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Complement-Mediated Glomerular Diseases: A Tale of 3 Pathways

Andrew S. Bomback[1], Glen S. Markowitz[2] and Gerald B. Appel[1]

[1]Department of Medicine, Division of Nephrology, Columbia University College of Physicians and Surgeons, New York, New York, USA; and [2]Department of Pathology, Columbia University College of Physicians and Surgeons, New York, New York, USA

A renewed interest in the role of complement in the pathogenesis of glomerular diseases has improved our understanding of their basic, underlying physiology. All 3 complement pathways—classical, lectin, and alternative—have been implicated in glomerular lesions both rare (e.g., dense deposit disease) and common (e.g., IgA nephropathy). Here we review the basic function of these pathways and highlight, with a disease-specific focus, how activation can lead to glomerular injury. We end by exploring the promise of complement-targeted therapies as disease-specific interventions for glomerular diseases.

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In clinical practice, a nephrologist evaluating a patient with a glomerular disease always begins with a simple, dichotomous classification scheme. The glomerular disease is considered either "primary" (intrinsic to the kidney) or "secondary" (a renal manifestation of a systemic disease that can also affect other organ systems). For example, in approximately 25% of patients whose kidney biopsies show the lesion of membranous nephropathy, a systemic disease process such as lupus, hepatitis B, or cancer will be identified as the underlying etiology of the lesion. Traditionally, the primary glomerular lesions have also been called idiopathic, often with the suggestion of an underlying, ill-defined autoimmune process. In recent years, advances in our understanding of the pathophysiology behind many of the glomerular diseases have gradually chipped away at this "idiopathic" nomenclature. One area of major advances has been through a heightened appreciation of the role of complement in glomerular injury. This complement-oriented approach has allowed nephrologists to come increasingly close to answering the question most commonly posed by patients—Why did this happen?—and has provided a guide to prognosis and treatment of a number of glomerular diseases.

Correspondence: Andrew S. Bomback, MD, MPH, 622 West 168th St., PH 4-124, New York, New York 10032, USA. E-mail: asb68@columbia.edu

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Overview of Complement Pathways

The complement system is divided into 3 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] The 3 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, the assembly of the membrane attack complex (MAC), which is also known as C5b-9, and subsequent cell lysis or sublytic cellular injury.

Although all 3 pathways converge at a similar level and therefore have similar downstream targets, the pathways are distinct in their points of origin. 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 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 trimolecular complex with 2 serine proteases and subsequent cleavage of C4 and C2, the next complement proteins in the cascade. In this pathway, C4b and C3b can bind to antigen-associated Igs as well as to microbial surfaces. The alternative pathway begins at the level of C3.

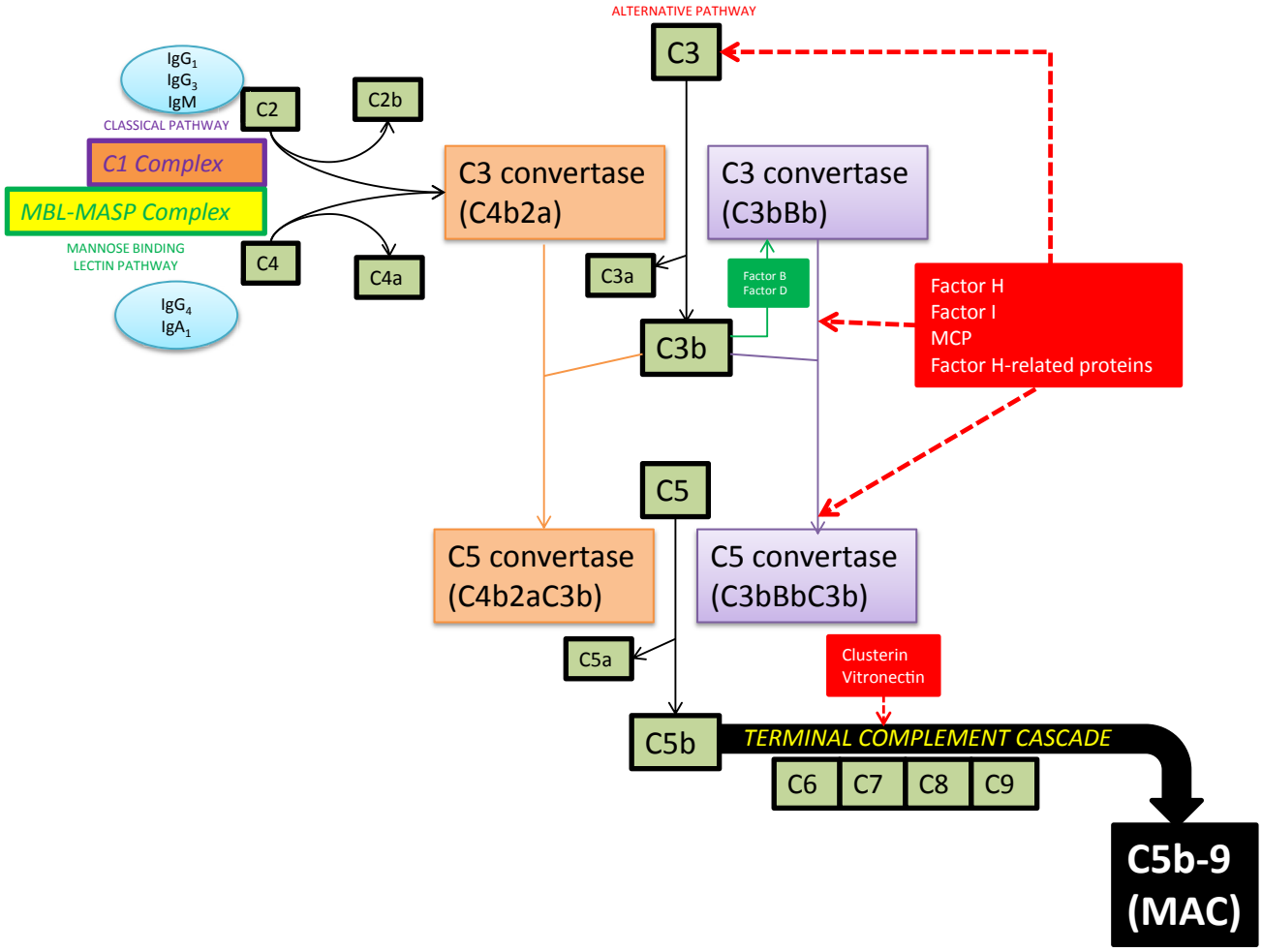

Figure 1. An overview of the complement cascade. The classical, mannose-binding lectin and alternative complement pathways converge at C3 to generate an enzyme complex known as C3 convertase that cleaves C3 into C3a and C3b. However, the pathways are distinct in their points of origin. The classical complement pathway is activated by either IgG (predominantly IgG_1 and IgG_3) or IgM antibodies bound to antigen; this immune complex exposes a binding site on the Ig for the first component of the classical pathway, C1, to form a C1 complex that cleaves C2 and C4. The lectin pathway is initiated by the binding of mannose-binding lectin (MBL) to the polysaccharide surface of pathogenic bacteria. This binding results in the formation of a trimolecular complex with mannose-binding lectin-associated serine proteases (MASPs) and subsequent cleavage of C2 and C4. IgG_4 and IgA_1 autoantibodies can also bind MBL and activate the lectin complement pathway. The alternative pathway begins at the level of C3 and is constitutively active via spontaneous hydrolysis of C3 to C3b, which binds factor B to yield the C3 convertase (C3bBb) of this pathway. Hence, activation of this complement pathway is generally considered antibody independent. MAC, membrane attack complex; MCP, membrane cofactor protein.

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 versus the triggered classical and lectin pathways, is manifest on immunofluorescence (IF) studies, which are performed routinely on all medical kidney biopsy specimens (Table 1). 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 and/or lectin pathway proteins (Figure 1), whereas the presence of C3 staining alone without Ig 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 work-up and treatment of the glomerular disease on (i) the trigger in classical or lectin pathway–mediated injuries, with attention toward infectious, autoimmune, malignant, or drug-induced etiologies, versus (ii) 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]