1 Introduction

Pattern recognition receptors (PRRs) are germline encoded receptors utilized by cells of the innate immune system for pathogen recognition. PRRs are classically activated by pathogen-associated molecular patterns (PAMPs) present in whole classes of pathogens, but not in mammalian cells, termed the “infectious nonself model” (Medzhitov and Janeway, 2002). It has also been recent appreciated that there are self-derived products released upon tissue injury or necrotic cell death that can activate PRRs (Morgan et al., 2005). PRR activation leads to opsonization, activation of complement and coagulation cascades, phagocytosis, activation of proinflammatory signaling pathways, and the induction of apoptosis (Janeway and Medzhitov, 2002; Matzinger, 2002). Additionally, activation of the innate immune system is crucial for the induction of adaptive immune responses and the eventual clearance of pathogens (Janeway and Medzhitov, 2002).

The CNS has long been considered to be an immunologically ‘privileged’ organ, largely due to early studies showing that rejection of allografts placed within the CNS was delayed or deficient in comparison to rejection of grafts placed at peripheral sites (Geyer et al., 1985; Head and Griffin, 1985). In recent years however, it has become clear that the CNS should be more accurately described as an immunologically ‘specialized’ organ. The CNS is constitutively monitored by the immune system, but at low levels compared to other sites (Hickey, 2001), making it crucial that CNS-resident cells be capable of rapidly recognizing and responding to infection. In this chapter, we discuss PRRs expressed by CNS resident cells and how they contribute to pro-inflammatory responses during CNS infection. We also discuss recent studies demonstrating that PRRs may contribute to neurodegenerative diseases when chronically activated, but their controlled activation may actually have neuroprotective functions.
2 Expression and Regulation of Pattern Recognition Receptors by CNS Resident Cells

2.1 Toll-like Receptors (TLRs)

TLRs are a large family of PRRs in the vertebrate immune system and are highly evolutionarily conserved, providing evidence of their importance in host defense (Roach et al., 2005). At least 13 TLR genes have been identified in mice, and the family is even larger in other vertebrate species, although ligands have not been identified for all of them and some may be pseudogenes in various species (Kawai and Akira, 2005; Roach et al., 2005). All known TLRs with the possible exception of TLR3 are believed to signal through the adaptor protein MyD88, which also is critical for interleukin-1 (IL-1) receptor signaling, and all lead to the activation of the transcription factor nuclear factor κB (NFκB) (Kawai and Akira, 2005). TLR3 and TLR4 can signal through an MyD88-independent pathway dependent on the adaptor TRIF and activate both NFκB and interferon response factor 3 (IRF3) (Kawai and Akira, 2005). Many of the most well known PAMPs signal through TLRs, including lipopolysaccharide (LPS) and double stranded RNA (dsRNA) or its synthetic mimic polyinosinic-polycytidylic acid (poly I:C) signal through TLRs. The complete signaling mechanisms have been reviewed elsewhere (Roach et al., 2005; Zuany-Amorim et al., 2002) and the ligands for the known TLRs are summarized in Table 1.

In the resting CNS, TLRs1-9 have been detected by quantitative real time PCR, with particularly strong expression of TLR3 (Bottcher et al., 2003; McKimmie et al., 2005). In order to determine regional variation in TLR expression, in situ hybridizations have been performed for TLR2 and TLR4 and demonstrated constitutive expression primarily in circumventricular organs (CVOs) and meninges, areas with direct access to the circulation (Laflamme and Rivest, 2001; Laflamme et al., 2001). More recent studies suggest that TLR4 may also be expressed in the parenchyma throughout the brain as well, although at lower levels (Chakravarty and Herkenham, 2005). Expression of TLRs are upregulated in the CNS in response to circulating LPS, bacterial and viral infections, and other neuroinflammatory diseases, although

| Table 1 Summary of mammalian TLRs with some known ligands [summarized from (Kawai and Akira, 2005; Zuany-Amorim et al., 2002)] |
|---------------------------------|
| **Toll-like receptor** | **Ligand(s)** |
|-------------------------|---------------|
| TLR1/2, TLR2/6 | Peptidoglycans, diacyl and triacyl lipopeptides, LPS, zymosan |
| TLR3 | dsRNA, poly I:C |
| TLR4 | LPS, respiratory syncitial virus proteins, saturated and unsaturated fatty acids, hyaluronic acid fragments |
| TLR5 | Flagellin |
| TLR7, TLR8 | Imidazoquinolines, ssRNA |
| TLR9 | Unmethylated CpG DNA |
| TLR11 | Uropathogenic bacteria |
the extent to which this is due to the CNS infiltration of TLR-expressing immune cells is unknown (Bottcher et al., 2003; Bsibsi et al., 2002; Laflamme and Rivest, 2001; Laflamme et al., 2001; McKimmie et al., 2005; Zekki et al., 2002).

Studies using purified cultured CNS cells have demonstrated TLR expression on multiple cell types, most commonly microglia and astrocytes. Primary murine microglia in vitro constitutively express TLRs1-9, while human microglia express robust levels of TLRs1-8 but low TLR9 levels (Bsibsi et al., 2002; Dalpke et al., 2002; Kielian et al., 2002; Olson and Miller, 2004). In comparison, astrocytes express much lower levels of TLRs, but also express a wide variety (Bowman et al., 2003; Carpentier et al., 2005; Olson and Miller, 2004). Human astrocytes express TLRs1-5 and 9 and primary murine astrocytes reportedly express TLRs1-9, although a fair amount of controversy still exists with regards to the particular TLRs expressed by astrocytes and at what levels (Bsibsi et al., 2002; Carpentier et al., 2005; Farina et al., 2005; Jack et al., 2005; McKimmie and Fazakerley, 2005). It is apparent however that astrocytes express particularly high levels of TLR3 (Bsibsi et al., 2002; Carpentier et al., 2005; Farina et al., 2005), suggesting that astrocytes may be particularly important for anti-viral responses in the CNS. Microglia and astrocytes in vitro significantly upregulate TLRs upon treatment with cytokines, TLR agonists, and following infection with various pathogens (Bowman et al., 2003; Carpentier et al., 2005; Esen et al., 2004; Kielian et al., 2002; McKimmie and Fazakerley, 2005; Olson and Miller, 2004), providing a mechanism for amplification of inflammatory responses to pathogens infecting the CNS. This amplification of receptor expression may particularly important in astrocytes and in the CNS parenchyma, where constitutive expression of TLRs is quite low.

Although several studies describe TLR expression on astrocytes and microglia, few report TLR expression on other CNS resident cells. Human oligodendrocytes constitutively express TLR2 and 3 in vitro (Bsibsi et al., 2002). Human NT2-N cells, a neuronal cell line, express TLRs1-4 in vitro, and upregulate TLR3, interleukin-6 (IL-6), interferon-β (IFN-β), tumor necrosis factor (TNF), and CCL5 transcripts in response to viral infection or treatment with poly I:C (Prehaud et al., 2005), but this observation has yet to be confirmed in primary cells or in the intact CNS. A murine cerebral endothelial cell line (MB114EN) constitutively expresses TLRs 2, 4, and 9 (Constantin et al., 2004), and human brain microvessel endothelial cells in vitro are able to respond to LPS with the upregulation of adhesion molecules and chemokines, suggesting a key role of TLR signaling in promoting leukocyte extravasation into the CNS (Shukaliak and Dorovini-Zis, 2000; Wong and Dorovini-Zis, 1992, 1995).

**2.2 Non-TLR Recognition of Virus**

All cells express machinery to recognize and respond to viral infection through the activation of ubiquitously expressed viral PRRs. The serine/threonine kinase dsRNA-activated protein kinase R (PKR) is constitutively expressed at low levels
in most cell types including CNS resident cells under normal physiological conditions and is activated by dsRNA, which may be present in viral genomes or produced during viral replication (Williams, 1999). Upon dsRNA binding, PKR autophosphorylates and also phosphorylates a number of substrates, the best characterized of which is the α subunit of eukaryotic initiation factor 2 (EIF-2α), leading to translation inhibition in the infected cell. Other functions of PKR include the induction type I IFNs, cytokines, and chemokines and the promotion of apoptosis (Williams, 1999). DExD/H box-containing RNA helicases retinoic acid inducible gene 1 (RIG-1) and melanoma differentiation associated gene 5 (Mda5) are also ubiquitously expressed PRRs activated by dsRNA and have reported roles in viral-induced upregulation of type I interferons (Yoneyama et al., 2004).

2.3 Non-TLR Recognition of Bacteria

There are also non-TLR PRRs which recognize various components of bacteria. CD14, a receptor which coordinates with TLR4 and TLR2 for signaling, is expressed on microglia in vitro and in vivo (Becher et al., 1996; Esen and Kiellian, 2005; Laflamme and Rivest, 2001). The mannose receptor is a type I transmembrane C-type lectin that recognizes mannose-containing carbohydrate structures found on bacteria (Apostolopoulos and McKenzie, 2001). Its functions include receptor-mediated endocytosis and phagocytosis, microbicidal activity, and induction of cytokines, cell adhesion molecules, and major histocompatibility complex class II (MHC II) molecules (Apostolopoulos and McKenzie, 2001). Both primary rodent microglia and astrocytes constitutively express mannose receptors in vitro, and mannose receptors can be detected in the adult CNS in perivascular microglia/macrophages as well as a subset of neurons and astrocytes (Burudi and Regnier-Vigouroux, 2001; Burudi et al., 1999; Marzolo et al., 1999). Interestingly, mannose receptor expression on perivascular macrophages is upregulated in the CNS after injury, but its expression on microglia and astrocytes in vitro is downregulated in response to pro-inflammatory cytokines or LPS (Burudi et al., 1999; Galea et al., 2005; Marzolo et al., 1999). The functional importance of the downregulation of this receptor in the presence of inflammatory and infectious stimuli is unclear.

Originally characterized on macrophages for their ability to bind low-density lipoproteins, scavenger receptors type A and BI (SR-A and SR-BI) and CD36 also recognize a variety of PAMPs including LPS and lipoteichoic acid, as well as whole bacteria (Husemann et al., 2002). The main roles of SRs in the immune system are in mediating phagocytosis and uptake of pathogens, although their activation may also induce antigen presentation functions and reactive oxygen species (ROS) formation (Mukhopadhyay and Gordon, 2004). Murine microglia express SR-A, SR-BI, and CD36 in vitro although resting expression in vivo is low or undetectable (Husemann et al., 2002). However, these receptors can be upregulated by microglia in response to LPS or CNS injury (Bell et al., 1994; Husemann et al., 2002). Astrocytes may also
express SR-BI, but lack SR-A and CD36 expression (Husemann et al., 2002; Husemann and Silverstein, 2001).

Nucleotide-binding oligomerization domain (NOD) molecules recognize bacterial peptidoglycans (PGNs) and LPS and are able to induce apoptosis and regulate inflammatory responses (Inohara and Nunez, 2003). Primary murine astrocytes constitutively express low levels of NOD1 and robust NOD2 mRNA. Following exposure to LPS, flagellin, CpG DNA, and bacterial pathogens astrocytes upregulate NOD2 in vitro (Sterka et al., 2006). Primary microglia express low levels of NOD1 mRNA, but NOD2 expression on microglia is undetermined (Sterka et al., 2006).

3 Role of CNS Pattern Recognition Receptors in Response to Infection

The limited immune surveillance of the CNS makes it crucial that resident cells be able to rapidly recognize and respond to infection. Glial cells express TLRs and other PRRs and respond to their ligation by upregulating a variety of pro-inflammatory functions. The immune functions of these cells are important for the early control of pathogen replication and direct the recruitment and activation of cells of the adaptive immune system.

3.1 PRR Stimulation Activates Innate Immune Functions of Glia Cells

It is well known that both astrocytes and microglia have the potential to contribute to innate immune functions in the CNS following exposure to pathogens or PAMPs, and many of these functions have direct anti-microbial consequences. LPS, poly I: C as well as viral infection induce type I IFN expression by microglia and astrocytes, important for control of infection through the inhibition of translation, degradation of dsRNA and upregulation of MHC class I and class II antigens required for antigen presentation in the CNS (Carpentier et al., 2005; Olson et al., 2001; Olson and Miller, 2004; Palma et al., 2003; Samuel, 2001). Engagement of TLR ligands also induce cultured glia to produce iNOS, leading to high levels of nitric oxide production which has microbicidal activity (Boje and Arora, 1992; Carpentier et al., 2005; Dalpke et al., 2002; Galea et al., 1994; Olson et al., 2001; Olson and Miller, 2004). Both microglia and astrocytes express iNOS in vivo in response to CNS infection as well (Mack et al., 2003; Oleszak et al., 1997; Sun et al., 1995). Additionally, LPS can induce human astrocytes to express β-defensin, a small anti-microbial molecule effective at killing Gram-negative bacteria, some viruses, and fungi (Hao et al., 2001).
In response to TLR stimulation, glia also express chemokines, adhesion molecules, and cytokines important for the recruitment, infiltration and activation of peripheral leukocytes. The anatomic proximity of astrocytic endfeet to CVEs producing chemokines may render astrocytic production of chemokines particularly potent. Pathogens, as well as isolated PAMPs LPS, poly I:C, PGN and CpG DNA can stimulate the production of the chemokines CCL2, CCL3, CCL4, CCL5 and CXCL10 in astrocytes and microglia (Aravalli et al., 2005; Carpentier et al., 2005; Esen et al., 2004; Hayashi et al., 1995; Hua and Lee, 2000; Kielian et al., 2002; Olson et al., 2001; Olson and Miller, 2004; Palma and Kim, 2001; Takeshita et al., 2001). Importantly, both astrocytes and microglia have been implicated as a major source of these chemokines in vivo during a variety of neuroinflammatory diseases [reviewed in (Ambrosini and Aloisi, 2004)].

Astrocytes also promote leukocyte invasion of the CNS via their expression of VCAM-1 and ICAM-1, which are known to be crucial for leukocyte infiltration (Ransohoff et al., 2003). Astrocytes in vitro express low constitutive levels of these molecules, that can be upregulated by LPS, poly I:C, or CpG DNA (Carpentier et al., 2005; Lee et al., 2004; Pang et al., 2001) Interestingly, when CVE expression of VCAM-1 is intact, but astrocytic expression is selectively lost, T cells accumulate perivascularly but do not penetrate into the CNS parenchyma (Gimenez et al., 2004) suggesting that astrocytic expression of adhesion molecules is crucial for the penetration of leukocytes into the CNS parenchyma. Microglia can also express high levels of adhesion molecules after stimulation via TLRs, although it is unknown how they contribute to leukocyte invasion (Dalpke et al., 2002; Olson and Miller, 2004).

Glial cells are also sources of cytokines that may impact developing adaptive immune responses in the CNS. Stimulation of astrocytes with flagellin, PGN, LPS, CpG, or poly I:C is effective in inducing IL-6, IL-1 and TNF production, the cytokines most frequently expressed by activated astrocytes (Bowman et al., 2003; Carpentier et al., 2005; Esen et al., 2004; Farina et al., 2005; Sharif et al., 1993; Takeshita et al., 2001). These cytokines are also produced by astrocytes in vivo during neuroinflammation (Maimone et al., 1997; Sun et al., 1995). Microglia also express TNF, IL-6, and IL-1β in response to the TLR agonists LPS, poly I:C, PGN and CpG DNA (Kielian et al., 2002; Lee et al., 1993; Olson and Miller, 2004; Takeshita et al., 2001). All of these molecules have the potential to activate a pro-inflammatory response in both the CNS and the periphery and have also been implicated in mediating BBB damage (de Vries et al., 1996) and promoting efficient leukocyte entry into the CNS. Microglia in vitro produce IL-12, IL-18, and IL-23, potent cytokines involved in Th1 differentiation, in response to many of these stimuli (Constantinescu et al., 1996; Dalpke et al., 2002; Li et al., 2003; Olson and Miller, 2004; Stalder et al., 1997; Takeshita et al., 2001). Astrocytes have been reported to express these molecules as well (Constantinescu et al., 1996, 2005; Stalder et al., 1997), although it is generally thought that microglia are the major CNS resident source of IL-12 and IL-23 (Wheeler and Owens, 2005). The complete roles of cytokines during CNS inflammation is discussed elsewhere in this volume.
TLR stimuli also promote the phagocytic activity of microglia which become bactericidal upon stimulation with CpG DNA, *E. coli* DNA, and *S. aureus* in vitro (Dalpke et al., 2002; Kielian et al., 2002). Increased phagocytic activity promotes the processing of antigens for presentation to T cells. Upon LPS, poly I:C, or CpG DNA stimulation, murine microglia upregulate cell surface expression of both costimulatory molecules and MHC I and II, which are critical for T cell activation (Dalpke et al., 2002; Kielian et al., 2002; Olson and Miller, 2004). Microglia become capable of processing and presenting antigen to CD4+ and CD8+ T cells following TLR ligand and IFN-γ exposure, indicating microglia may be relevant for activating CD4+ and CD8+ T cells infiltrating the CNS (Dalpke et al., 2002; Dhib-Jalbut et al., 1990; Frei et al., 1987; McMahon et al., 2005; Olson and Miller, 2004).

Although PAMPs are efficient at inducing innate immune functions of astrocytes, they are not effective at inducing antigen presenting cell functions of astrocytes (Carpentier et al., 2005). LPS or poly I:C stimulated astrocytes are not able to efficiently activate CD4+ T cells due to a deficiency of MHC class II expression, indicating that astrocytes are likely not involved in activation of T cells infiltrating the CNS early after infection. In contrast, astrocytes constitutively express low levels of MHC I which is increased by poly I:C stimulation or virus infection and these cells can therefore possibly activate or be lysed by CD8+ T cells (Carpentier et al., 2007; Cornet et al., 2000; Suzumura et al., 1986).

Several investigators have confirmed the necessity of TLRs for responses of glial cells to these ligands as well as to pathogens. As expected, CD14 and TLR4 are required for glial responses to LPS (Kitamura et al., 2001; Qin et al., 2005). Similarly, TLR3 is necessary for full glial activation by poly I:C (Park et al., 2006; So et al., 2006; Town et al., 2006) and TLR2 mediates glial responses to PGN (Esen et al., 2004; Kielian et al., 2005a). Interestingly, TLR2 also mediates astrocyte responses to intact *S. aureus*, but it is dispensable for microglial activation by the same bacteria (Esen et al., 2004; Kielian et al., 2005a), indicating that microglia, but not astrocytes, have multiple mechanisms by which recognition of this bacteria occurs. We have also noted that while TLR3−/− astrocytes display reduced responses to poly I:C, their responses to direct infection with Theiler’s virus are normal. Rather, it appears that PKR is the more important mediator of inflammation in virus-infected astrocytes (Carpentier et al., 2007). It is not surprising that responses to intact pathogens do not depend on a single TLR, but rather multiple pathways can be activated and compensate for loss or lack of another. Such redundancy is necessary for protective immunity, since so many pathogens have evolved mechanisms to block innate immune signaling pathways as a mechanism of immune evasion.

### 3.2 CNS Cells are Activated by Peripherally Administered PAMPs

It has long been recognized that peripheral infection has profound effects in the CNS, resulting in fever and stimulation of the hypothalamic-pituitary-adrenal axis. Peripheral infection or injection of LPS also causes a set of behavioral symptoms
collectively termed “sickness behavior”, including anorexia, modification of sleep patterns, decreased locomotor activity, libido, social and exploratory behavior (Roth et al., 2004). Peripheral injection of LPS results in a variety of molecular changes in the CNS, particularly the upregulation of pro-inflammatory cytokines like IL-6, IL-1β, and TNF, (Breder et al., 1994; Chakravarty and Herkenham, 2005; Vallieres and Rivest, 1997). Many of these effects can be mimicked by the intravenous injection of high levels of the recombinant cytokines, and blocking cytokine action in the periphery or CNS can partially inhibit the induction of fever and sickness behavior (Roth et al., 2004), suggesting that many of the infection-induced CNS effects result from the production of pro-inflammatory cytokines by peripheral immune cells. However, cytokine-targeting strategies to prevent LPS-induced fever are only partially effective, and the early response to LPS is often intact (Roth et al., 1998), indicating that other mechanisms must also be involved. The CNS response to pyrogens is thought to be initiated in the CVOs, which lack a blood–brain barrier and therefore are accessible to large circulating molecules. CVOs express high levels of TLR4 and CD14 in comparison to the rest of the CNS parenchyma (Chakravarty and Herkenham, 2005; Laflamme and Rivest, 2001), demonstrating the possibility that these organs can directly respond to circulating LPS. Recently, TLR4 expression on CNS resident cells was shown to be crucial for the induction and maintenance of pro-inflammatory cytokine expression in the CNS using bone marrow chimeras in which TLR4 was intact in the periphery, but absent on CNS resident cells (Chakravarty and Herkenham, 2005). Although best characterized for LPS, peripheral administration of other TLR ligands also induces sickness behavior and activation of CNS resident cells (Cremeans-Smith and Newberry, 2003; Katafuchi et al., 2003; Zhang et al., 2005).

3.3 In vivo Roles of PRRs in Control of CNS Infection

Recently, use of mice genetically deficient for various PRRs has allowed the study of their in vivo role during CNS infection. This field of study is still in its infancy, and the potential differential contributions of PRR signaling in the periphery vs. the CNS has not yet been thoroughly assessed. Even so, there appear to be some intriguing differences in how the CNS and periphery use PRRs in response to infection. MyD88−/− or TLR2−/− mice are more susceptible to fatal meningitis induced by Streptococcus pneumoniae or Listeria meningitis (Echchannaoui et al., 2002; Koedel et al., 2003, 2004). Two separate groups have reported increased clinical severity of S. pneumoniae-induced meningitis in TLR2−/− mice, associated with increased bacterial load in the CNS, massive although delayed leukocyte infiltration, and increased BBB permeability. In the first study by Echchannaoui et al. (2002), the authors found no differences in bacterial titer or cytokine production in the periphery of TLR2−/− and wild type mice, while Koedel et al. (2003) noted an increase in blood, but not splenic bacterial load in TLR2−/− mice. The differences between these two studies could potentially be explained by the route of infection: the former used an intracerebral route of infection with lower levels of bacteria, while
the latter infected intracisternally with higher numbers of bacteria, which led to higher peripheral bacterial load and faster onset of clinical symptoms.

Studies of the role of TLR2 in *Staphylococcus aureus* infection also demonstrate differences between peripheral and CNS responses. TLR2−/− mice are highly susceptible to intravenous *S. aureus* infection, resulting in increased mortality and increased bacterial titers in the blood (Takeuchi et al., 2000). In contrast, there was no difference between TLR2+/− and wild type mice in the survival, clinical symptoms or bacterial load associated with *S. aureus*-induced brain abscess (Kielian et al., 2005b). Despite the lack of clinical effect, TLR2−/− mice in this model displayed decreased TNF, CXCL2 and iNOS production in the brain, with a paradoxical increase in IL-17 (Kielian et al., 2005b). In accordance with these observations, it has been reported that TLR2 is important for the induction of cytokines from macrophages, but not microglia, incubated with intact *S. aureus* (Kielian et al., 2005a; Takeuchi et al., 2000). The additional mechanisms by which microglia recognize *S. aureus* have not yet been determined.

TLR2 is also important for mediating responses to herpes simplex virus 1 (HSV-1), as TLR2−/− mice show decreased peripheral inflammatory responses and serum cytokine levels after HSV-1 infection (Kurt-Jones et al., 2004). Interestingly, these mice are protected from lethal encephalitis which correlates with decreased CNS inflammation. Similarly, TLR3−/− mice are protected from lethal West Nile virus encephalitis (Wang et al., 2004). In the periphery, these mice have increased viral loads and decreased inflammatory responses. The decreased inflammatory response in the periphery failed to damage the BBB, and the virus was unable to access the CNS and cause fatal disease. In contrast, intracerebral infection of West Nile virus had identical effects in wild type and TLR3−/− mice, indicating that TLR3 in the CNS may not be important for responses to this virus (Wang et al., 2004). Mice which constitutively express a dominant negative PKR also show protection from fatal poliovirus infection associated with decreased inflammation but normal viral replication (Scheuner et al., 2003). These studies demonstrated that host inflammatory responses in the CNS during infection may be more responsible for self tissue damage than direct effects of the pathogen itself. Determination of the roles of TLRs specifically in CNS-resident cells during infection will require the use of bone marrow chimeric animals in which CNS resident cells and peripheral immune cells are mismatched with respect to TLR expression, studies which are ongoing in our and other laboratories.

4 Role of CNS Pattern Recognition Receptors in Neurodegeneration

4.1 PRR Stimulation Induces Neuron and Oligodendrocyte Death

Although the stimulation of TLRs on glial cells activate functions that are important for the elimination of pathogens, these same functions can be toxic to cells of the CNS that have limited regenerative capacity. Injection of poly I:C into the CNS causes strong glial activation and profound neurodegeneration in the surrounding tissue.
Injection of LPS also causes profound and long lasting glial activation (Hartlage-Rubsamen et al., 1999; Herber et al., 2006) associated with oligodendrocyte death, demyelination and increased vulnerability of neurons to injury, dependent on TLR4, MyD88 and CD14 (Lehnardt et al., 2002, 2003; Milatovic et al., 2004). Neural precursor cells appear to be exquisitely sensitive to the effects of LPS, as peripheral injection of even low levels of LPS reduces neurogenesis in the hippocampus and olfactory bulb and induces apoptosis of progenitor cells in the rostral migratory stream (Monje et al., 2003; Mori et al., 2005). The effects of LPS on neurogenesis can be blocked by the anti-inflammatory drug indomethacin, indicating the disruption of neurogenesis is due to inflammation in the CNS (Monje et al., 2003).

Many of these studies have implicated a role for glial cell-derived inflammatory mediators in the CNS damage induced by TLR stimuli. Cytokines produced directly by activated glial cells or by peripheral immune cells activated in the CNS can be toxic to CNS resident cells, which is highlighted by the observation that mice with transgenic overexpression of IL-6, TNF, or IFN-\(\gamma\) in the CNS develop severe neurologic disease (Wang et al., 2002). IFN-\(\gamma\) and TNF are also directly toxic to oligodendrocytes in culture (Selmaj and Raine, 1988; Vartanian et al., 1995).

The production of iNOS by TLR-stimulated glia has potential to be toxic in the CNS. Peroxynitrite (ONOO\(^-\)), the product of NO reacting with superoxide anions, is a potent oxidizing and nitrating agent, thought to mediate most of the damage observed in the presence of high levels of NO (Smith et al., 1999). Reactive oxygen species (ROS) are particularly damaging to neurons and oligodendrocytes, due to their low levels of antioxidant defenses and the high lipid to protein ratio (Smith et al., 1999). As previously discussed, iNOS is induced in microglia or astrocytes treated with a variety of TLR stimuli which subsequently produce high levels of NO. TLR-stimulated glial cultures are therefore toxic to cultured neurons and oligodendrocytes, and this toxicity can be blocked by pharmacologic inhibitors of NOS (Bal-Price and Brown, 2001; Boje and Arora, 1992; Iliev et al., 2004; Merrill et al., 1993). Inhibition of iNOS by amino-guanidine results in decreased inflammation, demyelination, axonal damage and necrosis after CNS viral infection (Rose et al., 1998), but whether this is a direct effect on cell death or an indirect effect on the immune response, BBB permeability, or other factors is unclear.

Cytokine and NO production can also enhance CNS injury from glutamate excitotoxicity. Levels of extracellular glutamate are normally tightly controlled by astrocytes which express high levels of glutamate transporters (Sonnewald et al., 2002). In oligodendrocytes and neurons, excess glutamate causes calcium overload, which leads to mitochondrial dysfunction, formation of ROS, activation of toxic proteases, and ultimately apoptosis (Arundine and Tymianski, 2004; Matute et al., 2001). Cytokines produced by TLR-stimulated glia such as IL-6 and TNF can enhance glutamate excitotoxicity in cultured neurons (Chao and Hu, 1994; Qiu et al., 1998). In vitro, glutamate uptake by astrocytes is inhibited in the presence of cytokines or poly I:C, which causes the accumulation of extracellular glutamate (Fine et al., 1996; Scumpia et al., 2005; Takahashi et al., 2003). Glutamate excitotoxicity is a major mechanism of CNS damage in vivo, since glutamate receptor antagonism can reduce virus-induced neurodegeneration (Nargi-Aizenman et al., 2004).
4.2 PRRs in Multiple Sclerosis

The neurodegeneration and demyelination induced by CNS administration of PAMPs has advanced the hypothesis that the activation of PRRs and ensuing inflammation may be involved in a variety of neurodegenerative diseases. Multiple sclerosis (MS) is believed to be a CD4+ T cell-mediated autoimmune demyelinating disease of the CNS (Sospedra and Martin, 2005). Although its exact etiology is unknown, it has been hypothesized that it may have an infectious trigger and infections are known to exacerbate disease episodes (Kurtzke, 1993). The principal murine model of MS is experimental autoimmune encephalomyelitis (EAE), in which an autoimmune response is primed in the periphery by the administration of myelin peptides or proteins emulsified in complete Freund’s adjuvant (CFA), which contains heat killed *Mycobacteria tuberculosis*, or by adoptive transfer of activated myelin-specific CD4+ T cells. In EAE and MS lesions, the expression of multiple TLRs are increased (Bsibsi et al., 2002; Prinz et al., 2006; Zekki et al., 2002), probably due to both increases in expression by CNS-resident cells as well by CNS-infiltrating peripheral TLR-expressing leukocytes. TLR and/or IL-1 signaling is crucial for the development of EAE because MyD88−/− mice do not develop EAE under the typical immunization protocol (Prinz et al., 2006). TLR9−/− and TLR4−/− mice also show decreased clinical disease after peripheral priming, although the effect is less dramatic than the loss of all MyD88-dependent pathways (Prinz et al., 2006). At least some of this effect is probably due to the inability to effectively prime Th1 responses, which is severely defective in mice with compromised TLR signaling (Schnare et al., 2001). Similar deficiency in priming likely occurs in encephalitogenic Th17 cells. Additionally, it was recently demonstrated that TLR4 is required for the action of pertussis toxin, which promotes leukocyte rolling and adhesion to CNS microvessels and CNS infiltration (Kerfoot et al., 2004). Not all roles for TLR signaling in EAE, however, are due to effects on the peripheral immune system, as MyD88−/− mice also developed decreased clinical disease after the transfer of activated wild-type, myelin-specific, CD4+ T cells and because chimeric mice specifically deficient in CNS expression of MyD88 also exhibit reduced clinical disease (Prinz et al., 2006). Mice deficient specifically in TLR9 in the CNS also develop delayed and reduced disease compared to wild type mice, with decreases in leukocyte infiltration as well as axonal and myelin damage (Prinz et al., 2006). These studies define important roles for both TLR9- and other MyD88-dependent pathways in CNS-resident cells during EAE-associated neurologic damage.

4.3 PRRs in Alzheimer’s Disease

Alzheimer’s disease (AD) is a devastating neurodegenerative disease characterized by progressive memory loss, cognitive decline and neuronal loss. Although there is no known infectious component, neuroinflammation is a major feature of disease (McGeer and McGeer, 2003). One pathologic hallmark of AD is the amyloid plaque, which consists of deposits of Aβ peptide, activated microglia and astrocytes, and dystrophic neurites (Nagele et al., 2004). A great deal of research has
focused on how Aβ deposits may lead to glial activation, and a variety of PRRs have been hypothesized to play a role.

Although no TLR to date has been identified which is directly activated by Aβ, CD14, which coordinates with either TLR4 or TLR2 for signaling, can bind to fibrilar Aβ and mediate its induction of nitrates, IL-6, and TNF (Fassbender et al., 2004). Whether TLR4 also contributes to CD14 signaling in response to Aβ has not yet been determined, but it is interesting to note that a human polymorphism in TLR4, but not CD14, has been linked to AD risk (Combarros et al., 2005; Minoretti et al., 2006).

The murine formyl peptide receptor 2 (mFPR2) is classically expressed in neutrophils and other phagocytic leukocytes and is activated by N-formylated peptides produced by bacteria (Le et al., 2002). This PRR is also expressed in microglia and CNS-infiltrating leukocytes of AD patients and in vitro is important for chemotaxis and oxidative stress induced by Aβ peptides (Le et al., 2001; Tiffany et al., 2001). Interestingly, while resting microglia express little or no mFPR2, the activation of TLRs on microglia by LPS, PGN or CpG induces its upregulation and function (Chen et al., 2006; Cui et al., 2002; Iribarren et al., 2005).

Finally, scavenger receptors are also upregulated in AD brains and have been reported to be expressed by both microglia and astrocytes (Christie et al., 1996; Husemann and Silverstein, 2001). SR-A was the first SR demonstrated to promote microglial adhesion to and uptake of Aβ fibrils and mediate production of ROS (El Khoury et al., 1996; Paresce et al., 1996). However, the generation of transgenic mice which develop AD and are deficient in SR-A did not reveal any differences in plaque formation or neurodegeneration (Huang et al., 1999), leading to questions of the in vivo relevance of these observations. Shortly thereafter, it was shown that SR-BI can mediate Aβ adhesion and internalization by microglia, although its ability to do so was only revealed in the absence of SR-A (Husemann et al., 2001; Paresce et al., 1996). CD36 may also bind fibrillar Aβ and is crucial for the induction of ROS, cytokines and chemokine in microglial cell lines or primary microglia stimulated with fibrillar Aβ (Bamberger et al., 2003; Coraci et al., 2002; El Khoury et al., 2003). CD36 also mediates Aβ-induced chemotaxis of microglia in vitro and in vivo after intracerebral injection of fibrillar Aβ, the first demonstration of the in vivo role of PRRs in microglial responses to Aβ (El Khoury et al., 2003).

5 Neuroprotection Mediated by PRR activation

Although chronic or dysregulated innate immunity in the CNS is potentially damaging to this tissue, its controlled activation may also have neuroprotective effects. Astrocytes stimulated with poly I:C or LPS induce the expression of ciliary neurotrophic factor (Bsibsi et al., 2006), a potent oligodendrocyte survival factor and a major protective factor in CNS demyelinating disease (Barres et al., 1993; Linker et al., 2002). Astrocytes stimulated with poly I:C, but not LPS, express a variety of other neurotrophic factors, including vascular endothelial growth factor, neurotrophin-4, brain derived neurotrophic factor, and glial growth factor 2, as well as the anti-inflammatory cytokines
transforming growth factor-β and IL-10 (Bsibsi et al., 2006). Accordingly, conditioned media from poly I:C-stimulated astrocytes can promote endothelial cell growth and survival of brain slices in vitro.

Additionally, IL-6 and TNF produced by astrocytes and microglia stimulated with PAMPs, although potently pro-inflammatory in the periphery, also have been demonstrated to have neuroprotective functions in the CNS (Wang et al., 2002). Cerebral infusion of IL-6 is neuroprotective in models of ischemia and excitotoxicity, perhaps through its induction of nerve growth factor by astrocytes (Kossmann et al., 1996; Loddick et al., 1998; Toulmond et al., 1992). TNF can also promote neuronal survival in vitro, even after a variety of challenges by glutamate or kainic acid, glucose deprivation, excess iron or Aβ (Barger et al., 1995; Bruce et al., 1996; Cheng et al., 1994). Mice deficient in TNF and lymphotoxin-α show worse outcome after traumatic brain injury, kainic acid lesions, and middle cerebral artery occlusion (Bruce et al., 1996; Scherbel et al., 1999). These mice also develop enhanced EAE, although this appears to be dependent on the genetic background and/or immunizing antigen (Eugster et al., 1999; Frei et al., 1997; Liu et al., 1998). Interestingly, the neuroprotective effects of TNF appear to be mediated specifically by the p75 receptor, since p75-deficient mice, but not p55 deficient mice, show exacerbated EAE and cuprizone-induced demyelination (Arnett et al., 2001; Eugster et al., 1999; Suvannavejh et al., 2000). This could be due to a direct effect on oligodendrocytes, since p75-deficient mice exhibit decreased oligodendrocyte progenitor proliferation and decreased remyelination after cuprizone withdrawal (Arnett et al., 2001). In accordance with a regenerative function, MS patients who underwent anti-TNF therapy, an effective treatment against other autoimmune disorders, exhibited exacerbations of their clinical disease (Lenercept Multiple Sclerosis Study Group, 1999).

Another surprising role for innate immunity in myelin repair has emerged from recent studies co-infusing LPS with neurotoxins. Ethidium bromide injection into the corpus callosum causes demyelination and loss of oligodendrocytes. LPS co-injection promoted the survival and/or regeneration of oligodendrocytes as measured by an increase in the number and broader distribution of cells expressing oligodendrocyte-specific genes (Glezer et al., 2006). LPS co-injection with Tween into the brain also limited tissue damage and promoted debris clearance from the site of injury (Glezer et al., 2006). Although the exact mechanism is unknown, it is possible that LPS activates phagocytic activities of microglia, induces cytokines with pro-regenerative properties, and/or neurotrophin expression by astrocytes. Collectively, these studies highlight that a properly controlled and limited innate immune response can be beneficial to protect cells of the CNS.

6 Conclusions

CNS resident cells, particularly microglia and to a lesser extent astrocytes, express a variety of PRRs that allow them to respond to almost any pathogen invading the CNS. The ligation of PRRs activates a host of pro-inflammatory responses from
these cells, including the production of type I interferons, nitric oxide, cytokines and chemokines. Additionally, microglia exposed to pathogens upregulate their ability to acquire, process and present antigen resulting in more efficient activation of activated T cells. In the CNS, PRRs are important for pro-inflammatory responses to pathogens. Interestingly, the inhibition of these pro-inflammatory responses can be beneficial or detrimental to host survival, depending on the particular pathogen and disease. Similarly, the chronic activation of PRRs may lead to neurodegeneration, but limited or controlled activation may be neuroprotective. These results suggest that the manipulation of PRR activation in the CNS may be a viable approach both in the treatment of CNS infections and neurodegenerative diseases, while dysregulation of this process may contribute to neuronal or oligodendrocyte cell death. This is a burgeoning field of research, and clearly more research is needed to determine the full range of PRR functions in the CNS.

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