Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
CHAPTER FIVE

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

Christine A. Vaine, Roy J. Soberman

Department of Medicine, Division of Nephrology, Massachusetts General Hospital, Boston, Massachusetts, USA

1Corresponding author: e-mail address: soberman@helix.mgh.harvard.edu

Contents

1. Inhibitory Receptors 192
   1.1 Decoy ligands for inhibitory receptors 193
2. The Inhibitory Receptor CD200R1 196
   2.1 Signaling through the CD200R1 cytoplasmic domain 196
   2.2 CD200:CD200R1 signaling and infectious diseases 197
3. Perspective 205

Acknowledgments 207

References 207

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.
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).
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).

**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).
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

### 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)         |
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

| 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                         |                                          | 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 find-
ings 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 pul-
monary 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 inflamma-
tory 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).

| Virus          | Gene    | Binds CD200R1? | References                                                                 |
|----------------|---------|----------------|----------------------------------------------------------------------------|
| HHV8           | vOX2 (K14) | Yes           | Foster-Cuevas, Wright, Puklavvec, Brown, and Barclay (2004), Misstear et al. (2012), and Shiratori et al. (2005) |
| RRV            | R15     | ?             | Langlaïs, 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).

ACKNOWLEDGMENTS
This work was funded by NIH grants R01AI068871, R01AI068871-04S1, and R01HL097796. We would like to thank M. Turman for review of the manuscript.

REFERENCES
Adams, S., van der Laan, L. J., Vernon-Wilson, E., Renardel de Lavalette, C., Dopp, E. A., Dijkstra, C. D., et al. (1998). Signal-regulatory protein is selectively expressed by myeloid and neuronal cells. *Journal of Immunology*, *161*, 1853.

Alblas, J., Honing, H., de Lavalette, C. R., Brown, M. H., Dijkstra, C. D., & van den Berg, T. K. (2005). Signal regulatory protein alpha ligation induces macrophage nitric oxide production through JAK/STAT- and phosphatidylinositol 3-kinase/Rac1/NADPH oxidase/H2O2-dependent pathways. *Molecular and Cellular Biology*, *25*, 7181.

Arase, H., & Lanier, L. L. (2004). Specific recognition of virus-infected cells by paired NK receptors. *Reviews in Medical Virolology*, *14*, 83.

Barclay, A. N., & Brown, M. H. (2006). The SIRP family of receptors and immune regulation. *Nature Reviews Immunology*, *6*, 457.

Bhatnagar, S., Shinagawa, K., Castellino, F. J., & Schorey, J. S. (2007). Exosomes released from macrophages infected with intracellular pathogens stimulate a proinflammatory response in vitro and in vivo. *Blood*, *110*, 3234.

Brooks, A. G., Borrego, F., Posch, P. E., Patamawenu, A., Scorzelli, C. J., Ulbrecht, M., et al. (1999). Specific recognition of HLA-E, but not classical, HLA class I molecules by soluble CD94/NKG2A and NK cells. *Journal of Immunology*, *162*, 305.

Cameron, C. M., Barrett, J. W., Liu, L., Lucas, A. R., & McFadden, G. (2005). Myxoma virus M141R expresses a viral CD200 (vOX-2) that is responsible for down-regulation of macrophage and T-cell activation in vivo. *Journal of Virology*, *79*, 6052.

Cameron, C. M., Barrett, J. W., Mann, M., Lucas, A., & McFadden, G. (2005). Myxoma virus M128L is expressed as a cell surface CD47-like virulence factor that contributes to the downregulation of macrophage activation in vivo. *Virology*, *337*, 55.

Carlyle, J. R., Jamieson, A. M., Gasser, S., Clingan, C. S., Arase, H., & Raulet, D. H. (2004). Missing self-recognition of Ocil/Clr-b by inhibitory NKR-P1 natural killer cell receptors. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 3527.

Caserta, S., Nausch, N., Sawtell, A., Drummond, R., Barr, T., Macdonald, A. S., et al. (2012). Chronic infection drives expression of the inhibitory receptor CD200R, and its ligand CD200, by mouse and human CD4 T cells. *PLoS One*, *7*, e35466.

Chapman, T. L., Heikeman, A. P., & Bjorkman, P. J. (1999). The inhibitory receptor LIR-1 uses a common binding interaction to recognize class I MHC molecules and the viral homolog UL18. *Immunity*, *11*, 603.

Chen, Z., Marsden, P. A., & Gorczynski, R. M. (2006). Cloning and characterization of the human CD200 promoter region. *Molecular Immunology*, *43*, 579.

Chen, Z., Marsden, P. A., & Gorczynski, R. M. (2009). Role of a distal enhancer in the transcriptional responsiveness of the human CD200 gene to interferon-gamma and tumor necrosis factor-alpha. *Molecular Immunology*, *46*, 1951.

Chlewicki, L. K., Velikovsky, C. A., Balakrishnan, V., Mariuzza, R. A., & Kumar, V. (2008). Molecular basis of the dual functions of 2B4 (CD244). *Journal of Immunology*, *180*, 8159.
Cortez, M., Huynh, C., Fernandes, M. C., Kennedy, K. A., Aderem, A., & Andrews, N. W. (2011). Leishmania promotes its own virulence by inducing expression of the host immune inhibitory ligand cd200. *Cell Host & Microbe, 9*, 463.

Cosman, D., Fanger, N., Borges, L., Kubin, M., Chin, W., Peterson, L., et al. (1997). A novel immunoglobulin superfamily receptor for cellular and viral MHC class I molecules. *Immunity, 7*, 273.

Costello, D. A., Lyons, A., Denieffe, S., Browne, T. C., Cox, F. F., & Lynch, M. A. (2011). Long term potentiation is impaired in membrane glycoprotein CD200-deficient mice: A role for Toll-like receptor activation. *The Journal of Biological Chemistry, 286*, 34722.

Daeron, M., Jaeger, S., Du Pasquier, L., & Vivier, E. (2008). Immunoreceptor tyrosine-based inhibition motifs: A quest in the past and future. *Immunological Reviews, 224*, 11.

De Albuquerque, N., Baig, E., Ma, X., Zhang, J., He, W., Rowe, A., et al. (2006). Murine hepatitis virus strain 1 produces a clinically relevant model of severe acute respiratory syndrome in A/J mice. *Journal of Virology, 80*, 10382.

Debierre-Grockiego, F., Campos, M. A., Azzouz, N., Schmidt, J., Bieker, U., Resende, M. G., et al. (2007). Activation of TLR2 and TLR4 by glycosylphosphatidylinositols derived from Toxoplasma gondii. *Journal of Immunology, 224*, 11.

Deckert, M., Sedgwick, J. D., Fischer, E., & Schluter, D. (2006). Regulation of microglial cell responses in murine Toxoplasma encephalitis by CD200/CD200 receptor interaction. *Acta Neuropathologica, 111*, 548.

Dentesano, G., Straccia, M., Ejarque-Ortiz, A., Tusell, J. M., Serratosa, J., Saura, J., et al. (2012). Inhibition of CD200R1 expression by C/EBP beta in reactive microglial cells. *Journal of Neuroinflammation, 9*, 165.

Farrell, H. E., Vally, H., Lynch, D. M., Fleming, P., Shellam, G. R., Scalzo, A. A., et al. (1997). Inhibition of natural killer cells by a cytomegalovirus MHC class I homologue in vivo. *Nature, 386*, 510.

Foster, S. L., Hargreaves, D. C., & Medzhitov, R. (2007). Gene-specific control of inflammation by TLR-induced chromatin modifications. *Nature, 447*, 972.

Foster-Cuevas, M., Westerholt, T., Ahmed, M., Brown, M. H., Barclay, A. N., & Voigt, S. (2011). The cytomegalovirus e127 protein interacts with the inhibitory CD200 receptor. *Journal of Virology, 85*, 6055–6059.

Foster–Cuevas, M., Wright, G. J., Puklávec, M. J., Brown, M. H., & Barclay, A. N. (2004). Human herpesvirus 8K14 protein mimics CD200 in down-regulating macrophage activation through CD200 receptor. *Journal of Virology, 78*, 7667.

Gorczyński, R. M. (2001). Transplant tolerance modifying antibody to CD200 receptor, but not CD200, alters cytokine production profile from stimulated macrophages. *Journal of Immunology, 167*, 2331.

Goulding, J., Godlee, A., Vekaria, S., Hilty, M., Snelgrove, R., & Hussell, T. (2011). Lowering the threshold of lung innate immune cell activation alters susceptibility to secondary bacterial superinfection. *The Journal of Infectious Diseases, 204*, 1086.

Hoek, R. M., Ruuls, S. R., Murphy, C. A., Wright, G. J., Goddard, R., Zurawski, S. M., et al. (2000). Down-regulation of the macrophage lineage through interaction with OX2 (CD200). *Science, 290*, 1768.

Houchins, J. P., Lanier, L. L., Niemi, E. C., Phillips, J. H., & Ryan, J. C. (1997). Natural killer cell cytolytic activity is inhibited by NKG2-A and activated by NKG2-C. *Journal of Immunology, 158*, 3603.

Karlofer, F. M., Ribaudo, R. K., & Yokoyama, W. M. (1992). MHC class I alloantigen specificity of Ly-49 + IL-2–activated natural killer cells. *Nature, 358*, 66.

Karnam, G., Rygiew, T. P., Raaben, M., Grinwis, G. C., Coenjaerts, F. E., Ressing, M. E., et al. (2012). CD200 receptor controls sex-specific TLR7 responses to viral infection. *PLoS Pathogens, 8*, e1002710.
Kretz-Rommel, A., Qin, F., Dakappagari, N., Cofiell, R., Faas, S. J., & Bowdish, K. S. (2008). Blockade of CD200 in the presence or absence of antibody effector function: Implications for anti-CD200 therapy. *Journal of Immunology, 180*, 699.

Kubagawa, H., Burrows, P. D., & Cooper, M. D. (1997). A novel pair of immunoglobulin-like receptors expressed by B cells and myeloid cells. *Proceedings of the National Academy of Sciences of the United States of America, 94*, 5261.

Kubagawa, H., Chen, C. C., Ho, L. H., Shimada, T. S., Garland, L., Mashburn, C., et al. (1999). Biochemical nature and cellular distribution of the paired immunoglobulin-like receptors, PIR-A and PIR-B. *The Journal of Experimental Medicine, 189*, 309.

Kuroki, K., Furukawa, A., & Maenaka, K. (2012). Molecular recognition of paired receptors in the immune system. *Frontiers in Microbiology, 3*, 429.

Kurt-Jones, E. A., Chan, M., Zhou, S., Wang, J., Reed, G., Bronson, R., et al. (2004). Herpes simplex virus 1 interaction with Toll-like receptor 2 contributes to lethal encephalitis. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 1315.

Langlais, C. L., Jones, J. M., Estep, R. D., & Wong, S. W. (2006). Rhesus rhadinovirus R15 encodes a functional homologue of human CD200. *Journal of Virology, 80*, 3098.

Lee, N., Llano, M., Carretero, M., Ishitani, A., Navarro, F., Lopez-Botet, M., et al. (1998). HLA-E is a major ligand for the natural killer inhibitory receptor CD94/NKG2A. *Proceedings of the National Academy of Sciences of the United States of America, 95*, 5199.

Long, E. O. (1999). Regulation of immune responses through inhibitory receptors. *Annual Review of Immunology, 17*, 875.

McVicar, D. W., Taylor, L. S., Gosselin, P., Willette-Brown, J., Mikhail, A. I., Gehlen, R. L., et al. (1998). DAP12-mediated signal transduction in natural killer cells. A dominant role for the Syk protein–tyrosine kinase. *The Journal of Biological Chemistry, 273*, 32934.

Mihrshahi, R., Barclay, A. N., & Brown, M. H. (2009). Essential roles for Dok2 and RasGAP in CD200 receptor-mediated regulation of human myeloid cells. *Journal of Immunology, 183*, 4879.

Mihrshahi, R., & Brown, M. H. (2010). Downstream of tyrosine kinase 1 and 2 play opposing roles in CD200 receptor signaling. *Journal of Immunology, 185*, 7216.

Misstear, K., Chanas, S. A., Rezaee, S. A., Colman, R., Quinn, L. L., Long, H. M., et al. (2012). Suppression of antigen-specific T cell responses by the Kaposi’s sarcoma-associated herpesvirus viral OX2 protein and its cellular orthologue, CD200. *Journal of Virology, 86*, 6246.

Mukhopadhyay, S., Plueddemann, A., Hoe, J. C., Williams, K. J., Varin, A., Makepeace, K., et al. (2010). Immune inhibitory ligand CD200 induction by TLRs and NLRs limits macrophage activation to protect the host from meningococcal septicemia. *Cell Host & Microbe, 8*, 236.

Nakamura, A., Kobayashi, E., & Takai, T. (2004). Exacerbated graft-versus-host disease in Pirb–/- mice. *Nature Immunology, 5*, 623.

Nakayama, M., Underhill, D. M., Petersen, T. W., Li, B., Kitamura, T., Takai, T., et al. (2007). Paired Ig-like receptors bind to bacteria and shape TLR-mediated cytokine production. *Journal of Immunology, 178*, 4250.

Odorizzi, P. M., & Wherry, E. J. (2012). Inhibitory receptors on lymphocytes: Insights from infections. *Journal of Immunology, 188*, 2957.

Ravetch, J. V., & Lanier, L. L. (2000). Immune inhibitory receptors. *Science, 290*, 84.

Reyburn, H. T., Mandelboim, O., Vales-Gomez, M., Davis, D. M., Pazmany, L., & Strominger, J. L. (1997). The class I MHC homologue of human cytomegalovirus inhibits attack by natural killer cells. *Nature, 386*, 514.

Rosenblum, M. D., Olasz, E., Woodliff, J. E., Johnson, B. D., Konkol, M. C., Gerber, K. A., et al. (2004). CD200 is a novel p53-target gene involved in apoptosis-associated immune tolerance. *Blood, 103*, 2691.
Sarangi, P. P., Woo, S. R., & Rouse, B. T. (2009). Control of viral immunoinflammatory lesions by manipulating CD200:CD200 receptor interaction. *Clinical Immunology, 131*, 31.

Shiratori, I., Yamaguchi, M., Suzukawa, M., Yamamoto, K., Lanier, L. L., Saito, T., et al. (2005). Down-regulation of basophil function by human CD200 and human herpesvirus-8 CD200. *Journal of Immunology, 173*, 4441.

Shlapatska, L. M., Mikhilap, S. V., Berdova, A. G., Zelensky, O. M., Yun, T. J., Nichols, K. E., et al. (2001). CD150 association with either the SH2-containing inositol phosphatase or the SH2-containing protein tyrosine phosphatase is regulated by the adaptor protein SH2D1A. *Journal of Immunology, 166*, 5480.

Smith, H. R., Heusel, J. W., Mehta, I. K., Kim, S., Dorner, B. G., Naidenko, O. V., et al. (2002). Recognition of a virus–encoded ligand by a natural killer cell activation receptor. *Proceedings of the National Academy of Sciences of the United States of America, 99*, 8826.

Snelgrove, R. J., Goulding, J., Didierlaurent, A. M., Lyonga, D., Vekaria, S., Edwards, L., et al. (2008). A critical function for CD200 in lung immune homeostasis and the severity of influenza infection. *Nature Immunology, 9*, 1074.

Soberman, R. J., MacKay, C. R., Vaine, C. A., Ryan, G. B., Cerny, A. M., Thompson, M. R., et al. (2012). CD200R1 supports HSV–1 viral replication and licenses pro-inflammatory signaling functions of TLR2. *PLoS One, 7*, e47740.

Ulbrecht, M., Martinozzi, S., Grzeschik, M., Hengel, H., Ellwart, J. W., Pla, M., et al. (2000). Cutting edge: The human cytomegalovirus UL40 gene product contains a ligand for HLA-E and prevents NK cell-mediated lysis. *Journal of Immunology, 164*, 5019.

Vance, R. E., Kraft, J. R., Altman, J. D., Jensen, P. E., & Raulet, D. H. (1998). Mouse CD94/NKG2A is a natural killer cell receptor for the nonclassical major histocompatibility complex (MHC) class I molecule Qa–1(b). *The Journal of Experimental Medicine, 188*, 1841.

Vely, F., & Vivier, E. (1997). Conservation of structural features reveals the existence of a large family of inhibitory cell surface receptors and noninhibitory/activatory counterparts. *Journal of Immunology, 159*, 2075.

Voigt, V., Forbes, C. A., Tonkin, J. N., Degli-Esposti, M. A., Smith, H. R., Yokoyama, W. M., et al. (2003). Murine cytomegalovirus m157 mutation and variation leads to immune evasion of natural killer cells. *Proceedings of the National Academy of Sciences of the United States of America, 100*, 13483.

Voigt, S., Mesci, A., Ettinger, J., Fine, J. H., Chen, P., Chou, W., et al. (2007). Cytomegalovirus evasion of innate immunity by subversion of the NKR-P1B:Clr-b missing-self axis. *Immunity, 26*, 617.

Voigt, S., Sandford, G. R., Ding, L., & Burns, W. H. (2001). Identification and characterization of a spliced C-type lectin-like gene encoded by rat cytomegalovirus. *Journal of Virology, 75*, 603.

Weikert, B. C., & Blumberg, E. A. (2008). Viral infection after renal transplantation: Surveillance and management. *Clinical Journal of the American Society of Nephrology, 3*(2), S76.

Willcox, B. E., Thomas, L. M., & Bjorkman, P. J. (2003). Crystal structure of HLA–A2 bound to LIR–1, a host and viral major histocompatibility complex receptor. *Nature Immunology, 4*, 913.

Wright, G. J., Cherwinski, H., Foster-Cuevas, M., Brooke, G., Puklavec, M. J., Bigler, M., et al. (2003). Characterization of the CD200 receptor family in mice and humans and their interactions with CD200. *Journal of Immunology, 171*, 3034.

Wright, G. J., Puklavec, M. J., Willis, A. C., Hoek, R. M., Sedgwick, J. D., Brown, M. H., et al. (2000). Lymphoid/neuronal cell surface OX2 glycoprotein recognizes a novel receptor on macrophages implicated in the control of their function. *Immunity, 13*, 233.

Yarovinsky, F., Zhang, D., Andersen, J. F., Bannenberg, G. L., Serhan, C. N., Hayden, M. S., et al. (2005). TLR11 activation of dendritic cells by a protozoan profilin-like protein. *Science, 308*, 1626.
Yu, K., Chen, Z., & Gorczynski, R. (2013). Effect of CD200 and CD200R1 expression within tissue grafts on increased graft survival in allogeneic recipients. *Immunology Letters, 149*, 1.

Zhang, S., Cherwinski, H., Sedgwick, J. D., & Phillips, J. H. (2004). Molecular mechanisms of CD200 inhibition of mast cell activation. *Journal of Immunology, 173*, 6786.

Zhang, S., & Phillips, J. H. (2006). Identification of tyrosine residues crucial for CD200R-mediated inhibition of mast cell activation. *Journal of Leukocyte Biology, 79*, 363.

Zhang, L., Stanford, M., Liu, J., Barrett, C., Jiang, L., Barclay, A. N., et al. (2009). Inhibition of macrophage activation by the myxoma virus M141 protein (vCD200). *Journal of Virology, 83*, 9602.