Review Articles

Advances in Immunology

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COMPLEMENT

First of Two Parts

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COMPLEMENT is part of the innate immune system and underlies one of the main effector mechanisms of antibody-mediated immunity. It has three overarching physiologic activities (Table 1): defending against pyogenic bacterial infection, bridging innate and adaptive immunity, and disposing of immune complexes and the products of inflammatory injury. In this review, each of these activities will be placed in a clinical context.

Complement was first identified as a heat-labile principle in serum that "complemented" antibodies in the killing of bacteria. We now know that complement is a system of more than 30 proteins in plasma and on cell surfaces. Complement proteins in plasma amount to more than 3 g per liter and constitute approximately 15 percent of the globulin fraction. The nomenclature of complement follows the historical order of discovery of the proteins and is one of the less friendly aspects of the complement system.

The first complement pathway that was discovered, the classical pathway, begins when antibody binds to a cell surface and ends with lysis of the cell. The proteins of this pathway are designated C1 through C9 (Fig. 1). It was subsequently discovered that the numbering of the proteins did not quite correspond with the order of the reaction, since C1 is followed in succession by C4, C2, C3, and C5, with numerical sanity restored from C6 through C9. Proteins of the second pathway to be discovered, the alternative pathway, are called factors, followed by a letter, such as factor B. Complement proteins on cell membranes can be receptors for activated complement proteins or proteins that regulate complement. They often have multiple names. Several complement proteins are cleaved during activation of the system, and the fragments are designated with lowercase suffixes — for example, C3 is cleaved into two fragments, C3a and C3b. Normally, the large fragment is designated "b," and the small fragment "a." Anarchy reigns with respect to the fragments of C2: the large fragment is designated C2a, and the small, C2b, for historical reasons.

The pathways leading to the cleavage of C3 are triggered enzyme cascades, analogous to the coagulation, fibrinolysis, and kinin pathways. The terminal complement pathway, leading to the formation of the membrane-attack complex, is a unique system that builds up a lipophilic complex in cell membranes from several plasma proteins. There are three pathways of activation of the complement system: the classical, mannose-binding lectin, and alternative pathways (Fig. 1 and Table 2).

The regulatory mechanisms of complement are finely balanced so that, on the one hand, the activation of complement is focused on the surface of invading microorganisms and, on the other hand, the deposition of complement on normal cells and tissues is limited. When the mechanisms that regulate this delicate balance go awry, the complement system may cause injury, and some of the resulting dis-

TABLE 1. THE THREE MAIN PHYSIOLOGIC ACTIVITIES OF THE COMPLEMENT SYSTEM.

ACTIVITY	COMPLEMENT PROTEIN RESPONSIBLE FOR ACTIVITY
Host defense against infection	
Opsonization	Covalently bound fragments of C3 and C4
Chemotaxis and activation of leukocytes	Anaphylatoxins (C5a, C3a, and C4a); anaphylatoxin receptors on leukocytes
Lysis of bacteria and cells	Membrane-attack complex (C5b–C9)
Interface between innate and adaptive immunity	
Augmentation of antibody responses	C3b and C4b bound to immune complexes and to antigen; C3 receptors on B cells and antigen-presenting cells
Enhancement of immunologic memory	C3b and C4b bound to immune complexes and to antigen; C3 receptors on follicular dendritic cells
Disposal of waste	
Clearance of immune complexes from tissues	C1q; covalently bound fragments of C3 and C4
Clearance of apoptotic cells	C1q; covalently bound fragments of C3 and C4

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eases will be discussed at the end of this review. Particular attention will be paid to illustrating the ways in which the meticulous study of patients with abnormalities of the complement system has illuminated our understanding of the immunobiology of complement.

This review is organized around the three main associations between complement and disease (Table 3): complement deficiency and susceptibility to infection, the consequences of abnormalities in the regulation of the complement system, and the role of complement deficiency in inflammatory diseases.

COMPLEMENT AND THE DEFENSE AGAINST INFECTION

Three types of complement deficiency can cause increased susceptibility to pyogenic infections: a deficiency of the opsonic activities of the complement system, which causes a general susceptibility to pyogenic organisms; any deficiency that compromises the lytic activity of complement, which can increase the susceptibility to neisserial infections; and deficient function of the mannose-binding lectin pathway.

Pyogenic Infections

Increased susceptibility to pyogenic bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae* occurs in patients with defects of antibody production, complement proteins of the classical pathway, or phagocyte function. Study of these patients shows that the normal pathway of defense against pyogenic bacteria is opsonization with antibody, followed by the activation of complement, phagocytosis, and intracellular killing. The most important complement opsonins in the defense against bacterial infection are C3b and iC3b, the covalently-bound cleavage fragments of C3.

Complement Deficiency and Neisserial Infections

The sole clinical association between inherited deficiency of components of the membrane-attack complex and infection is with neisserial disease, particularly *Neisseria meningitidis*.[1-3] This complex is necessary for the complement system to form a lytic channel in neisseriae. Extracellular lysis is a major mechanism of killing these organisms, which are capable of intracellular survival.

In parts of the world where meningococcal infections are highly endemic,[4,5] there appears to be a high prevalence of deficiencies of proteins of the membrane-attack complex. It has been argued that the homozygous deficiency of C6 offers a selective advantage by protecting against the deleterious effects of complement activation by endotoxin in infantile gastroenteritis.[5,6]

There are good data from epidemiologic studies in Japan on the association between a deficiency of proteins of the membrane attack complex and neisserial infection. A survey of nearly 150,000 consecutive blood donors[7] revealed 154 with the absence of one of these proteins (138 had a C9 deficiency, and 16 had a deficiency of C5, C6, C7, or C8), none of whom had a history of neisserial infection. However, among 17 patients with meningococcal disease ascertained from a register in Fukuoka, 8 had an inherited complement deficiency (4 of C7 and 4 of C9), and a 9th patient had systemic lupus erythematosus with acquired complement deficiency.[8] From incidence data for meningococcal disease,[8] the prevalence of complement deficiency among patients with sporadic cases of meningococcal disease, and the frequency of inherited complement deficiencies among Japanese blood donors,[7,8] the risk of meningococcal disease for a person with a complement deficiency in Japan can be calculated to be 0.5 percent per year. This is a relative risk of 5000, as compared with the incidence of meningococcal disease among Japanese persons without a complement deficiency.

Mannose-Binding Lectin Deficiency

In 1976[9] a group of children between the ages of six months and two years was described who had re-

Figure 1 (facing page). The Three Activation Pathways of Complement: the Classical, Mannose-Binding Lectin, and Alternative Pathways. The three pathways converge at the point of cleavage of C3. The classical pathway is initiated by the binding of the C1 complex (which consists of C1q, two molecules of C1r, and two molecules of C1s) to antibodies bound to an antigen on the surface of a bacterial cell. C1s first cleaves C4, which binds covalently to the bacterial surface, and then cleaves C2, leading to the formation of a C4b2a enzyme complex, the C3 convertase of the classical pathway. The mannose-binding lectin pathway is initiated by binding of the complex of mannose-binding lectin and the serine proteases mannose-binding lectin–associated proteases 1 and 2 (MASP1 and MASP2, respectively) to arrays of mannose groups on the surface of a bacterial cell. MASP2 acts in a fashion similar to that of C1s to lead to the formation of the C3 convertase enzyme C4b2a. MASP1 may be able to cleave C3 directly. The alternative pathway is initiated by the covalent binding of a small amount of C3b to hydroxyl groups on cell-surface carbohydrates and proteins and is activated by low-grade cleavage of C3 in plasma. This C3b binds factor B, a protein homologous to C2, to form a C3bB complex. Factor D cleaves factor B bound to C3b to form the alternative pathway C3 complex C3bBb. The binding of properdin stabilizes this enzyme. The C3 convertase enzymes cleave many molecules of C3 to C3b, which bind covalently around the site of complement activation. Some of this C3b binds to the C4b and C3b in the convertase enzymes of the classical and alternative pathways, respectively, forming C5 convertase enzymes. This C3b acts as an acceptor site for C5, which is cleaved to form the anaphylatoxin C5a and C5b, which initiates the formation of the membrane-attack complex. The activities of biologically active proteins and protein fragments of the complement pathway are described in Table 1.

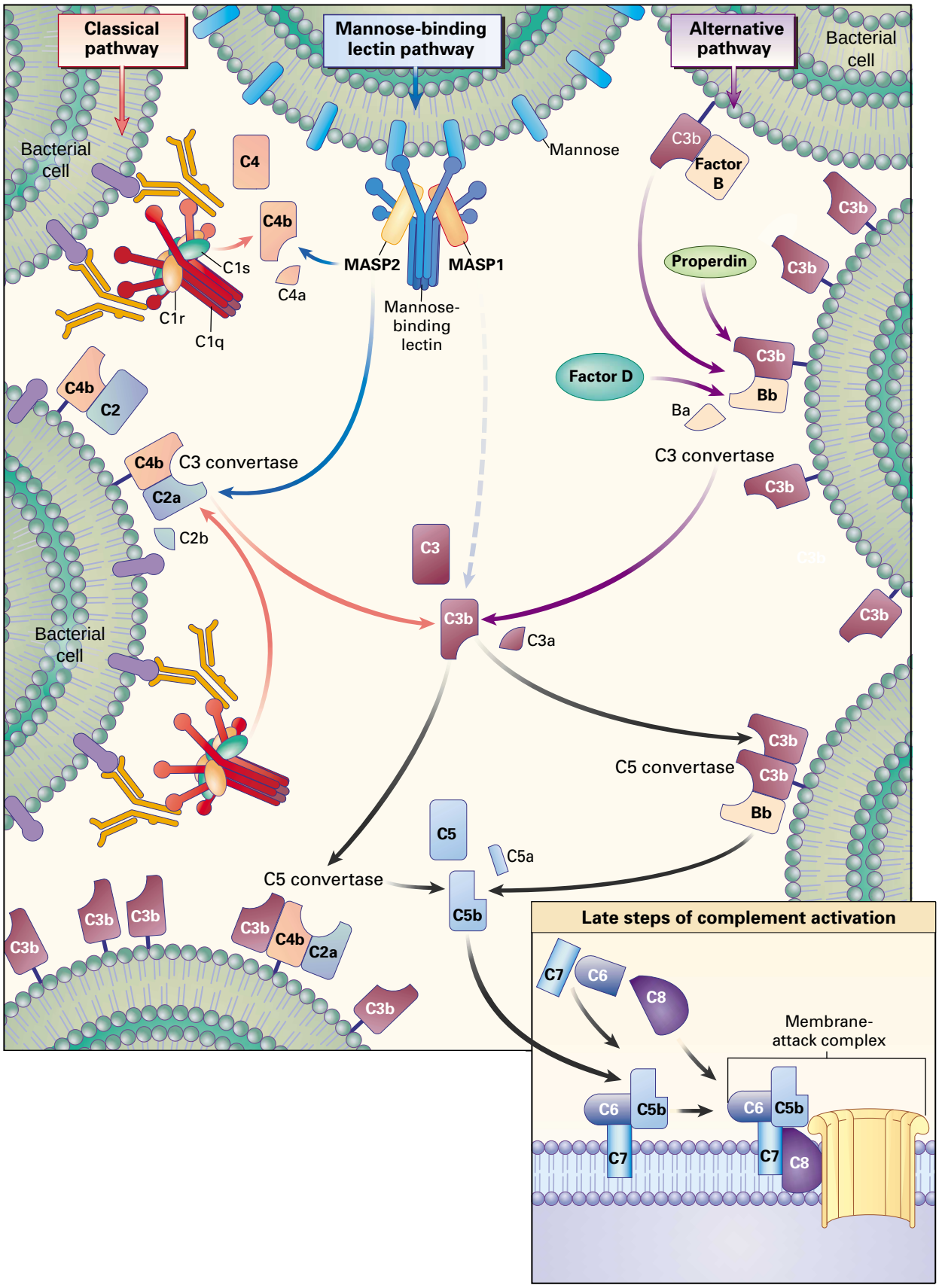

Classical pathway
Mannose-binding lectin pathway
Alternative pathway
Bacterial cell
Bacterial cell
Bacterial cell
C4
C4b
C4a
C1s
C1r
C1q
MASP2
MASP1
Mannose-binding lectin
Mannose
C3b
Factor B
Properdin
Factor D
Ba
Bb
C4b
C2
C4b
C2a
C3 convertase
C2b
C3 convertase
C3
C3b
C3a
C5 convertase
C5
C5a
C5b
C5 convertase
Late steps of complement activation
C7
C6
C8
Membrane-attack complex
C6
C5b
C7
C6
C5b
C7
C8

TABLE 2. INITIATORS OF THE THREE ACTIVATION PATHWAYS OF COMPLEMENT.

PATHWAY	INITIATORS
Classical	Immune complexes Apoptotic cells Certain viruses and gram-negative bacteria C-reactive protein bound to ligand
Mannose-binding lectin	Microbes with terminal mannose groups
Alternative	Many bacteria, fungi, viruses, tumor cells

current pyogenic infections and failure to thrive. Serum from these children failed to opsonize the yeast *Saccharomyces cerevisiae* with C3.[10] A similar opsonic defect was present in approximately 5 percent of an adult population without any obvious immunodeficiency. These results remained a mystery until it was found that the opsonic defect correlated with reduced serum levels of mannose-binding lectin.[11,12] Mannose-binding lectin is a member of a family of calcium-dependent lectins, the collectins (collagenous lectins), and is homologous in structure to C1q. Mannose-binding lectin, a pattern-recognition molecule of the innate immune system, binds to arrays of terminal mannose groups on a variety of bacteria.[13,14]

A deficiency of mannose-binding lectin is due to one of three point mutations in the gene for mannose-binding lectin, each of which reduces levels of the lectin by interfering with the oligomerization of the protein. A polymorphism in the promoter region of the gene also influences levels of the protein.[15,16]

The finding that the binding of mannose-binding lectin to mannose residues can initiate complement activation was followed by the discovery of the mannose-binding lectin–associated serine protease (MASP) enzymes. Mannose-binding lectin activates complement by interacting with two serine proteases called MASP1 and MASP2. MASP2 cleaves and activates C4 and C2, and MASP1 may cleave C3 directly.[17] These components of the complement system have been named the mannose-binding lectin pathway (Fig. 1).

The low levels of mannose-binding lectin in young children with recurrent infections[18] suggest that the mannose-binding lectin pathway is important during the interval between the loss of passively acquired maternal antibody and the acquisition of a mature immunologic repertoire. Surprisingly, there is a high frequency of dominantly expressed alleles of the gene for mannose-binding lectin that result in low levels of the protein in several ethnic groups. Perhaps this deficiency during early childhood is counterbalanced by an advantage later in life. There is epidemiologic evidence that low levels of mannose-binding lectin partially protect against mycobacterial infections, although at a population level the effect is not large.[19,20] In addition, one study found that Ethiopians with lepromatous leprosy had higher levels of serum mannose-binding lectin than their counterparts without the disease.[21] It is possible that the opsonization of intracellular organisms such as mycobacteria by mannose-binding lectin enhances the entry of such pathogens into cells. The other side of this coin is that pathogenic mycobacteria can synthesize a C4-like molecule that binds the serine esterase fragment of C2, C2a, leading to the cleavage of C3 and the deposition of C3b on mycobacterial-cell membranes.[22] This mechanism could enhance infection by increas-

TABLE 3. CLINICAL EFFECTS OF HEREDITARY COMPLEMENT DEFICIENCIES.*

COMPLEMENTARY DEFICIENCY	CONSEQUENCE OF COMPLEMENT ACTIVATION	CLINICAL ASSOCIATION
C3	Loss of major complement opsonin and failure to activate membrane-attack–complex pathway	Pyogenic bacterial infections, may be accompanied by distinctive rash Membranoproliferative glomerulonephritis
C3, properdin, membrane-attack–complex proteins	Failure to form membrane-attack complex	Neisserial infection
C1 inhibitor	Loss of regulation of C1 and failure to activate kallikrein	Angioedema
CD59	Failure to prevent the formation of membrane-attack complex on autologous cells	Hemolysis, thrombosis
C1q, C1r and C1s, C4, C2	Failure to activate the classical pathway	Systemic lupus erythematosus
Factor H and factor I	Failure to regulate the activation of C3; severe secondary C3 deficiency	Hemolytic–uremic syndrome Membranoproliferative glomerulonephritis

*C1 inhibitor, CD59, factor H, and factor I are regulatory proteins of the complement system. The other proteins are members of the activation pathways of complement (as shown in Fig. 1). C3 deficiency is associated with both infectious and inflammatory diseases.

ing the uptake of mycobacteria into macrophages. By contrast, low levels of mannose-binding lectin, by reducing opsonization, might confer resistance against mycobacteria.

COMPLEMENT AND THE PATHOGENESIS OF INFECTIOUS DISEASE

Many organisms take advantage of the complement system to enhance their virulence. Some viruses and intracellular bacteria use cell-bound complement regulatory molecules and receptors as a means of gaining entry to the cell.[23] The Epstein–Barr virus uses complement receptor type 2 (also called CD21) as a cellular receptor for its envelope glycoprotein gp350/220,[24,25] which explains the tropism of this virus for B cells with complement receptor type 2. Other examples are shown in Table 4. Some organisms activate host complement, thereby causing C3b to bind to their surface. This process allows the microbe to use C3 receptors to enter the cell. The human immunodeficiency virus (HIV) and pathogenic mycobacteria exploit this mechanism.[22,26]

Bacteria can evade complement if they have thick capsules that form a physical barrier against the membrane-attack complex or express proteins that inhibit the activation of complement.[27] Group A streptococci use the M protein to bind factor H,[28] which increases the catabolism of C3b and reduces the formation of C3 convertase enzymes. These bacteria also possess a peptidase that inhibits the inflammatory effects of C5a.[29]

Viruses have three ways of evading complement.[30] Some, such as HIV, incorporate complement regulatory proteins into the viral envelope.[31,32] Others have proteins that are structural mimics of complement regulatory proteins. For example, the vaccinia virus complement-control protein acts as a cofactor to complement factor I, which cleaves C4b and C3b, thereby inhibiting the activation of complement.[33] Still other viruses use proteins that have no structural homology to complement regulatory proteins but that nevertheless have similar functional properties. An example is the glycoprotein C of several herpesviruses, which binds C3b and renders the viruses resistant to destruction by complement.[34,35]

ABNORMALITIES OF COMPLEMENT REGULATION

Activation of C3

The three activation pathways of complement converge to generate C3 convertase, an enzyme that cleaves C3. This protein at the heart of the complement system contains an internal thioester bond. The cleavage of C3 to C3b by C3 convertase activates this bond and allows, for a very short period, the stable covalent binding of C3b to hydroxyl groups on carbohydrates and proteins in the immediate vicinity. Any C3 that does not bind in this way is inactivated by binding to water molecules. The covalent binding of C3 to hydroxyl groups is a key feature of the complement system. It tags invading microorganisms as foreign, and the bound C3 acts as a focus for further complement activation on and around the microbe. This leads to the production of anaphylatoxins and the assembly of the membrane-attack complex on the membrane of the invading pathogen (Fig. 1 and Table 1).

Regulation of the cleavage of C3 is critical (Fig.

TABLE 4. PROTEINS OF THE COMPLEMENT SYSTEM USED BY MICROORGANISMS TO ENTER HUMAN CELLS.

MICROORGANISM	MICROBIAL LIGAND OR MECHANISM OF ENTRY INTO HOST CELL	HOST RECEPTOR*	OTHER RECEPTORS AND CORECEPTORS	LOCATION OF RECEPTOR	TARGET OF INFECTION
Epstein–Barr virus	Glycoprotein 350/220	Complement receptor type 2	Possibly a receptor on epithelial cells	B cells	B cells, epithelial cells
Measles virus	Hemagglutinin	CD46 (membrane cofactor protein)		Many cells	Lymphocytes, macrophages, dendritic cells, neurons
Picornaviruses, such as echoviruses and coxsackieviruses	Capsid	CD55 (decay-accelerating factor)	Coxsackie and adenovirus receptor, $\alpha_2\beta_1$ integrin (very late antigen-2)	Many cells	Cells of alimentary tract and lymphoid tissues; can disseminate to most tissues
Mycobacterium tuberculosis	Deposition of host C3 fragments	Complement receptor type 3		Macrophages	Macrophages
Human immunodeficiency virus	Deposition of host C3 fragments	Complement receptor type 1, complement receptor type 2, complement receptor type 3	CD4, chemokine receptor CCR5, chemokine receptor CXCR4	Macrophages, some CD4 T cells, dendritic cells, follicular dendritic cells	CD4 T cells, dendritic cells, follicular dendritic cells, macrophages
Flavivirus, such as West Nile virus	Deposition of host C3 fragments	Complement receptor type 3		Macrophages	Macrophages, neurons

*The cell tropism of most microorganisms cannot be explained by their use of a single receptor to enter cells. Some of the other host receptors used by these organisms are indicated in the table.

2). Once C3 is deposited covalently as C3b on a membrane, it has two possible fates. The first is an amplification step, in which more C3 is cleaved and bound to the membrane. This process requires another complement protein, factor B. When factor B binds to C3b, it is activated by the complement enzyme factor D and forms the C3 convertase enzyme C3bBb. This enzyme cleaves more C3, causing many more C3b molecules to be set down on the membrane.

The second possible fate of bound C3b is catabolism to inactive products. This step is mediated by factor I, a regulatory enzyme of the complement system, and three other proteins: the plasma protein factor H and two cell-membrane proteins, complement receptor type 1 (also called CD35) and membrane cofactor protein (also called CD46) (Fig. 2). Factor H is the dominant complement-control protein, and in its absence the regulation of complement activation breaks down completely.

A key to the regulation of complement activation is whether factor B or factor H binds to C3b. The carbohydrate environment of bound C3b influences the outcome of the competition between factor B and factor H for binding to C3b on membranes.[36]

Defective regulation of C3 is typically associated with glomerulonephritis. The malfunction in these cases is due to C3 nephritic factor, which increases the stability of the C3 convertase enzymes, or to reduced function of factor H or factor I.

C3 Nephritic Factor

C3 nephritic factor is an autoantibody that binds to and stabilizes the C3 convertase enzyme C3bBb. This autoantibody is not usually connected with other conditions, but it is present in a few patients with systemic lupus erythematosus.[37] What triggers the production of C3 nephritic factor is unknown.[38]

C3 nephritic factor is associated with type II, dense-deposit, membranoproliferative glomerulonephritis (Fig. 3) and partial lipodystrophy. Membranoproliferative glomerulonephritis[39] is characterized by mesangial proliferation, thickening of the capillary wall, and subendothelial deposits of immunoglobulin and C3. Electron microscopy of kidneys affected by membranoproliferative glomerulonephritis type II reveals electron-dense deposits of unknown composition within the glomerular basement membrane. Partial lipodystrophy is a disfiguring condition that affects the body from the waist upward but spares the legs. The loss of fat in this condition was a mystery until it was discovered that adipose cells are the main source of factor D,[40] which completes the formation of the C3 convertase enzyme C3bBb by cleaving factor B bound to C3b. There is a gradient in the concentration of factor D in the fat cells of the body; more is present in the upper than the lower half of the body, which could explain the distribution of the fat loss.[41] It is likely that the C3 nephritic antibody in partial lipodystrophy stabilizes the C3bBb C3 convertase that forms in the immediate vicinity of adipocytes. The abnormally stabilized enzyme may then cleave enough C3 to allow assembly of the membrane-attack complex, which lyses adipocytes.

Factor H Deficiency

Membranoproliferative glomerulonephritis also occurs with factor H deficiency. The mechanism for this association is unknown, but in the absence of factor H, continuous activation and turnover of C3 in the vicinity of the glomerular basement membrane may cause C3b to bind to glomeruli and incite inflammation.

Some cases of homozygous factor H deficiency have also been associated with the hemolytic–uremic syndrome.[42-47] Familial cases of the hemolytic–uremic syndrome or membranoproliferative glomerulonephritis have been described in association with low levels of serum C3 but no obvious deficiency of factor H or factor I. However, in two of the families the disease was linked by genetic mapping to the gene for factor H.[48] In these families and in a number of sporadic cases of recurrent hemolytic–uremic syndrome, a heterozygous factor H deficiency has been identified. At present there is no test that will reliably identify heterozygous carriers of factor H deficiency, and the gene is not easy to sequence. A high index of suspicion for factor H deficiency is needed in patients with reduced levels of C3 and recurrent hemolytic–uremic syndrome or membranoproliferative glomerulonephritis.

C1 Inhibitor Deficiency

The main clinical feature of hereditary angioedema is recurrent angioedema, which may cause severe illness if it affects the intestinal submucosa or death by suffocation if it causes obstruction of the upper airways. In this autosomal dominant disease, the single normal allele of the gene for C1 inhibitor cannot ensure the production of physiologically adequate amounts of C1 inhibitor. This serine protease inhibitor inactivates the complement serine esterases C1r and C1s, kallikrein of the kinin system, and activated factors XI and XII of the coagulation system. Although C1 inhibitor is not an important inhibitor of plasmin, it is consumed by plasmin, and plasmin activation is probably the most important trigger of attacks of angioedema. In this disease, treatment by infusion of the deficient protein, C1 inhibitor, relieves attacks and may be lifesaving.[49]

The main cause of the increased vascular permeability in hereditary angioedema is the excess bradykinin[50] that results from the unregulated cleavage of high-molecular-weight kininogen by kallikrein. The angioedema associated with treatment with angiotensin-converting enzyme is also associated with elevated bradykinin levels,[50] and angiotensin-convert-

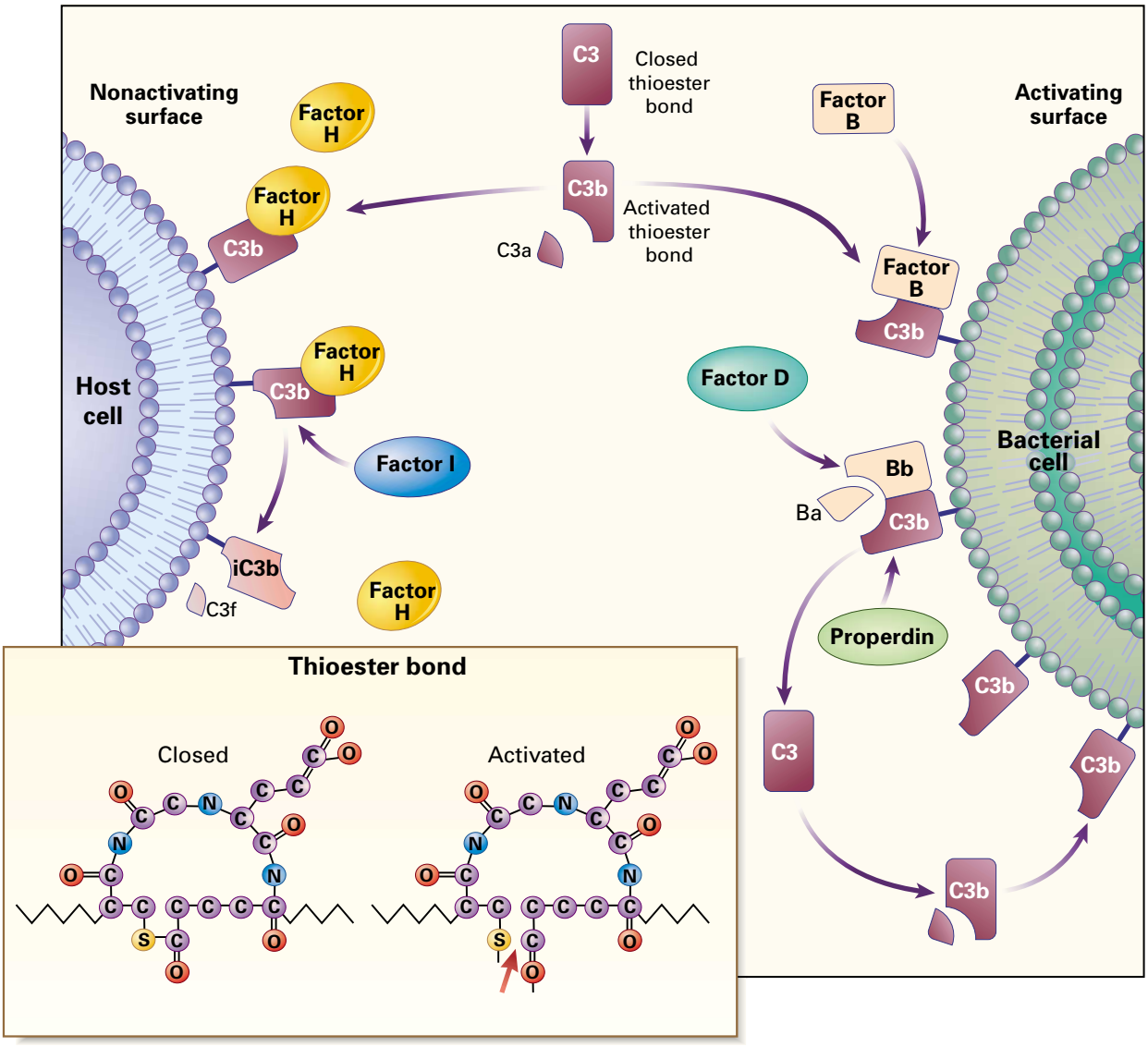
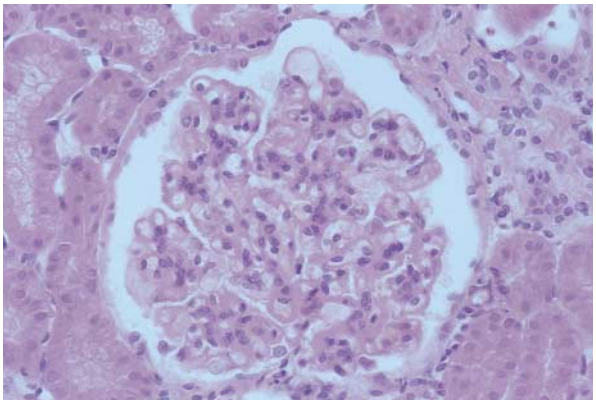


Figure 2. Regulation of the Cleavage of C3 by Factor H and Factor I.

The first product of the cleavage of C3 by a C3 convertase is C3b, which has an activated internal thioester bond. This bond enables C3b to bind covalently to hydroxyl groups on nearby carbohydrates and protein-acceptor groups. If the acceptor molecule is on a host cell surface, then protective regulatory mechanisms come into play. This is illustrated by the binding of factor H to C3b, which acts as a cofactor to the serine esterase factor I. Factor I cleaves the C3 into an inactive product, iC3b, releasing a small peptide, C3f. The iC3b can no longer participate in the formation of a C3 convertase enzyme. If C3b binds covalently to a bacterium, then the enzyme precursor factor B binds to the C3b. Factor B that is bound to C3b is susceptible to cleavage and activation by the enzyme factor D. This leads to the formation of the C3 convertase enzyme C3bBb, which is stabilized by the binding of properdin. This enzyme cleaves more C3, leading to the deposition of additional C3b on the bacterium. The carbohydrate environment of the surface on which the C3b is deposited determines the relative affinity of C3b for factor H or factor B. On host cell surfaces bearing polyanions such as sialic acid, factor H binds to C3b with a higher affinity than does factor B. On microbial surfaces that lack a polyanionic coating, factor B binds to C3b with a higher affinity than does factor H, leading to amplified cleavage of C3.

ing–enzyme inhibitors are absolutely contraindicated in patients with C1 inhibitor deficiency.

In type 1 hereditary angioedema, which accounts for approximately 85 percent of cases of the disease, a mutation prevents the transcription of the abnormal allele, and hence, plasma levels of C1 inhibitor are reduced. In type 2 hereditary angioedema, a point mutation in the gene for C1 inhibitor alters the amino acid sequence at or near the active center of the protein and abolishes its activity as a serine protease inhibitor.[51,52] The amount of inert C1 inhibitor in serum is normal or even elevated in patients with type 2



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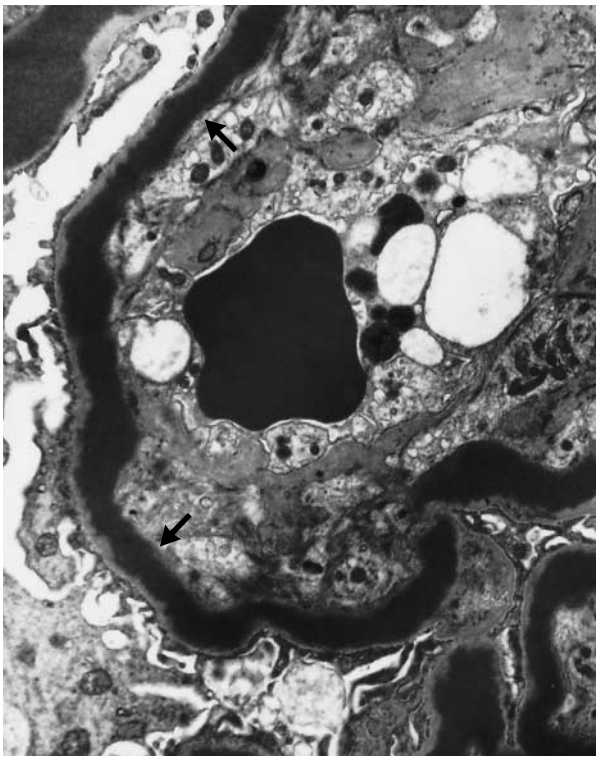

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Figure 3. Glomerulonephritis in the Presence of C3 Nephritic Factor.

Panel A shows a glomerulus from a patient with type II membranoproliferative glomerulonephritis (hematoxylin and eosin, ×200). There is mesangial expansion and hypercellularity, with thickening of glomerular capillary walls. Panel B shows the characteristic electron-dense deposits in the glomerular basement membrane (arrows) (×12,000). Photographs courtesy of Dr. Terry Cook, Department of Histopathology, Imperial College School of Medicine, Hammersmith Hospital, London.

hereditary angioedema, because the mutant protein is not consumed by activated serine proteases. It is easy to miss the diagnosis of this variant of hereditary angioedema if it is not understood that levels of C1 inhibitor can be normal or high in patients with the disease.

Another type of angioedema associated with C1 inhibitor deficiency is caused by the presence of autoantibodies against the protein. This syndrome usually occurs in elderly persons and is often associated with a lymphoproliferative disease.[53,54]

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria is a striking example of the consequences of the failure to regulate the formation of the membrane-attack complex.[55] In this disease, a somatic mutation in a clone of hematopoietic-cell precursors causes a deficiency of phosphatidylinositol glycan class A (PIG-A), a protein required for the synthesis of glycosylphosphatidylinositol phospholipid. Glycosylphosphatidylinositol is the lipid tail that anchors more than 40 proteins to cell membranes. As a result of the mutation in the *PIG-A* gene, many proteins are deficient on the surface of cells of patients with paroxysmal nocturnal hemoglobinuria.[56,57] The most likely cause of intravascular hemolysis in these patients is the increased susceptibility of red cells to complement. Two molecules anchored by glycosylphosphatidylinositol — decay-accelerating factor (also called CD55), which regulates the formation of C3 convertase, and CD59 (also called membrane inhibitor of reactive lysis), which restricts the formation of the membrane-attack complex — have been implicated. The discovery of isolated deficiencies of decay-accelerating factor and of CD59 showed that the deficiency of CD59 is responsible for the intravascular hemolysis that characterizes paroxysmal nocturnal hemoglobinuria.[58-61]

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