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Review

# New aspects in the regulation of human B cell functions by complement receptors CR1, CR2, CR3 and CR4

Anna Erdei [a,b,*], Kristóf G. Kovács [a], Zsuzsa Nagy-Baló [b], Szilvia Lukácsi [b], Bernadett Mácsik-Valent [b], István Kurucz [b], Zsuzsa Bajtay [a,b]

[a] Department of Immunology, Eötvös Loránd University, Budapest, Hungary
[b] MTA-ELTE Immunology Research Group, Eötvös Loránd University, Budapest, Hungary

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ABSTRACT

The involvement of complement in the regulation of antibody responses has been known for long. By now several additional B cell functions – including cytokine production and antigen presentation – have also been shown to be regulated by complement proteins. Most of these important activities are mediated by receptors interacting with activation fragments of the central component of the complement system C3, such as C3b, iC3b and C3d, which are covalently attached to antigens and immune complexes. This review summarizes the role of complement receptors interacting with these ligands, namely CR1 (CD35), CR2 (CD21), CR3 (CD11b/CD18) and CR4 (CD11c/CD18) expressed by B cells in health and disease. Although we focus on human B lymphocytes, we also aim to call the attention to important differences between human and mouse systems.

## 1. Introduction

The complement system is a major component of immune defense. As an integral part of innate immunity it provides a fast, first-line protection against invading pathogens. At the same time the activation products of the complement cascade induce inflammation and shape the adaptive immune response. The major component C3 is present in plasma at concentrations of 1.5–1.8 mg/ml. People with C3 deficiency display severe clinical manifestations, reflecting the central role of this complement component [1]. Activation of C3 is the point where the three routes of complement activation – the alternative, lectin-dependent and classical pathway – converge. Once activated, C3b, the first large cleavage product of C3 becomes attached covalently to the activating surface and, along with further degradation fragments such as iC3b and C3d, serves as a ligand for various complement receptors (Fig. 1.). Pathogens, antigens, autoantigens and immune complexes readily activate either of the three complement pathways, and become opsonized by such C3-derived fragments which may interact with different receptors, like CR1 (CD35), CR2 (CD21), CR3 (CD11b/CD18), CR4 (CD11b/CD18) – hereafter collectively designated as C3-receptors for simplicity – expressed by a wide variety of cell types.

First in line, the membrane glycoprotein that is the C3b receptor – termed by Nelson immune adherence receptor [2] – was identified on erythrocytes, polymorphonuclear leukocytes, B lymphocytes and monocytes [3]. This finding was shortly followed by the discovery of further cellular receptors binding iC3b, C3dg, and C3d, respectively, and several cell types were identified expressing one or more of the C3-receptors [4,5]. The indispensable role of C3 in opsonization, and the participation of CR1, CR3 and CR4 in the binding and uptake of C3-fragment bearing pathogens and immune complexes by erythrocytes, macrophages, neutrophil granulocytes and dendritic cells have been known for long [6–8]. Furthermore, the negative regulatory role of primate CR1 in complement activation has also been extensively studied [9].

Our knowledge regarding the expression and role of C3-receptors in human B lymphocytes under physiological and pathological conditions however, is just being expanded. Complexes of antigen, antibody and complement proteins formed *in vivo* may interact with complement receptors simultaneously with the occupancy of the B cell receptor (BCR) as well as Fc-receptors via the opsonizing antibodies and with Toll-like receptors (TLRs) binding to pathogen associated molecular patterns (PAMPs). All these interactions provide important feedback signals for the immune system.

Since the early findings of Pepys obtained by studying the humoral immune response in mice [10], numerous investigations have dealt with the role of complement in B cell functions. By now it has become clear

* Corresponding author at: University L. Eötvös, Pázmány Péter s. 1/C, 1117 Budapest, Hungary.
*E-mail address:* anna.erdei@ttk.elte.hu (A. Erdei).

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that there are major differences between humans and mice in this aspect, mostly due to profound differences between the cellular distribution and genetic background of various C3-receptors. Here we aim to summarize studies obtained with human B cells and call the attention to dissimilarities between the two species.

In addition to the implication of complement in B cell functions of healthy donors, various pathological conditions will also be discussed. Its importance is indicated by investigations where complement activation by autoantigens and immune complexes followed by the covalent deposition of the C3 fragments, as well as the role of the various C3-receptors have been studied in the progression of autoimmune diseases and in various B cell malignancies.

In this review the most important findings will be highlighted that show how complement might influence human B cell functions in health and disease.

## 2. Expression and function of CR1 (CD35)

### 2.1. Structure and ligands

Human complement receptor type 1 (CR1, CD35) is a 200 kDa, single-chain, type 1 transmembrane glycoprotein which belongs to the regulators of complement activation (RCA) family proteins [11] (Fig. 2.). It consists of a 43 amino acid long cytoplasmic domain, a 25 amino acid long transmembrane domain and an extracellular region that is mostly formed by 30 evolutionarily conserved complement control protein (CCP) modules. The CCP modules are also known as short consensus repeats (SCR) or sushi domains, and have a highly conserved structure with approximately 60 to 70 amino acids [12], including four cysteine residues forming internal disulfide bonds [13]. The 28 amino terminal CCPs of CR1 can be grouped into four long homologous repeats (LHRs A-D) [14]. Four allotypic forms of CR1 have been described based on molecular weight and glycosylation [14,15]. In addition, its polymorphism also gives rise to the Knops blood group system [16].

CR1 possesses both receptor and regulatory functions. It binds complement fragments C3b and C4b with high affinity [17] and iC3b with low affinity [18]. It also interacts with C1q [19], mannose binding lectin (MBL) [20] and Epstein-Barr virus (EBV) [21]. Multiple CCPs of different LHRs are responsible for the distinct interactions of CR1 [21]. In addition to its role in various B cell functions – detailed later – CR1 expressed on nucleated cells plays an important role in the regulation of the complement cascade as a member of the CCP superfamily by exerting decay accelerating activity for the C3/C5-convertases, and serving as a cofactor for factor I-mediated cleavage of C3b [22,23]. On

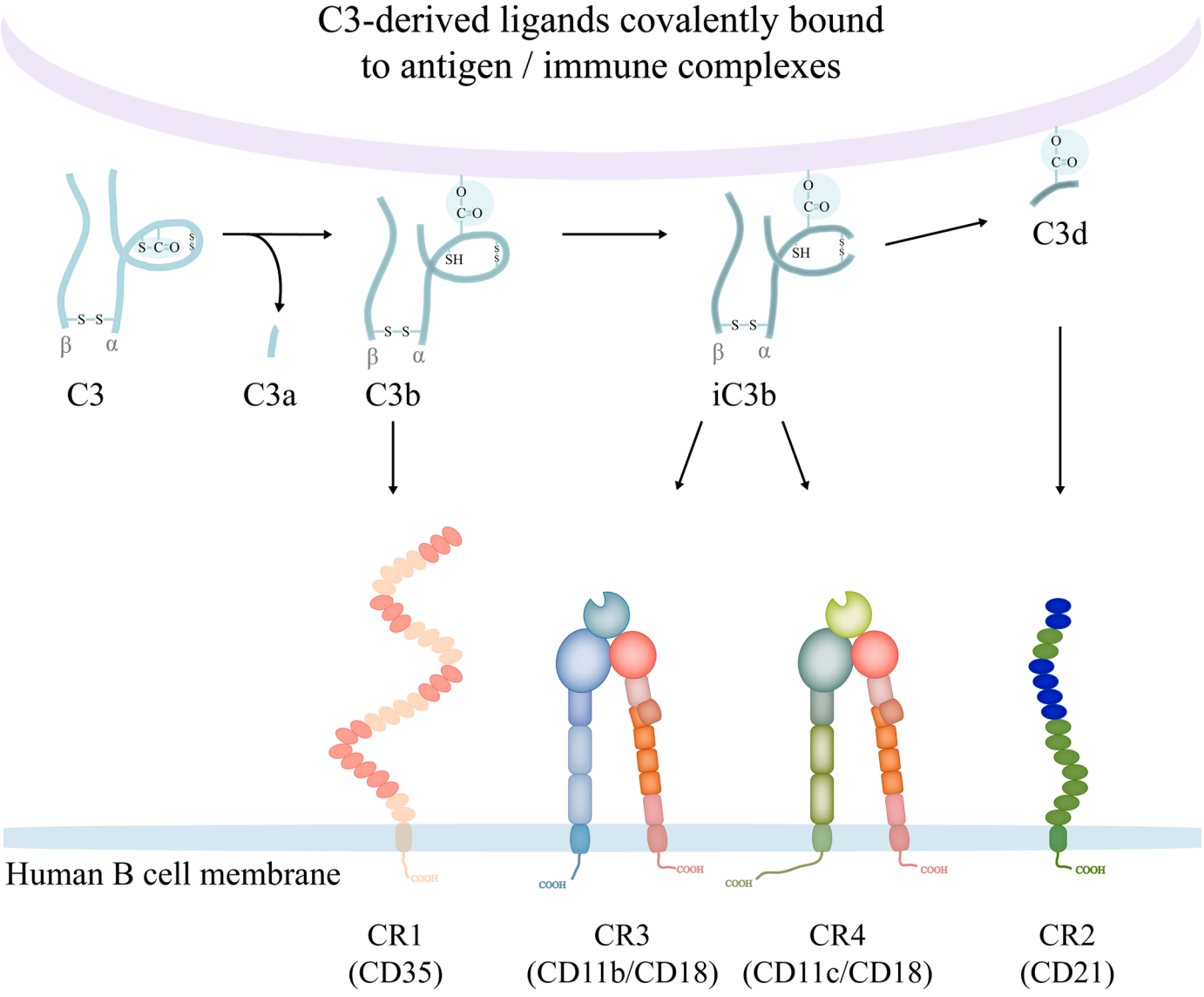


**Fig. 1. C3-derived covalently fixed ligands and their corresponding receptors expressed by B lymphocytes known to regulate BCR-induced functions.**

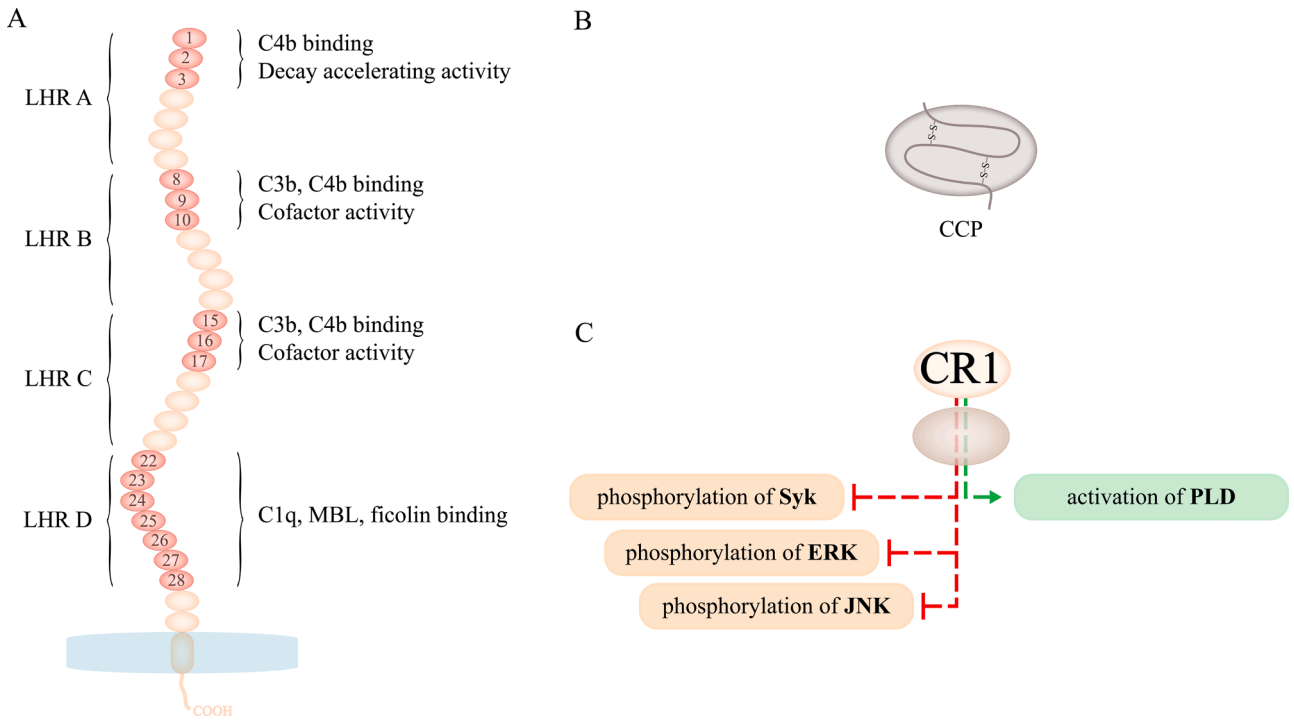


**Fig. 2. Human CR1 (CD35).**
Structure (A-B), involvement in intracellular signaling events (C).

primate erythrocytes CR1 mediates immune complex adherence and transport to the liver and spleen for phagocytosis [24].

The 25 amino acid long cytoplasmic tail of CR1 contains one potential threonine phosphorylation motif [25]. Triggering CR1 was shown to activate phospholipase D (PLD), which is the main signal for the phagocytosis of complement opsonized particles in human neutrophil granulocytes [26]. Regarding direct signaling via CR1 in human B cells no data are available. However, it has been described that upon the simultaneous engagement of CR1 and the BCR, the phosphorylation of key BCR-linked signaling molecules is inhibited, namely the Syk tyrosine kinase, as well as the mitogen-activated protein kinases (MAPKs) ERK and JNK [27].

In humans CR1 and CR2 are encoded by distinct genes, in contrast to mice, where one gene encodes the two alternatively spliced proteins [28] (Fig. 3.). In the membrane of human B cells a major portion of CR1 appears in complex with CR2 [29], as discussed later.

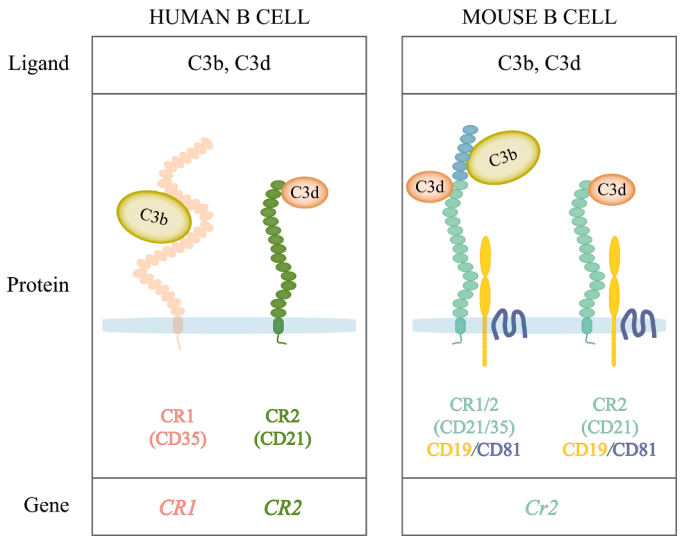


**Fig. 3. Differences between the genetic background and appearance of human and mouse CR1 (CD35) and CR2 (CD21) in the B cell membrane.**

### 2.2. Cellular distribution

CR1 is expressed in various human cell types. Its diverse functions – in addition to its cofactor activity which is universal on nucleated cells – are summarized in Table 1. CR1 is also present in plasma in a soluble form (sCR1), comprising the extracellular portion of the protein [30,31].

### 2.3. Role in B cells

#### 2.3.1. Role in mouse B cells

Mouse CR1 is significantly different from human CR1 in many aspects. It is encoded by the murine *Cr2* gene, which also gives rise to mouse CR2 through alternative splicing. Thus, mouse CR1, the bigger molecule is built up of CR2 containing the 15 CCP modules with additional 6 CCP modules at its N-terminal, hence this molecule is often

**Table 1**
**Cellular distribution and function of human CR1 (CD35).**

| Cell type | Function of CR1 |
|---|---|
| B lymphocyte | inhibition of several functions [27, 32–37] (discussed below in details), enhancement of antigen uptake and presentation [38–40] |
| T lymphocyte | inhibition of proliferation [41], generation of regulatory T cells [42] |
| follicular dendritic cell (FDC) | antigen retention [43] |
| red blood cell (RBC) | immune complex clearance [24] |
| monocyte, macrophage, basophil granulocyte, eosinophil granulocyte, neutrophil granulocyte, mast cell, endothelial cell, Langerhans cell, Kupffer cell | phagocytosis/endocytosis of complement opsonized particles [3,44] |
| glomerular podocyte, neuron, microglia cell, astrocyte, natural killer (NK) cell | inhibition of complement activation [45–47] |

designated as mouse CR1/2 (Fig. 3.). It forms trimolecular complexes with CD19 and CD81 [48,49]. The common signaling denotes that most of the functions of mouse CR1 are identical to mouse CR2 (discussed in the section on CR2), except for its C3b binding and Factor-I cofactor activity mediated by its first 6 CCP modules [50]. A recent study of a CR1 deficient mouse line confirmed the important role of mouse CR1 in the development of a humoral immune response and showed that in mice, the preferential expression of CR1 is characteristic for FDCs, whereas B cells predominantly express CR2 [51].

#### 2.3.2. Role in human B cells in health

Early studies regarding the role of human CR1 on B cells lead to ambiguous results, mainly due to the dissimilar experimental conditions and nonphysiological ligands applied. Daha et al. described that antibody production of B cells suboptimally stimulated by pokeweed mitogen (PWM) can be enhanced by clustering CR1 [52], while others found that C3b inhibited the same process under similar conditions [53,54]. Triggering CR1 with receptor-specific antibodies was demonstrated both to induce [55] and not to induce B cell differentiation to plasma cells [56]. Furthermore, while some groups showed that co-ligation of CR1 with BCR can suppress the proliferation of human B cells [57,58], others could not confirm this correlation [55,56,59].

Our research group studied intensively the effect of CR1 ligation on BCR-stimulated human cells using the natural, multimeric ligand of the complement receptor: C3b-like C3. We found that all the studied BCR induced functions were significantly and dose-dependently inhibited, including the increase of intracellular free $Ca^{2+}$ level [32], the phosphorylation of Syk, and mitogen-activated protein kinases (MAPKs) ERK and JNK [27], the expression of activation markers CD69 and CD40 [27], proliferation [27,32,33] as well as IgM and IgG production [27,33].

Further investigating the role of CR1 on human B cells, we revealed that it significantly inhibits not only the BCR induced B cell functions, but also the Toll-like receptor 9 (TLR9) dependent B cell activation [34]. Furthermore, we showed that ligation of CR1, together with either TLR7 or TLR9 stimulation, differentially regulates IL-6 secretion, proliferation and IgM production [34].

The role of CR1 and CR2 in the uptake and presentation of complexes formed by C3b covalently bound to tetanus toxin antigens has been shown by Arvieux et al. [38] and Colomb et al. [39]. They demonstrated that C3b-opsonized antigens enhance the proliferation of human T cell clones specific for tetanus toxin. It has also been shown that both antigen-specific and non-specific B cells were involved in this process [40].

#### 2.3.3. Role in human B cells in disease

Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are both chronic, inflammatory autoimmune diseases. Their pathogenesis is mediated by the formation of autoreactive B lymphocytes whose secreted autoantibodies form immune complexes with the autoantigens and activate the complement system. Complement receptors binding these complexes contribute greatly to the clinical manifestations of the diseases. The reduced expression of CR1 on most cell types – including red blood cells – is characteristic for both diseases [60–62]. Importantly however, our findings revealed that the decrease in the number of CR1 on B cells does not affect its inhibitory capacity, and even the reduced amount of CR1 of RA and SLE patients can induce significant inhibition of B cell functions [27,33]. Furthermore, we showed that the number of CR1 declines significantly during B cell differentiation from naïve or memory B cells toward plasmablasts both in RA patients and healthy controls [33], which suggests that instead of influencing the severity of an ongoing disease, CR1 most probably plays crucial roles in the maintenance of peripheral B cell tolerance.

In addition, recent studies have demonstrated the therapeutic potential in utilizing the B cell inhibitory role of CR1, studying *in vivo* systems [35–37]. Voynova et al. constructed a chimeric molecule consisting of a DNA-mimotope peptide and a CD35-specific antibody, which selectively suppressed the antibody production of DNA-specific, autoreactive B cells of SLE patients by co-crosslinking their BCR with CR1 [35]. Applying these constructs, Kerekov et al. reported a selective elimination of autoreactive B cells in the humanized mouse model of SLE [36]. Furthermore, Manoylov et al. demonstrated that similar constructs suppressed the antibody production of autoreactive B cells in Type 1 diabetes mellitus (T1DM) patients [37].

Genetic CR1 deficiency has not been reported in any individuals to date.

#### 2.3.4. Cooperation with other receptors

CR1, MCP (membrane cofactor protein, CD46) and factor H, all serve as cofactors during the factor I mediated limited proteolysis of C3b generating iC3b [22,63], which functions as a major opsonin facilitating phagocytosis of particles and immune complexes. A further degradation step, also mediated by factor I generates C3d(g) [23]. All these three cleavage products remain covalently attached to the complement activating agent, and may be transferred from CR1 to CR2 on the surface of human B cells [23,29]. This process is also essential in antigen retention on follicular dendritic cells (FDCs) [43].

The possible cooperation between CR1 and MCP has not been studied so far. Regarding the simultaneous engagement of CD46 and the antigen binding receptors on T cells the increase of cell proliferation and generation of a unique regulatory T cell phenotype have been described [64]. In contrast to this, the concurrent ligation of CD46 and BCR had no effect on the proliferation and antibody production of human B cells [65].

On human B cells Tuveson et al. revealed the existence of CR1/CR2 complexes [29], which suggests that the CR2 induced inhibitory functions (discussed in the section on CR2) are most probably mediated by the inhibitory CR1.

Recently a substantial cooperation between BCR, CR1 and TLR9 has been demonstrated, which serves as an additional level in the regulation of B cell functions [34]. It has been shown that ligation of CR1 on human B cells significantly inhibits not only the BCR induced, but also the Toll-like receptor 9 (TLR9) dependent B cell functions [34].

## 3. Expression and function of CR2 (CD21)

### 3.1. Structure and ligands

As mentioned earlier, in humans CR1 and CR2 are encoded by two distinct genes, in contrast to mice [28] (Fig. 3.), thus their structure and function are different.

Human complement receptor type 2 (CR2, CD21, also termed Epstein-Barr virus receptor) is a 145 kDa, single-chain, type 1 transmembrane glycoprotein, consisting of a 111 kDa polypeptide chain and *N*-linked oligosaccharides [66,67]. CR2 is a member of the RCA family proteins [11] (Fig. 4.).

Depending on alternative splicing, the extracellular part of human CR2 consists of 15 or 16 CCP modules [68], termed as CD21 short and long isoforms (CD21S and CD21L). CD21S which lacks CCP10 has been reported to be specifically expressed on B cells, whereas CD21L appears on FDCs [69]. The CCPs of CR2 can be organized as four LHRs [69]. The receptor comprises a 24 amino acid long transmembrane and a relatively short, 34 amino acid long intracellular region [70].

Overlapping but non-identical binding sites of the two N-terminal CCP modules (CCP1–2) are responsible for its complex formation with complement fragments iC3b [71], C3dg and C3d [72,73], the Epstein-Barr virus (EBV) envelope protein gp350/220 [74], IFN-α [75], FcεRII (CD23) [76] and DNA [77], whereas a further, glycosylation dependent interaction has been described between FcεRII and CCP5–8 [78].

CR2 can induce specific intracellular signaling in human B cells separately from the BCR and CD19 mediated signaling. Triggering CR2

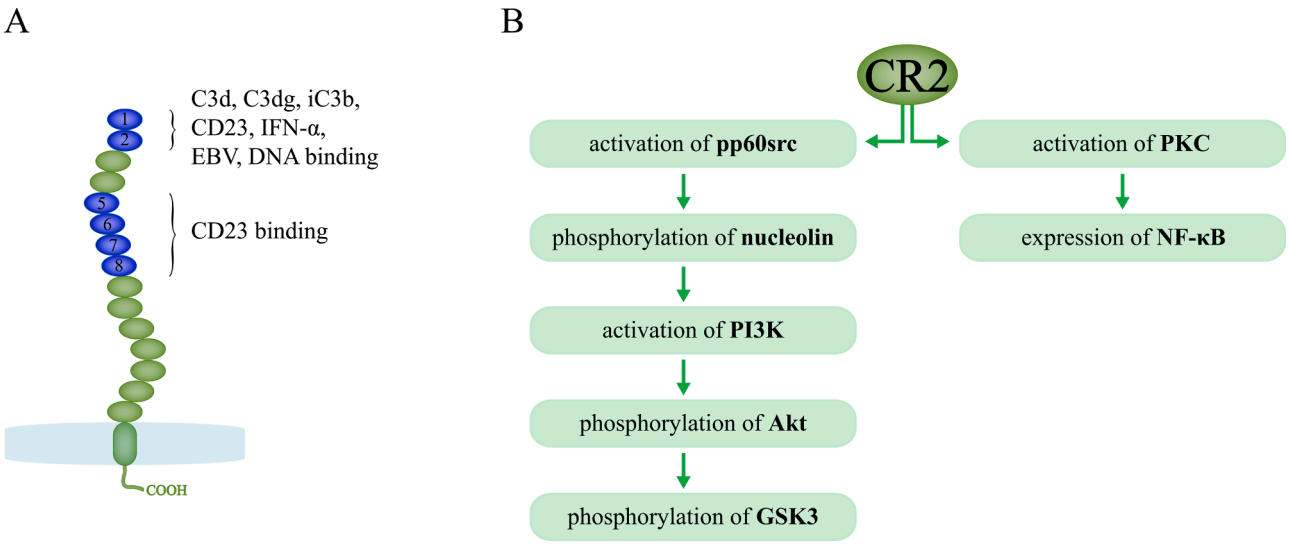


**Fig. 4. Human CR2 (CD21).**
Structure (A), involvement in intracellular signaling events (B).

activates the tyrosine kinase pp60src of Src family, which then phosphorylates nucleolin, independently of Syk tyrosine kinase [79]. Then, nucleolin interacts with the p85 subunit of phosphatidylinositol 3-kinase (PI3K) [80], resulting in the initiation of its kinase activity [81]. After that, PI3K phosphorylates the serine-threonine kinase Akt [79]. Subsequently, Akt phosphorylates the glycogen synthase kinase-3 (GSK3) [79], which is a serine-threonine kinase with numerous known substrates including NF-κB transcription factor in human B cells [82]. In addition to these, triggering CR2 with gp350 was also demonstrated to induce the expression of NF-κB via a protein kinase C (PKC) dependent pathway [83].

### 3.2. Cellular distribution

CR2 is expressed by several cell types in humans and plays various roles as summarized in Table 2. Its function in many cell types is still unidentified. In addition, a soluble form of CR2 (sCR2) can be found in serum [84–86].

### 3.3. Role in B cells

#### 3.3.1. Role in mouse B cells

Due to the identical membrane proximal, transmembrane and intracellular domains of mouse CR1 and CR2, all functional properties of CR2 apply to both receptors [97]. CR2 of mice and humans share only 65% homology in protein sequence [98], and – similarly to human CR2 – mouse CR2 was also shown to bind iC3b and C3d with high affinity [99,100]. In 1974, C3 fragments were demonstrated to affect murine B cell functions including antibody responses, revealing that complement fragments may serve as a link between innate and adaptive immunity [10]. Then, C3d was shown to control the growth of activated murine B cells [101,102]. Later, both the activation of naïve B cells and the survival of germinal center B cells toward memory B cells were shown to require a positive signal through CR2 [103,104]. As an important step, in 1996 Dempsey et al. demonstrated that co-ligation of mouse CR2 and BCR with antigen bound C3d dose-dependently augment the humoral immune response of mice by significantly lowering the threshold for B cell activation, identifying C3d as a molecular adjuvant in mice [105].

**Table 2**
**Cellular distribution and function of human CR2 (CD21).**

| Cell type | Function of CR2 |
|---|---|
| B lymphocyte | inhibition of several functions [87] (discussed below in details), enhancement of antigen uptake and presentation [38–40] |
| T lymphocyte | increase of intracellular free $Ca^{2+}$ concentration [88] |
| follicular dendritic cell (FDC) | antigen retention [43] |
| basophil granulocyte | increase of histamine release [89] |
| epithelial cell [90–92], keratinocyte [93], mast cell [94], astrocyte [46], thymocyte [95,96] | unknown function |

#### 3.3.2. Role in human B cells in health

The role of human CR2 has been studied intensively for many years, however, its involvement in boosting the antibody production of B cells has not been demonstrated adequately. Hence, the tempting idea to use C3d as a potent adjuvant for human vaccines had to be dismissed. Available data on the effects of CR2 on human B cell functions were contradictory due to the various experimental conditions applied to stimulate B cells including pokeweed mitogen, B cell growth factor, Staphylococcus aureus Cowan I, and IgM specific antibodies [57,106,107] as well as the different agents to ligate CR2 – such as CR2 specific antibodies and C3d [108,109]. Some studies were carried out using Sepharose or dextran conjugated anti-BCR and anti-CR2 antibodies [57,110]. These data show that both the synergistic enhancement and inhibition of proliferation have been described in the different experimental system.

Recent studies, in which C3d (the natural ligand of CR2) and anti-BCR antibodies were crosslinked via streptavidin, showed that co-ligation of CR2 with the BCR leads to the elevation of a suboptimal intracellular free $Ca^{2+}$ concentration to the extent obtained during an optimal BCR stimulation [87,111,112]. It has been proven that under these conditions the NFAT pathway is initiated instead of the NF-κB signaling route, which suppresses B cell functions [113,114]. Applying experimental conditions closer to the *in vivo* occurring situation, we have reinvestigated the role of human CR2 recently. Our findings revealed that co-clustering CR2 and BCR significantly and dose-dependently inhibits the expression of the early activation marker CD69 and the release of the cytokine IL-6 [87].

An early event of B cell activation is blastogenesis, which is essential for the formation of antibody secreting cells [115]. A series of our ongoing experiments very recently highlighted an important but so far unrevealed process namely, that the co-ligation of CR2 and the BCR

inhibits the plasmablast formation of human B cells. This is visibly displayed by the C3d induced inhibition of the increase in cell size upon B cell activation (Fig. 5.). Monroe et al. demonstrated that the diameter of B cells correlates to their cell cycle progression [115]. Our data clearly show that co-crosslinking of BCR and CR2 results in the arrest of cell cycle progression, as the mean cell diameter of the C3d-treated samples is significantly lower than that of the BCR-activated samples (Fig. 5.). Therefore, our work in progress suggests that in contrast to mice where C3d has a growth factor-like activity [101,102], in humans C3d arrests the cell cycle.

Importantly, we found that the BCR induced proliferation and antibody production (both IgM and IgG) are also dose-dependently and significantly inhibited by the co-ligation of CR2 and BCR on human B cells [87]. These experiments undoubtedly proved that human CR2 serves as an inhibitory coreceptor of BCR during B cell activation [87], opposite to its role in the mouse. These data are strengthened by the lack of publications stating otherwise and call the attention to the fact that results of mouse studies cannot always be applied directly to humans, and should be handled cautiously.

The molecular mechanism behind the inhibition of the BCR-induced processes by CR2 is most probably due to the fact that in the cell membrane of human B cells CR2 is present in association with the inhibitory CR1, furthermore CD19 is excluded from this complex [29]. Although some CR2 may appear together with CD19 [29], which may augment B cell activation under certain conditions, the signaling activity of these complexes is inactivated upon BCR activation [116], which further emphasizes the relevance of the inhibitory CR1/CR2 complexes on human B cells. The strong inhibitory effect of human CR1 on the BCR induced functions, as detailed in previous sections, has been demonstrated *in vitro* as well as *in vivo* [27,32–37].

### 3.3.3. Role in human B cells in disease

As discussed above, autoantibodies contribute greatly to the pathogenesis of both RA and SLE where the expression of CR2 on B cells is significantly reduced [60,117–119]. The degree of CR2 expression correlates negatively with both the SLE Disease Activity Index (SLEDAI) [117] and the RA Disease Activity Score of 28 joint counts (DAS28), showing that the severity of symptoms increases with the decreasing level of CR2 expression. This finding was further confirmed by comparing RA patients to healthy controls or to DMARD (disease modifying antirheumatic drug) treated follow-up patients after 6 months [119]. In addition, B cells taken from the synovial tissues of RA patients display significantly lower degree of CR2 expression than the peripheral B cells of the same patients [118]. These findings suggest that an insufficient level of CR2 expression may contribute considerably to the onset of B cell mediated autoimmune diseases.

We have recently revealed an indirect correlation between the degree of BCR induced B cell activation and CR2 mediated inhibition of B cell functions. We have found that the CR2 induced inhibition is the most potent in the case of a weak BCR stimulus, which might be the case at the initiation of an immune response [87]. We also demonstrated earlier that the level of CR2 expression gradually decreases while naïve B cells develop into memory cells and plasmablasts [33]. These findings, together with the discovery that CR2 can bind self-antigens like ssDNA, dsDNA, chromatin or histones [77], suggest a prominent role for CR2 in the maintenance of peripheral B cell tolerance, mediated by its inhibitory effects on the initial steps of peripheral B cell activation.

Genetic CR2 deficiency has recently been described. Wentink et al. found by comparing CR2-deficient patients to a patient with CD19 and CD81 deficiency, that whereas the commonly observed hypogammaglobulinemia in the latter case was due to defective BCR signaling, in

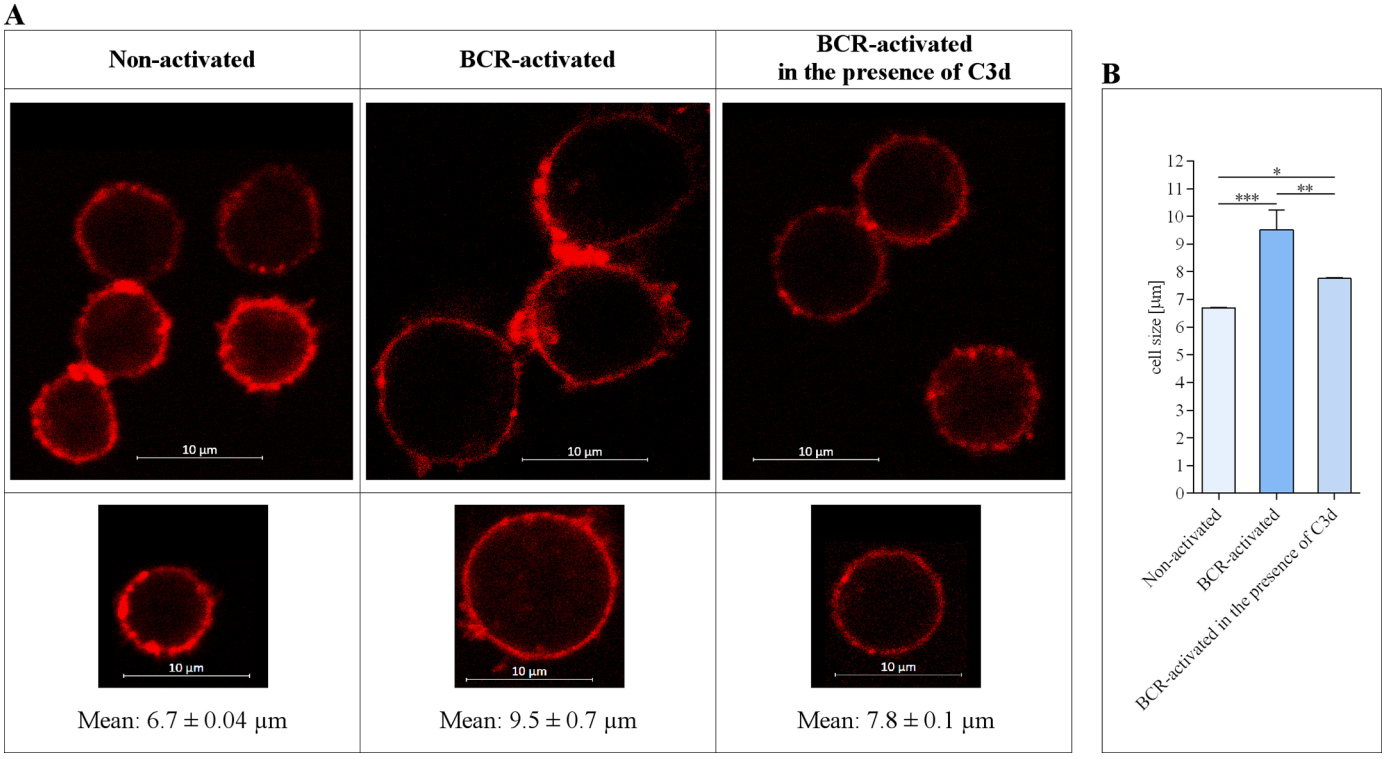


**Fig. 5. C3d inhibits the blastogenesis of human B cells by arresting the cell cycle progression.**
Human B cells were labeled with AF555-conjugated CD19-specific antibodies and analyzed by a Zeiss confocal laser scanning microscope immediately after isolation (Non-activated) and following 48 h of culturing with complexes consisting of streptavidin-conjugated biotinylated 5 µg/ml anti-IgG/A/M (BCR-activated), or streptavidin-linked biotinylated 5 µg/ml anti-IgG/A/M and biotinylated 3.8 µg/ml C3d (BCR-activated in the presence of C3d). Representative microscopic images and the mean cell diameter ± SD of the distinct samples obtained in three independent experiments are shown (**A**). Cumulative mean cell size ± SD is displayed with the statistical results of one-way analysis of variance (ANOVA) by GraphPad Prism (**B**). *p < 0.05, **p < 0.01, ***p < 0.001. The mean cell number investigated in each experiment was 310.

CR2-deficient patients the BCR induced signal transduction was intact [120]. Furthermore, Thiel et al. demonstrated that neither the activity of the complement system, nor the expression of CR1 is impaired in CR2 deficiency, therefore, the CR1 mediated inhibition is maintained and most probably leads to the diminished antibody response to certain vaccines [121]. These findings further support results obtained in *in vitro* experiments [87], showing that in humans CR2 is not a positive co-receptor for the BCR, in contrast to mice.

#### 3.3.4. Cooperation with other receptors

Based on its short C-terminal cytoplasmic domain, CR2 supposedly requires other molecules to induce signal transduction. CR2 is most often described as part of a complex with CD19, CD81 (TAPA-1) and Leu-13 [122–124]. However, CR2 was also demonstrated to form a bimolecular complex with the inhibitory CR1, in which case its association with CD19 is prohibited [29,125]. As both CR2 and Toll-like receptor 9 (TLR9) are receptors for DNA [77,126], recently, attention has been called to the proposed existence of their cooperation [127]. Our recent findings revealed that the TLR9 induced B cell activation is significantly inhibited by the activation of CR1 [34] (discussed in the section on CR1), which might be a consequence of the relocation of CR1 to the close proximity of TLR9 upon simultaneous DNA recognition by TLR9 and CR2, which may be required to facilitate CR1 to suppress the TLR9 induced signaling pathway. These suggest that the inhibitory CR1/CR2 complexes incorporate the majority of CR1 and CR2 present in the B cell membrane. However, to date, no quantitative analyses of the occurrence of these complexes have been conducted.

## 4. Expression and function of CR3 (CD11b/CD18) and CR4 (CD11c/CD18)

The complement receptors CR3 (CD11b/CD18, also known as Mac-1; $\alpha_M\beta_2$) and CR4 (CD11c/CD18, also known as p150,95; $\alpha_X\beta_2$) play an essential role in cell motility and the elimination of pathogens and apoptotic cells via phagocytosis. They belong to the leukocyte specific $\beta_2$-integrin family together with two other members: LFA-1 (CD11a/CD18, $\alpha_L\beta_2$) and CD11d/CD18 ($\alpha_D\beta_2$). CR3 and CR4 are generally thought to mediate overlapping functions, and although present day's examinations have proven a widening operational segregation between the receptors (reviewed recently in [128]) their similarity makes it reasonable to discuss them in parallel. In this review only their role in human B cells in health and disease (4.4.2, 4.4.3) will be covered separately.

### 4.1. Structure and ligands

These receptors are transmembrane heterodimers, consisting of non-covalently coupled α and β chains. They have a large extracellular region for ligand binding, a transmembrane domain and a short cytoplasmic tail (Fig. 6.), interacting with signaling molecules and the actin cytoskeleton [129,130]. The α subunit head consists of a β-propeller and I-domain (Inserted) and it is connected to an elongated leg region, including three domains with a β-sheet structure, the thigh, calf-1 and calf-2 [131]. The β subunit head is formed by an I-like domain and the leg includes a PSI (plexin-semaphorin-integrin), a hybrid, four I-EGF (integrin-epidermal growth factor) and a β tail domain (TD) [132,133].

The many ligands described for CR3 and CR4 include complement proteins (iC3b, C3d, factor H), ECM components (fibronectin, collagen, laminin), coagulation factors (fibrinogen, factor X) and adhesion molecules (ICAMs, VCAM-1), all recognised by the ligand binding site in the αI-domain [134–140]. With the crystal structures available for the I-domains of both receptors, Vorup-Jensen et al. showed a ridge of positively charged residues present only in CR4, that results in a differential ligand binding compared to CR3 [141]. While CR3 recognizes molecules with a positive charge, CR4 preferentially binds polyanionic species and molecules with a net negative charge [142,143]. Additionally an I-domain independent binding of fungal β-glucans was described for CR3 [144] and a site for bacterial lipopolysaccharides (LPS) was shown for both receptors [145,146].

The ligand binding affinity of these adhesion receptors is tightly regulated by a conformational change between an inactive bent and an activated extended conformation of the extracellular parts (Fig. 6.) [147]. The close interactions of the α and β transmembrane and cytoplasmic domains keep integrins in the inactive state, and to acquire an active conformation, these regions must be separated. This important process is regulated mainly by the cytoskeletal protein talin, which binds to the tail region of the β chain and disrupts the association of the two receptor chains and initiates the separation of the transmembrane domains [148,149].

### 4.2. Cellular distribution

The expression of CR3 and CR4 varies between cell types and species (Table 3 and 4) [128]. In humans both receptors can be found on

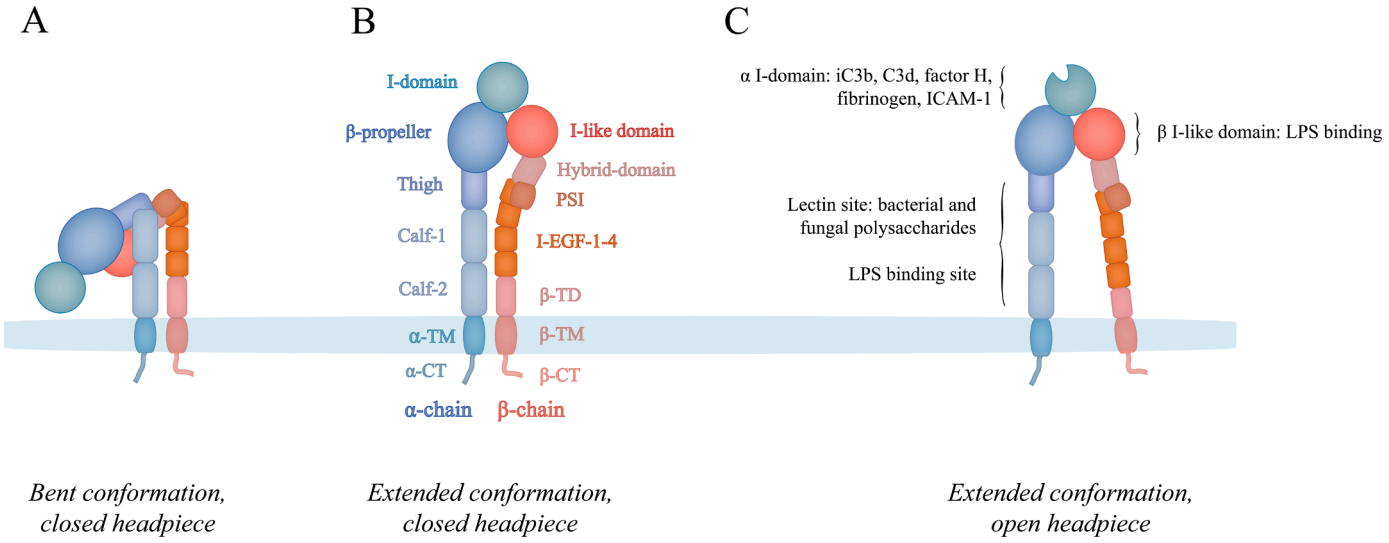


**Fig. 6. Structure and conformational states of iC3b binding $\beta_2$-integrins: CR3 and CR4.**
$\beta_2$-integrins can transition between a low affinity bent (A), an intermediate extended (B) and a high affinity extended (C) conformation. The ligand binding regions of CR3 are illustrated on (C).

**Table 3**
**Cellular distribution and function of human CR3 (CD11b/CD18).**

| Cell type | Function of CR3 |
|---|---|
| B lymphocyte | migration [160] |
| T lymphocyte | homing to inflammatory sites [161], inhibition of IL-2 secretion and proliferation [156] |
| monocyte | phagocytosis [162,163], adherence to endothelium [164] |
| macrophage | phagocytosis [165], podosome formation [166] |
| microglia | phagocytosis of apoptotic cells and debris in the CNS [167] |
| dendritic cell | phagocytosis, podosome formation [166,168] |
| neutrophil granulocyte | chemotactic migration [169], phagocytosis [170,171], NET release [172] |
| natural killer (NK) cell | enhancement of cytotoxic killing [173,174] |

**Table 4**
**Cellular distribution and function of human CR4 (CD11c/CD18).**

| Cell type | Function of CR4 |
|---|---|
| B lymphocyte | adhesion to fibrinogen [155,157], proliferation [155,157], migration [157] |
| T lymphocyte | conjugate formation with target cells [175] |
| monocyte | migration, adherence to endothelium [176] and fibrinogen [152,177] |
| macrophage | phagocytosis [178], adherence, migration, podosome formation [166,179] |
| dendritic cell | phagocytosis [180], adherence, migration, podosome formation [168,179] |
| neutrophil granulocyte | adhesion to endothelial cells [164], enhancement of anti-bacterial activity [181] |
| natural killer (NK) cell | complement dependent cellular cytotoxicity [182] |

myeloid cells, such as neutrophil granulocytes, monocytes, macrophages and dendritic cells [150–152]. On lymphoid cells they do not appear uniformly; while NK cells express CR3 constitutively [153,154], these $\beta_2$-integrins are usually present only on certain subpopulations of T and B lymphocytes [153], and may appear after activation [155–157] or during pathological conditions [158,159].

### 4.3. Role in myeloid cells

CR3 and CR4 provide the cell-cell and cell-ECM linkage to achieve the adhesion, spreading and migration of leukocytes [129]. For this purpose, immune cells of the monocytic lineage use specific adhesive structures, called podosomes, that mediate short-lived adhesion spots that are formed and quickly remodeled during migration [183]. High-resolution microscopy helped to understand the ultrastructure of podosomes, revealing that instead of a continuous ring, integrins are positioned in small islets around the F-actin core [184]. The importance of $\beta_2$-integrins in podosome formation is highlighted by studies showing that they are specifically recruited to podosomes in human dendritic cells on a fibronectin surface (in contrast to $\beta_1$-integrins), and that in a $\beta_2$-integrin-null mouse model podosome assembly is disrupted [168,185]. Our group also provided evidence, that in human monocyte derived macrophages (MDMs) and dendritic cells (MDDCs) attached to a fibrinogen coated surface, both CR3 and CR4 are located in the vicinity of podosome cores, and that this organization disappears upon LPS-induced podosome loss in MDDCs [166,179].

The other well accepted role of CR3 and CR4 is the phagocytosis of opsonized pathogens, tumor- and apoptotic cells. However, the participation of these receptors seems to depend on the cell type and the experimental conditions applied in the experiments. Whereas monocytes and neutrophil granulocytes preferentially use CR3 over CR4 for opsonic phagocytosis of several pathogens [140,163,165,166,170,171,186], the receptor utilization of macrophages is influenced by the subset of these cell types and the invading pathogen they encounter [165,166,171,178,187]. The outcome is also affected by the microbe to be ingested, since some pathogens are able to utilize complement receptors for the infection of host cells [188,189]. In addition to binding opsonized particles, CR3 and CR4 were shown to directly recognize bacterial or viral components as well [190,191].

Our group recently assessed the absolute number of cell surface CR3 and CR4 on human monocytes, neutrophil granulocytes, MDMs and MDDCs [128,152]. These data reveal that the expression level of the two receptors differs among these cell types. Comparing the ratio of CR3 and CR4 on the same cell type there is a strong shift in favor of CR3 in the case of monocytes and neutrophil granulocytes, whereas on MDMs and MDDCs the CD11b:CD11c ratio is close to 1:1. The notable differences in receptor number probably contribute to the functional diversity observed in the case of different immune cells.

### 4.4. Role in B cells

#### 4.4.1. Role in mouse B cells

In mice CR3 was found to regulate BCR signaling [192] as well as antibody class switching [193]. It was also shown, that CR3 contributes to the suppression of experimental autoimmune hepatitis [194]. These results suggest a general function for $CD11b^+$ B cells in the regulation of immune responses in mice. Furthermore, Rubtsov et al. showed that aged female mice acquire a $CD11b^+CD11c^+$ population of B cells, the so-called Age Associated B Cells (ABCs), which also appear in young lupus-prone mice and contribute to autoantibody production [195]. Interestingly however, while in mice $CD11b^-$ B1 cells were shown to be the progenitors of $CD11b^+$ B1 cells [196], human $CD11b^-$ B1 cells cannot be induced to express CD11b [197], highlighting important differences regarding the regulation of complement receptor expression in these two species. For this reason, it is important to point out, that data obtained in mouse systems cannot be applied to humans.

#### 4.4.2. Role in human B cells in health

*4.4.2.1. CR3 (CD11b/CD18).* Regarding the expression and role of CR3 on human B lymphocytes, numerous studies with often contradictory result can be found. According to Griffin and colleagues, around 10–13% of human B1 cells express CD11b, which are also positive for CD11c. These $CD11b^+$ B1 cells mostly belong to the $CD5^-$ subpopulation, in contrast to the majority of $CD11b^-$ B1 B cells which are positive for CD5. Importantly, these $CD11b^+$ cells do not derive from the $CD11b^-$ B1 cells, as both subsets retain their CD11b expression levels when separately cultured, moreover, stimulation of sorted $CD11b^-$ B1 cells failed to induce the expression of CD11b. These B1 cell populations fulfill different roles, as $CD11b^-$ B1 cells spontaneously secrete much more IgM than $CD11b^+$ B1 cells, while $CD11b^+$ B1 cells are able to stimulate allogeneic $CD4^+$ T cell expansion more efficiently [197]. Interestingly, while these $CD11b^+$ B1 cells drive T-cell proliferation with the help of elevated expression of the costimulatory molecule CD86, the same $CD11b^+$ B1 cell population has also been shown to secret IL-10 which suppresses CD3-mediated T-cell activation. For this reason, Griffin and Rothstein propose that $CD11b^+$ B1 cells should be termed “orchestrator” B1 cells [198]. It was shown that during self-protective immune reactions, *Trypanosoma cruzi*-derived protein-enriched fraction activates these $CD11b^+$ B1 B-cells in Chagas disease, and that this activation is associated with a beneficial clinical status [199]. However, the direct participation of CD11b in the observed functions was not investigated in these studies.

Beside CD11b expressing B-1 cells, Muto et al. found that approximately 20% of all blood B cells express CR3 [153], while Kawai et al. detected around 34% $CD11b^+$ cells among B lymphocytes, which were enriched in the $CD27^+$ memory population. The expressed CR3 was shown to contribute to the high migratory potential of this B cell population [160]. Kawai and colleagues also demonstrated that epigallocatechin gallate, the phenolic antioxidant exerted its

anti-inflammatory and anti-allergic effects by inhibiting the CR3 mediated adhesion and migration of blood B cells [200]. In contrast to these data, Postigo et al. detected no significant expression of CD11b on tonsillar or blood B lymphocytes, even after activation [155]. Our recent results are in line with the earlier findings of Postigo et al., confirming the lack of CR3 on human B cells [157,158]. At the same time, it is important to mention that according to Griffin and colleagues in healthy donors less than 1% of B cells belong to the $CD11b^+$ B-1 subset [197], thus they might easily escape the detection level of the different experimental conditions.

*4.4.2.2. CR4 (CD11c/CD18).* Regarding the expression of CR4 on human B lymphocytes the available data are rather variable. In 1990 Wormsley et al. found that approximately 20% of peripheral blood B cells express CD11c [159]. In contrast to this, Postigo et al. found that no significant expression of CR4 can be detected on resting tonsillar or blood B lymphocytes. However, after activation with PMA for three days most of the B cells became $CD11c^+$ [155].

In 2011 Rubtsov et al. identified a $CD11c^+$ population of B cells, which are present in low numbers in the blood of healthy donors but became expanded in rheumatoid arthritis and scleroderma patients, especially in older women [195]. These Age Associated B Cells (ABCs) were identified as $CD21^-$, $CD11c^+$, $CD19^{high}$ cells, and were further characterized as switched memory B cells. Rubtsov et al. showed in mice that the accumulation of these cells is driven by TLR7 [195]. This could explain the higher frequency of ABCs in women, as TLR7 is coded by an X-linked gene, and thus it is overexpressed in females [201].

In contrast to this however, Golinski et al. found that the number of $CD11c^+$ B cells does not correlate with gender, only with the age of the healthy donors, varying between 3 to 55 percentages. They also found that CD11c expression is upregulated by BCR-activation but not through TLR9 or TLR7 triggering [202]. These results might suggest a disparate regulation of CR4 expression in B cells of men and mice, but the contradictory results could also be ascribed to the different methods applied. In their study, Golinski et al. tested if CR4 expression on $CD11c^-$ cells can be induced via TLR9 and TLR7 stimulation, but it did not occur. Therefore, it is possible, that TLR stimuli drive the accumulation of $CD11c^+$ cells by inducing their proliferation and not by changing the expression profile of $CD11c^-$ cells. Regarding the characteristics of $CD11c^+$ B cells they found that their majority belongs to the switched memory ($CD27^+IgD^-$) pool, and only a smaller extent of the CR4 bearing cells could be found also in the unswitched ($CD27^+IgD^+$), naïve ($CD27^-IgD^+$) as well as in the double negative ($CD27^-IgD^-$) population. The fact that CD11c was detected in each subpopulation suggests a role for CR4 in all steps of B cell development [202].

In our recent study we analysed the expression of CR4 both on tonsillar and blood B cells of healthy donors. We detected only a slight CR4 expression on resting B cells, however after three days of BCR stimulation, up to 35% of the cells expressed CD11c. Analysing the kinetics of CD11c expression we found that CR4 molecules are newly synthesized, reaching the maximum surface expression on the third day of activation with the average of 9500 CD11c molecules on a cell surface. In line with the previous studies, we also found that the vast majority of both tonsil and blood derived $CD11c^+$ B cells belong to the switched memory pool. Moreover, we demonstrated that the ratio of switched memory B cells further increases among tonsillar $CD11c^+$ B cells after activation [157].

Regarding the role of CR4 on B cells it was demonstrated by Postigo et al. that the ligation of CD11c with receptor specific antibodies triggers proliferation and blocks attachment to fibrinogen [155]. Recently Golinski et al. demonstrated that $CD11c^+$ B cells differentiate into antibody-secreting cells upon activation, however, the exact role of CR4 in this process has not been addressed in this study [202].

We found, that CR4 mediates adhesion of BCR-activated human B cells to fibrinogen, the natural ligand of this $\beta_2$-integrin, leading to enhanced proliferation of B cells. We revealed a further important function of CR4 by demonstrating its contribution to the migration of activated B cells towards SDF-1 [157]. As Lefevre et al. found the surface of follicular dendritic cells (FDC) is covered with high amounts of fibrinogen in the dark zone of germinal centres of human tonsils [203], where both the generation and re-activation of memory B cells occur [204–207], we suggest that CR4 expressed by activated B lymphocytes is involved in their close contact with fibrinogen-covered FDCs. Moreover, since fibrinogen increased the proliferation of activated B lymphocytes, we suggest, that adhesion to fibrinogen by CR4 itself could be one of the supporting signals B cells receive from FDCs [157]. It is important to point out that while the majority of FDCs are located in the light zone of germinal centres, the fibrinogen-covered FDCs were found only in the dark zone [203], which is the primary site of intense B cell proliferation and somatic hypermutation [208]. The migration of B lymphocytes to this site is regulated by the expression of CXCR4 [209], which directs the cells towards the chemoattractant SDF-1, produced by the reticular cells of the dark zone [210]. The fact that CR4 contributes to the migration of B cells towards SDF-1 [157] indicates that it can be involved in the migration towards fibrinogen covered FDCs as well. It is also possible, that $CD11c^+$ B cells, as they differentiate into antibody-secreting cells upon activation [202], use CR4 during their homing into the bone marrow, where SDF-1 is also expressed [211]. Overall, it seems that the expression of CD11c on B lymphocytes is not only a passive marker of activation, but CR4 actively contributes to B cell functions during immune response.

### 4.4.3. Role in human B cells in disease

As it has been mentioned previously, the $CD11b^+CD11c^+$ population of B1 cells, can be considered "orchestrator" B1 cells, due to their capacity to regulate immune responses [197,198]. Interestingly, the derailment of this regulation seems to contribute to the pathomechanism of SLE, as the frequency of these cells is elevated in lupus patients, where they express more CD86 and have increased T cell–stimulating activity [197]. The $CD11c^+$ "Age Associated B Cells", defined by Rubtsov et al., were also found to become expanded in rheumatoid arthritis and scleroderma patients, but the exact mechanism of this process was not clarified [195].

Interestingly, CR3 and CR4 have also been detected in various B cell malignancies such as in Hodgkin's lymphoma [212], hairy cell leukaemia [213] or chronic lymphocytic leukaemia (CLL) [158, 213–219]. In the case of CLL the expression of CD11b and CD11c on the malignant B cells varies widely among patients, however the presence of either CR3 or CR4 was shown to be an unfavorable prognostic factor [214–217]. Since the anatomical distribution of different B-cell lymphomas can be partially explained by the profile of the adhesion molecules expressed on their surface [220], it is plausible to assume that CR3 and CR4 contribute to the adhesive and migratory behavior of the malignant B cells to accumulate in the bone marrow more efficiently. This hypothesis is further strengthened by the fact that the presence of either CR3 or CR4 correlates with the pattern of bone marrow infiltration [214].

In our attempt to decipher the role of CD11b and CD11c on leukemic B cells we demonstrated that both receptors are involved in the spreading of CpG-activated CLL B cells on fibrinogen [158]. We also demonstrated very recently, that both CR3 and CR4 contribute to the adhesion of CLL B cells, while CR4 has a dominant role in their migration towards the chemoattractant SDF-1 [233]. Knowing the essential role of the stromal microenvironment in the pathomechanism of CLL [221–223], the contribution of CR4 to the migration towards SDF-1 vindicates the association of CD11c expression with bone marrow infiltration.

### 4.4.4. Cooperation with other receptors

Some examples of the cooperation between these integrins and other cell-membrane proteins on myeloid cell types are well described in our

previous review regarding the crosstalk between CR3 and Fcγ receptors; CD14, TLR4 and CR3; uPAR and CR3; as well as between CR3 and CR4 [224]. However, our knowledge about the cooperation of these complement receptors with other proteins is limited on lymphoid cells, especially on human B lymphocytes.

Nevertheless, it is known, that chemokines can stimulate integrin functions via G-protein–coupled receptors as shown for SDF-1, which activates the $\alpha_4\beta_1$ integrin VLA-4 mediated adhesion of human B cells, thereby regulating B lymphopoiesis [225]. While $\beta_2$-integrins were not studied under these circumstances on B cells, SDF-1 (as well as other chemokines) was also shown to activate CR3 in monocytes and Jurkat T lymphoma cells. It was also clarified, that integrins sharing the same $\beta_2$-chain can be differentially regulated by chemokines, depending on the distinct α subunit cytoplasmic domains – however, CR4 was not investigated in this study [226].

Beside chemokines, B cell antigen receptor also affects integrin mediated functions on B lymphocytes. Amongst others, BCR stimulation was shown to induce both the LFA-1 [227] and VLA-4 mediated adhesion [228] of B cells. As a feedback, these receptors contribute to the interaction between tonsillar B cells and FDCs [229], moreover LFA-1 was demonstrated to facilitate the synapse formation of B cells, thereby lowering the threshold of B cell activation [230]. Importantly, BCR activation heavily increases the expression of CR4 on B lymphocytes [157,202], moreover, CR4 mediated adhesion was also found to boost the BCR-mediated proliferation of B cells [157]. This cooperation between BCR and integrins carries a major clinical relevance, as the chemotherapeutic drugs, ibrutinib and idelalisib, both exerts their functions by inhibiting BCR controlled integrin-mediated adhesion of malignant B cells [231,232], with ibrutinib having also a strong effect on chemokine signaling [231].

## 5. Conclusion

In this review we assembled the various new aspects of C3-receptors expressed by B cells, focusing on their role in health and disease (Fig. 7.). Recent studies revealed that in humans CR2 – similarly to CR1 – is a negative coreceptor for the BCR, since coengagement by its natural ligand causes inhibition of cytokine production, proliferation, and antibody production. In men these two complement receptors are encoded by separate genes, and they appear on the cell membrane in a complex devoid of CD19 – in contrast to mice. Thus the function of human CR1 and CR2 is profoundly different from their mouse counterpart, where C3d has been demonstrated to act as an adjuvant to enhance humoral immunity. These data may intensify further investigations and better understanding of the role of complement in shaping B cell responses. Furthermore, these findings may open up novel therapeutic strategies – *e.g.* by targeting the inhibitory CR1 and CR2 in autoreactive B cells. The differential expression and role of CR3 and CR4 on human B cells further support the notion that these $\beta_2$-integrins are "non-identical twins" [128]. Recent data prove that CD11c is not only a passive marker of human B cells but acts a functional driver of memory B cell responses.

As hepatocyte-derived complement components might not be available at high concentrations in various tissues where several immunological processes take place, the importance of locally synthesized complement should receive special emphasis in the future.

Finally, we find it important to emphasize that there are basic differences between human and mouse systems regarding C3-mediated processes mostly due to the differing expression and function of various C3-receptors in these two species. Due to this, mouse systems are not optimal for studying the role of complement in the function and manipulation of human B cells – despite of several known advantages. Translating findings from mouse to human must be done with great care.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Research Council in Hungary (TUKEB), 52088/2015/EKU. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

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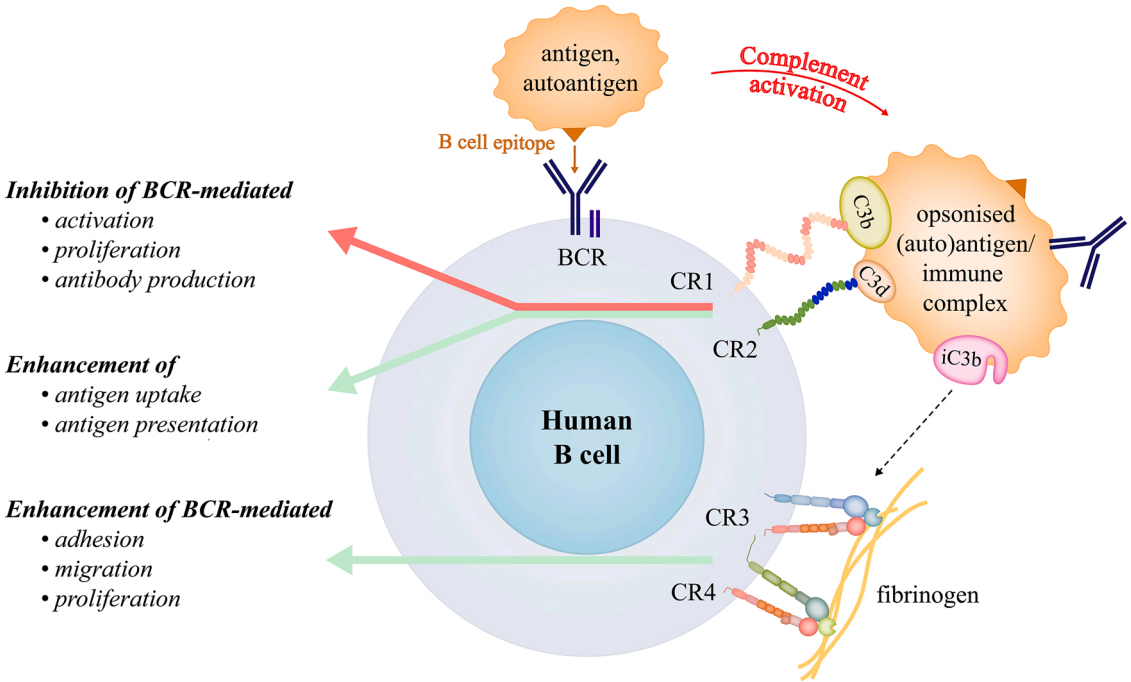


**Fig. 7. Function of C3-receptors expressed by human B cells.**

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