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Review Article

CD200-CD200R signaling and diseases: a potential therapeutic target?

Conelius Ngwa, Fudong Liu

Department of Neurology, The University of Texas Health Science Center at Houston McGovern Medical School, Houston, TX 77030, USA

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Abstract: CD200 and its receptor, CD200R, constitutes an endogenous inhibitory signaling, and is being increasingly recognized in studies of various central nervous system (CNS) disorders. Emerging data have demonstrated that neuronal CD200 binds to CD200R to modulate immune responses to pathogenic stimuli. However, on which component of the immune response that CD200-CD200R signaling acts is not well understood. In this review, we focused on cellular expression of the signaling, the effects on immune cell activation, and the function in pathological procedures of neurodegenerative diseases, in both clinical and experimental disease models. Essential functions of CD200-CD200R interaction and the treatment relevance have been elaborated. Immune responses to diseases under the control of CD200-CD200R axis were also discussed in the review.

Keywords: Brain, CD200, CD200R, immune responses, neuron

Introduction

Immune responses to brain tissue damage are triggered by the recognition of non-self or altered self-molecular patterns by professional cells including microglia, neurons, astrocytes, and oligodendrocytes [1, 2]. The recognition leads to activation of immune cells that is regulated by endogenous inhibitory pathways including CD200 signaling. The cluster of Differentiation-200 (CD200), a 41-47 KDa protein [3-11] characterized by two immunoglobulins superfamily (IgSF) domains [11], one transmembrane region, and a small cytoplasmic domain, is suggested to be devoid of intracellular signaling function [12]. However, primarily expressed in the somas, axons, dendrites and synapses of neurons, and in endothelial cells, CD200 is an important inhibitory ligand to interact with immune cells [10]. Genes encoding CD200 are located on chromosome 3, precisely 3q12-13. The homology between human and mouse CD200 is 77.6% for protein and 81.7% for DNA, which in the case of human vs. rat is 77.2% (protein) and 80.7% (DNA) [13]. CD200 receptor (CD200R) also has two IgSF domains but with a longer cytoplasmic tail [7, 21], constituting a cellular signaling domain [14]. CD200R is mainly expressed by myeloid cells [20, 26, 30], but also present on thymocytes [15], T and B cells [8, 24]. CD200R family include CD200-R1, R2, R3 and R4 in mouse; and CD200R1 and R2 in human [31, 32]. However, it was found that CD200 only binds to CD200R1 but is not the ligand for other CD200R isoforms [16, 17]. CD200R interacts with CD200 ligand through its N-terminal Ig V-type domain, forming an endogenous inhibitory signaling for immune responses [18]. The human CD200R gene spans a region of 52 kb consisting of nine exons and encodes a 348-amino-acid cell-surface protein [14]. In contrast to murine CD200R protein, the human membrane-bound and soluble CD200R proteins have an insertion of 23 amino acids at position 23, encoded by exon 2, which generates a putative dihydroxyacid dehydratase domain [14]. Despite these differences, CD200-CD200R signaling plays a pivotal role in modulating immune responses in both murine and human upon inflammatory stimuli.

Molecular mechanisms of CD200-CD200R signaling

CD200R does not contain any immunoreceptor tyrosine-based inhibitory motifs (ITIMs) which

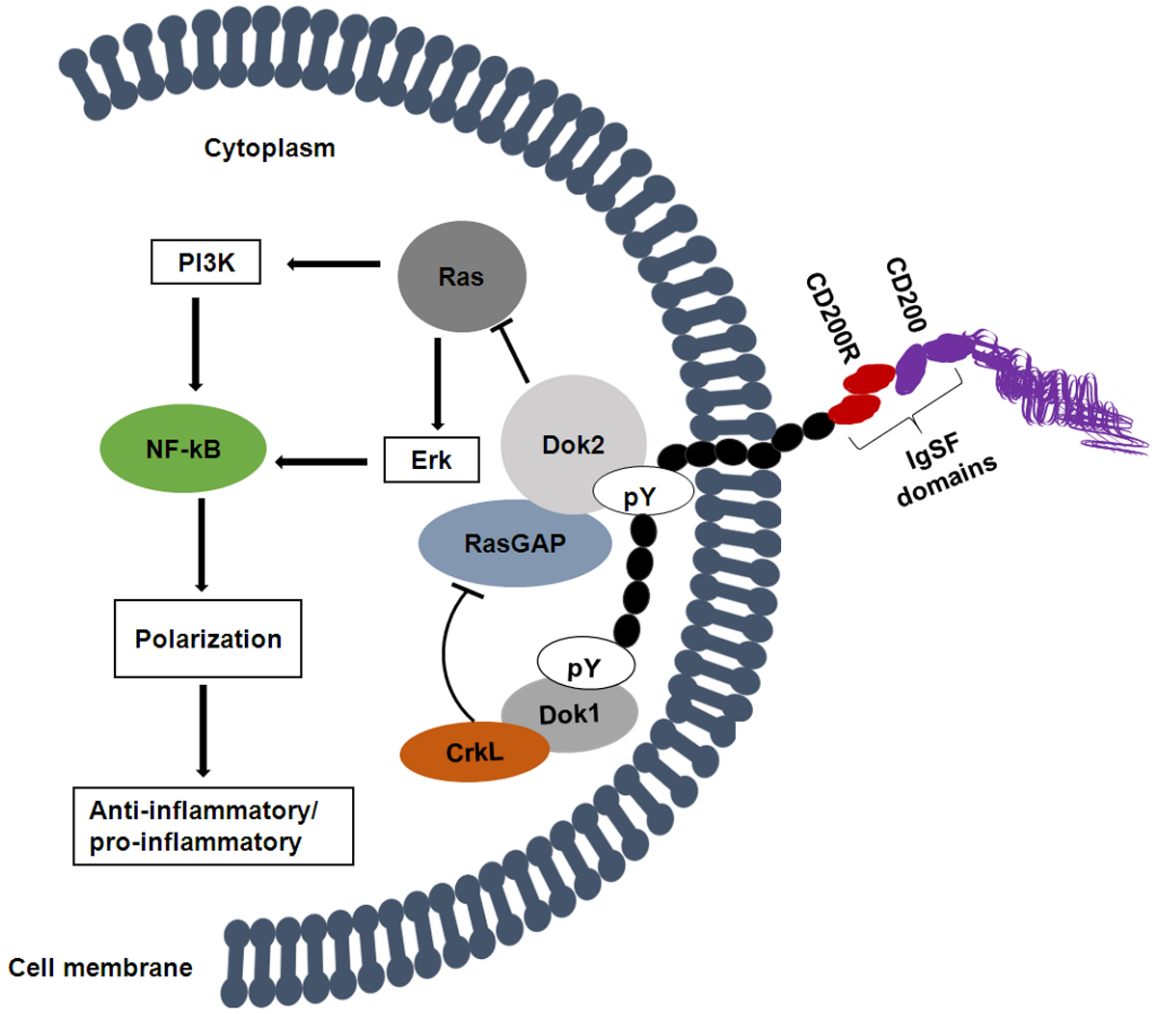

Figure 1. Presumptive mechanism of CD200-CD200R interactions underlying the activation of immune cells (monocytes, lymphocytes, etc.). The primary mechanism involves activation of Dok2 and RasGAP, leading to the inhibition of Ras activation and suppression of downstream effects on PI3K and Erk. Resultantly an increase of multiple anti-inflammatory signals occurs due to the inhibition of NF-kB. Activation of RasGAP can be inhibited by the combination of Dok1 and CrkL, leading to activation of NF-kB and the pro-inflammatory phenotype. pY: Phosphotyrosine. This illustration is based on the findings from [7, 22, 29, 69, 85, 86].

are usually present in a large number of inhibitory receptors and which mediate their inhibitory roles through the recruitment of protein tyrosine phosphatases such as Src homology 2 domain-containing phosphatase (SHP) 1, SH2, or the inositol phosphatase (SHIP) upon phosphorylation [19]. Instead, the molecular signaling mechanism of CD200R following activation involves direct interaction of the adaptor protein downstream to tyrosine kinase (Dok2), with the membrane distal tyrosine residue located within a phosphotyrosine-binding (PTB) domain recognition motif (NPxY) [20]. This interaction leads to binding and recruitment of RAS p21 protein activator (RasGAP) which is an SH2 domain containing protein [21, 22]. The formation of the Dok2-RasGAP complex inhibits Ras activation (**Figure 1**), leading to inhibition of other downstream inflammatory signals through inhibition of principal mitogen activated protein kinases including Phosphoinositide 3-kinase (PI3K) and Extracellular Signal-regulated Kinase (Erk) [10, 23-25]. According to Snelgrove et al. [26] the interaction between CD200 and CD200R induces phosphorylation of tyrosine residues, initiating a signaling cascade which recruits SHIP and RasGAP [27, 28]. Dok2 appears to be regulated by Dok1 through Crk Like

(CrkL)-RasGAP suppression; both Dok2 and Dok1 are recruited during CD200-CD200R interaction that leads to recruitment of RasGAP and SH2-containing inositol phosphatase [29]. As shown in **Figure 1**, Dok1 activation is initiated through binding to one of the three phosphotyrosine residues located on the cytoplasmic amino acid chain of CD200R. This Dok1-phosphotyrosine binding then suppresses Dok2's effect on Ras through activation of CrkL [30]. It has been demonstrated that knockdown of Dok2 but not Dok1 ameliorated the increase in IL-8 production following CD200R activation in U937 cells [29]. The regulatory effect of Dok2 by Dok1 was also confirmed by using macrophages with Dok1 knockdown, which shows increased phosphorylation of Dok2 and enhanced recruitment of RasGAP [14]. Thus, the activation and recruitment of Dok2, and the subsequent activation of RasGAP are the key events downstream to the CD200-CD200R interaction that induce immune regulatory function in immune cells [29].

Neuronal CD200 signaling

CD200 is mainly expressed by neurons and vascular endothelia cells [31-33], although relatively weaker expression was also found in astrocytes and oligodendrocytes [12, 25, 36], as well as in peripheral thymocytes [3, 24] and NK cells [34]. Neurons express the highest level of CD200 compared to other cell types [35], and execute their functions on immune cells where CD200 receptor (CD200R) is expressed, including macrophages and dendritic cells [39, 49], B and T cells [39, 45]. CD200 gene in the human brain is likely regulated differently compared with rodents [13]; however the characterization of human CD200 localization [14, 15] has shown a similar distribution on neuronal cell membrane as that of rodents [13, 35]. Microglial CD200R expression has been controversial, as low levels of CD200R have been detected in microglia from multiple sclerosis [35] and Alzheimer's disease (AD) [36] animal models. In another report CD200R was only present in macrophages but not microglia [37, 38]. In vitro studies showed that isolated microglia from AD human brains had low levels of CD200R mRNA and protein compared with that in blood-isolated macrophages [36], suggesting that monocytic cells are more sensitive to CD200-CD200R signaling. Our recent study examined CD200R expression in infiltrating immune cells in mouse brains subjected to experimental ischemic stroke model, and found microglia express near null CD200R; while robust signals of the receptor were found in lymphocytes with modest expression on monocytes [39]. The vast amount of infiltrating $CD200R^+$ leukocytes in the ischemic brain indicates the enhanced activation of these immune cells, which could be attributed to the loss of neuronal CD200 after stroke.

CD200R may not be the sole receptor for neuronal CD200. The addition of CD200 to primary neuronal cultures promoted neuronal survival and neurogenesis, an experiment performed through CD200 binding to the fibroblast growth factor receptor (FGFR) instead of CD200R1 [40]. Since the ultimate anti-inflammatory effect of FGFR activation was suggested being mediated by CD200 upregulation [28, 29], further research is warranted to investigate whether the protective effects of neuronal CD200 are derived from either a direct interaction with CD200R on immune cells or indirectly by binding to other putative receptors.

CD200 signaling with aging

CD200 levels in neurons reduce with age [41, 42]. Frank and his collaborators [41] compared the gene-expression profiles of the hippocampus from young (3 months) and aged (24 months) male F344xBN F1 rats. Their data showed a decrease in CD200 mRNA in the older animals accompanied by a significant increase in mRNA levels of inflammatory markers including the major histocompatibility complex (MHCII), Cluster of Differentiation-86 (CD86), and interferon gamma (IFN-γ). Microglial activation in the hippocampus of aged and β-amyloid (Aβ)-treated rats was accompanied by decreased expression of neuronal CD200, providing evidence that neurons can downregulate the microglial activation through CD200 signaling [43]. Data from this report also showed that the expression of CD200 was increased by IL-4 supplement, suggesting that IL-4 is also involved in the neuronal CD200 signaling to downregulate the activation of aged microglia under inflammatory conditions.

With the aim of characterizing CD200 and CD200R expression in elderly human brains, Walker et al. [13] found that many neurons in the cortex and hippocampus did not show

CD200 immunoreactivity. Quantitative studies on human AD brain tissues from averagely 84.4 year old patients (16 females and 15 males) showed a significant decrease in CD200 protein and mRNA in the hippocampus and inferior temporal gyrus, but not in the cerebellum [34]. A significant decrease in CD200R mRNA expression in AD hippocampus and inferior temporal gyrus, but not in cerebellum, was also detected. Low expression of CD200R by microglia was confirmed at the mRNA and protein level using cultured human microglia compared to blood-derived macrophages [34], and the treatment of cultured microglia and macrophages with IL-4 and IL-13 significantly increased the expression of CD200R. These data indicate that the CD200-CD200R axis may be deficient in AD brains and mechanisms aimed at increasing levels of CD200 and CD200R could be neuroprotective in human neurodegenerative diseases.

Ischemic stroke

Ischemic stroke, the leading cause of death and long-term disability in the USA [44, 45], accounts for > 80% of all stroke cases [46]. Post-stroke inflammation is a fundamental pathophysiological process that is tightly controlled by endogenous regulatory pathways including CD200-CD200R signaling. In the acute phase of brain ischemia, neuronal CD200 expression is markedly decreased in the brain due to the degeneration of CD200-expressing cells [11, 47]; however, increased expression of CD200 was found 5 days after stroke [11, 47, 48]. It was suggested that this unstable expression during ischemia disrupts the CD200-CD200R axis and triggers microglial activation [49]. Yang et al. [50] reported that the expression of CD200 was decreased within 48 h after permanent middle cerebral artery occlusion (pMCAO) accompanied by a decrease of neuron-specific enolase (NSE) expression. The loss of CD200 caused by neuronal death could be one of contributing factors in immune cell activation after cerebral ischemia.

We have found that CD200-CD200R inhibitory axis could be a critical regulator of peripheral immune response after brain ischemia, impacting animal survival rate and their susceptibility to post-stroke infection, as the loss of CD200R signaling leads to exacerbated leukocyte infiltration in the brain, greater spontaneous bacterial colonization of the lung, and worse stroke outcomes [39]. CD200R may also co-exist with CD200 in immune cells and functions through an autocrine mechanism. Using rat MCAO model, Matsumoto et al. [11] found that macrophage-like cells expressing CD200 have suppressive effects on activation of myeloid cells including microglia by interacting with CD200R. In this study CD200-mRNA and protein were detected in the ischemic core as well as the contralateral region, and in isolated spherical $Iba1^+$ macrophage-like cells. Similarly, it was reported that microglial CD200 interacts with CD200R to maintain microglia in an alternatively activated state, whereas interactions between neuronal CD200 and microglial CD200R keep microglial quiescent [51].

Interestingly, physical exercise and stem cell treatment have been found to boost the CD200-CD200R signaling in experimental stroke studies. Sun et al. [52] found that treadmill exercise significantly increased CD200 and CD200R levels in the ipsilateral hippocampus and cortex, and facilitated sensorimotor cognitive functional recovery after tMCAO. In addition, neural stem/progenitor cell proliferation, differentiation, and migration were enhanced in the ipsilateral subventricular and subgranular zones. Human placenta amniotic membrane-derived mesenchymal stem cells (AMSCs) transplanted into ischemic rat brains dramatically inhibited the expression of pro-inflammatory cytokines and increased CD200 expression in neurons, as compared with the sham-treated group [53]. The reason why stem cells promote CD200-CD200R signaling in stroke is not known, which might be delivered by the intrinsic protective mechanism conveyed by the new-born cells.

Alzheimer's disease

Alzheimer's disease (AD) is morphologically distinguished by the presence of senile plaques in the brain, composed mainly of different species of fibrillar amyloid-β (Aβ) produced by the cleavage of the Aβ precursor protein (APP), and neurofibrillary tangles composed of various isoforms of hyperphosphorylated and truncated tau proteins [54-57]. CD200 levels have been found decreased in AD brains mainly in hippocampus and inferior temporal gyrus [36, 58].

Data obtained from brain tissues of AD patients showed that there is not only a deficit of CD200 but also of CD200R [36]. It has been established that aggregated Aβ plaques activates microglia to a pro-inflammatory state, augmenting phagocytic and lysosomal activity, and capable of producing a wide range of neurotoxic mediators [43, 58, 69, 70]. Lyons et al. [59] examined the impact of CD200 deficiency on Aβ-induced changes in microglia and reported that the effect of Aβ was surprisingly reduced in microglia prepared from the CD200-deficient mice. It was previously shown that CD200FC administration reduced pro-inflammatory cytokine production in the presence of Aβ in microglia and attenuated the decrease in long-term potentiation (LTP) [60]. In summary, these data clearly showed that CD200-CD200R signaling is critical for Aβ removal and could be associated with other intrinsic molecules, and probably related to microglial phagocytosis.

Parkinson's disease

In one study using Parkinson's disease (PD) model created in rodents by 6-hydroxydopamine injection into substantia nigra (SN) neurons, blocking of CD200R resulted in significantly more severe PD-like movement dysfunction and a significantly greater loss of tyrosine hydroxylase-positive dopaminergic neurons in SN [37]. A 4-fold greater number of activated microglia was noticed in rats treated with CD200R blocking antibody compared with control animals, accompanied by 3 to 4-fold higher levels of TNF-α and IL-6 in the SN. Blocking CD200-CD200R interaction by anti-CD200R antibody resulting in microglial activation and intensified neurodegeneration in PD was also confirmed in monocyte-derived macrophages (MDMs) from 32 individuals with advanced PD [61], demonstrating an essential role of this CD200-CD200R axis in the regulation of PD.

Multiple sclerosis

Data of CD200 signaling in multiple sclerosis (MS) have been mainly from studies with Experimental Autoimmune Encephalomyelitis (EAE) which showed disruption of CD200-CD200R interaction due to neuronal damage leading to microglia activation [62-65]. According to Lyons et al. [59], both the severity and disease progression during the chronic phase of EAE in mice were ameliorated by CD200-Fc injection. Decreased CD200 mRNA expression has been reported in the rim and center of MS lesions, as well as in adjacent normal white matter compared with matched controls [66].

In both EAE and experimental autoimmune uveoretinitis (EAU) mice with CD200 deficiency, variations in peripheral immune cell infiltration were observed. The infiltration of monocyte-derived macrophages is increased after EAU or EAE induction [67-69], and blockade of CD200R leads to an increase in T-lymphocyte and monocyte-derived macrophage infiltration in both models [70-72]. Interestingly, the increase in these monocyte-derived macrophages and T-lymphocyte were reversed following administration of CD200-Fc [65, 70]. The involvement of CD200-CD200R in immune cell infiltration could be related to the expression of CD200 in capillary endothelial cells as immune regulatory agents [73-75]. Another explanation is that T-cell infiltration may be favored by an enhanced microglial activation state, as already shown in CD200-deficient mice, due to the release of an increased number of chemokines, including CCL-2, CCL-5, or CXCL-10 [74]. These reports reinforced the rational that CD200-CD200R is an important immunoregulatory signaling in autoimmunity, and suggested that targeting CD200-CD200R can dampen neuroinflammation and demyelination, and halt the progression of MS.

CD200-CD200R signaling in other diseases

Tumorigenesis: A number of groups have confirmed that high expression of CD200 in tumor cells is an independent prognostic factor predicting reduced overall survival rate in a number of hematological malignancies including multiple myeloma, acute myeloid leukemia (AML), and chronic lymphocytic leukemia (CLL) [76-78]. How CD200 signaling suppresses antitumor responses remains elusive although the malignity of CD200-expressing tumors may suggest a direct inhibitory signal delivered by the tumor against the anti-tumor response [79]. Bisgin et al. [80] examined the immunohistochemical expression and localization of CD200 and CD200R1 in rectal cancer patients; the results showed a strikingly high level of CD200 in tumor cells and high CD200R1 expression in normal mucosal epithelium and stromal cells. Kawasaki et al. [81] hypothesized that cancer

stem cells might be able to evade the immune system by generating a tolerogenic response facilitated by CD200. CD200 expression increases on a breast cancer cell line transplanted to immune competent mice in contrast to immune deficient mice [82], suggesting a CD200 mediated anti-inflammatory profile of CD200 positive cancer cells. In a word, CD200 signaling seems to benefit cancer by diminishing immune responses.

Allergy: Mast cells and basophils play a crucial role in allergic reactions in body tissues and blood respectively. It has been confirmed that CD200-CD200R interaction reduces their degranulation and attenuates the allergic inflammation [12, 27]. Administration of intratracheal CD200 recombinant to experimental asthmatic rats was reported to inhibit airway hyperresponsiveness by local alterations of T cell response and cytokine secretion [83].

CD200-CD200R signaling as a therapeutic target

The therapeutic potential of CD200 has been explored both in vitro and in vivo. Studies using neuron-microglia co-cultures suggested that CD200-CD200R interaction may be one of the mechanisms by which IL-10 protects neurons from inflammatory damage caused by microglia-induced cytotoxicity, as IL-10 increased the expression of CD200 in neurons [58, 84, 85]. An up-regulatory effect of IL-4 on CD200 expression has also been reported [43, 86]. IL-4-deficient mice showed low expression of CD200 in neurons, but IL-4 intracerebroventricular administration was able to reverse CD200 expression to normal levels [86]. Likewise, adeno associated viral gene-delivery of IL-4 in APP-PS1 mice restored CD200 expression in the hippocampus [84, 87], and treatment of cultured microglia from aged rodents with IL-4 resulted in the production of CD200 [13, 51]. These data indicate that it is feasible to manipulate CD200-CD200R signaling.

In AD brains, microglia are primarily classically activated but enhancing CD200R expression can promote alternative activation to confer neuroprotection. Up to date, it is not known yet how much of CD200 expression is sufficient to activate CD200R. In human brains the level of CD200R expression appears to be several orders of magnitude lower than that of CD200 [13, 36]; therefore, boosting CD200R may be more effective especially in diseases where the CD200R levels remain low.

Cannabinoids participate in the control of brain immune responses as well as in the protection of the CNS against injury [88-92]. Treatments with the endocannabinoid compound N-arachidonoylethanolamine (AEA) induced the recovery of CD200 and CD200R gene expression that was reduced in the Theiler's murine encephalomyelitis virus induced demyelinating disease (TMEV-IDD) model of MS [85]. This was accompanied by decreased inflammatory mediators and reduced microglial reactivity. Endocannabinoids may regulate CD200-CD200R axis through activating cannabinoid receptors expressed on immune cells including microglia, astrocytes, and neurons [91-94]. The endogenous ligand 2-arachidonoylglycerol (2-AG) binds and activates cannabinoid 2 (CB2) receptor [91, 95]. Neurons and glial cells produce 2-AG [96-99] suggesting CB2 receptors and 2-AG could play a role in the regulation of the CD200-CD200R axis especially in diseases where CB2 receptors are more likely to be expressed by immune cells.

Studies of manipulation of the CD200-CD200R axis have tested the effect of anti-CD200 monoclonal antibodies, and also soluble CD200R or fragments of CD200 [39, 71, 100]. A therapeutic trial based on the use of CD200 blocking antibodies in chronic lymphocytic leukemia (CLL) patients with ClinicalTrials.gov Identifier NCT00648739 [101] has recently been conducted. Of the 23 patients with advanced CLL enrolled, 21 patients received > 1 treatment cycle with samalizumab, a novel recombinant humanized monoclonal antibody that targets CD200. Treatment produced dose-dependent decreases in CD200 expression on CLL cells and decreased turnover of circulating $CD200^+$ $CD4^+$ T cells. This first-in-human investigation showed a good and safe treatment protocol that was associated with reduced tumor burden in a majority of patients [101], and support further development of samalizumab therapy for immune responses. Targeting CD200-CD200R signaling to modulate the immune response represents a promising therapeutic strategy for various inflammatory diseases. **Table 1** summarizes commonly used animal

Table 1. Summary of experimental CD200-CD200R axis

Disease	Animal model	Tissue	Function of CD200 signaling	Intervention of CD200-CD200R signaling	Ref.
Ischemic stroke	CD-1 mice	Cortex	Restored neural progenitor cell proliferation, differentiation, and migration.	Intracerebroventricular injection of recombinant CD200 protein after pMCAO. Decrease of Iba-1, IL-1β, TNF-α, and IL-10.	[50]
	Sprague-Dawley rats	Ipsilateral hippocampus and cortex		Sequential treadmill exercise for 4 weeks, with different speed and running times.	[52]
Alzheimer's	APP-PS1 mice	Hippocampus	Restored neural progenitor cell proliferation and differentiation in the subgranular and granular cell layers of dentate gyrus and reduce diffuse but not thioflavin-s^+ plaques.	AAV2/1-CD200 bilateral injection into the CA1 region of hippocampus at 6 months of age.	[84]
				AAV-IL-4 bilateral injection into mouse hippocampus at 3 months of age.	[87]
Parkinson's	Sprague-Dawley rats	Substantia nigra	Function loss due to depletion of dopaminergic neurons and decrease in tyrosine hydroxylase-immunoreactive neurons.	Injection into the right striatum with CD200R-blocking antibody, and then with 6-hydroxydopamine the next day injected unilaterally into the right ascending medial forebrain bundle.	[37]
EAE	C57BL/6 mice	Spinal cord	Attenuated the course of EAE and decreases axonal loss and demyelination.	Subcutaneous administration of CD200-Fc from onset of EAE to day 30.	[65]
GL261 glioma tumors	C57BL/6 mice	Brain	Negatively regulated immune response by activating CD200R on myeloid-derived suppressor cells promoting tumorigenesis.	Intradermal injection with CD200R antagonist peptide.	[105]

models for CD200 signaling study in neuroinflammatory diseases.

Summary

The neurobiological roles of CD200-CD200R signaling in CNS disorders have not been well understood. Probably owing to the differences between rodents and humans in the expression of CD200 and CD200R, data from literature about the pathway have been controversial. The development of humanized transgenic mice that express the human genes under their native promoters have been reported [102-104], which appears to be promising in the research of the field. As most of the experimental studies have involved application of CD200 protein or CD200R-blocking antibodies, an approach that has been questioned for human therapy, the development of suitable gene vectors that can target at neural cells, or embryonic stem cells could be more relevant. The research of CD200-CD200R signaling in neuroinflammatory diseases, including ischemic stroke, is still in its infancy; further studies at both the cellular and molecular levels are warranted to better understand the inhibitory signaling.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Fudong Liu, Department of Neurology, The University of Texas Health Science Center at Houston McGovern Medical School, 6431 Fannin Street, Houston, TX 77030, USA. Tel: 713-500-7038; Fax: 713-500-0660; E-mail: Fudong.Liu@uth.tmc.edu

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