REVIEW ARTICLE

CD200/CD200R PAIRED POTENT INHIBITORY MOLECULES REGULATING IMMUNE AND INFLAMMATORY RESPONSES; PART I: CD200/CD200R STRUCTURE, ACTIVATION, AND FUNCTION

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Summary: CD200/CD200R are highly conserved type I paired membrane glycoproteins that belong to the Ig superfamily containing a two immunoglobulin-like domain (V, C). CD200 is broadly distributed in a variety of cell types, whereas CD200R is primarily expressed in myeloid and lymphoid cells. They fulfill multiple functions in regulating inflammation. The interaction between CD200/CD200R results in activation of the intracellular inhibitory pathway with RasGAP recruitment and thus contributes to effector cell inhibition. It was confirmed that the CD200R activation stimulates the differentiation of T cells to the Treg subset, upregulates indoleamine 2,3-dioxygenase activity, modulates cytokine environment from a Th1 to a Th2 pattern, and facilitates an antiinflammatory IL-10 and TGF-β synthesis. CD200/CD200R are required for maintaining self-tolerance. Many studies have demonstrated the importance of CD200 in controlling autoimmunity, inflammation, the development and spread of cancer, hypersensitivity, and spontaneous fetal loss.

Key words: *CD200; CD200R; Inhibition mechanisms; Inflammation; IDO*

Short introduction of CD200 and CD200R

The main role of the immune system is to protect the organism against damage by ensuring an adequate response against various pathogens such as viruses, bacteria, fungi, parasites, environmental harm stimuli including allergens, haptens, and also from damage that may result from inappropriate immune system activation. The immune system, therefore, has to comprise mechanisms that maintain homeostasis, including both activatory and inhibitory mechanisms. CD200 and CD200R molecules are involved in the downregulation of myeloid and lymphoid cells. They provide immunomodulatory effects, are able to induce immune tolerance, regulate all differentiation, adhesion, and chemotaxis of various cell populations, mediators and cytokines release. This article aims to summarize the information addressing the regulatory activity of CD200 and CD200R membrane molecules and their putative potential in clinical applications, applications which are, for the moment, tested *in vitro* or *in vivo* animal models only.

CD200 and CD200R in detail

CD200 and CD200R, type I transmembrane-anchored glycoproteins, are structurally similar to immunoglobulins. Their extracellular N_2 terminal domain contains both C-type and V-type regions. CD200 and CD200R are identical in their extracellular parts, but they differ in their cytosolic COOH tails (4). In contrast to CD200R, CD200 have a minimal intracellular region which lacks the capacity to transmit either activatory or inhibitory signals, while the CD200R upon ligation is capable of downregulating the exaggerated activity of the immune system to protect the organism from harm caused by its overactivity. CD200 was first purified and described by Prof. A. N. Barclay and his team in 1981–1982, and it was originally referred to as OX-2. Using mouse monoclonal antibodies, the expression of CD200 was detected in rat lymphoid tissue (2, 3). CD200R was depicted later in 2000 by Wright and his team (45). To elucidate expression pattern, gene localization, isoforms and function of CD200 and CD200R, a variety of antibodies has been developed; monoclonal, polyclonal, chimeric, recombinant, together with receptor agonists, full length CD200, or synthesized 9–15 mer peptides defining discrete regions in N-terminal regions of CD200 (14). Finally, transgenic knock-out mice lacking CD200 were generated by using C57BL/6 embryonic stem cells.

1) Expression of CD200/CD200R

The receptor expression pattern and its ligand show marked differences. CD200 is expressed in a variety of cells both of hematopoietic origin, such as myeloid cells (mast cells, neutrophils, macrophages, dendritic cells), lymphoid cells (T, B cells), and nonhematopoietic origin, such as neurons, cardiomyocytes, endothelial cells, trophoblast

cells, retinal and optical nerve cells, and keratinocytes (9, 36, 43). Expression of CD200 is enhanced in response to the immune system activation during the inflammatory response. CD200 expression rapidly increases in the presence of TNFα, INFγ following the activation of TLR-4, scavenger receptor A (SR-A), NALP3 (NACHT-, LRR-, and PYD-containing protein 3), and NOD2 (nucleotide oligomerization domain 2) (7, 8, 29). Unsurprisingly, apoptotic cells bear a high amount of CD200 at the cell surface. Apoptosis is associated with p53 synthesis, which supports CD200 expression. CD200 gene contains p53 response element sequences that activate p53 mediated gene expression (35). CD200 in apoptotic cells prevents the development of autoimmune diseases. CD200R expression is restricted to lymphoid cells, to T, B cells, NK, and NKT cells, and to myeloid cells. Myeloid cells include dendritic cells, mast cells, eosinophils, basophils, neutrophils, and macrophages, especially subpopulation M2a regulatory macrophages (44). CD200R can be used as a specific marker for M2a macrophages. Differentiation of macrophages to the M2a subset is mediated by IL-4, IL-13, whereas differentiation to M2c macrophages is induced by IL-10 and glucocorticoids (25). The density of CD200R expression varies among distinct leukocyte subsets. The expression of CD200R was identified in mouse leukocytes harvested from the spleen using standard staining and flow cytometric analysis. It was shown that CD200R is highly expressed in $CD11b^+$ cells. It has been well documented that helper $CD4^+$ T cells showed more intensive expression of CD200R compared to $CD8^+$ cytotoxic T cells. Helper $CD4^+$ effector/memory cells express CD200R with a higher intensity compared to central memory and naive T cells. The expression of CD200R is significantly higher in Th1 T cells compared to Th2 T cells. B cell CD200R expression is more pronounced in memory cells and plasma blasts. It was discovered that the absence of CD200/CD200R ($CD200^{-/-}$ mice) does not result in any change in the absolute numbers of T, B, NK cells. The production of specific immunoglobulins showed no changes in mice, suggesting that immunoglobulin serum level is CD200R independent (33).

2) CD200 and CD200R gene encoding and isoforms

Genes encoding CD200 and CD200R are both located on chromosome 3. Precise localization of CD200 encoding gene on chromosome 3 is at position 3q12-13 (26). Finding CD200R encoding gene was more difficult. Vieites and his team mapped the CD200R gene to chromosome 3, region 3q13, using RT-PCR and cDNA cloning. (cDNA of CD200R encodes 325 amino acids, 28 in signal sequences, 215 in extracellular, 21 in transmembrane and 61 in cytoplasmatic domains.) They detected two different coding regions within chromosome 3 with homology to mouse CD200R encoding for isoforms CD200R2/CD200RLa. The mouse CD200 and CD200R genes are located on chromosome 16 (39). It was revealed that there are several related genes in the mouse genome that encode CD200R isoforms termed CD200RL (receptor like – CDR200RLa-e). CD200RL (including hCD200RLa) is characterized by a truncated cytoplasmatic tail with positively charged lysine residues compared to CD200R (1). There is evidence of its functional association with the DNAX-activating protein of 12 kDa (DAP-12) (31, 44). The expression of CD200RLs does not repeat the same pattern as CD200R. CD200RLa is highly expressed in resting mast cells and dendritic cells in the bone marrow. The Lb form is preferentially located in the activated mast cells. Concerning the fact that there are more isoforms, researchers had been challenging the question of whether CD200 is a ligand for all types of CD200R and CD200RL. Gorczynski's team announced that CD200 has an affinity to any form of receptor CD200R, including isoforms CD200RL (18). Recently it has been established by Deborah Hatherley's team that CD200 is not a ligand for CD200R isoforms (20). They confirmed their claim using highly specific monoclonal antibodies to CD200Fc fusion protein and BaF cells that express CD200R as well as isoforms of CD200RLs. It was demonstrated that CD200 binds only to CD200R. CD200RL binding by CD200 was very weak, almost undetectable. Hatherley pointed out that Gorzynski failed to consider the structural differences of N-terminal tails among CD200R and CD200RLs and their association with DAP-12 (40). Attention of late has focused on detailed mapping of CD200 molecule structure to find sequences that provide optimal interaction leading to effector cell inhibition. Molecular analysis has been elicited showing that CD200 comprises three domains – CDR1, CDR2, CDR3, typical for immunoglobulin molecules. It has also been recently revealed that both molecules CD200/CD200R interact through their extracellular NH_2 domains. More accurately, engagement depends on the "GFCC" amino acid sequence. After this discovery, 15-mer peptides from CD200 domains were synthesized to verify the hypothesis that these peptides are able to promote inhibition of the immune system as CD200 does. Surprisingly, some of these short peptides have shown an antagonistic effect on CD200R, and have canceled CD200-induced suppression. Antagonistic properties were observed in peptides from CDR1 and CDR3 regions, whereas peptides from the FR2CDR25 region functioned as agonists-amplified inhibition (14, 15). Further studies proved that there is a simultaneous expression of mRNA for two types of CD200, both the full-length and the short, truncated type. The synthesis of CD200 and CD200tr is controlled by SF2/ASF (alternative splicing factor/splicing factor 2). Exons contain specific short sequences affecting their ability to be spliced – ESE (exonic splicing enhancer). These sequences regulate alternative splicing of mRNA through their direct binding to regulatory protein SF2/ASF. CD200tr levels are determined by binding SF2/ASF to ESE. If there is a deficit of ESE, expression of full-length CD200 decreases. Increased expression of SF2/ASF leads to an increase of CD200 synthesis (23). The structural differences between CD200 and CD200tr are that mRNA for CD200tr

lacks exon-2. This property of mRNA for CD200tr is responsible for alternative splicing of mRNA, and the transcription starts from the second ATG codon and thus the alternative transcript of CD200 lacks the NH_2 domain (5). The CD200 truncated form was supposed to retain the same ability to suppress immune reactions as full-length CD200. It was shown that CD200tr is a natural antagonist of CD200. Its ligation to CD200R results in TNFα production and CTL activation. Both CD200tr and CD200 synthesis is promoted by the presence of LPS. Tumors and viruses block the production of CD200tr to protect themselves against immune responses. CD200tr does not bind isoforms of CD200RL (6).

3) CD200 and CD200R functions

Once the structure of CD200 and CD200R was described, research projects focused on identifying and describing biological functions of CD200 and CD200R. Transgenic knock-out mice lacking CD200 have allowed researchers to reveal the importance of CD200/CD200R interactions which dampen immune system overactivation. Heterozygous $CD200^{+/-}$ and homozygous $CD200^{-/-}$ mice were bred. Homozygous mice showed no CD200 expression in neurons, B cells, or follicular dendritic cells, whereas expression of CD4, CD8, CD220, CD11b molecules remained unaltered. The $CD200^{-/-}$ mice were found to exhibit an elevated spleen $CD11b^{+}$ cell population. The activated $CD11b^{+}$ cells were predominantly located in the red pulp of the spleen causing the spleen's enlargement but were found also in lymph nodes, especially in the mesenteric lymph nodes (45). There is evidence of increased susceptibility to external stimuli that contribute to autoimmune disease development in both $CD200^{-/-}$ animals and in normal mice after blocking CD200R by its antagonists. MOG (myelin oligodendrocyte glycoprotein) administered to such experimental animals induces experimental allergic encephalomyelitis, resembling multiple sclerosis (21). A vigorous inflammatory response was described in facial nerve transection. Lack of CD200 in neurons and microglias resulted in rapid progression of irreversible destruction of the nerve. Pronounced activation was detected at day 2 after transfection. The peak of reactivity was observed at day 4 in contrast to $CD200^{+/+}$ mice, in which the peak of activation occurs at day 7 after surgery (19). The disruption of the CD200/CD200R receptor interaction is also closely related to the increased susceptibility to collagen-induced arthritis. Wild mice ($CD200^{+/+}$) are resistant to this disease, as well as to the development of autoimmune uveitis (41). Gorczynski and his team clarified the function of CD200/CD200R interaction on the $NLDC145^{+}$ dendritic cell subpopulation, which is associated with better graft survival in mice. This subpopulation shows high expression of the CD200. Blocking of the CD200R by the administration of a CD200R-Fc fusion protein contributes to graft rejection (16, 17). It is useful to note that human CD200 and its receptor are highly conserved, sharing identical amino acid sequences with other mammals (rat, mice). The similarity was demonstrated by the administration of human CD200Fc, which displayed the ability to react with mice CD200R and vice versa (44). Recently, viral CD200 homologues (vOXs) were found in viruses, especially in HHV-6 poxviruses and the myxoma virus. It is supposed that vOX downregulates myeloid cell activity during viral infection, thus enabling the escape of viruses (13, 37).

CD200/200R signaling cascade

Immune response must be of sufficient intensity to eliminate exo- and endogenous antigens. To prevent excessive tissue damage, downregulation of the immune system activity is necessary. The immune system suppression is driven by a variety of biologically active substances and receptors. The majority of inhibitory receptors are closely related to the cytoplasmatic sequence ITIM (immunoreceptor tyrosine-based inhibitory motif). CD200R lacks ITIM domains and its cytoplasmatic tail contains three tyrosine residues (24, 46). The most membrane distal tyrosine residue is a part of a NpxY domain (27). This domain binds PTB (phosphotyrosine binding domain) sequences on other molecules – Dok1, Dok2, and Shc. Dok's phosphorylation triggers SH2, which modulates the interaction among Ras/GAP, Csk and SHIP molecules. Dok1 preferentially recruits Crk and CrkL (adaptor protein containing SH2 and SH3 src homology, CT10 sarcoma oncogene cellular homologue domains that activate Ras and Jun kinase), whereas Dok2 is closely related to RasGAP and NcK protein activation (non-catalytic region of tyrosine kinase adaptor protein) (28). To evaluate tyrosine residues and their role in signaling pathway, all three tyrosine residues were mutated to phenylalanine. As a result, the inhibitory function of CD200R was lost. Mutation of tyrosine residues showed the importance of these three tyrosines. Each of them plays an important role in the signal transmission (34). Zhang and his colleagues, in contrast, claimed that only the first and the third tyrosines are needed for signal conducting from CD200R. The second tyrosine residue was shown to have no significance (46). Upon binding of a ligand or agonist antibody, CD200R becomes phosphorylated on its tyrosine residues. This is associated with propagating the signal from the receptor and inducing the inhibitory adaptor protein Dok1 (downstream of tyrosine kinase) and Dok2. Doks are involved in the Ras GTPase (RasGAP) phosphorylation and activation. Dok1, in addition, recruits SHIP (SH2-containing inositol phosphatase). The activation of RasGAP and SHIP leads to inhibition of MAPK (mitogen-activated protein kinase) and NF-κB. Blocking of the MAPK activation results in decreased degranulation of mast cells, decreased synthesis of plethora of cytokines such as TNFα, INFγ, IL-1, IL-17, IL-6, IL-8, IP-10, MIG, and decreased iNOS activity, whereas the synthesis of anti-infammatory IL-10 and TGF-β cytokines increases (22, 32). The influence of various cytokines on the expression of CD200/CD200R molecules is shown in Fig. 1.

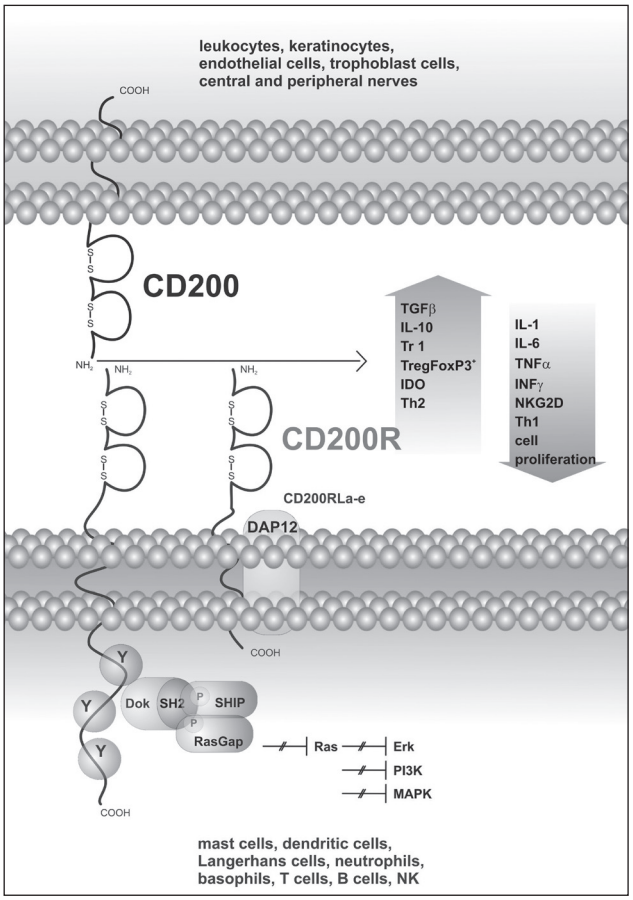

Fig. 1

Inhibition mechanisms

Direct inhibition of leukocytes is induced by cell-to-cell interaction mediated by CD200/CD200R, which is also responsible for indirect inhibition by polarization of T cells into either iTreg or Tr1 cells producing IL-10 and TGF-β. In addition, the shift from Th1 to Th2 cytokine environment or activation of the tryptophan catabolizing enzyme IDO (indoleamine 2, 3-dioxygenase) dependent inhibition pathway is also triggered by CD200/CD200R interaction. IDO is one of the three enzymes metabolizing tryptophan (10). Tryptophan is a substrate for NAD^+ (nicotinamide adenine dinucleotide) synthesis. Tryptophan is metabolized to kynurenines, which are strong propapoptotic signals. It was determined that IDO suppresses $CD4^+$ response to ovalbumin in allergic mice. IDO expression, more accurately toxic metabolites of tryptophan, are involved in $CD4^+$ T cell apoptosis. IDO is constitutively expressed by APC cells and trophoblast. However, dendritic cells $CD11c^+$ mPDCA-1^+ $120G8^+$ expressed IDO only after activation. The same holds for fibroblasts, astrocytes, eosinophils, and tumor cells. The crucial inducer of IDO expression is the CD200 molecule and its interaction with CD200R. CD200/CD200R interaction directly enables IDO expression or mediates its expression in DC by Treg after CTLA-4 ligation (38). IDO expression is also enabled in the presence of INFγ, CpG motifs of bacterial DNA. TNFα, IL-1, and LPS also strengthen IDO inhibitory potential (11, 42). IDO, whose expression is potentiated by CD200/CD200R interaction, suppresses APC cells to prevent autoreactivity and protects the fetus against spontaneous abortion. However, this IDO activity is penalized by an energy deficit as NAD^+ is decreased in this way (30). As mentioned above, a significantly higher expression of IDO is thought to be associated with inflammation and positively correlates with the severity of inflammation. It follows that a low level of tryptophan is a marker of poor prognosis in autoimmune disease as well as increased IDO expression. As already mentioned in the preceeding text, CD200 supports TGF-β synthesis in target cells. This cytokine, as a potent immune inhibitor, blocks the activation of lymphocytes and macrophages, and facilitates differentiation of T cells to $CD4^+CD25^+FoxP3^+$ Tregs, thereby possibly preventing transplanted organs from being rejected or controling and diminishing the autoimmune inflammation (12). The link between CD200/CD200R expression and various diseases is shown in Fig. 2.

Conclusion

All studies to date confirm that CD200/CD200R interaction promotes inhibitory activities of the immune system. These molecules play an irreplaceable role in maintaining homeostasis, suppressing inflammatory response to both external stimuli (pathogens, allergens, etc.) and internal stimuli (hypoxia, oxygen radicals, tissue damage, etc.). The distribution of CD200 expression is very broad, including immune-privileged tissues, whereas CD200R expression is restricted mainly to myeloid cells that are the first line of cell defense in an organism, the so-called sentinel cells. Downregulation of their activation results in both innate and adaptive immune system inhibition without any alteration of the total cell numbers or immunoglobulin production. Current studies of CD200 and CD200R are aimed at investigating their therapeutic potential for the treatment of diseases associated with increased immune system activity.

CD200/CD200R expression	increased		decreased	
cytokines, chemokines	IL-10 TGF-β IL-4 IL-5		IL-1, IL-6 IL-2, INFγ/α IL-12	MIP-1α MCP-1 IL-8
cells and adhesion molecules	Treg, Tr1, Tr3	immature state of leukocytes	CTL, leukocyte and microglia activation, adhesion, Ag presentation	MHC I, II, ICAM-1/2, VCAM-1,2, VLA-4, LFA-1
diseases	cancer invasivity and metastasis both hematopoietic and solid	immunotolerance self, allo graft acceptance osteoblastogenesis	autoimmunity rheumatoid arthritis, multiple sclerosis, Parkinson disease, Alzheimer disease, alopecia	viral infection, spontaneous fetal loss, allergy

Fig. 2

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Abbreviations

APC – Antigen-presenting cell
Csk – C-src tyrosine kinase
CTL – Cytotoxic T-lymphocytes
CTLA-4 – Cytotoxic T-Lymphocyte Antigen 4
DAP-12 – Immunoreceptor tyrosine-based activation motif-bearing adapter protein
Dok – Docking protein
ESE – Exonic splicing enhancer
IDO – Indolamine 2,3-dioxygenase
iNOS – Inducible nitric oxide synthese
JNK – Jun N-terminal kinase
LPS – Lipopolysaccharides
MOG – Myelin oligodendrocyte glycoprotein
NK – Natural killer
NKT – Natural killer T (NKT) cells
PTB – Phosphotyrosine binding domain
SF2/ASF – Alternative splicing factor/splicing factor 2
Shc – Phosphotyrosine-binding domain
SHIP – Inositol 5′ phosphatase
SH2 – Src homology 2 domain
TLR – Toll like receptor
Treg, Tr1 – Regulatory T cells
vOX2 – Viral CD200 homologue

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