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CHAPTER FIVE

The CD200–CD200R1 Inhibitory Signaling Pathway: Immune Regulation and Host–Pathogen Interactions

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Contents

Abstract

The CD200:CD200R1 inhibitory signaling pathway has been implicated in playing a prominent role in limiting inflammation in a wide range of inflammatory diseases. CD200R1 signaling inhibits the expression of proinflammatory molecules including tumor necrosis factor, interferons, and inducible nitric oxide synthase in response to selected stimuli. Unsurprisingly, due to the regulatory role that CD200R1 plays in multiple inflammatory pathways, an increasing number of parasitic, bacterial, and viral pathogens exploit this pathway to suppress host defenses. A complete understanding of the pathways regulated by CD200R1 signaling and the diverse mechanisms that pathogens have evolved to manipulate the CD200:CD200R1 pathway can help identify clinical situations where targeting this interaction can be of therapeutic benefit. In this review, we compare CD200R1 to other pathogen-targeted inhibitory receptors and highlight how this signaling pathway is utilized by a diverse number of pathogens and, therefore, may represent a novel targeting strategy for the treatment of infectious diseases.

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1. INHIBITORY RECEPTORS

Hosts and pathogens have evolved mechanisms to defeat each other in the battle for control over the host's immune system. A successful infection requires that the pathogen positively regulate its survival, replication, and spread while suppressing the pathogen-specific host immune response. Conversely, it is essential that the host immune response be appropriately controlled to respond to and remove pathogens while avoiding excessive production of cytokines, chemical mediators such as reactive oxygen species (ROS), and the release of proteolytic enzymes all of which can lead to increased tissue damage and morbidity and mortality.

Immune cells express receptors, such as toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors, which recognize and respond to pathogens with the induction of antivirulence genes and generation of chemical mediators. At the same time these cells express inhibitory receptors that limit the amplitude of the response to prevent immunopathology. The mechanisms by which inhibitory receptors limit the amplitude of proinflammatory responses have been described in detail (Long, 1999; Ravetch & Lanier, 2000). For the purpose of this review, we will focus on members of the inhibitory receptor superfamily that have been targeted by pathogens. Based on the structure of the extracellular domains, there are two major classes within the inhibitory receptor superfamily: the immunoglobulin (Ig) superfamily and the calcium-dependent carbohydrate-binding (C-type) lectin family (Long, 1999) (Fig. 5.1A).

Most members of the inhibitory receptor superfamily have an immunoreceptor tyrosine-based inhibitory motif (ITIM) in the cytoplasmic tail of the protein (Vely & Vivier, 1997) (Fig. 5.1). Upon activation of the receptor, phosphorylation of tyrosine residues in the ITIM recruits adaptor proteins such as src homology 2-containing protein tyrosine phosphatases (SHPs) and SH2 domain-containing inositol phosphatase-1 (SHIP-1) (Daeron, Jaeger, Du Pasquier, & Vivier, 2008). This ultimately leads to a decrease in immune functions including cytokine production, calcium release, migration, and proliferation (Ravetch & Lanier, 2000). Many inhibitory receptors also have paired activating receptors, which contain cytoplasmic immunoreceptor tyrosine-based activation motifs and associate with adaptor proteins like DNAX-activating protein of 12 kDa (DAP12) or the FcRγ chain through a positively charged residue in the transmembrane region (McVicar et al., 1998) to induce proinflammatory signaling events (Fig. 5.1).

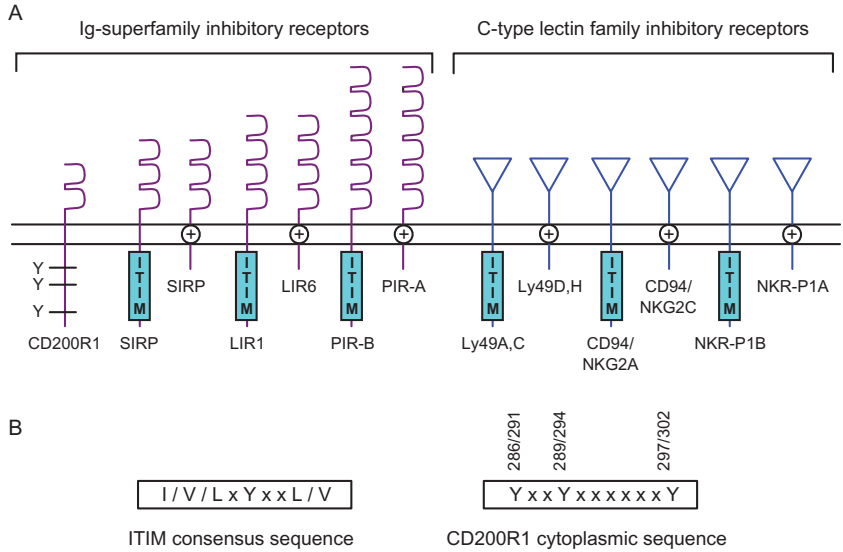

Figure 5.1 Classes and cytoplasmic signaling domains of the inhibitory receptor superfamily. (A) Classes of inhibitory receptors. Inhibitory receptors are separated into two major classes based on their extracellular domains: the immunoglobulin (Ig) superfamily and the carbohydrate-binding (C-type) lectin family. Many members of these inhibitory receptor families have affiliated activating receptors, which contain a charged residue in the transmembrane region, denoted by a plus sign. (B) Cytoplasmic inhibitory motifs. Most inhibitory receptors contain an immunoreceptor tyrosine-based inhibitory motif (ITIM) in its cytoplasmic region to recruit adaptor proteins upon activation, however the CD200R1 cytoplasmic region contains three tyrosine residues (locations listed as mouse/human), which play a role in adaptor protein interactions upon phosphorylation. LIR, leukocyte inhibitory receptor; PIR, paired Ig-like receptor; SIRP, signal-regulatory protein.

1.1. Decoy ligands for inhibitory receptors

Pathogens can express proteins that efficiently bind to a variety of inhibitory receptors that normally distinguish self from nonself. In this way, they avoid recognition and promote persistence in the host. Herpesviruses and poxviruses are exceptionally skilled at avoiding or subverting host immune responses (Table 5.1).

Murine cytomegalovirus (MCMV) expresses m157, which is structurally similar to MHC class I proteins and binds to the inhibitory receptor Ly49I in MCMV-susceptible mouse strains to prevent NK-mediated killing (Arase & Lanier, 2004; Arase et al., 2002). The mouse Ly49 family of molecules is expressed on NK cells that recognize the α1 and α2 subunits of H-2D MHC class I molecules (Karlhofer, Ribaudo, & Yokoyama, 1992).

Table 5.1 Viral decoy ligands for inhibitory receptors

Virus	Gene	Cellular homolog	Target receptor	References
MCMV	m157	MHC class I	Ly49I	Arase and Lanier (2004) and Arase, Mocarski, Campbell, Hill, and Lanier (2002)
	m144	MHC class I	?	Farrell et al. (1997)
HCMV	UL18	MHC class I	LIR-1	Chapman, Heikeman, and Bjorkman (1999), Cosman et al. (1997), and Reyburn et al. (1997)
	UL40	MHC class I peptide	CD94/NKG2A	Ulbrecht et al. (2000)
RCMV	RCTL	Clr-b	NKR-P1B	Voigt et al. (2007) and Voigt, Sandford, Ding, and Burns (2001)
Myxoma virus	M128L	CD47	SIRPα	Arase and Lanier (2004) and Cameron, Barrett, Mann, et al. (2005)

Interestingly, MCMV-resistant mouse strains, but not MCMV-susceptible strains, express the activating receptor Ly49H, which also binds to m157 but initiates NK killing of the infected cells (Smith et al., 2002). This suggests that virus and host together have evolved to modulate signaling through this receptor. In fact, when MCMV is continuously passaged in Ly49H positive cells in culture, the virus will quickly generate mutations in m157 to avoid binding to the activating receptor (Voigt et al., 2003).

Human cytomegalovirus (HCMV) expresses the protein UL18, a homolog of MHC class I antigens (Cosman et al., 1997; Reyburn et al., 1997). MCMV also expresses m144, which also functions as a MHC class I mimic and is required for efficient viral replication *in vivo* (Farrell et al., 1997). Both UL18 and m144 form the three α domains typical of MHC class I molecules and both can bind to β2M (Farrell et al., 1997; Reyburn et al., 1997). UL18 can bind to both CD94/NKG2 and leukocyte inhibitory receptor (LIR)-1 and it is thought that m144 may interact similarly. The CD94/NKG2 receptors recognize the nonclassical MHC class I molecules human HLA-E and mouse Qa1 (Brooks et al., 1999; Houchins, Lanier, Niemi, Phillips, & Ryan, 1997; Lee et al., 1998; Vance, Kraft, Altman, Jensen, & Raulet, 1998), which are expressed on all cell types except red blood cells (Kuroki, Furukawa, & Maenaka, 2012). Human LIR-1 recognizes epitopes shared by most MHC class

I molecules through interactions with the α3 and β2M domains (Chapman et al., 1999; Willcox, Thomas, & Bjorkman, 2003). In fact, LIR-1 binds to UL18 more tightly than host class I molecules (Chapman et al., 1999), indicating that this receptor may have evolved specifically to bind to UL18. Furthermore, the leader sequence of the HCMV protein UL40 is identical to the MHC class I, HLA-E associated peptide HLA-Cw03. CD94/NKG2A will recognize HCMV-infected cells as self based on presentation of the HLA-E-like peptide and will not kill them (Ulbrecht et al., 2000).

The rat cytomegalovirus (RCMV) C-type lectin-like gene (*rctl*) is characterized as an early gene whose structure closely resembles the mouse and rat C-type lectin related protein Clr-b (Voigt et al., 2001, 2007). The inhibitory receptor NKR-P1B, expressed mainly on NK cells (Voigt et al., 2007), recognizes Clr-b as a ligand, which is expressed on almost all hematopoietic cells (Carlyle et al., 2004). Following infection with RCMV, there is a rapid upregulation of RCTL, which counteracts downregulation of Clr-b expression by host cells in response to infection. Through a non-MHC class I recognition mechanism, RCTL inhibits NK cell-mediated lysis by directly interacting with NKR-P1B. Furthermore, RCTL-deficient virus exhibits decreased virulence and is more easily cleared from the host by NK cells (Voigt et al., 2007). Interestingly, the activation receptor NKR-P1A also recognizes RCTL, indicating that host defenses have evolved to counteract the ability of RCTL to evade recognition.

A variety of poxviruses encode a CD47 mimic (Arase & Lanier, 2004; Cameron, Barrett, Mann, Lucas, & McFadden, 2005), and based on evidence from other paired inhibitory/activation receptors, as described earlier, it has been suggested that these mimics may interact with signal-regulatory protein (SIRP)α to downregulate myeloid cell functions. SIRPα, expressed mainly on myeloid cells and neurons (Adams et al., 1998; Alblas et al., 2005), binds to CD47 to regulate leukocyte chemotaxis and proinflammatory cytokine production (Cameron, Barrett, Mann, et al., 2005). The myxoma virus CD47 mimic, M128L, is required for lethal infections in rabbits and appears to regulate macrophage activation and recruitment, as M128L-deficient virus-infected rabbits exhibit increased inducible nitric oxide synthase (iNOS)-positive cells at infection sites (Cameron, Barrett, Mann, et al., 2005). The activating receptor, SIRPβ does not bind to CD47, and its ligand is unknown, but may have evolved to counteract pathogen infections and/or recognize pathogen-infected cells (Arase & Lanier, 2004; Barclay & Brown, 2006).

In addition to viral decoys, several bacterial strains, including *S. aureus* and *E. coli*, can bind to the mouse paired Ig-like receptors (PIRs) PIR-B

and PIR-A1 and human LIR-1 to suppress macrophage proinflammatory responses (Nakayama et al., 2007). The murine PIRs, which are structurally similar to the human LIRs, recognize MHC class I molecules (Nakamura, Kobayashi, & Takai, 2004) and are expressed on a variety of cell types, including macrophages, dendritic cells, mast cells, and B cells (Kubagawa, Burrows, & Cooper, 1997; Kubagawa et al., 1999). These data suggest that many pathogens can take advantage of host inhibitory receptors to modulate inflammatory responses.

2. THE INHIBITORY RECEPTOR CD200R1

CD200R1 is an Ig superfamily transmembrane glycoprotein expressed on the surface of myeloid cells; it can also be induced in certain T-cell subsets (Caserta et al., 2012; Wright et al., 2000, 2003). CD200R1 interacts with CD200, which is also an Ig superfamily transmembrane glycoprotein, to down regulate myeloid cell functions. CD200 is expressed on the surface of a variety of cells including neurons, epithelial cells, endothelial cells, fibroblasts, lymphoid cells, and astrocytes (Caserta et al., 2012; Costello et al., 2011; Hoek et al., 2000; Snelgrove et al., 2008). The regulation of CD200R1 signaling can occur by posttranslational modification—namely, phosphorylation of tyrosines in the CD200R1 cytoplasmic tail—or by the inducible expression or downregulation of either CD200R1 or CD200. Each of these mechanisms can ultimately be exploited by pathogens.

2.1. Signaling through the CD200R1 cytoplasmic domain

Unlike most immune inhibitory receptors, CD200R1 does not contain an ITIM (Fig. 5.1). Instead, human CD200R1 contains three cytoplasmic tyrosine residues, Y291, Y294, and Y302 (Y286, Y289, and Y297 in the mouse), one of which, Y302/Y297, is located within a phosphotyrosine binding (PTB) domain recognition motif (NPxY). Stimulation by CD200 leads to the phosphorylation of these tyrosines by Src kinases, which recruit the adapter protein downstream of tyrosine kinase (Dok) 2 through its PTB domain (Mihrshahi, Barclay, & Brown, 2009; Mihrshahi & Brown, 2010; Zhang, Cherwinski, Sedgwick, & Phillips, 2004). Y302/Y297 and to a lesser extent Y291/Y286 are the major tyrosine residues required for CD200R1 association with Dok2 (Mihrshahi et al., 2009; Zhang & Phillips, 2006). Dok2 serves as the major initiator of signaling through CD200R1, beginning with binding to Ras-GTPase activating protein (RasGAP) and is required for CD200R1 function (Mihrshahi et al., 2009).

This is in contrast to ITIM containing inhibitory receptors, which utilize SHPs and SHIP-1 as the major initiator proteins and Dok proteins as secondary modulators of downstream signaling (Daeron et al., 2008; Mihrshahi et al., 2009).

2.2. CD200:CD200R1 signaling and infectious diseases

Pathogens have found ways to exploit the CD200:CD200R1 signaling pathway by altering expression of either CD200 or CD200R1, or by expressing a CD200 mimic to engage the host CD200R1 (Table 5.2). In

Table 5.2 Pathogen susceptibility to CD200:CD200R1 signaling

Pathogen	Effect on CD200/ CD200R1 expression	Disease severity (type of KO or treatment)	References
T. gondii	Increased CD200 and CD200R1	Decreased (CD200 KO)	Deckert, Sedgwick, Fischer, and Schluter (2006)
L. amazonesis	Increased CD200	Decreased (CD200 KO)	Cortez et al. (2011)
N. meningitidis	Increased CD200	Increased (CD200 KO)	Mukhopadhyay et al. (2010)
S. masoni	Increased CD200 and CD200R1		Caserta et al. (2012)
S. enterica	Increased CD200 and CD200R1		Caserta et al. (2012)
S. haematobium	Increased CD200R1		Caserta et al. (2012)
MHV		Decreased (CD200 KO)	Karnam et al. (2012)
Influenza A		Increased (CD200 KO); decreased (CD200-Fc)	Karnam et al. (2012) and Snelgrove et al. (2008)
		Decreased (CD200R1 KO)	Goulding et al., 2011
HSV-1 (ocular)	Increased CD200R1	Decreased (CD200-Fc)	Sarangi, Woo, and Rouse (2009)
HSV-1 (brain)		Decreased (CD200R1 KO)	Soberman et al., 2012

certain situations, the greatest threat to the host is the excessive inflammation seen in response to the infectious organism. In these cases, the disruption of the CD200:CD200R1 axis in model systems leads to the death of the host. In the cases of intracellular parasites, this can be deleterious to the pathogen as well, as these organisms benefit from the survival of the host for long-term growth and expansion. In other cases, the subset of antipathogen genes that are suppressed by the engagement of CD200R1 directly allows survival of the pathogen at the expense of the host.

Antipathogen molecules, such as ROS that include nitric oxide (NO), superoxide, and hydroxyl radicals, preformed mediators, and interferons (IFNs) are a subset of proinflammatory genes and mediators. As a protective measure against tissue damage, host macrophages adaptively modify chromatin to allow them to become unresponsive to repetitive or persistent signaling by TLRs (e.g., TLR4 and lipopolysaccharide (LPS) tolerance) (Foster, Hargreaves, & Medzhitov, 2007), leading to decreased pro-inflammatory signaling. Certain antipathogen molecules, however, are not dampened after prolonged TLR signaling because chromatin modification allows antipathogen genes to remain responsive to TLR4 in the presence of ongoing infection (Foster et al., 2007). Pathogens also employ various strategies to engage downregulatory mechanisms to suppress host defenses. These are illustrated by the mechanisms various pathogens use to manipulate the CD200:CD200R1 axis or to manipulate other inhibitory receptors.

2.2.1 Bacterial and parasitic pathogens

2.2.1.1 Toxoplasma

In WT mice, *Toxoplasma gondii* induces increased surface expression of CD200R1 and CD200 in microglia and blood vessel endothelial cells, respectively (Deckert et al., 2006). In CD200 KO mice, microglial cells exhibited increased proliferation, activation, and higher expression of MHC II, tumor necrosis factor (TNFα), and iNOS during infection in chronic *T. gondii* encephalitis. CD200 KO mice also exhibited decreased parasite burden and decreased mortality compared to WT mice following chronic infection. This is likely due to the fact that CD200 KO mice exhibit an increased inflammatory phenotype in response to the TLR ligands, including significantly higher IL-6 and TNFα release and IκBα phosphorylation (Costello et al., 2011). It is known that *T. gondii* stimulation of mouse TLR11 induces IL-12, which is key for the survival of the host (Yarovinsky et al., 2005). TLRs 2 and 4 have also been implicated in the inflammatory response to *T. gondii* (Debierre-Grockiego et al., 2007). These data show

that in the case of Toxoplasmosis, increased inflammatory responses, likely through TLR signaling, are detrimental to the pathogen.

2.2.1.2 Leishmania

Leishmania amazonensis, which causes severe disease in both humans and mice, induces CD200 mRNA and protein expression in bone marrow macrophages from WT mice (Cortez et al., 2011). Upregulation of CD200 was essential for replication and development of systemic Leishmaniasis as *L. amazonensis* replication and virulence are significantly decreased in CD200 KO mice. Virulence of *L. amazonensis* can be restored by treatment with soluble CD200-Fc. Not all species of Leishmania have evolved this mechanism, as *L. major*, which causes cutaneous but not systemic disease, does not induce CD200. However, CD200-Fc treatment in *L. major*-infected WT mice shifts its virulence to that of *L. amazonensis* (Cortez et al., 2011). *L. amazonensis* has evolved to utilize CD200 expression as a mechanism for inhibiting both NO production and induction of iNOS during infection. This was confirmed by treatment of macrophages with an iNOS inhibitor, which, in turn, lead to increased replication of *L. major*. Interestingly, *L. amazonensis* increased CD200 expression on macrophages. Macrophages have generally been found to express CD200R1, which can then interact with nonmyeloid cells expressing CD200. These findings suggest that, at least in the case of *L. amazonensis*, macrophages can inhibit neighboring macrophages by expressing both CD200R1 and CD200. Macrophages infected with intracellular pathogens can release exosomes, small vesicles containing various membrane proteins, which can provide signals to naïve macrophages (Bhatnagar, Shinagawa, Castellino, & Schorey, 2007). It may be that these exosomes contain CD200, which can then bind to CD200R1 on nearby macrophages. Whether or how this would occur is not clear, though it is certainly an interesting possibility. Alternatively, macrophages expressing CD200 may interact with activated T-cells expressing CD200R1.

2.2.1.3 Neisseria

CD200 KO mice are more susceptible to infection with *Neisseria meningitidis* than WT mice. While there was no significant difference in bacteremia between WT and CD200 KO mice, CD200 KO mice had higher systemic levels of IL-6 and TNFα, higher numbers of F4/80 + CD11b + macrophages, and expressed higher levels of MHC class II molecules on macrophages (Mukhopadhyay et al., 2010). Furthermore, CD200 expression is upregulated

in bone marrow macrophages following infection with *N. meningitidis*. This is likely due to recognition of Neisserial LPS by TLR4, since TLR ligation can increase CD200 surface expression in macrophages (Mukhopadhyay et al., 2010). These data suggest that in WT mice, CD200:CD200R1 signaling plays a role in regulating the response to *N. meningitidis*, but does not necessarily affect the survival of the pathogen. Therefore, increased mortality in this model is mediated by uncontrolled inflammation, not uncontrolled pathogen replication.

2.2.1.4 Schistosomes and salmonella

Both CD200 and CD200R1 are upregulated and coexpressed in chronically activated CD4 T-cells from mice infected with *Schistosoma mansoni* and *Salmonella enterica*. These cells also lost the ability to generate TNFα and exhibited increased IL-4 secretion. Furthermore, in patients chronically infected with *Schistosoma haematobium*, there was a correlation between CD200R1 expression and parasite load and almost all IL-4 secreting CD4 T-cells were CD200R1 positive. This suggests that chronic infections lead to increased expression of CD200 and CD200R1 and subsequently a decrease in antipathogenic mediators, allowing pathogen persistence.

How pathogens regulate CD200 expression is unclear. However, studies have shown that expression of CD200 is regulated by transcription factors and enhancer elements. Constitutive CD200 expression is regulated by the transcription factor CCAAT/enhancer binding protein β (C/EBPβ) (Chen, Marsden, & Gorczynski, 2006, 2009). Furthermore, there are three enhancer sites (*cis*-elements) upstream of the CD200 transcriptional start site, a NF-κB binding site, an IFNγ-activation site (GAS), and an IFN-stimulatory response element-2, that are important for inducible CD200 expression. NF-κB, STAT1, and IFN regulator factor-1 bind to these enhancer elements, respectively (Chen et al., 2009). Furthermore, it was determined that the NF-κB transcription factor, c-Rel, was required for TLR-induced upregulation of CD200 (Mukhopadhyay et al., 2010). Perhaps pathogens utilize these enhancer sites and transcription factors to induce CD200 expression following TLR recognition. CD200 is also a target of p53 and is upregulated on apoptotic cells to decrease responsiveness to self-antigen (Rosenblum et al., 2004).

The mechanisms that pathogens employ to induce the expression of CD200R1 are also unclear, although their interaction with TLRs is one mechanism (Dentesano et al., 2012; Mukhopadhyay et al., 2010). It has recently been discovered that inducible expression of CD200R1 is regulated

by C/EBPβ (Dentesano et al., 2012). Microglial cells exhibit a significant decrease in CD200R1 mRNA and protein expression following stimulation with LPS, a TLR4 ligand. This decrease is not seen in C/EBPβ KO cells. Additionally, overexpression of C/EBPβ led to a significant decrease in CD200R1 mRNA and protein expression. C/EBPβ directly binds to the CD200R1 promoter to inhibit expression in LPS-treated cells. Furthermore, it was found that histone deacetylase 1 interacts with C/EBPβ to downregulate CD200R1 expression.

2.2.2 Viruses

2.2.2.1 Coronaviruses

Loss of CD200R1 signaling, through use of CD200 KO mice, results in an increase in inflammatory signaling, specifically type I IFN in response to TLR7 ligands, including mouse hepatitis corona virus (MHV). MHV serves as an infection model for the severe acute respiratory syndrome coronavirus (De Albuquerque et al., 2006). Lack of inflammatory signaling control had a positive effect on MHV clearance as CD200 KO mice exhibited decreased viral replication and viral titers (Karnam et al., 2012). Infected CD200 KO mice also had increased levels of IFNα compared to WT mice. These findings indicate that coronavirus infections require a functional CD200:CD200R1 signaling interaction to limit type I IFN production.

2.2.2.2 Influenza virus

The opposite is true for influenza A where CD200 KO mice were highly susceptible to the effects of uncontrolled inflammation in response to pulmonary infection. These mice demonstrated more weight loss and increased mortality in response to influenza than WT mice (Karnam et al., 2012; Snelgrove et al., 2008), even though viral clearance was similar in both strains. CD200 KO mice also had higher levels of NO in lung homogenates, as well as increased levels of IL-6, TNFα, IFNγ, and macrophage inflammatory protein 1α in lavage fluids. Furthermore, the administration of CD200-Fc or anti-CD200R1 agonist was able to partially reverse the phenotype of CD200 KO mice, leading to less weight loss and lower cellularity than untreated CD200 KO mice following infection (Snelgrove et al., 2008). In WT mice, alveolar macrophages exhibit increased expression of CD200R1, which would serve to limit inflammatory responses to the virus, and thus, limit immunopathology (Snelgrove et al., 2008). In this case, the role of the CD200:CD200R1 axis is to protect the host from cytokine storm, which is the major cause of morbidity and mortality.

Influenza-infected CD200R1 KO mice show less bacterial load and exhibit decreased pathogenesis and mortality than WT mice following *S. pneumoniae* superinfection (Goulding et al., 2011). This is thought to occur because during the resolution phase of an influenza infection, apoptotic monocytes/macrophages in the lung express CD200 on their surface while alveolar macrophages upregulate CD200R1 surface expression. This leads to decreased alveolar macrophage responsiveness and increased susceptibility to bacterial superinfections. Interestingly, CD200R1 KO mice exhibit decreased viral pathogenesis and pathology in response to influenza infection (Goulding et al., 2011). These results seem counter-intuitive compared to the previous findings with CD200 KO mice. However, the authors suggest that this may be due to the limited expression of the receptor, compared to the broad expression of the ligand, but further studies need to be performed in order to prove this. Nonetheless, the increased inflammatory response seen in CD200R1 KO mice provides protection to the host in terms of a bacterial superinfection.

2.2.2.3 Herpesviruses

Herpes simplex virus (HSV)-1 mediated keratitis (stromal keratitis) is a chronic infection that causes an influx of CD200R1-expressing cells into the cornea, leading to inflammatory lesions and blindness (Sarangi et al., 2009). A variety of cell types, including myeloid cells, upregulate CD200R1 on their surface following ocular HSV-1 infection (Sarangi et al., 2009). CD200-Fc treatment of ocular HSV-1 infected mice caused decreased CD11b+ immune cells in the cornea, decreased inflammatory lesions, and decreased angiogenesis. These mice also had decreased cellularity in the spleen and draining lymph nodes and this was associated with a decrease in IFNγ-producing T-cells and an increase in FoxP3+ T-regulatory cells both in lymphoid tissue and the cornea. Treatment also mildly reduced lesions in chronically infected mice, though this would need to be combined with another drug to prove efficacious. These results indicate that CD200:CD200R1 signaling plays a key role in modulating inflammation during a viral infection and provides further evidence that decreasing the inflammatory milieu following a viral infection can actually have a beneficial role for unwanted immunopathology.

We have recently examined the role of the CD200:CD200R1 axis in the mouse model of HSV-1 encephalitis (Soberman et al., 2012). A significant component of the morbidity and mortality in this model is the release of cytokines and chemokines triggered by the interaction of HSV-1 with

macrophages and resident microglial cells through TLR2 (Kurt-Jones et al., 2004). Therefore, we predicted that CD200R1 KO mice would show increased morbidity and mortality in response to HSV-1 infection. However, CD200R1 KO mice were markedly protected against infection and exhibited a decrease in viral titers and HSV-1 glycoprotein expression in the brain. Furthermore, the levels of IFNβ were decreased in both the serum and brain, suggesting that the main driving force in survival was decreased viral replication (Soberman et al., 2012). Whether decreased viral titers are due to increased antipathogenic defenses in CD200R1 KO mice or due to a direct effect of CD200R1 on viral replication remains to be determined. When we examined the interaction of HSV-1 with thioglycollate-induced peritoneal macrophages we uncovered a potentially far more complex relationship between CD200R1 and cell signaling by TLR2. Rather than show an amplified generation of IL-6 in response to HSV-1, the cytokine response was blunted by 80%. This was not seen in response to LPS, a TLR4 ligand. Furthermore, the surface expression of TLR2 following HSV-1 infection of macrophages was not upregulated (Soberman et al., 2012).

2.2.3 Viral orthologs of CD200

Similar to other inhibitory receptors, several viruses have directly utilized the downregulatory signaling pathways mediated by CD200:CD200R1 interactions for their survival within the host. Members of the herpesviruses and poxviruses have incorporated or evolved orthologs of the host CD200 protein in their genome (Table 5.3).

Perhaps the best characterized is the Kaposi's sarcoma-associated herpesvirus or human herpesvirus 8 or (HHV8) *K14* gene, which encodes a viral ortholog of CD200 (vOX2) that is expressed on the surface of infected cells

Table 5.3 Viral CD200 orthologs

Virus	Gene	Binds CD200R1?	References
HHV8	vOX2 (K14)	Yes	Foster-Cuevas, Wright, Puklavec, Brown, and Barclay (2004), Misstear et al. (2012), and Shiratori et al. (2005)
RRV	R15	?	Langlais, Jones, Estep, and Wong (2006)
Myxoma Virus	M141R	?	Cameron, Barrett, Liu, et al. (2005) and Zhang et al. (2009)
RCMV	e127	Yes	Foster-Cuevas et al. (2011)

during the lytic phase (Foster-Cuevas et al., 2004). Although vOX2 shares 36–40% identity with human CD200, both vOX2 and CD200 bind to CD200R1 with equivalent affinity and avidity (Foster-Cuevas et al., 2004; Misstear et al., 2012). *In vitro*, vOX2 can downregulate TNFα, granulocyte colony-stimulating factor (G-CSF), and monocyte chemoattractant protein-1 release from macrophages activated with IFNγ and LPS (Foster-Cuevas et al., 2004). When comparing the function of CD200 and vOX2, Misstear et al. (2012) found that APCs (cell lines that express native HLA-A2 and HLA-B8) transduced to express either CD200 or vOX2 suppressed T-cell IFNγ secretion, ERK1/2 and AKT phosphorylation, and mobilization of CD107a. CD200 and vOX2 also contributes to maintenance of the homeostasis of antigen-specific T-cell responses *in vivo* by negatively regulating their activity in a manner similar to CTLA-4 and PDL-1/2 (Misstear et al., 2012). Human herpesviruses 6 and 7 also express CD200 orthologs that bind to human CD200R1 (Shiratori et al., 2005), though their function is not as well characterized.

Human CD200 and HHV8 vOX2 have also been found to function in downregulating basophil function. Basophils have the highest basal expression level of CD200R1 in human peripheral blood, and activation through FcεR1 engagement, measured by CD11b upregulation and histamine release, was blocked by cross-linking CD200R1 with either human CD200 or vOX2 soluble proteins (Shiratori et al., 2005). Interestingly, this inhibition was not seen when basophils were stimulated with IL-3, suggesting specificity for CD200 inhibitory functions.

Rhesus rhadinovirus (RRV) is a gammaherpesvirus similar to HHV8. RRV expresses a viral CD200 protein, R15, that is expressed on the surface of infected cells and released into the supernatant (Langlais et al., 2006). Similar to other viral CD200 orthologs, R15 decreases TNFα mRNA and cytokine release from PMA-activated THP-1 macrophages as well as primary rhesus monocytes/macrophages. These inhibition levels were similar to that of human CD200.

The myxoma virus CD200 ortholog, M141, can function as a global inhibitor of macrophage and lymphocyte activation, leading to increased pathology and viral spread (Cameron, Barrett, Liu, Lucas, & McFadden, 2005; Zhang et al., 2009). M141 is expressed on the virion of myxoma viruses and contains a single Ig-like domain, similar to the N-terminal region of cellular CD200 (Zhang et al., 2009). M141-deficient virus-infected rabbits exhibited significantly decreased pathology, including decreased lesion size and number as well as increased healing (Cameron, Barrett, Liu, et al., 2005).

There was also a significant increase in the number of iNOS+ cells recruited to sites of infection and activated T-cells in lymph nodes (Cameron, Barrett, Liu, et al., 2005). Additionally, mouse macrophages infected with M141-deficient virus exhibited an activated phenotype, including increased TNFα and G-CSF levels, whereas WT virus-infected macrophages did not, due to decreased NF-κB signaling (Zhang et al., 2009). This is thought to occur through interactions with CD200R1 but has not been proven.

Other viruses express CD200 orthologs, but its direct role in mediating viral fitness is unclear. Such is the case for the e127 CD200-like protein of rat CMV. With approximately 56% identity to the host CD200 protein, e127 binds to CD200R1 with equivalent affinity, however, it does not significantly affect viral replication or myeloid activity *in vitro* or *in vivo* (Foster-Cuevas et al., 2011). This suggests that although CD200 mimics provide an evolutionary advantage to a variety of pathogens, its role may not be entirely the same in each infection and its effect upon binding to CD200R1 may differ.

3. PERSPECTIVE

It is clear, based on the number of pathogens that have evolved to exploit CD200 and CD200R1 expression as well as the widespread expression of CD200 mimics in viral genomes, that the CD200:CD200R1 signaling pathway plays a major role in host:pathogen interactions and pathogen survival. Understanding how these infectious agents use the CD200:CD200R1 axis to downregulate host defenses can potentially be exploited in clinical settings. Furthermore, it is important to completely uncover how CD200R1 regulates immune responses, both dependent and independent of CD200 ligation, as this may provide important insight in the development of therapeutics.

An antibody that targets CD200 to block CD200R1 signaling (Kretz-Rommel et al., 2008) is currently in clinical testing for the treatment of cancer (ClinicalTrials.gov identifier: NCT00648739). This drug could also be used to treat pathogenic infections that are impacted by CD200:CD200R1 signaling. In addition to utilizing currently available therapeutics for the treatment of viral infections, it is an intriguing possibility to target viral CD200 orthologs to stimulate viral clearance, as opposed to blocking all signaling through targeting the host CD200 or CD200R1. This virus-specific targeting strategy would allow normal host immune response regulation to

continue, avoiding potential immunopathology, while blocking the ability of a virus to replicate unchecked.

Though the CD200:CD200R1 axis has been implicated to play a role in transplant tolerance (Gorczynski, 2001; Yu, Chen, & Gorczynski, 2013), one can speculate that disrupting this relationship in posttransplant patients, or other immunosuppressed patients may actually have short-term benefit under conditions where viral infections can become an issue. Viral infections in renal transplant recipients, for example, remain a significant problem (Weikert & Blumberg, 2008). In situations where they become difficult to control with antiviral therapy, the major option is to decrease immunosuppressive therapy and restore host antiviral defenses. Viruses most commonly associated with transplant tolerance include CMV, HSV-1, HHV8, Epstein–Barr, Varicella Zoster, BK, and PC viruses (Weikert & Blumberg, 2008). Though pretransplant screening combined with prophylactic treatment with antiviral therapy has been very effective in limiting morbidity caused by these infectious agents, there are times when this is not sufficient, especially with BK and PC viruses. Since some of these viruses target the CD200:CD200R1 signaling pathway, and likely more, blocking the interaction of CD200 with CD200R1 using an antibody or small molecule approach could support more efficient viral clearance while preserving immunosuppression.

There are still many questions about how CD200R1 regulates inflammatory responses in myeloid cells and T-cells. Only a few studies have looked at the signaling molecules within cells that associate with the cytoplasmic domain of CD200R1 following ligation with CD200. Furthermore, our recent findings that CD200R1 plays an immunomodulatory role in TLR2 surface expression and signaling add another level of complexity to an already multifunctional signaling interaction. The concept that inhibitory receptors can be multifunctional and may be required for proinflammatory signaling has emerged. For example, the T- and B-cell coreceptor CD150 contains a motif in its cytoplasmic tail, called the immunoreceptor tyrosine-based switch motif (ITSM), that can recruit either inhibitory or activating molecules (Shlapatska et al., 2001). Additionally, the NK cell receptor 2B4 can induce either inhibitory or activating signals depending on the level of expression, amount of receptor cross-linking, and availability of adaptor molecules (Chlewicki, Velikovsky, Balakrishnan, Mariuzza, & Kumar, 2008). Although CD200R1 has neither an ITIM nor an ITSM domain, it is possible that an alternative domain in the cytoplasmic tail can modulate anti- or proinflammatory signals. This is the case for the inhibitory receptors

CTLA-4, Tim-3, Lag-3, and CD160, none of which contain ITIM or ITSM motifs (Odorizzi & Wherry, 2012).

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