THE COMPLEMENT SYSTEM

The complement system includes serum and membraneebounproteins that function in both adaptive and innate host defense systems.

These proteins are highly regulated and interact via a series of proteolytic cascades. The term“complement” refers to the ability of these proteins to complement the effects of other components of the immune system (eg, antibody)

. Complement has several main effects:

(1) lysis of cells (eg, bacteria and tumor cells),

(2) production of mediators that participatein inflammation and attract phagocytes,

(3) opsonization of organisms and immune complexes for clearance by phagocytosis,

(4) enhancement of antibody-mediated immune responses.

Complement proteins are synthesized mainly by the liver and by phagocytic cells

Complement Activation

Several complement components are proenzymes, which must be cleaved to form active enzymes. The components of the classic pathway are numbered from C1 to C9, and the reaction sequence is C1-C4-C2-C3-C5-C6-C7-C8-C9.

Up to C5, activation involves proteolytic cleavage, liberating smaller fragments from C2through C5.

Activation of the complement system can be initiated either by antigen-antibody complexes or by a variety of nonimmunologic molecules.

Sequential activation of complement components occurs via three main pathways.

A. THE CLASSIC PATHWAY

Only IgM and IgG activate or fix complement via the classic pathway and 3 fix complement.

C1, which is bound to a site in the Fc region, is composed of three proteins: C1q, C1r, and C1s. that bind to the Fc portion of IgG and IgM. The antibody-antigen immune complex bound to C1 activates C1s, which cleaves C4 and C2 to form C4b2b.

The latter is an active C3 convertase, which cleaves C3 molecules into two fragments: C3a and C3b. C3a

. C3b forms a complex with C4b2b, producing a new enzyme, C5 convertase,

which cleaves C5 to form C5a and C5b

.C5b binds to C6 and C7 to form a complex that inserts into the membrane bilayer. C8 then binds to the C5b/ C6/C7 complex, followed by the polymerization of up to

sixteen C9 molecules to produce the membrane attack complex (MAC) that generates a channel or pore in the membrane

and causes cytolysis by allowing free passage of water across the cell membrane.

B. THE ALTERNATIVE PATHWAY

The alternative pathway begins with the activation of C3 and requires Factors B and D and Mg^{++} cation, all present in normal serum.

Many unrelated substances, from complex chemicals (eg, endotoxin) to infectious agents (eg, parasites), activate a different pathway. C3 is cleaved, and a C3 convertase is generated via the action of factors B, D, and properdin (factor P). these factors cleave C3and generate C3

convertase (C3Bb) that was generate during The alternative pathway produce more C3b.

The additional C3b binds to the C3 convertase to form C3bBbC3b, which is the alternative pathway C5 convertase that generates C5b, leading to production of the membrane attack complex described above.

C. MANNAN-BINDING LECTIN PATHWAY

In recent years, the concept of an additional pathway of complement activation has emerged—the MB lectin pathway. Its main constituent is a plasma protein termed MBL, which is short for mannan-binding lectin. MBL binds to sugar residues like mannose found in microbial surface polysaccharides such as LPS. The MBL complex, when bound to microbial surfaces, can activate C4 and C2. The rest of this pathway is the same as the classic pathway of complement activation.

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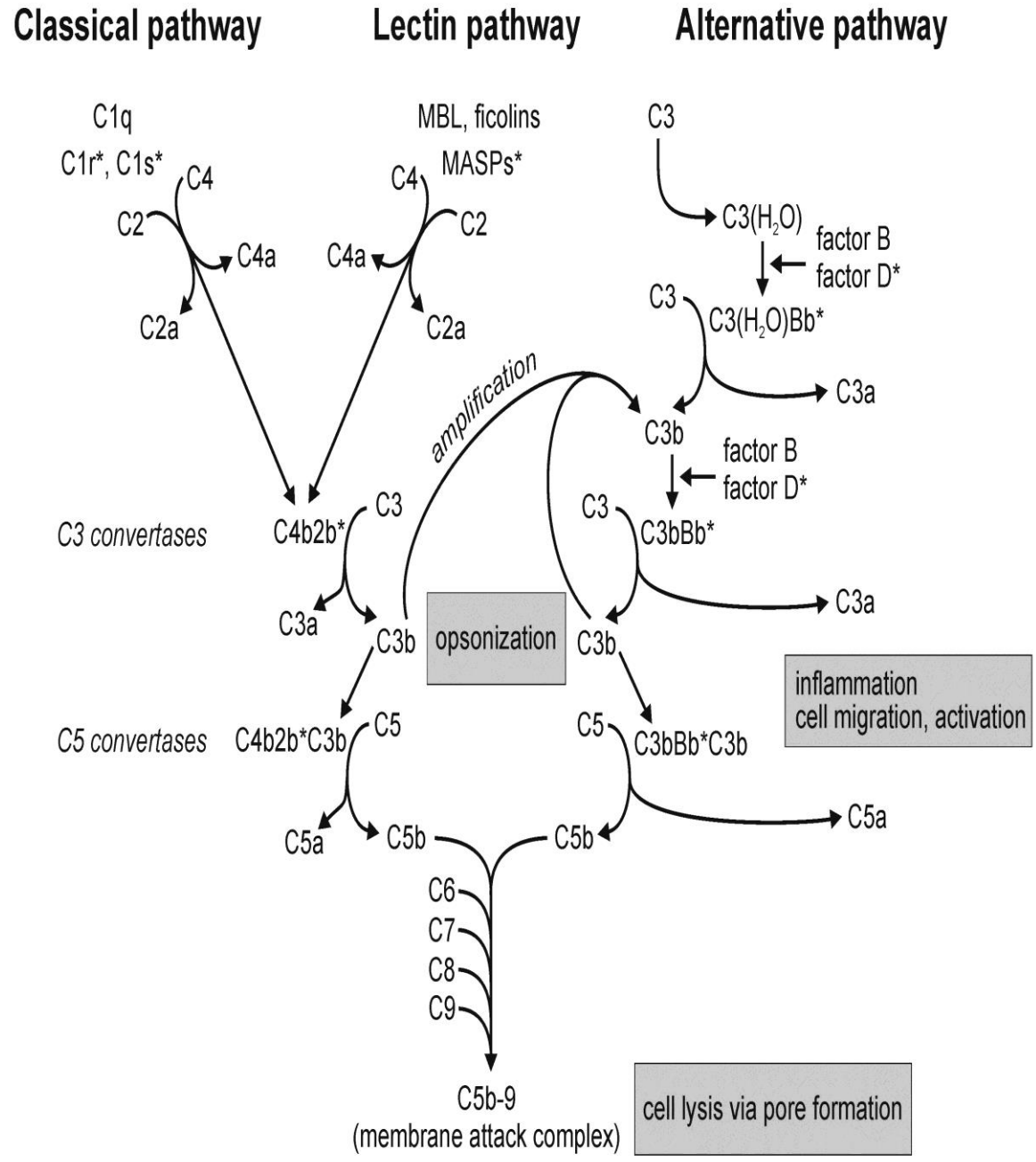
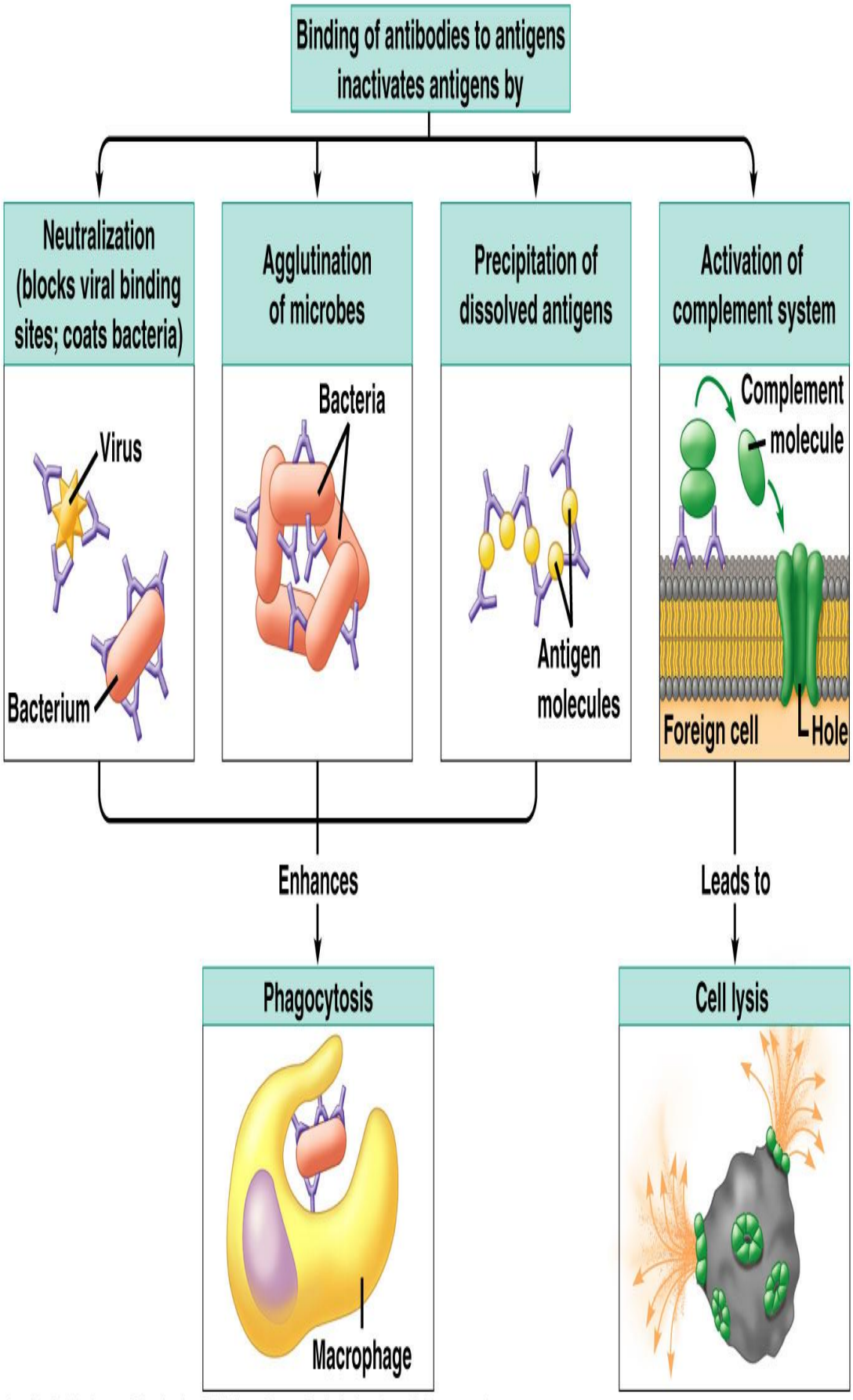
Clinical Consequences of Complement Deficiencies

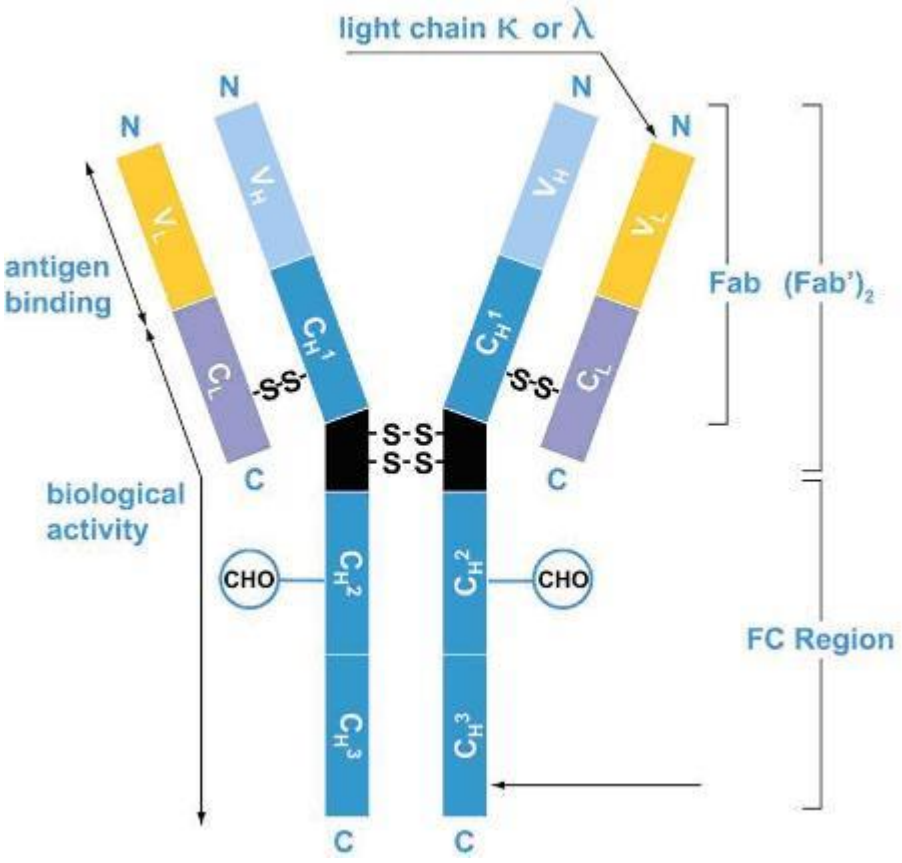
Many genetic deficiencies of complement proteins have been described, and these generally lead to enhanced susceptibility to infectious disease—for example,

C2 deficiency frequently leads to serious pyogenic bacterial infections. Deficiency in components of the membrane attack complex greatly enhances susceptibility to neisserial infections.

Deficiencies in components of the alternative pathway are also known—eg, properdin deficiency is associated with greater susceptibility to meningococcal disease.


Classical pathway
Lectin pathway
Alternative pathway
C1q
C1r*, C1s*
C4
C2
C4a
C2a
MBL, ficolins
MASPs*
C4
C2
C4a
C2a
C3
C3(H2O)
factor B
factor D*
C3
C3(H2O)Bb*
C3a
amplification
C3b
factor B
factor D*
C3
C3bBb*
C3a
C3 convertases
C4b2b*
C3
C3a
C3b
opsonization
C3b
inflammation
cell migration, activation
C5 convertases
C4b2b*C3b
C5
C5a
C5b
C5
C3bBb*C3b
C5a
C5b
C6
C7
C8
C9
C5b-9
(membrane attack complex)
cell lysis via pore formation

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