Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section

Review

CD22 (CD22 molecule)

Barnabas Nyesiga, Zahra El-Schich

Biomedical science, Health and society, Malmõ University, Malmõ, Sweden
nyesigabarnabas@gmail.com; zahra.el-schich@mau.se

Published in Atlas Database: April 2020

Online updated version : http://AtlasGeneticsOncology.org/Genes/CD22ID972ch19q13.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/70879/04-2020-CD22ID972ch19q13.pdf
DOI: 10.4267/2042/70879

Abstract

Sialic acid binding immunoglobulin-type lectin (Siglec) family are inhibitory receptors with diverse roles in the immune system. Siglec family contains 14 members in human and 9 in murine. Differentially expressed on various white blood cells. Here in this review we are focusing on CD22, also known as Sialic Acid-Binding Ig-Like Lectin 2 (Siglec-2). CD22 gene is located on 19q13.12 and is encoding a 140 kD type I transmembrane glycoprotein on the surface of B cells and is part of the immunoglobulin (Ig) superfamily and has been found only on B cells. CD22 has been shown to play a major role in establishing a baseline level of B-cell inhibition, and thus is a critical determinant of homeostasis in humoral immunity.

Keywords
B-cell inhibition; CD22; Sialic Acid; SIGLEC

Identity

Other names
B-cell receptor CD22, B-lymphocyte cell adhesion molecule, BL-CAM, CD22 antigen, FLJ22814, MGC130020, Sialic acid binding Ig-like lectin 2, Sialic acid-binding Ig-like lectin 2, SIGLEC-2, SIGLEC2, T-cell surface antigen Leu-14

HGNC (Hugo): CD22

Location: 19q13.12 by HGNC, Entrez Gene, Ensembl

Location (base pair)
19q13.12 The gene can be found on chromosome 19 at location: 1305228594023-121100029250780. (according to UCSC)

DNA/RNA

Description

The CD22 gene is spread over 22 kb of DNA and is composed of 15 exons (Wilson et al 1993).

Protein

Description

Siglec family are inhibitory receptors with diverse roles in the immune system. Siglec family contains 14 members in human and 9 in murine. Differentially expressed on various white blood cells. Binding site varied sialoside binding specificity.

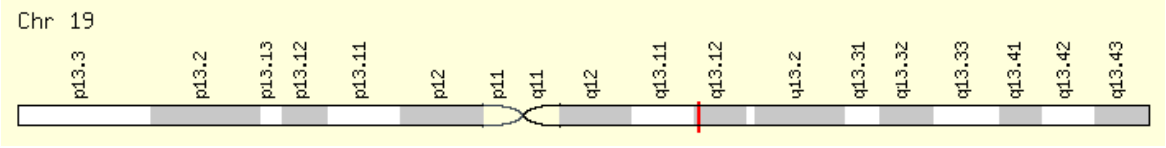

Figure 1: Mapping of CD22 gene on chromosome 19p13.12 (https://www.genecards.org/cgi-bin/carddisp.pl?gene=CD22).

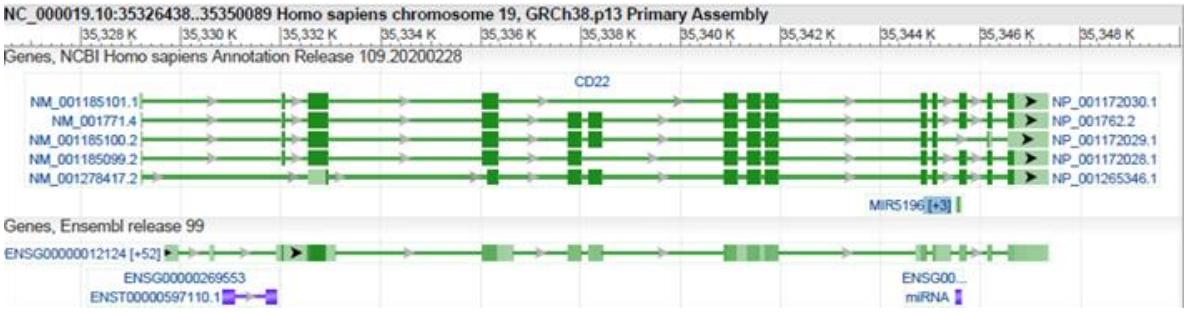

Figure 2: Homo sapiens CD22 molecule RefSeqGene on chromosome 19. 5 mRNA isoform transcript variants are presented (RefSeq NCBI et al., 2020).

Cytoplasmic domain; ITIM motifs regulate cell signaling, regulation of microdomain localization and endocytic mechanism (Crocker et al., 2007). One of the best described Siglecs is CD22, also known as Sialic Acid-Binding Ig-Like Lectin 2 (Siglec-2), is a 140 kD type I transmembrane glycoprotein on the surface of B cells and is part of the immunoglobulin (Ig) superfamily and has been found only on B cells. CD22 mediates B cell to B cell interactions and is implicated in the localization of B-cells in lymphoid tissues. CD22 acts as positive regulator via interaction with the Src family tyrosine kinases, in addition CD22 preform as an inhibitory receptor by recruiting cytoplasmic phosphatases (Walker et al., 2008). Anti-CD40 stimulation specifically up-regulated anti-IgM-induced phosphorylation of tyrosines within two ITIM motifs, Y762 and Y842, which was consistent with in vivo finding of the negative role of CD22 in CD40 signaling (Fujimoto et al., 2006).

CD22 (Siglec-2) is a 140-kDa B-cell-restricted membrane bound member of the immunoglobulin superfamily that binds glycan ligands containing α2,6-linked sialic acid through its two amino-terminal of seven extracellular Ig-like domains (Cyster et al., 1997, Tedder et al., 1997, Walker et al., 2008). The extracellular domain (ECD) of CD22 is composed of seven immunoglobulin (Ig) domains (d1-d7) and 12 putative N-linked glycosylation sites. The most N-terminal domain (d1) is of predicted V-type Ig-like fold and recognizes sialic acid containing α2,6-linkages (Powell et al.,1993). Whereas human CD22 is known to bind preferentially to sialic acid N-acetyl neuraminic acid (Neu5Ac), murine CD22 has higher specificity for the non-human N-glycolyl neuraminic acid (Neu5Gc) (Blixt et al., 2003), highlighting species-dependent specificities for CD22 ligand recognition. CD22, itself sialylated, forms homo-oligomers in cis on the surface of B cells (Han et al., 2005). CD22 oligomers are located in dynamic nanoclusters and create a signal threshold of antigen binding that must be achieved prior to B-cell activation (Gasparrini et al., 2016).

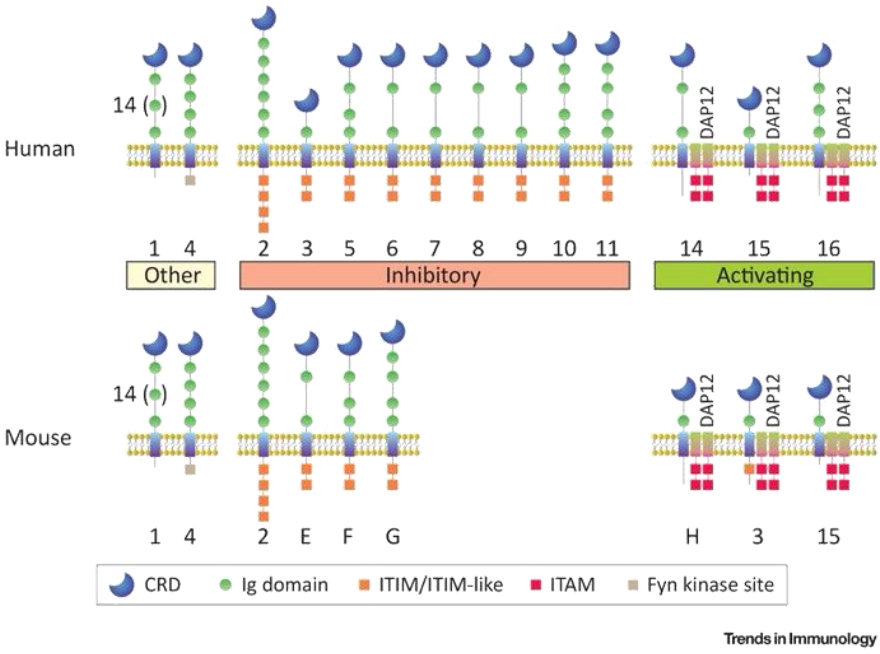

Figure 3: Overview image on the human and mouse Siglec family. Different Siglec have different functions, Ig domain and ITIM/ITAM (adopted from Zhou et al., 2018)

The activity of CD22 is mediated through the intracellular recruitment of phosphatases that enable dephosphorylation of stimulatory co-receptors (Nitschke, 2005). The trans engagement of sialic-containing ligands on antigen-bearing cells results in the recruitment of CD22 to the immunological synapse and inhibits BCR signaling in response to self-antigens (Leonard et al., 2007). The CD22 intracellular region contains immunoreceptor tyrosine-based inhibitory motifs (ITIMs). Phosphorylation of the tyrosine residues of the ITIMs with the ligand binding leads to activation of SHP-1 (Src homology region 2 domain-containing phosphatase-1), SHP-2 (Src homology region 2 domain-containing phosphatase-2) and SHIP-1 ((Src homology region 2 domain-containing inositol 5' polyphosphatase-1). These phosphatases are responsible for negative regulation of down-streaming signaling from B-cell receptors (Aujla et al., 2019). Ereno-Orbea et al. (2017) reported the crystal structure of human CD22 at 2.1 A resolution showing that the specificity for α2-6-linked sialic acid ligands is dictated by a pre-formed β -hairpin as a unique mode of recognition across sialic acid-binding immunoglobulin-type lectins. They showed that the CD22 ectodomain adopts an extended conformation that enables concomitant CD22 nanocluster formation on B cells and binding to trans ligands to prevent autoimmunity in mammals. They structurally portrayed the CD22 site targeted by the therapeutic antibody epratuzumab at 3.1 A resolution and determined a critical role for CD22 N-linked glycosylation in antibody engagement.

Expression

The highest level of CD22 gene expression is in lymph node (RPKM 101), ovary (RPKM 65), spleen (RPKM 63) and appendix (RPKM 38) (RefSeq NCBI et al., 2020). The human CD22 gene is expressed specifically in B lymphocytes and likely has an important function in cell-cell interactions. A full-length cDNA clone that encodes the CD22 protein was isolated by the use of subtractive hybridization and subsequent expression in COS cells for the first time by Wilson et al. in 1991 (Wilson et al., 1991). In 1992, Torres et al reported the isolation and expression of a molecular cDNA clone encoding the murine homologue of CD22 murine and human sequences overall have 62% identity, which includes 18 of 20 extracellular cysteines and six of six cytoplasmic tyrosines. (Torres et al 1992).

CD22 is one of the best described Siglecs whose expression is restricted to B cells (Walker et al., 2008). Expression of CD22 on human plasmacytoid DC tumors and follicular dendritic cells has also been reported (Ogata et al., 1996, Reineks et al., 2009). CD22 itself expresses its ligand as does surface IgM (sIgM) and PTPRC (CD45) and can associate with itself or other cell surface molecules on B cells in a 'cis' configuration or with ligands on other cells in a 'trans' configuration (Zhang et al., 2004, Macauley et al., 2014, Clark et al., 2018). Not all CD22 expresses its ligand, so CD22 can also be found on B cells in a ligand-free, 'un-masked' form (Clark et al., 2018). On murine B2 cells CD22 is down-regulated after BCR cross-linking with anti-IgM mAb, but it is up-regulated after stimulation with other stimuli such as LPS, anti-CD40 mAb, orIL4. CD22 expression is differentially regulated in B1 and B2 cells. Expression of CD22 can be regulated at the mRNA level (Lajaunias et al., 2002) or through CD22 endocytosis and recycling. In mice, the presence of CD22a allele has been associated with a decrease of CD22 expression (Clark et al., 2018). High expression of CD22 has been registered on marginal zone B cell precursors (Santos et al., 2008) and remains at high levels on mature B cells with some studies suggest that developing B cells in the bone marrow express low levels of CD22, starting at the Pre-B stage (Nitschke et al., 1997). Early CD22 expression during the ontogeny of B cells in the bone marrow and spleen and on B cells isolated from all the different lymphoid compartments has been reported. Additionally, in B cells stimulated through the B-cell antigen receptor (BCR), CD38 and CD40, an upregulated CD22 expression to maximal levels within 24 h after stimulation was observed but a decline in expression was observed at later times (48 and 72 h) (Moyron-Quiroz et al., 2002). Cell types such as hematopoietic cells, certain endothelial cells and T and B cells have been reported to express alpha 2,6-linked sialic acid ligands where the extracellular domain of CD22 binds (Clark et al., 2018). Expression of both CD22 and its ligands can vary depending on the maturation or activation state of B-cells. Maximum density expression of CD22 is registered in the periphery on human CD27-naive and transitional B cells whereas downregulation is observed in plasma cells (Dõrken et al., 1986, Daridon et al., 2010).

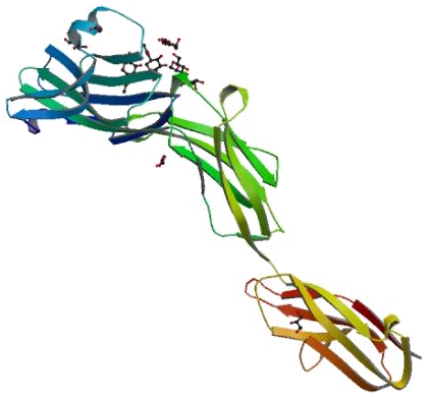

Figure 4: Crystal structure of human CD22 Ig domains 1-3 (adopted from Ereno-Orbea et al 2017).

Localisation

CD22 is an inhibitory co-receptor of the BCR and is required to modulate the antigen receptor signal in response to cues from the local microenvironment (Cyster et al., 1997). Nitschke et al improved already in 1996 the negative function of CD22 as a negative regulator of BCR signaling and suggest that CD22 mediates the negative regulation of the BCR signal through stimulation of the tyrosine phosphatase activity of PTPN6 (SHP-1) (Nitschke et al., 1997). The extracellular domain of CD22 is comprised of 7 Ig domains and 12 putative N-linked glycosylation sites (Powell et al., 1993). Engel et al identified the ligand-binding domains of the CD22 that uniquely binds a sialic acid-dependent ligand. The different epitopes identified by a large panel of CD22 monoclonal antibodies (Engel et al., 1995). The Siglec CD22 is a well-characterized inhibitory receptor of B cells and has up to four ITIMs. Its cis interactions with alpha 2-6-sialylated ligands are important for regulating signaling functions. CD22 is unique in having a strong preference for Neu5Acα2-6Gal and Neu5Gcα2-6Gal structures (Kelm et al., 1994). CD22 and Siglec-G have been shown to inhibit BCR signal and provide additional mechanisms to control the BCR signal. These mechanisms might be important to induce tolerance to self-antigens. Both CD22 and Siglec-G have also been linked to toll-like receptor signaling and may provide a link in the regulation of the adaptive and innate immune response of B cells (Lanoue et al., 2002, Jelluosova et al., 2012, Duong et al., 2010).

Macauley et al., showed that liposomal nanoparticles, displaying both antigen and glycan ligands of the inhibitory coreceptor CD22, induce a tolerogenic program that selectively causes apoptosis in mouse and human B cells (Macauley et al., 2015).

Function

CD22 has been shown to play a major role in establishing a baseline level of B-cell inhibition, and thus is a critical determinant of homeostasis in humoral immunity and as a result, CD22 knockout mice have an increased incidence of autoimmune disease and hyperactive B cells (O'Keefe et al., 1996). CD22 function is partly dependent upon binding to α-2,6 sialic acids. Disruption of this activity through mutation of the sialic acid-binding domain (CD22 R130E mutant) or impaired sialic acid generation (ST6galI enzyme deficiency) leads to decreased BCR calcium signaling (Nitschke, 2014, Müller et al., 2013, Hennet et al., 1998). When cross linked to B-cell receptors (BCR), CD22's tyrosine residues are phosphorylated, leading to the recruitment of PTPN6 (Src homology region 2 (SH2) domain-containing protein tyrosine phosphatase-1 SHP-1) and INPP5D (SH2 domain containing inositol 5'-phosphatase SHIP), the subsequent dephosphorylation of BCR-proximal signaling molecules, and the inhibition of BCR signaling (Zhu et al., 2008, Doody et al., 1995, Poe et al., 2000). CD22 also plays a role in the migration of recirculating B cells to the bone marrow (Clark et al., 2018). Dendritic cells (DCs) can directly regulate and activate B cells (Chappell et al., 2012), and CD22 can bind to ligands expressed on DCs. Immature DCs can inhibit B cell proliferation in a contact dependent manner that requires CD22 expression on B cells (Santos et al., 2008, Sindhava et al., 2012). CD22 is involved in the regulation of B cell responses to T cell-independent type 2 antigens, toll like receptor agonists and T cell-dependent antigens (Clark et al., 2018). Known to be recruited through binding CD22, SHP-1 is greatly involved in germinal center maintenance and memory cell development (Khalil et al., 2012, Li et al., 2014). This could be an indication that absence of CD22 could lead to decreased SHP1 recruitment required for efficient memory B cell development. (Clark et al., 2018).

There reports indicating that CD22 may be involved in regulating cell migration not simply through CD22L--CD22 interactions, but also indirectly, probably through regulation of chemokine receptor expression (Clark et al., 2018). As an endocytic receptor, CD22 recycles between the cell surface and the endosomes, where endosomal TLRs reside (O'Reilly et al., 2011). Sequestration of CD22 or other changes in the CD22 microdomain organization can have an effect on CD22 concentrations in the endosomes and further affect endosomal TLR signaling (Paulson et al., 2012). Cross-linking of CD22 with antibodies in vitro has been reported to increase cell proliferation, promote class switching and increase Ig secretion rate (Tuscano et al., 1996). In addition, apoptosis induced due to CD22 cross-linking has been reported (Chaouchi et al., 1995). Crosslinking of CD22 and the BCR activates phosphorylation of the CD22 cytoplasmic tail resulting in the activation of a number of signaling molecules responsible to either inhibition of the BCR signaling or promotion of the activation of JNK/SAPK and mitogen activated protein kinase MAPK1 ERK2 (Niiro et al.,2002 , Walker et al.,2008, Dõrner et al.,2012). Apart from regulating BCR signaling, CD22 has been shown to take part in the regulation of TLR-mediated signaling in B cells (Kawasaki et al., 2011). Additionally, Kawasaki et al. (2011) have shown that CD22 expression inhibits LPS-induced activation of nuclear factor-κB (NF-κB) downstream of TLR4.

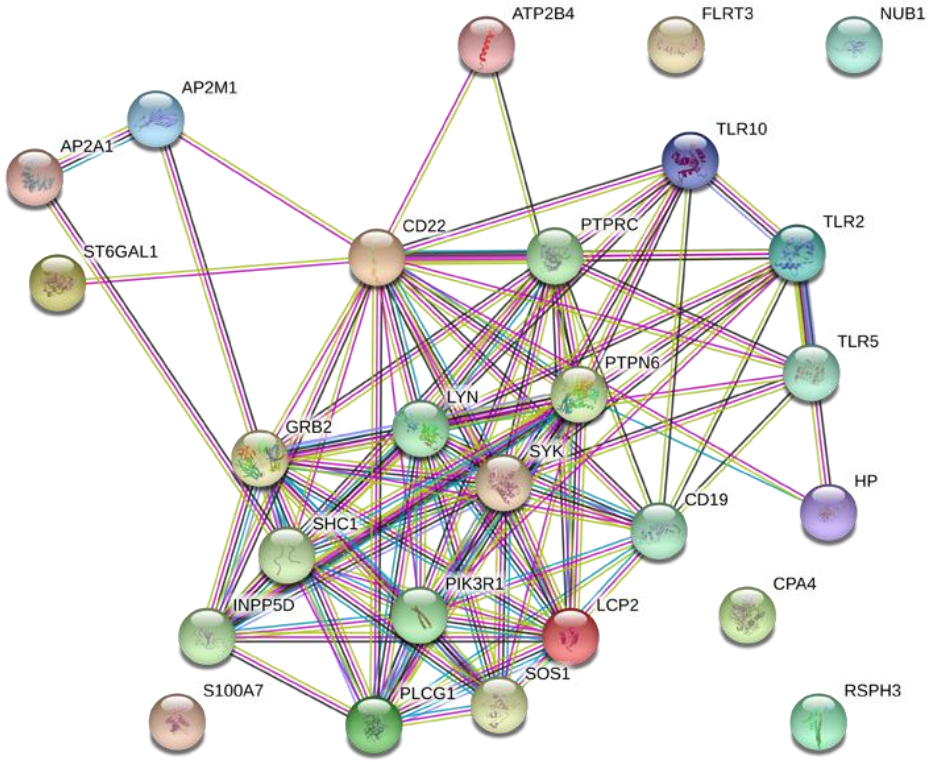

Figure 5: A typical association network in STRING. The input protein is CD22. The network is expanded to 25 proteins (Szklarczyk et al. Nucleic acids research 47.D1 (2018): D607-D613.2)

Chen et al. (2004) have reported that CD22 cytoplasmic tyrosine residues are required for association with plasma membrane calcium-ATPase (PMCA) and enhancement of calcium efflux. In addition they showed that CD22 regulation of efflux and the calcium response require tyrosine phosphatase SHP-1 and thus concluded that SHP-1 and PMCA provide a mechanism by which CD22, a tissue-specific negative regulator, can affect calcium responses.

Implicated in

B-cell acute lymphocytic leukemia (ALL)

CD22 is expressed in most (>90%) patients with B-cell ALL and represents a promising target for the treatment of ALL with anti-CD22 (Haso et al., 2013). Inotuzumab ozogamicin, an anti-CD22 antibody conjugated to calicheamicin, is active in acute lymphoblastic leukemia. Patients receiving inotuzumab ozogamicin versus standard care reached higher response and prolonged overall survival (Hagop et al., 2016).

Hairy cell leukemia (HCL)

Hairy cell leukemia (HCL) is a rare cancer of B lymphocytes. HCL cells have particularly high CD22 expression (Troussard and Cornet 2017).

A BRAF V600E (BRAF gene) somatic mutation was found and subsequently identified in up to 80-90% of HCL cases.

The mutation activates BRAF by autophosphorylation of the protein and downstream MEK-ERK signaling pathway.

MEK-ERK activation pathway lead to increased expression of genes involved in survival and proliferation (Tiacci et al 2011).

Rheumatoid arthritis, type 1 diabetes and systemic lupus erythematosus

Sialic acid esterase is an important enzyme that negatively regulates B lymphocyte antigen receptor signaling by enables ligand binding to CD22. Mutations in this enzyme has been found more and more in patients with autoimmune diseases such as rheumatoid arthritis, type 1 diabetes and Systemic Lupus Erythematosus (Pillai et al., 2009, Surolia et al., 2010, Chellappa et al 2013).

Primary Sjögrens syndrome (PSS)

CD22 is over-expressed in patients with primary Sjögrens syndrome (PSS).

Steinfeld et al determined that PSS patients get downregulation of CD22 over-expression by epratuzumab and suggested epratuzumab to be a promising therapy in active PSS (Steinfeld et al., 2006).

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This article should be referenced as such:

Nyesiga B, El-Schich Z. CD22 (CD22 molecule). Atlas Genet Cytogenet Oncol Haematol. 2020; 24(12):470-476.