Anti-Complement Therapy for Glomerular Diseases

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A major shift in our understanding of glomerular diseases is the focus on which components of the complement pathway are involved in mediating kidney injury. For example, the membranoproliferative glomerulonephritis lesion is no longer classified solely by ultrastructural findings on biopsy and is now divided into immune-complex-mediated lesions vs complement-mediated lesions. In turn, this emphasis on complement leads to interest in therapies that target complement as potential disease-modifying agents. Eculizumab, the first available anti-complement therapy, blocks at the level of C5 and has revolutionized the treatment of atypical hemolytic uremic syndrome. Whether this agent will work equally well for the far more heterogeneous entities of C3 glomerulonephritis and dense deposit disease remains unclear. Instead, newer agents that target C3 may turn out to be the most effective and specific therapy for these C3 glomerulopathies.

Key Words: Eculizumab, C3 glomerulopathies, Atypical hemolytic uremic syndrome, Complement, Anti-neutrophil cytoplasmic autoantibody

Introduction

The last decade has ushered in a renewed focus on the role of complement and, specifically, abnormalities in the alternative complement pathway in the pathogenesis of glomerular diseases. Lesions such as membranoproliferative glomerulonephritis (MPGN) have undergone a major reclassification into immune-complex-mediated vs complement-mediated disease, and the advent of anti-complement therapy has drastically altered the treatment paradigm of atypical hemolytic uremic syndrome (aHUS). The ability to selectively target components of the complement pathway offers unique avenues to change the natural history of glomerular diseases, but it also may be associated with unforeseen consequences, including unintended infectious adverse events, stimulation of earlier components of the complement pathway, and the potential need for lifelong therapy. This review surveys current data on the role of complement in various glomerular lesions and the progress, to date, in studying anti-complement therapies in these diseases.

Immune-Complex-Mediated Glomerulonephritis vs Complement-Mediated Glomerulonephritis

The complement system is divided into 3 initiating pathways: the classical, lectin, and alternative pathways. Proper functioning of each pathway is required for coordinated activity of innate and acquired immunity. The 3 initiating pathways all converge at C3 to generate an enzyme complex known as C3 convertase, which cleaves C3 into C3a and C3b (Fig 1). 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 comprises 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 (MAC; also known as C5b-9) and subsequent cell lysis. Although all 3 pathways converge at a similar level and therefore have similar downstream targets, the pathways are distinct in their points of origin. Furthermore, the alternative pathway is constitutively active (described below); therefore, enhanced activity of this system is generally due to a loss of regulation. In contrast, the classical and lectin pathways are not constitutively active and need a "trigger" to stimulate activity.

Until recently, the traditional view of complement's role in glomerulonephritis was focused on the classical complement pathway. Specifically, the glomerular diseases typified as "hypocomplementemic" glomerulonephritides, such as lupus nephritis, acute postinfectious glomerulonephritis, and cryoglobulinemic MPGN, are marked by immune complex deposition on immunofluorescence (IF) microscopy, which, in turn, signals the triggering of the classical complement pathway by antigen-antibody interactions. Indeed, the presence of immunoglobulin (Ig; IgG, IgM, and/or IgA) and complement (C1q and/or C3) on IF microscopy staining of immune-complex-mediated lesions infers that the classical pathway has been activated by an inciting cause or event that generally falls into 1 of 3 major categories: infectious (eg, acute postinfectious glomerulonephritis), autoimmune (eg, lupus nephritis), or malignancy associated (eg, proliferative glomerulonephritis in the setting of monoclonal gammopathy).[1] Therefore, treatment of these lesions was appropriately focused on the trigger for the classical pathway, exemplified by the use of high-dose and relatively nonspecific immunosuppression in lupus nephritis.

The last decade has seen a new focus on hypocomplementemic glomerular diseases because of the increasing

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awareness of proliferative glomerulonephritides that stain for complement (usually C3) without Ig. This IF pattern denotes an antibody-independent means of complement deposition and points to dysregulation of the alternative complement pathway. The alternative complement pathway is constitutively active at a low level. The term "tickover" has been used to describe this basal, physiologic activation of the alternative pathway by spontaneous hydrolysis of C3 and the production of C3b, which binds factor B to yield a fluid-phase C3 convertase (C3bBb).[2-4] However, this alternative pathway C3 convertase is under tight modulation by soluble or membrane-bound regulating proteins, including complement factor H, complement factor I, and membrane cofactor protein (Fig 2). Thus, a genetic or acquired (ie, via autoantibodies or monoclonal gammopathies) defect in either the activation or modulation of the C3 convertase could lead to a transformation from low-grade physiologic activity (tickover) to unrestrained hyperactivity (diseases of complement dysregulation).[3-10] In these instances, therapies aimed at specific components of the alternative complement pathway may prove to be effective, targeted therapies.

MPGN best exemplifies the importance of reclassifying lesions as immune-complex-mediated vs complement-mediated.[11,12] The MPGN lesion has traditionally been categorized according to ultrastructural findings on electron microscopy (EM). Subendothelial and mesangial deposits predominate in MPGN type I[13]; highly electrondense intramembranous and mesangial deposits are the hallmark of type II (also known as dense deposit disease [DDD])[14]; and in type III MPGN deposits can be subendothelial and subepithelial (Burkholder subtype) or produce complex intramembranous, subendothelial, and subepithelial formations with fraying of the lamina densa (Strife and Anders subtype).[15] However, this classification scheme was not without its problems; for example, within the same biopsy or the same glomerulus, pathologists may observe overlapping features among these subtypes.

The major drawback to the EM-based classification scheme was that it was based on histopathology patterns and not pathophysiology of disease. For example, many patients with intramembranous dense deposits, characteristic of MPGN type II, lacked an MPGN pattern altogether on light microscopy (LM). In a large study of the histology of MPGN type II, only 25% of patients had an MPGN pattern despite classic ultrastructural changes of electron densities along the glomerular basement membrane.[16] Subsequently, the designation MPGN type II was discarded in favor of the more accurate and inclusive term of DDD. In addition, pathologists began emphasizing in their reports the presence of isolated deposits of C3 in examples of MPGN type I and type III (similar to the C3-only staining pattern of DDD), setting these cases apart from the more common variants of type I and type III MPGN, which contained Ig. These Ig-negative lesions, initially called idiopathic MPGN with isolated C3 deposits, were also found to have other histologic patterns by LM and acquired the name C3 glomerulonephritis (C3GN).[17] The term C3 glomerulopathy, which encompasses DDD and C3GN, has been proposed as an umbrella classification for any glomerulonephritis with isolated C3 staining that, in turn, signals dysregulation of the alternative complement pathway.[18]

Just how far this umbrella extends is a fascinating and growing area of research. In addition to the C3 glomerulopathies and aHUS, diseases that are felt to be primarily mediated by genetic and/or acquired abnormalities in the alternative complement pathway, more common glomerular diseases, such as IgA nephropathy and diabetic kidney, have been associated with dysregulation in the complement cascade.[19] Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis has also recently emerged as a possible complement-mediated lesion. Although the hallmark finding on IF staining in ANCA-associated glomerulonephritis is a paucity of Ig and complement deposition, most cases have some focal complement deposition at sites of glomerular injury.[20] In ANCA-mediated disease, ANCA IgG activates cytokine-primed neutrophils that, in turn, release factors that stimulate activity of the alternative complement pathway. In mice, administration of anti-myeloperoxidase (MPO) IgG leads to a necrotizing, crescentic glomerulonephritis with neutrophil and macrophage infiltration alongside low-level glomerular IgG and C3 deposition. In contrast, co-administration of anti-MPO IgG with cobra venom factor, which depletes C3, protects against the development of such a lesion.[21] A similar "resistance" against anti-MPO-mediated glomerulonephritis was shown in knockout mice deficient in C5 and factor B (both

CLINICAL SUMMARY

- A classification scheme that divides proliferative glomerulonephritides into immune-complex-mediated versus complement-mediated disease can facilitate an understanding of which components of the complement cascade are involved in the pathogenesis of kidney injury.
- Eculizumab, a monoclonal antibody to C5, should be considered for all patients with atypical hemolytic uremic syndrome because dysregulation at the level of C5 is generally homogenous in this disease.
- The C3 glomerulopathies demonstrate variable degrees of C5 convertase dysregulation; therefore, they may not universally respond to anti-C5 therapy.
- Blockade at the level of C3 may be an alternative to eculizumab therapy, primarily in patients with C3 glomerulopathies associated with greater C3 convertase dysregulation than C5 convertase dysregulation.