



REVIEW ARTICLE

Utilization of complement receptors in immune cell–microbe interaction

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The complement system is a major humoral component of immunity and is essential for the fast elimination of pathogens invading the body. In addition to its indispensable role in innate immunity, the complement system is also involved in pathogen clearance during the effector phase of adaptive immunity. The fastest way of killing the invader is lysis by the membrane attack complex, which is formed by the terminal components of the complement cascade. Not all pathogens are lysed however and, if opsonized by a variety of molecules, they undergo phagocytosis and disposal inside immune cells. The most important complement-derived opsonins are C1q, the first component of the classical pathway, MBL, the initiator of the lectin pathway and C3-derived activation fragments, including C3b, iC3b and C3d, which all serve as ligands for their corresponding receptors. In this review, we discuss how complement receptors are utilized by various immune cells to tackle invading microbes, or by pathogens to evade host response.

Keywords: complement activation; complement receptors; complement-derived ligands; pathogen clearance; pathogen escape

The complement system consists of approximately 50 soluble, membrane-bound and regulatory proteins. Most of the circulating, inactive complement components are synthesized in the liver, although the local production of complement proteins in tissues has also

been proven to play an important role in several immune processes [1–3].

Activation of the complement cascade can occur *via* the classical, the lectin-dependent or the alternative pathway (Box 1).

Abbreviations

AIDS, acquired immune deficiency syndrome; BAD1, blastomyces adhesin 1; cC1q, collagen-like tail region of C1q; CCP, complement control protein; CLR, C-type lectin receptors; CR, complement receptor; CRD, carbohydrate recognition domain; CRlg, complement receptor of the immunoglobulin family; CRT, calreticulin; EBV, Epstein–Barr virus; Ecb, extracellular complement binding protein; GAS, group A *Streptococcus*; gC1q, globular head region of C1q; GPI, glycosylphosphatidylinositol; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV-1, human T-lymphotropic virus 1; ICAM-1, intercellular adhesion molecule 1; LAD, leucocyte adhesion deficiency; LPS, lipopolysaccharide; LTA, lipoteichoic acid; Mac, GAS Mac-1-like protein; MAC, membrane attack complex; MASP, MBL-associated serine protease; MBL, mannose-binding lectin; MyD88, myeloid differentiation primary response 88; NLR, NOD-like receptor; PfRh4, *Plasmodium falciparum* reticulocyte-binding-homologue-4; PMN, polymorphonuclear cells; PspA, pneumococcal surface protein A; RCA, regulators of complement activation; Sap, secreted aspartic protease; SARS, severe acute respiratory syndrome; SCR, short consensus repeat; SLE, systemic lupus erythematosus; TLR, Toll-like receptor; TRIF, TIR-domain-containing adapter-inducing interferon- β ; uPAR, urokinase-type plasminogen activator receptor; VSIG4, V-set and Ig domain-containing 4.

Box 1. Activation of the complement system

The classical pathway is triggered by C1q, a subunit of the trimolecular C1 complex, upon its reaction with the Fc portion of IgM or IgG antibodies bound to the antigen, or directly, upon recognizing pathogen surfaces and apoptotic cells. This step is followed by the activation of C1r then C1s, the two C1q-associated serine proteases. After cleavage of C2 and C4, the larger split products, C2b and C4b form the classical pathway's C3 convertase on the surface of the activating substance. This, in turn, activates C3, the major and central component of this cascade on which all three complement activation pathways converge.

The lectin pathway is activated by mannose-binding lectin (MBL) and ficolins. These pattern recognition molecules bind to microbial surface oligosaccharides and acetylated residues, and form complexes with MASP1 and MASP2, the MBL-associated serine proteases, which cleave C2 and C4 to generate C2bC4b, the classical C3 convertase.

The alternative pathway is constitutively activated at a low level by the spontaneous hydrolysis of C3 ('tick-over mechanism') in body fluids generating C3(H₂O). This C3b-like molecule binds factor B, which is cleaved by the serine protease factor D, giving rise to the formation of the initial, fluid-phase C3 convertase (C3(H₂O)Bb) of the alternative pathway. This enzyme produces further C3b fragments, resulting in a surface-bound C3bBb, the C3 convertase of the alternative pathway. Several substances can initiate this pathway, including bacterial LPS, zymosan and biomaterials. Of note, the alternative pathway serves as a strong amplification loop, as it can be triggered also by C3b generated by either the classical or the lectin pathways.

The three pathways converge at the level of the central complement component, C3. Activation of this major component leads to the generation of several biologically important C3 fragments. C3b, the first, larger cleavage product binds covalently to the activating surface and initiates the assembly of C5 convertase enzymes of either the classical (C4bC2bC3b) or the alternative (C3bBbC3b) pathway. Upon the cleavage of C5 by the C5 convertases, the generated C5b binds C6 followed by the formation of the trimeric C5b-7 complex, which associates with the cell membrane. In the next steps, the tetrameric C5b-8 complex is formed, which allows binding and polymerization of C9 molecules. In the final step, the C5b-9 complex (MAC) inserts into the plasma membrane, which causes cell death by lysis.

Since complement activation can potentially be destructive, fluid-phase and cell membrane-bound regulators control this system to protect host tissues. These regulators of complement activation (RCA) show structural homology, characterized by repeats of complement control protein (CCP) or sushi domains.

The central event in the activation cascade is the cleavage of the third component, C3. Its first split products are C3a and C3b. The small, soluble C3a peptide may bind to G-protein-coupled C3a receptors, while the larger activation fragment C3b, containing the exposed, reactive thioester group, has the capacity to bind covalently to the activating surface on the pathogen. Covalently fixed C3b is the main ligand of CR1 (CD35) and CR1g. C3b can be further processed to generate iC3b and C3d(g), which remain covalently attached to the antigen and interact with complement receptors CR3 (CD11b/CD18), CR4 (CD11c/CD18), CR1g and CR2 (CD21) expressed on several cell types. In addition to the covalently fixed C3- and C4-derived fragments, C1q and MBL are further opsonins (Table 1, Fig. 1).








Complement receptors are essential to empower immune cells to clear the circulation from invaders [4]. Here, we review data describing the interaction of these receptors with different pathogens – bacteria, viruses, fungi and parasites – mentioning also examples of how these receptors are utilized by pathogens to evade host responses (Table 2).

Complement receptor type 1 (CR1, CD35)

Human complement receptor type 1 (CR1, CD35) is expressed on the surface of various myeloid and lymphoid cells and also on erythrocytes [5]. It is an approximately 200 kDa single-chain transmembrane glycoprotein with a short cytoplasmic tail. In the most common human allotype, the extracellular portion of the molecule is composed of 30 SCRs (Short Consensus Repeat), each having 60–70 amino acids. CR1 binds activated fragments of C3 and C4, such as C3b and C4b and with lower affinity, iC3b [6]. It is also an important regulator of the complement cascade, since it possesses decay-accelerating activity for the C3/C5 convertases of both the classical and alternative pathways. Additionally, it serves as a cofactor for Factor I-mediated cleavage of C3b, thus blocks further activation of the complement cascade [7].

CR1 expressed by phagocytes – macrophages and granulocytes – plays an important role in the phagocytosis of C3-opsonized antigens. Its further roles include

Table 1. Complement receptors (For references see the text). Mo, monocyte; Mf, macrophage; DC, dendritic cell; Mast, mast cell; Bas, basophil granulocyte; Neu, neutrophil granulocyte; Eos, eosinophil granulocyte; RBC, red blood cell; FDC, follicular dendritic cell; NK, natural killer cell.

Name	Structure	Main ligand(s)	Distribution	Major function
cC1qR 	Calreticulin (CRT), 60 kDa, in complex with CD91	Collagenous region of C1q and MBL	Mo, Mf, DC, Mast, Bas, B cell	Phagocytosis, Chemotaxis, RO synthesis
gC1qR 	Homotrimer, 97 kDa	Globular heads of C1q and MBL	Ubiquitous	Inflammation
CR1, CD35 	Single chain, 200 kDa	C3b, C4b	Mo, Mf, Neu, Bas, Eos, B cell, T-cell subpop, RBC, FDC	Phagocytosis (Mf, Neu), IC clearance, immune adherence, antigen retention (FDC), human B-cell inhibition
CR2, CD21 	Single chain, 145 kDa in trimolecular complex CR2-CD19-CD81	C3d, EBV	B cell, FDC	Mouse B-cell coactivation, antigen retention (FDC)
CR3, CD11b/18 	Heterodimer, CD11b 170 kDa, CD18 90 kDa	iC3b, fibrinogen, ICAM-1, beta-glucan	Mo, Mf, DC, Neu, B-cell subpop, FDC, NK, platelet	Phagocytosis, RO/NO synthesis, migration
CR4, CD11c/18 	Heterodimer, CD11c 150 kDa integrin β chain, CD18 90 kDa	iC3b, fibrinogen, ICAM-1	Mo, Mf, DC, Neu, B-cell subpop, FDC, NK, platelet	Adherence, migration
CRlg 	Ig superfamily 56 kDa	iC3b, C3b	Kupffer cells, subset of tissue macrophages	Phagocytosis

transport of soluble antigen–antibody complexes from blood to the liver [8] and inhibition of human B-cell responses [9–12].

The expression of CR1 on human erythrocytes was shown to vary among healthy individuals. The CR1 gene is highly polymorphic, and an RFLP was

identified which correlates with CR1 expression levels on RBCs. A combination of the alleles linked to high (H) and low (L) expression levels – HH, HL and LL, respectively – gives rise to three distinct genotypes with high, intermediate and low expression of CR1 [13].

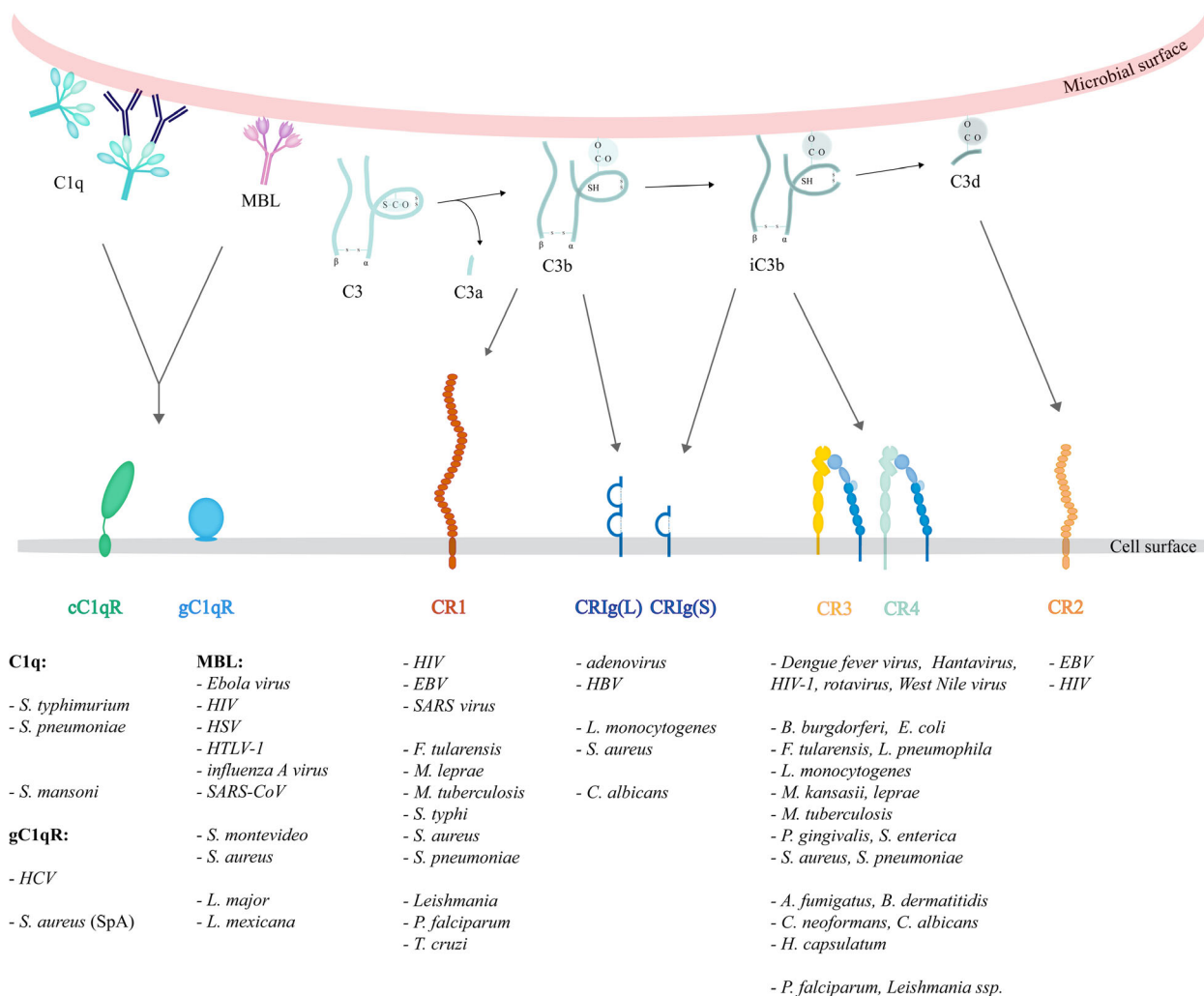


Fig. 1. Ligand specificity and microbial utilization of complement receptors. C1q may opsonize microbial surfaces directly or indirectly, via binding to the Fc region of bound antibodies. The globular head of C1q may interact with gC1qR, while its collagen-like tail binds to cC1qR. MBL directly bound to microbial surfaces presumably interacts with cC1qR. Complement activation leads to the deposition of complement fragments that are potent ligands for several complement receptors. The larger C3b fragment is recognized by CR1 and CR1g, the inactivated iC3b fragment interacts with CR1g, CR3 and CR4, whereas C3d is a ligand for CR2. Complement receptors interact with pathogens through the opsonins or by direct binding of microbial components. The viruses, bacteria, fungi and parasites utilizing these receptors are listed below the illustration.

The abundance of the receptor on the surface of various leucocytes makes these cells a potential target for intracellular pathogens. Phagocytosis – a crucial step in pathogen neutralization, regulating inflammation and antigen presentation – can be hijacked by microbes. Pathogens are able to adhere to or enter monocytes, macrophages and neutrophils via phagocytic receptors, while avoiding intracellular enzymatic digestion and subsequently contributing to disease development. Polymorphisms of CR1 have been linked to greater susceptibility to certain infections as well.

Viruses

Interaction between HIV (human immunodeficiency virus) and various immunocytes, as well as red blood cells, suggests a complex pathomechanism. Complement alone can target the virus to erythrocyte CR1, and antibodies only enhanced this effect [14]. Viral adherence was shown to be inhibited in the absence of complement, while undisturbed without IgG. Furthermore, blocking CR1 significantly diminished HIV adhesion. These experiments indicate that adherence of the virus to red blood cells is a complement-dependent phenomenon [15].

Table 2. List of pathogens binding to various complement receptors.

Receptor	Viruses	Bacteria	Parasites and Fungi
cC1qr–C1q		<i>Salmonella typhimurium</i> [133] <i>Streptococcus pneumoniae</i> [132]	<i>Schistosoma mansoni</i> [140]
cC1qr–MBL	Ebola virus [120] Human immunodeficiency virus (HIV) [119,124–126] Herpes simplex virus (HSV) [123] Human T-lymphotropic virus 1 (HTLV-1) [125] Influenza A virus [122,127–129] Severe acute respiratory syndrome (SARS-CoV) [121]	<i>Salmonella montevideo</i> [138,139] <i>Staphylococcus aureus</i> [135–137]	<i>Leishmania major</i> [141] <i>Leishmania mexicana</i> [141]
gC1qr	Hepatitis C virus (HCV) [130,131]	<i>Staphylococcus aureus</i> (SpA) [134]	
CR1	Epstein–Barr virus (EBV) [21] Human immunodeficiency virus (HIV) [14–16] SARS-virus [20]	<i>Francisella tularensis</i> [25] <i>Mycobacterium leprae</i> [30,31] <i>Mycobacterium tuberculosis</i> [29] <i>Salmonella typhi</i> [28] <i>Staphylococcus aureus</i> (Ecb) [26] <i>Streptococcus pneumoniae</i> [27]	<i>Leishmania major</i> [37,38] <i>Plasmodium falciparum</i> (PfRh4) [32–35] <i>Trypanosoma cruzi</i> [36]
CR2	Epstein–Barr virus (EBV) [21,39–43] Human immunodeficiency virus (HIV) [19,22]		
CR3/CR4	Dengue fever virus [51] Hantavirus [53] Human immunodeficiency virus (HIV-1) [46–48] Rotavirus [52] West Nile virus [49,50]	<i>Borrelia burgdorferi</i> [59] <i>Escherichia coli</i> [54] <i>Francisella tularensis</i> [25,63] <i>Legionella pneumophila</i> [65] <i>Listeria monocytogenes</i> [61] <i>Mycobacterium kansasii</i> [60] <i>Mycobacterium leprae</i> [30] <i>Mycobacterium tuberculosis</i> [55] <i>Porphyromonas gingivalis</i> [66–69] <i>Salmonella enterica</i> [58] <i>Staphylococcus aureus</i> [56,57] <i>Streptococcus pneumoniae</i> [64]	<i>Plasmodium falciparum</i> [78] <i>Leishmania</i> ssp.[80–82] <i>Aspergillus fumigatus</i> [74] <i>Blastomyces dermatitidis</i> [73] <i>Cryptococcus neoformans</i> [70] <i>Candida albicans</i> [54,75–78] <i>Histoplasma capsulatum</i> [71,72]
CR1g	Adenovirus [89] Hepatitis B virus (HBV) [95,96]	<i>Listeria monocytogenes</i> [85,99] <i>Staphylococcus aureus</i> [85]	<i>Candida albicans</i> [97,98]

Monocytes and macrophages also contribute to the progression of AIDS, as they express CD4 that HIV uses to enter these cells. In addition, it has been shown that the opsonization of HIV-1 and HIV-2 strains with complement results in higher and earlier productive infection – independently of CD4 – while blocking of CR1 (or CR3) attenuates the enhancing effect of complement [16]. The immune complex formation of virus envelope protein-specific antibodies and HIV-1 leads to opsonization and binding to CR1 on K562 leukaemia-derived cell line [14].

Certain human T lymphocyte subsets express CR1 (and CR2) receptors [17,18], making them suitable for complement-induced immune responses, but on the other hand, they become potential targets for infection. Similarly to monocytes and macrophages, opsonization of HIV-1 with complement leads to earlier and enhanced infection of CD4-expressing human T-cell lines in a CR1- or CR2-dependent manner, as blocking either of these receptors diminished the

positive effect of complement [19]. Certain HIV strains require no involvement of CD4 in the process of CR1- and CR2-mediated contagion of T cells. In addition to its crucial role in linking opsonized HIV to T lymphocytes, CR1 presumably facilitates viral attachment to CR2 by its cofactor activity during cleavage of C3b into smaller fragments that could interact with CR2 [19].

The genotype of CR1 could be a major factor in viral infections. Namely, severe acute respiratory syndrome (SARS) disease progression differs in patients with or without the high expression genomic type (HH) [20]. In the early stages of SARS disease, the number of CR1 receptors on RBCs decreases significantly but later returns close to physiological values. This phenomenon may have an impact on disease progression. While patients bearing HH and HL genotypes showed temporary reduction of CR1 levels, SARS patients with LL genotype had no change in their CR1 expression on erythrocytes, although this

might be a result of the small sample size, according to the authors. Thus, the correlation between the genotype of CR1 and progression of the SARS disease is not clear yet, but the dynamic change in the CR1 numbers during infection suggests its involvement in the process [20].

CR2 (CD21) was formerly considered the sole receptor for the major Epstein–Barr virus (EBV) glycoprotein gp350/220 [21]; however, there are data on EBV patients deficient in CR2 indicating an alternative CR2-independent process for viral entry. Experiments with CD21⁻ B-cell lines showed gp350/220 binding to CR1. In the presence of HLA type II complexes in the membrane, CR1 could mediate infection [22].

Bacteria

It is long known that CR1, in cooperation with CR3, has a major role in the phagocytosis of opsonized particles [23,24]. For instance, Schwartz *et al.* [25] demonstrated that neutrophils mediate the internalization of opsonized *Francisella tularensis* via CR1 and CR3.

During bacterial colonization, different ‘strategies’ allow survival and spreading depending on whether the species is extra- or intracellular. For example, evasion of phagocytosis can be beneficial for extracellular pathogens, while intracellular organisms can utilize phagocytic receptors for invasion, simultaneously inhibiting cytoplasmic killing mechanisms.

During *Staphylococcus aureus* infection, bacterial ligand Ecb (extracellular complement binding protein) has been shown to bind C3b and block direct interaction between the soluble form of CR1 (sCR1) and C3b. Thus, Ecb reduces cofactor activity of sCR1 in the process of proteolytic inactivation of C3b [26]. CR1 expressed in the membrane of neutrophils can also be utilized by *S. aureus* where Ecb binds to C3b and prevents CR1 engagement, resulting in impaired phagocytosis [26].

Pneumococcal surface protein A (PspA) has been shown to interfere with complement deposition onto *Streptococcus pneumoniae*. Results of a mouse study revealed that PspA impairs mouse CR1/2-, as well as CR3-, and CR4-mediated protection against pneumococcal infection, since the bacterial protein modulates opsonization by the components of the alternative pathway [27].

Intracellular survival of *Salmonella typhi* has been observed in human macrophages, and CR1 – along with CR3 – was found to be involved in its internalization. Correlation between CR1 mediated recognition of the bacteria and survival rate has been found as well [28].

Patients with *Mycobacterium tuberculosis* infection were shown to have more circulating immune complexes, a lower expression of CR1 on erythrocytes and a higher prevalence of the HH genotype than in healthy donors. The presence of the H allele of the *Cr1* gene may contribute to higher susceptibility to pulmonary tuberculosis [29].

CR1 and CR3 blocking reduced adherence and phagocytosis of *Mycobacterium leprae* by monocytes [30], while CR1 polymorphisms have also been associated with the infection. Susceptibility to leprosy is affected by the amount of soluble CR1 in blood which competes with cell membrane receptors for pathogen binding, subsequently affecting phagocytosis [31]. The uptake of opsonized *M. leprae* is enhanced in the case of a CR1 variant with a hidden cleavage site that results in a lower concentration of sCR1 or a polymorphism that leads to an elevated level of CR1 production [31].

Parasites

In the case of malaria, caused by the intracellular parasite *Plasmodium falciparum*, CR1 receptors expressed on infected red blood cells can presumably facilitate the infection by rosetting with uninfected erythrocytes [32]. This process correlates with the severity of the disease [33]. CR1 possibly serves as a point of entry for the obligate intracellular pathogen during erythrocyte invasion. PfRh4 (*P. falciparum* reticulocyte-binding-homologue-4) is a major *Plasmodium* ligand associated with sialic acid-independent invasion of red blood cells. Its recognition site has been located at the distal amino terminus of CR1 [34]. Simultaneous engagement of CR1 by C4b and PfRh4 specifically inhibits the receptor’s convertase decay-accelerating activity [34]. Moreover, sCR1 was also shown to bind PfRh4, resulting in the blocking of *Plasmodium* attachment to erythrocyte CR1 [35], demonstrating that CR1 has a complex role in disease progression.

Soluble CR1 can also be associated with infections with intracellular parasite *Trypanosoma cruzi*, responsible for Chagas disease (CD). Patients with chronic CD have a decreased amount of sCR1 compared to healthy controls. Certain haplotypes of CR1 have been linked to augmented risk of *T. cruzi* infection and developing chronic chagasic cardiomyopathy [36].

CR1 is a major receptor on macrophages for the obligate intracellular protozoa *Leishmania major*. Simultaneously blocking CR1 and CR3 significantly decreases pathogen attachment, and CR1 inhibition alone leads to attenuated binding. Data suggest higher survival rate when pathogens enter *via* CR1 [37,38].

Complement receptor type 2 (CR2, CD21)

In humans, CR2 (CD21) is composed of 16 SCRs, a transmembrane domain and a short cytoplasmic tail. The protein is encoded by the *CR2* gene, which is separate from the CR1 receptor coding gene, *CR1*. Contrarily, in mice both CR1 and CR2 are encoded by the same gene (*Cr2*) and alternative splicing gives rise to the two protein products. Thus, mouse CR2 is nearly identical to CR1 both in function and structure. CR2 binds fragment C3d, the final cleavage product of C3. CR2 has also been shown to serve as a receptor for viruses.

Viruses

A large body of evidence indicates that CR2 mediates EBV infection of human B lymphocytes *via* binding of a virus outer membrane glycoprotein, gp350/220 [21,39–43].

C3b-opsonized HIV was shown to bind to erythrocyte CR1 [14,15] that is followed by the cleavage of C3b to iC3b and C3d. This way C3d-bearing HIV targets CR2-expressing B cells and facilitates the B cell-mediated transmission of opsonized HIV to T cells [19,44].

Complement receptors CR3 (CD11b/CD18) and CR4 (CD11c/CD18)

Complement receptors CR3 ($\alpha_M\beta_2$, CD11b/CD18, Mac-1) and CR4 ($\alpha_X\beta_2$, CD11c/CD18, p150,95) are members of the β_2 -integrin family, expressed on most white blood cells. Both receptors bind multiple ligands – for example iC3b, fibrinogen, ICAM-1 or pathogen-related ligands like LPS – and thereby play an important role in phagocytosis, adherence and migration. Although it is clear that the two receptors exhibit nonoverlapping functions, comparative studies are barely available [45]. CR3 and CR4 are important phagocytic receptors, leading either effective antimicrobial responses against pathogens or noninflammatory phagocytosis of apoptotic cells under physiological conditions of a healthy individual. Some pathogens however evolved to hijack these functions of CR3 and CR4. Extracellular pathogens are likely to avoid phagocytosis by these receptors, by blocking their function or even cleaving them from the surface of phagocytes. In contrast, intracellular pathogens often use them as an effective entry route into host cells, thereby causing a more severe infection.

Viruses

As viruses are obligate intracellular pathogens, they can benefit from their ability to exploit complement-mediated phagocytosis. For instance, the opsonization of HIV-1 by complement causes an up to 10-fold higher productive infection of human dendritic cells compared to nonopsonized or only antibody-opsonized virus particles. Complement-dependent HIV infection is mediated by CR3 [46], which also modulates the signal transduction of Toll-like receptor 8 (TLR8). Modulated TLR8 signalling resulted in a lower expression of antiviral and inflammatory factors such as IL-1 β , IL-6, TNF- α , IFN- β , myxovirus resistance protein A and IFN-stimulated genes, leading to enhanced infection [47,48]. In addition, CR3 has been shown to mediate the complement-dependent enhancement of West Nile virus replication in mouse macrophages [49,50], and the infection of human monocytes with the Dengue fever virus [51]. The capsid of Rotavirus contains integrin ligand motif bearing viral peptides, which are shown to bind to β_1 and β_2 integrins including CR4, and thereby promoting viral entry to host cells [52]. A recent experiment suggests that complement receptors CR3 and CR4 also act as Hantavirus entry receptors [53].

Bacteria

As phagocytic receptors, both CR3 and CR4 have antimicrobial roles during the immune response to infections. Both CR3 and CR4 are involved in the uptake and killing of *Escherichia coli* [54] or *M. tuberculosis* [55]. Out of the two receptors, CR3 was shown to be the dominant mediator of phagocytosis over CR4 in the case of iC3b opsonized *S. aureus* on human monocytes, neutrophils, monocyte-derived macrophages and dendritic cells [56,57]. CR3 is also involved in the phagocytosis of *Salmonella enterica* [58], *Borrelia burgdorferi* [59] or *Mycobacterium kansasii* [60], and has a key role in the effective immune response against *Listeria monocytogenes* [61].

Phagocytosis *via* CR3 and CR4 is an effective antimicrobial immune response; however, some pathogens try to evade it. For instance, Group A *Streptococcus* (GAS), avoids phagocytosis by secreting the CR3 homologue GAS Mac-1-like protein (Mac). The Mac binds to CD16 (Fc γ RIII) on the surface of human polymorphonuclear cells (PMNs) and blocks receptor–antibody interactions as well as the binding of iC3b to CD11b, as CR3 and CD16 are physically and functionally linked. By that Mac inhibits

opsonophagocytosis and also the production of reactive oxygen species, thereby decreasing pathogen killing [62].

While some pathogens evolved the ability to avoid phagocytosis, others use this mechanism to enter host cells. As CR3 and CR4 have a main role in noninflammatory phagocytosis of apoptotic cells, it is an ideal target for intracellular pathogens to exploit for their entry, especially if additional danger signals are blocked by the microbe.

Uptake of *F. tularensis*, which is one of the most virulent pathogens known, is mediated by CR3 and CR4 in human dendritic cells. The internalization of *F. tularensis* is followed by its rapid growth inside cells resulting in cell death [63]. The same receptors are involved in the infection of human macrophages, while in human neutrophils it is mediated by CR1 and CR3 [25].

The RrgA adhesin containing pili of *Str. pneumoniae* enhances the CR3 dependent uptake of pneumococci by murine and human macrophages through a direct interaction with CR3. Macrophages harbouring higher numbers of viable bacteria are more likely to be destroyed prior to the complete eradication of the ingested particles. Moreover, the interaction between RrgA and CR3 leads to increased motility and migratory behaviour of macrophages, resulting in an earlier onset of septicaemia and a more rapid disease progression [64].

The obligate intracellular pathogen *M. leprae* invades host cells *via* phagocytosis and proliferates within mononuclear phagocytes. Both CR3 and CR4 (and CR1) were shown to be involved in that process [30].

The causative agent of Legionnaires' disease, *Legionella pneumophila*, multiplies in human monocytes and alveolar macrophages. CR1 and CR3 were shown to mediate the adherence of *Leg. pneumophila*, thereby contributing to the entry and intracellular proliferation of the bacteria, as these processes could be inhibited by specific antibodies for CR1 and CR3 [65].

Hajishengallis *et al.* described in detail the immune evasion mechanism of *Porphyromonas gingivalis*. The fimbriae of this bacteria serve as a ligand for CR3, which mediates its phagocytosis, thus proactively promoting its binding and entry into the host cells. The fimbriae activate the high-affinity conformation of CR3, which does not promote the killing but the persistence of *Po. gingivalis* after internalization and induces a selective suppression of IL-12 production [66–68]. Therefore, *Po. gingivalis* enhances its survival by exploiting CR3, as pharmacological blockade of CR3 promotes its killing and suppresses *Po. gingivalis*-induced periodontal bone loss in a mouse model [66,69].

Fungi

CR3 and CR4 were shown to be involved in the binding of *Cryptococcus neoformans* [70] and are dominant receptors in the uptake and killing of *Candida albicans* [54]. However, the fungal pathogen *Histoplasma capsulatum* evades antimicrobial defences and proliferates intracellularly in macrophages infected through CR3, CR4 and LFA-1. The host macrophages are destroyed by the multiplying yeast, and the released microbes are phagocytosed by other macrophages attracted to the infected site [71]. The major *H. capsulatum* ligand for CR3 on macrophages was identified as heat shock protein 60 (hsp60), whereas dendritic cells recognize it *via* a different ligand [72]. Similar to *H. capsulatum*, the related dimorphic fungal pathogen *Blastomyces dermatitidis* also expresses a CR3-interacting protein, BAD1 (blastomyces adhesin 1). BAD1 helps pathogen survival by binding *via* CR3 and CD14 that mediates its internalization and the suppression of TNF- α production of host cells [73].

The fungal pathogen *Aspergillus fumigatus* avoids opsonization and phagocytosis by expressing proteases that degrade complement proteins and CR3 [74]. As surface-bound factor H can enhance the antifungal activity *via* binding to CR3 and CR4, *C. albicans* avoid phagocytosis by releasing the secreted aspartic protease 2 (Sap2) to cleave both FH and the complement receptors CR3 and CR4 on macrophages [75]. Additionally, *C. albicans* expresses a CR3-like structure that mediates adhesion of the yeast to human endothelium [76–78].

Parasites

CR3 and CR4 also contribute to the phagocytosis of *P. falciparum*-infected erythrocytes [79], and *Leishmania* spp. are able to enter and survive in host macrophages in a CR3-mediated manner [80,81]. Moreover, *Leishmania* is known to inhibit IL-12 production in macrophages [82], which is also mediated by CR3, as signalling *via* CR3 by *L. major* reduces IL-12 production [83]. At the same time, dendritic cells were shown to take up *L. major* in a CR3-independent, Fc γ RI- and Fc γ RIII-mediated manner, which leads to a more effective antigen presentation, indicating that CR3-mediated uptake is likely to represent a 'decoy' mechanism for this pathogen [84].

CR1g

The complement receptor immunoglobulin [CR1g, also known as V-set and Ig domain-containing 4 (VSIG4)

and Z39Ig] is a phagocytic receptor expressed on macrophage subpopulations. First, Helmy *et al.* proved the expression of CRIg in CD68⁺ Kupffer cells in the liver, interstitial macrophages in the heart, adrenal gland macrophages, alveolar macrophages, Hofbauer cells, synovial macrophages and lamina propria histiocytes by immunohistochemistry [85]. In dendritic cells, two groups showed the expression of CRIg, but only at the mRNA level [86,87]. CRIg belongs to the immunoglobulin (Ig) superfamily. In humans, it has two splice variants. The long form (huCRIg(L)) contains a V- and a C₂-type Ig domain, and a short form (huCRIg(S)) encodes only a V-type Ig domain [88]. The murine muCRIg receptor comprises only of a single V-type Ig domain [85].

CRIg binds C3b and iC3b, providing the first line of defence in the liver and spleen by quickly eliminating opsonized pathogens. This receptor was shown to swiftly resurface through recycling endosomes after internalization, thus providing the means for a continuous phagocytosis [85]. In contrast to CR3 and CR4, which also bind iC3b-opsonized particles, CRIg is regarded to have an anti-inflammatory role as well. It is hypothesized that Kupffer cells internalize opsonized microbes and apoptotic cells first through CRIg, without the induction of inflammation [89,90]. A higher number of microbial agents in the blood will prompt the engagement of other pattern recognition and complement receptors, leading to the initiation of an immune response including leucocyte recruitment and inflammation.

CRIg is additionally involved in the promotion of immunological tolerance through the inhibition of the alternative complement pathway convertases [91,92] and the suppression of T-cell activation. However, the tolerogenic function of CRIg might support the progression of cancer with keeping T cells in an unresponsive state [93,94]. Recently, the downregulation of CRIg in chronic Hepatitis B virus (HBV) infection was shown to lead to a poor prognosis in hepatocellular carcinoma patients probably due to reduced virus clearance [95,96].

Studies on the CRIg-mediated phagocytosis proved that this receptor is indispensable in the rapid internalization of complement opsonized Adenovirus particles [89], *S. aureus* [85], *Li. monocytogenes* [85] and *C. albicans* [97,98]. The intracellular pathogen *Li. monocytogenes* survive inside macrophages by delaying phagosome maturation and escaping into the cytoplasm [99]. Kim *et al.* proved a multistep counter mechanism involving the engagement of CRIg. Signalling through CRIg facilitates phagosome acidification and fusion with lysosomes, enhancing the killing

of internalized bacteria [100]. In addition, the ligation of CRIg with opsonized *Li. monocytogenes* or an agonistic mAb induces autophagosome formation, enabling macrophages to eliminate cytoplasmic bacteria already escaped from the phagolysosome system [101].

Zeng *et al.* [102] proposed that the CRIg receptor is able to clear bacteria directly without opsonization, through the recognition of the gram-positive wall constituent, lipoteichoic acid (LTA). However, Broadley *et al.* [103] proved in a C3 knockout mouse, that Kupffer cells still internalize both gram-positive and gram-negative bacteria strains, but instead of CRIg, they use pattern recognition receptors, that is scavenger receptors for LTA. Further studies are required to clarify the individual participation of complement and pattern recognition receptors expressed by Kupffer cells, with consideration of the shear stress conditions present in the liver [104].

Receptors for C1q and MBL

C1q and MBL are soluble recognition molecules, which may serve as opsonins. Their structure is described briefly in Box 2. Binding of these complement proteins to pathogens may either mediate their direct uptake *via* their receptors expressed by phagocytes – including dendritic cells, macrophages and PMNs, or may initiate the complement cascade, resulting in the fixation of C3- and C4-derived fragments, leading to an enhanced engulfment of the microbe [5].

The attachment of C1q or MBL to microbial surfaces causes conformational changes in these molecules, which subsequently initiate functions such as complement activation and interaction with C1q or MBL binding molecules leading to the uptake of the microbe. MBL can act as a direct opsonin for microbes through interaction with a cellular receptor or binding protein [108,109]. The immunological significance of MBL as an opsonin was established in studies of MBL-deficient children with an opsonic defect [110].

Several cell membrane molecules have been shown to increase the binding of collectins and the structurally related C1q, including CD93 (C1qRp), CD35 (CR1) and cC1qR (calreticulin, CRT) in complex with CD91. Receptors for both the collagen-like tail (cC1qR) and globular head regions (gC1qR) of C1q, as well as receptors for MBL, have been proposed (Table 1, Fig. 1) [111–117]. The best-accepted candidate is cC1qR, a protein nearly identical with CRT, which is in complex with CD91. CRT, a chaperone and Ca²⁺-binding, ubiquitous intracellular protein, is

Box 2. Structure of C1q and MBL complexes

C1q, a subunit of the C1 complex, is a 460 kDa hexameric glycoprotein containing 18 polypeptide chains (A, B and C), which build up 6 identical units. The tulip-like structure possesses a globular head region (gC1q), a neck region and a collagen-like tail (cC1q) [105]. The globular heads bind to the Fc region of antigen-bound IgG or IgM, and it can also recognize various structures present on self, nonself and altered self molecules. In addition to these capacities, C1q has a distinguished role in clearing apoptotic cells, and therefore, C1q deficiency may provoke autoimmunity like SLE [106].

MBL, the pattern recognition molecule of the lectin pathway, is composed of three identical monomeric subunits of 32 kDa glycoproteins, forming 3–6 trimers. The bouquet-like structure of this collectin is mainly held together *via* disulphide bonds, similarly to that of complement C1q. Each polypeptide consists of a carbohydrate recognition domain (CRD), a neck domain and a collagen domain. MBL, a member of the collectin family, is important in host defence, especially in early childhood, when the adaptive immune response has not fully developed [107].

found in the membrane of cellular organelles, on the cell surface, and it can also be released as a soluble protein. It is unclear how CRT may become associated with the cell surface, but together with CD91, surface CRT is involved in the uptake and removal of cell remnants when opsonized with C1q [117]. gC1qR is specific to the globular head region, gC1q [115]. C1qRp – also known as the AA4 antigen in rodents – enhances the uptake of C1q-opsonized particles and is recognized by antibodies against CD93 [118].

In the next paragraphs, the biological consequences of the interaction of C1q and MBL and their receptors with various pathogens are summarized.

Viruses

MBL was shown to bind to HIV, SARS-CoV, Ebola, Herpes simplex virus (HSV) and influenza virus. Subsequent conformational changes of MBL were demonstrated to allow the molecule to initiate viral neutralization or kill them *via* complement activation and opsonization [119–123].

The direct interaction of C1q and MBL was studied in detail in the case of HIV [124] and Human T-lymphotropic virus 1 (HTLV-1) [125,126]. The

importance of MBL in opsonizing HIV was proved by the finding that the uptake of the opsonized virus by tissue macrophages leads to clearance of the virus from the blood [119].

Binding of MBL to Influenza A virus was shown to involve the CRD domain of the molecule and mannose oligosaccharides of the viral haemagglutinin and neuraminidase [127–129]. Interestingly, this interaction was found to result in virus inactivation in a complement activation independent way [129].

Hepatitis C virus core protein interaction with the gC1q receptor can contribute to the pathogenesis of multiple diseases associated with HCV infection [130]. Waggoner and colleagues demonstrated that binding of the HCV core protein to gC1qR on human monocyte-derived dendritic cells inhibited TLR-induced IL-12 production but not the production of other TLR-induced cytokines [131]. In addition, HCV core protein engagement of gC1qR on dendritic cells promoted the production of Th2 cytokines such as IL-4 by cocultured CD4⁺ T cells. These results suggest that the engagement of gC1qR on dendritic cells by HCV limits the induction of a Th1 response [131].

Bacteria

Agarwal *et al.* [132] demonstrated that the adherence of *Str. pneumoniae* is facilitated by the interaction of C1q collagen region with cC1qR resulting in an enhanced invasion of host epithelial and endothelial cells.

Using recombinant forms of the globular head regions of C1q, it was found that LPS derived from *Salmonella typhimurium* interacts specifically with the B-chain of the gC1q domain in a calcium-dependent manner. Since the LPS and the IgG-binding sites are overlapping, binding of the bacterium can modulate classical pathway activation [133].

In the case of *S. aureus*, the staphylococcal protein A (SpA) has been shown to bind to the gC1qR, which is highly expressed on the surface of activated platelets and endothelial cells [134]. The bacterium itself, however, was shown to bind MBL *via* peptidoglycan and lipoteichoic acid [135,136], and MBL was found to direct the bacterium to the phagosome [137].

It has been described that MBL served alone as an opsonin in the phagocytosis of *Salmonella montevideo* by PMNs [138]. However, when MBL binds to CR1, it cooperates with FcγRs in the process of the phagocytosis of *Sa. montevideo* by PMNs, as described by Ghiran *et al.* [139].

Parasites

C1q has been proven to enhance eosinophil mediated killing of schistosomula of *Schistosoma mansoni* [140]. Binding of MBL to *L. major* and *Leishmania mexicana* promastigotes by mannose-containing lipophosphoglycan was described by Green *et al.* [141] They suggested that MBL may opsonize the major developmental stages of *Leishmania* parasites.

Crosstalk of complement receptors with other cell-membrane proteins

Pathogens invading the body may get opsonized by plasma proteins other than complement – including antibodies, pentraxins [129] and fibronectin – furthermore, microbes contain a wide variety of PAMPS. All of these factors allow the interaction of the pathogens with more than one receptor on the interacting immune cell, providing an additional level of regulation. Still, in most studies only the effect of single receptor–ligand interactions is dissected (Fig. 2).

In addition to complement proteins, pathogen patterns can be recognized by several innate receptor families, such as C-type lectin receptors (CLR), NOD-like receptors (NLR) or Toll-like receptors (TLR). The complex microbial surfaces offer multiple binding sites for these receptors, which modulate host-cell response. Both synergistic and antagonistic interactions have been described for complement receptors and TLRs [142].

In the next paragraph, some examples of the cooperation between complement receptors and other sensors of nonopsonized and Ig-opsonized microbes are described briefly.

CR1-BCR

Simultaneous engagement of CR1 and BCR *via* complement opsonized antigens can significantly alter B-cell responses. Previously, our group was the first to show that in human system CR1 is a potent inhibitor of BCR-dependent B-cell activation – such as proliferation, cytokine and antibody production of cells – in both physiological and pathological conditions [9–12]. Since then the inhibitory function of CR1 was confirmed by others, using *in vivo* model systems as well [143–145].

CR1-TLR7, TLR9-BCR

In physiological and pathological conditions, when both complement and TLR activating microbial

products are present in the B-cell environment, the interaction between the two innate sensory systems has the potential to fundamentally alter or fine-tune B-cell responses. It has been shown recently that CR1 clustering has no effect on the TLR7-induced activation of tonsillar B cells. However, the TLR9-dependent responses of these cells were significantly and dose-dependently reduced by CR1 ligation [12]. These observations highlight diverse mechanisms of the interplay between CR1 and TLR7 or CR1 and TLR9, in regulating humoral immune responses.

CR2-BCR

In mouse system, it is well accepted that C3d-opsonized antigens, which crosslink CR2 with the BCR, augment antibody production by several order of magnitudes. Therefore, C3d is known as a molecular adjuvant with a capacity to bridge innate and adaptive immune responses [146]. However, in the case of human B cells the enhancement of antibody production by the C3-derived ligand has not been proven so far.

CR3-FcγRII, FcγRIII

Zhou and Brown reported that human neutrophils plated on a surface coated with both anti-CR3 and anti-FcγRIII antibodies, exert a strong respiratory burst. They showed that the lectin-like site of CR3, which is sensitive to saccharides, binds to the extensively glycosylated FcγRIIIB molecule. Furthermore, it has also been demonstrated that coligation of FcγRIII is required for the tyrosine phosphorylation of FcγRII. Thus, the cooperation of these three receptors leads to the FcγRII-dependent assembly of the NADPH oxidase [147].

CD14-TLR4-CR3

Hawley *et al.* [59] demonstrated that CD14, the GPI-linked LPS receptor expressed by phagocytes and CR3 are not associated under resting conditions; however, their interaction is rapidly induced in the presence of LPS, when they colocalize within lipid rafts.

Perera *et al.* [148] observed a combined participation of CR3, CD14 and TLR4 in the response to LPS and taxol, suggesting the formation of a receptor complex of these molecules on the surface of mouse macrophages. Later Han *et al.* [149] showed that TLR4 signalling activates CR3, which in turn provides negative feedback by enhancing the phosphorylation and subsequent degradation of TLR signalling molecules,

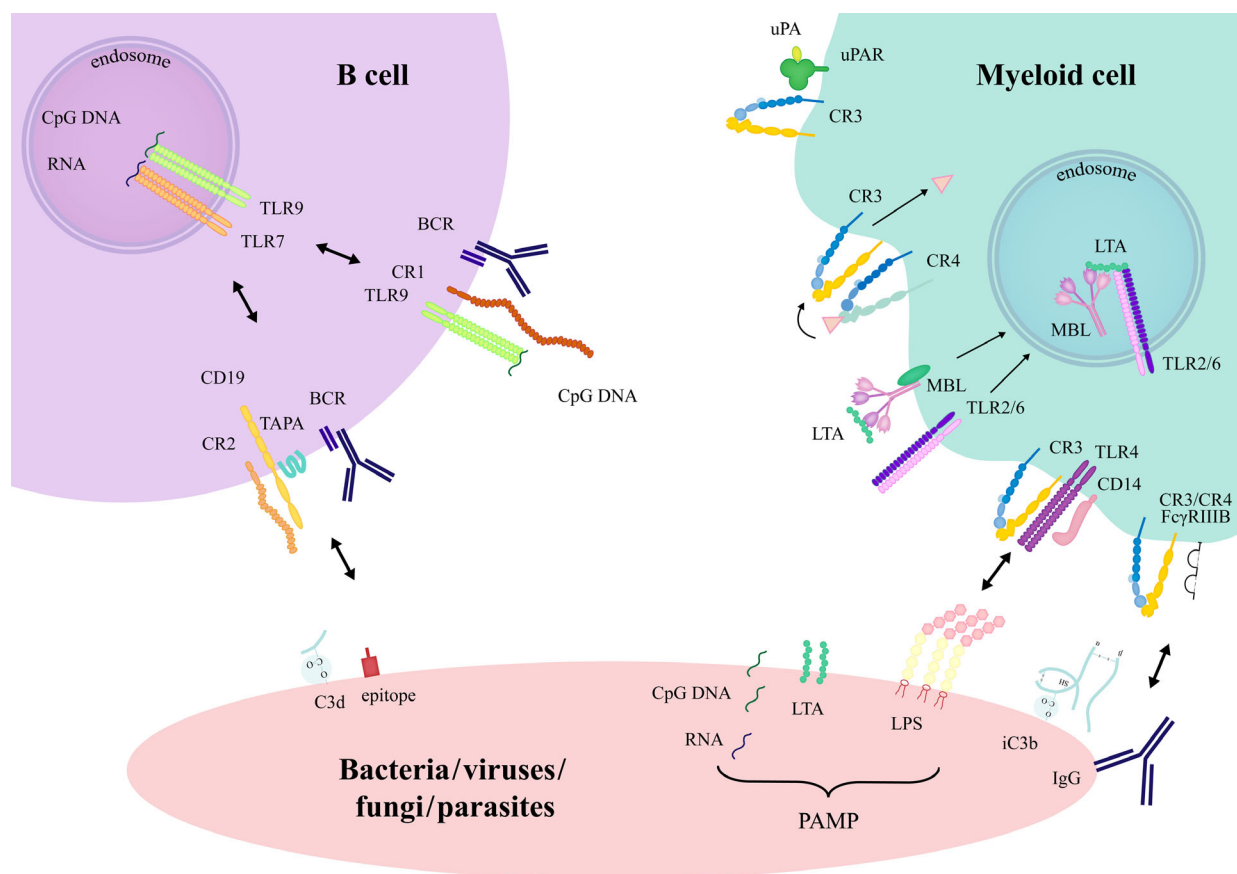


Fig. 2. Crosstalk between complement receptors and other host-cell membrane proteins induced by encountering pathogens. Crosstalk through direct association or *via* signalling cascade intersection has been described for complement receptors. The presence of pathogen-associated molecular patterns (PAMP) and opsonins on microbial surfaces promotes the simultaneous engagement of pattern recognition, complement, Fc-receptors and the BCR. CR3 may associate with FcγRIIIB and uPAR, and in the presence of LPS, it forms a complex with TLR4 and CD14. In macrophages, there is a division of labour between CR3 and CR4 in the binding and internalization of iC3b-opsonized particles. MBL and TLR2/6 both bind the bacterial lipoteichoic acid (LTA) and become associated in the phagosomes after internalization. The cooperation between CR1 and TLR7 or TLR9 inhibits human B-cell functions. In mouse, C3d-opsonized antigens crosslink CR2 with the BCR, which augments B-cell activation.

MyD88 and TRIF. This inhibitory effect of CR3 was also proved for the TLR7/8-induced inflammatory response on human macrophages [150].

uPAR-CR3

The most studied interaction between integrins and GPI-linked proteins involves the urokinase-type plasminogen activator receptor (uPAR; CD87) [151]. This receptor is expressed on a wide variety of cell types, including neutrophils and activated monocytes. uPAR-mediated calcium signalling was observed in the presence of CR3, while it did not occur in cells of leucocyte adhesion deficiency (LAD) patients or in normal neutrophils treated with anti-CR3 mAb. It has also been shown that complex formation with uPAR facilitates the adhesive functions of CR3 [152].

CR3-CR4

Our group found a division of work between CR3 and CR4 in the process of the phagocytosis of iC3b-opsonized *S. aureus*. In the case of monocyte-derived macrophages, we observed that blocking CR4 only decreased the amount of surface-bound particles, whereas internalization and digestion of the particles were dependent on CR3. While CR4 participates in the binding of iC3b-opsonized *S. aureus*, further steps leading to the digestion of the coccus are mediated by CR3 [56].

MBL-TLR2

MBL binds to the surface of *S. aureus* through lipoteichoic acid (LTA) that is also the ligand of TLR2/6. Ip *et al.* [137] showed that the presence of *S. aureus*

induced the association of MBL and TLR2 in phagosomes, and this interaction resulted in an enhanced inflammatory response.

Conclusion

The complement system is a major component of innate immunity, which contributes to the maintenance of host homeostasis. The activation of the complement cascade generates various biologically active complement protein-derived polypeptides that opsonize pathogens. Complement receptors interacting with these polypeptides are expressed by several cell types – including monocytes, macrophages, dendritic cells, neutrophil granulocytes, and T and B lymphocytes.

Engagement of the receptors leads to a wide array of responses, in many cases leading to the elimination of viruses, bacteria, fungi and parasites. On the other hand, pathogens utilize the same receptors to evade recognition and elimination. Learning more about the interaction and crosstalk between cells and microbes will help develop vaccines and treatment of infections.

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