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# Cortical and meningeal pathology in progressive multiple sclerosis: a new therapeutic target?

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**Abstract:** Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease that involves an intricate interaction between the central nervous system and the immune system. Nevertheless, its etiology is still unknown. MS exhibits different clinical courses: recurrent episodes with remission periods ('relapsing-remitting') that can evolve to a 'secondary progressive' form or persistent progression from the onset of the disease ('primary progressive'). The discovery of an effective treatment and cure has been hampered due to the pathological and clinical heterogeneity of the disease. Historically, MS has been considered as a disease exclusively of white matter. However, patients with progressive forms of MS present with cortical lesions associated with meningeal inflammation along with physical and cognitive disabilities. The pathogenesis of the cortical lesions has not yet been fully described. Animal models that represent both the cortical and meningeal pathologies will be critical in addressing MS pathogenesis as well as the design of specific treatments. In this review, we will address the state-of-the-art diagnostic and therapeutic alternatives and the development of strategies to discover new therapeutic approaches, especially for the progressive forms.

**Keywords:** animal models; cognitive impairment; cortical lesions; therapeutic agents.

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## Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of unknown etiology that is characterized by repeated inflammatory events, demyelination, and axonal damage and causes loss of function in the central nervous system (CNS). Although most authors suggested that an autoimmune response might be the cause, a primary inflammatory reaction is also plausible (Hutchinson, 2015; Louapre and Lubetzki, 2015). MS displays different clinical patterns: relapsing-remitting (RRMS), in which recurrent episodes with remission periods can progress to the secondary progressive form (SPMS), or primary progressive (PPMS), in which there is persistent progression from the onset of the disease. The clinical course of the different disease forms probably depends on different pathogenic mechanisms (Antel et al., 2012).

Although much progress has been made in the treatment of the RRMS form, there is currently only one treatment available for primary PPMS and none for SPMS. Thus, there is only one therapy available for more than 1 million patients, with the progressive form of MS among the 2.3 million MS patients worldwide (Zaratin et al., 2017).

MS was previously thought to exclusively involve white matter (Kidd et al., 1999); however, more recently, it has been described with neurodegenerative and demyelinating grey matter lesions that are mostly in the cortex. These cortical lesions are mainly found in PPMS and SPMS patients and contribute to their clinical disability and cognitive impairment (Nelson et al., 2011; Calabrese et al., 2012a, 2013).

Neuroinflammation and neurodegeneration play a key role in every form of the disease (RRMS, PPMS, and SPMS) (Losy, 2013), although their roles in the progression of the disease are still debated (Mahad et al., 2004; Hutchinson, 2015; Louapre and Lubetzki, 2015). Indeed, anti-inflammatory and immunomodulatory treatments that are beneficial in early stages of MS and in RRMS are ineffective in PPMS and SPMS, where neurodegeneration and cortical damage are more prominent (Watzlawik et al., 2010; Comi, 2013; Losy, 2013; Lorscheider et al., 2017).

Understanding the pathology of the progressive stages is necessary for developing new therapeutic strategies for these forms (Lassmann, 2007; Lassmann et al.,

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2012). To be effective, the designed drugs should be able to cross the repaired blood-brain barrier (BBB), regulate inflammation within the CNS, and inhibit neurodegeneration (Mahad et al., 2004).

## Cortical and meningeal human pathology

MS has historically been considered a white matter disease, but pathological and imaging analyses demonstrated that grey matter cortical lesions are quite frequent (Reynolds et al., 2011). The plaque of primary demyelination in the cortex is MS specific and it is not seen in any of the other chronic neuroinflammatory disorders (Fischer et al., 2013). Cortical lesions are more prominent in the progressive stages compared to RRMS, and their presence correlates with disease progression and cognitive impairment (Kutzelnigg et al., 2005; Nelson et al., 2011; Calabrese et al., 2012a, 2013; Eshaghi et al., 2014). Whole brain atrophy in MS occurs at rates of 0.5%–1.5% per year, and the rate is increased in the progressive forms of the disease and in grey matter (Thompson et al., 2018b). Indeed, in the SPMS form, the loss of grey matter volume is greater than the loss of white matter volume (Kapoor et al., 2010). However, there are no data regarding the pathology of the acute stages of cortical lesions, and this is probably because patients' deaths mostly occur in the chronic phases of the disease (Lucchinetti et al., 2011). Additionally, the cortex has a greater capacity for remyelination because of the presence of more myelinating oligodendrocytes compared to white matter (Albert et al., 2007; Staugaitis et al., 2012; Rodriguez et al., 2014). Cortical lesions, compared to white matter lesions, contain fewer reactive astrocytes, which express CD44 and inhibit oligodendrocyte differentiation and maturation molecules, such as hyaluronan and versican (Chang et al., 2012). Moreover, grey matter remyelination in PPMS patients is more extensive than in relapse-onset MS patients (Strijbis et al., 2017). Kidd et al. (1999) performed the first classification of cortical lesions. This classification described seven different types of lesions based on their location relative to the cerebral cortex venous supply (Kidd et al., 1999). The current classification system is based on the location of the demyelinated lesions within the cortical layers. Four cortical lesion types have been described: (a) type I or leukocortical lesions, which are located in the deeper layers of grey matter as well as in the adjacent white matter; (b) type II or intracortical lesions, which are small demyelinated lesions located within the cortex and are mostly confined to the periphery of blood vessels; (c) type III or subpial lesions, which are located on the outermost layer of the cortex and in close contact with the pia mater; and (d) type IV or pancortical (Peterson et al., 2001; Bo et al., 2003a,b; Dutta and Trapp, 2007; Lucchinetti et al., 2011; Kuhlmann et al., 2017).

Neurodegeneration, oxidative and mitochondrial damage, inflammation, and microglial activation all differentially contribute to the cortical demyelinating lesions depending on their type and location (Haider et al., 2016). For example, cortical lesions have less inflammation and substantially more neurodegeneration than white matter lesions (Peterson et al., 2001; Popescu and Lucchinetti, 2012b). These differences could be explained by different signals in the cortical microenvironment compared to white matter. Other reasons may include differences in microglia/macrophage activation, BBB permeability, myelin content, and T-cell removal (Merkler et al., 2006).

Recently, it was widely accepted that the lesions in progressive MS (PMS) do not have BBB breakdown (Lassmann et al., 2012). However, there is recent evidence that the cortical BBB could be damaged (Yates et al., 2017). On the contrary, the activation of microglia/macrophages in close relationships with neurons could indicate a possible role for inflammation in neurodegeneration (Peterson et al., 2001; Bo et al., 2003a). Oxidative damage in human cortical MS lesions has been associated with oligodendrocyte and neuronal injury (Fischer et al., 2013). Additionally, a dysregulation of fibrinolysis in the cortex has been described and demonstrates an association between fibrinogen deposits and increased neuronal loss (Yates et al., 2010). Microarray analysis demonstrated that cortical MS lesions had specific gene changes in three different molecular pathways: (1) inflammation through T-cell and macrophage activation, (2) oxidative stress with DNA and mitochondrial damage, and (3) degeneration and regeneration affecting oligodendroglia, neurons, and axons (Fischer et al., 2013).

At present, the mechanisms of tissue injury induction in cortical lesions remain unresolved. One possibility is that anterograde or retrograde neurodegeneration from white matter could play an important role in the induction and propagation of cortical pathology (Choi et al., 2012; Lassmann, 2012; Haider et al., 2016). Alternatively, another possibility is that cortical injury could also be explained by meningeal inflammation.

The meninges consist of three layers of connective tissue that surround the brain and the spinal cord: (1) the dura mater is the outermost and is located directly under the bone, (2) the arachnoid mater is the middle layer and is composed of flattened cells and filaments forming

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trabeculae that enclose the cerebrospinal fluid (CSF), and (3) the pia mater is the innermost layer and is located on the CNS. These structures, in spite of acting as the physical protection for the CNS (Russi and Brown, 2015), are considered sites of active immunity that serve as initial sites of immune responses (Magliozzi et al., 2007; Howell et al., 2011). One of the most important roles of the meninges is serving as the first-line defense against infections that threaten the CNS. Meningeal cells produce proinflammatory cytokines [tumor necrosis factor (TNF), interleukin (IL)-1β, inducible nitric oxide synthase (iNOS), and IL-6)] in response to inflammatory signals (Wieseler-Frank et al., 2007; Kivisakk et al., 2009; Russi and Brown, 2015; Figure 1).

Meningeal inflammation is a common feature in MS and is mainly associated with the cortical pathology in patients with progressive forms. The presence of meningeal inflammation is associated with a worse clinical prognosis in MS patients. Meningeal inflammation also plays a role in cortical grey matter pathology and contributes to the acceleration of the disease clinical course (Magliozzi et al., 2007; Howell et al., 2011; Choi et al., 2012; Popescu and Lucchinetti, 2012a; Hutchinson, 2014; Mainero and Louapre, 2015). Patients with

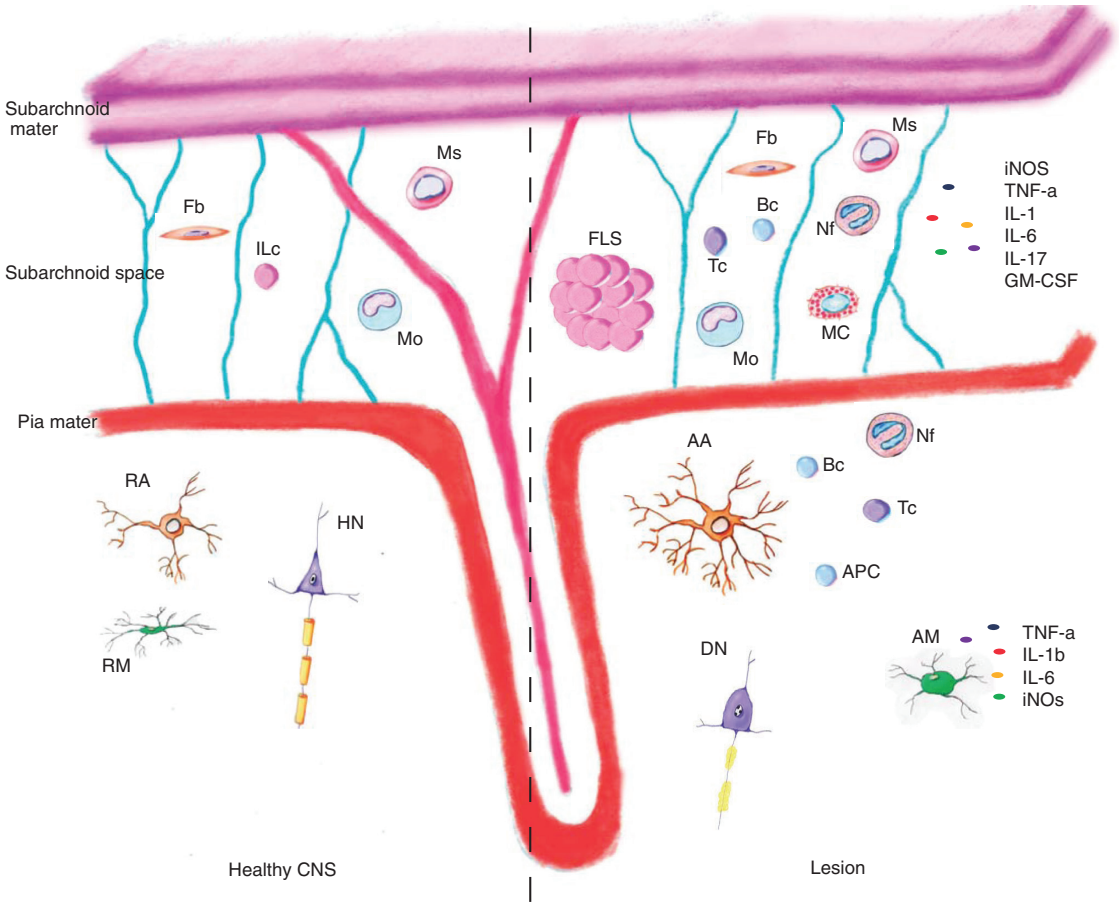



**Figure 1:** The mechanisms of cortical damage induction are unresolved, but the cortical injury could be explained by meningeal inflammation.

The subarachnoid space contains the CSF, which includes fibroblasts (Fb), macrophages (Mo), and meningeal cells (Ms). Meningeal cells produce proinflammatory cytokines (TNF, IL-1β, iNOS, and IL-6) in response to inflammatory signals. Meningeal inflammation can appear as either diffuse meningeal inflammation or tertiary lymphoid-like structures (FLS). These follicle-like structures are associated with the activation of type 3 ILCs, which reside in the meninges and express IL-17, IFN-γ, and GM-CSF. Peripheral immune cells enter the CNS in two 'waves'. The 'first wave' represents the immune surveillance of the CNS, where the T cells circulate from the bloodstream to the choroid plexuses and back. The interaction between myelin-specific T cells and myelin-loaded APCs triggers T-cell reactivation in the meninges, promoting the influx of peripheral leukocytes into the CNS and loss of local BBB integrity. The influence of meningeal mast cells (MC) and neutrophils (Nf) either in the onset or in the progression of the disease has been well documented. The proinflammatory environment induces microglia (AM) and astroglia activation (AA), which in turn induce proinflammatory cytokines inducing neurodegeneration (DN) and myelin breakdown and demyelination. Bc, B cells; HN, healthy neuron; RA, resting astrocyte; RM, resting microglia; Tc, T cells.

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PPMS and extensive meningeal inflammation presented a more severe clinical course, shorter disease duration, and younger age of death (Choi et al., 2012). Meningeal inflammation correlated with cortical neurodegeneration, demyelination, and activation of cortical microglia in these patients (Howell et al., 2011; Choi et al., 2012). Moreover, Lucchinetti et al. (2011) demonstrated that meningeal inflammation occurred early in the course of the disease and preceded the appearance of classic white matter lesions in many patients. Recently, it was demonstrated that a common intrathecal (meninges and CSF) inflammatory profile strongly correlates with increased cortical pathology, both at the time of diagnosis and of death. This suggests a role for detailed CSF analysis combined with magnetic resonance imaging (MRI) as a prognostic marker for more aggressive MS (Magliozzi et al., 2018).

Meningeal inflammation can appear as either diffuse meningeal inflammation or tertiary lymphoid-like structures (Serafini et al., 2004; Howell et al., 2011; Choi et al., 2012; Popescu and Lucchinetti, 2012a). Diffuse meningeal inflammation lacking tertiary lymphoid structures is characteristic of PPMS (Choi et al., 2012).

The follicle-like structures were found in SPMS patients and are composed of dendritic, T, and B cells. These aggregates are sites of B-cell reactivation and antibody production and are associated with chronic cortical inflammation, suggesting that soluble factors diffusing from these structures may have a pathogenic role in cortical damage (Serafini et al., 2004; Magliozzi et al., 2007). Additionally, the presence of these follicle-like structures was associated with the activation of type 3 innate lymphoid cells (ILCs; specifically, the ckit + subset that expresses CD30L and OX40L molecules and promotes T-cell memory), which reside in the meninges and express IL-17, interferon-γ (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Figure 1). These cytokines were found to be responsible for pathogenic actions in the experimental autoimmune encephalomyelitis (EAE) model and in MS (Serafini et al., 2004; Magliozzi et al., 2007; Spits et al., 2013; Walker et al., 2013) (Figure 1). These follicle-like structures could serve as sites for intrathecal subarachnoid antibody production and the sequestration and presentation of autoantigens (Serafini et al., 2004; Magliozzi et al., 2007; Aloisi et al., 2010).

The relationship between cortical damage and meningeal inflammation is still controversial. Recent studies have provided data that support the theory of a 'two-step' model, which explains the entrance of peripheral immune cells into the CNS in two 'waves'. The 'first wave' represents the immune surveillance of the CNS, where the T cells circulate from the bloodstream to the choroid plexus and back. Then, these cells cross the blood-CSF barrier from the choroid plexus and circulate through the ventricles toward the subarachnoid space of the meninges. The interaction between myelin-specific T cells and myelin-loaded antigen-presenting cells (APCs) triggers T-cell reactivation in the meninges, promoting the influx of peripheral leukocytes into the CNS and loss of local BBB integrity. This 'second wave' of inflammatory cells can mediate significant demyelination and neuronal damage leading toward lesion formation (Axtell and Steinman, 2009; Bartholomaus et al., 2009; Ransohoff, 2009; Reboldi et al., 2009; Wolburg and Paulus, 2010). In addition, the influence of meningeal mast cells and neutrophils either in the onset or in the progression of the disease has been well documented in animal models (Secor et al., 2000; Sayed et al., 2010, 2011; Christy et al., 2013; Russi and Brown, 2015) (Figure 1).

## Clinical relevance of cortical and meningeal pathology

Cortical pathology includes atrophy and subpial and leukocortical demyelination. Indeed, leukocortical and subpial lesion subtypes have different clinical relevance (Harrison et al., 2015). There is a correlation between increased Expanded Disability Status Scale score in MS and cortical lesions and cortical atrophy (Calabrese et al., 2009a,b, 2010; Roosendaal et al., 2009; Geisseler et al., 2016). Damage to grey and white matter occurs independently in MS. Grey matter damage, more so than white matter damage, is associated with physical and cognitive disability progression (Calabrese et al., 2012a). In addition, cortical atrophy seems to be a better predictor for future disability development than whole brain atrophy (Fisher et al., 2008; Popescu et al., 2015, 2016).

MRI, which is the most important complementary method for the diagnosis of all clinical forms of MS, lacks pathological specificity (Ontaneda et al., 2016). Despite knowing that cortical pathologies exist in MS, their *in vivo* visualization remains technically challenging (Calabrese et al., 2008; Sethi et al., 2012). The intracortical, leukocortical, and juxtacortical lesions cannot be reliably and consistently distinguished using conventional MRI clinical settings [according to the MAGNIMS (Magnetic Resonance Imaging in MS) Group 2016 Consensus Guidelines; Filippi et al., 2016]. The sensitivity of conventional MRI to detect cortical and subpial lesions is low (Klaver

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et al., 2015; Jonkman et al., 2016). However, the presence of cortical and juxtacortical lesions has been included in the 2017 McDonald criteria for RRMS and PPMS diagnoses (Thompson et al., 2018a). Different MRI techniques have been proposed to improve cortical lesion detection, including double inversion recovery, phase-sensitive inversion recovery, magnetization-prepared rapid acquisition with gradient echo sequences, and combination of magnetization-prepared two rapid gradient echo and T2*-weighted imaging at 7T (Geurts et al., 2005; Nelson et al., 2007, 2008; Sethi et al., 2012; Favaretto et al., 2015; Beck et al., 2018).

Cortical lesions have also been detected in pediatric-onset MS patients (Datta et al., 2017). This phenomenon supports the concept of early cortical involvement in MS (Geurts et al., 2012; Datta et al., 2017). In addition, grey matter atrophy was detected in a 3-year longitudinal study in a pediatric MS population (Calabrese et al., 2012b). However, Absinta et al. (2011) reported lower cortical lesion frequency in pediatric MS patients (<10% of lesions using 3T MRI) in comparison to adult MS patients.

Leptomeningeal MS pathology can be visualized with postcontrast 3T FLAIR MRI, although it is not specified for MS (Absinta et al., 2017). These MRI images correlate with findings from autopsy cases. In addition, it is suggested that the leakage of gadolinium into the CSF may be an indirect marker for meningeal inflammation in MS (Absinta et al., 2015). Therefore, considering the strong association between leptomeningeal pathology and cortical damage with disability and cognitive impairment, MRI studies could be used in assessing specific treatments for this pathology (Absinta et al., 2015). Furthermore, the presence of leptomeningeal contrast enhancement in 3T MRIs was also associated with cortical atrophy progression over 5 years (Zivadinov et al., 2017) and disability (Makshakov et al., 2017). In PMS, contrast-enhancing lesions occur less frequently than in RRMS, whereas grey matter abnormalities are more frequent (Antel et al., 2012). Indeed, a gradient of cortical pathology was demonstrated throughout stages of MS. In this gradient, changes were in the outer cortical layers during the earliest disease stages and in the deeper cortical layers in later MS stages, which could be related to meningeal inflammation (Mainero et al., 2015).

The presence of cortical lesions in MS is clinically relevant because it is associated with neurodegeneration, cortical thinning, physical disability, and cognitive impairment (Geurts et al., 2012). The imaging techniques currently used still require further progress and research to improve the understanding of MS pathology and in turn develop more specific treatments.

## Animal models of focal cortical pathology-associated meningeal inflammation

The development of experimental animal models of MS is key to clarifying the immune and pathological mechanisms of the progressive forms of this disease and to developing new therapeutic strategies. Although no single model represents all the pathophysiological characteristics of PPMS and SPMS, each animal model allows a different aspect of the disease to be studied.

The main challenges in modeling SPMS and PPMS are the difficulties of replicating the chronicity and the cortical injury pattern of these MS forms, which differ from those of RRMS. Furthermore, most of the current models do not reflect the irreversible nature of the damage that characterizes the progressive forms of MS (Fox et al., 2012). The EAE model has contributed to the study of MS pathophysiology and the development of therapeutic agents, but the scarcity of analyses of cortical lesions in the EAE model has led to some limitations in studying the cortical pathology and progressive forms of MS. As a limitation, areas of demyelinated axons do not occur in predictable locations; therefore, their use for studying the mechanism of local demyelination is limited (Ransohoff, 2006). The presence of cortical lesions has also been described in nonfocal EAE models developed in marmosets, mice, Lewis rats, and a modified cuprizone model (Gardner et al., 2013; Stassart et al., 2015; Bai et al., 2016).

On the contrary, focal cortical EAE models are based on myelin oligodendrocyte glycoprotein (MOG) immunization of animals along with focal injection of cytokines (TNF-α and IFN-γ) in the cortex. These lesions are characterized by demyelination, neuroinflammation, glial activation, and neuronal degeneration, which is associated with meningeal pathology in some models (Merkler et al., 2006; Stassart et al., 2015; Lagumersindez-Denis et al., 2017; Ucal et al., 2017). These features, as well as the chronicity of the lesions, vary according to the animal model (see Table 1). Merkler et al. (2006) developed a rat model of cortical pathology based on the stereotactical injection of proinflammatory cytokines in MOG-immunized rats. The focal cortical EAE model led to the typical pattern of intracortical and subpial demyelination, infiltration with inflammatory cells, complement deposition, acute axonal damage, and neuronal cell death, which were resolved within 2 weeks (Merkler et al., 2006) (Table 1).

However, a similar model in which TNF-α and IFN-γ were injected into the subarachnoid space instead of the cortex generated meningeal inflammation associated

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**Table 1:** Animal models of focal cortical pathology of MS (modified from Silva et al., 2018).

| References | Animal | Peripheral activation | Focal injection | Cortical pathology | Chronicity | Meningeal pathology |
|---|---|---|---|---|---|---|
| Merkler et al., 2006 | Lewis rat | Subcutaneous MOG immunization<br>Adaptive immunity | Prefrontal cortex: 250 ng TNF-α + 150 U IFN | – Cortical inflammation (ED1, CD4, CD8) and demyelination<br>– Neuronal apoptosis (maximum at 7 dpi)<br>– No MRI<br>– No behavioral test | 14 days | No |
| Gardner et al., 2013 | Dark Agouti rat | Subcutaneous MOG immunization<br>Adaptive immunity | Subarachnoid space: 1.25 μg TNF-α + 75 ng IFN | – Subpial demyelination, microglia activation<br>– No neuronal loss (maximum at 7 dpi)<br>– No MRI<br>– No behavioral test | 14 days | Meningeal inflammation |
| Stassart et al., 2015 | Marmoset | Subcutaneous MOG immunization<br>Adaptive immunity | Corpus callosum and its adjacent grey matter<br>2 mg TNF-α + 1.2 mg IFN-γ | – Cortical and callosal demyelination and inflammation (T-cell $CD3^+$), astroglia activation<br>– Perivascular foci of demyelination<br>– Axonal loss<br>– Visualization of cortical and callosal lesion by MRI<br>– No behavioral test<br>– Laquinimod prevents lesion development | 21 days | No |
| Ucal et al., 2017 | Dark Agouti rat | Subcutaneous MOG immunization<br>Adaptive immunity | Cortex: 500 μg/ml TNF-α + 300 U IFN-γ (catheter into the cortex) | – Cortical inflammation and demyelination<br>– Neuronal apoptosis (maximum at 15 dpi)<br>– Undetectable lesions by MRI<br>– No behavioral test | 30 days | Meningeal inflammation |
| Lagumersindez-Denis et al., 2017 | C57BL/6J mice | Subcutaneous MOG immunization<br>Adaptive immunity | Motor cortex: 50 ng TNF-α + 50 ng IFN-γ | – Inflammatory infiltrate ($CD3^+$, $NK^+$ macrophages, $CCR2^+$ macrophages)<br>– Subpial and perivascular demyelination<br>– Perivascular APP++ (maximum at 5 dpi)<br>– Motor deficiencies<br>– No MRI studies<br>– No behavioral test | 20–40 days | No |
| Silva et al., 2018 | Wistar rats | Adenovirus expressing IL-1β intravenously<br>Innate immunity | Prefontal cortex<br>Adenovirus expressing IL-1β | – Cortical inflammation (PMN in early stages; ED1, MHCII, and GFAP activation) and demyelination<br>– Neuronal apoptosis<br>– Neurodegeneration and axonal damage<br>– Visualization of cortical lesions on MRI<br>– Short-term memory impairment and anxiety-like symptoms | 50 days | Meningeal inflammation and follicle-like structures |



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with cortical subpial demyelination and microglial activation but no neuronal loss (Gardner et al., 2013). These pathology reversed 2 weeks after injection of the cytokines. These results sustain the hypothesis that proinflammatory molecules produced in the meninges may play an important role in cortical demyelination (Gardner et al., 2013).

To achieve a longer-lasting effect of cortical pathology, Ucal et al. (2017) placed a catheter in the cortex that allowed them to inject the same cytokines twice. The second injection was performed when the cortical lesion began to show signs of recovery (30 days after the injection) and prolonged the cortical damage for 15 more days. Cortical inflammation, demyelination, and neuronal apoptosis, associated with meningeal inflammation, were observed (Ucal et al., 2017) (Table 1).

Additionally, Lagumersindez-Denis et al. (2017) studied the contribution of the immune mechanisms on cortical demyelination. In an extensive study using several transgenic mouse lines, they demonstrated that $CCR2^{+}$ monocytes play a role in cortical demyelinating lesion pathogenesis (Lagumersindez-Denis et al., 2017).

EAE in the marmoset was also proposed as an alternative focal model featured as an intermediate step between animal models and clinical trials (Mangiardi et al., 2011; Stassart et al., 2015). Stassart et al. (2015) developed a focal model of EAE with stereotactic injection of proinflammatory cytokines. These animals present two different types of lesions: (a) large demyelinating lesions like those in human MS and (b) perivascular foci of demyelination. These lesions contain $CD3^{+}$ T cells and astroglia activation and can be observed by MRI. Interestingly, this EAE cortical lesion formation can be prevented by laquinimod (Stassart et al., 2015; Table 1).

Recently, our laboratory developed a new animal model based on the innate immune response. This model is based on the chronic expression of IL-1β in the adult rat cortex and the induction of peripheral inflammation, worsening the ongoing cortical damage. The main features of this model are neuroinflammation, demyelination, neurodegeneration, and meningeal inflammation along with cognitive impairment. These symptoms remained for almost 50 days, demonstrating the chronicity of the model (Silva et al., 2018) (Table 1).

The mentioned models above reflect different aspects of MS pathology, but the chronicity and behavioral symptoms vary according to the model (Table 1).

The development of experimental animal models that mimic the cortical damage of the progressive forms of MS with relevant similarities to the clinical setting is necessary to understand the pathophysiology of the disease. The main features of the chronic cortical lesions are demyelination, neurodegeneration, and neuroinflammation along with cognitive deficiencies such as those observed in human pathology. The animal models that feature these characteristics would allow us to understand the pathophysiology and therefore would help to design new therapeutic agents specific for the progressive forms of MS.

## Treatment of PMS

The new classification of the PMS course has been reorganized into two different categories of active and inactive inflammatory disease and by the presence or absence of gradual disease progression (Lublin et al., 2014). This classification allows for the clarification and improvement of PMS conceptualization and may eventually improve the recruitment of PMS patients into clinical trials (Ontaneda and Fox, 2015).

Several drugs are under investigation for their neuroprotective effects in PMS. Among them, high doses of biotin (or vitamin H) have been reported to have beneficial results. Biotin acts as a coenzyme for essential carboxylases that are involved in energy metabolism, fatty acid synthesis, and amino acid catabolism. In MS specifically, increasing fatty acid synthesis would contribute to improving remyelination and protecting from axonal degeneration secondary to hypoxia (Chataway, 2016; Tourbah et al., 2016).

On the contrary, in an EAE model, there is a direct effect of siponimod, a selective modulator of the S1P1 and S1P5 receptors of neurons, microglia, astroglia, and oligodendroglia. Siponimod prevented synaptic neurodegeneration, astrogliosis, activation of microglia, and lymphocytic infiltration in the CNS (Gentile et al., 2016). In another study, siponimod inhibited lysolecithin-induced demyelination in organotypic slice cultures and attenuated lipopolysaccharide or TNF-α/IL-17-induced IL-6 production in astrocytes and microglia (O'Sullivan et al., 2016). In the phase III clinical trial EXPAND, siponimod demonstrated a 26% reduction in disability worsening at 6 months versus placebo with a significant reduction in MRI activity (Chaudhry et al., 2017).

Laquinimod (quinolin-3-carboxamide) is an interesting oral drug that has shown more neuroprotective than anti-inflammatory effects in both experimental models and clinical trials. It has a significant effect in decreasing brain atrophy and disability progression, with greatest effects in long-term neurodegeneration in RRMS patients. Furthermore, *in vitro*, it decreases the production of

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proinflammatory cytokines and increases the production of anti-inflammatory cytokines from blood mononuclear cells in RRMS patients (Bruck and Wegner, 2011). *In vivo*, in animal models of MS, laquinimod inhibits the development of acute and chronic EAE and minimizes demyelination, inflammation, and axonal damage (Yang et al., 2004; Runstrom et al., 2006; Wegner et al., 2010; Kaye et al., 2016; Gentile et al., 2018).

Specifically, in a focal model of EAE, prophylactic therapy with laquinimod prevents the formation of such lesions in the corpus callosum and adjacent cortex (Stassart et al., 2015). However, the clinical trial for PPMS is still ongoing (Constantinescu and Constantinescu, 2016).

## Treatment for cortical and meningeal MS pathology

Until now, there are no treatments for MS focused on the cortex. Therefore, focal lesion models could be useful to monitor specific treatment effects on cortical lesions (Chaudhary et al., 2015). Chaudhary et al. (2015) tested lipoic acid, an antioxidant, in a focal cortical EAE mouse model and demonstrated decreased $CD4^+$ and galectin-$3^+$ immune cells and less infiltrated monocytes. In addition, a randomized controlled pilot trial with lipoic acid showed a 68% reduction in annualized brain volume percent change over 2 years in MS patients (Bittner et al., 2017; Spain et al., 2017).

Vitamin D is a prohormone belonging to the fat-soluble group of vitamins. Vitamin D receptor is activated by the vitamin D molecule, and it acts as a transcription factor and subsequently heterodimerizes with the retinoid X receptor. This allows for the regulation of protein expression of target genes involved in the immune response (de la Fuente et al., 2015). The study of vitamin D effects on RRMS and PMS, both in patients and animal models, has been relevant in recent years (Burton et al., 2010; Dorr et al., 2012; Adzemovic et al., 2013; Ascherio et al., 2014; Chiuso-Minicucci et al., 2015; Boontanrart et al., 2016). Regarding cortical pathology, one study has shown that the vitamin D3 administration in the cuprizone murine model induces myelination through an increase in MOG and CNPase expression in the cerebral cortex (Mashayekhi and Salehi, 2016).

Currently, no specific treatments target meningeal inflammation. Indeed, no pilot studies have been conducted in any of the animal models until now. However, some of the immunomodulatory drugs used for MS treatment are able to modulate the inflammatory meningeal response, affecting the permeability of the meningeal vasculature (Russi and Brown, 2015). Finally, complementary diagnostic methods should be developed and validated to define the patients with meningeal inflammation so that treatments that target this specific pathology can be applied.

## Conclusion

As pathophysiological mechanisms change over the course of the disease, treatments for the different stages and forms of the disease should be adapted. At present, animal models that represent the spectrum of the heterogeneous pathology and clinical presentations of human MS are not available. Given the heterogeneity of its pathology, several simple animal models will allow the analysis of individual components of MS pathology and the development of new treatments. The strong correlation between disability and cortical lesions reflects the importance of cortical research in MS studies.

The development of appropriate experimental models is necessary to understand the etiology, progression, and heterogeneous pathophysiology of different clinical forms of the human disease. The heterogeneous pathophysiology is the biggest challenge in treating demyelinating diseases such as MS. In particular, many laboratories are currently trying to find the pathophysiological differences between progressive and nonprogressive clinical forms, with the aim of finding specific and effective therapeutic agents for each clinical form of MS.

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