

Complement

M Claire H Holland, *University of Pennsylvania, Philadelphia, Pennsylvania, USA*

John D Lambris, *University of Pennsylvania, Philadelphia, Pennsylvania, USA*

The mammalian complement system consists of a complex group of more than 35 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, clearance of apoptotic cells and promotion of humoral immune responses.

Introduction

The existence of the complement system was first recognized close to 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. **See also:** Bordet, Jules Jean Baptiste Vincent; Ehrlich, Paul; History of immunology

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 non-complement 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 capable of interacting with its ligands. After activation, the C3 molecule can be inactivated to avoid self-damage, or becomes covalently attached to target surfaces where it leads to either opsonization, or cytolysis through the sequential activation of the membrane attack complex (MAC). C3 is one of the most abundant proteins in serum, its concentration generally ranging from 1.0 to 1.5 mg mL⁻¹. Most of the soluble complement proteins, including C3, are synthesized in the liver by hepatocytes, but other cell types can also be significant sources (see **Table 1**).

Introductory article

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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 at a low level of steady-state activation as a result of the hydrolysis of the thioester group of native C3, which leads to the formation of hydrolysed C3 (**Figure 2**). This low level of activation or ‘tickover’ allows the complement system to be quickly activated when potential pathogens are encountered. It is also necessary due to the short half-life of the active form of C3.

Once formed, C3(H₂O) is able to bind to factor B, the catalytic subunit of the alternative pathway, in the presence of Mg²⁺. Bound factor B is proteolytically activated and cleaved by a second serine protease, factor D, into the Bb (66 kDa) and Ba (33 kDa) fragments. The resulting complex (C3b, Bb) serves as the alternative pathway C3 convertase, which cleaves native C3 into C3a (10 kDa) and C3b. Release of the C3a fragment allows the C3b fragment to covalently bind to the surface of nearby activating particles via its metastable thioester bond (**Figure 2**). The smaller C3a anaphylatoxic fragment plays important roles in inflammatory processes (see later in this chapter). Most of the fluid-phase C3b, as well as the C3(H₂O), is instantaneously inactivated by factor I, in the presence of cofactor regulatory molecules (complement receptor 1 (CR1), factor H, membrane cofactor protein (MCP)). The surface-bound C3b, however, 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 newly generated C3b forms a new C3 convertase (C3b, Bb), which, stabilized by properdin, leads to the cleavage of more C3 molecules. Another enzyme complex, termed the C5 convertase (C3b, Bb, 3b), is

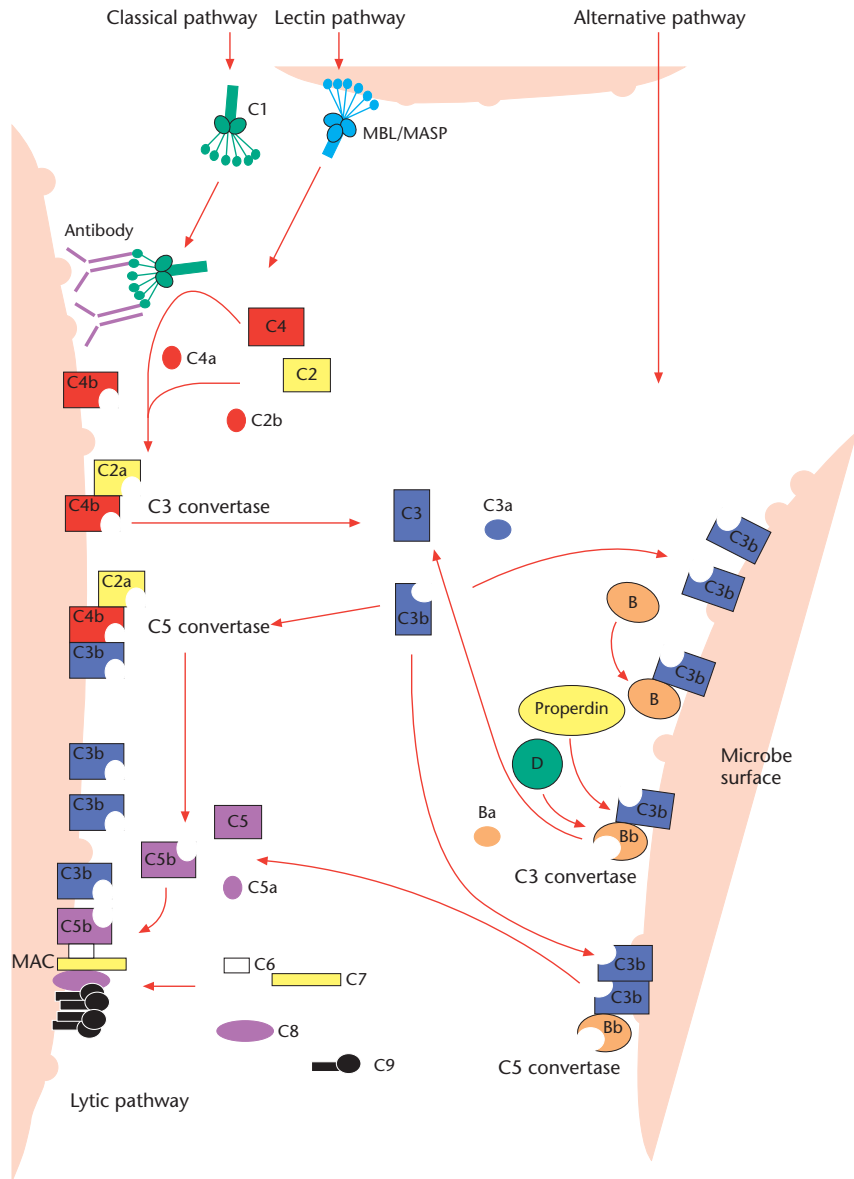


Figure 1 Schematic representation of the three complement activation pathways.

formed when a C3b molecule binds to the C3 convertase (C3b, Bb, 3b). The C5 convertase cleaves C5 into the active C5a and C5b fragments (**Figure 1**). The C5a anaphylatoxin is a potent mediator of inflammatory responses, while the C5b fragment is responsible for initiating the self-assembly of the MAC (lytic pathway), as will be discussed later. 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 regulatory molecule to C3b) will occur. **See also:** Complement: alternative pathway

Classical Pathway

Activation of the system by the classical pathway is primarily dependent on the immunoglobulins (IgM or IgG) present in immune complexes (**Figure 1**). However, it can also be activated by acute-phase proteins such as ligand-bound C-reactive protein or directly by certain viruses, bacteria and virus-infected cells. Binding of the C1q subunit of the Ca^{2+} -dependent C1 complex to this immunoglobulin leads to the activation of the C1r and C1s serine protease subunits of the C1 complex. Once activated, the C1s cleaves C4 into C4a and C4b. Since one molecule of

Table 1 Alternative, classical and lectin pathway proteins

Protein	Structure	Concentration ($\mu\text{g mL}^{-1}$)	Cellular sources	Key function
<i>Alternative pathway</i>				
Factor B	93 kDa	210	Hepatocyte, 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 ₂ O)
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	Hepatocyte, mononuclear phagocytes, epithelial and endothelial cells, adipocytes, fibroblasts	Activated C3 (C3b) covalently binds to activating surfaces and mediates phagocytosis and cytolysis. C3a is an inflammatory peptide It forms part of the C3 and C5 convertases Component of both alternative and classical pathways
Factor H	150 kDa	500	Hepatocyte, 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	Hepatocyte, mononuclear phagocytes, myoblasts, adipocytes, fibroblasts, B cells	C4b/C3b inactivator
<i>Classical pathway</i>				
C1q (462 kDa)	Hexamer: subunit contains ((x1)A + (x1)B + (x1)C) (x6) 26.5 kDa A chains (x6) 26.5 kDa B chains (x6) 24 kDa C chains	80	Hepatocyte, mononuclear phagocytes, fibroblasts, gastrointestinal epithelial cells	Binds to IgM or IgG or 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

Continued

Table 1 Continued

Protein	Structure	Concentration ($\mu\text{g mL}^{-1}$)	Cellular sources	Key function
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
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
<i>Lectin pathway</i>				
MBL (192-582 kDa)	Dimer to hexamer: sub- unit contains (x3) 32 kDa chain	1-4	Hepatocytes, astrocytes, kidney	Binds to mannans of microorganisms and initiates activation through the lectin pathway
MASP1	83 kDa	6	Hepatocytes, astrocytes	May be involved in the direct cleavage of C3
MASP2	83 kDa	6	Hepatocytes	Cleaves C2, C4
MASP3	105 kDa		Hepatocytes (?), astrocytes	Unknown, product of alternative splicing of MASP1
sMAP/MAP19	19 kDa			Unknown, truncated form of MASP2
<i>Late components</i>				
C5	110 kDa α chain 75 kDa β chain	75	Hepatocytes, mononuclear phagocytes, T/B lymphocytes, fibroblasts, epithelial, astrocytes	Initiates the assembly of MAC (C5b) and is involved in inflammatory processes (C5a)
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.

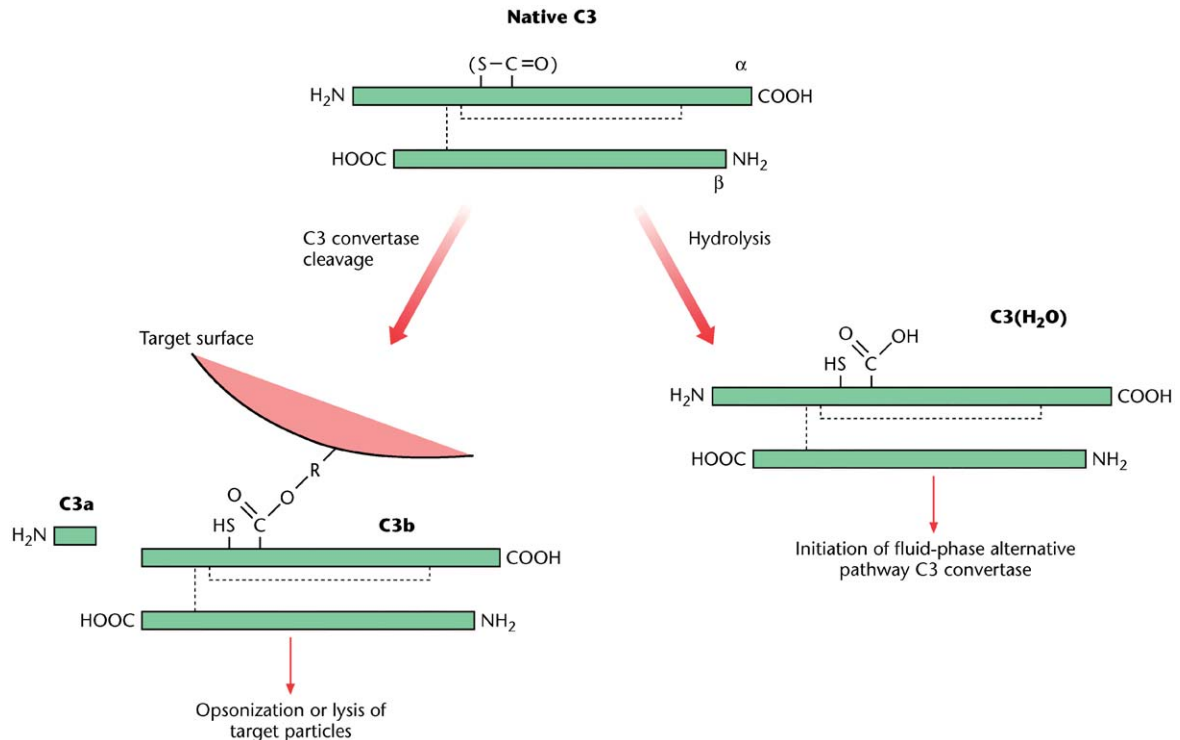


Figure 2 Native C3 is activated as a result of hydrolysis or C3 convertase cleavage. Hydrolysis of the protected, unreactive thioester bond in native C3 induces a conformational change that allows factor B to bind, resulting in the initiation of the alternative complement activation pathway. Cleavage of native C3 by the C3 convertase results in the release of the C3a fragment and the resulting conformational change of the remaining C3b molecule allows the thioester bond to react with target surfaces (e.g. microbes), leading to opsonization or lysis of the target cells. Dotted lines inside the C3 molecule indicate the presence of disulfide bonds.

activated C1s can cleave many C4 molecules, this step provides an important amplification mechanism of complement activation. Similar to C3b, C4b contains a thioester bond that can attach covalently to microbial surfaces via hydroxyl or amino groups present on their surface. The result of this antibody-mediated activation of the C1 complex is an aggregation of C4b molecules surrounding the antibody–C1 site. C2 is another serine protease cleaved by C1s, and the C2a fragment binds surface-bound C4b to form the classical pathway C3 convertase (C4b, 2a). Similar to the alternative pathway C3 convertase, this complex cleaves off the C3a fragment of C3, so that the resulting C3b fragment can be deposited on to the target surface. Surface-bound C3b serves as an opsonin (“tag”) and increases phagocytosis by binding to specific receptors on the surface of phagocytic cells. In addition, it can form a complex with the C3 convertase to give rise to the classical pathway C5 convertase (C4b, 2a, 3b), which cleaves C5 into C5a and C5b (lytic pathway). Thus, the classical pathway of complement activation provides a mechanism for linking adaptive (antibodies) and innate (complement) immune responses, and allows complement to serve as an important antibody effector mechanism. **See also:** Antibody classes; Complement: classical pathway

Lectin Pathway

The lectin pathway involves the recognition of specific carbohydrate groups, such as mannose and *N*-acetyl-glucosamine (GlcNAc), present on microbial surfaces by mannose-binding lectin (MBL), and the subsequent activation of the MBL-associated serine proteases (MASP1, MASP2 and MASP3) (Figure 1). Another nonprotease molecule, small MBL-associated protein (sMAP), has also been shown to be associated with MBL. The overall structure of the MBL/MASPs resembles that of the C1q/C1rC1s complex discussed earlier, and activation of both complexes leads to the proteolytic cleavage of C4 and C2, and the formation of the classical pathway C3 convertase (C4b, 2a). The enzyme component primarily involved in the C4 and C2 cleavage is MASP2. Although the enzymatic activity of MASP1 is generally low, it has been suggested to play a role in the direct cleavage of C3. The functions of MASP3 and sMAP are still unknown. Besides MBL, another group of carbohydrate-binding proteins called ficolins have been shown to activate the lectin pathway through association with MASPs, and these molecules have a similar overall structure to C1q and MBL. **See also:** Lectins

Lytic Pathway

All three pathways of activation converge to the production of the C5 convertase, which cleaves C5 into C5a and C5b, with the C5b initiating the self-assembly of the 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 (Figure 1). 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 ‘pores’ that are characteristic for 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. Similar to the classical and alternative pathways of complement activation, pore formation by the MAC is also under the control of serum and membrane regulatory proteins. It is interesting to note that the deposition of small quantities of MAC (sublytic MAC) on nucleated host cells mediates various responses related to cell cycle regulation, cell activation and cell survival. **See also:** Complement: terminal pathway

Phylogeny of the Complement System

It has now become clear that the complement system first arose in invertebrate species more than 600 million years ago. Several complement genes and proteins have been identified in 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 only C3, factor B and D or C3, MASP and MBL) with limited functions (e.g. only the opsonization of foreign material and C3a-mediated inflammatory responses). The classical pathway did not emerge until the antibodies first appeared in the cartilaginous fishes (e.g. sharks, rays). The lytic pathway may have first appeared in this group of primitive vertebrates, although a C6-type molecule has been identified in the amphioxus, suggesting that at least some of the components of the lytic pathway were already present before the evolution of the fishes. The functional and structural complexity that characterizes the complement system in modern vertebrate species arose from these few components, probably as a result of gene duplication and exon shuffling (Table 1).

The C3, C4 and C5 molecules are believed to be derived from a common ancestor gene, maybe the serum proteinase inhibitor α -2 macroglobulin, which is also present in

invertebrates. The primary sequences, structure and genomic organizations of the three components are very similar. All three molecules comprise individual chains (α - β in C3 and C5 and α - β - γ in C4), which are held together by single disulfide bonds. The C1s/C1r/MASPs appear to have descended from a common ancestor, since they possess similar domain/module structures and functional activities. Similarly, Bf/C2, which are both located in the major histocompatibility (MHC) class III region, and the members of the lytic pathway (C6/C7/C8/C9) are believed to each share common ancestry. Interestingly, teleost fish and birds (chickens) are known to possess a protein that seems to play the roles of both factor B and C2, suggesting that the gene duplication that gave rise to the individual C2 and Bf proteins occurred more recently. **See also:** Major histocompatibility complex (MHC)

Regulatory Proteins of Complement Activation

Complement activation can result in serious damage to cells, and it is of crucial importance that self-cells are protected from autologous attack. Therefore, complement activation is regulated by a number of regulatory proteins that, (1) degrade C3b and C4b into fragments that are incapable of participating in the complement amplification cascades, (2) disassemble the C3 convertases, (3) disrupt MAC assembly and (4) inactivate the C3a and C5a anaphylatoxins. Many of these regulatory and coregulatory factors mainly comprise short-consensus repeats (SCRs). SCRs, also called complement control modules (CCM), are tandem structural units of approximately 60–70 amino acids that contain two internal disulfide bonds. Complement regulatory proteins are expressed by almost all cell types and include soluble as well as membrane-bound proteins and complement receptors (see also Tables 1 and 2). Some of the complement components discussed earlier, such as factor B, C2, C1r/C1s, and MASPs also contain these SCR domains.

Serum-soluble regulatory proteins

Factor I is a serine protease that cleaves C3b at several positions, when in the presence of the cofactor molecules – factor H, MCP or CR1. The first C3 fragment that is generated after factor I cleavage is iC3b. This molecule is further cleaved by factor I into C3c and C3dg. Since C3dg contains the thioester site, this fragment maintains its covalent association with the surface to which it is attached, while the C3c fragment, containing the β chain and remainder of the α chain, is liberated. The C3dg fragment is further cleaved by other proteases to produce C3d and C3g, with the C3d fragment playing an important role in adaptive immune responses (CR2-mediated, see below).

Table 2 Complement receptors

Protein	Specificity	Structure	Cell type(s)	Key features
<i>Cell surface proteins</i>				
C1qRp (CD93)	C1q, MBL, SPA	126 kDa	Endothelial cells, platelets, neutrophils, glial cells, monocytes	Mediates phagocytosis of C1q-opsonized apoptotic cells, immune complexes and pathogens May play a role in leucocyte–endothelial cell interactions
cC1qR/CRT	C1q, MBL, SPA	46 kDa	Monocytes	Mediates phagocytosis of C1q/MBL-opsonized apoptotic cells
gC1qbp	C1q (MBL)	33 kDa	Platelets, mast cells	Function mainly unknown. May play a role in C1q mediated enhancement of P selectin by platelets and chemotaxis of mast cells
CR1	C3b, C4b iC3b, C3c, C1q, MBL	Four allotypes 160 kDa 190 220 250	Erythrocytes, eosinophils, monocytes, macrophages, neutrophils, B and some T lymphocytes, glomerular podocytes, follicular dendritic cells, mast cells, polymorphonuclear cells	Member of RCA, accelerates dissociation of CP and AP C3 convertases, cofactor for factor I, helps processing immune complexes, involved in phagocytosis of C3- and C1q-opsonized particles
CR2	iC3b, C3dg EBV gp 350	140 kDa	B cells, T cells, follicular dendritic cells	Member of RCA 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	Involved in phagocytosis of iC3b-coated particles, adhesion of neutrophils, cytotoxicity of cells bearing activated complement components, member of leucocyte integrins
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, eosinophils, basophils, monocytes/macrophages, T lymphocytes, platelets, bronchial and alveolar endothelial and epithelial cells, astrocytes and microglia	Depending on cell type, functions include chemotaxis, chemokinesis, cell aggregation and adhesion, release of lysosomal contents, may play a role in immunoregulation and haematopoiesis

Continued

Table 2 Continued

Protein	Specificity	Structure	Cell type(s)	Key features
C5aR	C5a, C5adesArg	40–55 kDa	Neutrophils, eosinophils, basophils, monocytes, macrophages, mast cells, liver parenchymal cells, lung vascular smooth muscle and endothelial cells, epithelial cells, astrocytes and microglia, dendritic cells, mesangial cells	Depending on cell type functions include chemotaxis, cell adhesion and aggregation, release of granular enzymes, superoxide anions and histamine, augments the humoral and cellular responses
C5L2	C5a, C5adesArg (possibly C3a, C4a and desArg products)	37–45 kDa	Immature dendritic cells, polymorphonuclear cells, monocytes, skin fibroblasts, adipocytes	Function unclear, may serve as a decoy receptor for C5a and mediate the acylation-stimulating properties of C3a-desArg
DAF	C3b, Bb C4b, 2a	75 kDa	Erythrocytes, all leucocytes, platelets	Lysosomal enzyme release, leucocytosis 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, cofactor for factor I, does not accelerate decay of C3 convertases
CD59	C8, C9	18–20 kDa	Widely expressed, all circulating cells, vascular endothelium, epithelial cells	Inhibits MAC on host cells
Undefined	C3 (β chain)		Neutrophils, eosinophils	Eosinophil cytotoxicity inhibitor of neutrophil adherence

CP, classical pathway; AP, alternative pathway; RCA, regulators of complement activation.

Factor H is a single polypeptide composed of 20 SCRs. It downregulates the amplification of the alternative pathway by acting as a cofactor for factor I in the first two factor I cleavages, or by binding to surface-bound or fluid-phase C3b and accelerating the decay of the C3b, Bb convertase. MCP and CR1 are membrane-bound proteins and will be discussed below. Factor I is also capable of cleaving C4b in the presence of C4 binding protein (C4bp), CR1, factor H and MCP. By serving as a cofactor for factor I, C4bp regulates the formation of the classical pathway C3 convertase. C4bp is composed of seven α chains and one β chain, which are linked by disulfide bonds and form a spider-like structure. The α and β chains are composed of eight and three SCRs, respectively.

Another regulator of the classical pathway is C1 inhibitor (C1-INH). This protein blocks the proteolytic activity of C1r and C1s. It is part of the serine protease inhibitor or serpin superfamily and lacks any characteristic modular structure.

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.

Carboxypeptidase N, also termed anaphylatoxin inactivator, and carboxypeptidase R cleave off the C-terminal arginyl residue of C3a, C4a and C5a. The resulting desArg derivatives of these anaphylatoxins generally possess reduced activities.

Membrane-bound proteins

Decay-accelerating factor (DAF or CD55) and MCP (or CD46) have similar structures, and downregulate complement activation to protect self-tissues from attack by complement. DAF contains four SCRs and 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. Similar to DAF, MCP contains four SCRs, but it differs from DAF in that it serves as a cofactor for factor I-mediated cleavage of surface-bound C3b and C4b. However, 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

Besides its role in the initiation of the classical pathway, C1q functions as an opsonin and plays a crucial role in the

removal of apoptotic cells, as well as immune complexes and pathogens. It may also be able to trigger several other cellular responses, such as chemotaxis, cytotoxicity and cytokine release. Four cell-associated molecules (C1qRp, CR1, cC1qR and gC1qbp; see **Table 2**) have been implicated in C1q binding; however, the nature of the binding interactions and their *in vivo* functions are still under debate.

C3/C4 receptors

Complement receptor type 1 (CR1 or CD35) is a transmembrane glycoprotein that contains 30 SCRs and is present on a wide variety of cells (**Table 2**). It functions mainly as a receptor for C3b and C4b, although it binds with lesser affinity to iC3b and C3c. More recently, it has been demonstrated that CR1 also binds C1q (and MBL) at a site distinct from the C3b binding site. Multivalent C3b binds CR1 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 convertases. (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. **See also:** Glycoproteins

Complement receptor type 2 (CR2, CD21 or C3d/EBV receptor) is a membrane glycoprotein containing 15–16 SCRs that binds the iC3b, C3dg and C3d fragments of C3. Epstein-Barr virus binds this receptor via one of its envelope glycoproteins (gp350), and requires the receptor for its pathogenicity. CD23, a low-affinity receptor for IgE, also binds CR2, an interaction that may influence the survival of B cells in germinal centres. CR2 plays a role in the regulation of B-cell function and is involved in antibody responses to T-cell-dependent and -independent antigens. **See also:** B lymphocytes; *Epstein-Barr virus*; Phagocytosis: enhancement

Complement receptor type 3 (CR3, CD11b/CD18) is an adhesion molecule belonging to the leucocyte-integrin family. Unlike CR1 or CR2, it does not contain any SCR modules. 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 Fc γ receptor III, *Leishmania* promastigote surface glycoprotein gp63, and others. When iC3b serves as a ligand, CR3 mediates phagocytosis of microorganisms, respiratory burst and degranulation of phagocytes, and enhances natural killer (NK) cell activity for C3-coated targets. **See also:** Integrins: Signalling and disease

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 some of its properties may be similar to those of CR3.

Anaphylatoxin receptors

C3a and C5a anaphylatoxin receptors are members of the superfamily of rhodopsin-type receptors, which contain seven transmembrane loops. C3aR and C5aR are involved in a variety of processes, including chemotaxis, cell aggregation and adhesion, and leucocyte granule release. A third receptor, C5L2, has been identified that binds C5a and C5a-desArg (and possibly also C3a and C4a), but its function is still unclear. **See also:** Complement receptors

Functions of the Complement System

Activation of the complement system results in the initiation of various biological processes some of which have already been mentioned earlier in this paper. In this section, we will discuss these functions in detail.

Opsonization of foreign material

This process involves the ‘tagging’ or ‘coating’ of viruses, bacteria, fungi, apoptotic cells and other particles in order to facilitate phagocytosis by leucocytes. C3 and C4 play important roles in this process, since the deposition of C3b and C4b on cell surfaces leads to the recognition of the opsonized particle by phagocytic leucocytes expressing the complement receptors CR1 and CR3. Binding of the covalently attached C3b (or C4b) molecules to these receptors results in the engulfment and destruction of the opsonized particles. In some cases, other stimulatory signals are needed to accelerate complement-mediated phagocytosis. C1q and MBL also have opsonizing capabilities, and are involved in the clearance of apoptotic cells, immune complexes and pathogens. **See also:** Neutrophils

Lysis of foreign material

After deposition of C3b or C4b on to foreign cells, these targets can be lysed via the formation of the MAC on its cell membrane. This process disrupts the integrity of the cell lipid membrane bilayer, killing the cell by osmotic lysis. Other mechanisms, such as the influx of Ca^{2+} and loss of ATP have also been implicated in the demise of target cells. Nucleated cells are generally more difficult to lyse than enucleated cells, such as erythrocytes. Due to the thick protective coat of Gram-positive bacteria, MAC deposition on these cells is without consequence. However, lysis by MAC is a major route for killing of Gram-negative bacteria, such as those of the genus *Neisseria*.

Solubilization and clearance of immune complexes

Clearance of immune complexes is necessary to prevent complement activation and, consequently, damage to self-tissues. 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 C3- (and C1q) opsonized immune complexes 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 systemic lupus erythematosus (SLE)) 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 these complexes are present. **See also:** Autoimmune disease; Macrophages; Systemic lupus erythematosus

Inflammatory processes

Complement activation results in the generation of the C3a, C4a and C5a anaphylatoxins. The C3a and C5a anaphylatoxins are the most studied of the three, and their effects are mediated through specific receptors present on the surface of various cell types (Table 2). Generally C5a is the most potent of the two. The overall role of these molecules is to recruit inflammatory cells, such as neutrophils and macrophages, to the site of injury, a process known as chemotaxis, and to trigger their responses. Both C3a and C5a are capable of increasing vascular adhesion and permeability (allowing cells to reach the place of injury) and inducing smooth-muscle contractions. Activation of mast cells, neutrophils and macrophages by the anaphylatoxins can result in the release of superoxide anions (respiratory burst), specific enzymes and various other important mediators, such as prostaglandins and cytokines. Due to their potent inflammatory activities, the anaphylatoxins have been implicated in several vascular, pulmonary, autoimmune, regenerative and degenerative neurological conditions. **See also:** Inflammation acute; Mast cells

Bridging innate and adaptive immune responses

Complement plays a fundamental role in mediating and enhancing humoral immunity. C3-opsonized particles are taken up by complement receptors (CR1, CR2) present on antigen-presenting cells (APCs), such as dendritic cells and B lymphocytes, which process the antigens and present them complexed to 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 C3-opsonized immune complexes by germinal centres. It has also been demonstrated that coligation of the CR2 complex (which includes CR2, CD19 and TAPA-1) with the B-cell antigen receptor (BCR) lowers the quantity of antigen required for B-cell activation by 10- to 100-fold. For example, when an antigen is coupled to the C3d fragment (the C3 fragment 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. Furthermore, complement has also been found to play an important role in B-cell tolerance, and through the actions of the C5a anaphylatoxin may modulate T-cell responses. **See also:** Antigen-presenting cells; B lymphocytes; B Lymphocytes: receptors; Immunological memory; Major histocompatibility complex (MHC); T lymphocytes: cytotoxic; T lymphocytes: helpers

Other functions of complement proteins

Recently, it has become evident that complement components may exert functions not directly related to immune or inflammatory processes. For instance, complement proteins have been shown to play important roles in skeletal (C1qRp and C3) and vascular (C1qRp and C3a) development, tissue regeneration (C3a and C5a), normal reproduction (C3, complement regulatory proteins and CRs), haematopoiesis (C3a), neuronal and CNS development (C5a and CRs), and cell proliferation and apoptosis (C3a, C5a and sublytic MAC). These novel functions demonstrate the existence of functional links between the innate immune system/complement and other cellular networks that influence normal developmental pathways.

Complement Deficiencies

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

Deficiencies in classical and lectin 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 all of these deficiencies is the autoimmune disease SLE. SLE is thought to develop as a consequence of the defect in clearing immune complexes that occur in individuals with classical pathway deficiencies. C1q deficiency has been associated with an accumulation of apoptotic cells, which, when not cleared

efficiently, can provide a source of autoantigens that drive the autoimmune responses seen in SLE. A deficiency in MBL has been associated with an increased susceptibility to various infections, and may affect the course of several noninfectious diseases, such as cystic fibrosis and rheumatoid arthritis. C2 and C4 deficiencies are not necessarily correlated with increased infections, implying that the alternative 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 -independent antigens. **See also:** Antigens; Glomerulonephritis; Systemic lupus erythematosus

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 lead 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 (*Neisseria* spp.). **See also:** Immune mechanisms against extracellular pathogens

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. 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. Deficiency in factor H has also been associated with an atypical form of haemolytic uraemic syndrome (factor H-associated HUS).

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. **See also:** Complement regulatory proteins; Complement: measurement

Further Reading

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