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Analysis of the Impact of CD200 on Neurodegenerative Diseases

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1. Introduction

Neuroinflammation, accompanied by neuronal loss and dysfunction, is a characteristic of neurodegenerative disorders like Alzheimer's disease (AD) and Parkinson's disease (PD). It is well documented that inappropriate activation of glia is the primary cause of neuroinflammation (Masocha, 2009), but their role in the pathogenesis of neurodegenerative diseases is not known. However it is certainly the case that dying neurons act to stimulate glia since they release alarmins which activate pathogen recognition receptors (PRR) and therefore the possibility exists that activation of glia especially microglia, may be a consequence, rather than a cause, of neurodegenerative processes which characterize diseases like AD and PD. Understanding microglial function remains a major goal since it is widely believed that modulating glial function will provide a possible strategy for limiting the progression of neurodegenerative diseases. Consequently it is imperative to increase our understanding of the factors which control microglial function and the mechanisms by which expression of these factors are controlled.

2. Microglia adopt different activation states

Secreted factors including neurotrophins and growth factors like transforming growth factor (TGF)-β, as well as anti-inflammatory cytokines, impact on microglial activation and help to maintain these cells in a relatively quiescent state. Similarly, the interaction of microglia with other cells affects their activation state. However the recognition that macrophages, the peripheral cells which are derived from the same myeloid precursors as microglia, adopt different activation states has led to the acknowledgement that microglia can also adopt different activation states (Gordon, 2003). As the primary immune cells in the brain, microglia express PRR and therefore pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) interact with these receptors and trigger the innate immune response (Blasko et al., 2004, Koenigsknecht and Landreth, 2004). Microglia, like macrophages, are activated by the secreted proinflammatory cytokine, interferon-γ (IFNγ) inducing classical activation, and by the anti-inflammatory cytokines interleukin (IL)-4 and IL-13 to induce the alternative activation state (Gordon, 2003). Humoral activation of microglia, involving the complement system has also been described

(Griffiths et al., 2010). In addition to the modulatory effect of secreted factors like pro- and anti-inflammatory cytokines and factors like TGFβ, a deactivation/suppression state of microglia has been described, and this state is controlled by neuroimmunoregulatory proteins (NIRegs).

2.1 Neuroimmunoregulatory proteins modulate microglial activation

NIRegs act on specific receptors expressed on microglia and ensure that cell activation is checked. These NIRegs include CD200, CD22, CD47, semaphorin and fractalkine which interact with CD200R, CD45, SIRPα, plexin B1 or CD72, and fractalkine receptor respectively. In most of these cases, expression of the receptors is relatively restricted to cells of the myeloid lineage, whereas expression of the ligands is more widespread.

CD47 is a membrane glycoprotein and a member of the immunoglobulin superfamily. It is expressed on neurons and endothelial cells and its expression on macrophages has also been reported (Reinhold et al., 1995). CD47 is a 'don't eat me' signal and circulating cells lacking CD47 are rapidly cleared. Activation of SIRPα by CD47 leads to activation of an inhibitory signal as a consequence of the interaction between tyrosine phosphatases SHP-1 and SHP2 with cytoplasmic tyrosine-linked inhibition motifs (Hatherley et al., 2009). SIRPα, and another receptor for CD47, thrombospondin, are expressed on microglia, although SIRPα is also expressed on neurons (Brown and Frazier, 2001; Lamy et al., 2007).

CD45 is expressed on microglia, albeit at low levels when cells are unstimulated, contrasting with the higher expression on macrophages. It is a transmembrane protein tyrosine phosphatase which has been identified as a negative regulator of microglial activation (Tan et al., 2000). It has been known for 20 years that CD22 is a ligand for CD45 (Stamenkovic et al., 1991), but the fact that CD22 is expressed on neurons, and also released from neurons, has been established only relatively recently (Mott et al., 2004). These authors identified a role for CD22 in modulating tumour necrosis factor (TNF)-α release from microglia.

Fractalkine (also known as CX_3CL1) is the only member of the CX_3C subfamily of chemokines (Bazan et al., 1997). In the brain, it is expressed mainly on neurons (Harrison et al., 1998, Maciejewski-Lenoir et al., 1999), whereas its receptor is expressed chiefly on microglial cells (Harrison et al., 1998). However this expression pattern is probably not exclusive with evidence indicating that the ligand is expressed on glia (Maciejewski-Lenoir et al., 1999) and the receptor is expressed on neurons (Hughes et al., 2002). The engagement of fractalkine with its receptor decreases microglial activation and inhibits lipopolysaccharide (LPS)-induced proinflammatory cytokine production (Zujovic et al., 2000; Lyons et al., 2009a). Evidence from this laboratory suggested that fractalkine expression was decreased in hippocampal tissue prepared from aged rats in which microglial activation is upregulated, and that the combination of these changes was coupled with a deficit in neuronal plasticity (Lyons et al., 2009a).

Although they were originally identified because of their importance as axon guidance molecules, an immunoregulatory role for some semaphorins has been described (Suzuki et al., 2008). SEMA4D (also referred to as CD100), a transmembrane protein which belongs to class 4 group of the semaphorin family, has been the focus of the studies designed to understand this immunomodulatory role. It is expressed on neurons, though not on microglia (Hirsch et al., 1999), whereas the 2 major receptors for SEMA4D, plexin B1 and CD72 are expressed on microglia (Toguchi et al., 2009). Soluble Sema4D inhibits LPS-induced microglial activation as assessed by a change in cell morphology, nitric oxide (NO) production and cell migration (Toguchi et al., 2009). It also prevents migration of monocytes

as a consequence of its interaction with plexin B1 (Chabbert-de Ponnat et al., 2005). However, in complete contrast to these findings, a Sema4D fusion protein has been reported to increase NO production in microglia and this was abolished in cells prepared from plexin B1-deficient mice (Okuno et al., 2010). The possible role of SEMA4D as a regulator of microglial function requires further examination.

3. CD200 and CD200R

3.1 Expression of CD200 and its receptor

Interest in understanding the roles of the NIRegs identified above has been increasing in the past few years and, to date, most emphasis has been placed on evaluating the role of the interaction between CD200 and its receptor on microglial activation. This interaction is recognized as a potent immune suppressor and therefore it is predicted that reduced inhibitory input from CD200 results in dysregulation of microglial function and the risk of inappropriate cellular activation and tissue damage.

CD200, previously known as OX2, is a 41-47 kDa type-1 cell surface glycoprotein with two immunoglobulin domains arranged in a typical V-/C2 set (Clark et al., 1985). The family of IgSF glycoproteins to which CD200 belongs includes neural cell adhesion molecule (NCAM), Thy-1 and L1, which are expressed on both lymphoid tissue and also neuronal tissue; CD200 was originally identified in the thymus and brain (Barclay, 1981) and thereafter in several tissues, and cells including neurons, T cells and astrocytes (Webb and Barclay, 1984, Preston et al., 1997, Wright et al., 2000). Expression of CD200 on vascular endothelium has been described with evidence of more intense staining on veins and venules rather than arteries, although staining in arteries was increased following injection with LPS. Distribution of CD200 in capillaries appears to be tissue-dependent and varies with the type of capillary; thus intense immunoreactivity is observed in continuous endothelia (both fenestrated and non-fenestrated) compared with relatively lower expression on discontinuous endothelia. Interestingly it has been shown that an anti-CD200 antibody blocked the adhesion of T cells to endothelial cells but did not affect the adhesion of macrophages; thus it was suggested that, whereas the primary role of the interaction between CD200 and its receptor may be to reduce activity of macrophages, a second role may be to modulate adhesion and migration of T cells into tissues (Ko et al., 2009). CD200 expression has also been examined on endothelial cells in the brain and it has been reported that expression in the hippocampus was evident only on the luminal surface of endothelial cells that made up the blood brain barrier (BBB), whereas in the area postrema, which lacks a BBB, clear staining was observed on the luminal and abluminal surfaces (Ko et al., 2009).

CD200 expression in brain tissue was found to be widespread with stronger staining in grey matter compared with white matter (Webb and Barclay, 1984). Immunostaining has been reported in the spinal cord, cerebellum and striatum, as well as the hippocampus and parietal cortex, and the evidence suggested that while it was expressed on the cell membrane in most brain areas, there was evidence of CD200 staining in the cytosol in hippocampal neurons. In the spinal cord, axons were CD200-positive whereas myelin did not stain for CD200 (Koning et al., 2009).

CD200 receptor (CD200R), CD200's cognate receptor is also a glycoprotein and, like the ligand, it contains two IgSF domains in a V/C2 set arrangement and cysteine residues in their V-like domains. To date, 5 CD200R family members (R1-R5) have been identified in mice (Gorczynski et al., 2008). The most studied receptor, CD200R1, is expressed primarily

on myeloid lineage cells such as microglia and macrophages (Meuth et al., 2008, Masocha, 2009) and also monocytes, granulocytes and dendritic cells (DC) (Wright et al., 2000, Wright et al., 2003). More recent flow cytometry data suggest that CD200R is also expressed on natural killer cells and B cells, as well as on CD4+ T cells which had been reported previously (Wright et al., 2003, Rijkers et al., 2008). It was suggested that CD200 is the natural ligand for only CD200R1 (Wright et al., 2003) although others suggest that this may not be the case (Gorczynski et al., 2004).

3.2 The signaling events induced by CD200R activation

Most inhibitory receptors contain immunoreceptor tyrosine-based inhibitory motifs (ITIM) which enables cell signalling through recruitment of Src homology 2 domain containing phosphatases (SHP), or SHIP, which is an inositol phosphataseSH2-containing inositol phosphatase (SHIP). This is not the case with CD200R; instead, CD200R has a long cytoplasmic tail of 67 amino acids (Figure 1).

This longer cytoplasmic domain on CD200R contrasts with the short intracellular domain of CD200, which contains 19 amino acids and no signalling motifs (Barclay et al., 2002). The cytoplasmic tail of CD200R includes an NPXY signalling motif which interacts with the phosphotyrosine-binding (PTB) domains present in several signalling adaptor molecules (Wright et al., 2000). The NPXY signalling motif contains 3 tyrosine residues, which are phosphorylated following the interaction between CD200 and CD200R (Wright *et al*., 2000: Snelgrove *et al.,* 2008). This initiates a signaling cascade, which involves recruitment and phosphorylation of adaptor proteins, downstream of tyrosine kinase (Dok) 1 and Dok 2 and the subsequent binding to RasGAP and SHIP (Mihrshahi et al., 2009); the downstream events include inhibition of the Ras/mitogen-activated protein kinase (MAPK) pathway (Zhang et al., 2004). Ultimately this results in a decrease in release of inflammatory cytokines. Thus CD200R agonists inhibited IFNγ-induced release of TNFα from peritoneal macrophages, although no effect on LPS-induced release was observed (Jenmalm et al., 2006). These agonists also increased IFNγ-induced and IL-17-induced release of IL-6, although production of monocyte chemoattractant protein-1 (MCP-1) was unaffected. Tetanus toxin-induced production of IL-5 and IL-13, but not other cytokines, was inhibited by CD200R agonists (Jenmalm et al., 2006). The effects of these agonists were cell-specific; activation of DC by several stimuli, including LPS and inflammatory cytokines, increased numerous markers of cell activation and resulted in release of many cytokines but these changes were resistant to modulation by CD200R agonists.

Recent evidence suggests that Dok 1 negatively regulates Dok 2-induced signalling (Mihrshahi and Brown, 2010) and that the negative regulation induced by CD200R activation is mediated by sequential activation of Dok 2 and RasGAP (Mihrshahi et al., 2009).

3.3 Characteristics of CD200-deficient mice

Deletion of the CD200 gene in mice provided a significant insight into the role of CD200 with the important observation that susceptibility of these mice to autoimmune diseases was markedly increased, with evidence of upregulated inflammatory responses (Hoek et al., 2000). The population of macrophages was increased in these animals and there was evidence of an enhanced activation state, even under resting conditions (Hoek et al., 2000). Specifically, macrophage numbers in the spleen and mesenteric lymph nodes were increased

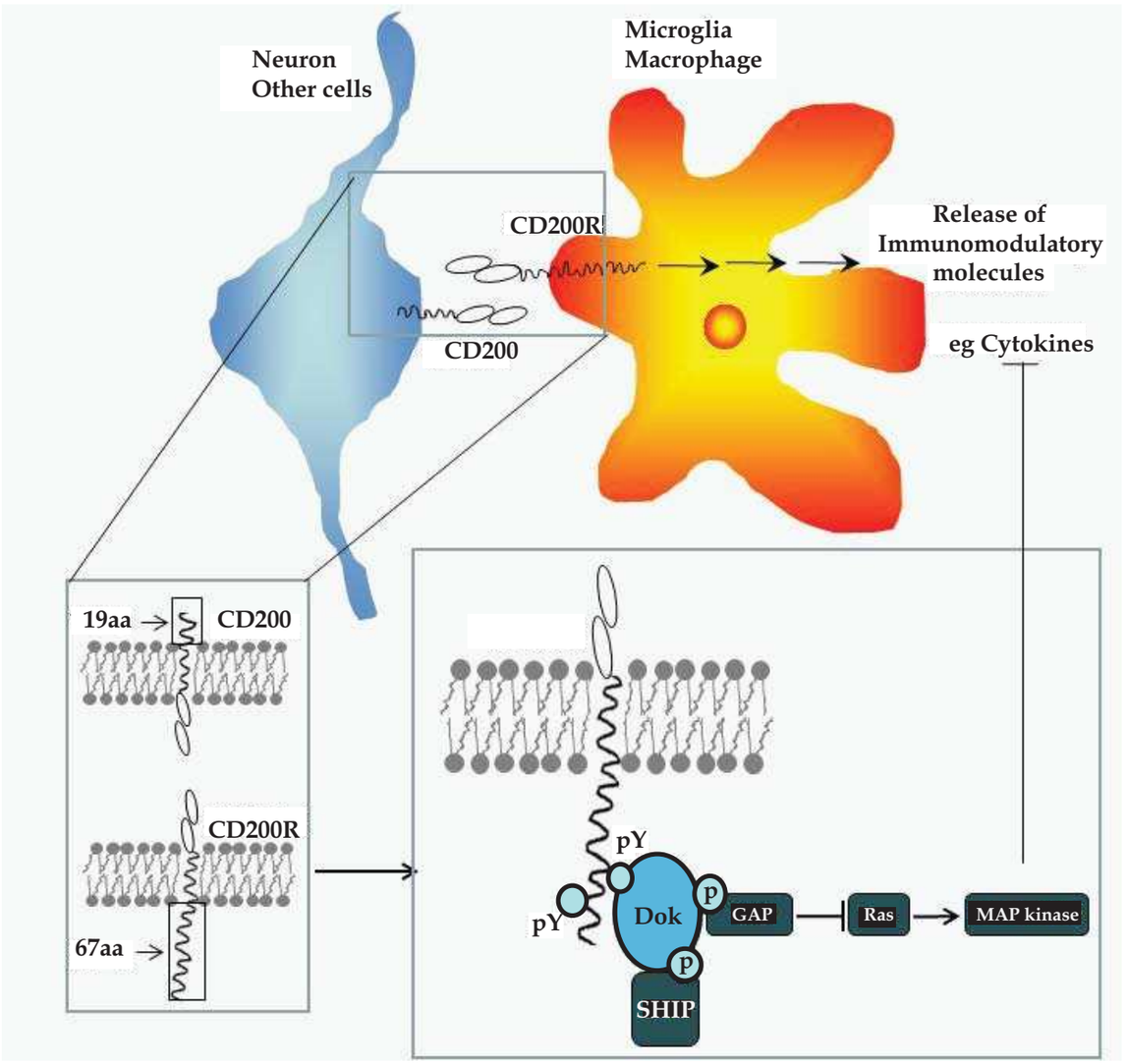

Fig. 1. CD200-induced signalling downregulates glial production of inflammatory cytokines. CD200 is expressed on several cell types including neurons and endothelial cells whereas expression of CD200R is relatively restricted to cells of the myeloid lineage. CD200 has a short cytosolic domain with no signalling capability whereas the signalling motif in the cytosolic domain of CD200R contains 3 tyrosine residues which, when phosphorylated, recruits Dok 1and Dok 2 which leads to activation of SHIP and RasGAP respectively, the latter of which leads to inhibition of MAP kinases thereby permitting increased production of inflammatory cytokines

and a defect in the organization of the mesenteric lymph nodes was described (Barclay et al., 2002). The findings of these studies indicated that CD200R activation provides a mechanism for negatively modulating cell responses and controlling responses of cells to immunological stimuli. An increase in the activation state of microglia was also reported with evidence of increased expression of CD11b and CD45, and the response of microglia to trauma is markedly enhanced in CD200-deficient mice where activated microglia cluster around the lesion area (Hoek et al., 2000). The clustering of activated macrophages or microglia in

tissues of CD200-deficient mice has suggested that CD200-CD200R interaction may not simply provide a mechanism by which these myeloid cells are maintained in a relatively quiescent state, but that this interaction may play a key role in controlling migration of cells (Nathan and Muller, 2001). Interestingly, one of the earliest papers on the actions of CD200 suggested that it was expressed on immature (as well as mature) neurons and that it may be involved in migration of these neurons during development of the CNS (Webb and Barclay, 1984).

Symptoms in several models of neurodegenerative and/or neuroinflammatory disease, or the responses to certain infections, or the effects of injury to neurons (detailed in Section 4 below) have been examined in CD200-deficient mice. The evidence consistently shows, across these experiments, that the symptoms are worse, the mortality rate is higher and activation of microglial cells or macrophages is more profound in CD200-deficient, compared with wildtype, mice. Thus CD200-deficient mice exhibit increased sensitivity to infections like influenza where evidence of greater macrophage activity was linked with prolonged symptoms and increased mortality (Snelgrove et al., 2008) and to *Toxoplasma gondii* where the increased macrophage infiltration, accompanied by increased activation of these cells and also microglia, was associated with poorer survival rates (Deckert et al., 2006). In a striking parallel with microglia from CD200-deficient mice, microglia prepared from mice lacking either Dok 1 or Dok 2 also respond more profoundly to LPS than cells from wildtype mice (Shinohara et al., 2005).

4. CD200 functions as a neuroimmunoregulatory protein

4.1 CD200-CD200R interaction maintains microglia in a quiescent state

The findings of several experiments indicate that the interaction between CD200 and CD200R maintains microglia or macrophages in a quiescent state whereas the absence of CD200 is linked with evidence of cell activation and inflammatory changes. Evidence from this laboratory has revealed that co-culture of neurons with mixed glia inhibited LPS-induced increases in release of IL-1β, IL-6 and TNFα. The effect of neurons was blocked when the incubation was carried out in the presence of a blocking anti-CD200 antibody (Lyons et al., 2009b) pinpointing a role for CD200 in modulating cytokine release. Similarly, the Aβ-induced release of IL-1β, IL-6 and TNFα from mixed glia is inhibited when cells are co-cultured with neurons and this effect of neurons is also inhibited by the presence of a blocking anti-CD200 antibody (Lyons et al., 2007a).

One factor which increases CD200 expression is IL-4 and, interestingly, a marked reduction in CD200 expression has been reported on neurons prepared from IL-4-deficient mice (Lyons et al., 2009b). Predictably, therefore, co-incubation of mixed glia with neurons prepared from IL-4-deficient mice did not attenuate Aβ-induced production of inflammatory cytokines (Lyons et al., 2009b), contrasting with the effect of neurons prepared from wildtype mice. As highlighted above, endothelial cells express CD200 and, like neurons, incubation of LPS-treated mixed glia with endothelial cells inhibits the LPS-induced release of IL-1β from mixed glia (Figure 2).

4.2 The age-related increase in microglial activation is associated with decreased CD200 expression

It has been recognized for several years that microglial activation is increased in the brain with age; the evidence suggests that expression of markers of activation, for example MHCII

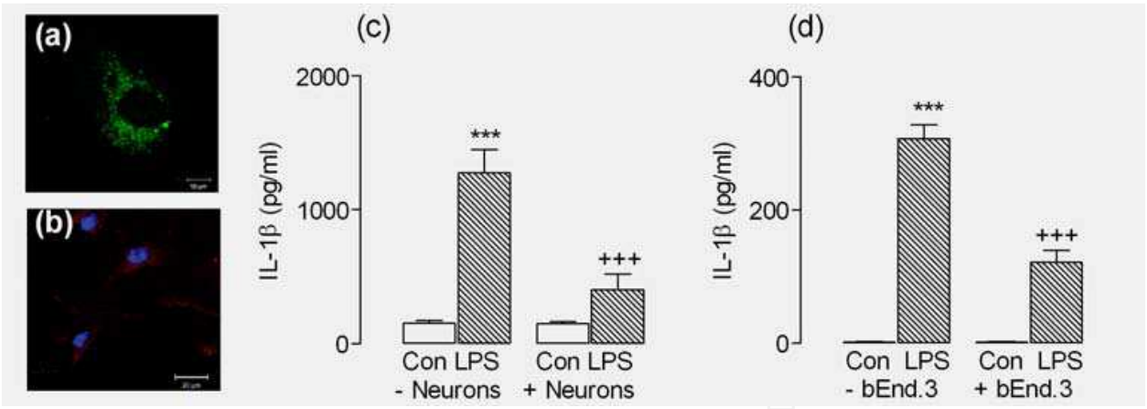

Fig. 2. Endothelial cells, which express CD200, modulate LPS-induced IL-1β production from glia in a manner which resembles the effect of neurons. a,b. Neurons (a) and endothelial cells (b; bEnd.3) express CD200. Mixed glia were incubated in the presence or absence of LPS (100ng/ml), and either neurons (1:2) or endothelial cells (bEnd.3; 1:8) were added. c,d. LPS significantly increased supernatant concentration of IL-1β (***$p < 0.001$; ANOVA) and this was significantly attenuated when mixed glia were co-cultured with either neurons or endothelial cells ($^{+++}p < 0.001$; ANOVA)

and CD11b, are increased in hippocampal and cortical tissue with age and these changes are accompanied by increased expression of inflammatory cytokines (Lynch, 2010). Evidence from this laboratory indicates that CD200 expression is decreased in hippocampal tissue prepared from aged, compared with young, rats. We have proposed that this significantly contributes to the age-related increase in microglial activation (Lyons et al., 2007a) and consequently the age-related decrease in synaptic plasticity, typified by the deficit in long-term potentiation (LTP). Recent evidence has revealed that intracerebroventricular injection of CD200Fc attenuated the age-related deficit in LTP (Cox et al., unpublished). Interestingly, amyloid-β (Aβ), which has been shown to decrease LTP (Lyons et al., 2007a, Lyons et al., 2007b) is associated with increased microglial activation as demonstrated by increased expression of the cell surface markers of microglial activation, MHCII (Lyons et al., 2007a, Lyons et al., 2007b), ICAM and CD86 (Clarke et al., 2007), increased production of inflammatory cytokines, IFNγ and IL-1β (Minogue et al., 2007) and increased production of chemokines MCP-1 and IP-10 (Clarke et al., 2007). Significantly Aβ also decreases CD200 expression *in vitro* while expression of CD200 is also decreased in hippocampal tissue prepared from rats which received an intracerebroventricular injection of Aβ (Lyons et al., 2007a).

4.3 CD200 is a protective molecule during apoptosis

Apoptosis is an ongoing process which is necessary to permit natural cell turnover. It is important to ensure that this occurs without production of inflammatory cytokines which can negatively impact on cells in the microenvironment; a key factor in ensuring maintenance of this steady state is the expression of immunoregulatory signals. Like other peripheral cells, apoptosis of DC occurs on an ongoing basis and, experimentally, apoptosis can be induced by growth factor deprivaton. Recent data have indicated that up to 75% of apoptotic $CD11c^+$ cells express CD200, whereas about one third of non-apoptotic $CD11c^+$ cells express CD200; the evidence indicates that expression of CD200 is p53- and caspase-

dependent. Similarly γ-irradiation, which induces apoptosis in C1498 leukemia cells, is associated with increased expression of CD200 (Rosenblum et al., 2004).
It has been proposed that CD200 also plays a role in tolerance. This has been demonstrated in a model of contact hypersensitivity which is induced by 2,4-dinitro-fluorobenzene. In this model, the inflammatory changes which typify contact hypersensitivity are attenuated by prior exposure to low dose ultraviolet light (UVB) and it has been proposed that UVB-induced apoptosis of epidermal DCs is the key to this tolerance. Significantly, and consistent with the findings obtained in vitro, this is dependent on CD200, since tolerance was absent when this experiment was conducted in CD200-deficient mice. The data suggest that CD200-CD200R interaction may be a key event in ensuring that inflammatory changes do not accompany steady-state ongoing apoptosis (Rosenblum et al., 2004). Interestingly several studies have highlighted a role for CD200 in tolerance following transplants (Clark et al., 2008, Gorczynski et al., 2009)

5. The importance of the interaction between CD200 and CD200R in modulating inflammation

CD200-CD200R interaction provides a regulatory signal to macrophages (Broderick *et al.*, 2002) and consequently macrophage numbers in the spleen are increased in $CD200^{-/-}$ mice compared with wildtype mice, while $CD200^{-/-}$ mice also have enlarged lymph nodes (Hoek et al., 2000). A similar regulatory signal modulates microglia and therefore the absence of CD200 is associated with microglial activation. Thus cells prepared from $CD200^{-/-}$ mice exhibited an activated phenotype, and had less ramified morphology and shorter processes, as well as increased expression of cell surface markers, CD11b and CD45, which are indicative of activation (Hoek et al., 2000). Microglia from $CD200^{-/-}$ animals also appeared to form aggregates, which occurs in neuroinflammatory and neurodegenerative, but not under normal, conditions (Hoek et al., 2000). Predictably, cells prepared from $CD200^{-/-}$ mice exhibited a greater response to stimuli including LPS and Aβ (Lyons et al., 2007a). These data indicate that disruption of this interaction between CD200-CD200R results in dysregulation of macrophages and microglia, with cells shifting to a more tonically active state (Hoek *et al.*, 2000).
Evidence from experimental conditions associated with inflammatory changes and microglial activation, adds support to the finding that CD200-CD200R interaction is an important regulator of neuroimmune function. For example, *Toxoplasma gondii*-induced encephalitis is characterized by lymphocytic infiltrates and microglial activation and it has been reported that infection induced a more profound microglial proliferation and greater expression of markers of activation in CD200-deficient, compared with wildtype, mice (Deckert et al., 2006). In addition, nerve injury is associated with microglial activation and it has been reported that facial nerve transaction induced a greater degree of microglial activation in CD200-deficient, compared with wildtype, mice (Hoek et al., 2000). Similarly the neurodegenerative changes that occurred following sciatic nerve crush was associated with a profound loss of CD200 and evidence of macrophage activation (Chang et al., 2011).

5.1 CD200-CD200R interaction in inflammatory diseases and models of disease

One of the most clearcut consequences of the loss of the interaction between CD200 and CD200R is the development of inflammatory changes (Masocha 2009), and therefore, as described above, $CD200^{-/-}$ mice are more susceptible to inflammatory stimuli and exhibit

exaggerated symptoms in models of autoimmune diseases (Feuer, 2007). The majority of studies which have examined the role of CD200 as a negative regulator of myeloid cells have focussed on three autoimmune disease models, collagen-induced arthritis (CIA), a model for rheumatoid arthritis, experimental autoimmune uveoretinitis (EAU), a murine model for uveitis and myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis.

5.1.1 CD200-CD200R interaction in CIA

Rheumatoid arthritis is a classical inflammatory disease of the joints, typified by infiltrates of inflammatory cells. The most widely-used model is CIA and the evidence indicates that the symptoms of the disease, including inflammation and joint pathology was much more severe in CD200$^{-/-}$ mice, compared with their wildtype counterparts (Hoek et al., 2000). In contrast, treatment of mice with recombinant CD200 at 3-day intervals, concomitant with collagen immunization, markedly reduced symptoms; this included a reduction in infiltration of inflammatory cells and reduced bone erosion (Melnyk et al., 2011). A similar reduction in the severity of the disease, pathology and production of inflammatory mediators was observed when mice were treated with CD200Fc (Simelyte et al., 2008). These findings suggest that an agonistic antibody to CD200R, as substitute for the CD200-CD200R interaction, might be a useful therapeutic strategy in CIA. Predictably, CD200Fc, an immunoadhensin, produced by fusing the extracellular domains of CD200 to a murine IgG2a Fc construct, decreases TNFα and IFNγ production following collagen injection and halted the progression of symptoms of CIA (Gorczynski et al., 2002).

5.1.2 CD200-CD200R interaction in EAU

EAU, which is induced by immunization with interphotoreceptor retinoid-binding protein, is characterized by destruction of the neuroretina and photoreceptors, and the evidence indicates that this is T cell mediated; the symptoms include leukocyte infiltration of the vitreous and retina, vasculitis and ultimately photoreceptor and ganglion cell death. Symptoms become evident more quickly and are more profound in CD200-/- mice, compared with wildtype animals with significant additional infiltration of CD45+ CD11b+ cells and evidence of photoreceptor death, coupled with increased expression of nitric oxide synthase (NOS)-2 (Broderick et al., 2002). These findings were replicated subsequently and extended to show that the progression of the disease was suppressed by an agonist CD200R antibody (Copland et al., 2007). The modulatory role for CD200 in EAU was also identified in a rat model and, in this case, the evidence indicated that blocking CD200-CD200R interaction by an antibody accelerated the onset and severity of symptoms (Banerjee and Dick, 2004). Experimentally-induced glaucoma, caused by injecting hypertonic saline into the superior episcleral aqueous drainage vein, is another inflammatory and degenerative condition of the eye which is associated with a time-related increase in microglial activation; like EAU a role for CD200-CD200R has been implicated by the finding that the microglial activation is coupled with a decrease in CD200 and evidence of retinal ganglion cell death (Taylor et al., 2011).

5.2 CD200-CD200R interaction and Multiple Sclerosis

Multiple sclerosis is a chronic, progressive, disabling autoimmune disease. The generally-accepted view is that the disease is caused by uncontrolled inflammatory T cell responses to

self antigens (myelin) in the brain and spinal cord. This results in a cascade of events which triggers inflammation, as a consequence of microglial and macrophage activation, and is followed by demyelination and degeneration of axons. One of the characteristics of this disease is the presence of inflammatory plaques, which are detected by magnetic resonance imaging (MRI), and post mortem examination has established that the brain lesions are associated with the presence of inflammatory cells (Frohman et al., 2006).

5.2.1 What factors contribute to the pathogenesis of EAE?

A great deal of progress in understanding the mechanisms which precipitate the disease has been made by examining changes which trigger disease symptoms in the widely-used animal model of multiple sclerosis, EAE. EAE is induced by stimulating an immune response directed against CNS antigens, such as myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG). EAE can be induced by immunisation with these myelin antigens in adjuvant or by adoptive transfer of myelin-specific T cells, both of which result in inflammatory infiltrates into the CNS and demyelination (Stromnes and Goverman, 2006).

Like multiple sclerosis, EAE is characterized by infiltration of macrophages and $CD4^+$ T cells into the CNS, accompanied by microglial activation which, together, are responsible for the temporary paralysis that typifies the disease. The symptoms have been shown to be exaggerated, and the onset of the symptoms is hastened, when CD200-CD200R interaction is attenuated (Hoek et al., 2000, Wright et al., 2000, Meuth et al., 2008). Specifically, initial symptoms following MOG injection appeared 2-3 days earlier in $CD200^{-/-}$ mice than in wildtype mice, and expression of iNOS and CD68 were markedly increased in spinal cord of these mice 7 days after immunization (Hoek et al., 2000), while more severe symptoms were also observed (Wright et al., 2000). Consistently, an anti-CD200R antibody increased the severity of the symptoms and, in parallel, increased T cell infiltration and macrophage numbers in the spinal cord of MOG-treated mice (Meuth et al., 2008). Furthermore, the Wld^s mouse, which exhibits unique protection against neurodegenerative conditions, including EAE, overexpresses CD200 (Chitnis *et al*., 2007). Interestingly, CD200 expression was reported to be decreased, in parallel with another NIReg, CD47, in laser-dissected active lesions of the post mortem brain of individuals with multiple sclerosis, although CD200R expression was unchanged and there was also no evidence of a change in SIRPα expression (Koning et al., 2007). However more recent studies revealed that CD200 was expressed on astrocytes associated with lesions in multiple sclerosis (Koning et al., 2009).

5.2.2 The development of EAE is associated with altered CD200 expression

MOG-induced EAE is typified by the development of clinical signs which appear initially at about day 7 post-immunization; the well-defined changes progress from the initial flaccid paralysis manifest by a limp tail and developing to paralysis in hindlimbs and ultimately the forelimbs (Stromnes and Goverman, 2006). We have investigated the accompanying changes induced in microglial activation and CD200 in the spinal cord following immunization (Figure 3). CD40 mRNA, which is indicative of microglial activation, increased after immunization whereas CD200 mRNA expression decreased and a significant inverse relationship between the 2 measures was observed. IL-4, which modulates CD200 expression, was decreased at the end of the experiment, paralleling the change in CD200. Similar data were obtained in the hippocampus (not shown).

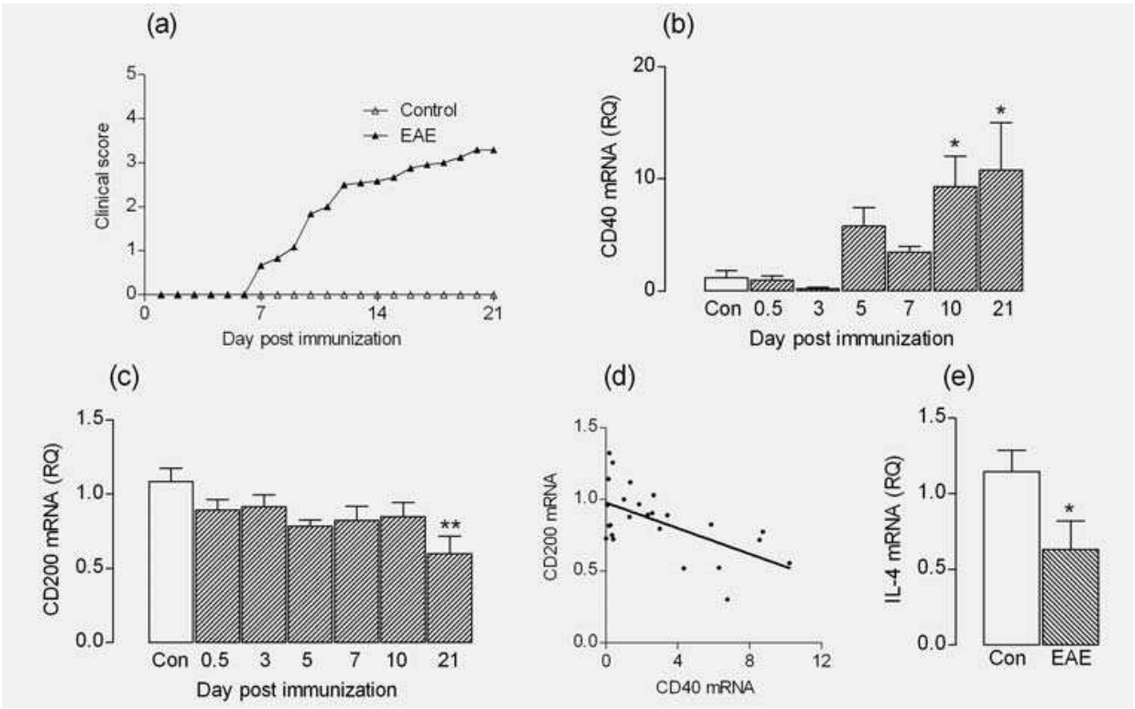

Fig. 3. Immunization with MOG increases microglial activation and decreases CD200 expression. Immunization of mice with MOG induced clinical signs which became evident after 7 days. This was accompanied, in the spinal cord, by a time-related increase in CD40 mRNA, which was significant 10 and 21 days post-immunization (*$p < 0.05$; ANOVA; Figure 3b) and a significant decrease in CD200 mRNA (**$p < 0.01$; ANOVA; Figure 3c). A significant inverse correlation between CD200 mRNA and CD40 mRNA is demonstrated ($p = 0.0017$; Figure 3d). IL-4 mRNA expression was significantly decreased in tissue prepared from animals with EAE (*$p< 0.05$; ANOVA; Figure 3e)

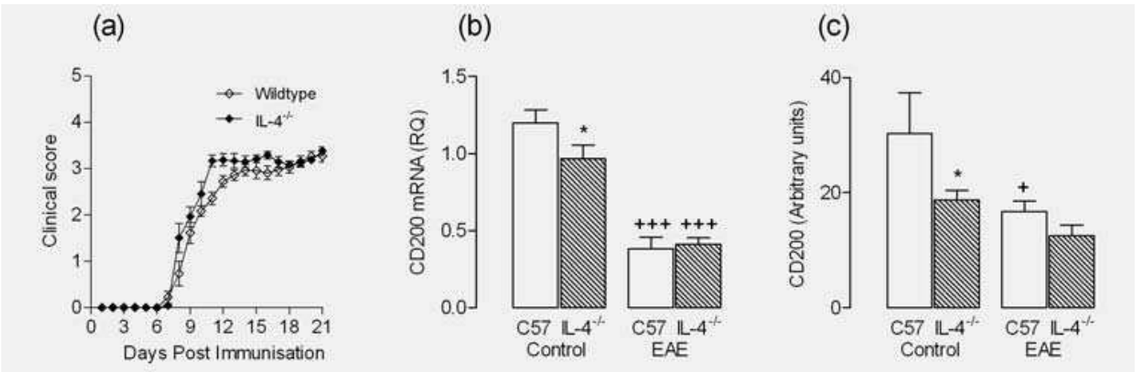

Fig. 4. The loss of IL-4 leads to more profound clinical symptoms of EAE. The symptoms of EAE developed more rapidly in IL-4-deficient mice compared with wildtype mice (Figure 3a). CD200 mRNA (Figure 3b) and CD200 protein (Figure 3c) were both decreased in tissue prepared from mice with EAE at the end of the 21-day experiment ($^{+}p < 0.05$; $^{+++}p < 0.001$; ANOVA; Figure 3b,c) and a decrease in both was identified in tissue prepared from IL-4-deficient, compared with wildtype, mice (*$p < 0.05$; ANOVA; Figure 3b,c)

5.2.3 IL-4 modulates CD200 expression and the course of EAE

Because the evidence indicates a close parallel between IL-4 and CD200, and because CD200 appears to be linked with the increase in microglial activation which contributes to the inflammatory changes in EAE, the onset and severity of clinical symptoms were compared following MOG immunization in wildtype and IL-4$^{-/-}$ mice. The evidence indicates that loss of IL-4 exacerbates the clinical symptoms (Figure 4a) and CD200 mRNA expression (Figure 4b), as well as CD200 protein (Figure 4c) was decreased in spinal cord prepared from IL-4$^{-/-}$ mice, compared with wildtype mice. Moreover, the decrease in both measures was significantly greater in mice with EAE compared with controls.

5.2.4 CD200R ligation on specific T cell subtypes may contribute to the development of EAE

A comprehensive analysis of the expression of CD200R on cells and tissue prepared from mouse and humans revealed that expression levels were greatest on macrophages, mast cells and dendritic cells, and in lymph nodes, spleen, bone marrow and, to a lesser extent, in lung and liver (Wright et al., 2003). However the receptor was also found on polarized Th2 cells, whereas expression on polarized Th1 cells was markedly less; this differential expression on T cells was observed in mice and human cells (Wright et al., 2003). Subsequent analysis indicated that CD200R was expressed to a greater extent on CD4^{+} effector memory cells compared with central memory cells and naïve cells. Similarly CD8^{+} central memory cells had higher expression than naïve cells (Rijkers et al., 2008). Clearly these findings suggest that CD200R ligation can modulate T cell function in addition to myeloid cell function; this may contribute to the exaggerated symptoms in autoimmune diseases, for example EAE.

6. Evidence of a role for CD200-CD200R interaction in other neurodegenerative diseases

6.1 Parkinson's Disease

PD is the most common movement disorder and the second most common neurodegenerative disease. It shares some characteristics with AD. Both are, at least to some extent, age-related disorders, characterized by neuroinflammatory changes accompanied by increased expression of inflammatory cytokines. PD is a chronic and progressive disorder, resulting in the selective loss of dopaminergic neurons within the substantia nigra (SN) of the midbrain. As the disease progresses there is gradual circuitry degeneration and neuronal loss within the nigrostriatal pathway, producing cognitive and psychiatric symptoms, as well as disturbances in movement (Braak et al, 2003). Cytoplasmic accumulations of insoluble proteins are likely to significantly contribute to the neuronal loss apparent in both AD and PD. Cognitive dysfunction is particularly marked in AD but there is also evidence of deterioration in cognition in PD. It has been suggested that the microglial activation which is prevalent in hippocampus and parahippocampal regions, coupled with the decrease in hippocampal volume (Laakso et al., 1996) and associated neuronal loss in the limbic areas (Emre, 2003a, b) may account for the cognitive dysfunction in PD. Although clinical trials have failed to show that NSAIDs are effective in treating AD or PD, epidemiological studies have suggested that chronic treatment with NSAIDs reduces the risk of both diseases suggesting that inflammatory changes may contribute to the

progression of the diseases. Interestingly, the protective effects in AD may be confined to particular subpopulations. Recent retrospective studies indicated that statin therapy reduced the risk of developing PD and AD.

It is unclear whether microglial activation directly contributes to neuronal loss in PD (or indeed AD) but post mortem examination has established that activated microglia are clustered at high density in the SN (McGeer et al., 1988), the most vulnerable area of the brain in PD due to the low intracellular glutathione concentration and high iron level within nigrostriatal dopaminergic neurons (Sian et al., 1994). Indeed dopaminergic neurons are especially vulnerable to LPS-induced neurodegeneration (Smidt, 2009). Interestingly the number of MHCII-positive cells in this area increases in parallel with neuronal loss (Imamura *et al.* 2003). Similarly, an inverse relationship between ^{11}C-(R)-PK11195 binding (which is indicative of microglial activation) in the midbrain and binding of [^{11}C]CFT to the dopamine transporter (which reflects the viability of presynaptic dopaminergic neurons) in the putamen has been described. It has been reported that the combination of binding of these 2 tracers positively correlates with motor deficits in early PD (Ouchi *et al.* 2009). The correlative changes suggest a role for microglial activation in the pathogenesis of PD but do not address the question whether microglial activation plays an explicit role in dopaminergic cell death; animal models have been used to explore this. Environmental factors including pesticides have been implicated in the aetiology of PD and therefore experimental models of the disease include those in which animals are treated with rotenone or paraquat (Cicchetti et al., 2009); the loss of dopaminergic neurons in these models appears to be mediated by microglia since the superoxide which is considered to be pivotal to inducing cell damage was generated from microglia (Gao et al., 2002, Wu et al., 2005). Another animal model of PD involves prenatal exposure to LPS, which ultimately causes protracted inflammation and loss of dopaminergic neurons which progresses with subsequent insults; data from this model suggests that the priming of microglia is responsible for the ongoing degeneration and has led to the development of the 'multiple hit' hypothesis (Ling *et al.* 2006). An important tenet of this theory is that prolonged inflammation, rather than an acute inflammatory response, is responsible for the progressive neuronal loss (Park *et al.* 2009, Long-Smith et al. 2009). Interestingly, an age-related increase in microglial-activation in the SN has been reported (Beach et al., 2007) and the suggestion is that this 'priming' may contribute to development of the disease.

The most commonly-used models of PD which lead to neurodegeneration of dopaminergic neurons and induce Parkinson-like symptoms involve injection of rotenone or 6-hydroxydopamine (6-OHDA). It has recently been reported that rotenone+iron-induced dopaminergic neurotoxicity is mediated by microglia and that the toxicity is enhanced by a CD200R blocking antibody (Wang et al., 2011). The evidence indicated that microglia were the source of superoxide, that production was enhanced by the antibody and that inhibiting CD200R activation in microglia has detrimental effects on neuronal function. In addition to the Parkinson-like symptoms, injection of 6-OHDA also induces marked microglial activation (Long-Smith et al., 2009). These findings and the observations of other groups over many years (Chen et al., 1998, Le et al., 2001, Liu and Hong, 2003, Kim and Joh, 2006, Purisai et al., 2007) have provided significant support for the thesis that activated microglia play an important part in the onset and/or progression of PD.

In an effort to further address this question, and specifically to evaluate whether CD200 may play a role in modulating microglial activation which accompanies the loss of dopaminergic neurons following 6-OHDA injection, we examined the expression of CD200 in the ipsilateral and contralateral SN of rats following unilateral injection of 6-OHDA into the medial forebrain bundle. Immunocytochemical analysis of sections prepared from these animals revealed that there was marked dopaminergic cell loss in the side of the brain in which the 6-OHDA injection was made, as shown by decreased expression of tyrosine hydroxylase (Figure 5d), but that there was no evidence of cell loss on the contralateral side (Figure 5c). No cell loss was evident on either the ipsilateral or contralateral side of sham-treated rats Figure 5a,b). The data show that the marked 6-OHDA-induced dopaminergic cell loss in the ipsilateral SN was coupled with a marked decrease in CD200 expression (Figure 5d) whereas there was no discernible loss in the contralateral side of 6-OHDA-injected animals (Figure 5c) or the ipsilateral or contralateral side of sham-treated rats (Figure 5a,b). The loss of dopaminergic neurons was also associated with marked microglial activation as indicated by increased OX42 staining (red; Figure 5h); this is consistent with previous evidence indicating that loss of CD200 is linked with microglial activation (Lyons et al., 2007a). There was no evidence of microglial staining in sections prepared from the contralateral side of 6-OHDA-injected animals (Figure 5g) or the ipsilateral or contralateral side of sham-treated rats (Figure 5e,f).

6.2 Alzheimer's Disease

Despite an enormous effort, the molecular/cellular events which trigger AD remain unknown. It is undoubtedly the case that neuroinflammatory changes characterize the disease with evidence of profound microglial activation and, specifically, activated microglia and astrocytes clustered around Aβ-containing plaques (Xiang et al., 2006) and blood vessels (McGeer and McGeer, 2003) where amyloid deposits are also observed. As indicated above, several reports suggest that NSAID treatment reduces the risk of developing AD (McGeer and McGeer, 1999, Szekely et al., 2008, Vlad et al., 2008, Breitner et al., 2009) but NSAIDs are of little value in treating the disease. One possible explanation for this might be that inflammatory changes occur very early in the disease, prior to development of symptoms, and that preventing or delaying inflammation is beneficial because it is factor which contributes to the later neurodegenerative changes. A corollary to this previously-rehearsed proposal is that anti-inflammatory agents will not be beneficial once neurodegenerative changes are advanced. In support of this view, it has been consistently shown that inflammatory cytokines like IL-1β, IL-6 and TNFα negatively impact on neuronal and synaptic function (Lynch, 2010), and that these cytokines can contribute to neuronal cell death (Thornton et al., 2008, Long-Smith et al., 2010). Since activated glia, particularly microglia, are responsible for releasing these cytokines, it could be argued that targeting these cells might be a reasonable strategy for the treatment of AD, at least in its very early stages. This argument has been advanced by Walker and colleagues, who reported that CD200 expression was decreased in brains of individuals with AD. Thus sections prepared from inferior temporal gyrus of non-demented individuals exhibited colocalization of CD200 with NeuN but a marked loss of CD200 immunoreactivity was observed in sections prepared from post-mortem brains of AD patients. An AD-associated decrease in CD200R was also observed. Furthermore, the evidence suggested that the plaque density, and also the neurofibrillary tangle score, was inversely related to CD200R expression (Walker et al., 2009).

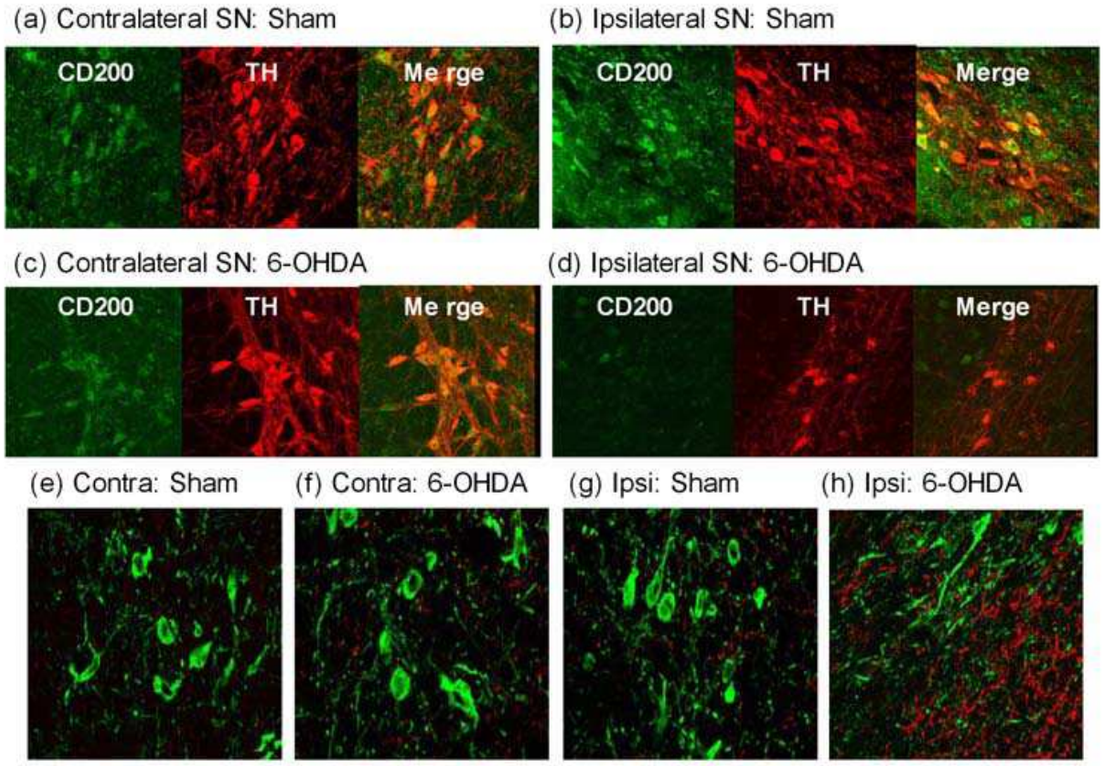

Fig. 5. 6-OHDA injection leads to dopaminergic cell loss and a marked reduction in CD200 immunoreactivity, coupled with microglial activation. Rats were anaesthetized with equal amounts of xylazine hydrochloride and ketamine hydrochloride (0.2ml/100g body weight; 1.5 ml of each compound dissolved in 7 ml PBS). Rats received a single injection of 6-OHDA (2μg/μl) into the medial forebrain bundle (AP –2.2 mm, ML + 1.5 mm from bregma; depth 7.8 mm). Rats were killed 10 days later. a-d: CD200 immunoreactivity (green) and tyrosine hydroxylase (TH) immunoreactivity was evident in contralateral and ipsilateral SN and there was clear evidence of co-localization indicating the presence of CD200 on dopaminergic neurons. There was a marked decrease in TH immunoreactivity in sections prepared from the ipsilateral SN of rats which received 6-OHDA, indicative of substantial dopaminergic cell loss but no changes were observed in the other treatment groups. TH loss was accompanied by a loss in CD200 immunoreactivity. e-h: TH expression (green) was similar in the contralateral SN obtained from sham- or 6-OHDA-treated rats and in the ipsilateral side of sham-treated rats. In contrast, a marked change in morphology indicative of dopaminergic cell loss was observed in sections prepared from the ipsilateral SN of rats which received 6-OHDA. Microglial activation was assessed by evaluating OX42 immunoreactivity (red staining); marked staining was observed in sections prepared from the ipsilateral SN of rats which received 6-OHDA but in none of the other groups

6.3 Stroke

Ischaemia induces a profound disturbance in homeostasis and significant pathology in the brain. Among the earliest changes is infiltration of neutrophils into the brain parenchyma and the evidence indicates that, in the endothelin model of stroke, these cells accumulated in the core of the lesion 2 weeks after injection and correlated with the infarct volume (Weston

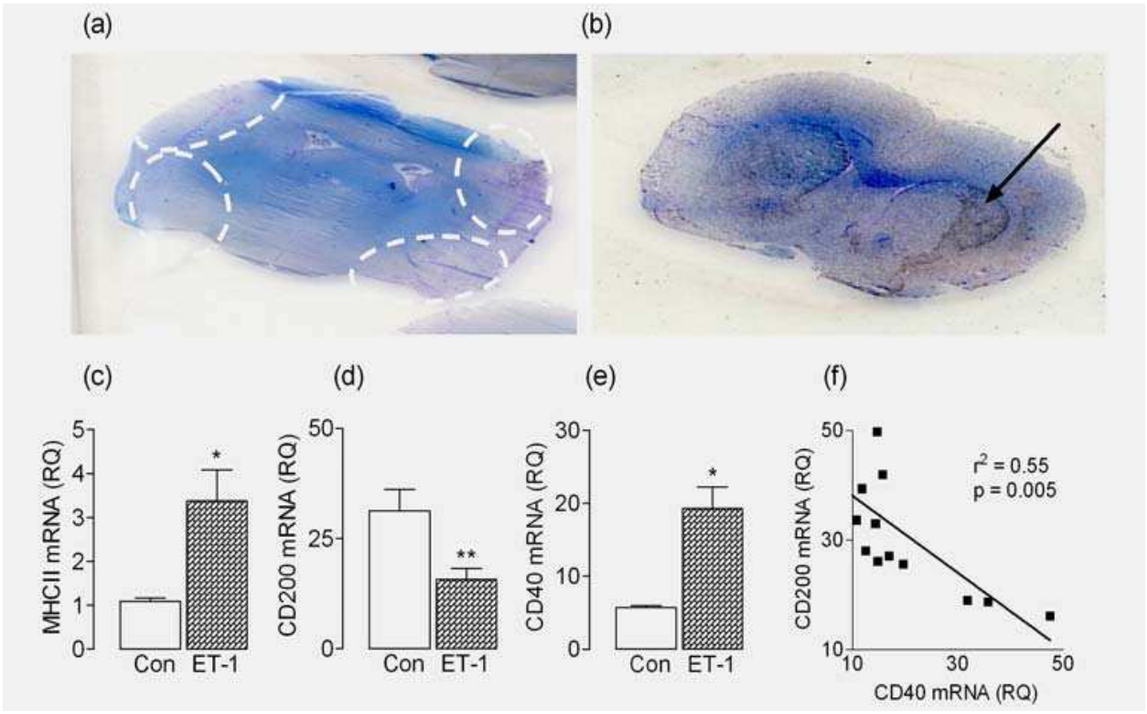

Fig. 6. CD40 mRNA is increased and CD200 mRNA is decreased in striatum following endothelin injection. Male Wistar rats (3 months; 270-350g; BioResources Unit, Trinity College, Dublin, Ireland) were anaesthetized with isofluorane (5% in O_2), placed in a stereotaxic frame and injected with endothelin-1 (ET-1; 600pmol; 3 µl), delivered through a drill hole (0.52 cm lateral to midline, 0.05 cm posterior to bregma; depth 0.05cm from the base of the skull) (Moyanova et al., 2003). Animals were killed and brain tissue harvested 7 days after injection. Cryostat sections were prepared from part of the brain and striatum was taken from the remaining brain tissue to analyse expression of CD40 and CD200 mRNA. Endothelin induced significant neuronal loss (Figure 1a) and microglial activation, as assessed by OX6 staining, particularly in striatum (Figure 1b). Analysis of striatal tissue indicated that MHCII mRNA and CD40 mRNA were significantly increased in tissue prepared from endothelin-1-injected animals (*$p < 0.05$; student's t test for independent means; Figure 1c,d) whereas CD200 mRNA was significantly decreased (**$p < 0.01$; student's t test for independent means; Figure 1e); a significant inverse relationship between CD40 mRNA and CD200 mRNA was observed ($p = 0.0039$; Figure 1f)

et al., 2007). Neutrophils have also been shown to contribute to the increase in BBB permeability following stroke (McColl et al., 2007). Neutrophils release inflammatory cytokines, chemokines and reactive oxygen species, all of which contribute to the pathology, and also recruitment of immune cells (Denes et al., 2010). However microglia can also act similarly and the evidence has indicated that microglial activation is increased following ischaemia but the effect of this activation remains unclear. On the one hand, these cells may contribute to the cell damage because of their ability to secrete inflammatory molecules but their reparative role has also been clearly identified (Denes et al., 2010). It has been known for almost 2 decades that release of the inflammatory cytokine, IL-1β, was increased following ischaemia and that the endogenous antagonist, IL-1 receptor antagonist (IL-1ra)

reduced the associated neurodegenerative changes (Relton and Rothwell, 1992). However, more recent findings have indicated that the reduction in synaptic responses following ischaemia, and the decrease in LTP, were partially reversed following intra-arterial injection of microglia into rats (Hayashi et al., 2006). Thus microglia exert both a positive and negative impact.

We investigated microglial activation 7 days after endothelin-1 injection and demonstrate that markers of activation were increased while CD200 was decreased. Thus staining of the tissue revealed that there was marked cell loss (Figure 6a) and extensive OX6 staining (Figure 6b), with particularly marked staining in the striatum. PCR analysis revealed that there was a significant increase in expression of MHCII mRNA (Figure 6c) as well as another marker of microglial activation, CD40 mRNA (Figure 6e), in striatal tissue prepared from endothelin 1-treated rats compared with controls (*$p < 0.05$). CD200 mRNA was markedly decreased in striatal tissue prepared from endothelin-1-injected animals and, interestingly, there was a significant inverse relationship between these CD200 mRNA and CD40 mRNA ($p = 0.0039$; Figure 6f). These findings indicate that there is a persistent increase in microglial activation following ischaemia which has been reported previously (Denes et al., 2010). The underlying cause of this increase has not been fully explained. The present results suggest that the decrease in CD200, which might be anticipated to accompany the loss of neurons, may be a contributory factor.

6.4 Conclusions

In the past decade or so, it has become clear that microglia are maintained in a non-activated state by soluble factors including growth factors and anti-inflammatory cytokines, as well as cell-cell interactions. Among the ligand-receptor pairs which play a key role in modulating microglial activation is CD200-CD200R and the evidence indicates that when CD200R activation is disrupted, for example in CD200-deficient mice, the result is activation of microglia and macrophages, accompanied by inflammatory changes, and exacerbation of changes in models of autoimmune disease. The experimental evidence certainly suggests that targeting the interaction between CD200 and its receptor is a powerful weapon in attenuating inflammation and there is a growing body of evidence suggesting that disruption of the interaction, in combination with microglial and/or macrophage activation occurs in

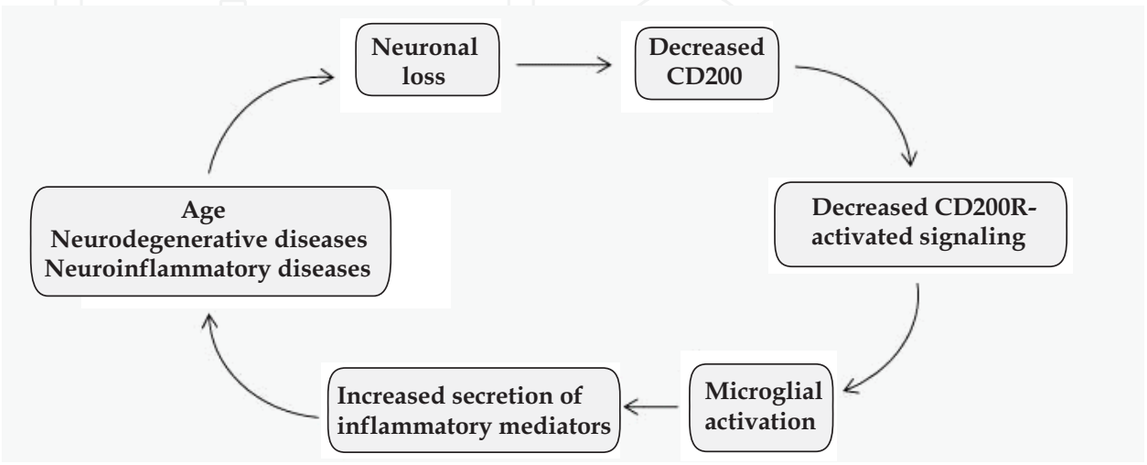

Fig. 7. Proposed role for CD200-CD200R interaction in neurodegenerative changes

models of neurodegenerative diseases. Figure 7 presents a schematic diagram which suggests that CD200R activation plays a pivotal role in modulating microglial activation. It is proposed that the secretion of immunomodulatory molecules from activated microglia contributes to the development of neurodegenerative changes which characterize neurodegenerative and neuroinflammatory diseases, and which also occur with age, these changes are inextricably linked with neuronal loss and consequently CD200 expression is decreased resulting in a decrease in signalling through CD200R, completing the continuing cycle of events.

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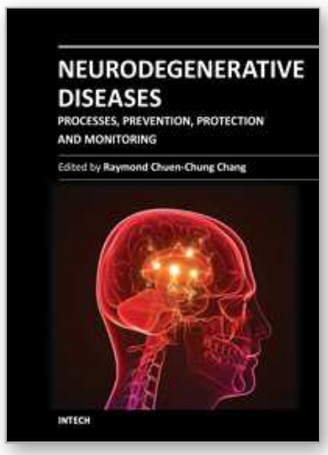

Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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