Europe PMC Funders Group
Author Manuscript
Crit Rev Immunol. Author manuscript; available in PMC 2008 July 09.

Published in final edited form as:
Crit Rev Immunol. 2006 ; 26(3): 213–230.

Is The CD200/CD200 Receptor Interaction More Than Just a Myeloid Cell Inhibitory Signal?

Konstantinos Minas and **Janet Liversidge**[*]
Department of Ophthalmology, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, UK AB25 2ZD

Abstract

The membrane glycoprotein CD200, which has a widespread but defined distribution and a structurally similar receptor (CD200R) that transmits an inhibitory signal to cells of the hematopoetic lineage, especially myeloid cells, has been characterized. CD200R expression is restricted predominantly to cells of the myeloid lineage indicating that this ligand/receptor pair has a specific role in controlling myeloid cell function. In addition to CD200R, several related genes have been identified. Whether these gene products also regulate immune function is controversial. CD200R is also expressed by certain subsets of T cells and CD200 may be expressed by antigen-presenting cells, adding additional layers of complexity to the CD200/CD200R axis. Because monocytic myeloid cells provide a link between the innate and adaptive immune response, mechanisms to control their function through receptors such as CD200R will have therapeutic potential. Regulation of immune responses is accomplished by the concerted, but opposing, activity of kinases and phosphatases, fine control often being achieved through paired receptors. In this review, we will consider whether CD200R signaling functions within a framework of paired activating and inhibitory receptors and whether the inhibitory signal delivered has functional consequences beyond inhibition of myeloid cell proinflammatory activation.

Keywords

monocyte-macrophage; dendritic cells; autoimmunity; allergy; transplantation

I. INTRODUCTION

A. Regulation by Myeloid Cells

Mononuclear cells of the myeloid lineage are central to the regulatory mechanisms that enable the immune system to respond to foreign or infectious organisms while remaining tolerant, or nonresponsive to self.1,2 After infection is controlled, an active process of immunosuppression or immunoregulation ensues to re-establish immunological homeostasis. This involves terminating lymphocyte survival and growth and induction of programmed cell death by apoptosis3 and reprogramming of proinflammatory monocyte macrophages toward alternative functions such as humoral immunity and wound healing.4 Broad control of these functions is cytokine driven,5-7 but fine control is now thought to depend upon activating and inhibitory receptors expressed by myeloid cells.8,9 In particular,

© 2006 by Begell House, Inc.

[*] Author to whom all correspondence should be addressed; Tel.: (44)1224 559548; Fax: (01144) 1224 555944; j.liversidge@abdn.ac.uk.

Referee: Professor A. Neil Barclay, Sir William Dunn School of Pathology, University of Oxford, South Parks Road, Oxford OX1 3RE, UK

Europe PMC Funders Author Manuscripts
Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

the integration of positive and negative signals through these cell-surface receptors is now thought to control induction and maintenance of immune-regulatory mechanisms responsible for maintaining immune steady-state in the normal individual. Defects in these mechanisms lead to acute inflammation, autoimmunity, or allergy.[10-12] Myeloid cells, including monocyte macrophages and dendritic cells (DC), express a multitude of plasma membrane receptors that mediate their functional response to endogenous or exogenous environmental signals. The diversity of these receptors underlines the potential heterogeneity and pivotal role that these cells play in orchestrating immune responses. Many of these receptors can be grouped into structurally related families with specific or overlapping functions.[11] Among those paired, activating and inhibitory receptors have been identified. It is now clear that an expanding number of myeloid inhibitory receptors can pair with closely related gene products with activating or inhibitory function, the activating isoforms lacking an ITIM, but containing a charged residue in the transmembrane region that can associate with adaptor proteins such as DAP-12.[13] Two distinct types have been identified: those belonging to the immunoglobulin domain superfamily and those belonging to the C-type lectin family. These may express on natural killer (NK) cells as well as myeloid cells, suggesting a role in innate immunity to infection.[14] The immunoglobulin superfamily members include the paired immunoglobulin-like receptors (PIRs) in mice,[15-17] immunoglobulin-like receptors (ILTs) in humans,[18,19] signal-regulatory proteins (SIRPS),[19-21] and triggering receptors expressed by myeloid cells (TREMs).[11] The CD200 (or OX2) receptor family has now been identified, and they too may represent functional-paired activating and inhibitory isoforms. Whether they act in concert with, or share an overlapping function with, other paired receptor families is at present under examination. In contrast to many of the other activating or inhibitory receptors that are orphans, the ligand (CD200) for at least one CD200 receptor is known.

B. The Role of CD200 in Immunoregulation

The relevant cytokine and receptor signals generating antigen-specific immunity or tolerance at the level of the T-cell receptor (TCR)/peptide/MHC interaction are well studied, and various therapies based on manipulating this interaction to modulate disease have been developed.[22,23] In contrast, we know comparatively little about the crucial cell-surface interactions that control the activity and function of monocyte/macrophages despite the fact that macrophages play a vital role in the response to injury or infection. This is in part because of their extreme functional and phenotypic heterogeneity as they respond or adapt to changes in their microenvironment.[4,9,24-26] Consequently, the early observation that CD200 appeared to deliver a strong “off” signal to myeloid cells created an interest in using this interaction therapeutically.

In comparison with other potential myeloid immunoregulatory molecules, the volume of research is limited and most of it has been carried out by, or in collaboration with, three research groups. Some of the data are contradictory, some data are unconfirmed or speculative, and large areas are as yet completely unexplored. In this article, we review the existing literature; examine the data presented; and in light of the evidence, attempt to evaluate the role of CD200/CD200 receptor signaling in regulating immune responses and in context with other related signaling complexes. We also identify key areas for further investigation.

II. THE CD200 (OX2) GENE

A. Distribution of OX2 Protein

The rat OX2 protein was first purified and characterized as a 41- to 47-kDa cell-surface glycoprotein in 1982[27] and was found to be expressed on a variety of cell types, including

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

rat thymocytes, B cells, activated T cells, follicular dendritic cells, endothelium28 neurons in the central nervous system (CNS) (including retina and optic nerve),29,30 and cells in reproductive organs.31 This distribution was found to be conserved in humans, and expression confirmed in kidney glomeruli.32 More recently, expression on a subpopulation of murine keratinocytes has been observed but is yet to be confirmed in human skin.33 This conserved, unusual, and specific rather than ubiquitous distribution, indicated a particular and important biological function for OX2. Sequence analysis showed that in common with many other leukocyte membrane proteins, OX2 was a member of the immunoglobulin superfamily (IgSF),34 and further characterization showed it contained two IgSF domains: a single transmembrane domain and a short cytoplasmic domain.27,35 By analogy with other proteins containing IgSF domains, it seemed likely that OX2 mediated specific cell-surface recognition events via a second cell-surface receptor.

B. Identification of the OX2 Receptor

Recombinant DNA technology was used to produce a soluble chimeric protein bearing the extracellular domains of OX2 expressed as a fusion protein with domains 3 and 4 of rat CD4 and coupled to fluorescent beads.36 This approach has the advantage of detecting even low-affinity binding, typical of other known leukocyte ligand/receptor interactions. OX2 protein was found to bind to a ligand present on peritoneal macrophages. OX2 protein was designated CD200 at the Seventh International Leukocyte Typing Workshop in 2000, and using a high-affinity monoclonal antibody (mAb), OX 102 raised to a macrophage cell-surface antigen that blocked OX2 binding; the OX2 receptor was purified from rat spleen cells. This protein was cloned, expressed and identified as another novel protein, similar in structure to OX2. It contained two IgSF domains, but with a larger cytoplasmic domain having potential signaling capacity.37 Further phenotypic analysis also revealed that the receptor recognized by OX102 was expressed by cells of the myeloid lineage.37 Thus, the distribution of OX2 and its receptor has similarities with the CD47-CD172a (SIRP-α) interaction in that CD47 is widely distributed, and its receptor CD172a is mostly expressed by myeloid cells. Signaling via CD172a has been shown to downregulate myeloid cells through tyrosine phoshatases SHP1 and SHP2.20

The OX2 gene is also closely linked genetically to the costimulatory molecules CD80 and CD86. These molecules are expressed by antigen-presenting cells and are ligands for the activating receptor CD28 and inhibitory receptor CD152 expressed by T cells, and are structurally related to OX2, having one IgV and one IgC-like domain. Based on this association with CD80 and CD86, experiments were designed to test the hypothesis that CD200 may also be a co-stimulatory molecule. Thus, OX2 CHO cell transfectants were found to stimulate $CD4^{+}$ T-cell proliferation in response to CD3 ligation, but did not generate IL-2, IL-4 or IFN-γ, cytokines associated with T-cell growth and immune activation, indicating that costimulation was incomplete or deviant. This response was independent of the CD28/CD152 pathway, and, apparently, the receptor recognized by OX102, raising the possibility of additional receptors for CD200,38 although these have not subsequently been identified. These experiments have not been repeated, possibly due to variation in transfected CHO cells that also have costimulatory molecules,39 and no further work confirming the role of OX2 as a costimulatory molecule has appeared in the literature.

Meanwhile, analysis of the role of OX2 protein in biological systems was raising tantalizing questions concerning the function of OX2 within the immune system. Gorczynski and colleagues reported increased expression of OX2 on a subpopulation of $NLDC145^{+}$ dendritic cells associated with increased graft survival in their in vivo mouse model of allo- and xenograft transplantion.40 Increased graft survival could be reversed using a mAb specific for mouse OX2 (3B3) or enhanced using an OX2Fc fusion protein.41,42 These data implied a predominantly immunosuppressive role for constitutively expressed OX2 in vivo

and Gorczynski et al. argued that the effects were related to T-cell function via an immune-deviation process, although this was not proved. OX2-deficient mice were developed by Sedgwick and colleagues,43 and these mice confirmed a role for OX2 in immune regulation. The resultant conclusion was that the effects were mediated through direct myeloid cell regulation through OX2-OX2R interactions.

C. The CD200 (OX2)-Deficient Mouse Indicates a Role for CD200 in Myeloid Regulation

To generate mice lacking functional CD200 (OX2), an *Eco*-47III-*Sal* 1 fragment of a CD200 genomic clone, isolated from a C57Bl/6 genomic library, was used to construct a targeting construct in which the *Nco* I fragment was replaced with a PGK-neo^r cassette. This construct was used to transfect C57Bl/6 strain embryonic stem cells that were microinjected into BALB/c blastocysts. Chimeras were mated with C57Bl/6 mice and CD200$^{-/-}$ offspring generated by crossbreeding offspring expressing the deleted germ-line DNA.43 The mice generated were essentially normal in appearance, with normal breeding and life span. Phenotypic analysis of cells and tissues from these mice showed that CD200 expression was lacking from neurons in CNS and from endothelium, B cells and follicular DC in splenic tissue. Phenotypic differences between leukocytes from CD200$^{+/+}$ (wild type, WT) and CD200$^{-/-}$ were found only in the CD11b$^+$ population, a population that largely did not express the missing CD200 molecule. Within the spleen, CD11b$^+$ myeloid cells were significantly increased in number from 4×10^{-6} in WT to 8×10^{-6} in CD200$^{-/-}$ mice. The increased numbers of cells appeared to be located within the splenic red-pulp areas with increased expression of F4/80$^+$ on tissue macrophages.44 MOMA-1$^+$ metallophylic marginal-zone macrophages45 were also prominent, the normal single-cell wide zone appearing as multilayered in the CD200$^{-/-}$ mice. Crucially, higher levels of the immunotyrosine-activating motif (ITAM)-containing intracellular protein DAP1246 were also detected in the marginal zone and on DC within the T-cell areas of the white pulp, suggesting elevated levels of activation in the CD200$^{-/-}$ mice.47,48 Significant alterations in the phenotype of microglia were also observed. In the normal brain, microglia display branched or stelate morphology, are distributed relatively evenly through the tissue, express only very low levels of MHC class I and Class II molecules, and are usually CD11b^{low} and CD45$^{low.}$ In contrast, in CD200$^{-/-}$ mice, a subfraction of microglia were strongly CD11b$^+$ and CD45$^+$ and formed aggregates, particularly in the spinal chord.

On the basis that it was myeloid cells that were most dysregulated, and the evidence49 that the CD200R were expressed by macrophages, Hoek et al. hypothesized that the CD200$^{-/-}$ phenotype represented a state of myeloid cell tonic activation as a result of myeloid cell expressed CD200R lacking a restraining signal from CD200. This was tested in the facial nerve transection model,50 in two autoimmune models, in myelin oligodendrocyte (MOG)-induced EAE,51 and in collagen-induced arthritis.52 In the facial nerve transection model, the microglial response was indeed accelerated with detectable activation at day 2, peaking at day 4 after surgery in CD200$^{-/-}$ mice, compared with WT mice where peak activation was not observed until day 7. In addition, in EAE, onset of disease was 3 days earlier in CD200$^{-/-}$ mice and loss of CD200 rendered the normally resistant C57Bl/6 mouse strain susceptible to induction of CIA. Disease in both EAE and CIA are self-antigen-specific T-cell dependent, but no evidence could be found for hyperreactivity of T cells in these models, and indeed no evidence for a direct effect on T-cell proliferation in response to antigen presentation has been demonstrated53,54 Disease induction in EAE was also characterized by the enhanced expression of NOS2 by inflammatory macrophages within the CNS lesions. This led Hoek et al. to conclude that CD200 molecules bind CD200R expressed by myeloid cells including macrophages, transmitting an inhibitory signal that downregulates macrophage activity to prevent or reduce tissue damage caused by macrophages.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Comparatively few other studies using CD200$^{-/-}$ mice have been published, but to date all seem to support an inhibitory role for CD200R signaling, and further imply a role in immune tolerance, or immunological nonresponsiveness (Table 1). Outside the CNS, expression of CD200 by follicular epithelium in the skin was found to attenuate immune responses in an alopecia model,33 supporting the notion that the distribution of CD200 on specific cell types is linked to a specialized rather than a generalized function connected with myeloid cell regulation. Within the CNS, microglia in the retina of CD200$^{-/-}$ mice differ from those in the brain as they have normal morphology, possibly as a result of lower density of these cells in the retina compared with the brain. Retinal microglia are normally resistant to classical activation by stimuli such as LPS-IFN-γ and are considered to be conditioned toward an alternatively activated phenotype by TGF-β present in the retinal microenvironment.55 But this conditioning appears to be overridden in the CD200$^{-/-}$ mouse retina, as microglia express NOS-2 constitutively and are present in larger numbers than in WT.56 A role for CD200 in maintaining MG potential to migrate has been identified in human retinal tissue,56 but to date there is no evidence for a role in directing leukocyte trafficking in inflammation. Accelerated onset of experimental autoimmune uveoretinitis (EAU) in these mice has been reported, but contrary to expectation, overall disease severity was not increased in CD200$^{-/-}$ mice,53,56 implying a more complex role for CD200 in immune regulation.

III. CD200 RECEPTOR FAMILY

The discovery and characterization of membrane receptors and their intracellular components has been facilitated by the availability of expressed sequence tag (EST) and genomic databases. Once a new molecule of interest is identified, searching for nearby genes or sequences with homology can be used to identify isoforms generated by alternative RNA splicing, and to uncover new gene families. Using this approach, two groups have independently described an extended family of CD200R-related molecules.57,58 These molecules are in addition to the actual CD200R originally identified by Wright,37 and their ligand partners and biological function are at present still largely speculative.58,60,61

A. The Definitive Inhibitory CD200 Receptor (CD200R)

The inhibitory receptor CD200R was originally cloned by Barclay and colleagues in Oxford, 37 and there is consensus that CD200 is its natural ligand. The rat CD200R gene was cloned and sequenced using an antisense- degenerate primer designed from the amino terminal protein sequence to amplify the 5′ untranslated region and leader sequence and the full-length cDNA was subsequently obtained using a 3′ RACE RT-PCR protocol. A closely related protein was also identified in mouse, and phylogenetic analysis of the extracellular sequences with other members of the IgSF revealed that as well as having structural similarities, the CD200R is closely related to CD200, implying evolution from a common ancestral protein.37 The human gene was independently characterized and mapped to chromosome 3q12-13.62 The sequence, chromosomal location, and tissue distribution of CD200R has since been confirmed by Gorczynski and colleagues in Toronto, and in their nomenclature is referred to as CD200R1.60

An unusual feature of the CD200R was the high content of N-linked glycosylation sites, 8 in the rat and 10 in the mouse.36 In addition, the cytoplasmic region of the receptor contained a NPXY motif that can interact with PTB/PID-binding domains present in several signaling adaptor molecules. Kinetic analysis of rat CD200R binding to soluble CD200 using BIAcore-chip assays, indicated that in common with many interactions between leukocyte cell-surface proteins, immobilized receptor bound soluble CD200 with comparatively low affinity (K_D = 2.5 μM), typical of interactions between migratory cells.63,64 Significantly, for application to human disease, the human homologue of murine CD200R has also now

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

been characterized and shown to have a high degree of sequence homology, particularly the tyrosine residues and associated amino acids in the cytoplasmic domain, with a conserved phosphotyrosine binding site (NPXY) for the signaling protein Shc.58 In addition, these studies showed that $CD4^{+}$ T cells, especially in blood, can express CD200R, and further identified CD200R mRNA highly expressed in polarized Th2 cells, mast cells, and dendritic cells in both mice and humans, suggesting that this receptor may have wider functions within the immune system, particularly in regulation of Th2-mediated responses.

That CD200R is an inhibitory receptor principally affecting myeloid cell function appears beyond doubt,37,43,59 but in contrast to other well-described myeloid-inhibitory immune receptors, such as FcεRIIB, GP49B1 or paired Ig-like receptors (PIRs), CD200R does not contain an immunotyrosine-based inhibitory motif (ITIM).8 ITIMs are phosphorylated on tyrosine, usually by Src family kinase. By recruiting phosphatases such as SHP1 or SHIP, ITIM-bearing receptors suppress cell activation by promoting dephosphorylation reactions. Zhang et al.65 recently reported that engagement of CD200R by soluble CD200-mIg fusion protein did indeed cause a rapid CD200R tyrosine-phosphorylation event in mouse mast cells over expressing CD200R. Activation of ERK, JNK and p38MAPK were all subsequently inhibited. The key phosphorylation was mediated through the CD200R-associated NPXY motif, phosphorylating Dok1 and Dok2 proteins that subsequently bound RasGAP and SHIP, and downstream inhibition of the RasMAPK pathways. Thus, the CD200R is an inhibitory receptor that appears to trigger a novel myeloid cell inhibitory pathway, distinct from more typical ITIM-like receptors.

Site-directed mutagenesis indicates that CD200R and CD200 interact through the GFCC' faces of their N-terminal domains, facilitating molecular interactions within the topography of the hypothesized signaling synapse between activated T cells and myeloid antigen-presenting cells.13,66 In addition, there is evidence for CD200R and/or ligand density affecting intensity or efficiency of signaling. In both murine and human systems, a dose-dependent relationship between receptor expression and cell function has been demonstrated. Cytokine production by CD200R transfected U937 cells correlated with CD200R expression levels, and in the same study, mCD200R agonists inhibited IFN-γ and IL-17 induced IL-6 secretion by murine-resident peritoneal macrophages.54 From this, together with the signaling potential through an inhibitory pathway distinct from other myeloid-regulatory molecules and the highly specialized distribution of CD200 in tissues outside the lymphoid system, we can hypothesize that the CD200/CD200R axis may function as an additional or enhancing inhibitory control on potentially damaging proinflammatory myeloid cell activity in vulnerable tissues. Such a role is certainly consistent with the mild phenotype of the CD200-deficient mouse.

In addition to confirming the sequence of CD200R, which they dubbed CD200R1, Gorkcynski and colleagues59 also showed that antibodies to a peptide sequence of CD200R1 could mimic the immunomodulatory effects of a CD200Fc fusion protein, reducing cytotoxic lymphocyte (CTL) generation in spleen mixed lymphocyte cultures (MLC). They also identified expression on a subpopulation of activated T cells. Further characterization of functional epitopes was carried out using a series of 15mer synthetic peptides.67 The ability of these molecules to block binding of CD200R1 to CD200 was studied using competitive ELISA and CD200Fc fusion protein. Results were duplicated in a FACS-based assay also using CD200Fc fusion protein, and infusion of these peptides also abrogated the protective effects of CD200Fc fusion proteins in a mouse allograft model indicating in vivo activity.68 That short, linear peptides were able to exert these effects, particularly in vivo,, is remarkable. But the mechanisms involved remain to be proven.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

B. CD200R Family Gene Products

Characterization of genes closely related to CD200R in mice and humans, revealed at least four mouse CD200R-related genes termed mCD200RLa-d (for CD200R-like), but only a single related human gene, designated hCD200RLa.58 Mouse CD200RLc was isolated only as a partial cDNA clone, and mCD200RLd was only identified as genomic sequence, so only the CD200La and Lb isoforms were characterized further. Both showed close sequence homology to CD200R in the extracellular regions, with short cytoplasmic regions containing a positively charged lysine residue in the transmembrane region. It was surmised that this residue would form a salt bridge with DAP12 to enable signal transduction and this was confirmed by immunoprecipitation. Human CD200RLa was also found to have a positively charged amino acid in the transmembrane region. More recently, the CD200Le gene expressed in the NOD mouse, but not C57/Bl/6 strains of mice, has also been characterized. 69

The distribution of the CD200RLa and Lb genes was determined by RT-PCR and protein expression determined by a set of mAbs. The highest level of mCD200RLa was observed in resting mast cells, but deceased on activation via FcεR1. Strong expression was also observed on bone marrow-derived DC and macrophages, with lower expression on Th2 cells. In contrast, mCD200Lb was primarily expressed in activated mast cells, polarized Th2 cells, to a lesser degree in cultured DC, but was virtually undetectable in cultured macrophages. This differential distribution suggests these genes may have specific rather than redundant functions in the immune response in mice. Although cDNA for human CD200RLa could be isolated from peripheral blood, amino acid analysis showed that it lacked two cysteine residues critical for expression and it is likely that the gene is nonfunctional, indicating that only CD200R is expressed in humans. Key points were that (1) none of these CD200RL molecules bound CD200, (2) the human CD300RLa was not expressed as a functional protein, (3) it is likely that these are activating receptors, and (4) the ligands have not been identified.58,61

Using EST, 5′-RACE, cDNA and genomic DNA clone analysis, Gorczynski and colleagues also cloned and sequenced a family of CD200 receptors in addition to the CD200R(1) described above. These were dubbed CD200R2 (corresponding to CD200RLc), and CD200R3 (corresponding to CD200Lb), and CD200R4 (corresponding to CD200La).60 Comparison of sequence data from Wright58 indicated NH_2-terminal differences for CD200R2 and R3 compared with RLc and RLb. Charged residues in the cytoplasmic domains of CD200R2-4 were found, but whether they associated with ITAMS was not determined. Using predicted amino acid sequence comparisons, hydrophobicity predictions and three-dimensional modelling of the isoform sequences, peptides were synthesized to generate rabbit polyclonal or rat monoclonal antibodies to CD200R1-4. Antibodies with relative specificity for CD200R2 and R3 were also obtained, as well as antibodies, for a cross-reactive epitope on CD200R1 and R4. Using flow cytometry, COS7 cells transfected with all CD200R isoforms appeared to bind FITC-labelled CD200Fc, contradicting previous reports that only the inhibitory CD200R bound CD200.58 However, these experiments were conducted in the absence of DAP12 expression by the transfected cells and it is probable that positive binding observed in these studies was an artifact, as CD200RLa is not expressed well in absence of DAP12, and CD200RLb is only expressed at the cell surface in the presence of DAP12.58 The necessity for coexpression of DAP-12 has also been confirmed independently for CD200R3 (CD200RLb).69 These proteins are therefore predicted to transmit activating signals through the DAP12 adaptor protein, placing the CD200R family in the same category as other paired receptor families such as the SIRPs, Ly49 natural killer cell, Ig-like receptors and PILR, which have both activating and inhibiting isoforms.13,70-72

It has now been definitively shown that only the inhibitory isoform, CD200R, binds CD200.61 Mouse CD200R, CD200RLa, and CD200RLb were expressed at high levels in BaF3 cells, and a DAP12 construct was cotransfected with CD200RLa and CD200RLb, enabling their expression at the cell surface and their detection using highly specific monoclonal antibodies. Using flow cytometry, only cells expressing CD200R bound a CD200-Fc fusion protein. This was confirmed at the protein level using surface plasmon resonance. The expressed receptors CD200R, CD200RLa, and CD200RLb, as well as protein products of the genes CD200RLc and CD200Le, were generated as chimeric proteins with a biotinylation sequence and with two domains of rat CD4 as an antigenic tag. Only CD200R was found to bind to either the monomeric or dimeric CD200 fusion proteins. A range of concentrations were tested and the affinity of binding of CD200R calculated as $K_d \sim 4\ \mu M$. Binding of CD200RLa was too weak to measure accurately and is therefore unlikely to be physiologically relevant, and no binding of CD200RLb, CD200RLc, or CD200RLe could be detected using this sensitive assay.

The fine specificity of binding between CD200 and CD200R can be appreciated through sequence comparison and analysis of the nonbinding receptors. Analysis of the sequence similarities of the extracellular regions of the receptors showed that the strain-specific gene CD200RLe appears to be the most closely related (91%) to CD200R, compared with CD200RLa (84%), CD200RLc (83%), and CD200RLb (39%).61 The binding site of the human CD200R has also been studied by mutagenesis analysis and residues in the predicted β strands C and F identified as important for binding human CD200. Importantly, a single residue change in this area was sufficient to prevent binding.66 Analysis of this region between the binding receptor CD200R and the nonbinding CD200RLe was also highly conserved. These observations have significant implications for potential therapies targeting the CD200/CD200R axis.

C. Evolutionary Origins of the CD200R Family

Why do multiple isoforms of the CD200R exist (at least in mice) and if CD200 is not their natural ligand, what is their function? A large proportion of leukocyte membrane proteins contain one or more IgSF domains.73 Almost half of these are similar to CD200 in having two Ig domains, binding ligand via the N-terminal Ig domain, and have arisen as the adaptive immune response has evolved, possibly reflecting their function as protein or peptide recognition molecules.74 Receptor ligand pairs with close-sequence homology are thought to have evolved from single gene products that originally mediated homophylic binding.75 Phylogenetic analysis of the CD200R extracellular sequence compared with other members of the IgSF, place it very close to CD200, implying that the two proteins have evolved from a common ancestral protein. Viral homologues of CD200 have also been identified, notably in the Herpesviridae and Poxviridae families that are highly adapted to coexist asymptomatically with their host. Viruses frequently acquire genes from infected host cells, and as IgSF domains are rare in viruses, it is likely that the CD200-related open reading frames (ORFs) found in a range of diverse viruses have been acquired independently on more than one occasion.13,74 For instance, the human herpesvirus 8 K14 protein can inhibit proinflammatory cytokine secretion (eg, TNF-α) by macrophages76 or histamine release from basophils,77 and the myxoma virus M141R gene product is predicted to reduce macrophage or DC ability to prime T cells through CD200/CD200R-specific mechanisms.78

The ability to downregulate host immune responses via inhibitory CD200R would have strong survival benefits for the virus, and would provide a strong evolutionary pressure on the host to evolve alterative, activation receptors to override detrimental pathogen-induced inhibitory responses. Accumulating evidence that this has occurred for other DAP12-pairing receptors79 raises the possibility that the non-CD200-binding receptors described above have evolved to stimulate the innate immune response by recognizing related microbial

Europe PMC Funders Author Manuscripts
Europe PMC Funders Author Manuscripts

proteins, and deliver activating rather than inhibitory signals aimed at eliminating or at least suppressing virus activity within the host.

IV. PHYSIOLOGICAL FUNCTION OF CD200/CD200R INTERACTION

All the evidence offered to date supports an immunoregulatory role for CD200. In particular, interaction with CD200R expressed constitutively by monocytic myeloid cells such as macrophages and dendritic cells represses proinflammatory activation in vivo,[33,41,43,53,80] reduces activation of MAPK's in mononuclear cells, and represses degranulation of human mast cells and basophils.[65,77,81] It is also probable that CD200 expressed by endothelium has a role in controlling circulating neutrophil degranulation, but this has not been directly tested. There is no evidence for spontaneous neutrophil degranulation in the $CD200^{-/-}$ mouse, and given the serious consequences of systemic degranulation (septic shock), it is evident that additional controlling mechanisms have evolved to restrain this event. There is evidence for CD200R expression by T-cell subsets in humans and mice, adding additional pathways for regulation.[58] A role for dysfunctional regulation through CD200 has been identified in various pathological models. As CD200R is the only definitively characterized receptor for CD200, and functional ligands for the activating isoforms of the receptor have yet to be found in humans or mice, only inhibitory signaling via CD200R will be considered further in this review.

A. Regulation of Allergy

Mast cells reside in most tissues of the body and are frequently found adjacent to blood vessels, where they provide a vital sentinel function for the innate immune response through clearance of immune complexes and complement-opsonized particles via Type-1 receptors. In common with other granulocytic cells of the myeloid series, they also respond directly to microbes and other mediators promoting an inflammatory response. Mast cells can also affect the magnitude or kinetics of the acquired immune response including autoimmunity via cell-surface interactions with DC and with T and B lymphocytes or through release of cytokines and chemokines.[82] They are also capable of an antigen-specific response via cross-linking of surface-bound IgE molecules. This results in the release of granule contents such as histamine and serine proteases, making mast cells the major effector cells for allergic or immediate hypersensitivity reactions. Expression of highly glycosylated CD200R by mast cells[37,58] is therefore a potential regulatory mechanism to control excessive allergic responses.

A model mast cell degranulation assay was developed by Zhang et al., [65] whereby cross-linking of FcεR1-bound TNP-specific IgE by varying concentrations of the contact sensitizing compound TNP-KLH, resulted in dose-dependent degranulation of the mast cells. This assay was used to study the molecular mechanisms of CD200 inhibition of mast cell activation demonstrating a novel inhibitory pathway, as discussed earlier in this review. Additional studies with this in vitro system showed that degranulation and secretion of IL-13 and TNF was markedly reduced following CD200 engagement of mast cell expressed CD200R, suggesting that CD200R might regulate the activation threshold of inflammatory immune responses.[81] More importantly for therapeutic applications, when normal human mast cells, expressing normal levels of CD200R, were treated with an agonist antibody that triggers CD200R signaling, a slight but consistent inhibition of degranulation could be achieved. The effect was dependent on the concentration of anti-hFcεR1 used to initiate degranulation, and was significantly enhanced by CD200 engagement, together with cross-linking of CD200R at the mast cell surface, reinforcing the notion that CD200-CD200R interactions are involved in regulating the threshold at which an inflammatory response might occur, as well as regulating the magnitude or duration of that response.[13]

Europe PMC Funders Author Manuscripts
Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

These in vitro observations were also tested in vivo in a murine model of passive cutaneous anaphylaxis.81 Although overexpression or cross-linking of CD200R on cultured mast cells was required to prevent degranulation in vitro, systemic administration of an agonist antimouse CD200R mAb inhibited FcεR1-dependent responses in vivo in a system in which no artificial cross-linking was used. The increased sensitivity of the response in vivo may be attributed to the higher constitutive expression of CD200R on mast cells in vivo compared with cultured cells, or perhaps other cell-cell interactions that occur in vivo lower the threshold for inactivation. The in vivo data clearly underline the potential of CD200R targeting as a therapeutic strategy in allergic responses.

B. Regulation of Organ-Specific Autoimmunity

If the function of CD200 expression on particular cells or tissues is to limit inflammatory damage to those cells and tissues, then a role in limiting autoimmune responses in vulnerable tissues might be predicted. In the limited number of studies carried out, this would appear to be the case.

CD200 is notably expressed on neurons within the CNS and would be predicted to modulate activation of $CD200R^{+}$ microglia. Consistent with this concept, some microglia in the brain form aggregates in the absence of CD200,43 and in the retina, microglia numbers are increased and show evidence of proinflammatory activation through de novo expression of NOS-2.56 These changes are linked to accelerated onset of MOG-induced EAE43 and of retinal antigen peptide-induced EAU in $CD200^{-/-}$ mice.30,53 A direct regulatory role for CD200 in controlling classical activation4 of microglia and retinal macrophages in retinal diseases is also supported by increased expression of CD200 on retinal neurons seen when CD200R signaling is interrupted using a blocking mAb. This treatment resulted in augmented NOS-2 expression by retinal macrophages and more severe disease in a rat model of EAU.83

Outside the CNS, other models of autoimmunity have indicated that in addition to attenuating local inflammatory reactions, CD200/CD200R may also promote immune tolerance or nonresponsiveness. In collagen-induced arthritis (CIA), although CD200 is not expressed in the joint, increased susceptibility to disease was seen in $CD200^{-/-}$ mice on the normally resistant C57Bl/6 background. CIA could also be induced in wild-type mice treated with a CD200R-Ig fusion protein that prevented the association between CD200 and CD200R.43 The inflammation was dominated by macrophages, with pannus formation and erosion of cartilage and bone, suggesting CD200-CD200R interactions outside the target tissue were also involved in regulating induction and progression of autoimmune disease. The powerful nature of this effect was confirmed by experiments in the susceptible DBA/1 mouse, where infusion of (presumably agonist) anti-CD200R antibody, or a CD200Fc fusion protein could halt disease progress and significantly reduce established arthritic disease.84 Reduced disease scores were accompanied by reduced TNF-α and IFN-γ ðproduction by lymphoid cells restimulated with antigen in vitro, but whether this reflected a direct and specific effect on collagen-specific T-cell responsiveness as a result of the treatment rather than the effect of reduced macrophage activity and reduced disease activity, was not proven.

More evidence for systemic regulation was observed in a murine-contact hypersensitivity model where $CD200^{-/-}$ mice were found to be resistant to ultraviolet (UV)-mediated induction of tolerance.85 This effect was linked to expression of CD200 in the skin, and specifically, MHC class II negative keratinocytes in the outer root sheath of the murine hair follicle.33 A syngeneic skin graft model of alopecia was developed to study the possible role of CD200 in maintaining immune tolerance to hair follicle associated autoantigens. In this model, it was observed that skin grafts from $CD200^{-/-}$ mice grafted onto syngeneic WT mice developed hair loss with significant perifollicular and intrafollicular inflammation. The

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

effect was localized and did not spread to CD200$^{+/+}$ skin on WT recipients or, surprisingly, to CD200$^{-/-}$ skin on KO recipients, suggesting both graft-localized effects and systemic effects that protected CD200$^{-/-}$ hair follicles outside the graft. Adoptive transfer of alopecia from WT mice that had received CD200$^{-/-}$ grafts to CD200$^{-/-}$ hosts indicated tissue-specific autoimmune mechanisms were involved, but disease was patchy and localized, and in time, normal hair growth in affected areas was restored. The mechanisms of hair follicle destruction were not elucidated, but may be linked to the tissue trauma associated with the grafting procedure. This is consistent with induction of inflammatory alopecia, in both host and graft tissue at the time of grafting, that failed to resolve in the absence of CD200. It was proposed that failure to regulate degranulation of CD200R^{+} skin mast cells responding to injury in CD200$^{-/-}$ tissue may underlie the persistent inflammatory response.33 As well as tissue- localized effects, this study also identified a wider role for CD200 in control of autoreactivity. Similar observations that indicated alternative regulatory responses in the absence of CD200 were also made by the present authors in the EAU model.53

In agreement with other studies in CD200$^{-/-}$ mice, we observed an earlier onset of retinal inflammation compared with WT mice in our model of EAU. We observed prominent expression of NOS2 in the retina at disease onset, consistent with tonic activation of microglia and macrophages.53,86 However, disease incidence and overall severity was actually reduced in CD200$^{-/-}$ mice compared to WT over time. This was unexpected and the reasons for this were not immediately apparent. Analysis of a range of cellular immune responses to lymphoid cell restimulation, with eliciting antigenic peptide, showed no significant differences between immunized CD200$^{-/-}$ mice and WT mice. These assays included proliferation, cytokine secretion, and enumeration of CD3/CD4/CD25^{+} regulatory T cells, but no significant differences were found. We hypothesized that there is redundancy in the regulatory mechanisms controlling potentially damaging inflammation, and in the absence of default and necessary CD200/CD200R signaling, other regulatory mechanisms are invoked during inflammation to convert the classically activated myeloid phenotype to an alternatively activated, healing and immunomodulatory phenotype. Some evidence for this was found in the spleen and lymph nodes of naïve mice, where STAT4 protein levels were significantly lower in CD200$^{-/-}$ mice than in WT, suggesting a constitutive bias away from Th1-cytokine responses in the absence of CD200/CD200R signaling. As Th2 cells also express CD200R, some evidence of elevated Th2 activity in the absence of expressed CD200 ligand might be expected,58 but as yet, the function of Th2-expressed CD200R is unknown, and no difference in STAT6 protein expression was found in naïve mice. However, marked upregulation of STAT6 did occur in spleens and cervical lymph nodes of CD200$^{-/-}$ mice compared to WT when exposed to antigen intranasally in a protocol designed to induce immunological tolerance to that antigen.87,88 The increased expression was highly significant and translated into profound suppression of retinal inflammation when EAU was induced. This was accompanied by suppression of T-cell proliferative responses, elevated levels of IL-4 and IL-5 in response to antigen challenge, significantly elevated numbers of CD3/CD4/CD25^{+} regulatory T cells, and the emergence of IL-10 secreting CD11b^{+} and CD11c^{low} myeloid cells, consistent with induction of immune regulation. Although the Th2 switch in our tolerized CD200$^{-/-}$ was highly significant compared to tolerized WT mice, a direct link between Th2 bias and the generation of immunological nonresponsiveness has not been established, and Th2 responses can also cause pathology.89-91

C. Regulation of Alloimmunity

Successful pregnancy involves establishing and maintaining tolerance to the fetus, and is a physiological state where regulation of alloimmunity is essential. Similar mechanisms are required for maintaining tolerance to grafts in the nonphysiological setting of organ

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

transplantation. Both involve a bias away from Th1 responses towards IL-4, IL-10, and TGF-β production.92-94 The effects of these cytokines often act locally, and a suppressive role for CD200R$^+$ γδ T cells have been implicated in both.95-99 Alloantigen recognition is also essential, inferring a crucial role for antigen-presenting cells. The high rate of spontaneous abortion in the CBA × DBA/2 model can be reduced by preimmunization with cells bearing paternal major and minor histocompatibility antigens,98 and organ graft survival was enhanced following donor-specific cell transfer.99-101 These effects were attributed to enhanced Th2 bias and reduced CTL and NK activity that could be reversed by antibodies to donor-specific antigens. A common rejection mechanism in termination of pregnancy and graft rejection is thrombin activation via Th1-cytokine induction of fibrinogen-like protein (fgl2).102,103 This leads to clotting, activation of neutrophils and endothelium, and blockage of the vasculature.

Thus maintenance of both pregnancy and graft survival requires a balance between pro-rejection and antirejection stimuli. Cytokine bias clearly plays a role, but this is too fragile a mechanism to sustain homeostasis, and represents general rather than specific immunosuppression. Other more robust cell receptor controlled mechanisms involving antigen-presenting cells are predicted to deliver specific signals to T cells generating effective immune tolerance. Several studies have implicated DC in renal allograft survival, and cross talk between CD200 expressing DC and CD200R$^+$ macrophages are hypothesized to be involved.40,68,104 How this interaction causes polarization to Th2- cytokine production and reduces CTL and NK activity is as yet unexplained. The same group105 has shown that bone- marrow-derived DC, incubated with a CD200R(1) mAb inhibited induction of CTL and Th1-type cytokine production in mixed lymphocyte reactions, but this study needs confirmation in controlled experiments utilizing F(ab')$_2$ antibody fragments. Other more recent studies106,107 have also attempted to define mechanisms, but whether the mAbs used were agonists or antagonists was not determined, making interpretation of data difficult.

In the CBA × DBA/2 spontaneous abortion model, infusion of CD200$^+$ BALB/c cells, expressing the same MHC as DBA/2 cells, induces production of protective cytokines. It is presumed that paternal DBA/2 cells express lower levels of the crucial Class I antigen Qa-2 and possibly other as yet unidentified minor antigens. Onset of abortion is gestation day 8.5-9.5 in this model, but infusion of the Balb/c cells as late as gestation day 7.5 can prevent fetal loss. This very short timescale supports the idea that suppression or tolerance induction involves receptor costimulation as well as a permissive cytokine bias. In addition to CD200, the secretory glycoprotein MD-1 is also expressed at the fetal/maternal interface and reciprocal expression of these molecules has been implicated in these alloresponses.108-111 In situ hybridization studies have revealed that CD200 mRNA and MD-1 mRNA are differentially expressed within trophoblast tissue. In untreated mice, approximately 80% of implantation sites expressed CD200, whereas fewer than 50% expressed MD-1. This pattern was reversed when abortion was induced by treatment with TNF and IFN-γ,112 but the link between CD200R and MD-1 signaling and increased or decreased allograft survival was not elucidated in these models.

V. IMMUNOSUPPRESSION AND CD200

From the in vivo models discussed earlier, it would appear that the CD200/CD200R axis has a role in maintaining immunological nonresponsiveness.53,105 Expression by thymocytes and cells in vulnerable tissue locations imply that both central and peripheral tolerance to self-antigens may be regulated, but the antigen specificity of suppressed responses remains to be proven. Central tolerance does not appear to be compromised in the CD200$^{-/-}$ mouse, as there is no evidence that these mice succumb to spontaneous autoimmune disease as

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

observed in other models, but a functional role for CD200 in reinforcing the process of peripheral tolerance has been indicated in two separate systems.

Immune tolerance as a functional consequence of presentation of antigens processed from apoptotic cells by DC has been demonstrated in many systems and is believed to be one of the mechanisms underlying maintenance of peripheral tolerance,113,114 defects leading to T_{reg} failure and autoimmunity.115,116 To date, there is no evidence that the CD200/CD200R axis has a direct role in generating T_{reg}, but in an elegant study, Rosenblum and colleagues have shown that CD200 expression was increased on DC undergoing apoptosis in vivo as well as in vitro. This was attributed to CD200 being a p53 target gene. In addition, a second caspase-dependent pathway that was independent of p53, was also identified for CD200 upregulation, implying an important physiological role for increased CD200 expression by apoptotic cells. Increased CD200 expression diminished proinflammatory cytokine production to self-antigens and was required for induction of tolerance in a contact hypersensitivity model.33,85 The authors hypothesized that upregulation of CD200 may represent a novel mechanism for reinforcing suppression of immune reactivity to self-antigens under steady-state conditions in the absence of other overt tolerizing signals.

A second mechanism may involve tryptophan metabolism by the enzyme indoleamine 2,3-dioxygenase (IDO). Suppression mediated by IDO is very powerful, with a strong bystander effect,117,118 and high levels of IDO expression are associated with inhibition of alloreactivity and T_{reg} function.112,119-125 Various cell types can be induced to express IDO, but myeloid cells, principally DC and in particular plasmacytoid DC, are thought to be involved in IDO-induced tolerance after exposure to IFN-γ and/or TNF or CTLA4.119 Significantly, CD200R ligation using a CD200 Ig fusion protein stimulated plasmacytoid DC to upregulate IDO expression and function, mimicking the effects of B7/CTLA4 signaling.126 The authors therefore hypothesized that the CD200/CD200R axis acts to reinforce the tolerogenic properties of certain DC subsets over the adjuvant activity of immunogenic subsets. Further support for this hypothesis was found in their subsequent studies that showed that CD200R-Ig signaling upregulated IDO via type-1 IFN induction, whereas CTLA-4-Ig induced IDO induction was IFN-γ-dependent, providing an additional or alternative route to IDO expression and regulation.127

Further experiments to determine the role of CD200R in regulating antigen-presenting cell function are required, but the experiments described above certainly suggest a regulatory role. Cytokine bias is clearly affected by CD200R signaling. Recent in vitro studies by Jenmalm et al. now show that CD200R agonists selectively inhibited macrophage cytokine and chemokine secretion induced by IFN-γ and IL-17. CD200R inhibition of IFN-γ-induced cytokine secretion was not universal as macrophages responses to innate activation signals by LPS were unaffected in these studies, suggesting a homeostatic role that could be overridden in the presence of infection.54 The expression of CD200R by polarized Th2 cells is also particularly intriguing.57 As CD200/CD200R signaling can inhibit proinflammatory TNF-α secretion from activated macrophages76 and mast cells,81 it is possible that the switch to anti-inflammatory cytokine secretion is a result of alternative pathways induced through TNF-driven regulatory mechanisms.128 Failure of such regulatory mechanisms could predispose individuals to inflammatory diseases.

VI. CONCLUSIONS

The apparently mild phenotype in the $CD200^{-/-}$ mouse supports the notion that CD200/CD200R interactions are either redundant or part of a more complex signaling system involving other receptor ligand pairs with overlapping or enhancing actions. The constitutive expression of CD200 on specific cell types, and in specific locations indicates that CD200

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

may have a specialized rather than a generalized function, and argues against a redundant function. The distribution of expression, particularly on tissues associated with sites of immune privilege (CNS, trophoblasts, and keratinocyes) and on cells associated with central and peripheral tolerance (thymocytes, plasmacytoid DCs and apoptotic cells), as well as the observation that there are two independent pathways to upregulate CD200 expression in apoptotic cells, is significant and would suggest a role in maintaining immune homeostasis in concert with other signaling events.[85,127]

Barclay has suggested that the interaction between CD200 and CD200R, and that between the thrombospondin receptor (CD47) and SIRP-α (CD172a), represent a new family of receptor pairs that allow the fine tuning of myeloid cell function, possibly by altering the threshold of responses by myeloid cells to activating stimuli such as FcR or complement-mediated phagocytosis.[13] This is an attractive hypothesis, and these elegant biochemical and molecular studies do show that the topology of the CD200/CD200R binding would facilitate molecular interactions within the hypothesized myeloid cell synapse. Functional studies are now required to support this notion, and determine whether the pairs of receptors act independently or in concert to deliver the observed inhibitory effects. Certainly all studies to date confirm that the CD200/CD200R interaction initiates an inhibitory signal to myeloid cells, and there is accumulating evidence that this signal may function as an additional or enhancing inhibitory control on potentially damaging proinflammatory myeloid cell activity in vulnerable tissues. The distribution of CD200 ligand in immune-privileged tissues and in sites exposed to antigen challenge does suggest that CD200/CD200R interactions are involved in reinforcing anti-inflammatory responses at these particular sites.[36] The breadth of downstream effects on both innate and adaptive immune responses from this interaction underline the important physiological consequences of this regulatory activity. In addition, the apparent lack of naturally expressed activating receptors that might bind CD200, particularly in humans, may reflect evolutionary pressure to specifically protect areas of immune privilege. An adaptation that may now be exploited by pathogens.[76,77]

From the evidence published to date, and discussed in this review, we can conclude that the interaction between CD200 and CD200R induces immune suppression. Some studies, particularly in alloantigen models have suggested that the CD200/CD200R axis generates a deviant immune response.[104] Other studies have focused on in vitro models that allow dissection of CD200R signaling at the cellular and molecular level.[54,65,76,81] These studies all indicate that CD200 binding to CD200R directly inhibits cellular activity as originally proposed by Hoek,[43] and the evidence that manipulation of CR200R signaling in mast cells can be used to control degranulation in vivo holds real promise for future therapies for allergies.[81] Given the exclusive nature of CD200 binding to the inhibitory CD200R and what we now know about the wider distribution of both CD200 and CD200R, interpretation of in vivo observations and the many ex vivo cell-mediated experiments described is difficult. Consequently, many of the hypotheses about the mechanisms of the suppression generated from these studies remain speculative. Specificity of reagents and an understanding of how they function as agonists or blocking reagents has been shown to be crucial for understanding the role of this receptor/ligand pair in immune responses. More studies of this type are required to understand the function of CD200R expression by nonmyeloid cells. Studies into the role of CD200 expressed by B cells and follicular dendritic cells are also required to explore the role of the CD200/CD200R axis in humoral immunity.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Acknowledgments

Work in the Authors Lab is supported by The Wellcome Trust, National Eye Research Centre, Tenovus-Scotland and NHS Grampian Endowments. We are grateful to Jon Sedgwick and Andrew Dick for useful discussions and critical reading of the manuscript.

REFERENCES

1. Gordon S. Pattern recognition receptors: doubling up for the innate immune response. Cell. 2002; 111:927–30. [PubMed: 12507420]
2. Hawiger D, Inaba K, Dorsett Y, Guo M, Mahnke K, Rivera M, Ravetch JV, Steinman RM, Nussenzweig MC. Dendritic cells induce peripheral T cell unresponsiveness under steady state conditions in vivo. J Exp Med. 2001; 194:769–79. [PubMed: 11560993]
3. Van Parijs L, Abbas AK. Homeostasis and self-tolerance in the immune system: turning lymphocytes off. Science. 1998; 280:243–48. [PubMed: 9535647]
4. Gordon S. Alternative activation of macrophages. Nat Rev Immunol. 2003; 3:23–35. [PubMed: 12511873]
5. Moore KW, de Waal MR, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol. 2001; 19:683–765. [PubMed: 11244051]
6. O'Garra A, Arai N. The molecular basis of T helper 1 and T helper 2 cell differentiation. Trends Cell Biol. 2000; 10:542–50. [PubMed: 11121747]
7. Nagy ZS, Ross J, Cheng H, Stepkowski SM, Kirken RA. Regulation of lymphoid cell apoptosis by Jaks and Stats. Crit Rev Immunol. 2004; 24:87–110. [PubMed: 15581392]
8. Ravetch JV, Lanier LL. Immune inhibitory receptors. Science. 2000; 290:84–9. [PubMed: 11021804]
9. Taylor PR, Martinez-Pomares L, Stacey M, Lin HH, Brown GD, Gordon S. Macrophage receptors and immune recognition. Annu Rev Immunol. 2005; 23:901–44. [PubMed: 15771589]
10. Lucas M, Daniel L, Tomasello E, Guia S, Horschowski N, Aoki N, Figarrella-Branger D, Gomez S, Vivier E. Massive inflammatory syndrome and lymphocytic immunodeficiency in KARAP/DAP12-transgenic mice. Eur J Immunol. 2002; 32:2653–63. [PubMed: 12207350]
11. Colonna M. TREMs in the immune system and beyond. Nat Rev Immunol. 2003; 3:445–53. [PubMed: 12776204]
12. Oldenborg PA. Role of CD47 in erythroid cells and in autoimmunity. Leuk Lymphoma. 2004; 45:1319–27. [PubMed: 15359629]
13. Barclay AN, Wright GJ, Brooke G, Brown MH. CD200 and membrane protein interactions in the control of myeloid cells. Trends Immunol. 2002; 23:285–90. [PubMed: 12072366]
14. Hamerman JA, Tchao NK, Lowell CA, Lanier LL. Enhanced Toll-like receptor responses in the absence of signaling adaptor DAP12. Nat Immunol. 2005; 6:579–86. [PubMed: 15895090]
15. Kubagawa H, Chen CC, Ho LH, Shimada TS, Gartland L, Mashburn C, Uehara T, Ravetch JV, Cooper MD. Biochemical nature and cellular distribution of the paired immunoglobulin-like receptors, PIR-A and PIR-B. J Exp Med. 1999; 189:309–18. [PubMed: 9892613]
16. Blery M, Kubagawa H, Chen CC, Vely F, Cooper MD, Vivier E. The paired Ig-like receptor PIR-B is an inhibitory receptor that recruits the protein-tyrosine phosphatase SHP-1. Proc Natl Acad Sci U S A. 1998; 95:2446–51. [PubMed: 9482905]
17. Maeda A, Kurosaki M, Kurosaki T. Paired immunoglobulin-like receptor (PIR)-A is involved in activating mast cells through its association with Fc receptor gamma chain. J Exp Med. 1998; 188:991–95. [PubMed: 9730901]
18. Samaridis J, Colonna M. Cloning of novel immunoglobulin superfamily receptors expressed on human myeloid and lymphoid cells: structural evidence for new stimulatory and inhibitory pathways. Eur J Immunol. 1997; 27:660–65. [PubMed: 9079806]
19. Cella M, Dohring C, Samaridis J, Dessing M, Brockhaus M, Lanzavecchia A, Colonna M. A novel inhibitory receptor (ILT3) expressed on monocytes, macrophages, and dendritic cells involved in antigen processing. J Exp Med. 1997; 185:1743–51. [PubMed: 9151699]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

20. Kharitonenkov A, Chen Z, Sures I, Wang H, Schilling J, Ullrich A. A family of proteins that inhibit signalling through tyrosine kinase receptors. Nature. 1997; 386:181–6. [PubMed: 9062191]
21. Dietrich J, Cella M, Seiffert M, Buhring HJ, Colonna M. Cutting edge: signal-regulatory protein beta 1 is a DAP12-associated activating receptor expressed in myeloid cells. J Immunol. 2000; 164:9–12. [PubMed: 10604985]
22. Brown EJ, Frazier WA. Integrin-associated protein (CD47) and its ligands. Trends Cell Biol. 2001; 11:130–5. [PubMed: 11306274]
23. Anderton S, Burkhart C, Metzler B, Wraith D. Mechanisms of central and peripheral T-cell tolerance: lessons from experimental models of multiple sclerosis. Immunol Rev. 1999; 169:123–37. [PubMed: 10450513]
24. Greenwald RJ, Boussiotis VA, Lorsbach RB, Abbas AK, Sharpe AH. CTLA-4 regulates induction of anergy in vivo. Immunity. 2001; 14:145–55. [PubMed: 11239447]
25. Stout RD, Jiang C, Matta B, Tietzel I, Watkins SK, Suttles J. Macrophages sequentially change their functional phenotype in response to changes in microenvironmental influences. J Immunol. 2005; 175:342–49. [PubMed: 15972667]
26. Stout RD, Suttles J. T cell signaling of macrophage function in inflammatory disease. Front Biosci. 1997; 2:197–206. [PubMed: 9206987]
27. Barclay AN, Ward HA. Purification and chemical characterisation of membrane glycoproteins from rat thymocytes and brain, recognised by monoclonal antibody MRC OX 2. Eur J Biochem. 1982; 129:447–58. [PubMed: 6129975]
28. McMaster WR, Williams AF. Monoclonal antibodies to Ia antigens from rat thymus: cross reactions with mouse and human and use in purification of rat Ia glycoproteins. Immunol Rev. 1979; 47:117–37. [PubMed: 398324]
29. Webb M, Barclay AN. Localisation of the MRC OX-2 glycoprotein on the surfaces of neurones. J Neurochem. 1984; 43:1061–7. [PubMed: 6147390]
30. Dick AD, Broderick C, Forrester JV, Wright GJ. Distribution of OX2 antigen and OX2 receptor within retina. Invest Ophthalmol Vis Sci. 2001; 42:170–6. [PubMed: 11133863]
31. Bukovsky A, Presl J, Zidovsky J. Association of some cell surface antigens of lymphoid cells and cell surface differentiation antigens with early rat pregnancy. Immunology. 1984; 52:631–40. [PubMed: 6146566]
32. Wright GJ, Jones M, Puklavec MJ, Brown MH, Barclay AN. The unusual distribution of the neuronal/lymphoid cell surface CD200 (OX2) glycoprotein is conserved in humans. Immunology. 2001; 102:173–9. [PubMed: 11260322]
33. Rosenblum MD, Olasz EB, Yancey KB, Woodliff JE, Lazarova Z, Gerber KA, et al. Expression of CD200 on epithelial cells of the murine hair follicle: a role in tissue-specific immune tolerance? J Invest Dermatol. 2004; 123(5):880–7. [PubMed: 15482475]
34. Williams AF, Gagnon J. Neuronal cell Thy-1 glycoprotein: homology with immunoglobulin. Science. 1982; 216:696–703. [PubMed: 6177036]
35. Clark MJ, Gagnon J, Williams AF, Barclay AN. MRC OX-2 antigen: a lymphoid/neuronal membrane glycoprotein with a structure like a single immunoglobulin light chain. EMBO J. 1985; 4:113–18. [PubMed: 2862025]
36. Preston S, Wright GJ, Starr K, Barclay AN, Brown MH. The leukocyte/neuron cell surface antigen OX2 binds to a ligand on macrophages. Eur J Immunol. 1997; 27:1911–8. [PubMed: 9295026]
37. Wright GJ, Puklavec MJ, Willis AC, Hoek RM, Sedgwick JD, Brown MH, Barclay AN. Lymphoid/neuronal cell surface OX2 glycoprotein recognizes a novel receptor on macrophages implicated in the control of their function. Immunity. 2000; 13:233–42. [PubMed: 10981966]
38. Borriello F, Tizard R, Rue E, Reeves R. Characterization and localization of Mox2, the gene encoding the murine homolog of the rat MRC OX-2 membrane glycoprotein. Mamm Genome. 1998; 9:114–8. [PubMed: 9457671]
39. Gaglia JL, Mattoo A, Greenfield EA, Freeman GJ, Kuchroo VK. Characterization of endogenous Chinese hamster ovary cell surface molecules that mediate T cell costimulation. Cell Immunol. 2001; 213:83–93. [PubMed: 11831870]

Europe PMC Funders Author Manuscripts

40. Gorczynski RM, Chen Z, Fu XM, Zeng H. Increased expression of the novel molecule OX-2 is involved in prolongation of murine renal allograft survival. Transplantation. 1998; 65:1106–14. [PubMed: 9583873]
41. Gorczynski RM, Cattral MS, Chen Z, Hu J, Lei J, Min WP, Yu G, Ni J. An immunoadhesin incorporating the molecule OX-2 is a potent immunosuppressant that prolongs allo- and xenograft survival. J Immunol. 1999; 163:1654–60. [PubMed: 10415071]
42. Gorczynski RM, Chen Z, Kai Y, Lei J. Evidence for persistent expression of OX2 as a necessary component of prolonged renal allograft survival following portal vein immunization. Clin Immunol. 2000; 97:69–78. [PubMed: 10998319]
43. Hoek RM, Ruuls SR, Murphy CA, Wright GJ, Goddard R, Zurawski SM, Blom B, Homola ME, Streit WJ, Brown MH, Barclay AN, Sedgwick JD. Down-regulation of the macrophage lineage through interaction with OX2 (CD200). Science. 2000; 290:1768–71. [PubMed: 11099416]
44. Hume DA, Ross IL, Himes SR, Sasmono RT, Wells CA, Ravasi T. The mononuclear phagocyte system revisited. J Leukoc Biol. 2002; 72:621–7. [PubMed: 12377929]
45. Kraal G, Janse M. Marginal metallophilic cells of the mouse spleen identified by a monoclonal antibody. Immunology. 1986; 58:665–9. [PubMed: 3733156]
46. Lanier LL, Bakker AB. The ITAM-bearing transmembrane adaptor DAP12 in lymphoid and myeloid cell function. Immunol Today. 2000; 21:611–4. [PubMed: 11114420]
47. Tomasello E, Olcese L, Vely F, Geourgeon C, Blery M, Moqrich A, Gautheret D, Djabali M, Mattei MG, Vivier E. Gene structure, expression pattern, and biological activity of mouse killer cell activating receptor-associated protein (KARAP)/DAP-12. J Biol Chem. 1998; 273:34115–9. [PubMed: 9852069]
48. Tomasello E, Cant C, Buhring HJ, Vely F, Andre P, Seiffert M, Ullrich A, Vivier E. Association of signal-regulatory proteins beta with KARAP/DAP-12. Eur J Immunol. 2000; 30:2147–56. [PubMed: 10940905]
49. Preston S, Wright GJ, Starr K, Barclay AN, Brown MH. The leukocyte/neuron cell surface antigen OX2 binds to a ligand on macrophages. Eur J Immunol. 1997; 27:1911–8. [PubMed: 9295026]
50. Graeber MB, Lopez-Redondo F, Ikoma E, Ishikawa M, Imai Y, Nakajima K, Kreutzberg GW, Kohsaka S. The microglia/macrophage response in the neonatal rat facial nucleus following axotomy. Brain Res. 1998; 813:241–53. [PubMed: 9838143]
51. Bakker AB, Hoek RM, Cerwenka A, Blom B, Lucian L, McNeil T, Murray R, Phillips LH, Sedgwick JD, Lanier LL. DAP12-deficient mice fail to develop autoimmunity due to impaired antigen priming. Immunity. 2000; 13:345–53. [PubMed: 11021532]
52. Campbell IK, Hamilton JA, Wicks IP. Collagen-induced arthritis in C57BL/6 (H-2b) mice: new insights into an important disease model of rheumatoid arthritis. Eur J Immunol. 2000; 30:1568–75. [PubMed: 10898492]
53. Taylor N, McConachie K, Calder C, Dawson R, Dick A, Sedgwick JD, Liversidge J. Enhanced tolerance to autoimmune uveitis in CD200-deficient mice correlates with a pronounced Th2 switch in response to antigen challenge. J Immunol. 2005; 174:143–54. [PubMed: 15611236]
54. Jenmalm MC, Cherwinski H, Bowman EP, Phillips J, Sedgwick JD. Regulation of myeloid cell function through the CD200 receptor. J Immunol. 2006; 176:191–9. [PubMed: 16365410]
55. Robertson M, Erwig LP, Liversidge J, Forrester JV, Rees AJ, Dick AD. Retinal micro-environment determines both resident and infiltrating macrophage function during experimental autoimmune uveoretinitis (EAU). Invest Ophthalmol Vis Sci. 2002; 44:3034–41. [PubMed: 12824249]
56. Broderick C, Hoek RM, Forrester JV, Liversidge J, Sedgwick J, Dick AD. Constitutive retinal CD200 expression regulates resident microglia and activation state of inflammatory cells during experimental autoimmune uveoretinitis. Am.J Pathol. 2002; 161:1669–77. [PubMed: 12414514]
57. Carter DA, Dick AD. CD200 maintains microglial potential to migrate in adult human retinal explant model. Curr Eye Res. 2004; 28:427–36. [PubMed: 15512951]
58. Wright GJ, Cherwinski H, Foster-Cuevas M, Brooke G, Puklavec MJ, Bigler M, Song Y, Jenmalm M, Gorman D, McClanahan T, Liu MR, Brown MH, Sedgwick JD, Phillips JH, Barclay AN. Characterization of the CD200 receptor family in mice and humans and their interactions with CD200. J Immunol. 2003; 171:3034–46. [PubMed: 12960329]

Europe PMC Funders Author Manuscripts
Europe PMC Funders Author Manuscripts

59. Gorczynski RM, Chen Z, Clark DA, Kai Y, Lee L, Nachman J, Wong S, Marsden P. Structural and functional heterogeneity in the CD200R family of immunoregulatory molecules and their expression at the feto-maternal interface. Am J Reprod Immunol. 2004; 52:147–63. [PubMed: 15274657]
60. Gorczynski R, Chen Z, Lee L, Wong S, Marsden PA. CD200 is a ligand for all members of the CD200R family of immunoregulatory molecules. J Immunol. 2004; 172:7744–9. Kai (2 Y. [PubMed: 15187158]
61. Hatherley D, Cherwinski HM, Moshref M, Barclay AN. Recombinant CD200 protein does not bind activating proteins closely related to CD200 receptor. J Immunol. 2005; 175:2469–74. [PubMed: 16081818]
62. Vieites JM, de la TR, Ortega MA, Montero T, Peco JM, Sanchez-Pozo A, Gil A, Suarez A. Characterization of human cd200 glycoprotein receptor gene located on chromosome 3q12-13. Gene. 2003; 311:99–104. [PubMed: 12853143]
63. van der Merwe PA, Barclay AN. Analysis of cell-adhesion molecule interactions using surface plasmon resonance. Curr Opin Immunol. 1996; 8:257–61. [PubMed: 8725949]
64. van der Merwe PA, Brown MH, Davis SJ, Barclay AN. Measuring very low affinity interactions between immunoglobulin superfamily cell-adhesion molecules. Biochem Soc Trans. 1993; 21:340S. [PubMed: 7907555]
65. Zhang S, Cherwinski H, Sedgwick JD, Phillips JH. Molecular mechanisms of CD200 inhibition of mast cell activation. J Immunol. 2004; 173:6786–93. [PubMed: 15557172]
66. Hatherley D, Barclay AN. The CD200 and CD200 receptor cell surface proteins interact through their N-terminal immunoglobulin-like domains. Eur J Immunol. 2004; 34:1688–94. [PubMed: 15162439]
67. Chen DX, He H, Gorczynski RM. Synthetic peptides from the N-terminal regions of CD200 and CD200R1 modulate immunosuppressive and anti-inflammatory effects of CD200-CD200R1 interaction. Int Immunol. 2005; 17:289–96. [PubMed: 15684038]
68. Gorczynski RM. Transplant tolerance modifying antibody to CD200 receptor, but not CD200, alters cytokine production profile from stimulated macrophages. Eur J Immunol. 2001; 31:2331–7. [PubMed: 11477545]
69. Voehringer D, Rosen DB, Lanier LL, Locksley RM. CD200 receptor family members represent novel DAP12-associated activating receptors on basophils and mast cells. J Biol Chem. 2004; 279:54117–23. [PubMed: 15471863]
70. Long EO. Regulation of immune responses through inhibitory receptors. Annu Rev Immunol. 1999; 17:875–904. [PubMed: 10358776]
71. Veillette A, Latour S, Davidson D. Negative regulation of immunoreceptor signaling. Annu Rev Immunol. 2002; 20:669–707. [PubMed: 11861615]
72. Seiffert M, Brossart P, Cant C, Cella M, Colonna M, Brugger W, Kanz L, Ullrich A, Buhring HJ. Signal-regulatory protein alpha (SIRPalpha) but not SIRPbeta is involved in T-cell activation, binds to CD47 with high affinity, and is expressed on immature CD34(+) CD38(-) hematopoietic cells. Blood. 2001; 97:2741–9. [PubMed: 11313266]
73. Barclay, AN.; Birkeland, ML.; Brown, MH.; Beyers, AD.; Davis, SJ.; Somoza, C.; Williams, AF. Leukocyte antigens factsbook. London: Academic Press; 2005.
74. Barclay AN. Membrane proteins with immunoglobulin-like domains—a master superfamily of interaction molecules. Semin Immunol. 2003; 15:215–23. [PubMed: 14690046]
75. Williams AF, Barclay AN. The immunoglobulin superfamily—domains for cell surface recognition. Annu Rev Immunol. 1988; 6:381–405. [PubMed: 3289571]
76. Foster-Cuevas M, Wright GJ, Puklavec MJ, Brown MH, Barclay AN. Human herpesvirus 8 K14 protein mimics CD200 in down-regulating macrophage activation through CD200 receptor. J Virol. 2004; 78:7667–76. [PubMed: 15220441]
77. Shiratori I, Yamaguchi M, Suzukawa M, Yamamoto K, Lanier LL, Saito T, Arase H. Down-regulation of basophil function by human CD200 and human herpesvirus-8 CD200. J Immunol. 2005; 175:4441–9. [PubMed: 16177086]

78. Cameron CM, Barrett JW, Liu L, Lucas AR, McFadden G. Myxoma virus M141R expresses a viral CD200 (vOX-2) that is responsible for down-regulation of macrophage and T-cell activation in vivo. J Virol. 2005; 79:6052–67. [PubMed: 15857991]
79. Arase H, Mocarski ES, Campbell AE, Hill AB, Lanier LL. Direct recognition of cytomegalovirus by activating and inhibitory NK cell receptors. Science. 2002; 296:1323–6. [PubMed: 11950999]
80. Gorczynski RM, Yu K, Clark D. Receptor engagement on cells expressing a ligand for the tolerance-inducing molecule OX2 induces an immunoregulatory population that inhibits alloreactivity In vitro and In vivo [In Process Citation]. J Immunol. 2000; 165:4854–60. [PubMed: 11046009]
81. Cherwinski HM, Murphy CA, Joyce BL, Bigler ME, Song YS, Zurawski SM, Moshrefi MM, Gorman DM, Miller KL, Zhang S, Sedgwick JD, Phillips JH. The CD200 receptor is a novel and potent regulator of murine and human mast cell function. J Immunol. 2005; 174:1348–56. [PubMed: 15661892]
82. Galli SJ, Kalesnikoff J, Grimbaldeston MA, Piliponsky AM, Williams CM, Tsai M. Mast cells as “tunable” effector and immunoregulatory cells: recent advances. Annu Rev Immunol. 2005; 23:749–86. [PubMed: 15771585]
83. Banerjee D, Dick AD. Blocking CD200-CD200 receptor axis augments NOS-2 expression and aggravates experimental autoimmune uveoretinitis in Lewis rats. Ocul Immunol Inflamm. 2004; 12:115–25. [PubMed: 15512981]
84. Gorczynski RM, Chen Z, Lee L, Yu K, Hu J. Anti-CD200R ameliorates collagen-induced arthritis in mice. Clin Immunol. 2002; 104:256–64. [PubMed: 12217336]
85. Rosenblum MD, Olasz E, Woodliff JE, Johnson BD, Konkol MC, Gerber KA, Truitt RL. CD200 is a novel p53-target gene involved in apoptosis-associated immune tolerance. Blood. 2004; 103:2691–8. [PubMed: 14644999]
86. Dick A, Broderick C, Forrester JV, Liversidge J, Hoek R, Sedgwick J. CD200 regulation of myeloid cell activation and distribution during experimental autoimmune uveoretinitis. J Neuroimmunol. 2001; 118:27.
87. Dick AD, Cheng YF, Liversidge J, Forrester JV. Intranasal administration of retinal antigens suppresses retinal antigen-induced experimental autoimmune uveoretinitis. Immunology. 1994; 82:625–31. [PubMed: 7835927]
88. Dick AD, Sharma V, Liversidge J. Single dose intranasal administration of retinal autoantigen generates a rapid accumulation and cell activation in draining lymph node and spleen: implications for tolerance therapy. Br J Ophthalmol. 2001; 85:1001–6. [PubMed: 11466262]
89. Chang HC, Zhang S, Kaplan MH. Neonatal tolerance in the absence of Stat4- and Stat6-dependent Th cell differentiation. J Immunol. 2002; 169:4124–8. [PubMed: 12370340]
90. Nakamura T, Terajewicz A, Stein-Streilein J. Mechanisms of peripheral tolerance following intracameral inoculation are independent of IL-13 or STAT6. J Immunol. 2005; 175:2643–6. [PubMed: 16081840]
91. Grunig G, Banz A, de Waal MR. Molecular regulation of Th2 immunity by dendritic cells. Pharmacol Ther. 2005; 106:75–96. [PubMed: 15781123]
92. Shurin MR, Lu L, Kalinski P, Stewart-Akers AM, Lotze MT. Th1/Th2 balance in cancer, transplantation and pregnancy. Springer Semin Immunopathol. 1999; 21:339–59. [PubMed: 10666777]
93. Dallman MJ. Cytokines and transplantation: Th1/Th2 regulation of the immune response to solid organ transplants in the adult. Curr Opin Immunol. 1995; 7:632–8. [PubMed: 8573305]
94. Li XC, Zand MS, Li Y, Zheng XX, Strom TB. On histocompatibility barriers, Th1 to Th2 immune deviation, and the nature of the allograft responses. J Immunol. 1998; 161:2241–7. [PubMed: 9725217]
95. Gorczynski RM, Chen Z, Fu XM, Levy G, Cohen Z. Gamma delta TCR+ cells regulate rejection of small intestinal allografts in rats. Transplant Proc. 1997; 29:863–4. [PubMed: 9123557]
96. Mincheva-Nilsson L. Pregnancy and gamma/delta T cells: taking on the hard questions. Reprod Biol Endocrinol. 2003; 1:120. [PubMed: 14651751]
97. Imamura M, Tanaka J. Immunoregulatory cells for transplantation tolerance and graft-versus-leukemia effect. Int J Hematol. 2003; 78:188–94. [PubMed: 14604276]

Europe PMC Funders Author Manuscripts
Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

98. Clark DA. Hard science versus phenomenology in reproductive immunology. Crit Rev Immunol. 1999; 19:509–39. [PubMed: 10647748]

99. Starzl TE, Rao AS, Thomson AW, Murase N, Demetris AJ. Donor-recipient microchimerism and tolerance induction. Transplantation. 1996; 61:169–72. [PubMed: 8560563]

100. Chung SW, Yoshida EM, Cattral MS, Hu Y, Gorczynski RM. Donor-specific stimulation of peripheral blood mononuclear cells from recipients of orthotopic liver transplants is associated, in the absence of rejection, with type-2 cytokine production. Immunol Lett. 1998; 63:91–6. [PubMed: 9761370]

101. Koga S, Luke PP, Specht SM, Rominski B, Jaquins-Gerstl A, Hoffman RA, Thomson AW, Jordan ML. Inhibition of the allograft response by donor specific blood transfusion: association with reduced local TH1 cytokines and nitric oxide but enhanced prostaglandin E2 production. Transplantation. 2000; 70:1788–96. [PubMed: 11152112]

102. Ghanekar A, Mendicino M, Liu H, He W, Liu M, Zhong R, Phillips MJ, Levy GA, Grant DR. Endothelial induction of fgl2 contributes to thrombosis during acute vascular xenograft rejection. J Immunol. 2004; 172:5693–701. [PubMed: 15100314]

103. Clark DA, Chaouat G, Arck PC, Mittruecker HW, Levy GA. Cytokine-dependent abortion in CBA × DBA/2 mice is mediated by the procoagulant fgl2 prothrombinase. J Immunol. 1998; 160:545–9. [PubMed: 9551885]

104. Gorczynski RM, Yu K, Clark D. Receptor engagement on cells expressing a ligand for the tolerance-inducing molecule OX2 induces an immunoregulatory population that inhibits alloreactivity in vitro and in vivo. J Immunol. 2000; 165:4854–60. [PubMed: 11046009]

105. Gorczynski RM, Chen Z, Kai Y, Wong S, Lee L. Induction of tolerance-inducing antigen-presenting cells in bone marrow cultures in vitro using monoclonal antibodies to CD200R. Transplantation. 2004; 77:1138–44. [PubMed: 15114074]

106. Yu K, Chen Z, Wang S, Gorczynski R. Decreased alloreactivity using donor cells from mice expressing a CD200 transgene under control of a tetracycline-inducible promoter. Transplantation. 2005; 80:394–401. [PubMed: 16082336]

107. Gorczynski RM, Lee L, Boudakov I. Augmented induction of CD4+CD25+ Treg using monoclonal antibodies to CD200R. Transplantation. 2005; 79:1180–3. [PubMed: 15880066]

108. Clark DA, Yu G, Arck PC, Levy GA, Gorczynski RM. MD-1 is a critical part of the mechanism causing Th1-cytokine-triggered murine fetal loss syndrome. Am J Reprod Immunol. 2003; 49:297–307. [PubMed: 12854734]

109. Gorczynski RM, Chen Z, Clark DA, Hu J, Yu G, Li X, Tsang W, Hadidi S. Regulation of gene expression of murine MD-1 regulates subsequent T cell activation and cytokine production. J Immunol. 2000; 165:1925–32. [PubMed: 10925274]

110. Hadidi S, Gorczynski RM. MD-1 expression regulates direct and indirect allorecognition. Tissue Antigens. 2004; 63:132–41. [PubMed: 14705984]

111. Zhang X, Chen BC, Xiang FL, Chang S, Zhou HM, Du DF, Yuan J, Chen ZK. Inhibition of MD-1 expression by immunosuppressants or antisense oligodeoxynucleotides on skin allograft survival in mice. Transplant Proc. 2005; 37:1965–7. [PubMed: 15919519]

112. Gorczynski RM, Hadidi S, Yu G, Clark DA. The same immunoregulatory molecules contribute to successful pregnancy and transplantation. Am J Reprod Immunol. 2002; 48:18–26. [PubMed: 12322892]

113. Steinman RM, Turley S, Mellman I, Inaba K. The induction of tolerance by dendritic cells that have captured apoptotic cells. J Exp Med. 2000; 191:411–16. [PubMed: 10662786]

114. Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. Annu Rev Immunol. 2003; 21:685–711. [PubMed: 12615891]

115. Mahoney JA, Rosen A. Apoptosis and autoimmunity. Curr Opin Immunol. 2005; 17:583–8. [PubMed: 16214321]

116. Seddon B, Mason D. Peripheral autoantigen induces regulatory T cells that prevent autoimmunity. J Exp Med. 1999; 189:877–82. [PubMed: 10049952]

117. Munn DH, Sharma MD, Hou D, Baban B, Lee JR, Antonia SJ, Messina JL, Chandler P, Koni PA, Mellor AL. Expression of indoleamine 2,3-dioxygenase by plasmacytoid dendritic cells in tumor-draining lymph nodes. J Clin Invest. 2004; 114:280–90. [PubMed: 15254595]

Europe PMC Funders Author Manuscripts

118. Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. Nat Rev Immunol. 2004; 4:762–74. [PubMed: 15459668]

119. Grohmann U, Bianchi R, Orabona C, Fallarino F, Vacca C, Micheletti A, Fioretti MC, Puccetti P. Functional plasticity of dendritic cell subsets as mediated by CD40 versus B7 activation. J Immunol. 2003; 171:2581–7. [PubMed: 12928409]

120. Grohmann U, Fallarino F, Bianchi R, Belladonna ML, Vacca C, Orabona C, Uyttenhove C, Fioretti MC, Puccetti P. IL-6 inhibits the tolerogenic function of CD8 alpha+ dendritic cells expressing indoleamine 2,3-dioxygenase. J Immunol. 2001; 167:708–14. [PubMed: 11441074]

121. Mellor AL, Baban B, Chandler P, Marshall B, Jhaver K, Hansen A, Koni PA, Iwashima M, Munn DH. Cutting edge: induced indoleamine 2,3 dioxygenase expression in dendritic cell subsets suppresses T cell clonal expansion. J Immunol. 2003; 171:1652–5. [PubMed: 12902462]

122. Bauer TM, Jiga LP, Chuang JJ, Randazzo M, Opelz G, Terness P. Studying the immunosuppressive role of indoleamine 2,3-dioxygenase: tryptophan metabolites suppress rat allogeneic T-cell responses in vitro and in vivo. Transpl Int. 2005; 18:95–100. [PubMed: 15612990]

123. Bozza S, Fallarino F, Pitzurra L, Zelante T, Montagnoli C, Bellocchio S, Mosci P, Vacca C, Puccetti P, Mellor AL. A crucial role for tryptophan catabolism at the host/Candida albicans interface. J Immunol. 2005; 174:2910–8. [PubMed: 15728502]

124. Funeshima N, Fujino M, Kitazawa Y, Hara Y, Hara Y, Hayakawa K, et al. Inhibition of allogeneic T-cell responses by dendritic cells expressing transduced indoleamine 2,3-dioxygenase. J Gene Med. 2005; 7:565–75. [PubMed: 15543532]

125. Munn DH, Zhou M, Attwood JT, Bondarev I, Conway SJ, Marshall B, Brown B, Mellor AL. Prevention of allogeneic fetal rejection by tryptophan catabolism. Science. 1998; 281:1191–3. [PubMed: 9712583]

126. Fallarino F, Asselin-Paturel C, Vacca C, Bianchi R, Gizzi S, Fioretti MC, Trinchieri G, Grohmann U, Puccetti P. Murine plasmacytoid dendritic cells initiate the immunosuppressive pathway of tryptophan catabolism in response to CD200 receptor engagement. J Immunol. 2004; 173:3748–54. [PubMed: 15356121]

127. Fallarino F, Orabona C, Vacca C, Bianchi R, Gizzi S, Asselin-Paturel, Fioretti MC, Trinchieri G, Grohmann U, Puccetti P. Ligand and cytokine dependence of the immunosuppressive pathway of tryptophan catabol ism in plasmacytoid dendritic cells. Int Immunol. 2005; 17:1429–38. [PubMed: 16172135]

128. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). Prog Retin Eye Res. 2004; 23:617–37. [PubMed: 15388077]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

TABLE 1

CD200 KO Disease Model	Refs.
Experimental autoimmune encephalitis	42
Collagen-induced arthritis	42
Experimental autoimmune uveoretinitis	52, 55
Alopoecia	32
Contact hypersensitivity	85
Skin grafts	32
Facial nerve transection	42