Review Article

**Complement receptor 2 (CR2/CD21)**

Rozaleen Dash1*, Nibhriti Das2

1Department of Chemical Engineering, Indian Institute of Technology, Delhi, Hauz Khas, New Delhi-110016, India
2Department of Lab Medicine, Nayati Multi Super Specialty Hospital, NH- 2, Mathura- 281003, Uttar Pradesh, India

Received: 14 February 2017
Revised: 22 February 2017
Accepted: 09 March 2017

*Correspondence:
Dr. Rozaleen Dash,
E-mail: rozaleendash@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

**ABSTRACT**

Human complement receptor type 2 (CR2/CD21) is a surface-associated glycoprotein which binds to a variety of endogenous ligands, including the complement component C3 fragments iC3b, C3dg and C3d, the low-affinity IgE receptor CD23, and the type I cytokine, interferon-alpha. This receptor serves as an important interface between the complement system and adaptive immunity. It is expressed on B-lymphocytes, follicular dendritic cells, some epithelial cells, peripheral blood T cells. CR2 also play an important role in enhancing humoral immunity to T-dependent and T-independent foreign antigens and in regulating T-cell immunity to self and non-self-antigens. It is an important receptor that amplifies B lymphocyte activation by bridging the innate and adaptive immune systems. CR2 ligands include complement C3d and Epstein-Barr virus glycoprotein 350/220. Regions of EBV have structural similarity to C3dg, which allows it to bind CR2, and thereby gain access to cell’s interior. It also acts as receptor for other components or activators of innate immunity such as IFN-α, an anti-viral cytokine and DNA-DNA containing complexes such as chromatin. The binding of CR2 to IFN-α is speculated to cause B cell activation but their roles are still not clear. Variations or deletions of the CR2 gene in humans, or the Cr2 gene in mice associate with a variety of autoimmune and inflammatory conditions.

**Keywords:** Autoimmunity, B cell signalling, Complement receptor 2 (CR2/CD21), Regulators of complement activation

**INTRODUCTION**

Complement receptor type 2 (CR2/CD21) is a 145-kDa glycoprotein with specificity for the complement fragments iC3b and C3dg. It is also the site of attachment for Epstein–Barr virus (EBV), the causative agent of infectious mononucleosis. The complement receptor type II belongs to the super gene family of regulators of complement activation. CR2 is the functional receptor for C3d fragments on immune complexes and the Epstein-Barr virus (EBV) envelope protein gp350.1 Human CR2 is the receptor for the C3d/C3b in addition to Epstein Bar virus CEBL, CD23 and expressed on all mature B-lymphocytes, follicular dendritic cells and also on T-lymphocytes.2 CR2 on B-lymphocytes plays on Antigen dependent enhancing role in the immune response by triggering proliferation of preactivated cells and augmenting calcium signals induced in response to cross-linking of SigM.3 Functional role of CR2 on T-cells is not clear. Recent evidences emphasize the potential role of receptor on T-cells in the regulation of immune response and infection with lymphocytotropic viruses.4

**Structure of CR2**

CR2 is a member of the RCA (Regulators of Complement Activation) family. It is expressed as two alternatively spliced gene products (140 kDa glycoprotein) encoding 15 or 16 SCRS; where the additional SCR in the longer version lies between SCR10
and SCR11 of the shorter CR2. C-terminal to the SCR lies a 24-amino acid transmembrane segment and 34 amino acid cytoplasmic tail. Electron microscopy of CR2 has revealed that the extracellular portion of the receptor is highly flexible. Allelic polymorphism (at least three alleles in humans) has been reported for both versions.

![Diagram of CR2](image)

The short consensus repeats (SCR) of CR2 are represented as ovals. The exon 11 variant in the long form of CD21 is indicated by an arrow. The ligands binding to their respective SCR are shown on the right and the antibodies against respective epitopes are shown on the left.

**Figure 1: Structural features of CR2.**

**Cellular distribution**

CR2 is expressed on mature B-lymphocytes and B cell lines, but not on early pre- and pro B cells and late developmental stages. It is also expressed on peripheral blood and thymic T cells, T cell lines and a number of other cell types.

**Function of CR2**

Functionally, CD21 on B cells and follicular dendritic cells (FDC) is implicated in the recognition and binding of immune complexes while the function in T cells and all other cell types is not known. In T cells, the expression of CD21 is developmentally regulated as double negative thymocytes express membrane bound CD21. Ligation of CD21 results in various signals that are critical for normal B cell responses. Crosslinking CD21 with C3d or certain anti CD21 antibodies in the presence of T cell factors leads to B cell proliferation and differentiation. Crosslinking CD21 with membrane IgM promotes T cell-independent proliferation. On mature B cells, CD21 forms a non-covalent signal transduction complex in the plasma membrane together with the CD81, Leu-13 and the pan-B cell antigen CD19. This complex amplifies the signal transmitted through the B cell receptor by specific antigen and thereby reduces the threshold of antigen necessary to initiate cell proliferation. The mechanism involved appears to be synergism between the IL-4R and BCR-CD21 signalling pathways in promoting the progression of resting B cells past an early G1 checkpoint. In addition, CD21 plays a key role in determining B cell survival by limiting apoptosis induced through ligation of membrane IgM and through accumulation of Bcl-2.

Alternatively, CD21 participate in the generation of a normal immune response by internalizing and directing C3-bound Ag into the class II processing pathway of B cells. CD21 is also shown to have a direct influence on B cell-T cell signal exchange by simultaneous up-regulation of CD80 and CD86 on murine splenic B cells. The other functions of CD21 reported in literature though not yet clear are in development and maintenance of B1 cells. In human pro- and pre- B cells the expression of the CD21 gene is silenced by methylation of a CpG island in its promoter. Expression in mature B cells is accompanied by the loss of CpG-methylation. C3 depositions on B cells may enhance their interaction with CD21 on FDC and vice versa. CD21 in FDC plays a very important role in rescuing antigen-activated B cells from apoptosis, promotion of somatic hypermutation and class switch.

CD21 is also found in a soluble form (sCD21) generated by shedding from lymphocytes in culture and in human plasma24,25 have purified a 72 kDa form of sCD21 from lymphoblastoid cell lines by affinity chromatography on sepharose-coupled BU34, BU33 and BU36 mAbs followed by DEAE ion exchange chromatography. Later, by metabolically labelling the LICR-LON-Hmy cell line with S, they could isolate several proteins of molecular range from 30-130 kDa. In addition to a range of proteins isolated from tissue culture supernatants, cell-associated CD21 from cell lysates was detected as a 120-140 kDa molecule and was reduced to 115 kDa upon treatment with endoglycosidase. sCD21 affinity-purified from human serum with THBS5 and BU32 mAbs showed a 135 kDa and a 90kDa protein. Moreover, sCD21 circulates as a complex with cleavage fragments of C3 and a trimeric form of soluble CD23 (sCD23). CD21 isolated from human serum showed a smear of 135-190 kDa under non-reducing conditions.

**Signalling of CR2**

CR2 possesses only a short cytoplasmic tail and is unlikely to act directly as a signal transducer. However, by virtue of its association with the trimolecular glycoprotein complex CD19/CD81 (TAPA-1)/Leu 13, CR2 plays a pivotal role in augmenting the B-cell response to opsonized antigen by bringing CD19 into close proximity with the BCR. Colligation of CD19 with BCR reduces the threshold for stimulation via BCR by at least two orders of magnitude. CD19 becomes tyrosine phosphorylated upon ligation with BCR and associates with the protein tyrosine kinases (PTK), Lyn and Fyn, PI3 kinase and the Rac guanine nucleotide

---

International Journal of Research in Medical Sciences | April 2017 | Vol 5 | Issue 4 | Page 1157
exchange factor Vav, which is responsible for activating the MAPK cascade. The enhancement of BCR signal transduction by CD19 is thought to involve at least two elements: (1) phosphorylation, by CD19-bound Lyn, of potential substrates in the BCR complex and (2) Ca2+ mobilization by a PI3 kinase dependent mechanism, distinct from the phospholipase Cg-mediated mobilization initiated by BCR.28

**Disease association of CR2**

CD21 has been associated to a number of diseases, especially to EBV-related ailments, as CD21 serves as its receptor, and to autoimmune diseases. SCD21 levels are often altered in pathologic conditions including various lymphoproliferative leukaemia, such as B-CLL (B cell-type chronic lymphocytic leukaemia) acute EBV-infection and other virus-associated diseases and autoimmune diseases.29

Significantly large expansion of CR2 bearing T-cells (80%) of the total CD3 in a patient with lupus nephritis has been document decline in CR2 had been reported during the development of autoimmunity in a mouse model but a quantitatively lower level of CR2 gene transcript in the synovial fluid B-lymphocytes from patients with RA had also been documented.30,31

B-cell expression of human CR2 and CR1 had been studied in number of human autoimmune diseases; one striking finding is that patients with SLE reproducibly demonstrate abnormal expression. B-cells CR2 and CR1 are below 50% of the normal.32 It is however, not known whether the disease in B-cell receptor precedes the development on parallels clinical disease activity. EBV is the best studied member of the herpes virus family and is involved in the pathogenesis of several human malignancies, as endemic Burkitt’s lymphoma, nasopharyngeal carcinoma, Hodgkin’s lymphoma, polyclonal lymphomas in immuno-compromised individuals and many more.33 sCD21 has been described as a marker of B-cell activation in humans and elevated sCD21 levels were found in patients with EBV-associated malignancies. Furthermore, sCD21 can inhibit EBV-binding and infection of B-cells.

However, as sCD21 is able to bind its ligands in plasma, the increased amounts of sCD21 caused by EBV-infection may contribute to the immuno-regulatory dysfunctions observed in EBV-associated diseases. Also, CD21 and its soluble form (sCD21) have been described to bind to the low-affinity IgE-receptor CD23 and to sCD23, thereby modulating IgE responses and monocyte activation and differentiation. Therefore, an imbalance of sCD21 and sCD23 may contribute to the development of allergic reactions.26

The mechanism by which CD21 might regulate B-cell reactivity to auto antigens has not been clarified yet. It may involve direct effects on B-cell tolerance or indirect effects on T-cell tolerance. The involvement of CD21/CD35 in the control of self-tolerance was shown by Prodeus et al, where CD21/CD35-deficient mice where crossed in mice expressing transgenic anti-hen-egg lysozyme (HEL) specific antibodies.34 In the presence of both HEL in the blood and anti-HEL transgenic B-cells, B-cells were rendered unresponsive in the periphery. CD21-deficient B-cells were able to up-regulate CD86 and the BCR, but still did not respond with antibody secretion. Hence, CD21 has some role in the induction of energy. CD21-expression has been linked to enhanced susceptibility for systemic lupus erythematosus. As BAFF independently regulates CD21 and CD23 expression and BAFF over expression leads to auto antibody production, seen in SLE, primary Sjögren’s syndrome (pSS) and rheumatoid arthritis (RA), some close link between over-activation of B-cells, CD21-expression and the development of autoimmunity may be drawn.35

Moreover, treatment of SLE mice with a BAFF protein antagonist ameliorates disease progression and enhances survival.36 In patients with SLE, an autoimmune disease characterized by antibodies specific for nuclear antigens such as dsDNA, sCD21 levels are reduced.24 Low sCD21 levels are also found in the Sjögren’s syndrome, a disease characterized by autoantibodies directed against salivary and lacrimal glands. In juvenile arthritis, though, sCD21 levels were not altered.

These data together with data from patients with autoimmune rheumatoid arthritis having reduced expression levels of CD21 in synovial B- and T-cells and significantly lower sCD21 plasma levels indicate a role for CD21 in autoimmunity. Interestingly, in SLE, pSS and RA, sCD21 levels have been described to be up-regulated.36

An inverse relationship between SLE disease activity index (SLEDAI) and the expression of complement receptor 2 (CR2) on SLE B cells suggest that CR2 on B-cells may emerge as an additional laboratory tool in the assessment of SLE activity.37 CR2 variants alter the maintenance of tolerance and autoantibody production in the secondary lymphoid tissues where B cells and FDCs interact.38 Recent studies have shown that CR2 is also centrally involved in innate immunity, and one key area is the development of potentially pathogenic natural antibodies that target neo-epitopes revealed in ischemic tissue undergoing reperfusion.

**CONCLUSION**

The review has summarized current knowledge of structure, function and disease association of CR2, a membrane glycoprotein which functions as the B-lymphocyte receptor for C3dg and EBV. The molecular mechanisms and biochemical events which mediate the functional reactions are yet to be elucidated. Ongoing studies in many laboratories using contemporary and
biochemical and genetic techniques will undoubtedly soon elucidate the importance and modulation of CR2.

**Funding:** No funding sources  
**Conflict of interest:** None declared  
**Ethical approval:** Not required

REFERENCES


