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Involvement of Fc Receptors in Disorders of the Central Nervous System

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Abstract

Immunoglobulins (Igs) are proteins with a highly variable antigen-binding domain and a constant region (Fc domain) that binds to a cell surface receptor (FcR). Activation of FcRs in immune cells (lymphocytes, macrophages and mast cells) triggers effector responses including cytokine production, phagocytosis and degranulation). In addition to their roles in normal responses to infection or tissue injury, and in immune-related diseases, FcRs are increasingly recognized for their involvement in neurological disorders. One or more FcRs are expressed in microglia, astrocytes, oligodendrocytes and neurons. Aberrant activation of FcRs in such neural cells may contribute to the pathogenesis of major neurodegenerative conditions including Alzheimer's disease, Parkinson's disease, ischemic stroke and multiple sclerosis. On the other hand, FcRs may play beneficial roles in counteracting pathological processes; for example, FcRs may facilitate removal of amyloid peptides from the brain and so protect against Alzheimer's disease. Knowledge of the functions of FcRs in the nervous system in health and disease is leading to novel preventative and therapeutic strategies for stroke, Alzheimer's disease and other neurological disorders.

Introduction

Identification of Fc receptors (FcRs) more than 3 decades ago has evolved into a comprehensive understanding of their biological consequences. Isotypes of immunoglobulins (Igs) in mammals include IgA, IgD, IgE, IgG, and IgM, and a specific FcR exists for each antibody (Ab) sub-class, with FcαR binding IgA, FcγR binding IgG, FcδR binding IgD, FcεR binding IgE and FcμR binding IgM. Activation of FcRs in immune cells initiates a range of biological responses that includes triggering of phagocytosis, degranulation, cytolysis and the transcriptional activation of cytokine genes leading to inflammatory cascades (Nimmerjahn et al., 2005; Roopenian and Akilesh, 2007; Nimmerjahn and Ravetch, 2008). Most cells express both a stimulatory FcR and an inhibitory FcRs (for example, FcγRIIb) so that responses of the cells to immunoglobulins can be finely tuned (Baerenwaldt and Nimmerjahn, 2008). In addition, FcRs are able to internalize Ab-ligand immune complexes leading to homeostatic degradation of these complexes (Akilesh et al., 2008).

Roles for various FcRs expressed on brain cells such as neurons, oligodendrocytes, astrocytes and microglia have been recently reported and are reviewed below. Several studies have also stressed the importance of FcRs in the inflammatory response in immunological (Seiwa et al., 2007) and neurodegenerative (Deane et al., 2009) diseases of the central nervous system (CNS).

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Microglia and astrocytes play key roles in the immune responses in the brain. Accumulating evidence shows that FcRs in these two types of glial cells play an important role in CNS disorders including multiple sclerosis (MS) (Nakahara and Aiso, 2006), ischemic stroke (Komine-Kobayashi et al., 2004), Parkinson disease (PD) (Orr et al., 2005) and Alzheimer's Disease (AD) (Deane et al., 2005) were also reported. Moreover, FcRs play a role in inducing rapid morphological differentiation with upregulation of myelin basic protein in oligodendrocyte precursor cells (Nakahara et al., 2003). More recently, it was shown that FcRs play critical roles in the functional establishment in the cerebellum because FcγRIIb-deficient mice have impaired development of Purkinje neurons, enhanced paired-pulse facilitation of parallel fiber-Purkinje cell synapses, and poor rotarod performance at increased velocities (Nakamura et al., 2007). Sensory neurons also express FcRs (Andoh and Kuraishi, 2004b), and activation of FcRs in mouse dorsal root ganglion (DRG) neurons results in an increased concentration of Ca²⁺ ions suggesting that FcRs may influence sensory processes (Andoh and Kuraishi, 2004a). This review discusses evidence for expression of FcR in the CNS, their involvement in CNS disorders, and the therapeutic potential of agents that modify FcR signalling.

FC receptors

Ig consists of a highly variable Fab region that contains a binding site for antigen, and an Fc region that interacts with either FcRs or other effector molecules such as complement proteins. The different FcRs and their interactions with Ig are discussed below, and the nomenclature used for the many different FcRs is summarized in Table 1.

FcγR

IgG binds to FcγRs. The complexity of the FcγR family is mirrored by the presence of four different IgG subclasses such as IgG1–IgG4 in humans (Takai et al., 2003) and IgG1, IgG2a, IgG2b and IgG3 in mice, which bind with varying affinity and specificity to different FcγRs. So far, four different classes of FcγRs (FcγRI, FcγRII, FcγRIII and FcγRIV) have been reported (Hulse and Woodfolk, 2008; Nimmerjahn and Ravetch, 2008). FcγRs include activating and inhibitory receptors that bind the same Fc portion of the IgG. In mice, FcγRI and FcγRIII are the activating receptors (along with FcγRIIa that contains a cytoplasmic activation domain and exists solely on myeloid cells). Innate immune effector cells, such as monocytes, macrophages, dendritic cells, basophils and mast cells express both activating and inhibitory FcγRs. FcγRI binds monomeric, as well as complexed IgG, with specificity for IgG2a and IgG2b (Ravetch and Bolland, 2001). FcγRIII is a low-affinity receptor for complexed IgG1, IgG2a and IgG2b (Sibéril et al., 2006). The inhibitory FcγRIIb is a broadly expressed FcγR, and is present on almost all leukocytes with the exception of natural killer (NK) cells that express the activating receptor FcγRIII and T lymphocytes. FcγRIIb, has two distinct isoforms called FcγRIIb1 and FcγRIIb2 which are generated by alternative mRNA splicing (Van den Herik-Oudijk et al., 1995). FcγRIIb1 is exclusively expressed on B cells, the FcγRIIb2 form is expressed on all other cell types (Minskoff et al., 1998; Lyden et al., 2001; Joshi et al., 2006). The balanced signalling through activating and inhibitory FcγR regulates the activity of various cells in the immune system.

FcεR

FcεRs include high- and low-affinity receptors, FcεRI and CD23, respectively. While most human and murine FcRs are members of the immunoglobulin super-family, the low affinity CD23 belongs to the C-type (calcium dependent) lectin super-family, and is distinguished structurally from almost all other immunoglobulin receptors (Turner and Kinet, 1999; Wurzburg et al., 2006; Gould and Sutton, 2008). IgE and FcεRI have long been known to be key players in allergic reactions (Dierks et al., 1993; Grant et al., 1997), and so is highly

expressed on mast cells and basophils, human antigen-presenting cells (APCs), monocytes, eosinophils and platelets (Dessaint and Capron, 1990; Abramson and Pecht, 2007). The IgE receptor network extends beyond FcεRI and CD23. Galectin 3 has the ability to bind complexed IgE and FcεRI via β-galactose containing oligosaccharide chains, thereby activating mast cells or basophils (Kimata, 2007).

FcαR

IgA is divided into closely related subclasses, IgA1 and IgA2. IgA2 differs from IgA1 by the absence of a 13-amino acid sequence in the hinge region (Frangione and Wolfenstein-Todel, 1972). Five types of IgA receptors are now recognized. Although they are not structurally related, three of them are considered genuine FcαRs. The first one, the polymeric Ig receptor (pIgR), is involved in transport of IgM and polymeric IgA across epithelial barriers. The second type is designated FcαRI (or CD89) and is specific for IgA (Yoo and Morrison, 2005; Wines and Hogarth, 2006). FcαRI expression is restricted to cells of the myeloid lineage including neutrophils, eosinophils, most of monocytes/macrophages, interstitial dendritic cells, Kupffer cells, and cell lines corresponding to these cell types (Monteiro and Van De Winkel, 2003). The third receptor, Fcα/μR is expressed on mature B cells and macrophages, but not on granulocytes, T cells or NK cells. It is also found in the liver, small and large intestines, kidney, testis and placenta (Monteiro and Van De Winkel, 2003). Two additional alternative IgA receptors are the asialoglycoprotein receptor (ASGPR) and the transferrin receptor (TfR) (Stockert, 1995; Monteiro and Van De Winkel, 2003). ASGPR is expressed on hepatocytes and recognizes terminal Gal residues on serum glycoproteins, including IgA (Monteiro and Van De Winkel, 2003). ASGPR is proposed to be involved in IgA clearance from the blood (Roccatello et al., 1993). The major pathway for IgA2 clearance was recently shown to be mediated by the liver ASGPR. Unlike other IgA receptors, TfR is not fully expressed on mature blood leukocytes, but it is expressed in cultured renal mesangial cells. In addition, it was shown that TfR is expressed in B lymphocyte cell lines, such as Daudi cells (Moura et al., 2001). The presence of TfR in the brain has been reported by several investigators (Hill et al., 1985; Mash et al., 1990). Within brain cells TfR have been identified in capillary endothelial cells (Pardridge et al., 1987), and neurons (Moos et al., 1999). In addition, TfRs have been detected in amoeboid microglia (Kaur and Ling, 1999) and reactive astrocytes (Orita et al., 1990).

Other FcRs

The recent identification of a large family of FcR-like molecules has considerably broadened the FcR network and some of which are termed FcR homology (FcRH)I to FcRH6 (Davis et al., 2002). The FcRHs, identified on the basis of sequence similarity with previously identified FcRs, are encoded by genes that reside near their closest FcR relatives on human chromosome 1 (q21–22) (Davis et al., 2001; Davis et al., 2002). At the transcript level, the FcRH genes are differentially expressed by B lineage cells and over-expressed in some B-cell malignancies (Davis et al., 2001). Fc receptors specific for IgM (Ohno et al 1990; Nakamura et al., 1993), and IgD (Lakshmi Tamma et al., 2001) have been reported, but these receptors have not been extensively investigated in the brain.

Alternative ligands to FcRs

One of the most neglected, and perhaps at the same time, most interesting aspects of FcR signaling, is the ability of non-Ig ligands to bind various FcRs. Soluble FcR (sFcR) were found to bind to non-Ig ligands found on the surface of various cell types. Human sFcγRIIIB binds to complement receptor (CR) 3 and to CR4. CR3 and CR4 are mainly expressed by monocytes, neutrophils and distinct populations of T and B cells. The result of CR3-sFcγRIIIB binding is the release of IL-6 and IL-8 from monocytes and IL-1β, IL-6, IL-8, IL-12 and GM-CSF from monocyte-derived dendritic cells (Galon et al. 1996). Similarly, human sFcεRII was also found

to bind to various non-Ig ligands, namely: CR2, CR3 and CR4. When bound to CR3, sFcεRII induces production of TNF- α , IL-1 β , IL-8 and GM-CSF (Heyman B. 2000). An emphasis should be placed on the implication of it on CNS related pathologies. Probably the most relevant implication is in ischemic stroke, in which the BBB is compromised, enabling infiltration of neutrophils, monocytes and other immune cells in the vicinity of neuronal cells. This mechanism offers an additional layer of complexity in the initiation of inflammatory response in the CNS during ischemic brain stroke.

Fc receptor signaling

Classical immunoreceptors like B-cell receptors (BCR), T-cell receptors (TCR) and FcRs utilize a common signal transduction mechanism, which relies on immunoreceptor tyrosine-based activation motifs (ITAMs) present in the receptor complex (Underhill and Goodridge, 2007; Ivashkiv, 2009). Phosphorylation of ITAMs is correlated with the activation of several sets of cytoplasmic protein tyrosine kinases, such as the SRC and SYK family kinases. Signals generated by these tyrosine kinases merge with signals generated by other immune receptors which results in an increased concentration of intracellular Ca²⁺, and activation of the PKC and Ras pathways.

FcγRs signalling

Activation of FcγRs in immune cells leads to phagocytosis, endocytosis, antibody-dependent cell-mediated cytotoxicity, release of inflammatory mediators, and the regulation of B cell activation and antibody production (Cox and Greenberg, 2001; Coggeshall, 2002). However, engagement of the inhibitory FcγRIIb, down modulates these effector responses. FcγRIIb is a single chain molecule that contains an ITIM in its cytoplasmic portion (Malbec et al., 2002; Brauweiler and Cambier, 2003). The signalling pathways initiated by the different activating FcγRs (FcγRI, FcγRIIa, FcγRIII and FcγRIV) are similar and start with tyrosine phosphorylation of the ITAMs in the receptor-associated adaptor molecules by kinases of the Src family (Park et al., 1999; Suzuki et al., 2000; Mina-Osorio and Ortega, 2004). This leads in turn to the recruitment of Syk-family kinases, which result in activation of various downstream targets including the linker for activation of T cells (LAT), multimolecular adaptor complexes, and phosphoinositide-3kinase (PI3K) (Ninomiya et al., 1994; Johnson et al., 1995; Ting et al., 1995; Ebel et al., 2001). By generating phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P₃), PI3K creates membrane-docking sites for Bruton's tyrosine kinase (BTK) and phospholipase Cγ (PLCγ) (Mukhopadhyay et al., 2001; Jakus et al., 2009). Activation of PLCγ leads to an increased intracellular calcium level and triggering of further downstream signalling events such as extracellular signal-regulated kinases (ERK), JUN N-terminal kinase (JNK) and p38 (Bracke et al., 1998; Cote-Vélez et al., 1999; Mukhopadhyay et al., 2001; Mangin et al., 2003). Besides calcium dependent pathways, the Ras–Raf–MAPK (mitogen activated protein kinase) pathway is of central importance for FcγR mediated cell activation (Rose et al., 1997; Renedo et al., 2001). IgG- FcγRIIb triggering of ITIM results in the recruitment of phosphatases such as SHIP (SH2- domain-containing inositol polyphosphate 5' phosphatase) and SHP1 (SH2-domain-containing protein tyrosine phosphatase 1) which inhibit cell activation (Bruhns et al., 2000; Huang et al., 2003). This prevents the recruitment of BTK or PLCγ, to the cell membrane, thereby diminishing downstream events such as the increase in intracellular calcium levels. In addition, FcγRII2 activation leads to B-cell apoptosis through ITIM-and SHIP-independent signalling pathways that involves the cABL kinase family, BTK and JNK (Muraille et al., 2000; Tarasenko et al., 2007).

FcεRs signalling

As in other FcRs, phosphorylation of ITAMs plays a crucial role in FcεRs intracellular signaling. Lyn is the first kinase activated after FcεRI activation, and the Lyn-dependent

molecular pathway has long been known as the key pathway for mast cell activation (Rivera et al., 2008). Phosphorylated ITAMs serve as binding sites for the Syk kinase that is activated by Lyn (Goldstein et al., 2002). Syk kinase by itself is considered a downstream cellular signal amplifier. Several adapter proteins have been identified in a molecular pathway following Syk activation. Among these, LAT plays a crucial role in mast cell activation (Amir-Moazami et al., 2008). After Syk is phosphorylated it forms a membrane-associated molecular complex that includes other adapter proteins, such as SH2-containing leukocyte-specific protein of 76 kDa (SLP-76), growth factor receptor-bound (Grb)2, hematopoietic-specific guanine nucleotide exchange factor (Vav1), and PLC γ (Manetz et al., 2001; Sada and Yamamura, 2003). Phosphorylated PLC γ of the complex hydrolyzes phosphatidylinositol-4,5-bisphosphate (PIP2) to inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) (Tkaczyk et al., 2003; Urtz et al., 2004). IP3 causes initial release of calcium ions from intracellular magazines, while DAG activates protein kinase C (PKC), responsible for promoting the activation of many molecular pathway transcription factors, which results in the production of pro-inflammatory cytokines and growth factors (Kopeć et al., 2006). In addition, the hematopoietic-specific guanine nucleotide exchange factor Vav and the adapter protein Grb2, other components of the LAT-molecular membrane signaling complex, play a crucial role in the initiation of the MAPK pathway (Jabril-Cuenod et al., 1996; Kopeć et al., 2006).

The molecular pathways of Fc ϵ Rs signalling described above are Lyn kinase dependent. Recent studies have showed that The Fyn kinase-dependent signaling pathway also plays a role in Fc ϵ Rs signaling (Olivera et al., 2006). This was initially shown in Lyn-deficient mast cells as Fyn kinase activity is responsible for the intense degranulation (Nishizumi and Yamamoto, 1997). Fyn activation induces rapid phosphorylation of Grb2-associated binder protein 2 (Gab2) and formation of a signaling complex organized around Gab2 which contains tyrosine phosphatase and PI3K (Kopeć et al., 2006; Olivera et al., 2006; Yu et al., 2006). Activation of PI3K results in the production of PIP3, which plays an important role in calcium influx. PIP3 acts as an activator of PI3K-dependent kinase 1 (PDK1), which is an effector of Gab signaling (Williams et al., 2000; Gu et al., 2001). This leads to protein kinase Akt activation by PDK1. Akt activation leads to activation of transcription factors, such as nuclear factor (NF)- κ B and AP-1, crucial for the expression of the pro-inflammatory cytokine genes (Kitaura et al., 2000; Wang et al., 2009).

Fc α Rs signalling

Similar to Fc γ Rs and Fc ϵ Rs, Fc α RI-IgA triggers ITAM phosphorylation by the Src kinase Lyn, which leads to recruitment of a number of tyrosine kinases including Syk, BTK, PI3K, and PLC γ . This triggers calcium release from intracellular stores in leukocytes (Monteiro and Van De Winkel, 2003) and induction of NADPH oxidase activity in neutrophils (Lang et al., 2000; Monteiro and Van De Winkel, 2003). Fc α RI activation is also associated with Grb2, SHIP, and SLP-76 (Monteiro and Van De Winkel, 2003). Furthermore, Fc α R-IgA can also activate the ERK1/2 MAP kinase pathway and serine/threonine kinases such as PKC, and protein kinase B (PKB) (Ouahiri et al., 2002).

FC receptors in the brain

The Innate immune response is comprised of various pathogen-sensing protein families, which act both redundantly and in concert. Some of these defence systems exist within the CNS including Toll like receptors (TLRs) (Ma et al., 2006; Tang et al., 2007; Tang et al., 2008; Okun et al., 2009), chemokine receptors (Mélis-Parsadaniantz and Rostène, 2008) and the Complement system (Johnson et al., 1996; Arumugam et al., 2007; Stevens et al., 2007; Arumugam et al., 2009). Similarly, FcRs expressions within the CNS have been demonstrated on periventricular tissues, microglia, astroglia, oligodendrocytes and more recently on neurons (Nakahara et al., 2003b; Song et al., 2004). This section will focus on the expression and

function of FcRs in different CNS cell types, followed by a consideration of the roles of FcRs in neurodegenerative conditions.

Microglia

Microglial cells are bone marrow-derived macrophage-like cells that reside within the CNS. Constituting about 10% of all cells in the adult CNS, they mediate neural - immune interactions under both physiological and pathological conditions (Alliot et al., 1999). Microglia are capable of detecting invading pathogens using FcRs, complement, and TLRs (Falsig et al., 2008) and subsequently remove them via phagocytosis. FcRs have been studied extensively in microglia in different diseases (Song et al., 2004; Ueyama et al., 2004), and all classes of FcRs have been identified on microglia *in vitro* and *in vivo* (Vedeler et al., 1994). A role for FcγRs in microglial cells was observed by Ulvestad and colleagues who found that incubation of cultured microglia with immune complexes (IgG-coated red blood cells) induced phagocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and oxidative bursts. These responses were triggered by interaction of FcγRs with opsonized antigens, emphasizing a probable role for FcγRs as mediators of tissue injury within the CNS (Ulvestad et al., 1994). Furthermore, *Cryptococcus neoformans* complexed with murine IgG1, IgG2a and IgG3 but not IgG2b, were shown to be effective in inducing macrophage inflammatory protein (MIP)-1α and phagocytosis in primary human microglia via activation of FcγRs (Song et al., 2002). It was also shown that the Src inhibitor PP2 and the Syk inhibitor piceatannol inhibited phagocytosis and MIP-1α release, as well as phosphorylation of extracellular-regulated kinase (ERK) and Akt in human microglia, consistent with Src/Syk involvement early in FcγR signaling. FcγRs activation stimulated the transcription factor NFκB which induced the expression of MIP-1α (Song et al., 2004; Jin et al., 2006). These results indicate that FcγRs are involved in MIP-1α production in microglia via signaling pathways involving ERK and NF-κB.

The basal levels of FcRs in microglia are relatively low under normal physiological conditions, but are strongly upregulated during active disease states such as in MS lesions (Ulvestad et al., 1994). A study by Woodrooffe et al. showed that IFNγ treatment of adult rat-derived microglia resulted in enhanced expression of FcR and increased production of superoxide anions (Woodrooffe et al., 1989). Importantly, in a separate study the Fc binding capacity of microglia was found to be significantly greater than that of peritoneal cells, underlining the potential role of microglia in immune-mediated neurodegenerative disorders such as T-cell mediated demyelination in the case of MS (Woodrooffe et al., 1989). Microglia display enhanced expression of Fc receptors upon treatment with IFNγ, tumour necrosis factor-α (TNFα), interleukin-1 (IL-1), IL-4 and lipopolysaccharide (LPS) (Loughlin et al., 1992; 1993). The first major evidence for a role for microglial FcRs in brain disease was found when Peress and colleagues compared the expression of FcγRs in normal and AD brains. They showed FcγRI, FcγRII and FcγRIII immunoreactivity in senile plaques and on ramified microglia throughout the cortex and white matter of normal and AD brains (Peress et al., 1993). FcγRI, FcγRII and FcγRIII immunoreactive microglia were present in active MS lesions, in contrast to little or no expression of these IgG receptors in the same brain regions of normal control subjects, suggesting a role for these Fcγ receptors in MS pathogenesis (Ulvestad et al., 1994).

Astroglia

Astrocytes have been regarded as the matrix of the CNS and as providers of nutritional, metabolic support to neurons. In contrast to microglia, astrocytes are the least studied CNS cell type in respect to FcR expression and function. The few studies that have been made are outdated and vague. Primary cultured murine astrocytes express FcRs (Nitta et al., 1992). A physiological role for astrocyte FcγRs was shown when murine astrocytes prepared from newborn BALB/c mice demonstrated killing activity against allogeneic T cell leukemia by

ADCC (Nitta et al., 1992). After treatment with the macrophage activating factor, IFN γ , both the expression of Fc γ Rs and the killer activity of astrocytes were augmented. Another recent study investigated the role of Fc γ R in astrocytes as well as in microglial cells using a transient blood-brain-barrier (BBB) opening model (Li et al., 2008). Real-time PCR analysis showed that epinephrine-induced BBB opening significantly increased Fc γ RI mRNA expression in brain tissue homogenates (Li et al., 2008). Double-label immunostaining for Fc γ RI and Iba1 (a specific marker for microglia) or Fc γ RI and GFAP (a specific marker for astrocytes) showed that increased Fc γ RI expression was mainly in microglia and astrocytes (Li et al., 2008). Importantly, reactive and migrating rat astrocytes may sequester IgG, IgM and IgA as a critical function in restoring homeostasis to the injured or diseased nervous system (Bernstein et al., 1993).

Oligodendrocytes

Most of the studies of FcR in oligodendrocytes were made by Nakahara J et al. Evidence suggests that oligodendrocytes express a set of Fc γ R. Nakahara and colleagues showed basal mRNA expression of Fc γ R in established oligodendrocytes and their precursor cells (OPCs) expressing A2B5, Olig2 and NG2, both in vitro and in vivo (Nakahara et al., 2003a). Fc γ R activation in these cells stimulates Fyn signalling and induces rapid morphological differentiation with upregulation of myelin basic protein (MBP) expression levels (Nakahara et al., 2003a). Interestingly, mice deficient in Fc γ R are hypomyelinated and have reduced MBP content (Nakahara et al., 2003a). Another recent study by same group further showed that the expression of Fc α R/Fc μ R in OPCs is observed in monopolar, bi-polar, tri-polar or more differentiated multi-polar cells. In-vivo, Fc α / μ R is observed primarily in the subventricular zone (SVZ) of the lateral ventricle, where OPCs are born. Cells positive for Fc α / μ R, with a morphology of immature oligodendrocytes also observed, primarily in the corpus callosum adjacent to the lateral ventricle. Similar to *in vitro* findings the expression of Fc α / μ R in these cells had a unique polarity (Nakahara et al., 2003b).

Neurons

The expression and functionality of FcRs in neurons is still controversial as several early studies failed to identify FcRs in neurons (Perry et al., 1985). Andoh and Kuraishi published the first direct evidence for neuronal FcRs expression (Andoh and Kuraishi 2004a; Andoh and Kuraishi 2004b). This study showed that the high affinity IgG receptor Fc γ RI, but not the low affinity receptors Fc γ RII and Fc γ RIII, is expressed on mouse dorsal root ganglion (DRG) neurons, especially small- or medium-sized neurons (Andoh and Kuraishi 2004a). Furthermore, they showed that IgG bound to DRG neurons formed a complex with ragweed pollen, increasing the concentration of Ca²⁺ ions in the DRG neurons. This increase was inhibited by a Ca²⁺ chelator, Ca²⁺ channel blockers, and anti- Fc γ RI antibody. IgG-antigen complex released substance P from DRG neurons; thus, IgG and antigen combine on primary sensory neurons to directly activate them, perhaps playing a role in pain and inflammatory signaling (Andoh and Kuraishi 2004a). The same group investigated whether IgE receptors are expressed on sensory neurons in mice. Immunostaining revealed that the high affinity IgE receptor Fc ϵ RI was expressed in cultured DRG cells and that Fc ϵ RI-immunoreactive cells were mainly positive for a neuronal marker (Andoh and Kuraishi 2004b). In addition, Fc ϵ RI immunoreactive cells were also positive for the high affinity IgG receptor Fc γ RI, and the expression level of Fc ϵ RI was lower than that of Fc γ RI (Andoh and Kuraishi 2004b). Mohamed and colleagues have demonstrated that in amyotrophic lateral sclerosis (ALS) patients IgG can be taken up by motor neuron terminals and can alter the function of neuromuscular synapses, such as increasing intracellular calcium levels and spontaneous transmitter release from motor axon terminals after passive transfer (Mohamed et al., 2002). Furthermore they found that Fc γ Rs appear to participate in IgG uptake into motor neurons as well as IgG-mediated increases in intracellular calcium levels and acetylcholine release from motor axon terminals (Mohamed

et al., 2002). Finally, a more recent study indeed showed that neurons in the CNS also express FcRs. Nakamura et al. (2007) showed that FcγRIIb along with CD3 are involved in cerebellar functions. FcγRIIb was expressed on Purkinje cells in the cerebellum and FcγRIIb-deficient mice showed an impaired development of Purkinje neurons. In the adult, rotarod performance of FcγRIIb-deficient mice was impaired at high speeds. These results indicated for the first time that FcRs may play critical roles in the developmental and functional establishment in the cerebellum (Nakamura et al., 2007).

Fc receptors in neurological diseases

Accumulating evidence suggests that FcRs not only participate in immune-related physiological processes, but are also critically involved in neurological disease pathogenesis. For example, recent studies have pointed the critical roles of FcRs expressed on microglia in the inflammatory cascade in neurological disorders. This section summarizes our current knowledge of the role of FcRs in the pathogenesis of brain disorders such as ischemic stroke, Alzheimer's disease, Parkinson's disease and multiple sclerosis.

Ischemic stroke

Ischemic brain injury results in increased permeability of the BBB to vascular proteins and blood-borne leukocytes (Arumugam et al., 2005; Arumugam et al., 2009). Ischemic stroke also enhances the interactions of vascular endothelial cells with extravascular brain cells (astrocytes, microglia, and neurons) and intravascular cells (platelets and leukocytes), interactions that may contribute to the injury process (Yenari et al., 2006). There is a large body of evidence that implicates leukocytes in the pathogenesis of stroke injury and the pathophysiological significance of lymphocyte recruitment into the brain after ischemic stroke was recently reported (Arumugam et al., 2005; Arumugam et al., 2006; Ishikawa et al., 2005; Yilmaz et al., 2006; Liesz et al., 2009; Shichita et al., 2009).

Experimental and clinical studies have documented increased levels of oxidative stress during all forms of stroke injury. In addition, certain resident cell populations within the brain are able to secrete proinflammatory mediators following an ischemic insult including microglia, endothelial cells, astrocytes and neurons, which greatly contribute to brain injury. Reactive oxygen species involved in stroke-induced brain injury include superoxide anion radical, hydroxyl radical and nitric oxide (NO). Reactive oxygen species can also be generated by activated microglia and infiltrating peripheral leukocytes via the NADPH oxidase system during ischemic injury (Love, 1999; Haberman et al., 2007; Breckwoldt et al., 2008). Both oxygen free radicals and reactive nitrogen species are involved in activating several pathways involved in cell death following stroke, including apoptosis and inflammation. In the ischemic brain, microglia and infiltrating leukocytes are the major source of inflammatory cytokines (Arumugam et al., 2005). Therefore, inhibition of microglial activation can protect against stroke associated pathological changes (Yenari et al., 2006). After ischemia, microglial activation results in a series of functional and morphological modifications that involve proliferation (Lalancette-Hébert et al., 2007).

Recently, Komine-Kobayashi and colleagues assessed the role of FcγR in ischemic stroke using the middle cerebral artery (MCA) occlusion/reperfusion model in FcγR knockout (FcγR^{-/-}) mice and bone marrow chimeric FcγR^{-/-} mice (Komine-Kobayashi et al., 2004). FcγR^{-/-} mice have reduced mortality (20%) and smaller infarcts compared to FcγR^{+/+} mice at 72 hours after reperfusion. The same study showed that FcγR contributes to the activation of microglia, induction of iNOS followed by generation of reactive oxygen species, and infiltration of bone marrow-derived macrophages during cerebral I/R. Immunoblotting revealed that microglial activation and induction of inducible nitric oxide synthase were reduced in FcγR^{-/-} mice compared with wild-type mice. Komine-Kobayashi and colleagues showed that microglial

activation was markedly suppressed in ischemic lesions from the early stage of reperfusion in FcγR^{-/-} mice compared with WT mice, which provides strong evidence that FcγR plays a crucial role in the initiation and progression of neuronal damage by activation and proliferation of microglia (Komine-Kobayashi et al., 2004). Activation and migration of FcγR^{+/+} bone marrow-derived macrophages is markedly reduced in FcγR^{-/-} mice even at 7 days following reperfusion. This study demonstrated that the neuroprotective effect of FcγR deficiency may be primarily attributable to suppression of inflammatory cell activation and infiltration. However, a role for neuronal FcRs in ischemic stroke induced brain injury was not investigated. Our preliminary data show that all four FcγRs are expressed in neuronal cells (Arumugam et al., unpublished observations). Future studies investigating the role of neuronal FcγRs in ischemic stroke-induced neuronal cell death may reveal the therapeutic importance of FcRs in stroke.

Intravenous immunoglobulin (IVIG) is a therapeutic modality approved for the treatment of various conditions, and is increasingly used for autoimmune disorders to suppress immune-mediated tissue damage, particularly in neuro-autoimmune diseases. We have recently shown that administration of IVIG to mice subjected to experimental stroke almost entirely eliminated mortality and reduced the size of brain infarction by 50-60% (Arumugam et al., 2007). Moreover, within the ischemic region of the cerebral cortex neurons were spared and only occasional cell loss was observed in IVIG treated mice (Arumugam et al., 2007). The efficacy of IVIG against stroke-induced brain injury in our study was due, in part, to its ability to selectively bind complement components and reduce cell adhesion molecule production and subsequent infiltration of inflammatory cells, thus reducing inflammation in the infarcted region (Arumugam et al., 2007). In additional studies we provided evidence that IVIG can directly protect neurons against ischemia-like conditions. However the mechanism by which IVIG directly protects neurons under ischemic conditions is not yet understood. We found that oxygen and glucose deprivation (OGD) in cultured neurons caused an increase in levels of cleaved (enzymatically active) caspase-3 (a marker of apoptosis) and a progressive decrease in neuronal viability. Treatment with IVIG suppressed the OGD-induced increases in activated caspase-3 levels suggesting the IVIG protect against neuronal cell death directly by unknown mechanisms (Arumugam et al., 2007).

The majority of the activities conferred by IVIG may be mediated through FcγR in immunocompetent cells because protection is seen with the Fc fragment of IVIG alone and does not require classical antibody-binding components (Ravetch et al., 2001). The binding of infused IgG molecules to FcγR on the surface of phagocytic cells that invade the target tissues of patients with various autoimmune neurologic diseases can prevent FcγR-mediated phagocytosis of antigen-bearing target cells or inhibit antibody-dependent cell-mediated cytotoxicity by saturating or altering the affinity of the FcγR (Bayry et al., 2007). Ravetch and colleagues established a framework for the cellular basis of a sustained anti-inflammatory IVIG effect. IVIG indirectly up-regulates the expression of inhibitory FcγRIIb on inflammatory macrophages, which would be expected to oppose activating FcγR signaling, thereby suppressing the antibody-triggered inflammatory response (Andersson et al., 2005). As mentioned above, under certain conditions, neurons in the CNS express FcR. However, the expression and the role of FcR in neuronal cells in ischemic stroke injury are not well established. Our preliminary study shows that the expression of some FcR in neurons changes in response to OGD *in vitro* (unpublished data). As we have already shown that IVIG directly protects neurons against OGD induced neuronal cell death, FcγR subtypes in neurons and activation of these FcγRs on neurons may contribute to the neuronal cell death and IVIG treatment may protect neurons by modulating activity of FcγRs. However, further researches needed to establish how IVIG protects neurons directly in ischemic conditions.

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by memory loss and other cognitive and behavioral deficits. Definitive diagnosis of AD is based on the presence of extracellular amyloid plaques comprised of neurotoxic amyloid β -peptide ($A\beta$), which is generated by proteolysis of the β -amyloid precursor protein (APP), and intracellular neurofibrillary tangles composed of hyperphosphorylated insoluble forms of tau protein (Mattson, 2004). Genetic factors that either cause or predispose to AD include mutations in APP and presenilins 1 and 2 (which cause early-onset autosomal dominant inherited AD) and polymorphisms in apolipoprotein E (ApoE4 increases the risk of AD). Activation of the innate immune response by reactive glia is a consistent pathological event in AD. Neuroinflammation in AD brain is concentrated at sites of $A\beta$ plaques, which exhibit increased levels of pro-inflammatory cytokines, complement components and proteases (Akiyama et al., 2000; McGeer et al., 2006). $A\beta$ plaques are surrounded and infiltrated by activated astrocytes and microglia, which are believed to be the major source of local inflammatory components (Akiyama et al., 2000). Neuroinflammation is proposed to play a major role in AD pathogenesis, as long term treatment with non-steroidal anti-inflammatory drugs reduces AD risk and may delay disease progression (Beard et al., 1998; Scali et al., 2000).

Early studies by Peress and colleagues have found Fc γ RI, Fc γ RII and Fc γ RIII immunoreactivity in senile plaques and on ramified microglia throughout the cortex and white matter of normal and AD (Peress et al., 1993). More recently, roles for FcRs in $A\beta$ clearance by microglial cells were reported by various groups. Treatment with anti- $A\beta$ antibodies resulted in attenuation of $A\beta$ deposition and associated pathologies (Bard et al., 2000, 2003; Wilcock et al., 2003) as well as prevent cognitive deficits in mice (Holtzman et al., 2002; Rakover et al., 2007; Wilcock and Colton, 2009). Bard et al. (2000) have shown that antibodies against $A\beta$ -peptide triggered microglial cells to clear plaques through FcR mediated phagocytosis and subsequent peptide degradation. However, recent studies by Das and colleagues have examined the efficacy of $A\beta$ immunization in amyloid precursor protein (APP) mutant transgenic mice crossed lacking Fc γ R^{-/-}. In APP transgenic mice lacking Fc γ R^{-/-}, $A\beta$ immunization significantly attenuated $A\beta$ deposition, as assessed by both biochemical and immunohistological methods. The reduction in $A\beta$ accumulation was equivalent to the reduction in deposition seen in $A\beta$ immunized, age-matched, FcR^{+/+} APP transgenic mice. Results from this study showed that the effects of anti- $A\beta$ antibodies on $A\beta$ deposition in APP Tg2576 transgenic mice are not dependent on FcR-mediated phagocytic events (Das et al., 2003). Another study demonstrated that clearance of amyloid deposits *in vivo* may involve a non-Fc-mediated disruption of plaque structures (Bacskai et al., 2002). Bacskai and colleagues used antibodies which lack the Fc region IgG2b (3d6) applied directly to the brains of 18-month-old Tg2576 or 20-month-old PDAPP (PDGF promoter expressing amyloid precursor protein) mice. Using *in vivo* multiphoton microscopy, they found that FITC-labeled F(ab')₂ fragments of 3d6 (which lack the Fc region of the antibody) also led to clearance of 45% of the deposits within three days. This result suggests that direct disruption of plaques, in addition to Fc-dependent phagocytosis, is involved in the antibody-mediated clearance of $A\beta$ deposits *in vivo* (Bacskai et al., 2002). Furthermore, Levites and colleagues (2006) confirmed anti- $A\beta$ monoclonal antibody either indirectly enhancing clearance of $A\beta$ or targeting a low abundance aggregation intermediate. Levites and colleagues (2006) have examined the *in vivo* binding properties, pharmacokinetics, brain penetrance, and alterations in $A\beta$ levels after a single peripheral dose of anti- $A\beta$ antibodies to both wild-type and young non- $A\beta$ depositing APP and BRI- $A\beta$ 42 mice. The rapid rise in plasma $A\beta$ observed after antibody administration is attributable to prolongation of the half-life of $A\beta$ bound to the Ab. Despite dramatic increases in plasma $A\beta$, no evidence that total brain $A\beta$ levels are significantly altered (Levites et al., 2006). Finally, only a tiny fraction of anti- $A\beta$ antibodies entered the brain (Levites et al., 2006).

Parkinson disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the selective loss of dopaminergic neurons from the substantia nigra compacta (SNc) region of the midbrain and the presence of Lewy body inclusions in residual neurons. Many studies indicate that PD is associated with several factors including genetic predisposition, innate characteristics of the nigrostriatal dopaminergic system of the brain, and exposure to environmental toxins (Hirsch and Hunot, 2009; Lees et al., 2009). Increasing evidence also suggests the involvement of immune and inflammatory systems in PD (Hirsch and Hunot, 2009). It has been suggested that degeneration of dopaminergic neurons in the substantia nigra (SN) can be caused by immune-mediated processes (Appel et al., 1992; Le et al., 1995), indicating a potential role for immune mechanisms in the destruction of SN neurons.

Antibodies to dopaminergic neurons have been found in the cerebrospinal fluid of some PD patients (McRae- Degueurce et al., 1988; Dahlstrom et al., 1990) and PD cerebrospinal fluid may contain factors that cause specific dopaminergic neuronal cell injury (Le et al., 1999), further supporting a possible autoimmune mechanism for SNc dopaminergic neurodegeneration in PD. Particularly, IgG from the serum of PD patients can selectively induce degeneration of mesencephalic dopaminergic neurons by activating microglia in vitro and in vivo (Chen et al., 1998; He et al., 2002). IgG from PD patients has also been demonstrated to activate microglia via the FcγRs on them (He et al., 2002). He and colleagues have recently shown the involvement of microglial FcγR in IgG-induced lesions of SN in vivo. They have shown that the tyrosine hydroxylase (TH)-positive cell loss in SNc in mice lacking FcγRs^{-/-} mice was significantly reduced compared to wild type control animals. Furthermore, the injection of F(ab')₂ fragments of PD IgG was able to induce TH-positive neuronal loss in the SNc only when the injected animals raised antibodies against the injected human IgG fragments, which confirmed the importance of the FcγR in microglial activation and nigral injury (He et al., 2002).

Roles for other FcR subtypes in PD have also been suggested. Hunot et al. (1999) have shown that FcεRII was found in both astroglial and microglial cells in PD patients. Combined treatment with IFNγ, interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) induced the expression of FcεRII in glial cells. Ligation of FcεRII with specific antibodies resulted in the induction of iNOS and the subsequent release of NO. The activation of FcεRII also induced TNFα expression, which was dependent on NO release. In the SN of PD patients, a significant increase in the density of glial cells expressing TNFα, IL-1β, and IFNγ was observed. Altogether, these data demonstrate the involvement of FcR-mediated glial cell activation in the pathophysiology of PD (Hunot et al., 1999).

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease in which the CNS is attacked by infiltrating immune cells leading to demyelination of axons. In rodents, MS is simulated by various forms of experimental autoimmune encephalomyelitis, in which T cells (more specifically, TH-17 cells), antibodies, cytokines and complement factors interact with the CNS myelin proteins and lead to inflammatory damage.

Early reports found abnormalities in the proportions of total T lymphocytes in peripheral blood lymphocytes (PBL) of patients with MS that were accompanied by high proportions of T lymphocytes with FcRs for IgG (T_γ cells) (Merrill et al, 1980a). Moreover, MS patients have a higher proportion of total T cells, T_γ cells and T_γ/μ (T cells expressing FcRs for IgG as well as IgM) cells in their CSF and their peripheral blood compared to the same cell populations in samples from normal control subjects (Merrill et al, 1980b). In active MS lesions, reactive microglia are strongly stained for FcγRI, FcγRII, and FcγRIII (Ulvestad et al, 1994). Robbie-

Ryan et al. (2003) tested the myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE) model using two different FcγR^{-/-} DBA/1 mouse strains. The first were the FcγR chain-deficient mice, which lack FcγRI, FcγRIII and FcεRI, while the second strain lacked only FcγRII. Interestingly, while the lack of FcγRII enhances the disease susceptibility with associated increased CNS demyelination, FcγR^{-/-} littermates were protected despite initial peripheral autoimmune responses to MOG. Mice reconstituted with FcγR^{-/-} bone marrow-derived mast cells (BMMCs) or FcγRIII^{-/-} BMMCs exhibited less severe clinical symptoms similar to controls mice, while reconstitution with FcγRIIb^{-/-} BMMCs resulted in disease significantly more severe. Notably, mice reconstituted with FcγRIII^{-/-} BMMC exhibit a relapsing-remitting course of disease. The importance of this study is that both activating and inhibitory FcRs expressed on mast cells influence the course of EAE (Robbie-Ryan et al. 2003).

Urich and colleagues found that the functional expression of FcγR on systemic accessory cells, but not CNS-resident cells, is vital for the development of CNS inflammation, independent of antigen-presenting cell function or Ab involvement (Urich et al., 2006). Interestingly, injection of anti MOG-Abs drastically worsens disease severity, inflammation, and demyelination. Using FcγR^{-/-} and C1q^{-/-} mice, it was shown that the demyelinating capacity of such auto Ab in vivo relies entirely on complement activation and is independent of FcR (Urich et al. 2006).

Conclusions

The role of FcR in the innate immune system has been widely studied. The roles of FcRs in the physiology and pathology of the CNS have only recently begun to be appreciated. Very little is known of the pathways affected by FcR activation in astrocytes and neurons, and we know even less on the interaction between FcRs and other innate immune related receptors in the cells. Several immune-related receptor pathways have been implicated in the pathogenesis of neurodegenerative disorders. The use of mouse strains deficient in one or more FcRs has provided clues as to their involvement in disease pathology. Similar to the experiments described above for studies of MS in which FcR^{-/-} mouse strains were employed, it will be of considerable interest to cross FcR-deficient mice with mouse models of AD, PD, HD and ALS. Activation of FcRs in glial cells and neurons may have either deleterious or beneficial affects on the processes (amyloidogenesis, α-synuclein and huntingtin pathologies) involved in neuronal dysfunction and death. Finally, FcRs may provide novel targets for therapeutic intervention in a range of neurological disorders, as suggested by studies of the neuroprotective action of IVIG in animal models of stroke and MS. Refinement of this research to elucidate the specific isotypes of Igs that suppress inflammation and protect neurons will be required to enhance the specificity and tolerability of therapeutic agents that target FcRs.

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Figure 1.

The outcomes of FcR activation during ischemic injury. FcRs are activated by natural antibodies and induce JNK, p-38, NFκB and AP-1 activation in neurons, glial cells, endothelial cells, and infiltrating leukocytes. This culminates in proinflammatory cytokine and chemokine secretion. In neurons, the JNK/AP-1 pathway is activated, which promotes further lipid peroxidation and apoptosis. FcRs activation promotes leukocyte adhesion and infiltration, endothelial cell dysfunction and causes blood-brain barrier permeability. IVIG treatment activates FcγR2B which inhibits FcR activation during ischemic stroke.

Fc receptor nomenclature**Table 1**

Receptor	Ligand	Isoforms
Fc γ R1	IgGs	Ia, Ib1, Ib2, Ic
Fc γ R2	IgGs	IIa1, IIa2, IIb1, IIb2, IIb3, IIc
Fc γ RIII	IgGs	IIIa, IIIb
Fc γ RIV	IgGs	
Fc ϵ R1	IgEs	
Fc ϵ R2	IgEs	
Fc α R1	IgAs	Ia1, Ia2
Fc μ R	IgMs	
Fc δ R	IgDs	

Table 2
Fc receptor expression and function in CNS cells

Cell type	FcR expression	Function of FcR	References
Neurons	FcγRI FcεRI (on DRG cells)	Increasing the concentration of Ca ²⁺ ions in the DRG neurons.	Andoh and Kuraishi 2004a
		FcγRs participates in IgG uptake into motor neurons FcγR increases intracellular calcium levels and acetylcholine release from motor axon terminals.	Mohamed et al., 2002
	FcγRIIb was expressed on Purkinje cells in the cerebellum		Nakamura et al., 2007
Astrocytes	FcγRI	FcγRI is activated and results in anti-inflammation in astrocytes after transient BBB opening	Li et al., 2008
		killing activity against allogeneic T cell leukemia by ADCC	Nitta et al., 1992
Oligodendrocytes	FcγR FcαR/FcμR	FcγR stimulates Fyn signalling and induces rapid morphological differentiation with upregulation of myelin basic protein (MBP) expression levels	Nakahara et al., 2003a
		Mice deficient for FcγR are hypomyelinated and have reduced MBP content	Nakahara et al., 2003a
Microglia	Express all FcRs		Vedelr et al., 1994
		FcγR activation induces phagocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC), and oxidative bursts	Ulvestad et al., 1994
		FcγR activation causes macrophage inflammatory protein (MIP)-1a and phagocytosis	Song et al., 2002
		FcγR activation stimulates the transcription factor NFκB which induced the expression of MIP-1a	Song et al., 2004; Jin et al., 2006
		that IFNγ treatment of adult rat-derived microglia resulted in enhanced expression of FcR and increased production of superoxide anions	Woodroffe et al., 1989
		Microglia display enhanced expression of Fc receptors upon treatment with IFNγ, tumour necrosis factor-alpha (TNFα), interleukin-1 (IL-1), IL-4 and lipopolysaccharide (LPS)	Loughlin et al., 1992; 1993
		FcγRI activation results in anti-inflammation in microglia after transient BBB opening	