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MINI-REVIEW

Multiple sclerosis: a battle between destruction and repair

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Abstract

Multiple sclerosis (MS) is a chronic neurodegenerative disease of the CNS in which an unrelenting attack from the innate and adaptive arms of the immune system results in extensive demyelination, loss of oligodendrocytes and axonal degeneration. This review summarizes advances in the understanding of the cellular and molecular pathways involved in neurodegeneration following autoimmune-mediated inflammation in the CNS. The mechanisms underlying myelin and axonal destruction and the equally important interaction between degenerative and repair mechanisms are discussed. Recent studies have revealed that the failure of CNS regeneration may be in part a result of the presence of myelin-associated growth inhibitory molecules in MS lesions. Successful therapeutic intervention in MS is likely to require suppression of the inflammatory response, in concert with blockade of growth inhibitory molecules and possibly the mobilization or transplantation of stem cells for regeneration.

Keywords: experimental autoimmune encephalomyelitis, inflammation, multiple sclerosis, neurodegeneration, neuroregeneration, stem cells.

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Multiple sclerosis (MS) is a chronic neurodegenerative disease of the CNS in which relentless attacks of autoimmune-mediated inflammation result in demyelination, loss of oligodendrocytes and axonal degeneration. This, in turn, results in a multiplicity of neurological deficits, such as paralysis, sensory loss, limb weakness, fatigue, cramps, incontinence and cognitive defects (Noseworthy *et al*. 2000). MS is most frequently diagnosed during early adulthood, has a clear gender bias towards females (2–3 : 1) and is estimated to affect 2.5 million people worldwide. In most patients (80%), MS develops as a relapsing–remitting disease, characterized by intermittent attacks of neurological dysfunction amid periods of remission with partial or complete recovery. However, over time, recurrent bouts of inflammation lead to the accumulation of CNS damage with the persistence of neurological impairment, resulting in a secondary progressive disease without remission. In other patients (20%), a primary progressive disease is apparent from the onset, in which there is gradual deterioration (Keegan and Noseworthy 2002).

Pathogenesis

The clinical heterogeneity of MS is well described, but it is now clear that MS lesions and the underlying pathological mechanisms involved in CNS destruction are also heterogeneous (Lassmann *et al*. 2001). However, the common inflammatory pathology of MS lesions suggests that autoimmune responses targeted against CNS myelin components may play a principal role in the destruction of myelin in MS. This concept is supported by the high level of oligoclonal immunoglobulin in the cerebrospinal fluid, genetic linkage to the major histocompatibility complex (MHC) locus, expansion of myelin-reactive T and B cells within MS lesions and the fact that immunization with myelin proteins induces an MS-like disease in experimental animals (experimental autoimmune encephalomyelitis, EAE). Autoreactivity to several myelin proteins, including myelin basic protein,

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Abbreviations used: BBB, blood–brain barrier; EAE, experimental autoimmune encephalomyelitis; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN-γ, interferon-γ; IL, interleukin; LFA-1, leucocyte function-associated antigen-1; MHC, major histocompatibility complex; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; OPC, oligodendrocyte precursor cell; RANTES, 'regulated upon activation, normal T cell expressed and secreted'; VLA-4, very late antigen-4.

proteolipid protein, myelin-associated glycoprotein and myelin oligodendrocyte glycoprotein (MOG), has been observed in MS patients (Bernard and de Rosbo 1991; Sun *et al*. 1991; Kerlero de Rosbo *et al*. 1993; Sellebjerg *et al*. 1998; Egg *et al*. 2001; Hellings *et al*. 2001; Markovic *et al*. 2003; O'Connor *et al*. 2003). However, it has been documented that T cells from MS patients exhibit a predominant activity to MOG relative to other myelin proteins (Kerlero de Rosbo *et al*. 1993), and anti-MOG antibodies have been identified bound to disintegrating myelin around axons in lesions of acute MS (Genain *et al*. 1999), implicating it as a dominant autoantigen. Moreover, sensitization with MOG reproduces the full clinical, demyelinating and axonal degenerative pathology of MS in the rodent and primate models of MS (Johns *et al*. 1995; Bernard *et al*. 1997; Genain and Hauser 1997; Storch *et al*. 1998; t Hart *et al*. 2000; Gold *et al*. 2006).

It is generally assumed that CNS inflammation is initiated by the activation of autoreactive, myelin-specific T cells in the periphery, which permeate the blood–brain barrier (BBB) and locally trigger a cascade of events that promotes tissue destruction leading to neurological dysfunction. However, unlike EAE, in which the autoimmune response is induced by immunization, the mechanism resulting in the induction of autoreactive T cells in MS remains unclear. In addition, MS is a spontaneous disease with unknown aetiology; thus, it is possible that, at least in some patients, inflammation is secondary to tissue destruction.

Autoreactivity to autoimmunity

It is apparent that central tolerance to self-antigens in the thymus is not absolute and that many autoreactive T cells escape deletion and enter the circulation. However, there are several peripheral mechanisms which also operate to maintain self-tolerance. Depending on the co-stimulation received when encountering antigens in the periphery, T cells can undergo activation or, alternatively, be deleted (by apoptosis) or inhibited. Also, T cells that are physically separated from their specific antigen by anatomical barriers remain ignorant (Kamradt and Mitchison 2001). Loss of tolerance in MS could result from unmasking and novel presentation of CNS antigens to the immune system, from antigen-specific mechanisms, such as molecular mimicry, or, alternatively, from non-specific mechanisms, such as bystander activation of ignorant T cells (Benoist and Mathis 2001). Reports of association between infections and MS relapses (Buljevac *et al*. 2002; DeLorenze *et al*. 2006) have been extensive, but no single infectious agent has been detected reproducibly. Perhaps infection in the CNS might instigate the onset of autoimmunity via molecular mimicry, or by creating an inflammatory environment within the CNS that is capable of activating natural autoreactive T-cell populations (Panoutsakopoulou *et al*. 2001). It is also possible that tissue destruction in MS may precede inflammation. Whatever the mechanism, autoreactivity is a relatively common finding, yet autoimmune phenomena are still rare, suggesting that the induction of autoreactive T cells alone is insufficient to induce autoimmunity. The presence and persistence of autoreactive T cells in the CNS, however, may be a major factor governing the transition from autoreactivity to autoimmune diseases of the CNS.

Historically, the CNS was considered to be an immunologically privileged site, but research performed over the last decade has indicated that this notion no longer holds true (Perry *et al*. 1997; Hickey 2001). Although most immune cells are denied entry to the CNS by the BBB, both naive and activated T cells possess the ability to traffic across the BBB and patrol the brain parenchyma; however, these cells usually exit the CNS swiftly or die rapidly via apoptosis (Hickey 2001). Clinical disease in EAE requires the reactivation and clonal expansion of T cells within the CNS (Krakowski and Owens 2000; Kawakami *et al*. 2005). In the CNS, antigen presentation is generally negligible because of the lack of MHC expression. However, given the right cytokine milieu, microglia and/or astrocytes can be stimulated to become professional antigen-presenting cells through stimulation by cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF) and interferon-γ (IFN-γ). Resting microglia, isolated from the brain, have been shown to generate a population of immature brain dendritic cells on exposure to GM-CSF (Fischer and Reichmann 2001). Thus, depending on the local cytokine environment and type of interaction (co-stimulation), these activated glial cells could potentiate the re-stimulation of autoreactive T cells and promote the retention of these cells in the CNS (Matyszak *et al*. 1999). Indeed, several studies have implicated microglia and/or astrocytes as critical to the effector phase of EAE (Slavin *et al*. 2001; Girvin *et al*. 2002). This scenario is also supported by the observation of local expression and/or up-regulation of MHC antigens in EAE and MS lesions (Traugott 1987).

The inflammatory cascade

The BBB is responsible for the selective transport of molecules and cells from the circulation into the CNS. Penetration of the BBB initially involves tethering of leucocytes to endothelial cells via selectins. Leucocytes then adhere to the endothelium by ligand–receptor interactions of cell adhesion molecules, and directional migration through the endothelium is driven by locally produced chemokines (Ransohoff 1999). Leucocyte function-associated antigen-1 (LFA-1) and very late antigen-4 (VLA-4) are members of integrin-type adhesion molecules that are predominantly involved in leucocyte trafficking and extravasation. LFA-1 is exclusively expressed on leucocytes

and interacts with its ligands, intercellular adhesion molecules-1/-2/-3, to promote a variety of cell adhesion events required for normal and pathological functions of the immune systems. VLA-4 is expressed mainly on lymphocytes, monocytes and eosinophils, and interacts with its ligand, vascular cell adhesion molecule-1, during chronic inflammation (Ransohoff 1999; Yusuf-Makagiansar *et al*. 2002). In MS and EAE, it has been well documented that adhesion molecules, such as E-selectin, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, are expressed on CNS microvessel endothelial cells in active lesions (Lee and Benveniste 1999). LFA-1 and VLA-4 have also been found on leucocytes infiltrating the brain in MS lesions (Bo *et al*. 1996). Any activated T cells expressing adhesion molecules may bind to corresponding adhesion molecules on the surface of the endothelium and begin penetration of the endothelium, the first component of the BBB. The necessity of this process in disease progression is highlighted by the observation that the blockade of VLA-4 in EAE can reverse clinical paralysis and prevent relapses (Yednock *et al*. 1992; Carrithers *et al*. 2000; Cannella *et al*. 2003). Following extravasation of the endothelial layer, activated T cells en route to the perivascular tissue must still pass through the subendothelial basement membrane composed of type IV collagen. Collagen type IV is a specialized form of collagen that is found only in basement membranes and contains a distinct binding site for α1-integrins, which may play a role in leucocyte binding to the BBB basement lamina (Kern *et al*. 1994; Sacca *et al*. 2003). To facilitate transmigration of the basement lamina, T cells utilize enzymes known as matrix metalloproteinases, and other matrix-degrading enzymes, which make selective clips in the extracellular matrix components. Type IV collagen is specifically targeted by matrix metalloproteinases 2 and 9, which are both detected in the CSF in MS and EAE (Gijbels *et al*. 1992; Graesser *et al*. 2000; Steinman *et al*. 2002). It has also been reported that treatment with minocycline, which has been shown to inhibit matrix metalloproteinase 9 production, is efficacious against EAE (Brundula *et al*. 2002; Popovic *et al*. 2002).

Chronic inflammation in the CNS begins when T cells, that have crossed the BBB, recognize endogenous antigen presented locally by microglia and/or astrocytes. This encounter results in local amplification of pro-inflammatory molecules, including cytokines, chemokines, adhesion molecules and matrix-degrading enzymes, that increase the permeability of the BBB and promote increased leucocyte trafficking and persistence in the CNS (Fig. 1). In MS, there is mounting evidence implicating chemokines as major players in the development of chronic inflammatory lesions (Gerard and Rollins 2001). Chemokine expression is thought to follow the earliest infiltration of lymphocytes in EAE, thereby advancing the recruitment of inflammatory cells into the CNS (Glabinski *et al*. 1995). Several reports indicate that the appearance of 'regulated upon activation, normal T cell expressed and secreted' (RANTES), osteopontin, macrophage inflammatory protein-1α, macrophage inflammatory protein-1β, IFN-γ-inducible protein-10 and monocyte-chemoattractant protein-1 mRNA and protein correlate with inflammatory lesions (Godiska *et al*. 1995; Hvas *et al*. 1997; Karpus and Ransohoff 1998; Ransohoff 1999; Chabas *et al*. 2001). Once the BBB is breached, other inflammatory cells, including CD4+ and CD8+ T cells, macrophages, granulocytes and B cells, rapidly invade the CNS in response to chemotactic stimuli and spread into the white matter (Ransohoff 1999; Prat *et al*. 2002). Inflammatory lesions in MS are dominated by macrophages and T lymphocytes, but B lymphocytes and antibody-producing plasma cells are also present (Esiri 1977; Prineas and Connell 1978; Prineas and Wright 1978; Traugott *et al*. 1983; Ozawa *et al*. 1994). It is well documented that CD4+ T cells are vital contributors to the pathogenesis of EAE and MS, as demonstrated by the induction of EAE in naive animals by passive transfer of autoreactive CD4+ T cells. Within the CNS, the CD4+ T cells that are re-stimulated by perivascular macrophages/dendritic cells are thought to orchestrate the disease process via a complex network of cytokines that regulate and mediate the immune response. Pro-inflammatory cytokines, such as IFN-γ, tumour necrosis factor-α, tumour necrosis factor-β, lymphotoxin, interleukin (IL)-1α, IL-2, IL-6 and IL-12 are thought to potentiate and intensify inflammation in the CNS, whereas anti-inflammatory cytokines, such as IL-4, IL-5, IL-10, IL-13 and transforming growth factor-β, regulate and alleviate disease (Hjelmstrom *et al*. 1998). CD8+ T cells, which are more abundant in active lesions, also contribute to the milieu of cytokines and intensify the inflammatory pathology in MS and EAE (Booss *et al*. 1983; Hayashi *et al*. 1988; Gay *et al*. 1997; Babbe *et al*. 2000).

Natural resolution of the inflammatory process in MS and EAE may be explained in part by the existence of a subpopulation of regulatory T cells that specialize in the suppression of aberrant T-cell responses. CD4+ CD25+ T cells possess potent regulatory activity *in vitro* and *in vivo* (Maloy and Powrie 2001). CD4+ CD25+ regulatory T cells effectively inhibit both proliferation and cytokine production by MOG_{35-55}-specific T cells *in vitro* and confer significant protection from EAE (Kohm *et al*. 2002), and show diminished activity in MS patients (Viglietta *et al*. 2004). Activated natural killer T cells have also been implicated as cells that can suppress myelin antigen-specific T-helper-1 responses and/or promote myelin antigen-specific T-helper-2 cell responses to provide protection against EAE (Jahng *et al*. 2001; Singh *et al*. 2001). Finally, apoptosis of autoreactive T cells is also considered to be one of the factors that regulates the clinical expression of EAE. We have shown that the suppression of T-cell apoptosis influences disease severity during the chronic phase of EAE (Okuda *et al*. 2002).

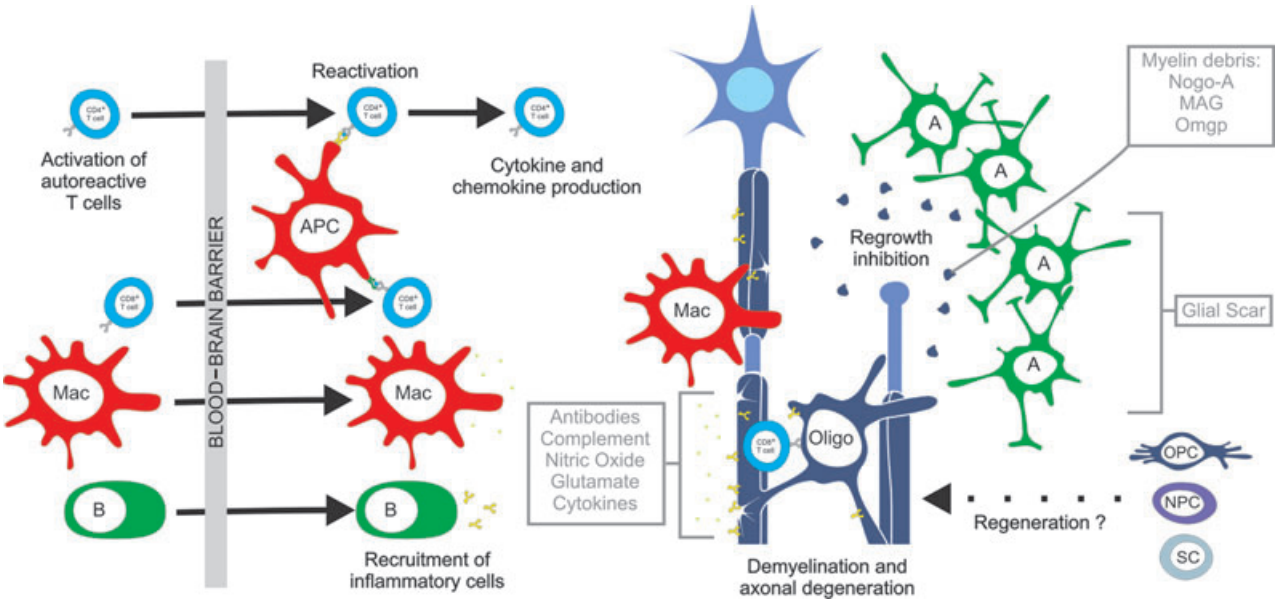

Fig. 1 Degeneration and repair in multiple sclerosis (MS). Inside the CNS, autoreactive CD4+ T cells, which encounter antigen presented by perivascular macrophages/dendritic antigen-presenting cells, are reactivated and retained in the CNS. The secretion of various cytokines and chemokines then results in recruitment and activation of other inflammatory cells, such as macrophages (Mac), CD8+ cytotoxic T cells and B cells (B). These cells are thought to be the proximate mediators of demyelination, loss of oligodendrocytes (Oligo) and axonal degeneration. Attempts at remyelination and axonal regeneration are limited in the CNS by the inhospitable environment of the degenerating lesion caused by reactive astrocytes (A) in the glial scar and growth inhibitors, including those in the myelin debris. However, blockade of these inhibitory molecules may unlock the regenerative potential of the CNS, allowing oligodendrocyte precursor cells (OPCs), neural precursor cells (NPCs) or stem cells (SCs) to potentially differentiate into myelinating oligodendrocytes or functional axons.

Demyelination and axonal degeneration

The neurological impairment typical of MS and EAE has been attributed in the past to extensive demyelination and subsequent loss of saltatory conduction; however, it is now thought that cumulative axon loss correlates with the development of permanent disability in MS (Losseff *et al*. 1996a,b; Trapp *et al*. 1998, 1999; Arnold 1999). Recurrent episodes of autoimmune-mediated inflammation can cause demyelination via a plethora of mechanisms, and axons are susceptible to both inflammation and disruption of axonal/glial interactions (Fig. 1). Previously, axonal loss in EAE and MS was thought to be secondary to demyelination, but, from our own work and that of others, it is becoming increasingly evident that extensive axonal degeneration occurs from the earliest stages of disease (Ferguson *et al*. 1997; Kornek *et al*. 2001; Onuki *et al*. 2001; Kuhlmann *et al*. 2002; Wujek *et al*. 2002; Wang *et al*. 2005; Kim *et al*. 2006). Axons may be vulnerable to damage by proteases, inflammatory cytokines, nitric oxide and glutamate, which are expressed by activated immune cells and glial cells (Bjartmar *et al*. 2003). Axonal loss as a consequence of demyelination and lack of myelin-derived trophic support may occur in later stages of disease following persistent failure of remyelination (Kornek *et al*. 2000). To improve treatment outcomes in MS, it is necessary to understand the complicated association between inflammation, demyelination and axonal degeneration.

The direct contribution of CD4+ T cells in local tissue destruction is likely to be limited to the secretion of cytokines, which, further to their role in mediating the inflammatory cascade, may contribute directly to the loss of oligodendrocytes and axons through direct cytotoxic effects. CD8+ cytotoxic T cells can recognize antigen in MHC class I molecules on the surface of target cells, which are upregulated in the CNS during inflammation, and induce cell death through their cytotoxic granules, containing perforin and granzymes, or through receptor-mediated cytotoxicity, such as Fas/FasL interactions (Bauer *et al*. 2001). T-cell populations infiltrating active MS lesions are dominated by CD8+ T cells (Booss *et al*. 1983; Hayashi *et al*. 1988; Gay *et al*. 1997; Babbe *et al*. 2000). The encephalitogenic potential of these cells was established in animal models of MS by adoptive transfer of CD8-enriched MOG-specific T cells, which, on transfer, could induce a severe, progressive form of disease (Huseby *et al*. 2001; Sun *et al*. 2001). CD8+ T cells appeared to have enhanced tissue-damaging effect and to persist in the animal for long periods (Huseby *et al*. 2001; Sun *et al*. 2001; Cabarrocas *et al*. 2003; Ford and Evavold 2005). Recent immunopathological analyses of MS tissue have revealed that the underlying mechanisms of tissue

destruction are profoundly heterogeneous from patient to patient. At least four different patterns of demyelination have been recognized, with tissue destruction mediated predominantly by T cells and phagocytic cells, antibody and complement, hypoxia-like tissue injury or extensive oligodendrocyte degeneration (Lucchinetti *et al*. 1996).

Despite the indispensable role of T cells in autoimmunity, studies have shown that disease severity in both MS and EAE often correlates with the number of infiltrating macrophages in the CNS, supporting a central role for these cells in tissue destruction (Berger *et al*. 1997; Lassmann *et al*. 2001). Deactivation (Martiney *et al*. 1998) or depletion (Huitinga *et al*. 1990, 1995; Tran *et al*. 1998) of macrophages has been shown to inhibit the progression of EAE. We have also shown that the blockade of GM-CSF, a cytokine intimately involved in macrophage development and function, is essential for the maintenance of CNS inflammation and EAE progression (McQualter *et al*. 2001). Activated macrophages and microglia may perpetuate the inflammatory response via antigen presentation and reactivation of T cells in the CNS (Martin *et al*. 1992; Owens and Sriram 1995). They are also an abundant source of matrix metalloproteinases, proteases and various other soluble factors which can induce myelin and axonal damage. The release of excessive quantities of the neurotransmitter glutamate by macrophages (Piani *et al*. 1991) can cause excitotoxicity and death of neurons (Okayama *et al*. 1993) and oligodendrocytes (Matute *et al*. 1997). Markers for glutamate production (glutaminase) and glutamate receptors are up-regulated in MS lesions and appear to correlate with disease severity and axonal damage (Werner *et al*. 2000, 2001; Geurts *et al*. 2003; Sarchielli *et al*. 2003). In EAE, blockade of glutamate receptors (Smith *et al*. 2000; Groom *et al*. 2003) or glutamate transporters (Gilgun-Sherki *et al*. 2003) results in substantial amelioration of disease, increased oligodendrocyte survival and reduced axonal damage. Axons and oligodendrocytes are also susceptible to damage by nitric oxide, which, in concert with reactive oxygen species, is thought to have a potent cytotoxic activity in MS and EAE (Willenborg *et al*. 1999). Inducible nitric oxide synthase is expressed by activated macrophages, microglia and astrocytes and has been detected in high levels in MS lesions (Bagasra *et al*. 1995; De Groot *et al*. 1997); treatment with inducible nitric oxide synthase inhibitors suppresses EAE (Willenborg *et al*. 1999).

In addition to the intense cellular response in MS, there is a great deal of evidence incriminating B cells, plasma cells and antibodies in the disease process (Cross *et al*. 2001). Most MS patients show evidence of increased production of polyclonal immunoglobulin in CSF, yet concurrent elevations are generally not observed in serum, indicating that antibodies are produced locally within the CNS (Kabat *et al*. 1948; Siden 1979; Ebers 1984). Antibodies reacting to a multitude of CNS antigens, including myelin basic protein, proteolipid protein, myelin-associated glycoprotein and MOG, and complement products have been identified in the CSF and/or serum of MS patients (Cross *et al*. 2001; Markovic *et al*. 2003), and the presence of antibody and complement has been detected in MS lesions (Lucchinetti *et al*. 1996, 2000). The demyelinating capacity of MOG-reactive antibodies has been widely demonstrated in EAE models (Hjelmstrom *et al*. 1998; Stefferl *et al*. 2000). Almost three decades ago, it was revealed that demyelination in spinal cord homogenate-induced EAE was due, at least in part, to antibodies specific for MOG (Lebar *et al*. 1976). Further studies have since established that the administration of anti-MOG antibodies can accelerate the clinical and pathological course of disease and promote demyelination in murine (Schluesener *et al*. 1987; Lassmann *et al*. 1988; Linington *et al*. 1988) and primate (Genain *et al*. 1995) models of EAE. Antibodies can potentiate myelin and axonal degeneration through the promotion of opsonization (Prineas and Graham 1981; Moore and Raine 1988; Genain *et al*. 1999), antibody-dependent cell-mediated cytotoxicity via linking of antibody bound to target tissue with the Fc receptor of natural killer cells, granulocytes and macrophages, or by activation of complement (Piddlesden *et al*. 1993; Mead *et al*. 2002).

Regeneration and repair

Although some promising outcomes have been achieved in minimizing CNS destruction via immunomodulatory therapies that help to resolve inflammation, effective strategies for the rehabilitation of MS patients have yet to be developed (Keegan and Noseworthy 2002). One of the major challenges in treating MS is that regeneration in the CNS inherently fails. The regenerative failure in the CNS is no longer considered to be a result of an intrinsic lack of regenerative potential of CNS axons, but rather to be a consequence of the inhospitable lesions of the degenerating adult CNS. This non-permissive growth environment is associated with the formation of the glial scar and the presence of myelin-associated inhibitory molecules. Reactive astrocytes, meningeal fibroblasts and oligodendrocyte precursor cells (OPCs) form the foundation of the glial scar, which most probably serves to re-establish a barrier to isolate inflammation in the brain. However, the expression of axon growth inhibitory molecules, including chondroitin sulphate proteoglycans and semaphorins, which are up-regulated in response to injury, is detrimental for subsequent neurogenesis and impedes regeneration (Fawcett and Asher 1999). Myelin debris in the scar tissue also contains several potent axon growth inhibitory molecules, including myelin-associated glycoprotein (McKerracher *et al*. 1994; Mukhopadhyay *et al*. 1994; Liu *et al*. 2002; Lamhamedi-Cherradi *et al*. 2003), oligodendrocyte myelin glycoprotein (Wang J. *et al*. 2002) and Nogo-A (Chen *et al*. 2000; GrandPre *et al*. 2000; Prinjha *et al*. 2000;

Buchli and Schwab 2005). These three molecules act via a common receptor complex, consisting of the Nogo receptor, LINGO-1 and either the low-affinity neurotrophin receptor (p75NTR) or TROY, to induce growth cone collapse via the small GTPase Rho-A (Fournier *et al*. 2002; Wang K. C. 2002; Wong *et al*. 2002; McKerracher and Higuchi 2006). Several studies have shown that targeting the Nogo-A molecule might unlock the intrinsic growth potential of CNS axons (Buchli and Schwab 2005; McKerracher and Higuchi 2006). We and others have demonstrated that Nogo-A has an influential role in the disease pathology of EAE. Ablation of Nogo-A activity by active and passive vaccination against Nogo-A or gene deletion attenuates clinical symptoms, demyelination and axonal damage (Fontoura *et al*. 2004; Karnezis *et al*. 2004). In addition, anti-Nogo antibodies have been detected in the serum and CSF of MS patients, and appear to be more frequent in those with remitting MS in comparison with chronic progressive MS, suggesting a possible role in the mediation of disease remission (Reindl *et al*. 2003). There is increasing evidence that neurogenesis occurs in the adult brain and that neural stem cells reside in the adult CNS (Murray and Lledo 2006), but axonal regeneration in EAE and MS still requires the mobilization and recruitment of neural precursor cells to the lesion site.

There are strong data suggesting that remyelination occurs during the early course of MS and is associated with disease resolution (Prineas *et al*. 1989, 1993; Raine and Wu 1993; Lucchinetti *et al*. 2000). However, in later stages of disease, remyelination inevitably fails (Prineas *et al*. 2001; Compston and Coles 2002). OPCs are thought to be responsible for this remyelination attempt, but there is a suggestion that repeated bouts of demyelination may exhaust the pool of OPCs (Johnson and Ludwin 1981; Carroll *et al*. 1998; Keirstead *et al*. 1998; Franklin and Hinks 1999). Others have suggested that the degenerating CNS, as for axonal growth, may be non-permissive for OPC recruitment and differentiation into remyelinating oligodendrocytes (Wolswijk 2000; Franklin 2002). Recent studies have shown that myelin can impair the differentiation of OPCs, possibly via similar pathways to myelin-associated axon growth inhibition (Kotter *et al*. 2006). Nevertheless, OPCs have been shown to be efficient in anatomical and functional restoration of myelinating oligodendrocytes in various chemically induced models of demyelination (Redwine and Armstrong 1998; Levine and Reynolds 1999; Zhang *et al*. 1999). Neural stem cells from the subventricular zone have also been shown to migrate towards inflammatory lesions in EAE and to give rise to oligodendrocytes (Picard-Riera *et al*. 2002). However, in MS and EAE, there is an incessant battle between destruction and repair, whereby the differentiation of precursor cells may be negatively affected within the lesion environment.

During chronic inflammatory diseases, such as MS, the inflammatory processes may not only induce extensive CNS destruction, but, in contrast, may also promote neuroprotection and CNS repair via the production of neurotrophic factors (Besser and Wank 1999; Hohlfeld *et al*. 2000; Kerschensteiner *et al*. 2003; Villoslada and Genain 2004). Nerve growth factor (Kuhlmann *et al*. 2006) has been suggested to have trophic and tropic effects on nerve growth and regeneration, and also to regulate and mediate inflammation such as that observed in EAE (Villoslada and Genain 2004). Moreover, neurotrophic factors, such as leukaemia inhibitory factor and ciliary neurotrophic factor, are thought to modulate autoimmune-mediated demyelination by preventing oligodendrocyte death (Butzkueven *et al*. 2002; Linker *et al*. 2002). In EAE, neutralization of leukaemia inhibitory factor significantly worsens disease severity (Butzkueven *et al*. 2006), and treatment with ciliary neurotrophic factor suppresses the disease (Kuhlmann *et al*. 2006). Thus, it is likely that the provision of such neurotrophic support may enhance any regenerative therapies for the treatment of MS.

Stem cell transplantation

Although the manipulation of the local environment through the blockade of inhibitory molecules may unlock the regenerative potential of the CNS, it is thought that inadequate mobilization or loss of endogenous stem cell populations may account for the transitory regenerative attempts in chronic diseases such as MS. One method by which this may be overcome is stem cell transplantation. Stem cells are defined by their capacity for long-term self-renewal and retain the ability to differentiate into multiple lineages. Embryonic stem cells have the ability to differentiate into any type of tissue within the body. This makes them a very attractive candidate for cell replacement therapies and tissue regeneration. However, the clinical application of embryonic stem cells is complicated by various problems, such as differentiation into heterogeneous tissue, teratoma formation and ethical issues. Adult stem cells may represent an alternative source of renewable cells for transplantation therapies. It has been shown that adult stem cells exist within discrete niches throughout the body. Although they retain much lower potency than embryonic stem cells, they display multilineage plasticity (Moore and Lemischka 2006). Neural stem cells and bone marrow stem cells, including haematopoietic and mesenchymal stem cells, have been shown to be capable of differentiating into neural cells, including oligodendrocytes, microglia, astrocytes and neurons (Jiang *et al*. 2002; Mezey *et al*. 2003; Alexanian 2005; Goldman 2005; Lu and Tuszynski 2005; Zhao *et al*. 2005). Recent studies have demonstrated that bone marrow stem cell transplantation leads to the improvement of neurological function in models of traumatic brain (Lu *et al*. 2006) and spinal cord (Koda *et al*. 2005) injury, with the expression of neural cell markers on bone marrow stem cell-derived cells suggesting

possible integration of new neural cells into the brain. In MS, the expression of chemokines, such as stromal cell-derived factor-1, may play an important role in the recruitment of stem cells for regeneration and repair of the CNS (Imitola *et al*. 2004; Kucia *et al*. 2004). The migration and differentiation of transplanted neural precursor cells into the white matter during EAE was found to coincide with inflammation (Ben-Hur *et al*. 2003). Thus, following systemic transplantation, CNS inflammation may encourage the migration of stem cells into the degenerating CNS and contribute to the repair process. It has been shown that the transplantation of bone marrow cells (Herrmann *et al*. 2005; Zappia *et al*. 2005; Zhang *et al*. 2005) or neurospheres (Einstein *et al*. 2003; Pluchino *et al*. 2003) can ameliorate EAE, possibly by exerting immunomodulatory effects, as well as being a source of cells for remyelination and neuroregeneration (Pluchino *et al*. 2005; Uccelli *et al*. 2006).

In summary, recent years have seen tremendous advancement in the understanding of the various cellular changes that contribute to the disease process in MS, including those that contribute directly or indirectly to inflammation and local tissue destruction and those that obstruct the regeneration of tissue in the CNS. However, as the increasing complexity of the disease process becomes clearer, so too does the realization that it is unlikely that any single intervention can completely halt the disease process and reverse the consequences of demyelination and axonal degeneration. Unfortunately, it seems that any regenerative attempts in MS are negated by the unrelenting inflammatory attack. Thus, we believe that successful therapeutic intervention may only be achieved by a combination of strategies, including long-term suppression of the inflammatory reaction or elimination of autoreactive T cells, supply of trophic support, blockade of myelin- and glial scar-associated growth inhibitors and mobilization or transplantation of stem cells for regeneration.

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