially important contribution from the alternative and lectin complement pathways (6). IgA1 can activate both pathways in vitro, and pathway components are present in the mesangial deposits, including properdin and factor H in the alternative pathway and mannann binding lectin, mannann binding lectin-associated serine proteases 1 and 2, and C4d in the lectin pathway. Indeed, intensity of C3 staining and deposition of mannann binding lectin (as well as increases in urine complement components) have been shown in small studies to correlate with severity of IgA nephropathy (7–9).

How can these new findings affect treatment?

A better understanding of the role of complement in glomerular diseases, in turn, yields questions about targeting therapies at the complement pathways (10). The most logical target of therapy for diseases mediated by classical complement pathway activity is the trigger or inciting event that led to complement consumption—a documented infection, for example. In patients whose trigger is not apparent or in glomerular lesions where the lectin or alternative pathways seem to be playing the dominant role, complement-directed therapies may offer a more precise mode of treatment than traditional use of nonspecific immunosuppression. Anticomplement therapies, such as eculizumab, a mAb that targets C5 and prevents the generation of membrane attack complex, have already shown benefit in atypical hemolytic uremic syndrome and some forms of C3 glomerulopathies. Other complement-targeting therapies are currently being studied in a variety of glomerular diseases, including lupus nephritis, IgA nephropathy, and antineutrophil cytoplasmic antibody-associated GN. The advent of therapies aimed at the complement cascade, now in the earliest phases, may promise breakthroughs in disease-specific treatments that will change the natural history of disease.

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References


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Rapid changes are occurring in the healthcare environment, with greater emphasis placed on the care experience, its value/cost, and health outcomes. These changes are outpacing educational reforms, leading to growing gaps between medical education and clinical practice. Particularly concerning is trainee readiness for such gap areas as systems redesign, quality improvement and patient safety, population health, and interprofessional practice. Medical education must continue to evolve to address these gaps, and nephrology is at the cutting edge of these transformations.

Greater attention is being paid to the continuum of medical education and the competencies needed to advance from undergraduate medical education (UME; medical students) to graduate medical education (GME; residents and fellows) to clinical practice. Competency-based assessment of entrustable professional activities such as ability to perform a history and physical, or form a differential diagnosis, is becoming the preferred method of assessing performance. As a consequence there is a move from the traditional block rotation of clinical clerkships to more longitudinal clinical experiences. The classic Flexnerian model of UME with two years of foundational knowledge (anatomy, genetics, biochemistry, histology, and others) followed by two years of clinical education, is changing to earlier and more meaningful clinical education experiences, a shorter time for learning the foundational knowledge, and greater integration of basic and clinical science across all years of medical school. Incorporating public health, health policy, quality improvement, and interprofessional practice into the curriculum is narrowing gaps between medical education and clinical practice.

Integrating basic and clinical science
Nephrology exemplifies how the understanding of basic science can greatly inform the clinical approach to patients. For example, understanding the action of antidiuretic hormone in the cortical collecting duct, or the trafficking of aquaporin 2 can inform the differential diagnosis of diabetes insipidus or the approach to hyponatremia. Part of the teaching of clinical fluid and electrolyte disorders is simultaneous re-education in renal physiology. Similarly, renal histology informs the interpretation of kidney biopsies, and understanding the basics of complement regulation can help with the approach to glomerular diseases.

Focusing on population health
In the US, funding for the treatment of patients with end-stage renal disease (ESRD) is unique in that every American with kidney failure is eligible for Medicare coverage under the Medicare End-Stage Renal Disease (ESRD) Program, regardless of age or income. As a consequence, ESRD is a disease that is monitored closely. The United States Renal Data System (USRDS) established in 1988 is the national data registry that collects, analyzes, and reports information on ESRD patients in the US. USRDS reports on the epidemiology of ESRD including incidence and prevalence, trends in mortality, and demographic characteristics of the ESRD population. This data enables investigation into relationships among demographics, treatment modalities, and clinical