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REVIEW ARTICLE

Neuroinflammation in Demyelinating Diseases: Oxidative Stress as a Modulator of Glial Cross-Talk

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Abstract: Myelin is a specialized membrane allowing for saltatory conduction of action potentials in neurons, an essential process to achieve the normal communication across the nervous system. Accordingly, in diseases characterized by the loss of myelin and myelin forming cells -oligodendrocytes in the CNS-, patients show severe neurological disabilities. After a demyelinated insult, microglia, astrocytes and oligodendrocyte precursor cells invade the lesioned area initiating a spontaneous process of myelin repair (i.e. remyelination). A preserved hallmark of this neuroinflammatory scenario is a local increase of oxidative stress, where several cytokines and chemokines are released by glial and other cells. This generates an environment that determines cell interaction resulting in oligodendrocyte maturity and the ability to synthesize new myelin. Herein we review the main features of the regulatory aspect of these molecules based on recent findings and propose new putative signal molecules involved in the remyelination process, focused in the etiology of Multiple Sclerosis, one of the main demyelinating diseases causing disabilities in the population.

Keywords: Multiple Sclerosis, neuroinflammation, oxidative stress, glial cross-talk, remyelination.

1. INTRODUCTION

The myelin sheath is a specialized extension of glial plasma membrane that encloses axons, conferring fast saltatory nerve impulse propagation and trophic support to the axon [1, 2]. It is now clear that suitable myelination is required for fine functional overall integration of the central nervous system (CNS). In the CNS, oligodendrocytes are the glial cells in charge of continuously production and renewal of myelin that enwraps a given axon [2, 3]. Demyelinating diseases are irreversible progressive pathologies characterized by myelin loss leading to axon degeneration and consequently neuronal loss, causing serious and several neurological impairments [4, 5]. Demyelination is roughly classified as primary, when is due to a focused insult to oligodendrocytes, or secondary (Wallerian demyelination) when this process is caused by axonal degeneration. Broadly, there are two major causes of primary demyelination in the CNS: acute inflammatory damage to myelin and oligodendrocytes and genetic vulnerability that affect glia (leukodystrophies). We will focus our discussion on the demyelinating inflammatory diseases, among which multiple sclerosis (MS) is the archetypical case [4-6].

MS is one of the world's most common neurologic disorders, characterized by an inflammatory autoimmune demyelinating process that causes disability and symptoms differing among patients, challenging a clear diagnosis. Some of the most prevailing symptoms are vision impairment, weakness, posture instability, spasticity and loss of bladder control [7]. Inflammation in demyelinating diseases only affects CNS, suggesting that are specific CNS antigens that recruited T- and B-cells. The pathogenic immune responses to CNS autoantigens lead to tissue damage that triggers a second wave of immune responses and eventually promoting microglia activation (see below). Upon MS progression, the immune responses become restricted to CNS, in which the injury pattern of the white matter changes from focal to diffuse (associated with microglial activation). Activated microglia could contribute to disease pathology by secreting proinflammatory cytokines, chemokines, free radicals and glutamate [6]. The main clinical feature of MS is a neuronal/axonal loss that leads to permanent patient's disability and therefore, the development of the neurobiological aspects of MS depends strongly on both the location of the lesion and the extent of the inflammatory process within the CNS [8]. In this regard, one of the most commonly used models to study the pathogenic mechanism of the MS (and other demyelinating diseases) preserving some clinical symptoms and the inflammatory process, is the experimental autoimmune encephalomyelitis (EAE) paradigm, in which the autoimmune response is induced by injecting a mouse with myelin-related peptides. Complementary, acute inflammatory lesion of the optic nerve triggers optic neuritis characterized by visual impairments associated with the demyelination, providing another animal model that preserves important clinical hallmarks of the disease [9]. Although both experimental models are complex and several variables should be considered, the evidences suggest that the main factors linking (total or partial) loss of timely-nerve impulse propagation and pathologic signals are proinflammatory cytokines, nitric oxide and demyelination process [10]. An additional complexity at this early stage is that $CD4^+$T cells differentiation, and therefore the autoimmune response that targets myelin, depends strongly on the nature and magnitude of the original insult. For instance, in a scenario in which interleukin-4 (IL-4) is the most abundant secreted cytokine, $CD4^+$T cells derived mainly into Th2 cells, a phenotype that has been associated with attenuation of the autoimmune response [11, 12]. On the other hand, when there is an early prevalence of IL-23, $CD4^+$T cells differentiate mainly to Th17 phenotype [13], which promotes autoimmune tissue injuries by secreting proinflammatory cytokines (IL-17, IL-22) that in turns recruit other immune cells such as neutrophils [14]. Th17 cells have been implicated in the pathogenesis of demyelinating inflammatory diseases in the CNS [15]. Moreover, evidences arising from mixed cultured glial cells suggest that at least the protective role of Th2 cells is due to the suppression of proinflammatory cytokines secreted by Th1 and Th17 cells [16], focusing on the idea that the outcome of the

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early autoimmune response is determined by the surrounding microenvironment [17].

Thus, in order to understand demyelinating diseases (or any other autoimmune neurodegenerative disease), a key question to answer is how a self-limiting, tissue-repairing immune response becomes harmful to the CNS. In this regard, the role of microglia as the main resident immune cells in the CNS, is crucial. Quiescent microglia contribute to CNS homeostasis by an ongoing release of anti-inflammatory and neurotrophic factors [18]. But upon tissue injury and/or pathogen infection, these "CNS sentinels" are the first cells to respond by becoming activated and releasing proinflammatory cytokines that in turn trigger the innate inflammatory response [19]. A key issue is that astrocytes are also activated, either directly by the insult or indirectly by microglial mediators such as IL1-β [20] and interferon-γ (INF-γ) [21]. A robust body of evidences show that astrocytes activation promotes neuronal survival, at least in part by secretion of several neurotrophic growth factors, such as nerve growth factor (NGF), brain-derived growth factor (BDNF), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), among others [22-25]. Interestingly, it has been shown that in response to the electrical activity of the neighboring axons, astrocytes secrete LIF, which in turn promotes myelination by mature oligodendrocytes [22]. Additionally, activated astrocytes secrete CNTF, which further increases astrocytic supporting function and even astrogliosis [25-27]. In fact, activated astrocytes can promote hippocampal neural stem cell differentiation and, therefore neurogenesis [28]. Regarding demyelinating diseases, it is also known that CNFT-activated astrocytes, but not quiescent ones, support myelination [29]. Further evidence suggests that local increases in IL1-β in early stages of the inflammatory response stimulates astrocytic CNTF production, an event related to myelination [20, 28, 30]. Thus, in the intricated chain of events determining the fate of the neuroinflammatory response both, microglia and astrocytes play a key role and the delicate balance of their relative contribution to this response, is regulated by a myriad of local signals (mainly cytokines and reactive oxygen species; see below).

2. OLIGODENDROCYTES PRECURSOR CELLS IN DEMYELINATION/REMYELINATION.

Although the etiology of demyelinating diseases (such as MS) is still not known, there is a wide consensus regarding that they are characterized by a progressive autoimmune attack upon myelin. Several evidences point at myelin-reactive $CD4^+$T cells as key actors that dysregulate the inflammatory response by overactivation of microglia and astrocytes, leading to unbalanced amounts of proinflammatory cytokines and thus, initiating the demyelinating insult. However, after a demyelinating injury, there is an innate remyelinating process, whose success into a functional recovery depends on the multiple variables that also define the progression of the demyelinating disease [4, 5, 17]. In fact, evidences from different mammal models show that remyelination, which is normally never completed or unsuccessfully achieved (i.e. thinner myelin sheath), can partially reestablish myelin conduction properties and neurological function under certain experimental manipulations [31–34]. In this context, it is worth to have in mind that myelination is an ongoing process throughout adulthood that depends on the renewal of the myelinating oligodendrocyte population from a highly proliferative and motile oligodendrocyte progenitor cells (OPCs) [5, 35]. In fact, OPCs are constantly renewed in the adult (mice) brain [36, 37] and interestingly, some evidences show that adult oligodendrocytes have a very narrow time window to produce new myelin sheaths (in the *in vivo* zebrafish model) [38], highlighting the importance of OPCs as the main source of remyelinating oligodendrocytes. Interestingly, as remyelination started, polarized (M2) microglia secretes activin-A (a member of the transforming growth factor (TGF) β superfamily) that promotes oligodendrocytes differentiation [39]. Moreover, chlodronate-induced macrophage depletion impairs oligodendrocyte but not Schwann cells remyelination in the injured spinal cord model, suggesting a positive and active role of the innate immune system in promoting oligodendrocytes remyelinating activity [40]. Accordingly, MS remission tightly depends on OPCs migration to the injury zone and differentiation into myelin-forming oligodendrocytes [5, 41]. In line with this, the analysis of *postmortem* MS samples indicates that OPCs migration is a key event defining the remyelinating response [42]. Furthermore, cuprizone-induced acute demyelination leads to OPCs activation and expression of proinflammatory mediators (such as IL1-β and chemokine Ccl2) that in turn promotes OPCs migration and differentiation in the injury zone [43]. On the other hand, if the proinflammatory scenario becomes increasingly hostile, OPCs capability to respond to myelin damage falls, therefore, limiting remyelination capacity [44]. This declined capacity of myelin regeneration has prompted efforts to find tools and strategies to enhance the remyelination process [5]. However, the evidences suggest that there is not a single sequence of events but a diverse array of variables to consider, largely the relative contributions of both microglia and astrocytes.

In fact, microglia have a robust contribution to the early disease pathology that would largely define the beneficial or detrimental outcome of the immune response. Activated microglia produces several signaling molecules, including tumor necrosis factor α (TNF- α), a master regulator of the immune system that promotes inflammation and IL-6 which enhances microglia activation and, in conjunction with IL-1β and INF-γ, promotes astrogliosis and subsequently astrocyte activation [18, 45]. In addition, type-1 interferons from the CNS in combination with tryptophan derivatives from gut flora modulate astrocytes and suppress CNS inflammation [21]. As we will discuss later, activated microglia increases the production of reactive oxygen species (ROS) mainly due to increased NADPH oxidases (NOXs) activity and/or mitochondrial metabolism [46], triggering a mismatch between oxidative stress and antioxidant defenses which induces redox signal-dependent expression of genes for inflammatory mediators and/or protective mechanisms [18]. Microglia can become chronically activated (even by a single stimulus) and thus leading to a cumulative, progressive neuronal loss that supports the chronic nature of the disease [47]. Accordingly, the inhibition of microglial overactivation minimizes neurotoxic events and promotes neuron survival in the early stages of the disease [18].

In a second stage, the progression of the demyelinating diseases is characterized by the demyelination, axonal retraction/loss that underlies the clinical symptoms [6]. Another hallmark at this stage is the astrocytes contribution: microglia would define whether astrocytes become slightly activated -and promote glial scar and OPCs survival, proliferation, and differentiation- or highly reactive astrocyte likely detrimental to OPCs and myelin itself [17, 25]. In this regard, evidence suggests that reactive astrocytes would favor the demyelination at early stages of the myelin loss, but later promoting the remyelination. However, most of this evidence comes from studies *in vitro*, or *in vivo* approaches that do not clearly define the time window analyzed, precluding more definitive conclusions on the role of astrocytes in the remyelination. Nonetheless, this dual role of astrocytes is known to be related to a shift in gene expression of adhesion molecules, antigen presentation molecules, cytokines, growth factors, receptors, enzymes and protease inhibitors [25, 27]. An early role of active astrocytes is to facilitate peripheral immune cell trafficking by regulation of several tight junction adhesion proteins that contribute to an increased blood-brain barrier permeability [48,49]. In addition, astrocytes release IL-23, which induces $CD4^+$T differentiation and the maintenance of the proinflammatory Th17 lineage [50], a key immune cell type in the pathogenesis of several inflammatory and autoimmune diseases, including demyelinating diseases in the CNS [15]. Another important cytokine secreted by astrocytes is TNF-α, a well-known promoter of inflammation that correlates with myelin and oligoden-

drocyte damage *in vitro* and *in vivo* [25, 51, 52]. Transgenic mice overexpressing TNF-α in the brain show spontaneous demyelination [53], and TNF-α RNA expression correlates positively with the degree of demyelination and negatively with oligodendrocyte numbers in the vicinity of the lesion in brain biopsies of MS patients [54]. Nevertheless, TNF-α, by activating TNFR-2 receptors, could favor oligodendrocyte viability by promoting the secretion of different signaling molecules such as platelet-derived growth factor and LIF [55, 56] and therefore it could have a role in promoting remyelination. In addition, astrocyte-derived TGF-β1 inhibits neuroprotective inflammatory response by microglia and T cells, accelerating the neurodegenerative progression in amyotrophic lateral sclerosis [57]. While there is no robust information on the putative role of astrocytic TGF-β1 in MS, there are evidences suggesting that TGF-β undermines the ability of microglia to promote oligodendrocyte differentiation from OPCs, and therefore remyelination [58]. On the other hand, TGF-β1 induces astrocytosis and an alteration of the translation/elongation of myelin genes in oligodendrocytes [59]. Hence, astrocyte-derived TGF-β1 could be a therapeutic target to promote remyelination that requires further attention (see below).

3. OXIDATIVE STRESS DEFINES THE SEVERITY OF DEMYELINATING DISEASES BY MODULATING GLIAL CROSS-TALK

Several factors contribute to the development of oxidative stress in this proinflammatory scenario. Thus, a mild increase in oxidative stress during inflammation plays a beneficial role by triggering an antioxidant response and killing invading microorganisms [60, 61], an overproduction of ROS (such as hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\cdot-}$) and hydroxyl radical (·OH)) and reactive nitrogen species (RNS) (i.e. nitric oxide (NO) and peroxynitrite ($ONOO^-$)) generates a more aggressive oxidative stress. The latter triggers a detrimental response, contributing to define the severity of the autoimmune/neurodegenerative disease, including MS and other well studied neurodegenerative pathologies such as Alzheimer's and Parkinson's diseases [62, 63]. In fact, increased oxidative stress enhances the sensitivity of microglia to proinflammatory stimuli, which has been implicated in aging and neurodegenerative diseases [18, 45]. In MS, *postmortem* samples shown DNA and lipid oxidation associated with ongoing demyelination and neurodegeneration [64]. Furthermore, oligodendrocytes, axons and neurons death and/or damage in MS are linked to extensive cytoplasmic and nuclear oxidative distress [64]. Recent evidence suggests not only that oligodendrocytes are the most vulnerable CNS cells to DNA oxidation following injury in the rat optic nerve, but also newly derived mature oligodendrocytes had reduced myelin regulatory factor gene mRNA, indicating that the myelination potential of these cells might be reduced [65]. Besides, there are evidence that glutathione confers antioxidant defenses to cultured (spinal cord) OPCs under oxidative stress, promoting OPCs survival and, therefore regenerative potential [66]. Moreover, the clinically tested ROS scavenger *edaravone* diminishes OPCs death rate under oxidative stress, *in vivo* and *in vitro* [67]. Thus, oxidative stress is very effective in restraining a pathogenic event but, if not regulated, could trigger serious progressive damage to the CNS. In this regard, it is necessary to point out that microglia have a robust antioxidant defense that not only protect themselves but to the surrounding tissue [68]. Likewise, primary cultured rat microglia respond to an H_2O_2 challenge releasing 2'-AMP (non-canonical nucleotides), suggesting an autocrine/paracrine mechanism that attenuates the overactivation of microglia during oxidative stress [69]. On the other hand, astrocytes respond to oxidative damage in MS with enhanced antioxidant enzyme expression (including superoxide dismutases and catalase) suggesting an adaptive defense against oxidative cytotoxicity [70]. However, under severe stress, the astrocytic functional profile switches from protective to detrimental (i.e. release of proinflammatory factors; [18, 25]).

Regarding the intimacy of the mechanism that defines if oxidative stress runs from adaptive to maladaptive process, it is known that the "proinflammatory activation" increases NADPH catalytic activity in both, microglia and astrocyte [71], leading to an increased ROS/RNS production. Additionally, agents causing ROS production -such as rotenone and diesel exhaust compounds- amplify the proinflammatory response in microglia [72, 73]. It is note to worth that microglia express the highly regulated "phagocyte NOX", the NOX2 isoform which increases ROS production in response to pathogens, therefore playing a key role in antimicrobial host defense and in regulating inflammation [74]. In addition, NOX2 deficiency has been implicated in the pathogenesis of a broad range of pathologies including neurodegenerative diseases [75]. Furthermore, upon inflammatory activation a human microglial cell line switches the expression of NOX2 to NOX4, an isoform that produces large amounts of H_2O_2 constitutively, leading to a constant tonic release of IL-6 [46]. This opens a new mechanism for understanding the deregulated inflammatory response that progresses into an autoimmune disease. NOX4 has been characterized as the "oxygen sensor" that triggers erythropoietin synthesis [76] and its overactivity contributes to the inflammatory component of several progressive diseases [77]. Furthermore, inflammatory stimuli, such as LPS and TNF-α induce ROS production through the activation of NOX4 in vascular endothelial cells [78, 79], suggesting a ubiquitous role for NOX4 in the deregulation of the inflammatory response going beyond the CNS environment.

Another important targets of ROS/RNS are common regulatory transcription factors, such as nuclear factor E2-related factor 2 (Nrf2), nuclear factor kappa beta (NF-κB) and hypoxia-inducible factor 1 alpha (HIF-1α) [80]. Among them, NF-κB is of particular interest not only as a master modulator of oxidative stress responses, but because it can be activated by diverse stimuli, including inflammatory mediators, growth factors, and various types of cell stress, such as oxidative stress [81]. In turn, activated NF-κB plays a critical role in inflammatory diseases (including MS and the EAE model) by regulating inflammation and cell viability [80, 81]. Although NF-κB favors adaptive responses to stress and therefore is recognized as a cytoprotective transcription factor, some authors suggest that NF-κB facilitates the progression of demyelinated diseases. Accordingly, in MS brain samples, an increased NF-κB activation in microglia, astrocytes, oligodendrocytes and infiltrated macrophages has been reported [81]. Microglia exposed to H_2O_2 showed impaired NF-κB function generating microglia overactivation, and mice lacking the expression of a specific NF-κB subunit (NF-κB p50) showed persistent inflammatory response to LPS [82]. In addition, NF-κB protects oligodendrocytes against inflammation. *In vitro* studies show that NF-κB activation promotes oligodendrocytes survival against INF-γ-induced apoptosis and that suppression of the NF-κB signaling leaves oligodendrocytes more susceptible to cytotoxicity evoked by ROS or RNS [83]. It has also been shown that controlled expression of NF-κB prevented TNF-α-induced apoptosis in an OPC cell-line [84]. More recently, it has been reported that inhibitors of NF-κB decrease oligodendrocytes viability and promote hypomyelination in developing mice [85], linking directly the NF-κB activity with myelin viability, at least in the CNS (contradictory effects have been described at the peripheral nervous system [86, 87]. It seems that the main source of NF-κB in response to an inflammatory event in the CNS are astrocytes, mainly due to their activation by IL-1β and INF-γ from microglia and infiltrated macrophages [25, 45, 77]. In line with this, by using the EAE model in transgenic mice, specific inhibition of astroglial NF-κB reduces the inflammatory response, leading to a significant improvement in locomotor recovery and white matter preservation after spinal cord injury (Brambilla et al., 2005). Afterward, the same authors show that this specific astroglial NF-κB inhibition not only improves myelin preservation but enhances remyelination, suggesting that astrocytes are key players in the pathophysiology of EAE and eventually in demyelinating diseases [88]. In agreement

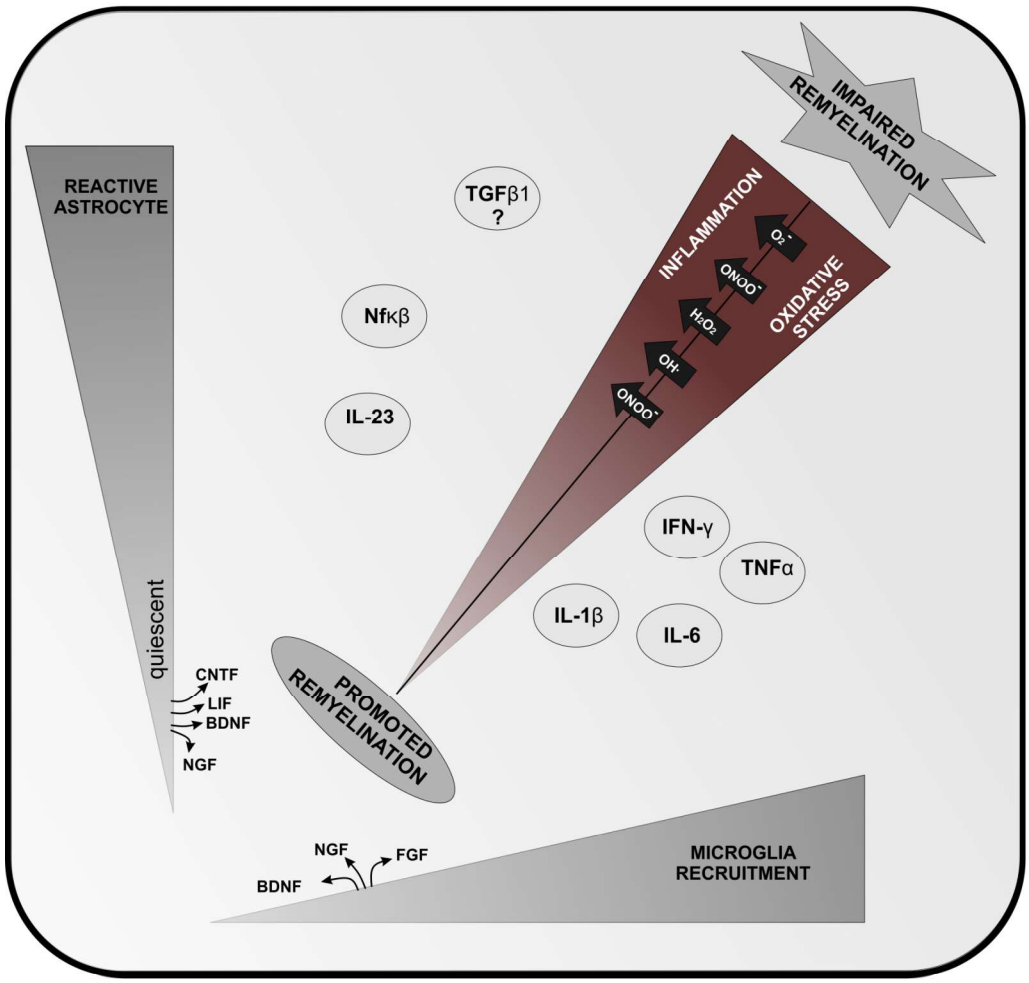

Fig. (1). Main signaling molecules involved in myelin repair progression. Early after a demyelinated insult cytokines and chemokines released by astrocytes and microglia (i.e CNTF, LIF, BDNF, NGF, FGF, among others) promote OPC proliferation or differentiation into mature oligodendrocytes which in turn synthetize new myelin, promoting remyelination. Microglia recruitment and polarization modify astrocyte stage by releasing cytokines (i.e. INF-γ and IL-1β) inducing its activation. Active (reactive) astrocytes in turn release molecules sucha as IL-23 and NFk-β which contribute to the increase in oxidative stress and the concomitant inflammatory environment. TGF-β1 is also released by astrocytes in this condition, putatively (?) contributing to the impairment of remyelination (see main text). CNTF; ciliary neurotrophic factor; LIF; leukaemia inhibitory factor; NGF; nerve growth factor; BDNF; brain-derived growth factor; FGF; Fibroblast growth factor; IL-1 β ; Interleukin 1β; IL-6; Interleukin 6; IFN-γ; Interferon γ; TNF-α; tumor necrosis factor α; IL-23; Interleukin 23; NFk-β; nuclear factor kappa β; TGF-β1; transforming growth factor β-1. *This figure considers the main signaling molecules discussed in this review but does not intend to summarize all published data. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

with the main role for astroglial NF-κB on demyelination progression, after 5 weeks of cuprizone-induced demyelination, inhibition of NF-κB activation in astrocytes but not oligodendrocytes protect mice from myelin loss [89]. In order to identify mechanisms to link inflammatory response, oxidative stress, and the numerous effects this transcriptional factor could trigger, it is worth mentioning that upon recognition of LPS, activated Toll-like receptor 4 (TLR4) directly activates NOX4 and NF-κB [90].

In summary, the ongoing, physiological oxidative stress becomes unbalanced when an early inflammatory response takes place, and ROS/RNS levels are increased. In MS, this scenario could lead to further microglia and/or astrocyte activation that, through a complex cocktail of chemical signals (Fig. **1**), inhibits the remyelination process mainly by doing both, promoting degeneration (and eventually death) of mature oligodendrocytes and preventing OPCs differentiation [45].

4. POTENTIAL THERAPEUTIC TARGETS

Numerous treatments have been approved for tackling MS progression, mainly by targeting neuroinflammation and, indirectly, neurodegeneration [5, 6]. Nevertheless, these approaches show low efficacy. In fact, only the humanized anti-CD20 monoclonal antibody *ocrelizumab* (i.e. an immunosuppressive drug) has shown to be able to stop the development of the disease in patients with primary progressive MS [91, 92]. Many other immunosuppressor drugs have a higher risk of serious adverse effects (infections, etc.) [6]. Several treatments have the potential to slow the progression of new lesions; however until an eventual prevention of MS is achieved, the current efforts should be focused in promoting repair of existing lesions. In this regard, the quest for discovery of molecules that allow effective pharmacological treatment of MS have been focused on CNS remyelination. Indeed, some promising results have been achieved with muscarinic antagonists that directly stimulate oligodendrocytic differentiation [93, 94]. Importantly, a recent pre-clinical study showed that *Clemastine*, an approved antihistaminic drug with anticholinergic activity, induced the recovery of the visual function in MS patients with chronic demyelinating optic neuropathy [95]. Nevertheless, many of these compounds are not selective anticholinergic agents but instead target other proteins as well, making difficult to identify a precise mechanism of action.

Other potential strategy is to point at the leucine-rich repeat and immunoglobin-like domain-containing protein 1 (LINGO1), that it is expressed by OPCs and regulates myelination. In fact, in LINGO1$^{-/-}$ mice, OPCs differentiation and oligodendrocyte maturation are enhanced, leading to an earlier and heightened myelination [96, 97]. Accordingly, the function-blocking monoclonal antibody against LINGO1 *Opicinumab* shows potential as future neuroregenerative drug [98], although its effectiveness in MS is questionable [98]. Finally, it has been reported that semaphorin 4D inhibits remyelination through several mechanisms (including OPCs survival and differentiation) the monoclonal antibody *Antisemaphorin* has been tested as a potential therapeutic drug in a model for Huntington' disease, positioning a novel approach for tackling neurodegeneration [99, 100] . Yet again, since the initiation and progression of MS is a multivariable progressing scenario, it is unlikely that pharmacological strategies pointing at a unique molecular target turn out to be fully effective.

CONCLUDING REMARKS

Demyelinating diseases, such as MS are complex in its etiology, clinical expression and treatment. In this scenario, the finding of new molecular targets tackling the complex cross-talk between glial cells is of pivotal interest. Among them, cytokines, ROS and RNS represent major putative targets giving the inflammatory scenario that characterize demyelinating diseases. Further attention to molecules involved in these pathways in another neurodegenerative diseases (e.g. TGF-β1), should shed light on the molecular and cellular pathways involved in the neuroinflammatory process, hopefully leading to new potential therapeutic strategies in demyelinating pathologies, particularly in MS.

AUTHORS CONTRIBUTION

RV and FCO conceived the major ideas developed in the manuscript. RV and FCO designed the Figure. RV wrote the manuscript under the supervision of FCO. Both authors read, edit and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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