Diagnosis of complement alternative pathway disorders

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Kidney diseases resulting from abnormal control of the complement alternative pathway include atypical hemolytic uremic syndrome, C3 glomerulonephritis, and dense-deposit disease, as well as atypical postinfectious glomerulonephritis. Although clinically diverse, they all result from loss of surface or fluid-phase complement control, caused by acquired or genetic defects in the complement alternative pathway. As such, the diagnostic approach is similar and includes a comprehensive biochemical, genetic, and pathologic analysis of the complement pathway. The biochemical test battery includes functional activity measurements of the entire complement pathway, functional and quantitative analysis of individual components and regulators, and quantification of activation products. In patients with a thrombotic microangiopathy, ADAMTS-13 activity should be determined to exclude a thrombotic thrombocytopenic purpura. The spectrum of genes currently known to be involved in the pathogenesis of alternative pathway disorders is rapidly expanding. Pathologic analysis of a kidney biopsy specimen is sophisticated with *ad hoc* immunofluorescence studies and laser microdissection with mass spectrometry. The identification of the underlying defect in the alternative pathway based on this comprehensive analysis will allow treatment to be directed to the site of dysregulation.

Kidney International (2016) **89,** 278–288; http://dx.doi.org/10.1016/j.kint.2015.12.003

KEYWORDS: alternative pathway; atypical hemolytic uremic syndrome; C3 glomerulonephritis; C3 glomerulopathy; classical pathway; complement; dense-deposit disease; glomerulonephritis

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Received 20 June 2015; revised 13 August 2015; accepted 19 August 2015

A number of kidney diseases result from uncontrolled activation of the alternative pathway (AP) of complement. Atypical hemolytic uremic syndrome (aHUS) is a primary thrombotic microangiopathy (TMA), clinically characterized by acute kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia. C3 glomerulopathy, comprising C3 glomerulonephritis (C3GN) and dense-deposit disease (DDD), is a pathologic entity defined by dominant C3 accumulation with absent or scanty immunoglobulin deposition. The term atypical postinfectious glomerulonephritis has been used to describe a disease course where the diagnosis of postinfectious glomerulonephritis is not followed by resolution, but by persisting hematuria and proteinuria and even development of end-stage kidney disease. It is likely that atypical postinfectious glomerulonephritis falls in the continuum of C3GN and DDD. In other glomerular disorders, including antineutrophil cytoplasmic antibody–associated vasculitis, activation of the AP contributes to the pathophysiology of the disease.[1]

Despite phenotypic differences, these glomerular diseases share dysfunction of the AP as the defining pathophysiology. Thus, the diagnostic approach to these disorders should be similar. The causal abnormality in the complement pathway, be it either genetic or acquired, may not be clinically evident until a triggering condition, such as infection or pregnancy, disrupts the fragile balance between complement activation and restraint. A collaborative effort of the clinicians, biochemical and genetic laboratory, and pathologists is required to unravel the underlying defects in the AP.

The purpose of this communication is to provide a comprehensive discussion of the diagnostic evaluation of the AP, conducive to support the practicing nephrologist in the difficult task of interpreting the results while avoiding the pitfalls of these tests.

THE NORMAL COMPLEMENT PATHWAY

The complement system is an essential part of innate immunity and provides a first-line defense against invading pathogens and abnormal self-derived components.[2,3] The complement system is a proteolytic cascade, comprising more than 30 proteins,[4] where serine proteases activate each other

in a strictly ordered manner. The complement components are available in soluble form, called the fluid phase, or expressed on the cell membrane, the solid phase.

Three distinct activation pathways belong to the complement system: the classical, lectin, and alternative pathways.[5] These pathways each converge to the central step of the complement system, that is, the cleavage of C3 by C3 convertases (Figure 1). The cleavage products C3a and C3b subsequently set in motion downstream effector functions. The crucial effector steps are opsonization, anaphylatoxin-mediated inflammation, and formation of terminal membrane attack complex. Rigorous active control mechanisms are required to prevent damage to self.

Complement pathway activation

In the classical pathway, the cascade is initiated by the interaction between C1q and immunocomplexes, consisting of a single IgM or at least 2 IgG1–3 subclass molecules and the antigen. C1q has 6 binding sites that associate with the constant immunoglobulin (Fc) fragments of IgM or IgG. The serine proteases C1r and C1s are then activated by binding to the C1q–immunoglobulin complex. Initially, 1 molecule of C1r binds and autoactivates, subsequently cleaving a second C1r molecule and both C1s molecules. Activated C1s cleaves C4 to C4a and C4b, and C2 to C2a and C2b. The C4b fragment combines with the lipid bilayer of the target cell and C2a to form the C3 convertase of the classical pathway, C4b2a.

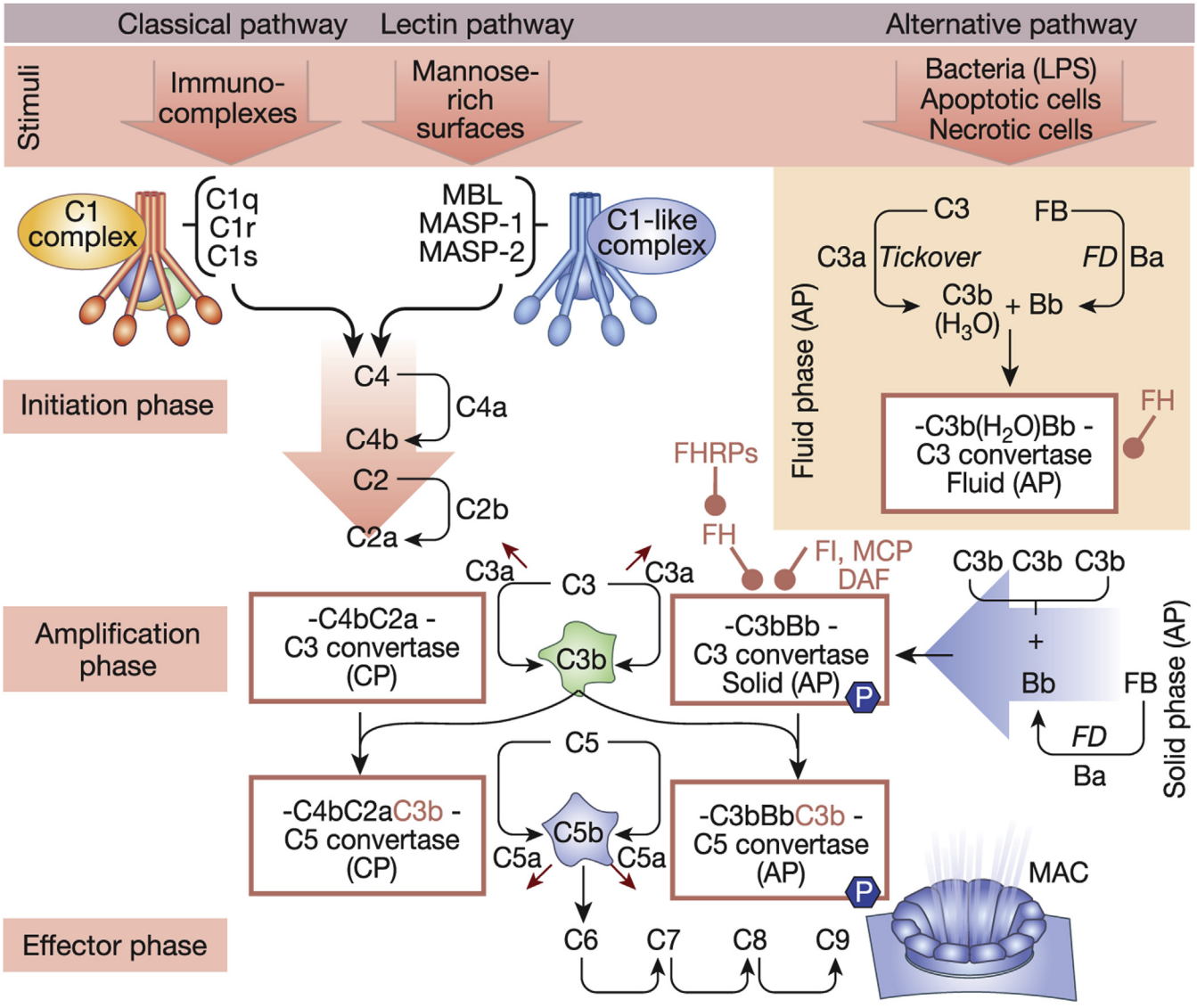

Figure 1 | Schematic overview of the normal complement pathway. The complement system can be activated by the classical, lectin, and alternative pathways, all resulting in the formation of C3 convertases. The C3 convertases continuously cleave C3 in a powerful amplification loop. The terminal complement cascade is initiated by the C5 convertase and ultimately generates the MAC complex that inserts pores into cell membranes to induce cell lysis. AP, alternative pathway; CP, classical pathway; DAF, decay-accelerating factor; FB, factor B; FD, factor D; FH, factor H; FHRPs, factor H–related proteins; FI, factor I; LPS, lipopolysaccharide; MAC, membrane attack complex; MBL, mannose-binding lectins; MASPs, MBL-associated serine proteases; MCP, membrane cofactor protein. Red arrows, anaphylatoxins; white boxes, convertases; red circles, inhibitors; P, properdin.

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