Peripheral Inflammation and Demyelinating Diseases

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Abstract In recent decades, several neurodegenerative diseases have been shown to be exacerbated by systemic inflammatory processes. There is a wide range of literature that demonstrates a clear but complex relationship between the central nervous system (CNS) and the immunological system, both under *naïve* or pathological conditions. In diseased brains, peripheral inflammation can transform "primed" microglia into an "active" state, which can trigger stronger pathological responses. Demyelinating diseases are a group of neurodegenerative diseases characterized by inflammatory lesions associated with demyelination, which in turn induces axonal damage, neurodegeneration, and progressive loss of function. Among them, the most important are multiple sclerosis (MS) and neuromyelitis optica (NMO). In this review, we will analyze the effect of specific peripheral inflammatory stimuli in the progression of demyelinating diseases and discuss their animal models. In most cases, peripheral immune stimuli are exacerbating.

Keywords Demyelinating diseases · Systemic inflammation · Microglia · Multiple sclerosis · Neuromyelitis optica · Experimental autoimmune encephalomyelitis

Abbreviations and Acronyms

AQP4	Aquaporin-4
BBB	Blood–brain barrier
CCL2	Chemokine CC motif ligand 2
CCR2	Chemokine CC motif receptor 2
CD	Cluster of differentiation

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CNS	Central nervous system
CSF	Cerebrospinal fluid
CXCR2	CXC motif chemokine receptor type 2
EAE	Experimental autoimmune encephalomyelitis
GC	Glucocorticoids
HPA	Hypothalamic-Pituitary-Adrenal
HPG	Hypothalamic-Pituitary-Gonadal
IFN	Interferons
IgG	Immunoglobulin G
IL	Interleukin
iNOS	Inducible nitric oxide synthase
MHC	Major histocompatibility complex
MS	Multiple sclerosis
NMO	Neuromyelitis optica
PMN	Polymorphonuclear
PPMS	Primary progressive MS
RRMS	Relapsing remitting multiple sclerosis
SGK1	Serum glucocorticoid kinase 1
SPMS	Secondary progressive multiple sclerosis
TGF-β	Transforming growth factor beta
Th	T helper
TLR	Toll-like receptors
TNF-α	Tumor necrosis factor α
WBC	White blood cells

Peripheral Inflammation and Neurodegenerative Diseases

Inflammation can be viewed as one of the primary responses of the immune system to infections or body injury. Systemic inflammation is associated with several chronic diseases, including obesity, type 2 diabetes, atherosclerosis, liver disease, and cancer (reviewed in Wilson et al. 2010; Fung et al. 2012). Additionally, it may also be associated with an acute stimulus, such as infection, surgery, and acute organ injury (Ottani et al. 2009). Systemic inflammatory stimuli that circulate in the blood may induce the synthesis of cytokines in the central nervous system (CNS) (Besedovsky and del Rey 1996; Pitossi et al. 1997; Combrinck et al. 2002; Dantzer et al. 1998, 2008; Londono and Cadavid 2010). In a diseased brain, this production of proinflammatory molecules exacerbates ongoing brain damage in several neurodegenerative diseases, such as Alzheimer's disease, multiple sclerosis (MS), Parkinson's disease, prion disease, and stroke (Perry et al. 2002; Cunningham et al. 2005a, b; McColl et al. 2007; Palin et al. 2008; Ferrari and Tarelli 2011; Murta and Ferrari 2013). In this review, we will discuss the influence of specific systemic

proinflammatory stimuli on different demyelinating diseases and animal models, and the role of several cells and molecules in this phenomenon.

Microglia as a Mediator of Systemic Inflammation and Neurodegenerative Diseases

Microglia are the resident immune cells of the CNS; their main role is monitoring the local environment and triggering an immune response after specific stimuli in the nervous tissue. As discussed in Chapters "Glial cells and Integrity of the Nervous System", "Microglia function in the normal brain", and "Purine Signaling and Microglial Wrapping", microglia activation is characterized by morphological and physiological changes such as secretion of proinflammatory and anti-inflammatory cytokines. Therefore, microglia can exert either cytotoxic or repairing actions, and these are referred as the M1-like and M2-like responses (Samad et al. 2001).

Resting microglia have a ramified morphology and represent a more quiescent basal state of this cell type. Systemic infections or mild central neurodegenerative processes can activate and prime the resting microglia. **Priming of microglia** precedes a further neurotoxic activation, which a secondary inflammatory stimulus can transform into an "**active**" **state** (Samad et al. 2001; Cunningham et al. 2005b; McColl et al. 2007). Microglia activation to an M1 phenotype increases neurotoxicity and, therefore, contributes to neurodegeneration through the release of free radicals such as superoxide radicals and nitric oxide (through the action of inducible nitric oxide synthase, iNOS) (Minghetti et al. 1999; Czlonkowska et al. 2002; Arimoto and Bing 2003), and immunomodulatory cytokines such as interleukin (IL) 1β, tumor necrosis factor α (TNFα), IL6, IL8, IL12, IL15, and IL10 (Kim and de Vellis 2005; Dilger and Johnson 2008; Henry et al. 2009). Therefore, ongoing inflammatory degenerative processes can be accelerated by systemic inflammation through the stimulation of "primed" microglial cells toward a more aggressive state, which in turn exacerbates damage in the nervous tissue (Fig. 1).

Communication Between the Periphery and the CNS

The brain used to be considered an "immune-privileged" organ isolated from the peripheral immune system. Nowadays, it is well known that a bidirectional pathway between the brain and the peripheral immune system exists.

Circulating cytokines and other inflammatory molecules can affect the brain through several routes, mainly through the neural or humoral pathways. The neural pathway is mainly related to the transmission of peripheral inflammatory signals

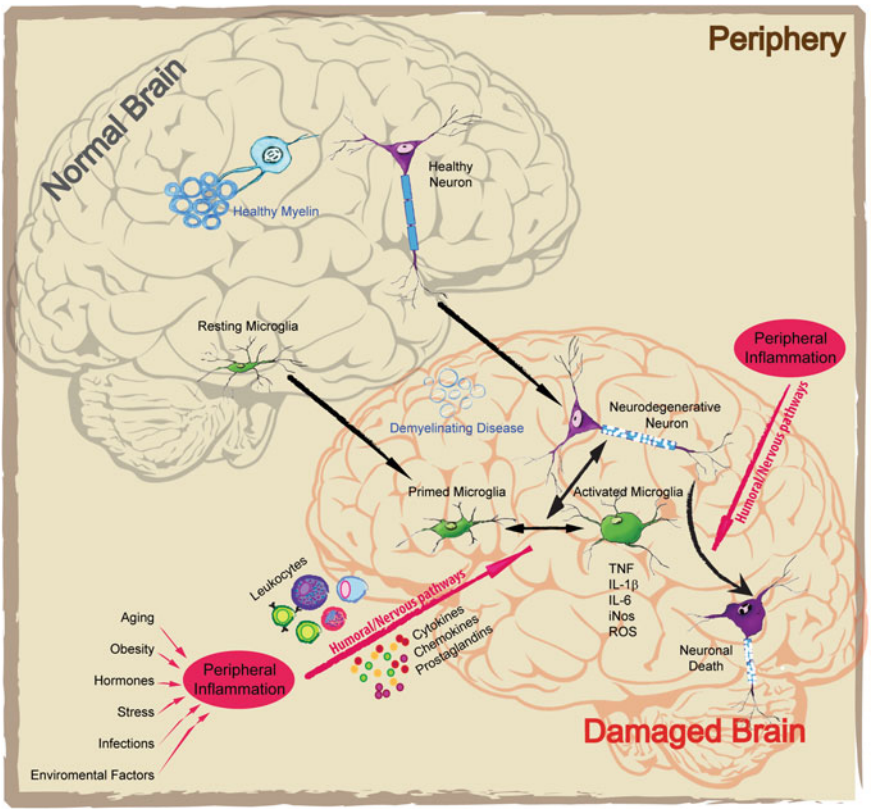

Fig. 1 Schematic diagram showing the relationship between peripheral inflammation and demyelinating diseases. Demyelinating diseases are characterized by microglia activation; in which microglia change their morphology from resting (ramified) towards an activated round-shaped stage. The intermediate stage, "primed microglia," represents the microglial stage, which precedes a further neurotoxic microglial activation as a consequence of a secondary proinflammatory stimulus. The peripheral stimuli come from the periphery either through neural or humoral pathways and influence microglia activation. Activated microglia releases proinflammatory cytokines which can, in turn, act on myelin sheath integrity, thereby inducing demyelination, axonal loss and neurodegeneration

through the vagal afferent nerve (Perry et al. 2003; D'Mello et al. 2009; Gautron and Laye 2009; Teeling and Perry 2009; Campbell et al. 2010). The humoral pathway involves the direct action of peripheral proinflammatory cytokines (e.g., IL1β, TNFα, and IL6) and type I interferons (IFNα and IFNβ) that can initiate the synthesis of cytokines within the CNS, through blood–brain barrier (BBB) dependent or independent pathways (Perry et al. 2003; Teeling and Perry 2009).

Demyelinating Diseases

As mentioned in Chapter "Glial cells and Integrity of the Nervous System", demyelinating diseases are a group of neurodegenerative diseases characterized by inflammatory lesions associated with demyelination, which in turn induces axonal damage, neurodegeneration, and progressive loss of function. Among them, the most important are MS, neuromyelitis optica (NMO), acute demyelinating encephalomyelitis, multifocal leukoencephalopathy, Guillain Barré syndrome, and acute disseminating encephalomyelitis. This review will mostly focus on MS and NMO, which are the most frequent in humans, and the most studied.

Multiple Sclerosis

MS is a chronic inflammatory disease characterized by multifocal and repeated inflammatory events associated with demyelination–remyelination and axonal damage, which leads to poor conduction of the nervous impulse and eventual loss of sensory and motor function.

MS follows a varied clinical course, but most patients exhibit a course of repeating exacerbation and remission from the onset (relapsing/remitting MS or RRMS) eventually leading to secondary progressive multiple sclerosis (SPMS), which worsens the patients' quality of life (Playfair and Chain 1979; Neumann et al. 1998). A minority of patients exhibit primary progressive MS (PPMS), which is characterized by a constant decline from the onset with no recovery in neurological function (Playfair and Chain 1979; Loddick and Rothwell 2002).

Despite the fact that BBB breakdown is a major MS hallmark (McQuaid et al. 2009; Larochelle et al. 2011), some components of the inflammatory response contribute to the pathology even with an intact BBB (Buljevac et al. 2002; Lindquist et al. 2011). Although it has been proposed that in RRMS BBB breakdown allows the invasion of inflammatory cells, in the progressive forms inflammation remains enclosed behind an intact BBB (Playfair and Chain 1979).

Relapsing and Remitting MS

RRMS is the prevalent clinical type of MS and is characterized by recurrent episodes of new or worsened symptoms. Exacerbations or relapses are followed by periods of partial or complete remission, with apparent clinical stability between relapses. Relapsing episodes are unpredictable; however, peripheral inflammation may exacerbate these events (see below). Infections and other proinflammatory events have been postulated as possible triggers of the pathology and/or of relapsing episodes, and some authors have hypothesized that the autoimmune response could be a consequence of a primary central proinflammatory event (Barnett and Prineas 2004).

Progressive Multiple Sclerosis

The progressive forms of MS lead to a continuous and irreversible evolution of the disease, inducing decline of the quality of life either from the onset (PPMS) or after a course of relapsing and remitting episodes (RRMS), named SPMS. SPMS is diagnosed as a worsening after relapsing-remitting phases, with or without acute exacerbations during the progressive stage (Wagner 1996). PPMS is a distinct, non-inflammatory, or less inflammatory pathologic form of MS. The progressive forms of MS are characterized by gray matter atrophy, which could be involved in physical and cognitive disability (Rivest et al. 2000; Pocock and Kettenmann 2007; Qian et al. 2012). Cortical lesions have peculiar inflammatory and demyelinating hallmarks, characterized by lack of BBB disruption, differential inflammatory process, and reactive microglia, suggesting different immunopathogenic mechanisms (Vitkovic et al. 2000). However, anti-inflammatory or immunomodulatory therapies have no effect on neurodegeneration and cognitive impairment in the progressive forms of MS (O'Connor et al. 2005; London et al. 2013). This could be related to the fact that in progressive MS, the inflammation creates an environment that favors retention of inflammatory cells within the lesions (Konsman et al. 1999; Godbout et al. 2005).

Neuromyelitis Optica

NMO, or Devic's disease, is a demyelinating disease characterized by inflammatory demyelinating lesions mainly in the spinal cord and optic nerve, potentially leading to paralysis and blindness. It used to be considered a subtype of MS, but the pathology and clinical features make them different diseases (Mosher et al. 2001). NMO is characterized by seropositivity for immunoglobulin G (IgG) antibodies against the astrocytic water channel aquaporin-4 (AQP4), and secondary inflammation with granulocyte and macrophage infiltration, BBB disruption, and oligodendrocyte injury. Therefore, an adaptive immune response to AQP-4 underlies the chronic demyelinating in NMO.

The etiology of the disease is still unclear, but infections and BBB permeabilizing factors could be involved in triggering the overproduction of AQP4-IgG, and its access to the CNS (Schafer et al. 1999; Galiano et al. 2001). Uzawa et al. (2010) demonstrated a significant difference in the levels of some cytokines/chemokines (e.g. IL-6 for NMO) in the cerebrospinal fluid (CSF) of patients with NMO or MS, supporting the view that different immunological and pathophysiological mechanisms exist between them.

Current NMO therapies are directed toward reducing the inflammatory response and the NMO–IgG load, such as B cell depletion and plasmapheresis. However, most MS treatments, such as IFNβ, fingolimod, and natalizumab, exacerbate NMO. Therefore, it is necessary to better comprehend the diseases' underlying mechanisms and differentiate NMO from MS.

MS and Peripheral Inflammation

MS is a neurodegenerative disease mainly characterized by inflammatory processes. Activation of systemic immunity affects primed microglia in the CNS, reactivating lesions and increasing parenchymal inflammation. Although relapsing episodes in RRMS are unpredictable, most relapses are concomitant with peripheral inflammation (Buljevac et al. 2002). RRMS patients show increased serum levels of IL1β, IL2, IL4, IL12p70, IFNγ, and TNFα during the relapse phase (Nathan 2006; Edwards et al. 2011; Trenova et al. 2011), as well as higher numbers of IL1β, IL6, and TNFα secreting cells (Ysrraelit et al. 2008), and increased levels of T helper (T_h)17 and Treg cells in the periphery (Edwards et al. 2011). Moreover, a change in CSF cytokine profile is observed during relapses; ranging from high levels of IL1β, TNFα, and transforming growth factor beta (TGFβ) to lower levels of IL-10 (Hauser et al. 1990; Edwards et al. 2011). However, the treatment of MS patients with TNFα inhibitors results in the exacerbation of central lesions (reviewed in Perry et al. 2003).

Differences in cytokine expression patterns are described when comparing progressive MS and RRMS (during relapses). SPMS patients present elevated levels of chemokine CC motif receptor 2 (CCR2) in T cells, increased serum/CSF levels of chemokine CC motif ligand 2 (CCL2) (Brinkmann et al. 2004), and decreased plasma/CSF values of TNFα and IL4 (Schmitz and Chew 2008). Peripheral blood mononuclear cells of both remitting RRMS and SPMS patients express low levels of IL10 mRNA, which return to basal levels during relapses in the RRMS form (Berkenbosch et al. 1987). Additionally, the progressive forms are characterized by a permanent peripheral type 1 immune activation, which could contribute to CNS damage during the progressive phase of the disease (Playfair and Chain 1979; Hampton et al. 1998). Thus, the peripheral blood of SPMS patients seems to reflect the inflammatory response accumulated in the CNS (Playfair and Chain 1979). On the other hand, RRMS is characterized by waves of T helper (Th)1 and Th17 cells, which are recruited into the brain causing the attacks (Neumann et al. 1998).

Inflammatory Stimuli Associated with MS

Although there is a clear association between systemic inflammation and the onset or progression of different neurodegenerative pathologies, the particular nature of these inflammatory phenomena is also relevant. Numerous studies, cited below, have investigated the role of specific systemic proinflammatory stimuli including acute or chronic stimuli, physiological imbalances, or external infections and injuries. A summary of the roles of distinct proinflammatory stimuli in MS will be addressed in the following section.

Obesity

During the last few years, a strong connection between metabolism, immunity, and inflammation was described. Obesity is considered an inflammatory disease, associated with metabolic and cardiovascular complications. Adipocyte tissue acts as an endocrine organ releasing adipocytokines, and is associated with increased levels of tissue and circulating inflammatory biomolecules (Oh et al. 1998). Excessive adipose tissue increases the number and activity of macrophages, mast cells, neutrophils, and lymphocytes (Ott et al. 1994; Kossmann et al. 1995). Moreover, leptin (an adipocyte-derived cytokine) has a role in regulating both innate and adaptive immunity (Bradl and Lassmann 2009), promoting the production of cytokines such as TNFβ, IL6, IL12, IL15, and granulocyte colony-stimulating factor in macrophages, and increasing their phagocytic activity, as well as inducing the chemotaxis of neutrophils (Bradl and Lassmann 2009; Lee et al. 2011; Golde et al. 2013; Procaccini et al. 2014). High levels of leptin have also been reported in both active inflammatory lesions and serum of MS patients (Batocchi et al. 2003).

Clinical data have demonstrated that obesity worsens the onset and progression of most autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, MS, type-1 diabetes, and psoriasis. Additionally, it impairs a positive response to the treatments usually given for these diseases (Cardona et al. 2008). Data show that 18-year old obese people are twice as likely to develop MS as their normal weight age mates (Banisadr et al. 2005). However, even if it seems quite clear that obesity and diet may influence the progression of MS, few studies have linked a caloric restriction diet to reduced MS progression (Procaccini et al. 2014).

Aging

Aging processes induce a generalized proinflammatory state in the organism. This change is induced by increased immune responses in the periphery, disruption of the periphery-CNS immune communication, and an increment in "primed" microglia, which increases CNS reactivity (reviewed in Veenstra and Ransohoff 2012). Microglia in aged brains exhibit upregulated major histocompatibility complex (MHC) class II, complement receptors, toll-like receptors (TLR) 4, and cluster of differentiation (CD) 14 expression (see Chapter "Age-Dependent Changes in the Activation and Regulation of Microglia" for further reading). Therefore, peripheral innate immune stimulation induces microglial cells in aged brains to have an exaggerated inflammatory response compared with younger cohorts (Sly et al. 2001; Dilger and Johnson 2008).

PPMS and SPMS manifest around 10 years later than RRMS, therefore the timeline at which patients develop neurological deficit in PPMS and SPMS is

remarkably similar, and both include aging as a major risk factor for MS progression (reviewed in Kutzelnigg et al. 2005).

Infections

Infectious pathogens have been described as important factors involved in the development of MS. Moreover, clinical studies revealed an association between infections and relapses, which worsen neurological damage even after the infection is gone (Buljevac et al. 2002; Panitch 1994). Pathogens associated with the exacerbation include bacteria (such as *Mycoplasma pneumonia*, *Chlamydia pneumoniae*, and *Staphylococcus aureus*-produced enterotoxins), virus (Epstein-Barr virus and human herpes virus, and human endogenous retrovirus), and the protozoan (*Acanthamoeba castellanii*). Viral infections that trigger MS episodes can be reduced with IFN-γ treatment (Panitch 1994; Andersen et al. 1993).

Studies of MS patients and of animal experimental models have demonstrated the influence of these infectious agents on the development and/or exacerbation of MS (Krieger et al. 1992). However, not all infections cause progression of MS, since it has been reported that infections with some parasites, such as helminthes, can protect against the exacerbation phase of the disease (Correale and Farez 2011a, b; Krieger et al. 1992). This protection is associated with the induction of CD4+, CD25+ T cells secreting IL10, and TGFβ (Correale and Farez 2011a).

Immune Regulation by the Neuroendocrine System

The neuroendocrine system exerts its action on the immune system through finely tune regulation. Glucocorticoids (GCs) induce the production of pro- and anti-inflammatory cytokines, specifically causing a shift from Th1 to Th2 immune response. GCs inhibit the production of Th1 related cytokines (IL1 and IL6, IL2, IL12, IFNγ) and increase the secretion of anti-inflammatory Th2 cytokines (IL4 and IL10) (Haak et al. 2009). However, GCs can increase both peripheral and central inflammatory responses to a systemic challenge if they are administered before the peripheral stimuli (Sorrells and Sapolsky 2010; Frank et al. 2010). Therefore, GCs can prime the immune response and, as a consequence, increase proinflammatory cytokine production and exacerbation of MS symptoms.

The Hypothalamic–Pituitary–Adrenal (HPA) Axis

Clinical and experimental studies have demonstrated that abnormalities in the HPA axis, which influences the immune response, may exacerbate MS symptoms (Hofstetter et al. 2005; Seo et al. 2013). Thus high cortisol levels are often

correlated with acute relapses (Hofstetter et al. 2005; Seo et al. 2013), whereas prolactin increases the peripheral production of IFNγ and IL12 by T cells (Du and Dreyfus 2002).

The Hypothalamic–Pituitary–Gonadal (HPG) Axis

MS affects predominantly women in comparison with men, therefore, considering that gender affects the course of autoimmune diseases, the influence of sex hormones is critical (Dunn et al. 2015a, b). In particular, 17β-estradiol induces an increase of Th2 cytokines (IL10 and IL4) and a decrease of Th1 cytokines (TNFα and IFNγ) (van Riemsdijk et al. 2001; Janik et al. 1997). Estrogens, in addition to their anti-inflammatory effects, appear to be neuroprotective in CNS diseases, such as MS and Alzheimer's, disease (Nicot 2009; Gao and Tsirka 2011). Additionally, both clinical symptoms and relapse rates of MS are decreased during pregnancy, whereas the postpartum period increases the risk for exacerbation of the disease (Ling et al. 1997).

The increased secretion of estrogen, progesterone, and cortisol during pregnancy is associated with increased production of Th2 cytokines and decreased production of Th1 cytokines (Takii et al. 1992, 1994). Additionally, progesterone also inhibits NFκB and increases IL4 production, demonstrating its anti-inflammatory effect (Piccinni et al. 1995; Nishiyori et al. 1997). Male hormones, such as testosterone, also inhibit both innate and adaptive immune systems by enhancing the production of IL5 and IL10, and decreasing IFNβ secretion, thus promoting a Th2 response (Murphy and Sturm 1923).

Environmental Factors and Peripheral Inflammation

Environmental factors have influence on most autoimmune diseases. Epidemiological risk factors for MS, including low vitamin D and elevated salt intake, are associated with peripheral inflammation. Recent studies have shown that components of the daily diet and gut microbiota can strongly affect the levels of effector T cells in the gut (Ransohoff et al. 2007).

On the other hand, high sodium chloride concentrations induced expression of serum glucocorticoid kinase 1 (SGK1) in T cells, which in turn stimulate the induction of Th17 cells from CD4+ T cells, promoting autoimmune diseases (Glabinski et al. 1997). However, direct correlation between salt intake and incidence of autoimmune disease is yet to be demonstrated (Tsai et al. 2002).

Vitamin D plays an important role in the regulation of the immune responses (Semple et al. 2010), modulating many inflammatory mechanisms including: (a) the regulation of inflammatory mediators, such as cytokines (IL1β, TNFα, IL6, TGF1β) and cyclooxygenases, (b) the interference with transcription factors, such as NFκB, and (c) the activation of signaling cascades, such as MAP kinases

(Xia and Hyman 2002; Bakshi et al. 2011; Semple et al. 2010; Perry and Teeling 2013). MS exacerbation correlates with low levels of Vitamin D, whereas vitamin D supplementation has a protective effect (Aubert et al. 1995; Romeo et al. 2001; Varvel et al. 2012).

NMO and Peripheral Inflammation

There is not much evidence for peripheral inflammation affecting NMO, in contrast with MS. However, recent work shows that the peripheral immune system affects the progression of NMO. The CSF of NMO patients shows white blood cells (WBC) ≥50 cells/mm^3 or ≥5 neutrophils/mm^3 compared to control patients, whose counts are <5 WBC/mm^3 (Campbell et al. 2008). Additionally, removing inflammatory mediators from the blood of MNO patients alleviates the symptoms (Okada et al. 2006).

NMO can occur concomitantly with systemic autoimmune disorders such as Sjogren's syndrome and systemic lupus erythematous, which likely reflects an underlying predisposition for these patients to develop autoimmune disorders. Moreover, the presence of other systemic disease can increase the mortality rate in relapsing NMO patients (Krady et al. 2008).

Finally, the seropositivity for NMO–IgG represents a key factor for predicting future relapses; indeed, it is a prognostic marker for NMO. Additionally, humoral immune mechanisms, including the activation of B cells and the complement pathway, have been said to play a role in NMO pathogenesis (Quan et al. 2013; Kim et al. 2011).

Experimental Models of Demyelinating Diseases

Experimental models of demyelination help in understanding the pathophysiology of such demyelinating diseases as MS (Denic et al. 2011) and NMO (Linington et al. 1992). Animal models can be divided into two groups: those which attempt to replicate the disease as accurately as possible and others that provide a reductionist approach to the diseases by studying demyelination and remyelination processes (e.g., ethidium bromide, lysolecithin, and cuprizone) (reviewed in Blakemore and Franklin 2008). For MS, the most common models have been virus-induced encephalomyelitis and various forms of Experimental Autoimmune Encephalomyelitis (EAE) (reviewed in Dai et al. 2003).

A clear distinction between NMO and MS only became possible in the past decade, and nowadays the most frequently used NMO models are NMO/EAE, NMO-IgG/complement intracerebral injection, and cytokine-injection NMO (Linington et al. 1992). Some of the main features present in these experimental models are summarized in Table 1. Consistent with the human diseases, animal

Table 1 Summary of the main features of MS and NMO experimental models

Experimental model	Disease features	Reference
Lysolecithin and Ethidium Bromide Demyelination	**MS and NMO** Demyelination–Remyelination NO autoimmune component Microglial and Astroglial activation	Blakemore (2008)
Cuprizone induced Demyelination	**MS and NMO** Demyelination–Remyelination No autoimmune component Microglial and Astroglial activation Cytokine mediated inflammatory response Growth factors involved in remyelination	Wilkins et al. (2001)
Virus- induced Encephalomyelitis	**MS** BBB breakdown Demyelination Axon pathology Cytokine upregulation Central and systemic inflammatory response Autoimmune component Involvement of different immune cells (T cells, B cells) Microglial and Astroglial activation	Grigoriadis and Hadjigeorgiou (2006)
EAE (active, passive, or transgenic models)	**MS** Relapsing-remitting and progressive forms BBB breakdown Demyelination (sometimes remyelination) Axon pathology Cytokine upregulation Central and systemic inflammatory response Autoimmune component Involvement of different immune cells (depending on the model): T cells, B cells, granulocytes Microglial and Astroglial activation	Dai et al. (2003)
NMO/EAE	**NMO** Autoimmune component (AQP4 IgG) BBB breakdown Loss of AQP4 expression Presence of astrocyte destructive lesions Neutrophil and T cell infiltration to the CNS Activation of microglia/macrophages Demyelination Oligodendrocyte death	Linington et al. (1992) Bradl and Lassmann (2014)
NMO-IgG/complement	**NMO** Autoimmune component (AQP4 IgG) BBB breakdown Loss of AQP4 expression Presence of astrocyte destructive lesions Neutrophil and macrophage infiltration to the CNS Demyelination Neuronal death	Linington et al. (1992)

(continued)

Table 1 (continued)

Experimental model	Disease features	Reference
Cytokine-injection NMO	**NMO** Autoimmune component (AQP4 IgG) BBB breakdown Loss of AQP4 expression Presence of astrocyte destructive lesions Neutrophil infiltration to the CNS Demyelination Activation of microglia/macrophages	Linington et al. (1992)

experimental models show the influence of peripheral inflammation on the progression of the disorders.

The importance of humoral components of the immune system is evident in EAE. For example, a specific cytokine profile appears during the different phases of acute the EAE model: decreased IL21 expression on the peak phase and high IL22 expression during the induction phase that decreases during recovery (Almolda et al. 2011). Additionally, systemic TNFα causes clinical signs to recrudesce and induces relapses in EAE (Crisi et al. 1995).

MS Animal Models and Systemic Inflammation

Obesity

Immunomodulatory effects of leptin, the adipocyte-derived hormone, are involved in the induction and progression of EAE (Matarese et al. 2001, 2008). In this context, the use of leptin antagonists improved the course of EAE (De Rosa et al. 2006). Moreover, the leptin-deficient (*ob/ob)* mice do not develop EAE; however, exogenous leptin treatment renders *ob/ob* mice susceptible to EAE development (Matarese et al. 2001). On the other hand, caloric restriction, (associated with low levels of leptin in plasma) can significantly increase the overall survival in several experimental animal models of autoimmune diseases (Oka et al. 2007).

Infections

Peripheral infection with enterotoxin A or B exacerbates clinical signs and induces relapses in EAE (Brocke et al. 1993; Crisi et al. 1995; Schiffenbauer et al. 1993). A single dose of peripheral LPS can induce increased inflammatory, demyelinating and axonal damage in EAE lesions (Serres et al. 2009; Moreno et al. 2011) as well

as CD4+ cells activation (Nogai et al. 2005). Additionally, respiratory tract pathogens (*Streptococcus pneumonia* and *Chlamydia pneumonia*) aggravate EAE symptoms (Du et al. 2002; Herrmann et al. 2006; Tauber et al. 2007).

On the other hand, some data have been published demonstrating beneficial effects of peripheral LPS. In those studies, pretreatment with LPS prior to EAE induction lead to a delay in the onset of the disease by suppressing antigen presentation and altering the expression of inflammatory mediators (Buenafe and Bourdette 2007).

The presence of blood-derived peripheral polymorphonuclear neutrophils (PMN) expressing CXC chemokine receptor type 2 (CXCR2) is requisite for oligodendrocyte death, demyelination, and BBB breakdown in both EAE and cuprizone models (Liu et al. 2010; Carlson et al. 2008). Peripheral PMN are considered the first key effector leukocytes in the pathogenesis of EAE; they produce cytokines and chemokines that in turn induce lymphocyte and monocyte activation (Carlson et al. 2008).

Moreover, the importance of PMN neutrophils for the development of a demyelinating lesion in the CNS of rats has been seen in a model of chronic neuroinflammation and demyelination in response to a sustained expression of IL1β in the CNS (Ferrari et al. 2004). Furthermore, a *relapsing-like* lesion was achieved in the same model by inducing a peripheral sustained expression of IL1β (Murta et al. 2015). Here, the involvement of CXCR2 + PMN neutrophils from the periphery was also proven central for the development of the relapse.

Immune Regulation by the Neuroendocrine System

Estrogen inhibits clinical and histological symptoms of EAE, and pretreatment with low doses of 17beta-estradiol (E2) diminishes the symptoms of EAE by inhibiting cell migration into the CNS and promoting axon and myelin survival (Wolswijk 1998; reviewed in Murta and Ferrari 2013). Moreover, in EAE animals progesterone decreases proinflammatory cytokine secretion (IL12, IL17), increases IL10 production, and increases the CD19 + and CD8 + populations (Chang et al. 2002).

Environmental Factors

Diet also represents an important factor in experimental animal models. In EAE mice, a high salt diet increases the number of Th17 cells, worsening the disease (Tsai et al. 2002). Conversely, vitamin D (or its metabolite 1.25-dihydroxyvitamin D3) reverses the EAE symptoms by inhibiting chemokine and inducible nitric oxide synthase (iNOS) synthesis, and CD11b + monocyte trafficking into the CNS

(Moynagh 2005). Moreover, this vitamin also suppresses EAE female selectivity (Byravan et al. 1994).

Another environmental factor associated with EAE progression is UV irradiation: several authors have shown that UV irradiation suppresses EAE by inducing immunosuppression through an alteration of dendritic and regulatory T cells, independently of vitamin D production (Hauser et al. 1984; Waxman 1998; Lappe-Siefke et al. 2003; Ng et al. 2013).

Moreover, the influence of the microbiome on different pathological conditions has been investigated. In some models of EAE, gut microflora-free animals are resistant to the induction of RR-EAE and have decreased Th17 and B cell responses (Tsunoda and Fujinami 2002; Tsunoda et al. 2003; Huitinga et al. 2000).

Concluding Remarks

Systemic inflammatory insults are risk factors in both the etiology and progression of demyelinating diseases. The interaction between damaged brain and systemic inflammation may be responsible for the progression of neurodegenerative diseases. However, certain systemic stimuli may be beneficial for both disease progression and repair. Primed microglial cells in the diseased CNS are viewed as one of the key components in the exacerbation of central damage due to systemic inflammatory stimuli in most CNS diseases. Additionally, the peripheral immune system contributes significantly to the pathophysiology of the demyelinating diseases discussed in the present review and their animal models, and the environment appears also to be important. Better understanding of the mechanisms of CNS and immune system communication should improve therapeutics for immune mediated diseases.

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