Complement

Introductory article

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The mammalian complement system consists of a complex group of more than 30 soluble proteins and receptors that play an important role in innate and acquired host defence mechanisms against infection, and participate in various immunoregulatory processes. The functions mediated by complement activation products include phagocytosis, cytolysis, inflammation, solubilization of immune complexes and promotion of humoral immune responses.

Article Contents

Introduction

The existence of the complement system was first recognized near the end of the nineteenth century, when normal sheep blood was found to possess a mild bactericidal activity that was lost when the blood was heated to 55°C. This labile bactericidal activity was later termed alexin by Bordet. By 1900 Paul Ehrlich had proposed a scheme for humoral immunity in which he identified the heat-stable immune sensitizer component of serum as 'amboreceptor' (antibody), while the heat-labile factor in serum (Bordet's alexin) was termed 'complement'. Since then an impressive number of complement components have been, and are being, added to the list of molecules that make up the complement system as we know it today.

The complement system is activated by three different pathways, termed the classical, alternative and lectin pathways. All three pathways are activated in a sequential manner, with activation of one component leading to the activation of the next (**Figure 1**). Activation of complement through any of the three pathways leads to activation of C3, the central protein of the complement system. C3 is a fascinating molecule that has the capacity to interact with more than 20 different proteins of complement and noncomplement origin. Native C3 is not a functional molecule, and all of the ligand-binding sites on C3 are hidden until the molecule is activated. As we shall see in the following sections, native C3 contains a thioester group that upon activation makes C3 a functional protein that is able to interact with its ligands. After activation the C3 molecule can either be inactivated to avoid selfdamage, or

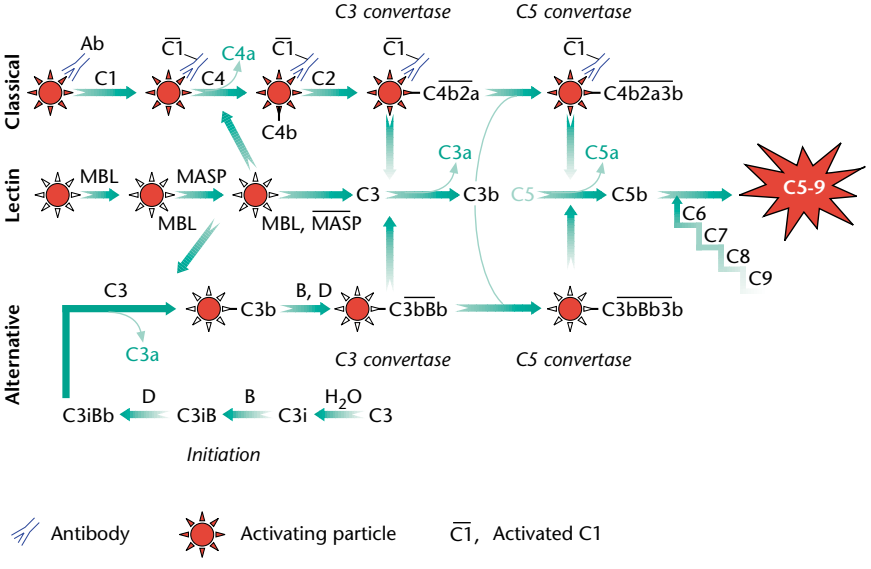

Figure 1 Pathways of complement activation.

it can be covalently attached to target surfaces where it leads to either opsonization, or cytolysis through the sequential activation of the membrane attack complex (MAC).

Alternative Pathway

The alternative pathway is activated by a variety of microorganisms including viruses, bacteria, fungi and protozoans. Although the initiation of activation is essentially antibody-independent, aggregated antibody has been shown to enhance the activation process. The alternative pathway is kept in a low level of steady state activation as a result of hydrolysis of the thioester group of native C3, which forms C3(H_2O) (hydrolysed C3). This low-level activation is essential since it makes 'functional' C3 continuously available and ready to react with potential pathogens. It is also necessary because the half-life of the active form of C3 is very short.

Once formed, C3(H_2O) is able to bind to factor B, the catalytic subunit of the alternative pathway. Factor B is proteolytically activated and cleaved to Bb (66 kDa) and Ba (33 kDa) fragments by a second serine protease, factor D, to generate the enzyme C3 convertase (C3b,Bb). C3 convertase is able to cleave native C3 to C3a and C3b; C3b can then covalently bind to the surface of nearby particles (including viruses, bacteria and fungi) via its metastable thioester bond. Most of this resulting C3b, as well as the C3(H_2O), is instantaneously inactivated by factor I in the presence of cofactor regulatory molecules (CR1, factor H, MCP). The C3b that is not inactivated (the C3b bound to activating surfaces) is involved in an amplification loop of the activation process, an essential feature of the activation of the alternative pathway. Binding of factor B to the newly generated C3b forms a new C3 convertase (C3b,Bb), which is further stabilized by properdin. Close association of another C3b molecule with the C3b,Bb complex forms the enzyme C5 convertase (C3b,Bb,3b), which cleaves C5 into C5a and C5b (**Figure 1**). Activation of the pathway is very much dependent upon the microenvironment surrounding the C3b bound molecule; conditions therefore determine whether amplification (binding of factor B to C3b) or abrogation of the pathway (binding of a regulator molecule to C3b) will occur.

Classical Pathway

Activation of the system by the classical pathway is primarily dependent on the immunoglobulin M (IgM) or IgG present in immune complexes, which binds to the C1 complex via the C1q subunit (**Figure 1**). Binding of antibody induces conformational changes in the C1 complex and leads to the activation of its C1r and C1s serine protease subunits. Once activated, the C1s can cleave C4 to C4a and C4b; one molecule of activated C1s can cleave many C4 molecules. Like C3b, C4b contains a thioester bond that can attach covalently to surfaces via their hydroxyl or amino groups. The result of this antibody-mediated activation of the C1 complex is an aggregation of C4 molecules surrounding the antibody–C1 site. The next protein to bind to the complex is C2, another serine protease. C2 binds to C4b in a Mg^{2+}-dependent manner and is cleaved by C1s to C2a and C2b. The association of C2a (which contains the catalytic site) with C4b leads to the formation of the classical pathway C3 convertase (C4b,2a). This enzyme is capable of binding and cleaving C3 to C3b, which is then deposited in large amounts onto the target surface. This deposition of C3 serves to opsonize the target surface and facilitate its phagocytosis, while initiating the terminal reaction sequence by forming C5 convertase (C4b,2a,3b). With the C2a fragment again supplying the catalytic subunit, C5 convertase cleaves C5 to C5b, which is then added to the complex.

Lectin Pathway

Lectins can also directly activate the complement system, through the binding of mannans to the complex compound of mannose-binding lectin (MBL) and the MBL-associated serine protease (MASP1 and MASP2). Once MBL binds to mannans on the surface of various microorganisms, MASP becomes capable of cleaving and activating C3, C4 and C2. The distinct roles of MASP1 and MASP2 are as yet unclear.

Lytic Pathway

All three pathways of complement activation converge with the production of a C5 convertase which cleaves C5 to C5b and C5a. C5b then initiates the self-assembly of the MAC C5b–C9 (see below).

Components of the Complement System

It has now become clear that the complement system arose first in invertebrate species more than 600 million years ago, since complement genes have already been cloned, and the molecules they encode have been purified, from echinoderms and tunicates. In these animals, or perhaps even more primitive species, the complement system may have emerged as a simple system comprising a small number of components (perhaps C3, factor B and D and/or C3, MASP and MBL) with limited functions (perhaps only

the opsonization of foreign material). A combination of gene duplication in combination with exon shuffling, including sequential addition or deletion of several types of modules or domains from various proteins, has produced the functional and structural complexity that characterizes the complement system in vertebrate species (**Table 1**).

From a functional point of view, complement proteins can be grouped into three major categories: (1) those involved in the activation sequences of the three pathways, (2) those involved in the regulation of these activation sequences, and (3) those that act as receptors for complement proteins. Several of the complement proteins may belong to more than one of these three groups, since they have several functional roles within the complement system.

Components Involved in the Activation Sequences

Complement components C1q and MBL (mannose-binding lectin) share a similar molecular architecture, and they play analogous roles in the activation of the classical and lectin pathways, respectively. The C1q molecule has a hexameric structure, and each of the six subunits is made of three different chains, A, B and C. The N-terminal portion of each chain has a collagen-like sequence with a triple-helical structure: the C-terminal portion contains a globular head region. Modules with similarity to C-terminal portion of the A, B and C chains are also present in the C-terminal regions of noncomplement proteins, including human type VIII and X collagens and precerebellin. The globular head region of the C1q chains is involved in the binding of C1q to the Fc regions of IgM and IgG antibodies.

MBL is a collectin with collagen-like stalks similar to those of C1q; like C1q, MBL also has a hexameric structure. However, in contrast to C1q, each of its six subunits is composed of three identical chains. The N-terminal region of each chain forms a triple-helical collagen-like structure, and the C-terminal region contains a C-type lectin carbohydrate-recognition domain that is involved in the binding of the MBL molecule to the mannan groups on the surfaces of microorganisms.

Complement components with serine protease domains

The complement components that contain a serine protease domain are factor D, C1r, C1s, MASP1, MASP2, factor B and C2. Factor I also has a serine protease domain, but this complement component falls within the group of regulatory proteins. Except for factor D, all the other serine protease domain-containing molecules are protein mosaics that are made up of different domains or modules. Beginning from the N-terminus, C1r, C1s, MASP1 and MASP2 consist of two noncontiguous C1r/C1s/UEGF/BMPI (CUB) modules (found also in extracellular proteins playing roles in developmental processes), an epidermal growth factor (EGF)-like domain, two short consensus repeat (SCR) domains and a serine protease domain at the C-terminal part of the molecule. The four molecules appear to have descended from a common ancestor, since they share very similar domain structures and functional activities. It is interesting to note that MASP2, C1r and C1s are similar to the serine protease domain of haptoglobin (a haemoglobin-binding serum protein) in being encoded by a single exon; in addition, the haptoglobin 2 molecule also contains two CCP (complement control protein) modules. Therefore, an evolutionary relationship appears to exist between haptoglobin and the MASP2, C1r and C1s molecules.

Factor B and C2 share the same genomic organization and are localized in tandem within the major histocompatibility complex (MHC) class III region. They also share the same domain structure and are both composed of three SCR domains, a Von Willebrand domain and the serine protease domain (N- to C-terminus). Because of their similarities it is believed that factor B and C2 have arisen by gene duplication from a common ancestor. A factor B-like molecule has been cloned from the sea urchin (echinoderm), suggesting that the alternative pathway is very primitive in nature and is thus by far the most ancient pathway characterized in animal species. It is not known in which animal species the ancestral factor B molecule was duplicated and diverged to give the C2 molecule. However, teleost fish (trout) and birds (chickens) are known to have a protein that seems to play the roles of both factor B and C2.

Components C3/C4/C5

In contrast to most of the other complement components, C3, C4 and C5 contain neither repeating structures nor evident modules. However, the primary sequences and genomic organizations of the three components are very similar, leading to the belief that the three proteins arose from a common ancestral molecule. C3, C4 and C5 are similar in size ($\sim$ 200 kDa), subunit structure, and order of their chains (α-β in C3 and C5 and α-β-γ in C4); all three also possess arginine linkers between chains, and both C3 and C4 contain an active thioester site in the α chain.

The thioesters located in the C3d and C4d region of C3 and C4, respectively, are responsible for the covalent binding of these components to their acceptor molecules. The His residue at position 1126 of human C3, as well as the Gln located two amino acids upstream, is very important in determining the binding specificity of the thioester; indeed, the presence of His 1126 is believed to be essential for the

Table 1 Alternative, classical and lectin pathway proteins

Protein	Structure	Concentration ($\mu g\ mL^{-1}$)	Cellular sources	Key function
Alternative pathway (AP)				
Factor B	93 kDa	210	Hepatocytes, mononuclear phagocytes, epithelial and endothelial cells, adipocytes, fibroblasts	Catalytic subunit of AP C3 convertase, forms part of the C5 convertase
Factor D	24 kDa	1–2	Mononuclear phagocytes, adipocytes	Cleaves factor B that is bound to C3b or $C3(H_2O)$
Properdin	55–220 kDa monomer to tetramer	25	Mononuclear phagocytes	Stabilizes AP C3 convertase
C3 (185 kDa)	110 kDa α chain 75 kDa β chain	1300	Hepatocytes, mononuclear phagocytes, epithelial and endothelial cells, adipocytes, fibroblasts	Activated C3 (C3b) covalently binds to activating surfaces. It forms part of the C3 and C5 convertases. Forms part of both alternative and classical pathways
Factor H	150 kDa	500	Hepatocytes, mononuclear phagocytes, epithelial and endothelial cells, fibroblasts, B cells, keratinocytes, myoblasts	Accelerates the dissociation of AP C3 convertase. Cofactor for factor I
Factor I	88 kDa	35	Hepatocytes, mononuclear phagocytes, myoblasts, adipocytes, fibroblasts, B cells	C4b/C3b inactivator
Classical pathway (CP)				
C1q (462 kDa)	Hexamer. Subunit contains: ((×1)A+(×1)B+(×1)C) (×6) 26.5 kDa A chains (×6) 26.5 kDa B chains (×6) 24 kDa C chains	80	Hepatocytes, mononuclear phagocytes, fibroblasts, gastrointestinal epithelial cells	Binds to IgM or IgG or C-reactive protein (CRP) and initiates the classical pathway
C1r	83 kDa	50	Hepatocytes, mononuclear phagocytes, fibroblasts, gastrointestinal epithelial cells	Cleaves C1s
C1s	83 kDa	50	Hepatocytes, mononuclear phagocytes, fibroblasts, gastrointestinal epithelial cells	Cleaves C4 and C2
C4 (205 kDa)	97 kDa, α chain 75 kDa, β chain 33 kDa, γ chain	600	Hepatocytes, mononuclear phagocytes, fibroblasts, genitourinary and alveolar type II epithelial cells	Activated C4 (C4b) covalently binds to activating surfaces. Forms part of classical C3 convertase
C2	110 kDa	20	Hepatocytes, mononuclear phagocytes, fibroblasts, genitourinary and alveolar type II epithelial cells	Catalytic subunit of the CP C3 convertase. Forms part of the C5 convertase

Table 1 – *continued*

Protein	Structure	Concentration ($\mu g\ mL^{-1}$)	Cellular sources	Key function
C4bp	460–540 kDa 70 kDa α chain 45 kDa β chain	250	Hepatocytes, mononuclear phagocytes	Cofactor for factor I. Accelerates the decay of CP C3 convertase
Lectin pathway				
MBL (192–582 kDa)	Dimer to hexamer. Subunit contains (×3) 32 kDa chain	1–4		Binds to mannans of microorganisms, activating the lectin pathway
MASP1 (83 kDa)	Monomer	6		Cleaves C2, C4 (?), C3
MASP2 (83 kDa)	Monomer	6		Cleaves C2, C4
Late components				
C5	110 kDa α chain 75 kDa β chain	75	Hepatocytes, mononuclear phagocytes, T/B lymphocytes, fibroblasts, epithelial cells, astrocytes	Initiates the assembly of MAC
C6	120 kDa	45	Hepatocytes, neutrophils, astrocytes	Participates in the formation of MAC
C7	105 kDa	55	Hepatocytes, mononuclear phagocytes, fibroblasts, astrocytes	Participates in the formation of MAC
C8	64 kDa α chain 64 kDa β chain 22 kDa γ chain	80	Hepatocytes, pneumocytes, astrocytes	Participates in the formation of MAC
C9	71 kDa	60	Hepatocytes, astrocytes, fibroblasts, macrophages, monocytes, platelets	Participates in the formation of MAC

CP, classical pathway; AP, alternative pathway; MAC, membrane attack complex; MBL, mannose-binding lectin; MASP, MBL-associated serine protease.

binding of C3 and C4 to hydroxyl groups. This binding preference is clearly illustrated in the case of mammalian C4; in humans C4 exists as two isoforms, C4A and C4B. Although the two molecules have very few amino acid differences (13 substitutions in 1722 residues), C4A (which contains an Asp instead of the His residue) binds preferentially to surfaces carrying amino groups, whereas C4B (which contains the His) binds to those containing hydroxyl groups. It is noteworthy that, unlike any other species, the C3 molecule of teleost fish is encoded by various genes and that the multiple C3 proteins present in an individual fish have the ability to bind with different specificities to a variety of complement-activating surfaces. It has been hypothesized that this functional and structural C3 diversity allows these animals to expand their innate immune recognition capabilities.

C3, C4 and C5 are cleaved by their respective convertases to produce C3a, C4a and C5a anaphylotoxins, and both C3 and C4 are inactivated by factor I in the presence of cofactors to generate similar cleavage products. Except for the C-terminal region, the overall structure and gene organization of C3, C4 and C5 very much resemble that of the serum proteinase inhibitor α_2-macroglobulin, suggesting that the ancestral molecule from which the three complement components were derived might have been originated by gene duplication from an ancestral α_2-macroglobulin-like molecule.

Late components

All three pathways of activation converge to the production of a C5 convertase which cleaves C5 to C5b and C5a, with the C5b initiating the self assembly of the membrane attack complex (MAC). The MAC is a supramolecular organization of molecules that contains C5b, C6, C7, C8, together with numerous molecules of C9, and is responsible for creating the transmembrane channels that lead to cell lysis. The assembly of MAC and its insertion into the cell membrane occurs by the following sequence of events. The C5b–C6 complex binds C7 and exposes hydrophobic sites that are concealed within the molecule. This allows insertion of the C5b–C7 complex into a discrete site on target membrane and it now serves as a receptor for C8. The C5b–C8 complex can then bind multiple molecules of C9 (n = 1–18) and the polymerization of C9 molecules results in the membrane lesions that are characteristic of MAC. Although polymerization of C9 is not essential for lysis of erythrocytes and nucleated cells, it is believed to be required for the killing of bacteria. Like the classical and alternative pathways of complement activation, channel formation by the MAC is also under the control of serum and membrane regulatory proteins.

Regulatory Proteins

Serum-soluble proteins

C1 inhibitor (C1-inh) regulates the classical pathway by blocking the proteolytic activity of C1r and C1s subcomponents of C1. It is part of the serine protease inhibitor or serpin superfamily and lacks any characteristic modular structure. C4b-binding protein (C4bpA and C4bpB) regulates the formation of the classical pathway C3 convertase by serving as a cofactor in the inactivation of C4b by factor I. There are three isoforms of C4bp. The major form is composed of seven α chains (each 70 kDa) and one β chain (75 kDa) that are linked by disulfide bonds to form a spider-like structure. As is true of many of the regulatory C3b- and C4b-binding proteins, C4bp also contains SCRs. The α and β chains are composed of eight and three SCRs, respectively.

Factor H is a single polypeptide chain of 150 kDa composed of 20 SCRs. It downregulates amplification of the alternative pathway by binding either to surface-bound or fluid-phase C3b and accelerating the decay of the C3b,Bb convertase, or by acting as a cofactor for factor I. Properdin is required for the stabilization of the C3b,Bb convertase, allowing rapid amplification of surface-bound C3b. It contains six thrombospondin repeat type 1 (TSP1) domains.

Factor I is an 88-kDa serine protease with an unusual structure; from its N-terminus to its C-terminus it is composed of a factor I/membrane attack complex (FIMAC) module, a scavenger receptor cysteine-rich (SRCR) module, two low-density lipoprotein receptor class A (LDLRA) modules and a serine protease domain. Factor I cleaves C3b and C4b (in the presence of various cofactor molecules) at several positions in the molecules.

S-protein (vitronectin) and clusterin (SP-40-40) are soluble plasma inhibitors of MAC formation that bind to the C5b-7 complexes and prevent their insertion into cell membranes. S-protein is a glycoprotein that contains a fibronectin-like integrin-binding region and a heparan-binding domain. Clusterin is a heterodimeric protein with a thrombospondin-like N-terminal domain.

Carboxypeptidase N, also termed anaphylatoxin inactivator, inactivates C3a, C4a and C5a by removing their C-terminal arginyl residue.

Membrane-bound proteins

Decay-accelerating factor (DAF or CD55) and membrane cofactor protein (MCP or CD46) have a similar structure, and both downregulate complement activation to protect self tissue from attack by complement. DAF is a 75-kDa glycoprotein that contains four SCRs followed by a serine/threonine/proline (STP) domain. The C-terminal portion ends with 24 hydrophobic residues that serve as a membrane anchor. DAF becomes anchored to the cell

membrane via a covalent linkage to a glycosylphosphatidylinositol (GPI) and may be involved in signal transduction. The role of DAF is to dissociate the C3 and C5 convertases by releasing C2a or Bb from the convertases. MCP is a single-chain glycoprotein that ranges in size from 45 to 75 kDa, depending on the degree of glycosylation. MCP is present in four different isoforms in humans. Like DAF, MCP contains four SCRs, but it differs from DAF in that it serves as a cofactor for factor I-mediated cleavage of C3b and C4b deposited on self tissue; also in contrast to DAF, MCP is devoid of decay-accelerating activity.

CD59 is an 18–20-kDa GPI-linked membrane protein which binds to C8 and C9 and inhibits the formation of the MAC on host cells.

Complement Receptors

C1q receptors

Three molecules have been shown to act as C1q receptors. cC1qR is a calreticulin-like molecule that also binds to MBL or surfactant protein A (SP-A). $C1qR_{02}$ only interacts with C1q and appears to trigger superoxide production. $C1qR_p$, the best characterized receptor, is a 66.5-kDa type I membrane glycoprotein. From the N-terminus to C-terminus $C1qR_p$ is composed of a C-type lectin domain (CRD domain), five EGF-like modules, and a cytoplasmic tyrosine phosphorylation motif that is involved in transducing cellular activation signals. $C1qR_p$ is also important in mediating phagocytic processes following binding of C1q, MBL or SP-A-containing complexes.

C3/C4 receptors

Complement receptor type 1 (CR1 or CD35) is a type I transmembrane glycoprotein of 220 kDa that contains 30 SCRs and is present in a wide variety of cells (**Table 2**). CR1 presents four different allotypes with different molecular masses of 160 (C form), 190 (A form), 220 (B form) and 250 (D form) kDa. It functions mainly as a receptor for C3b and C4b, although it binds with lesser affinity to iC3b and C3c. Multivalent C3b binds more strongly than does monovalent C3b, a difference which might have physiological relevance for the CR1-mediated functions. CR1 has two functions: (1) As a regulatory protein, it serves as a cofactor for the factor I-mediated cleavage of C3b or C4b, and it also has decay-accelerating activity for the C3 convertase. (2) As a receptor, CR1 promotes the binding and phagocytosis of C3b- and C4b-coated particles by phagocytic cells, and is also involved in the clearance of immune complexes.

Complement receptor type 2 (CR2, CD21 or C3d/EBV receptor) is a 140-kDa membrane glycoprotein that binds to iC3b, C3dg and C3d fragments of C3. It also binds to gp350, an Epstein–Barr virus envelope glycoprotein, and mediates the binding of the virions at the cell surface. CD23, a low-affinity receptor for IgE, also binds to CR2, an interaction that may influence the survival of B cells in germinal centres. CR2 is implicated in the regulation of B-cell responses and is involved in antibody responses to T-cell-dependent and -independent antigens.

Complement receptor type 3 (CR3, CD11b/CD18), with a 170-kDa α chain and a 95-kDa β chain, is an adhesion molecule belonging to the leucocyte–integrin family. Unlike CR1 or CR2, it does not contain any SCR modules. The β chain of CR3 (CD18) is common to other members of the leucocyte–integrin family such as CD11a/CD18 (LFA-1) and CD11c/CD18 (CR4), whereas the α chain (CD11b) is a type I transmembrane glycoprotein that is associated noncovalently with the β chain. CR3 binds specifically to the iC3b form of C3 in a divalent cation-dependent manner. It also binds to several other molecules, such as coagulation factor X, fibrinogen, lipopolysaccharide, zymosan, soluble Fcγ receptor III, *Leishmania* promastigote surface glycoprotein gp63, and others. When iC3b serves as the ligand, CR3 mediates opsonization and phagocytosis of microorganisms, as well as enhancement of natural killer (NK) cell activity for C3-coated targets.

Complement receptor type 4 (CR4, CD11c/CD18) is also an adhesion molecule of the leucocyte–integrin family. It is very similar to CR3, and it also binds iC3b in a divalent cation-dependent manner. The physiological role of CR4 is not clear, but its properties may be similar to those of CR3.

C3a and C5a anaphylotoxin receptors are members of the superfamily of rhodopsin-type receptors, which contain seven transmembrane loops. C3aR (95 kDa) and C5aR (43 kDa) are involved in a variety of processes, including chemotaxis, cell aggregation and adhesion, and release of lysosomal contents.

Functions of the Complement System

Activation of the complement system results in the initiation of various biological processes. The complement system plays very important roles in the following.

Opsonization of foreign material

This process involves the covalent binding of C3b and/or C4b to viruses, bacteria, fungi and other microorganisms. The opsonized surface becomes a target that can then be recognized and engulfed by phagocytic leucocytes bearing C3b or C4b receptors on their surfaces.

Table 2 Complement receptors

Protein	Specificity	Structure	Cell type(s)	Key features
Cell surface proteins				
CR1	C3b, C4b, iC3b, C3c	4 allotypes: 160 kDa 190 kDa 220 kDa 250 kDa	Erythrocytes, eosinophils, monocytes, macrophages, neutrophils, B and some T lymphocytes, glomerular podocytes, follicular dendritic cells, mast cells, polymorphonuclear cells	Member of RCA family Accelerates dissociation of CP and AP C3 convertases Cofactor for factor I Helps to process immune complexes Involved in phagocytosis
CR2	iC3b, C3dg, EBV gp350	140 kDa	B cells, T cells, follicular dendritic cells	Member of RCA family Plays a role in immunoregulation
CR3	iC3b, C3dg	170 kDa α chain 95 kDa β chain	Polymorphonuclear cells, monocytes, natural killer cells, some B and T lymphocytes	Member of the leucocyte–integrin family Involved in phagocytosis of iC3b-coated particles, adhesion of neutrophils, cytotoxicity of cells bearing activated complement components
CR4 (p150, 95)	iC3b	150 kDa α chain 95 kDa β chain	Monocytes, macrophages, NK and ADCC effector lymphocytes, neutrophils	Functions in cell adhesion
C3aR	C3a, C4a	95 kDa	Mast cells, neutrophils, basophils, monocytes, T lymphocytes, eosinophils	Depending on cell type, functions include chemotaxis, chemokinesis, cell aggregation and adhesion, release of lysosomal contents, may play a role in immunoregulation
C5aR	C5a	43 kDa	Neutrophils, eosinophils, monocytes, macrophages, liver parenchymal cells, lung vascular smooth muscle and endothelial cells, bronchial and alveolar epithelial cells, astrocytes	Depending on cell type, functions include directed chemotaxis, cell adhesion and aggregation, release of granular enzymes and histamine Augments the humoral and cellular responses
C3eR	C3dk, C3e	Not characterized	Neutrophils, monocytes	Lysosomal enzyme release, leucocytosis
DAF	C3b,Bb, C4b,2a	75 kDa	Erythrocytes, all leucocytes, platelets	Accelerates decay of CP and AP C3 convertases
MCP	C3b, iC3b, C4b	45–70 kDa	Neutrophils, monocytes, platelets, reticulocytes, most lymphocytes, granulocytes, endothelial cells, epithelial cells, mesenchymal cells	Member of RCA family Cofactor for factor I Does not accelerate decay of C3 convertases
CD59	C8, C9	18–20 kDa		Inhibits MAC on host cells
Undefined	C3 (β chain)		Neutrophils, eosinophils	Eosinophil cytotoxicity inhibitor Inhibitor of neutrophil adherence

CP, classical pathway; AP, alternative pathway; RCA, regulators of complement activation; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; DAF, decay-accelerating factor; MCP, membrane cofactor protein.

Lysis of foreign material

After deposition of C3b or C4b onto the surface of a microorganism, the microorganism can be lysed by the insertion of the MAC into its cell membrane. This process disrupts the integrity of the cell lipid membrane bilayer, killing the microorganism by osmotic lysis.

Inflammatory processes

Complement activation results in the generation of the C3a, C4a and C5a anaphylotoxins. The effect of these molecules is mediated through specific receptors present on the surface of various cell types (**Table 2**). The overall role of these anaphylotoxins is to recruit cells that play particular roles in inflammation, as well as to trigger their responses. C3a, C4a and C5a generally induce an increase in vascular permeability (allowing cells to reach the place of injury) and smooth muscle contraction. Activation of mast cells by these three anaphylotoxins results in the release of various mediators with similar activities. C5a is much more active than C3a and C4a and induces degranulation and respiratory burst activation in neutrophils. In addition, C5a promotes the production of prostaglandins and eicosanoids.

Solubilization and clearance of immune complexes

Clearance of immune complexes is necessary to prevent damage to autologous tissue resulting from complement activation. Activation of complement through the classical pathway inhibits the formation of precipitating antigen–antibody complexes. The alternative pathway is responsible for the solubilization of precipitated antigen–antibody complexes. In humans the immune complexes with deposited C3 are cleared from the circulation by erythrocytes through binding to CR1 present on their surfaces. Macrophages from the liver and spleen remove and degrade the complexes present on the surface of the erythrocytes without affecting the erythrocyte integrity. In some autoimmune diseases (such as lupus erythematosus) the formation and deposition of immune complexes can be massive, and in such cases the action of complement can damage the surface of the cells on which the complexes are present.

Bridging innate and adaptive immune responses

Complement plays a fundamental role in mediating and enhancing humoral immunity. As a result of complement activation, foreign particles acquire C3b or C3 fragments which are covalently bound to their surfaces. These particles are taken up by complement receptors (CR1, CR2) present on many antigen-presenting cells (APCs), including B lymphocytes, which process the antigens and present them on MHC class II molecules to T cells. Complement is important for the formation of memory B cells, as has been shown by the CR2-mediated localization and retention of immune complexes by germinal centres. It has also been demonstrated that coligation of the C21(CR2)/CD19/TAPA-1 coreceptor with the B-cell antigen receptor (BCR) lowers by 10- to 100-fold the quantity of antigen required for B-cell activation. For example, when an antigen is coupled to the C3d fragment (the protein of C3 containing the thioester site), the antibody response is dependent upon binding of C3d to CR2 and is greatly enhanced; in fact, C3d acts as a natural adjuvant, bridging the innate with the acquired immune response, through CR2. Complement, furthermore, has also been found to play an important role in B-cell tolerance.

Complement Deficiencies

Deficiencies of specific complement components have been identified in the classical, alternative and terminal pathways, as well as in regulatory proteins and complement receptors.

Deficiencies in classical pathway complement components

Deficiencies in C1q, C1r, C1s, C2 (the most common) or C4 produce deficiencies in classical pathway activation. A common disorder that is associated with of all these deficiencies is the autoimmune disease systemic lupus erythematosus (SLE). SLE is thought to develop as a consequence of the defect in clearing immune complexes that occur in individuals with classical pathway deficiencies. C2 and C4 deficiencies are not necessarily correlated with increased infections, implying that the alternative and/or lectin pathways are sufficient for the elimination of most foreign microorganisms. However, deficiencies in C3 are normally associated with a higher susceptibility to infection. In addition, C3 deficiencies are also associated with glomerulonephritis, a pathologic condition characterized by kidney damage resulting from complement activation that has been stimulated by the presence of immune complexes in the basement membranes of blood vessels in the renal glomerulus. This pathology reflects the importance of C3 in immune complex clearance. In general, C3 deficiencies (and any deficiency that results in a defect in C3 activation or deposition on foreign particles), produce an impairment of the immune response to T-cell-dependent and T-cell-independent antigens.

Deficiencies in alternative pathway

These deficiencies are less common than those of classical pathway components. Deficiencies in properdin (the most common of the alternative pathway deficiencies) and factor D result in abnormal activation of the alternative pathway. Recurrent infections are not common in individuals with a deficiency of only one protein of the alternative pathway, but have been observed in individuals with various factor D deficiencies. Meningococcal infections are the most frequently detected in alternative pathway deficiencies.

Deficiencies in late components

Deficiencies of any of the late complement components leads to inability to form the MAC, which results in failure to kill foreign pathogens by complement-mediated lysis. The infections most frequently associated with deficiencies of late components, with the exception of C9, are meningococcal or gonococcal infections.

Deficiencies in complement regulatory proteins and complement receptors

Deficiencies in C1 inhibitor, factor I and factor H are commonly associated with regulation problems in the alternative or classical pathways of complement activation, and in C3 consumption. C1 inhibitor deficiency is associated with the development of hereditary angioneurotic oedema, which is characterized by the accumulation of oedema fluid in skin and mucosa. Factor I and H deficiencies are characterized by a complete consumption of C3 from plasma, as a result of a continuous formation of fluid-phase C3 convertase. Consequently, individuals become more susceptible to infection by pyogenic bacteria. Impairment in the clearance of immune complexes in these deficiencies leads to glomerulonephritis.

Deficiencies in membrane regulators such as DAF and CD59 produce a deregulation of C3 convertase activity and a higher susceptibility of erythrocytes to complement-mediated lysis. Paroxysmal nocturnal haemoglobinuria (PNH) is a disease associated with DAF and CD59 deficiencies and is characterized by erythrocyte lysis throughout the vascular system, leading to chronic haemolytic anaemia and venous thrombosis, among other disorders. Deficiencies in CR3 and CR4 are associated with the disease known as leucocyte adhesion deficiency, which results in recurrent pyogenic infections.

Further Reading

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