

Gene Section

Review

CD200 (CD200 molecule)

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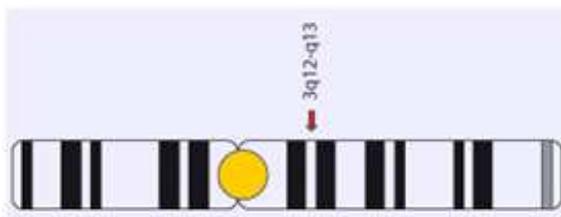
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Identity

Other names: MOX1; MOX2; MRC; OX-2

HGNC (Hugo): CD200

Location: 3q13.2



DNA/RNA

Description

29744 bp.

Transcription

mRNA variant 1 (isoform a): predominant transcript (Pubmed ID NM_005944) is 2226 bp in length, contains 7 exons, and is further represented by sequences AL832529, BC022522 and DA544134 in Pubmed.

mRNA variant 2 (isoform b): In-frame, yet has a much longer N-terminus. (Pubmed ID NM_001004196.2) is 2301 bp in length, also contains 7 exons, and is further represented by sequences AL832529, BI547787, CR62029 and DA544134 in Pubmed.

mRNA variant 3 (isoform c): (Pubmed ID NM_001004197) is 2085 bp in length and is missing an exon in the coding region, which results in a frameshift and an early stop codon, compared to variant 1. The predicted protein is encoded by the upstream open reading frame and is very short

when compared to variant 1. Translation of a 153-aa protein from a downstream open reading frame may occur.

Protein

Description

The CD200 molecule is a single-pass type I membrane protein spanning the membrane once, with its N-terminus on the extracellular side of the membrane and subsequent processing results in removal of its signal sequence. Variant 1 produces a protein that is 269 amino acids in length, variant 2 yields a protein that is 294 amino acids, and variant 3 has yet to be experimentally validated for its product. CD200 is a highly conserved member of the immunoglobulin superfamily containing both an Ig-like C2-type (immunoglobulin-like) domain as well as Ig-like V-type (immunoglobulin-like) domain.

Expression

CD200 is commonly expressed on cells originating from the hematopoietic cells, specifically those of the myeloid lineage such as macrophages, dendritic cells, neutrophils, mast cells, and eosinophils, yet it can also be expressed on B cells, activated T cells, endothelial neuronal cells and cells of the reproductive organs (ovaries and placental trophoblasts). This molecule exerts its effect by binding to its cognate receptor CD200R (also on chromosome 3 and containing two Ig-like domains) which is expressed on cells specifically derived from the myeloid lineage and certain populations of T cells. This interaction can only occur when the cell carrying the receptor and the cell expressing CD200 are in close contact to one another.

Cell type	Membrane protein			
	CD200	CD200R	CD47	CD172a
Thymocyte	+	-	+	-
T cell	+/-	-	+	-
Activated T cell	+	-	+	-
B cell	+	-	+	-
Activated B cell	+/-	-	+	-
Dendritic cell	+/-	+	+	+
Monocyte/macrophage	-	+	+	+
Endothelium	+	-	+	-
Neuron	+	-	+	+
Platelets	-	ND	+	-
Erythrocyte	-	-	+	-

CD200 and membrane protein interactions in the control of myeloid cells. Neil Barclay, Gavin J. Wright^b, Gary Brooke and Marion H. Brown. Trends in Immunology. Volume 23, Issue 6, 1 June 2002, Pages 285-290.

Unlike the CD200 molecule itself, the CD200R has 67 amino acids in its cytoplasmic domain compared to 19 for CD200, and it contains tyrosine residues that can be phosphorylated to carry on further signal transduction. A recent review has further summarized the tissue distribution of CD200 and its receptor in rat, mouse and human samples.

Localisation

Single-pass type I plasma membrane protein or plasma membrane associated protein.

Function

The function of CD200 was originally identified using mice lacking the CD200 gene where the mice developed an earlier onset of disease in experimental models of both autoimmune encephalomyelitis (EAE), collagen-induced arthritis (CIA), and autoimmune alopecia. The mice have increased numbers of macrophages in the spleen and after immunological stimulation, these macrophages demonstrate a more active phenotype *in vivo*. These studies demonstrate the importance of CD200 in maintaining self-tolerance and further studies have demonstrated that CD200 acts as an important molecule in controlling autoimmunity,

inflammation and adaptive immune responses implicating it as a key immunosuppressive molecule. The CD200-CD200R interaction exerts its inhibitory signal to myeloid cells that suppresses INF (Interferon)-gamma-induced proliferation, activation and secretion of nitrous oxide (NO), IL5, IL13 and IL6. Interestingly, a few phylogenetically distinct viruses including poxviruses and KSHV, the agent that causes Kaposi sarcoma and other human cancers, have been shown to attenuate the host antiviral immune response by expressing a viral CD200 homolog.

Homology

			% Identity	
			Protein	DNA
Homo sapiens				
CD200	vs. Pan troglodytes (Common Chimpanzee)	CD200	99.3	99.4
	vs. Canis lupus familiaris (Domestic Dog)	CD200	77.1	82.7
	vs. Bos taurus (Domestic Cow)	CD200	80.2	84.8
	vs. Mus musculus (The House Mouse)	CD200	77.6	81.7
	vs. Rattus norvegicus (Norway Rat)	CD200	77.2	80.7
	vs. Gallus gallus (Domesticated Fowl)	CD200	36.8	51.0

NP_001004196.2		-----	
XP_516648.2	1	MP LHGVQDES LS DWFS LAEDKKT LRYVAA LG IGHRAARHHS FQD IYFERS	50
XP_849283.1		-----	
NP_001029792.1		-----	
NP_034948.3		-----	
NP_113706.1		-----	
NP_001025958.1		-----	
NP_001004196.2	1	---MERLTLTRTIGGFLLTATLLGKTTINDYQVIRMPFCHLSTYSLVWV	46
XP_516648.2	51	IRNTVMEITLTRTIGGFLLTATLLGKTTINDYQVIRMPFCHLSTYSLVWV	100
XP_849283.1	1	---MSSGFAFRNSGEAWIGAVTCQG--ASRQVFRALPCQLSTCGLIWL	44
NP_001029792.1	1	-----MQCLVFRRLVCHLSTFQLIWF	21
NP_034948.3	1	-----MG-----SLVFRFRFFCHLSTYSLIWF	21
NP_113706.1	1	-----MG-----SPVFRFRFFCHLSTYSLIWA	21
NP_001025958.1	1	-----MTFQALVLS	9
NP_001004196.2	47	MAAVVLCTAQVQVVTQDEREQLYTPASLRCSLQNAQDALIVTWQKKRAVS	96
XP_516648.2	101	MAAVVLCTAQVQVVTQDEREQLYTPASLRCSLQNAQDALIVTWQKKRAVS	150
XP_849283.1	45	IARVMLCRAQ--VVTQDERRLINTPASLRCSLQNPPEVLIVTWQKVPVS	92
NP_001029792.1	22	IAFLILCRAQ--VVTQDVRGLINTPASLRCSLKRPQEVIVTWQKIKAVS	69
NP_034948.3	22	MAAVALSTAQVEVVTQDERKALHTTASLRCSLKTSQEPVIVTWQKKRAVS	71
NP_113706.1	22	IAAVALSTAQVEVVTQDERRLHTTASLRCSLKTTQEPVIVTWQKKRAVS	71
NP_001025958.1	10	LVCVVLGKAKVVTQTEQRVVKAGNSVTLSCALTEPRD IVQVTWQKDSLKS	59
NP_001004196.2	97	FENMVTFSRNHGVVIQPAYKDKINITQLGLQNSTITFWNITLEDEGCYMC	146
XP_516648.2	151	FENMVTFSRNHGVVIQPAYKDKINITQLGLQNSTITFWNITLEDEGCYMC	200
XP_849283.1	93	LENMVTFSRNHGVVQPAYKDKINVTQLELKNSTITFWNITLEDEGCYRC	142
NP_001029792.1	70	FENMITYSRNHGVVQPAYKDKINITQLGIMNSTITFWNTLEDEACYRC	119
NP_034948.3	72	FENMVTYSRNHGVVIQPAYKDKINVTQLGLWNSITITFWNTLEDEGCYMC	121
NP_113706.1	72	FENMVTYSRNHGVVIQPAYKDKINITELGLLNTSITITFWNTLDDDEGCYMC	121
NP_001025958.1	60	QSNIAIYSKSTGLKIQKPYQNRMLNLSLMLNNTSITITFWNARIDDTGCVLC	109
NP_001004196.2	147	LFNTFGFGKI SGTACLTVYVQPIVSLHYKFS EDHLNITC SATAR PAFMVF	196
XP_516648.2	201	LFNTFGFGKI SGTACLTVYVQPIVSLHYKFS EDHLNITC SATAR PAFMVF	250
XP_849283.1	143	LFNTFGSGKI SGTACLTLVQPTVFLHYNFFEDQLNITCFANAR PAFVIS	192
NP_001029792.1	120	LFNTFGSGKI SGTACLTLVQPTVFLHYNYS EDHLNITC SATAR PAFMIS	169
NP_034948.3	122	LFNTFGSQKV SGTACLTLVQPIVHLHYN YF EDHLNITC SATAR PAFVIS	171
NP_113706.1	122	LFNMFSGSKV SGTACLTLVQPIVHLHYN YF EDHLNITC SATAR PAFVIS	171
NP_001025958.1	110	LFNTFPLG SF SGRSCLGVYG- LNASIHYNVS EGHLIATC SAVGV PEPTIS	158
NP_001004196.2	197	WKVPRSGIENSTVILSHPNGTTSVTSILH IKDPKNQVGR EVICQVLHLGT	246
XP_516648.2	251	WKVPRSGIENSTVILSHPNGTTSVTSILH IKDPKNQVGR EVICQVLHLGT	300
XP_849283.1	193	WKVAGSGIENSTEVLLHPNGTTSVTSVLHVKDFKRVGR EVCQVLHLGT	242
NP_001029792.1	170	WKVFGSGIENSTEIVSHPNGTTSVTSILQ IKDPKTVGR DVICQVLHLGT	219
NP_034948.3	172	WKGTTGIENSTESHFHSNGTTSVTSILRVKDFKTVGR EVICQVLYLGN	221
NP_113706.1	172	WKGTTSGIENSTESHSHNGTTSVTSILRVKDFKTVGR EVICQVLYLGN	221
NP_001025958.1	159	WNNVFN-YTPTQERFTYENGVSITSELKVYDSQNISKE DLT CRVNSESE	207
NP_001004196.2	247	VIDFRQTVNKGWFSVP-LLL SI VSLVILLV LIS ILL YWKRHRN QDREP-	294
XP_516648.2	301	VIDFRQTVNKGWFSVP-LLL SI VSLVILLV LIS ILL YWKRHRN QDREP-	348
XP_849283.1	243	VISLRQTVNKGWFSVP-LLL SI VSLVILLV LIS ILL YWKRHRN QDRATQ	291
NP_001029792.1	220	VIDYRETVNKGWFSVP-LLL SI VSLVILLV LIS ILL YWKRHRN QDREP-	267
NP_034948.3	222	VIDYRQSLDKGWFSPVP-LLL SI VSLVILLLI LIS ILL YWKRHRN QERGES	270
NP_113706.1	222	VIDYRQSLDKGWFSPVP-LLL SI VSLVILLV LIS ILL YWKRHRN QERGES	270
NP_001025958.1	208	EMELPISMKKKEGLRFLGLAVAVTSLVILV LVLVLIALRWRK KICRKS---	254
NP_001004196.2		-----	
XP_516648.2		-----	
XP_849283.1	292	RFWEPQKEVILP LRSVVGLDYVRCQCSVVL SRGYWILNQ	329
NP_001029792.1		-----	
NP_034948.3	271	SGGMQRMK-----	278
NP_113706.1	271	SGGMQRMK-----	278
NP_001025958.1		-----	
Protein Acc.	Gene	Organism	
NP_001004196.2	CD200	Homo sapiens	
XP_516648.2	CD200	Pan troglodytes	
XP_849283.1	CD200	Canis lupus familiaris	
NP_001029792.1	CD200	Bos taurus	
NP_034948.3	Cd200	Mus musculus	
NP_113706.1	Cd200	Rattus norvegicus	
NP_001025958.1	CD200	Gallus gallus	

Mutations

Region	Contig position	mRNA pos	dbSNP rs# cluster id	Heterozygosity	Function	dbSNP allele	Protein residue	Codon pos	Amino acid pos
exon_1	18547206	145			start codon				1
exon_3	18554914	<u>251</u>	<u>rs1131199</u>	0.427	missense	G	Cys [C]	2	36
					contig reference	C	Ser [S]	2	<u>36</u>
exon_4	18558996	<u>355</u>	<u>rs2272022</u>	0.301	missense	A	Thr [T]	1	71
					contig reference	C	Pro [P]	1	<u>71</u>
	18559029	<u>388</u>	<u>rs11553079</u>	N.D.	missense	A	Lys [K]	1	82
					contig reference	C	Gln [Q]	1	<u>82</u>
	18559087	<u>446</u>	<u>rs35465733</u>	0.017	missense	G	Gly [G]	2	101
					contig reference	T	Val [V]	2	<u>101</u>
	18559233	<u>592</u>	<u>rs34710949</u>	0.043	missense	C	Pro [P]	1	150
					contig reference	A	Thr [T]	1	<u>150</u>
exon_5	18561622	<u>712</u>	<u>rs36015707</u>	0.036	missense	T	Cys [C]	1	190
					contig reference	C	Arg [R]	1	<u>190</u>
	18561708	<u>798</u>	<u>rs1050572</u>	0.297	synonymous	A	Thr [T]	3	218
					contig reference	G	Thr [T]	3	<u>218</u>

Germinal

None noted.

Somatic

Restricted CD200R isoform expression at the fetomaternal interface suggests CD200-CD200R interactions may serve important function(s) determining the successful outcome of pregnancy.

Implicated in

Cancer

Note

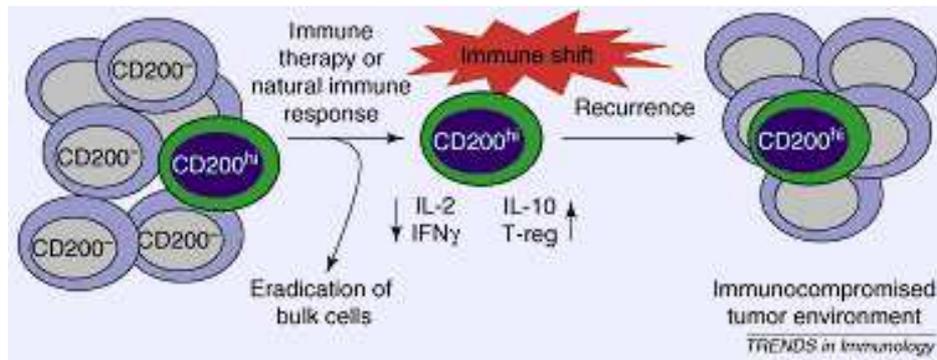
The expression of CD200 has been found in expressed several cancer cell lines or tissues, including ovarian, melanoma, head and neck carcinoma, testicular, malignant mesothelioma, neuroblastoma, renal cell carcinoma, chronic lymphocytic leukemia, prostate, breast and colon cancer. In multiple myeloma (MM) and acute myeloid leukemia (AML) CD200 has been implicated as a prognostic factor. In MM patients, CD200 was expressed in 78% of samples analyzed and for AML patients, in 43% of the patient samples. Patients who demonstrated expression of CD200 on their leukemic cells also demonstrated a decrease in survival overall. With regards to cancer progression, expression of CD200 is associated with metastasis or a relapse in bladder, lung, CML (chronic myeloid leukemia), breast, melanoma and prostate cancers. The

expression of CD200 on cancer cells has been linked to the theory of tumor immunity since mice treated with a CD200-Fc fusion protein (which blocks function of CD200) were able to clear injected leukemic cells, unlike mice who did not receive the antibody.

Cancer Stem Cells

Note

A relatively new hypothesis about cancer progression has suggested that cancer stem cells (CSCs) mediate solid tumor initiation and progression. The theory suggests that CSCs are only a minor subpopulation of cells (generally <1%) within the tumor that self-renew and also give rise to differentiated tumor cells, while the bulk of tumor cells are highly differentiated, have limited proliferative potential and are non-tumorigenic. Several markers exist to identify CSCs. For example CD44, CD133, $\alpha 2\beta 1$ integrin and flow cytometry-based 'side-populations' are all associated with CSCs. In 2007, CD200 was found to be co-expressed with the CSC markers CD44 and CD133 in a number of cancer cell lines including breast, prostate, brain, colon and melanoma, as well as in normal mesenchymal stem cells. In addition, the expression of CD200 was found to be 3-fold higher in CSCs compared with non-CSCs. This research has supported the theory that expression of CD200 defines a CSC population that can evade the tumor immune responses the host would normally provide (Figure below).



A hypothetical model of how CD200 might be involved in cancer stem cell (CSC) immunoevasion. CD200-expressing CSCs survive immune therapy or a natural immune response and induce a shift away from a Th1 response. These immunosuppressive effects of CD200+ CSCs could be mediated by events such as deviations in cytokine production, increased proliferation and/or induction of regulatory T cells (Treg). The altered immune response to the tumor might indefinitely dampen future immune reactions to the tumor, thus resulting in tumor cells that are resistant and free to proliferate in an immunocompromised tumor microenvironment. Kawasaki, B.T. et al. (2008) Cancer stem cells, CD200 and immunoevasion. Trends in Immunology Vol. 29 No. 10 (464-468).

Experimental autoimmune encephalomyelitis (EAE)

Note

EAE is a model of the human disease multiple sclerosis, which results from activation of peripheral T lymphocytes, macrophages, and granulocytes. These activated cells migrate to the Central Nervous System and can lead to microglial activation, tissue damage, and neurological deficits including paralysis. In these EAE mice, loss of CD200 resulted in an increase of disease onset and progression compared to mice expressing the gene. Using cultured rat hippocampal neurons, it was found that if the CD200-CD200R signalling pathway is blocked using an anti-CD200R-Fc antibody, the INF-gamma induced IL6 response of macrophages is increased and macrophage-mediated cell death of the neurons occurred.

Collagen-induced arthritis (CIA)

Note

CIA is a model of human rheumatoid arthritis which is an inflammatory autoimmune disease of the joints, and like EAE involves tissue-specific influx of T cells, macrophages, and granulocytes. Disruption of CD200-CD200 receptor interaction using cd200 KO mice increased susceptibility to mice normally resistant to this disease. The animals developed moderate to severe arthritis with synovial inflammation and formation of invasive pannus which results in degradation of cartilage and bone.

Skin Graft Rejection/Transplantation

Note

Experiments from mice have demonstrated that when wild-type tail skin from a male mouse was grafted onto the flank of a strain matched female, the skin was rejected at 59 days. However, if the male skin was CD200-deficient, it was only rejected after only 25 days.

Alopecia

Note

When expression of CD200 is lost from follicular keratinocytes the CD200R-positive cells (Langerhans cells and dendritic cells) switch to having an activated phenotype. Any additional trauma to the skin can initiate a full activation of CD200 positive cells and cause folliculocentric inflammation. The chronic inflammation that ensues leads to recruitment and activation of autoreactive T cells which are specific for hair follicles and lead to their destruction.

Autoimmune uveoretinitis (EAU)

Note

EAU is an organ-specific autoimmunity in the eye, a tissue with extensive neuronal and endothelial CD200 expression. One experiment demonstrated that mice lacking CD200 expression had increased numbers of retina-infiltrating macrophages. In addition, these mice displayed an increase in nitric oxide responses. When DX109 (a monoclonal antibody to CD200) was administered, it suppressed EAU despite maintained T-cell proliferation and IFN-gamma production and resulted in an earlier resolution of disease. Thus promoting CD200R-mediated signaling can successfully prevent full expression of IFN-gamma-mediated macrophage activation and protect against tissue damage during autoimmune responses.

Recurrent Abortion/Pre-Eclampsia

Note

A number of immunoregulatory cells have been shown to help prevent abortions and/or play a role in pre-eclampsia. For CD200, when male lymphocytes from aborting mice were immunized (inactivated), this stimulated female gdT CD4 cells to secrete Th2 cytokines via a CD200-dependent mechanism and reversed the abortive affects.

Microglia activation and Parkinsons Disease (PD)

Note

A number of studies have demonstrated that CD200 down-regulates microglia activation through binding to CD200R. Microglia are the primary immune cells in the brain and play an important role in the progression of PD. Similar to true myeloid cells, microglia in CD200-deficient mice exhibited more activated characteristics, such as shorter glial processes and less of a disordered arrangement, as well as an increase in inducible nitric oxide synthetase (specific to immune cells). To further support this, Frank et al. in 2006 demonstrated that expression of CD200 mRNA (measured by PCR) in the hippocampus decreased with increase in aging. Thus, the CD200-CD200R signaling pathway should be considered as target for developing therapies against PD.

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