Novel roles of complement in renal diseases and their therapeutic consequences

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The complement system functions as a part of the innate immune system. Inappropriate activation of the complement pathways has a deleterious effect on kidneys. Recent advances in complement research have provided new insights into the pathogenesis of glomerular and tubulointerstitial injury associated with complement activation. A new disease entity termed 'C3 glomerulopathy' has recently been proposed and is characterized by isolated C3 deposition in glomeruli without positive staining for immunoglobulins. Genetic and functional studies have demonstrated that several different mutations and disease variants, as well as the generation of autoantibodies, are potentially associated with its pathogenesis. The data from comprehensive analyses suggest that complement dysregulation can also be associated with hemolytic uremic syndrome and more common glomerular diseases, such as IgA nephropathy and diabetic kidney disease. In addition, animal studies utilizing genetically modified mice have begun to elucidate the molecular pathomechanisms associated with the complement system. From a diagnostic point of view, a noninvasive, MRI-based method for detecting C3 has recently been developed to serve as a novel tool for diagnosing complement-mediated kidney diseases. While novel therapeutic tools related to complement regulation are emerging, studies evaluating the precise roles of the complement system in kidney diseases will still be useful for developing new therapeutic approaches.

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The complement system is a cascade of proteins that mediate important innate immune functions, but this system's inappropriate activation has been implicated in kidney disease. In this review, we discuss recent advances for identifying the roles of complement activation in the development and progression of kidney disease.

ACTIVATION AND EFFECTOR FUNCTIONS OF COMPLEMENT

The complement system, which is an important mediator of inflammation and tissue injury, is a family of more than 20 serum and cell-surface proteins that function as a cascade (Figure 1). Immune complexes formed by IgG and nephritogenic antigens bind to complement factor C1q and activate the C1 complex, leading to the formation of C3 convertase and the enzymatic cleavage of the central complement component C3. C3 activation results in the release of the chemotactic factor C3a and covalent attachment of the C3b fragment to host cells, which is an important step for amplification through the alternative pathway and for continued formation of the terminal membrane attack complex C5b-9. Under normal conditions, complement activation is strictly regulated by a series of circulating and cell-bound complement regulatory proteins.

Complement activation induces inflammation and damages the host through the production of chemotactic factors. C3a and C5a function in a synergistic manner with Fc-receptor cross-linking to stimulate inflammatory cells. Interestingly, a recent study by Karsten *et al.*[1] has demonstrated novel regulatory mechanisms for complement-FcγR cross talk. They have demonstrated that immune complexes with highly galactosylated IgG suppress the C5a receptor (C5aR)–mediated inflammatory response by promoting an interaction between the inhibitory IgG receptor FcγRIIB and the C-type lectin-like receptor dectin-1. Thus, the inhibitory effect of highly galactosylated IgG–immune complexes may serve as a feedback loop to control complement- and chemokine-mediated inflammation.

The nephritogenic effects of complement activation are also mediated by the generation of the membrane attack complex C5b-9. Although C5b-9 creates pores in the cell membrane and lyses cells without nuclei, such as erythrocytes, C5b-9 induces the activation of nucleated cells, converting resident kidney cells into effector cells to cause injury.

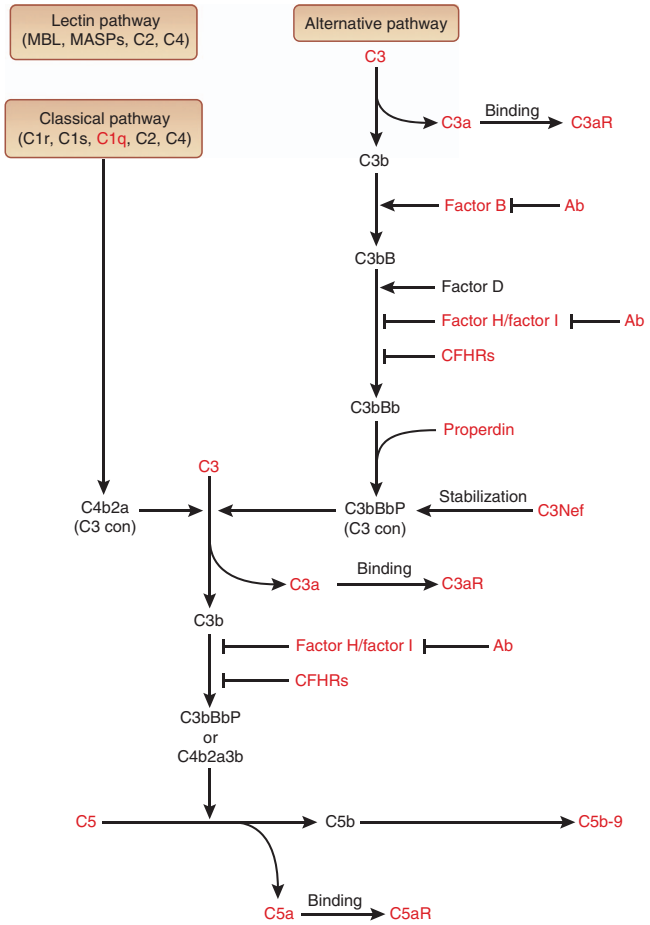

Figure 1 | Complement components and related molecules implicated in abnormal activation. The pathways of complement activation are depicted, with particular emphasis on the alternative pathway. The molecules highlighted in red are the complement components and the related molecules specifically discussed in this review. Ab, antibody; C3 con, C3 convertase; C3Nef, C3 nephritic factor; C3aR/C5aR, C3a receptor/C5a receptor; CFHRs, complement factor H–related proteins; MASPs, mannose-binding protein–associated serine proteases; MBL, mannose-binding lectin.

Recent advances in complement research have revealed an unexpected role for complement. Komuro and colleagues[2] reported that C1q has a role in impairing the regenerative capacity of skeletal muscle in aged animals by activating canonical Wnt signaling, which was induced by cleavage of LRP6, a Wnt coreceptor. This finding is important, because it suggests that the complement system may be associated with aging and that the modulation of C1q-dependent activation of Wnt signaling may provide a therapeutic option for diseases related to dysregulated Wnt signaling.

DETECTION OF COMPLEMENT ACTIVATION

Histological findings in renal biopsy specimens provide important information for diagnosing kidney diseases, but renal biopsy is an invasive procedure. Recently, Thurman and colleagues[3] developed an magnetic resonance imaging–based method for detecting glomerular C3. By using this method, they tracked glomerular C3b/iC3b/C3d deposition in the MRL/lpr mouse model of lupus nephritis, using superparamagnetic iron oxide nanoparticles conjugated to complement receptor type 2 as a targeting agent. This noninvasive measure of complement activation in the kidney using magnetic resonance imaging may be a good biomarker of disease.

COMPLEMENT AND GLOMERULAR INJURY

C1q glomerulopathy

C1q nephropathy is defined by conspicuous C1q in glomerular immune deposits in patients with no evidence of systemic lupus erythematosus or membranoproliferative glomerulonephritis (MPGN) type I. Vizjak *et al.*[4] described the clinicopathologic correlations and outcomes for 72 patients with C1q nephropathy. The light microscopic findings included focal segmental glomerulosclerosis, proliferative glomerulonephritis, and various other lesions. The clinical presentations were heterogenous even within a patient group with the same histological lesion. The mechanisms underlying C1q nephropathy include C1q binding to poly-anionic substances (DNA, RNA, Gram-negative bacterial proteins, viral proteins, etc.) or to C1q receptors, C1q production by dendritic cells and macrophages, and C1 inhibitor abnormalities.[5]

At this point, there is no specific therapy for C1q nephropathy, and patients with C1q nephropathy may be treated with the protocols for the underlying microscopic lesions, such as minimal-change disease or focal segmental glomerulosclerosis.

C3 glomerulopathy

MPGN is generally characterized by mesangial interposition and the duplication of glomerular basement membranes, which are typically associated with immune deposits in the peripheral capillary walls. MPGN was initially classified into three types based on electron microscopic findings. MPGN type I is characterized by a membranoproliferative phenotype with subendothelial and mesangial deposits.[6] In MPGN type II, also known as dense deposit disease (DDD), highly electron-dense intramembranous and mesangial deposits were the histopathological hallmarks.[7] MPGN type III is characterized by subendothelial and subepithelial (Burkholder subtype) deposits or complex intramembranous, subendothelial, and subepithelial deposits with fraying of the lamina densa (Strife and Anders subtype).[8] However, because our understanding of the pathogenesis of MPGN has illuminated the field, the classification is now being replaced with a more mechanistic classification based on the presence of immunoglobulins and/or C3 deposits by immunofluorescence microscopy.[9] Recently, Pickering and colleagues[10] proposed that glomerulonephritis characterized by the presence of C3 in the absence of immunoglobulins or components of the classical pathway of complement activation (C1q and C4) should be called 'C3 glomerulopathy.' C3 glomerulopathy is a disease entity that includes DDD and C3 glomerulonephritis, both of