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Review

Influence of Peripheral inflammation on the progression of multiple sclerosis: Evidence from the clinic and experimental animal models

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory disease characterized by demyelination, remyelination and loss of functions. Even though its etiology is unknown viral, genetic and environmental factors are considered triggers of the disease. MS shows a heterogeneous clinical course, but most patients exhibit exacerbations and remissions from the onset, eventually leading to secondary progressive multiple sclerosis. Systemic inflammatory events are known to signal into the central nervous system (CNS), and can induce a general response known as sickness behavior. Several research papers have demonstrated that a peripheral stimulus can induce the synthesis of cytokines in the brain. In different neurodegenerative diseases peripheral inflammation generates exacerbation to ongoing damage in the brain. In MS, relapsing and remitting episodes are unpredictable; however, peripheral inflammation may exacerbate these events. Clinical studies revealed an association between infections and relapses, which may lead to the worsening of neurological damage. A similar scenario was described in MS animal models demonstrating that peripheral inflammation recrudesced a central ongoing demyelinating lesion. In this paper, we reviewed the existing data on the inflammatory component of MS, with special attention on the effect of peripheral infections in the etiology and progression of MS and its effect on the relapsing and remitting episodes. We also analyzed data concerning the effect of peripheral inflammatory events in MS experimental animal models. This article is part of a Special Issue entitled 'Neuroinflammation in neurodegeneration and neurodysfunction'.

Contents

Abbreviations: γδ, gamma delta; AD, Alzheimer's disease; APC, antigen presenting cells; BBB, brain blood barrier; CCL2, chemokine CC motif ligand 2; CCR2, chemokine CC motif receptor 2; CNS, central nervous system; CSF, cerebrospinal fluid; CXCR2, CXC chemokine receptor type 2; EAE, experimental autoimmune encephalomyelitis; GA, glatimer acetate; GC, glucocorticoid; IFN-α, interferon alpha; IFN-β, interferon beta; IFN-γ, interferon gamma; IL-1β, interleukin 1 beta; IL-10, interleukin 10; IL-12, interleukin 12; IL-17, interleukin 17; IL-2, interleukin 2; IL-21, interleukin 21; IL-23, interleukin 23; IL-4, interleukin 4; IL-6, interleukin 6; LPS, lipopolysaccharide; MCP-1, monocyte chemotactic protein 1; MHC I, major histocompatibility complex type 1; MHC II, major histocompatibility complex type 2; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; PD, Parkinson's disease; PMN, polymorphonuclear neutrophils; PP, primary progressive; PrD, prion disease; SP, secondary progressive; RR, relapsing-remitting; TGF-β, transforming growth factor beta; Th1, T helper 1; Th17, T helper 17; Th2, T helper 2; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cells; VEGF, vascular endothelial growth factor.

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Introduction

MS: an autoimmune disease

Multiple sclerosis (MS) is a chronic inflammatory disorder of the brain and spinal cord characterized by demyelination and remyelination events, accompanied by loss of sensory and motor functions. With time remyelination becomes incomplete and leads to persistent symptom accumulation. MS shows a heterogeneous clinical course, but the vast majority of the patients present relapsing-remitting (RR) episodes from the onset, eventually leading to secondary progressive (SP) MS, that worsens the patients' quality of life (Bradl and Lassmann, 2009; Weiner, 2008). A minority of patients exhibit primary progressive (PP) MS, which is characterized by a constant decline from the onset with no recovery in their neurological functions (Bradl and Lassmann, 2009; Dutta and Trapp, 2011).

Although MS is an autoimmune disease, its etiology is still unclear. Many people now believe it to be of multifactorial origin. Epidemiological studies have clearly shown that both genetic and environmental factors influence MS incidence, suggesting that people with certain genetic risk factors, are more likely to develop the disease given specific features of their surroundings (reviewed in Compston and Coles, 2008). Infections and other pro-inflammatory 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 pro-inflammatory event (Barnett and Prineas, 2004).

Although therapeutic interventions are able to reduce the frequency of new relapsing episodes, they fail to reduce disability or influence the progressive phase of the disease. Moreover, second generation drugs are usually powerful immunological treatments that may induce serious adverse secondary effects. Questions have been raised about the safety of the long term use of these drugs (reviewed in Chataway and Miller, 2011). Immunomodulatory treatments that were demonstrated to be beneficial in the relapsing form of the disease have very little effect in progressive phases. These data might indicate that both the pathogenesis and the immunological mechanisms are different between relapsing and progressive MS (Kutzelnigg et al., 2005). In addition, the same authors demonstrated that SPMS and PPMS patients had generalized inflammation in the whole brain along with cortical demyelination and diffuse white matter injury. These characteristic signs of PPMS and SPMS patients are rare in the acute or relapsing stage (Kutzelnigg et al., 2005).

MS and inflammation

MS is described primarily as an inflammatory autoimmune disease (Lindquist et al., 2011; Lucchinetti et al., 2004). Multifocal inflammation, mainly in the white matter of the brain and spinal cord, is associated with the RR phase of the disease, while the progressive period has been related to the events of axonal loss and neurodegeneration (Slavin et al., 2010). Like most autoimmune disorders, unveiling the role of the different inflammatory components is essential, but has been proven to be a challenge.

Immune cells

Lymphocytes and macrophages have been considered as the principal pathological players for years, since they were the main cell type found in MS plaques. It is well established that activated T cells entering the CNS drive at least part of the immune mediated damage (Frohman et al., 2006; Hafler et al., 2005). Inflammatory cells in progressive MS patients were observed in perivascular cuffs, while their location in the parenchyma is sparse. In addition, lymph follicle-like structures are formed in the meninges and perivascular spaces (Bradl and Lassmann, 2009; Kutzelnigg et al., 2005). The germinal centers of this follicle are composed of B cells and a network of dendritic cells. On the contrary, both perivascular and parenchymal infiltration by immune cells are seen in acute and relapsing MS lesions (Bradl and Lassmann, 2009).

In the past years, several subtypes of T cells have been implicated in the pathology of MS.

(1) CD4 + T helper 1(Th1) cells have been considered key players in both MS pathology and experimental autoimmune encephalomyelitis (EAE) pathology for a long time due to the fact that most histopathological and clinical conditions could be explained by the involvement of these cells and their leading cytokine IFN-γ (Leibowitz et al., 1966). In fact, adoptive transfer of myelin specific Th1 cells is a very potent inducer of EAE, whereas IFN-γ has been found in MS lesions and its administration has exacerbated MS pathology by triggering relapses (Gold, 2011; Panitch et al., 1987).

(2) In the early 2000s novel CD4 + T helper 17 (Th17) cells became highly associated with EAE because mice deficient of interleukin 23 (IL-23), the main interleukin 17 (IL-17) stimulator, were found to be resistant to the induction of the pathology (Cua et al., 2003). Since then more evidence has supported the involvement of these cells in MS pathology, including their presence in the inflamed CNS of EAE animals (Pepper et al., 2010), and the fact that IL-17 is one of the main up-regulated cytokines in MS patients (Lock et al., 2002).

(3) Gamma delta (γδ) T cells have also been implicated in MS pathology since they were found in active MS acute lesions and in the cerebrospinal fluid (CSF) of early diagnosed patients (Shimonkevitz et al., 1993; Wucherpfennig et al., 1992). In the EAE animal model high amounts of IL-17 producing γδT cells were found during the induction phase of the pathology (Sutton et al., 2009). They were also implicated in an exacerbation of autoimmunity because of their ability to restraint regulatory T cell (Treg) activity (Petermann et al., 2010).

(4) Even though there is a lot of evidence that implicates different types of Treg cells in MS pathology, the interpretation of experimental data has been difficult due to the lack of markers. In spite of this, adoptive transfer and neutralization experiments have proven that Tregs render resistance to EAE (reviewed in Fletcher et al., 2010).

(5) Finally, CD8 + T cells were found in the lesions, CSF and blood of MS patients, and their CNS abundance has been positively correlated with the intensity of axon damage (reviewed in Saxena et al., 2011). In EAE, some studies have suggested a pathogenic role for CD8 + T cells (Huseby et al., 2001; Sun et al., 2001), while CD8 + Treg cells have a suppressing role (Chen et al., 2009).

The presence of B cells in recent MS plaques was first described in 1980 (Esiri, 1980), since then they were found to play a significant role in the pathology of the disease (reviewed in Wootla et al., 2011). As previously said, Baranzini et al. were able to prove that a germinal center-like reaction takes place during the immune attack against CNS structures, with the production of antibodies within the plaques (Baranzini et al., 1999; Bradl and Lassmann, 2009; Kutzelnigg et al., 2005). Some of the roles attributed to these cells in MS pathology are: myelin-specific antigen presentation (acute demyelination and contribution to MS progression), abnormal cytokine production (decreased production of IL-10 may be responsible for the activation of pro-inflammatory T cells), and the production of immunoglobulins involved in demyelination or remyelination (reviewed in Wootla et al., 2011).

Antigen presenting cells (APC) are involved in multiple stages during the pathogenesis of MS in animal models: (1) upon encountering myelin antigen they activate T cells in the lymph nodes (Bailey et al., 2007; Guermonprez et al., 2002), (2) depending on the cytokines produced they influence the resulting T cell subtype (Zhu and Paul, 2010), (3) they re-stimulate mature T cells once they

are in the brain (Tompkins et al., 2002). Under non-pathological conditions macrophages are the main MCH II expressing APCs in the CSF, but they are not the only ones able to present myelin antigens: monocytes, dendritic cells, microglia and astrocytes have also been implicated in antigen presentation in demyelinating disorders (Bauer et al., 1995; Constantinescu et al., 2005; Cudrici et al., 2007; Pattison et al., 1996).

Finally, some less specific effector cells have been related to MS. Mast cells have been associated with MS plaques since 1990 (Wootla et al., 2011), and more recently it was evidenced that these cells were involved, in high association with myelin autoantibodies, in both MS and EAE (Kruger et al., 1990; Secor et al., 2000). Mast cells are able to secrete a wide range of cytokines, and therefore influence the differentiation pattern of both T and B lymphocytes, tilting the scale towards an effector or regulatory profile. In EAE, mice lacking mast cells developed a milder form of the pathology (Secor et al., 2000), and also showed a reduced response of autoreactive T cells (Gregory et al., 2005). On the contrary, a recent report demonstrated that mast-cell deficient mice presented a more severe form of the disease (Bennett et al., 2009). Moreover, mast cells also contributed to EAE severity by interacting with other immune cells in secondary lymphoid organs (Tanzola et al., 2003).

Neutrophils are leukocytes that respond to several infectious stimuli. In the past years they have been found to cooperate extensively with the Th17 cell response by means of a chemokine-dependent reciprocal cross-talk between them. Due to the fact that neutrophils have a highly indiscriminate and histotoxic potential, their activation has to be finely regulated and consists of a priming first step prior to the fully active state. Neutrophil priming was evidenced in some inflammatory and autoimmune pathologies such as rheumatoid arthritis or autoantibody-associated vasculitis (Harper et al., 2001; Wright et al., 2010). Indeed, in MS primed neutrophils are numerous in patients (Naegele et al., 2011). Moreover, CXC chemokine receptor type 2 (CXCR2 +) neutrophils have been seen to contribute to the development of lesions in EAE and cuprizone (Carlson et al., 2008; Liu et al., 2010) models.

Cytokines

Cytokines are polypeptides traditionally involved in orchestrating immune responses. Taking into consideration the wide range of functions they have individually and as a complex network, fully understanding the mechanisms behind their involvement in MS pathology has been difficult (for a more detailed review see Codarri et al., 2010). Information taken from animal models has, time after time, failed to translate into the clinics; and most hypotheses had to be revised in light of the results of clinical trials.

Tumor necrosis factor alpha (TNF-α) is elevated in the CSF, serum and active lesions of MS patients, and correlates with disease progression (Maimone et al., 1991; Sharief and Hentges, 1991). Even though preclinical results in animal models were encouraging, patients treated with different TNF-α blockers deteriorated with the treatment (Anon., 1999).

Something similar was seen with interferon gamma (IFN-γ) and interleukin 12 (IL-12) therapies, where preclinical results in animal models pointed to a specific beneficial (IFN-γ) or a detrimental (IL-12) role of these cytokines, but the opposite was seen in the clinical trials (Leonard et al., 1995; Panitch et al., 1987; Willenborg et al., 1996).

The denominated IL-23/IL-17 axis, which includes interleukin 23 (IL-23), interleukin 17 (IL-17) and interleukin 21 (IL-21) among other cytokines, has been associated in the past years with MS. Although IL-23 has a vital role in the development of EAE, blocking it did not result in any significant therapeutic benefit in a clinical trial (Segal et al., 2008). Even though Th17 cells have been clearly implicated in both MS pathology and EAE pathology (see above), neutralizing IL-17 or the lack of the cytokine did not provide resistance to EAE (Haak et al., 2009; Hofstetter et al., 2005).

Taking this into consideration and many other data, it becomes clear that the comprehension of the mechanisms behind the involvement of cytokines in MS is crucial for a better and global insight into MS pathophysiology. Given the pleiotropic and multi-functional traits of cytokines we need to be careful in the interpretations of the data available from both animal model research and clinical trials.

Inflammation and BBB

Blood brain barrier (BBB) breakdown and inflammation appear to play a major role in the pathology of numerous neurodegenerative diseases compromising the vascular unit and inducing leukocyte migration within the brain parenchyma (Stolp and Dziegielewska, 2009). BBB disruption is a major hallmark in MS (Larochelle et al., 2011; McQuaid et al., 2009; Watzlawik et al., 2010). The entry of leukocytes into the CNS is considered an early phenomenon that induces BBB breakdown and neuroinflammation (Larochelle et al., 2011). Activated peripheral lymphocytes infiltrate the CNS and trigger an immune response that damages the myelin and eventually leads to axonal loss (Lindquist et al., 2011). Indeed, it was described that leukocyte migration modifies BBB integrity in MS lesions (Larochelle et al., 2011). However, it was also described that components of the inflammatory response contribute to the disease independent of BBB integrity (Buljevac et al., 2002; Lindquist et al., 2011). RRMS and progressive MS differ mainly in the state of the BBB. RRMS lesions are characterized by BBB breakdown which allows new lesions to flare up as inflammatory cells enter the CNS. But, the inflammation remains trapped behind a close BBB in the progressive phase of the disease (Bradl and Lassmann, 2009).

Several cytokines associated with MS are known to affect BBB integrity: (1) intravenous administration of TNF-α in mice resulted in BBB breakdown (Tsuge et al., 2010), (2) in vitro TNF-α and IFN-γ alter the architecture of junction proteins in primary cultures of BBB-endothelial cells (Alvarez et al., 2011), (3) interleukin 1beta (IL-1β) increases the vascular endothelial growth factor (VEGF) during MS relapses which in turn generates an increase in BBB permeability (Argaw et al., 2006; Su et al., 2006), and (4) IL-17 increases BBB permeability and promotes lymphocyte and monocyte migration (Kebir et al., 2007).

MS and systemic inflammation

Communication between periphery and CNS

Systemic inflammatory stimuli that circulate in the blood can get into the brain, inducing the synthesis of cytokines in the CNS, which are responsible for changes in behavior and the general state known as sickness behavior (Besedovsky and del Rey, 1996; Combrinck et al., 2002; Dantzer et al., 1998, 2008; Londono and Cadavid, 2010; Pitossi et al., 1997). This sickness behavior is evidenced by fever, anorexia, fatigue, sleep and memory disturbances (Dantzer, 2004; Dantzer et al., 1998, 2008; Holden et al., 2008).

Circulating cytokines and other inflammatory molecules can affect the brain through several routes, mainly through the neural or humoral pathways. The neural pathway is related to the transmission of peripheral inflammatory signals through the autonomic nervous system, almost exclusively through the vagal afferent nerve (Campbell et al., 2010; D'Mello and Swain, 2011; Gautron and Laye, 2009; Perry et al., 2003; Teeling and Perry, 2009). IL-1β and prostaglandin E_2 receptors were reported in vagal ganglia close to the liver and lymphatic nodes (Goehler et al., 1999). Subdiaphragmatic surgical vagotomy or chemical deafferentation (capsaisin) attenuates brain cytokine production, anorexia and behavioral effects after a systemic challenge (Gaykema et al., 2007; Gaykema and Goehler, 2009; Ge et al., 2001; Gibb et al., 2008; Giovambattista et al., 2000).

The humoral pathway involves the direct action of pro-inflammatory cytokines on the CNS. It is known that peripherally induced cytokines (e.g. IL-1β, TNF-α, and interleukin 6 [IL-6]) and type I interferons (IFNα and IFNβ) can initiate the synthesis of cytokines within the CNS (Perry et al., 2003; Teeling and Perry, 2009). The BBB regulates the passage of substances from the blood to the brain (reviewed in Larochelle et al., 2011). BBB disruption normally occurs as a response to any damage in the brain.

Cytokines secreted in the periphery cannot diffuse through the intact BBB, but there are some mechanisms to avoid this barrier: (1) substances can diffuse from the circulation through BBB deficient areas, such as the circumventricular organs and choroid plexus. (2) Cytokines and amines can actively cross the BBB using specific transporters. (3) Cytokines can stimulate BBB endothelial cells inducing the expression of factors that activate either neurons or microglia in the CNS (Dantzer, 2004; Dantzer and Kelley, 2007; Goehler et al., 2006). (4) Active leukocyte recruitment into the brain can disrupt BBB integrity allowing lesion formation.

Recently a new pathway was proposed using a model of inflammatory liver injury (D'Mello et al., 2009). The authors suggested that activated monocytes were recruited into the brain acting as cellular messengers (D'Mello et al., 2009). Activated monocytes secreted messenger molecules, such as TNF-α and monocyte chemotactic protein 1 (MCP-1), within the brain during systemic inflammatory diseases (D'Mello et al., 2009; Rostene et al., 2007).

MS and systemic inflammation: evidence from the clinics

As described previously, systemic inflammation has an effect on the CNS (Cunningham et al., 2005a; Dantzer et al., 1998, 2008). Indeed, peripheral pro-inflammatory stimuli can also trigger the secretion of pro-inflammatory molecules in the injured brain (Perry et al., 2002). Neurodegenerative diseases present "primed" and "activated" microglia as one of the main hallmarks. The term "primed" microglia describes the atypical state which precedes further neurotoxic microglial activation, consequence of a secondary pro-inflammatory stimulus (Cunningham et al., 2005b; McColl et al., 2007). Central or peripheral inflammation can transform the "primed" state microglia into an "active" state microglia, which can trigger exacerbated responses towards neurodegeneration.

In fact, peripheral inflammation exacerbates central ongoing damage in several neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), prion disease (PrD), stroke, and Wallerian degeneration (Cunningham et al., 2005a, 2005b; McColl et al., 2007; Palin et al., 2008; Perry et al., 2007; Spencer et al., 2007), leading to the worsening of clinical symptoms. MS was also described to flare up the symptoms after peripheral inflammation. Systemic inflammations are considered a risk factor for relapsing episodes in MS (Perry et al., 2003).

Both innate and adaptive immune systems are involved in the different MS phases (Weiner, 2008). But, it was described that the peripheral innate immune system changes from the relapsing/remitting to the progressive phase (Weiner, 2008).

In the case of RRMS, relapsing and remitting episodes are unpredictable; however, these events seem to be related to the presence of peripheral inflammation (Buljevac et al., 2002). RRMS patients showed increased serum levels of IL-1β, IL-2, IL-4, IL-12p70, IFN-γ and TNF-α during the relapse phase (Edwards et al., 2011; Mikulkova et al., 2011; Trenova et al., 2011). The number of IL-1β, IL-6 and TNF-α secreting cells is higher in RRMS patients only during exacerbations (Ysrraelit et al., 2008). Also, the levels of Th17 and Treg cells in the periphery are higher in MS patients undergoing a relapse (Edwards et al., 2011). The CSF cytokine profile can change from remission to relapse stage, with the up-regulation of IL-1β, TNF-α, transforming growth factor beta (TGF-β), and the down-regulation of IL-10 (Edwards et al., 2011; Hauser et al., 1990). Despite the important association between ubiquitous TNF-α increase and relapses, treatment of MS patients with TNF-α inhibitors resulted in the exacerbation of central lesions (reviewed in (Perry et al., 2003)).

Several publications have shown that there are some differences regarding the cytokine expression pattern when comparing different forms of the disease. Compared with RRMS patients, SPMS patients presented elevated levels of chemokine CC motif receptor 2 (CCR2) in T cells, and increased chemokine CC motif ligand 2 (CCL2) in the serum and CSF (Miller, 2012). Moreover, the TNF-α and IL-4 levels were diminished in the CSF and plasma of SPMS patients when compared with the levels observed during relapses of RRMS (Obradovic et al., 2012). Another difference between the RR and SP forms of the disease was seen regarding IL-10 mRNA levels in peripheral blood mononuclear cells: low levels of this cytokine were seen in SP and remitting RR patients, which returned to basal reading during relapses in the RR form (van Boxel-Dezaire et al., 1999). Regarding the inflammatory cell pattern, PPMS and SPMS patients exhibited a sustained increase in the number of Th1 and T cytotoxic type 1 cells in peripheral blood, suggesting that the progressive phase of the disease is characterized by a permanent peripheral type 1 immune activation, which is not the case for RRMS patients (Frisullo et al., 2012). RRMS is characterized by waves of Th1 and Th17 cells, which are recruited into the brain causing the attacks (Weiner, 2008). The peripheral type 1 response could contribute to CNS damage during the progressive phase of the disease (Bradl and Lassmann, 2009). Thus, the peripheral blood of SPMS patients seems to reflect the inflammatory response accumulated in the CNS (Bradl and Lassmann, 2009).

CNS leukocyte infiltration is essential for viral immunosurveillance (Ransohoff, 2005). The entrance of anti-inflammatory Th2 lymphocytes has been shown to contribute to CNS repair in MS (Doerck et al., 2010). Therefore, the delicate balance between pro- and anti-inflammatory processes should be taken into account when considering therapeutic options for different MS patients.

Clinical studies revealed an association between infections and relapse episodes, which induce worsening of neurological damage that remains even when the infection is gone (Buljevac et al., 2002; Panitch, 1994). Viral infections of the upper respiratory tract and gastrointestinal tract are important triggers of MS episodes, and can be reduced with IFN-γ treatment (Andersen et al., 1993; Panitch, 1994). Additionally, increased serum levels of leptin, a hormone involved in the immune response, has been correlated with the pathogenic Th1 profile in MS (reviewed in (Matarese et al., 2010; Matarese et al., 2008)). Stress was also associated with increased relapses in RRMS (Buljevac et al., 2003). The authors suggested that stress can suppress the immune response, therefore increasing the susceptibility to opportunistic infections. Indeed, recent data demonstrated that glucocorticoids (GCs), considered as potent anti-inflammatory molecules, under certain circumstances can exert pro-inflammatory effects (reviewed in (Sorrells et al., 2009)). GCs increased both the peripheral (liver) and central inflammatory response to a systemic challenge if they are administrated before the peripheral stimuli (Frank et al., 2010; Sorrells and Sapolsky, 2010). The timing between the stressor and the peripheral challenge influenced the effect of stress on inflammatory responses (Frank et al., 2010). Therefore, stress can prime the immune response, increase pro-inflammatory cytokine production and exacerbate MS symptoms.

Interestingly, not all infections are detrimental for the progression of MS symptoms. It was reported that infections with some parasites can protect against MS (Correale and Farez, 2011a, 2011b. This was associated with the induction of CD4+, CD25+ T cells secreting IL-10 and TGF-β (Correale and Farez, 2011a). In accordance with previous data, the hygiene hypothesis, that suggested that early exposure to germs strengthen the immune system (Leibowitz et al., 1966; Olszak et al., 2012), can be applied to the evidence that the risk of developing MS increased among patients who, during their childhood, lived with high sanitation levels (reviewed in (Bach, 2002; Correale and Farez, 2011a)).

Taking into consideration the information exposed above, knowledge on the fine tuning between periphery–brain communications would help to develop specific therapeutic tools to improve the quality of life of RRMS patients.

MS and drugs used in clinical trails

Although a detailed description of drugs used in MS treatments is beyond this review, we consider that it is worthy to briefly mention the most important MS drugs and its influence on the inflammatory components of the disease. As previously said, MS etiology is still unknown and to find a cure is still a challenge. The main hallmark of the disease appears to be inflammation and several agents were designed to decrease inflammation. These drugs, designed especially for the relapsing forms of the disease, focus on targeting specific components of the immune system in order to decrease the inflammatory processes, but none of them cure or reverse previous damage caused by the disease (Loma and Heyman, 2011). IFN-β and glatiramer acetate (GA) were the first drugs approved for MS treatment and are used as first-line agents with similar efficacy in reducing the relapse rate (reviewed in (Saidha et al., 2012)). IFN-β reduces the production of pro-inflammatory cytokines and induces the expression of anti-inflammatory molecules, whereas GA switches the cytokine profile to a regulatory type, increasing the expression of IL-10, TNF-α and IL-4 (Loma and Heyman, 2011).

Monoclonal antibodies (natalizumab and alemtuzumab among others) were also used as therapy agents. These drugs inhibited leucocyte migration across the BBB and, therefore, reduced the relapse rate (Loma and Heyman, 2011; Pucci et al., 2011; Saidha et al., 2012). In addition, an emerging second-line of treatments was developed. These agents have greater efficacy but many safety concerns (reviewed in (Gasperini and Ruggieri, 2009; Killestein et al., 2011; Saidha et al., 2012)). Most of them (e.g. fumaric acid, cladribine, teriflunomide, laquinimod) decrease the inflammatory processes either by reducing the number of immune cells or shifting the pro-inflammatory profile to an anti-inflammatory one (Gasperini and Ruggieri, 2009, 2011; Gold, 2011; Killestein et al., 2011; Loma and Heyman, 2011; Saidha et al., 2012). Anti-inflammatory therapies appeared to be an interesting option, however since most of them are cytotoxic myelosuppresion is a side effect. Therefore an augmented incidence of opportunistic infections represents another known risk during immunosuppressive drug administration. The balance between pro- and anti-inflammatory mechanisms represents an important issue in the drug design. As previously said, the appearance of systemic infections should be considered as a risk factor while administering these treatments.

MS experimental models and systemic inflammation

Several animal models of demyelination have helped understand the pathophysiology of MS (Denic et al., 2011). As reviewed in Blakemore and Franklin (Blakemore and Franklin, 2008), animal models can be divided into two groups: those which attempt to replicate the disease as accurately as possible, like virus induced encephalomyelitis and EAE, and others that provide a more reductionist approach which allow studying specific aspects of the disease (e.g. ethidium bromide, lysolecithin, cuprizone). The viral encephalomyelitis model is based on the theory that viral infections play a role in the development of autoimmunity in the CNS. It is characterized by extensive demyelination and the course is chronic progressive with no RR phase. The EAE model is based on the principle that MS is an autoimmune disease.

MS experimental models also demonstrated the influence of peripheral inflammation on ongoing CNS lesions. The importance of the humoral components of the immune system was emphasized in EAE. A specific cytokine profile was demonstrated along the different phases of the acute EAE model: decreased IL-21 expression on the peak phase and high IL-22 expression during the induction phase that decreased during recovery (Almolda et al., 2011). In order to develop a model of RR EAE, immunization with myelin oligodendrocyte glycoprotein (MOG_{35-55}) in (B6×SJL) F1 H-$2^{b/b}$ mice is required (Skundric et al., 2003, 2005). In the experimentally induced acute disease the activation of T cell clones occurs in the periphery; however, in the relapsing disease this activation may occur either in the CNS or periphery (Steinman, 2001).

The peripheral challenge with lipopolysaccharide (LPS) enhanced the pathogenicity in a Theiler's virus demyelinating model (Palma et al., 1996). Peripheral infection with enterotoxin A or B, and systemic TNF-α recrudesces clinical signs and induces relapses in EAE (Brocke et al., 1993; Crisi et al., 1995; Schiffenbauer et al., 1993). The adipocyte-derived hormone leptin, involved in the regulation of the immune response, was also demonstrated to increase the susceptibility to EAE ((Matarese et al., 2001); reviewed in (Matarese et al., 2008)). In this context, the use of leptin antagonists improved the course of EAE (De Rosa et al., 2006). In addition, *Streptococcus pneumonia* and *Chlamydia pneumonia*, two pathogens of the respiratory tract, were demonstrated to aggravate EAE symptoms (Du et al., 2002; Herrmann et al., 2006; Tauber et al., 2007). A single dose of LPS induced an increased inflammatory and demyelination response in EAE lesions (Serres et al., 2009), and also promoted EAE relapses by the activation of CD4+ cells (Nogai et al., 2005). Recently it was published that a peripheral challenge with LPS induced a stronger response in lesion associated microglia, increasing the axonal damage in an EAE model (Moreno et al., 2011).

On the other hand, some data have been published demonstrating beneficial effects of peripheral LPS: pretreatment 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). In addition, neonatal exposure to LPS induced a modulation in the inflammatory response (down-regulation of IL-17 and IFN-γ), which in turn provided a neuroprotective effect on EAE development in adult rats (Li et al., 2010).

The presence of blood-derived peripheral polymorphonuclear neutrophils (PMN) expressing CXC chemokine receptor type 2 (CXCR2) is mandatory to induce oligodendrocyte death, demyelination and BBB breakdown in both EAE and cuprizone models (Carlson et al., 2008; Liu et al., 2010). Therefore, the presence of cuprizone toxicity is necessary but not enough to induce demyelination (Liu et al., 2010). The early presence of CXCR2-expressing PMN contributes to both disease initiation and relapse in an EAE model (Carlson et al., 2008). PMN are considered the first key effector leukocytes in the pathogenesis of EAE, by producing cytokines and chemokines that induce in turn lymphocyte and monocyte activation (Carlson et al., 2008). Moreover, the administration of an antibody against CXCR2 induced and increased clinical symptomatology of the disease, and also enhanced demyelination during inflammatory demyelination initiated by a viral infection of the CNS (Hosking et al., 2010). Taking these data together, the presence of peripheral inflammatory elements is required to induce demyelination in both cuprizone and EAE models.

However, some conflicting data were reported in the cuprizone model. An acute or repeated challenge with LPS after 5 weeks of cuprizone treatment did not influence the central nor peripheral expression of IL-1β, TNF-α or IL-6 (Urbach-Ross and Kusnecov, 2007). Indeed, the systemic infection with LPS inhibited early re-expression of myelin proteins but had beneficial effects on remyelination, inducing oligodendrocyte precursor proliferation, and microglia activation during early remyelination. This translated into diminished axonal damage, therefore demonstrating that systemic LPS improves remyelination in a cuprizone model (Skripuletz et al., 2011).

The responsiveness of the disease to infectious agents should be carefully studied in experimental models in order to achieve an exhaustive knowledge on the peripheral–central interactions that can help elucidate the complex RRMS mechanisms.

Conclusions

We have reviewed evidence that some peripheral infections exacerbate the immune response in both MS experimental models and patients. Peripheral infectious agents may aggravate the symptomatology of the disease and increase the risk of relapses and remitting episodes. The importance of early treatments of infectious diseases should be taken into account in MS patients in order to improve the quality of life and progression of the disease. In addition, treatments with anti-inflammatory agents should be carefully studied in order to get specific therapeutic tools for each phase of the disease.

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