Genetics of Immune-Mediated Glomerular Diseases: Focus on Complement

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Summary: The spectrum of immune-mediated glomerular diseases is wide, ranging from rare diseases with well-recognized genetic origins to more common and multifactorial diseases. Immune-mediated glomerular injury is complex and involves both the innate and the adaptive immune systems. In the past 20 years a huge effort has been undertaken to unravel the genetic basis of immune-mediated glomerular diseases. The discovery of abnormalities in genes encoding proteins of the alternative pathway of complement in more than 50% of patients with atypical hemolytic uremic syndrome (aHUS), and in approximately 20% of patients with membranoproliferative glomerulonephritis (MPGN), has highlighted the role of this complement pathway in the pathogenesis of immune-mediated glomerular diseases. aHUS-associated complement gene abnormalities mainly result in complement dysregulation restricted to the cell surface, whereas complement activation in the fluid phase prevails in most, but not all, genetic cases of MPGN. Results achieved in aHUS and MPGN have boosted interest in the impact of complement gene abnormalities and variations in the predisposition to more common, multifactorial kidney diseases, including IgA nephropathy and lupus nephritis. Emerging findings in these complex diseases have broadened our understanding of the fragile balance between the protective and harmful functions of the complement system.

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Immune-mediated damage to glomerular structures largely is responsible for the pathogenesis of the majority of glomerular diseases. These include atypical hemolytic uremic syndrome (aHUS), membranoproliferative glomerulonephritis (MPGN), IgAN, lupus nephritis (LN), acute poststreptococcal glomerulonephritis, anti–glomerular basement membrane (GBM) antibody disease, membranous nephropathy, and many others.[1] Immune-mediated glomerular injury is complex and implies the activation of both the innate and the adaptive immune system. Many immune-mediated glomerular diseases are rare and disease clusters have been reported often in families, suggesting the existence of genetic determinants that may contribute to disease risk. In the past 20 years a huge effort has been made to unravel the genetic basis of immune-mediated glomerular diseases based on direct sequencing of candidate genes, whole-genome linkage analysis in families, and genome-wide association studies (GWAS). Hundreds of risk variants in genes of the HLA system and of the innate and adaptive immune response have been reported.

The discovery that mutations in genes encoding proteins of the alternative pathway of complement are associated with two rare glomerular diseases, aHUS[2] and MPGN,[3] has highlighted the importance of genetic variations in the complement system in determining predisposition to glomerular injury, and encouraged research on complement genetics in more complex multifactorial immune-mediated glomerular diseases such as IgAN and LN. In this article we provide an overview of the known and emerging genetic evidence regarding the role of genetic variations in complement genes in the pathogenesis of these diseases.

THE COMPLEMENT SYSTEM

The complement system is part of innate immunity and functions as a first-line defense against pathogens, but also plays a central role in the clearance of immune

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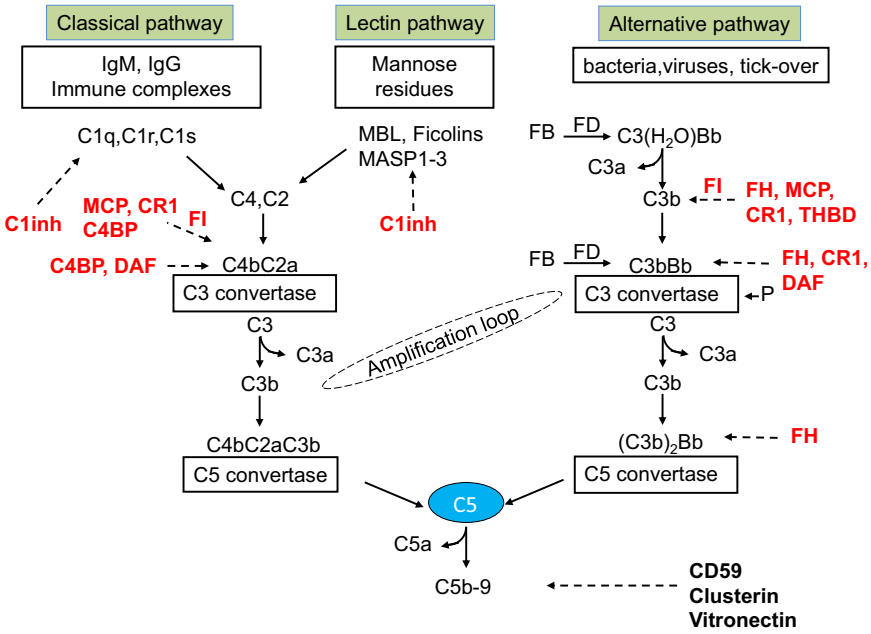

Figure 1. The three complement pathways. The classic pathway is activated by the binding of the Fc region of IgG or IgM antibodies to the complement complex C1, comprising one C1q molecule, two C1r molecules, and two C1s molecules. The lectin pathway is triggered by the binding of MBL or ficolins to sugar molecules on pathogens or altered self, which leads to the activation of MBL-associated serine proteases (MASP-1, MASP-2, and MASP-3). The classic and lectin pathways converge into the cleavage of complement components C2 and C4, leading to the formation of the C3 convertase (C4bC2a) of the classic/lectin pathways. The alternative pathway is activated continuously in plasma by low-grade hydrolysis (tick-over) of C3 that forms C3(H_2O). The latter binds to FB, which in turn is cleaved by factor D (FD) to form the alternative pathway fluid-phase C3 convertase. The C3 convertases cleave C3 into C3a, an anaphylotoxin, and C3b that deposits on cell surfaces. C3b contributes to the formation of the alternative pathway surface C3 convertase that cleaves additional C3 molecules, resulting in an amplification loop. In addition, C3b contributes to the formation of the C5 convertases that cleave the complement component C5, producing the anaphylatoxin C5a and C5b. C5b initiates the late events of complement activation, leading to the formation of the membrane-attack complex (C5b-9 complex). Self-surfaces are protected against complement damage by protein regulators (red characters). C1inh, C1 inhibitor, inactivates C1r and C1s, MASP-1, and MASP-2; C4BP, C4b-binding protein, binds to C4b and has decay accelerating activity for the classic pathway C3 convertase and cofactor activity for factor I–mediated C4b cleavage; CD59, protectin, vitronectin, and clusterin, prevents C5b-9 formation; CR1, has decay accelerating activity as well as cofactor activity for factor I–mediated C3b and C4b cleavage; DAF, has decay accelerating activity on C3/C5 convertases of the classic and alternative pathways; FH, binds C3b, exerts cofactor activity for factor I–mediated C3b cleavage, and dissociates (decay accelerating activity) the alternative pathway C3 and C5 convertases; MCP, has cofactor activity for factor I–mediated C3b and C4b cleavage; FI, it degrades C3b and C4b aided by cofactors.

complexes (ICs) and damaged cells, and in the regulation of adaptive immune response.[4] Complement components and regulators are organized into three activation pathways: the alternative, classic, and lectin pathways, the activation of which results in the formation of C3 convertases, which are protease complexes that cleave C3 into C3a and C3b. The binding of additional C3b to the C3 convertases forms the C5 convertases that cleave C5, producing C5a and C5b. At this stage the three pathways converge into a common terminal pathway that leads to the formation of the terminal complement complex C5b-9 (Fig. 1).

Activated complement generates three major groups of effector molecules: (1) anaphylatoxins (C3a and C5a), which attract and activate leukocytes through interaction with C3a and C5a receptors; (2) opsonins (C3b, inactivated C3b [iC3b], and C3d), which covalently bind to target surfaces to facilitate transport and favor the removal of target cells or IC by leukocytes; and (3) the terminal C5b-9 complex that lyses pathogens or damaged self-cells (Fig. 1).

The classic pathway is triggered by interaction between C1q and antigen–antibody IC in the circulation or on target cells, whereas the lectin pathway uses mannose binding lectins (MBLs) and ficolins to identify carbohydrate ligands on the surface of microbes or damaged host cells.[4]

The alternative pathway always is activated at a low degree in fluid phase by hydrolysis of C3, which through the formation of the alternative pathway initiation C3 convertase leads to the deposition of low amount of C3b onto cell surfaces. C3b binds factor B (FB), and forms the surface alternative pathway C3 convertase (Fig. 1) that cleaves additional C3 molecules. C3b generated by any of the three pathways can form the alternative pathway C3 convertase, which