Complement: Alternative Pathway

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Secondary article

Article Contents

The alternative pathway of complement is a powerful and evolutionarily old defence system of innate immunity that inactivates invading microorganisms and pathogens. For survival in an immunocompetent host microbes, viruses, pathogens or modified tissue cells must provide means to interfere with and control alternative pathway reactions at several levels.

Introduction

The alternative pathway, the phylogenetically oldest and most important activation pathway of the complement system, provides a highly e cient defence mechanism against invading microorganisms and bacteria. Formation of C3b occurs spontaneously and continuously, while the further activation of this central component is tightly controlled by a large number of both soluble and membrane-bound regulatory proteins. These regulators restrict activation to the surface of foreign cells and microorganisms and simultaneously protect self cells from the destructive e ects of this defence system. If left uncontrolled, the activated alternative pathway deposits C3b molecules on the surface of infectious agents (microorganisms) to prepare them for phagocytosis or lysis, and the activation products (chemotactic anaphylatoxins) induce inflammatory reactions by recruiting and stimulating immune e ector cells.

Description of Pathway

The alternative pathway of complement is a host defence system that assists in maintaining the integrity of an organism by inactivating invading organisms, pathogens and modified tissue cells.

Activation

Activation of the pathway starts in the fluid phase, in plasma, by a spontaneous conformational change of C3 which leads to the formation of an enzyme complex that cleaves further C3 molecules and sets in motion an amplification reaction leading to complement activation and deposition of a large number of C3b molecules on the cell surface.

A cleaved and activated C3b molecule is highly reactive and covalently interacts with any molecule in its vicinity. Attachment allows powerful amplification reactions by the formation of C3b-generating enzymes, i.e. C3 convertases, that use plasma C3 as a substrate. This positive feedback amplification loop generates increasing amounts of surface-bound C3b in the close vicinity of the initial enzyme. On foreign particles, unrestricted activation leads to the powerful initiation of the complement cascade, while on self cells and tissues these reactions are tightly controlled by inhibition of enzyme complex formation and inactivation of deposited molecules.

Initiation

Activation of C3 is pivotal and central to the alternative pathway. It is initiated by a spontaneous and continuous turnover of fluid-phase C3, which is present in plasma in a high concentration of 1.5 mg mL^{-1} (Lambris, 1988). In human plasma, formation of C3(H_2O) (also known as iC3), a molecule with a 'C3b'-like function, occurs slowly (0.005% per min) and results from a spontaneous reaction of the internal thioester bond with water. This tickover mechanism generates a 'C3b-like molecule' which has the C3a part attached to the α chain and can associate with factor B. After enzymatic cleavage the active Bb fragment remains attached to C3(H_2O), forming the initial C3 convertase C3b(H_2O)Bb of the alternative pathway. This spontaneously formed C3(H_2O)Bb molecule can generate metastable C3b, a molecule which has the C3a part removed and which exposes the highly reactive internal thioester. The reactive C3b molecule has the ability to form covalent bonds between its internal thioester and any adjacent molecule.

The rapid activation and amplification of C3b is restricted to the vicinity of newly formed molecules. Most of the thioester bonds of the activated C3(H_2O) interact with water and are not further active, but a small fraction interacts with nearby molecules and cell surfaces. These covalently attached C3 molecules can form functional C3 convertases, allowing the activation and amplification of the pathway. While the initial reaction occurs at a low rate, it proceeds continuously and an amplification reaction

triggered by the activated C3(H_2O) molecules induces alternative complement pathway activation. A large number of regulatory proteins present in the fluid phase and on cell surfaces control the fate of the newly generated C3 molecules. They allow activation to proceed at the surface of pathogens and microorganisms, but inactivate this powerful and destructive system on the surface of host cells.

Generation of AP convertase

If left uncontrolled, C3b associates in the presence of Mg^{2+} ions with factor B, a serine protease. Factor B attached to the C3(H_2O) complex becomes accessible for another serine protease, factor D, and is cleaved to the fragments Ba (30 kDa) and Bb (60 kDa). The smaller cleavage product, Ba, is released, while the larger Bb fragment remains attached to C3(H_2O). The C3(H_2O)bBb complex forms the initial alternative complement C3 convertase, which in the presence of C3, factors B and D and Mg^{2+} ions catalyses the cleavage of native C3 molecules to C3a and C3b. The newly generated C3b also associates with factors B and D and forms AP C3 convertase C3bBb. This proteolytic protein complex sets in motion the amplification of the alternative complement pathway by formation of more metastable C3b molecules, building further C3bBb convertases, resulting in the surface deposition of C3 molecules, or allowing the formation of C5 convertases, which initiate the lytic pathway. Thus a feedback amplification loop initiated by a spontaneously formed alternative complement pathway convertase allows the formation of a large number of C3b molecules and a powerful amplification of the pathway (**Figure 1**).

Stabilization

Under physiological conditions, the C3bBb complex is rather unstable and dissociates irreversibly with a half-life of about 90 s. However, *in vivo*, the complex is stabilized by properdin (factor P) which increases the half-life of the protein complex about 10-fold (Pillemer *et al*., 1954). The action of properdin is mimicked *in vitro* by Ni^{2+} ions, which stabilize the C3bBb complex in a similar manner.

Deposition of C3b

Deposition of C3b on the surface of particles is essential for alternative pathway activation and the fate of such surface-attached C3b is determined by the surface composition of the particle. Surface molecules influence whether a particle serves as activator or nonactivator of the pathway (Kazatchkine *et al*., 1979). Thus, a delicate balance determines the fate of the newly attached C3b molecules as to whether amplification occurs or inactivation by regulators and surface-bound suDtabiivator andj0B

of and coating of C3b molecules on foreign cells or particles (opsonization) that allows binding and interaction of several cellular C3 receptors (CR1, CR2, CR3 and CR4) expressed on phagocytic cells. Receptor interaction results in rapid and e cient phagocytosis of these particles. (2) The initiation of the lytic pathway by formation of the membrane attack complex. (3) Pro-inflammatory reactions induced by the release of the cleavage products C3a and C5a. These anaphylatoxins are potent inducers of inflammatory reactions. Pro-inflammatory reactions must be restricted to foreign particles and prevented on host cells and tissues. Thus, activation, in particular the initial reactions of the alternative pathway at the level of C3b and C3bBb, has to be tightly controlled. Formation, stability and dissociation of the complexes is regulated by the plasma proteins factor H and reconectin/FHL-1 and by three membrane-bound proteins called complement receptor 1 (CR1/CD35), membrane cofactor protein (MCP/CD46) and decay-accelerating factor (DAF/CD55). The membrane-bound regulators are expressed by a wide range of cells and tissues and CR1/CD35, MCP/CD46 and DAF/CD55, are present on almost all human peripheral blood cells. Due to their insertion into the cell membrane, the site of action of these proteins is restricted to the cell surface. In contrast, action of the widely distributed fluid-phase regulators (factor H and reconectin/FHL-1) is not limited to the cell membrane, but occurs in the fluid phase and at the extracellular matrix. By interacting with sialic acids, polyanions and other components of the extracellular matrix, factor H and reconectin/FHL-1 can control a larger area surrounding the cell surface. Thereby, these plasma proteins control C3b formation and reduce the number of C3b molecules that attach directly to the cell surface.

Alternative complement activation initiates the lytic pathway, i.e. the formation of membrane attack complexes that incorporate holes in the plasma membrane of the labelled cells and cause cell lysis. This pathway in itself is tightly controlled; again, several fluid-phase and surface bound regulators control the individual reaction steps of this pathway and limit activation and pore formation to foreign cells and particles.

Components

The complement proteins are a prime example of protein families with diverse, but overlapping, functional properties defined by conserved common structural elements. The structure and organization of the genes coding for the complement proteins emphasize that the evolution of new protein function occurs via gene duplication, gene modification and exon shu ing. Most of the complement proteins show a modular, multidomain structure and several of the genes are tightly linked in gene clusters (Hourcade *et al*., 1992). The modular composition of the exons and the conservation of structural domains in proteins with related functions is consistent with the common evolution of the individual components of the complement system. The conserved protein domains display common three-dimensional structures which are defined by conserved and structurally essential amino acid residues and amino acid substitutions at surface-exposed locations of the protein domains that provide unique properties for substrate binding, protein interaction and membrane insertion.

Effector proteins

C3

The plasma glycoprotein C3 (183 kDa) is the pivotal complement component and the central element of the activation cascade. It is the centre where the three complement activation pathways (i.e. the alternative, the classical and the lectin pathway) merge. With a concentration of 1.0–1.5 mg mL^{-1}, C3 is one of the most abundant human plasma proteins. The intramolecular thioester of C3 allows the molecule to form covalent bonds with biomolecules, cell surface components and immune complexes. Thus, C3 has the potential to attach to a variety of molecules and bind to various targets.

C3 is synthesized as single-chain precursor and the native protein is composed of two disulfide-bonded polypeptide chains: the 115-kDa α chain and the 75-kDa β chain (**Figure 2**; Lambris, 1988). Central to the function of C3 is the internal thioester bond formed between Cys988 and Gln991. Two other components of the complement systems, C4 and α_2-macroglobulin, also have internal thioester bonds. In the native C3 protein, this site is not accessible, but under physiological conditions, spontaneous conformational changes occurring at a rate of less than 1% make the thioester reactive and accessible to attack by nearby nucleophilic groups. These reactions allow the glutamine residues to react covalently via hydroxyl or amino groups to any other molecule.

C3 activation is initiated by the C3 convertases formed in all three complement activation pathways. In the alternative complement pathway, a spontaneously formed $C3(H_2O)Bb$ protein is the first convertase and provides the source for an amplification reaction leading to formation of further convertases and deposition of C3b molecules on the surfaces of particles. In its default setting, this reaction results in an unrestricted and excessive amplification of the complement cascade.

Activation of C3

Spontaneous conformational changes in C3 directly expose the internal thioester bond, making it accessible for nucleophilic attack by either H_2O or nucleophiles, such as amine or hydroxyl groups. In a newly formed C3b

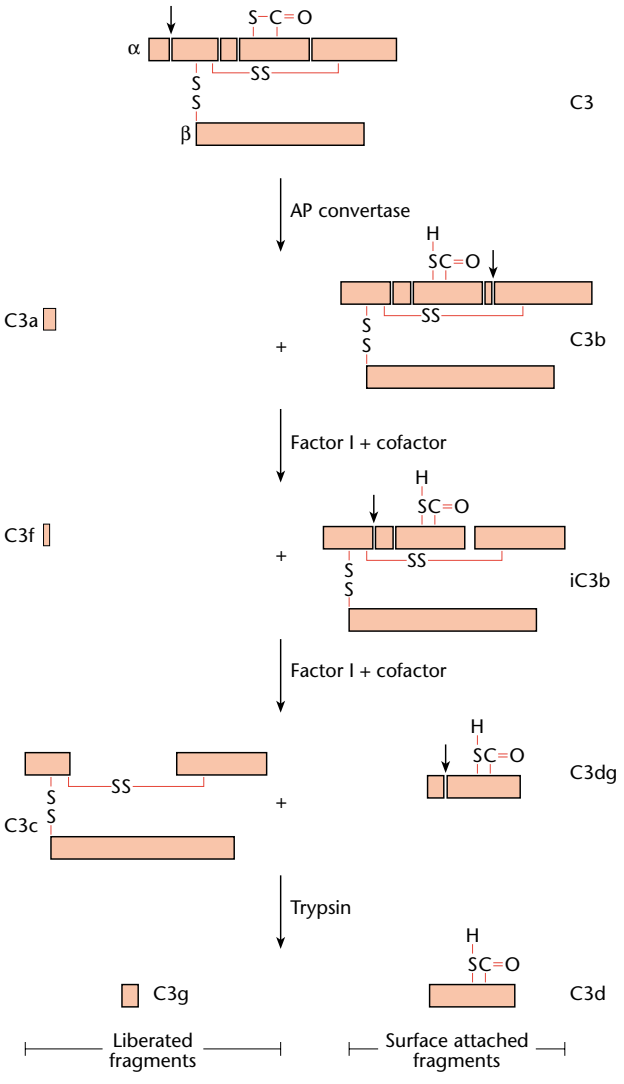

Figure 2 Processing of C3 in the alternative pathway. A continuously and spontaneously formed C3 convertase cleaves plasma C3 to C3b and the anaphylactic C3a fragment. The thioester of C3b interacts with molecules in its vicinity and binds to cell surfaces. C3b is inactivated by factor I in combination with various cofactors in several steps. The first cleavage results in the inactive form of iC3b and the release of fragment C3f. A second cleavage liberates the large C3c fragment and leaves the smaller C3dg fragment attached to particles or biomolecules. Further cleavage forms the C3d fragment. The various fragments represent ligands for several C3-binding proteins and specific C3 receptors.

molecule, this thioester is exposed for a brief period of time (60 μs) before the molecule is inactivated. This short half-life restricts alternative pathway activation locally and, in time, ensures that activation proceeds within the immediate vicinity. Both the classical and alternative complement convertases cleave C3 between Arg726 and Ser727, resulting in release of the anaphylactic C3a fragment. The newly formed C3b expresses multiple binding sites for complement components which are not accessible in the C3 molecule. The thioester of the newly formed metastable C3b molecule is highly reactive, allowing attachment of the C3b proteins to nearby molecules and surfaces close to the site of activation. Binding of the complement components to newly formed C3b either leads to generation of the C3 convertases and amplification reactions by interaction with factor B, factor D and properdin, or to inactivation of C3b by MCP (CD46), CR1 (CD35), factor H, reconectin/FHL-1, C4bp or factor I (**Figure 2** and **Table 1**).

Table 1 to be inserted here

Role of C3-degradation products

C3b is inactivated by factor I, which cleaves the protein at several sites within the α chain and which requires one of several cofactor molecules for its activity (**Figure 2** and **Table 1**). The cofactors induce conformational changes in C3b and make the molecule accessible for the protease. C3 is degraded in an orderly manner and the various degradation fragments serve distinct biological functions. The first cleavage by the specific protease factor I, together with a cofactor, produces iC3b and a 2-kDa C3f fragment, which is liberated. This conversion results in a conformational change of the protein and the inactivated iC3b no longer participates in complement activation. Further cleavage of the α chain forms the fragments C3c and C3dg. As the thioester site is contained within the C3dg fragment, the C3dg fragment remains attached to the surface, while the C3c fragment is released. Surface-bound and soluble C3 fragments that are generated during complement activation bind specifically to several surface receptors expressed on a number of immune e ector cells, such as CR1 (CD35), CR2 (CD21), CR3 (CD11b,CD18), CR4 (CD11c,CD18) and C3a receptor (**Table 1**). The binding of C3 fragments to their specific receptors results in a variety of biological responses. In particular, the anaphylatoxin C3a triggers the release of soluble inflammatory mediators, such as histamine, and serves as a chemotactic factor which attracts immune e ector cells to the site of inflammation. In addition, multiple complement receptors recognize C3 fragments on the surface of particles and local interaction induces phagocytosis and elimination of the coated particle.

Factor B

Factor B is a single-chain, 93-kDa polypeptide. Its association with C3b makes the protein susceptible for proteolytic cleavage by factor D. The smaller cleavage product, the released Ba fragment (33 kDa), is represented by three short consensus repeat (SCR) domains, which are each encoded by a separate exon. The larger Bb fragment (60 kDa) is encoded by 13 exons and contains domains with homology to the catalytic chains of other serine proteases. Each of the functionally relevant domains of the active site is contained on a separate exon. Factor B of the alternative

Table 1 Components of the alternative pathway

Protein	Function	Molecular weight (kDa)	Plasma concentration ($\mu g\ mL^{-1}$)	Domain structure
Activators				
C3	Central component		1000–1600	Thioester
Factor B	Serine protease	93	200	Ba SCR Bb serine protease
Factor D	Serine protease	24	2	Serine protease
Properdin	Stablilizers C3 and C5 convertases	53	25	
Regulators – soluble				
Factor I	Inactivation of C3b in the presence of cofactors serine protease	88	35	Serine protease
Factor H	Accelerates decay of C3b, Bb; Cofactor for I; Binding to host cells, adhesion molecule	155	*c*. 500	SCR
Reconectin/FHL-1	Accelerates decay of C3b, Bb; Cofactor for I; adhesion molecule		25–50	SCR
FHR-1	?	37, 42		SCR
FHR-2	?	24, 29		
FHR-3	C3-binding protein	34–56		
FHR-4	C3-binding protein	86		
Regulators – membrane bound				
CR1 (CD35)	Accelerates decay of C3b, Bb; cofactor for I	190 (most common allotype)		SCR
DAF (CD55)	Accelerates decay of C3b, Bb	70		SCR
MCP (CD46)	Cofactor for I	45–68		SCR

SCR, short-consensus repeat.

complement pathway shows structural and functional homology to the classical pathway regulator C2.

Factor D

The serine protease factor D is a 24-kDa single-chain protein present in human plasma at a rather low concentration. Apparently factor D circulates in plasma in an active form. The human protein displays a 60% amino acid homology to mouse adipsin, a mouse serine protease expressed in adipocytes which functions in lipid metabolism.

Properdin

Properdin was the first of the alternative pathway proteins to be identified (Kazatchkine *et al*., 1979). Its function is to stabilize the alternative complement pathway convertase. In plasma, the properdin glycoprotein appears in cyclic polymers consisting of tetramers and trimers, composed of several subunits of 53 kDa which bind to each other in a head to tail fashion. Each subunit contains repeating motifs of the thrombospondin type 1 repeats.

Plasma regulators

Factor I

Factor I is a member of the serine protease family and acts in both the alternative and the classical complement pathway by cleaving C3b and C4b. Factor I is a central complement regulator and several cofactors are essential for its proteolytic degrading activity. The protein is

composed of two disulfide bond chains of 50 and 38 kDa and several carbohydrates are attached to the secreted protein. The protein has a modular composition and the β chain contains two low-density lipoprotein receptor repeats, and a repeat shared with C6 and C7. The light chain possesses a serine protease structure.

Factor H

Factor H is a single-chain, 155-kDa glycoprotein that is present in human plasma in a concentration of about 500 μg mL^{-1} (Zipfel and Skerka, 1994). The secreted form of the protein is composed of 20 repetitive domains termed short consensus repeats (SCRs). Factor H is a multidomain, multifunctional protein with regulatory activities in the complement system and has additional functions outside of the complement system. The complement regulatory domains have been localized to the N-terminus of the protein and SCRs 1–4 are both essential and su cient for cofactor and decay-acceleration activity. Additional functional domains have been identified within the intact molecule, including a total of three C3-binding domains, three heparin-binding domains, and the amino acid motif RGD (Arg-Gly-Asp), which is a major site of adhesion proteins for interaction with integrin type receptors. Factor H has been shown to bind to the integrin-type receptor Mac-1 (CD11b/CD18, or complement receptor CR3) and to L-selectin.

Reconectin/FHL-1

The factor H-like protein 1 (FHL-1), also termed reconectin, is derived from the factor H gene by means of alternative processing. Expression of the two transcripts is regulated in a tissue- and mediator-specific way and apparently the reconectin/FHL-1 mRNA is the default transcript. The corresponding protein represents the N-terminal seven SCRs of factor H with four additional amino acids added to the C-terminal end. Reconectin/FHL-1 is a multidomain multifunctional protein and acts as a regulator of the alternative complement pathway and also displays cell adhesion functions (Zipfel and Skerka, 1999). In addition to the conserved complement regulatory N-terminal SCR 1–4, the protein includes a heparin-binding domain in SCR 7 and the RGD-adhesion domain, located within SCR 4, confers attachment to cell surface receptors of the integrin type. The plasma concentration of reconectin/FHL-1 is about 10–50 μg mL^{-1} and a local action of this protein is suggested due to its smaller size that results in fast di usion.

Factor H-related proteins (FHRs)

The factor H-related proteins (FHR-1 to FHR-4) represent additional members of the factor H protein family and are present in human plasma and in lipoproteins in di erently glycosylated forms (Zipfel and Skerka, 1994). The FHR-1 protein exists as a 43- and 37-kDa protein, and FHR-2 as a 27- and 24-kDa. The FHR-3 protein is present in several glycosylated forms ranging from 49 to 58 kDa, and the FHR-4 protein exists in plasma and in lipids as a dimeric glycoprotein of 87 kDa. Each protein is encoded by a unique gene, all of which seem located within the RCA (Regulators of Complement Activation) gene cluster. The precise function of the various proteins is under investigation. In addition to their structural and sequence homology and their immunological crossreactivity with factor H and reconectin/FHL-1, the FHR proteins display cofactor activity and control the fate of C3.

Membrane-bound regulators

The three membrane-bound regulators of the alternative complement pathway belong, together with other complement control proteins, to the regulators of complement activation gene cluster on human chromosome 1 (region 1q32). The three proteins are structurally related, as their extracellular region is composed of SCR domains, and as membrane-bound regulators, they serve important control function in both the alternative and the classical complement pathway.

CR1

CR1 is a single-chain membrane protein involved in complement regulation, as it displays cofactor and decay-accelerating activity. Expressed in nearly all human peripheral blood cells, CR1 is a highly polymorphic protein and, in the most dominant form, is composed of 30 SCR domains. The SCRs are arranged in long homologous repeats, each containing seven contiguous SCRs (i.e. SCRs 1–7, 8–14, 15–21 and 22–28). Within each repeat domain, the binding sites for the ligands are located within the N-terminal part, providing also the basis for multiple interaction sites for C3b.

Membrane cofactor protein (MCP/CD46)

The membrane cofactor protein (MCP) is a membrane-bound regulator that has cofactor activity for factor I in the degradation of membrane-attached C3b proteins. The N-terminal extracellular domain of MCP is composed of four SCR domains that are followed by a stretch of serine, threonine and proline residues (STP region) and a transmembrane region. In the case of MCP, the STP region occurs in polymorphic forms due to alternative splicing of an exon.

Decay accelerating factor (DAF/CD55)

The decay-accelerating protein is a membrane-bound complement regulator that controls the formation and reduces the stability of membrane-attached convertases. The protein is composed of four SCR domains followed by an extensively *O*-glycosylated STP region and a stretch of 24 hydrophobic residues. The protein is attached to the

membrane by a glycosylphosphatidylinositol (GPI) anchor.

Control

The alternative complement pathway C3 convertase is the step where the activation cascade becomes amplified. While a powerful amplification is desirable and required on foreign surfaces, self cells and tissues in general, and particularly host cells in the direct vicinity of a pathogen, must be protected from this destructive and harmful system. The importance and relevance of protection can be concluded from the large number of regulatory and inactivator proteins, which actually exceeds the number of e ector proteins. Several of the major control proteins act on the stage of alternative pathway C3 convertases formation. These regulators dissociate any preformed convertases and prevent formation of a new convertase (decay-accelerating activity) or, by binding to C3b, they make this protein accessible for the serine protease factor I that proteolytically degrades and inactivates C3b (cofactor activity). Regulatory proteins that control complement activity exist in plasma and also on cell surfaces (**Table 2**).

Microbes

As an evolutionarily old defence system, the alternative complement pathway is the major e ector mechanism of innate immunity to attack, inactivate and eliminate microbes and pathogens. However, during evolution, microbes have evolved means to cope with the host immune system and to interfere and control complement activity. Increasing evidence indicates that host complement proteins not only act as mammalian complement regulators, but also are a target for pathogenic microorganisms. Many pathogens have developed the capacity to evade the pro-inflammatory and destructive e ects since they control alternative complement activation on their surface. The importance of the alternative pathway in host defence is envisioned by the fact that several independent evasion mechanisms have evolved and are being used by microbes to restrict complement deposition and amplification on the surface. Similar to the protective mechanisms employed by mammalian cells, pathogens control complement activation at distinct levels and steps. Regulatory proteins used by pathogens either represent host-like antigens encoded within the microbial genome or they are regulatory proteins acquired from their hosts by absorption. Several microbial proteins and genes have been identified on a functional, as well as a genetic level. These proteins are expressed either on the surface of a pathogen or are released into the medium. Several of these proteins that mimic functions of the endogenous regulators are related in structure and domain composition to the host proteins.

Distinct strategies are employed by pathogens to interfere with complement activation. One resistance mechanism is the development of an antiphagocytic capsule that physically prevents the access of C3 receptors presented on the surface of phagocytes to C3b deposited on the cell wall of bacteria. A second strategy is the mimicry of complement regulators. A number of pathogens and bacteria express proteins that restrict C3 activation either by controlling C3 convertase assembly or by acting as cofactors for the cleavage of bound C3b. A first example was the identification of a CR1-like molecule in herpes simplex virus (HSV) type I and II (Fishelson, 1994). Several domain motifs and structures of the mammalian complement components and regulators are also found in microbial proteins (Rother *et al.*, 1994). One example of a secreted microbial complement regulatory protein is the 35-kDa vaccinia virus complement control protein (VCP), a virally encoded protein that is secreted by cells upon infection with the virus (Kotwal and Moss, 1988). This protein is composed of four SCR domains that share amino acid homology to the α chain of C4BP. The protein has decay-accelerating and cofactor activity in the classical and the alternative complement pathway. By being secreted it can protect viral particles from complement-mediated attack and can augment viral virulence.

A third strategy is the acquisition of host regulators to enable bacteria and pathogens to control C3b deposition. Thus, pathogens limit the number of newly formed C3b molecules in the vicinity of the cell and further inactivate C3b molecules at the cell surface. Gram-positive bacteria are not e cient activators of the alternative pathway. In particular, the presence of sialic acids and complement regulator binding proteins have been shown on *Escherichia coli* K1, *Neisseria meningitidis* and *Streptococcus pyogenes* to be important for complement control. One example is the streptococcal M protein, a major virulence factor that mediates resistance to complement-induced lysis. M protein binds the two human complement regulators factor H and reconectin/FHL-1. In plasma absorption experiments, the reconectin/FHL-1 preferentially binds to M5 protein and, in a bound configuration, the protein retains its complement regulatory functions. The two human regulators bind to di erent sites of the bacterial protein. The binding site for reconectin/FHL-1 is located within the hypervariable, surface-exposed region of the M5 protein, while that of factor H is located in the conserved region in the middle of the protein (Zipfel and Skerka, 1999). Acquisition of the host regulators downregulates C3 deposition on the streptococcal surface and, thus, explains why the hypervariable region of M proteins is essential for phagocytosis resistance. A related mechanism is being used by viruses, as during the budding process viruses like HIV capture membrane-bound complement regulators of the host cell and incorporate these proteins into the viral

Table 2 Proteins interacting with C3 and its proteolytic fragments

Protein	Alternative pathway complement protein
C3	Convertases C3bBb
C3b	Factor B
	Factor H
	Reconectin/FHL-1
	FHR-3
	FHR-4
	Factor I
	Properdin
	CR1 (CD35)
	DAF (CD55)
	MCP (CD 46)
iC3	Factor B
	Factor H
	Factor I
	CR1 (CD35)
iC3b	Factor H
	Factor I
	CR1 (CD35)
	CR2 (CD21)
	CR3 (CD11b/CD18)
	CR4 (CD11c/CD18)
C3dg	CR2 (CD21)
	FHR-3
	FHR-4
C3a	C3a receptor

envelope. These host complement regulators help the virus to inactivate complement attack.

In addition to their role in complement control, host membrane regulators are used by microorganisms as entry points into cells. Following internalization, the pathogens are not further accessible to complement. The CR2 (CD21) protein on B and T lymphocytes serves as a receptor for Epstein–Barr virus (Nemerow *et al*., 1989), the RCA proteins MCP (CD46), and DAF (CD55) act as receptors for measles and echovirus, and the CR1 (CD 35) receptor seems to be recognized by a protein expressed on the surface of *Plasmodium falciparum*-infected erythrocytes.

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