Glial-derived transforming growth factor β1 (TGF-β1): a key factor in multiple sclerosis neuroinflammation

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Glial cell activation and neuroinflammation in multiple sclerosis (MS): MS is an irreversible and progressive central nervous system (CNS) disease which originates in the autoimmune attack of lymphocytes against CNS myelin. This specialized membrane, synthesized by oligodendrocytes (OL) in the CNS, provides metabolic support to axons and allows for saltatory conduction in neurons. The lack of myelin (i.e., demyelination) leads to axonal degeneration, neuronal death, and the consequent neurological disabilities (Franklin and Ffrench-Constant, 2017). Although the causes of MS are still matter of active investigation, the early events preceding the demyelination onset have been characterized in deep. Evidence indicates that there is an increase in the blood-brain barrier (BBB) permeability, followed by the infiltration of $CD4^+$ T lymphocytes, which, in turn, induces the overactivation of microglia and astrocytes present in the white matter. The latter leads to the dysregulation of the inflammatory response, being characterized by an increased concentration of proinflammatory cytokines promoting myelin loss (recently reviewed in Varas and Ortiz, 2019).

After this demyelinating insult, oligodendrocyte precursor cells (OPCs) migrate to the lesioned area, thus giving rise to remyelinating OLs. However, this spontaneous regenerative process is not normally completed, resulting in a low quality (i.e. less dense) myelin, which consequently leads to a functional failure, hence aggravating the neurological symptoms of MS patients (Franklin and Ffrench-Constant, 2017).

Even though there are not available regenerative therapies for MS, one of the most promising treatments is based on the re-generation of OLs which could, in turn, synthesize new myelin in the lesion (Franklin and Ffrench-Constant, 2017). These new OLs must maturate in a complex cellular environment, characterized by glial cell activation and a neuroinflammatory response. As previously stated, early during the demyelination onset, microglia become activate and release proinflammatory cytokines which triggers an inflammatory response. Astrocytes are also activated, either directly by the tissue injury or indirectly by microglial-derived factors such as interleukin 1β (IL-1β), transforming growth factor β1 (TGF-β1) and interferon-γ (INF-γ). Additionally, astrocytes release IL-23, IL-1β, tumor necrosis factor alpha (TNF-α), and IFN-γ, all together contributing to the inflammatory scenario (Varas and Ortiz, 2019; Traiffort et al., 2020).

The role of microglia on MS progression has been extensively studied. Activated microglia contributes to disease pathology by secreting proinflammatory cytokines, chemokines, free radicals, and glutamate (Varas and Ortiz, 2019). Besides, microglia would exert a dual role in the process of remyelination. Evidence shows that microglia and peripherally-derived macrophages polarized in the M1 stage would impair myelin repair in a model of lysolecithin-induced demyelinating lesions (an experimental model of MS) by secreting pro-inflammatory interleukins, such as IL-1 β, IL-2 and TNF-α. In the same experimental model, M2-macrophages and microglia promotes remyelination by inducing the differentiation of OPCs into OLs (Miron et al, 2013; Traiffort et al., 2020).

Astrocytes would play a dual role by potentiating the demyelination in early stages of the lesion progression, and also promoting myelin repair in later stages of the remyelination process (Varas and Ortiz, 2019; Traiffort et al., 2020). Studies from different groups indicate that astrocytes can induce and potentiate myelin loss and neurodegeneration (compelling evidence on this subject has been recently summarized by Traiffort et al., 2020). Particularly important to this proposal, inhibition of pro-inflammatory activity in astrocytes (i.e., secretion of IL-1β, TNF-α, IFN-γ, TGF-β1, among others) reduces the demyelination extent in *in vitro* lysolecithin-induced demyelination lesions, and also reduces the clinical score in the experimental autoimmune encephalomyelitis (EAE) model of MS (Traiffort et al., 2020). Besides, astrocytes could also provide a neuroprotective environment, thus favoring remyelination. Astrocyte-derived leukemia inhibitory factor favors OL survival, which correlates with a decrease in the EAE mice signs. In the same line, *in vitro* activation of astrocyte TNFR2 receptor led to an increase in the maturation of co-cultured OPCs into OL, being this effect mediated by leukemia inhibitory factor. Importantly, astrocytic brain-derived neurotrophic factor induced the maturation of OPCs into OL in cultures, while in an *in vivo* model of white matter damage (cerebral hypoperfusion) brain-derived neurotrophic factor deletion in astrocytes correlated with an impairment myelination (Traiffort et al., 2020).

Thus, among many other essential functions, microglia and astrocytes play a key role in determining the neuroinflammatory environment in MS and other neurodegenerative scenarios by secreting several regulatory cytokines, including IL-1β, IFN-γ, IL-23 and TGF-β1 (Traiffort et al., 2020). Importantly, recent studies have pointed out TGF-β1 as a central signaling molecule controlling oligodendroglia maturation and myelin synthesis (Baror et al., 2019; Hamaguchi et al., 2019). Nonetheless, the cellular source/s and its/their putative active pathway/s have been poorly characterized in demyelinating conditions.

TGF-β1 signaling on oligodendroglia dynamics and MS: TGF-β is a superfamily of cytokines, including activins, inhibins, and bone morphogenic factors, which play essential roles in neurogenesis, synapse formation, regulation of growth, gliogenesis and angiogenesis (Diniz et al., 2019). TGF-β1 to -β3 have been implicated in inflammatory process. TGF-β receptor I (TGF-βRI) and TGF -βRII are expressed in neurons, astrocytes, OLs, and microglia (Diniz et al., 2019). In the CNS, glial-derived TGF-βs modulate cell proliferation and differentiation in several systems, particularly under inflammation. Importantly, TGF-β1 promotes OL differentiation *in vitro* by modulating the effect of PDGF as a determinant factor to achieve OPC differentiation (Diniz et al., 2019). During development, a combination of TGF-β1/β3, and activins induced OL maturation and myelination in the spinal cord. Similarly, the activation of TGF-β receptors I and II (TGF-βRI and -II) in OPCs from neonatal brain lysates modulates OPC cell cycle through the activation of their conventional effectors SMAD 1, 2 and 3. Thus, during developmental stages, TGF-β1 plays a key role in determining the timing of myelination (Diniz et al., 2019).

What is known about TGF-β1 signaling in MS? Clinical studies report increased blood levels of TGF-β1 in MS patients from both relapsing remitting and progressive forms of the disease (Flauzino et al., 2019), but the role of this cytokine is still elusive. As described for glial cells in demyelinating lesions, the evidence suggests that TGF-β1 has a dual role on MS progression. For instance, it has been shown that TGF-β1 might induce astrogliosis and triggers an OL defective genetic program in MS patients (Nataf et al., 2017). However, TGF-β1 could reduce both the neuroinflammatory response of lesioned areas in progressive MS patients as well as the activation of B-lymphocytes in a EAE model of MS (Bjarnadóttir et al 2016; Nataf et al 2017), moreover, it has been also reported that TGF-β1 favors remyelination in the EAE and toxin-induced demyelination models of MS (Hamaguchi et al., 2019)

TGF-β1 as a deleterious signal in MS: In physiological conditions, the formation and maturation of the BBB rely on endothelial cells-astrocyte interactions depending on TGF-β-mediated activation of the

integrin avβ8 pathway (Diniz et al., 2019). Interestingly, by controlling BBB tight junction proteins, active astrocytes contribute to one of the first events in MS onset: the increase of BBB permeability. The latter allows the lymphocyte infiltration, thus leading to the neuroinflammation (Varas and Ortiz, 2019). Importantly, treatment with TGF-β1 induced the disruption of an *in vitro* BBB model, constituted by a brain endothelial human cells line (Derada Troletti et al., 2019). Although MS represents a different scenario, the evidence allows to speculate that an altered glial TGF-β1 signaling could disrupt the BBB under pathological conditions (**Figure 1**). Additionally, TGF-β1 activates the glial fibrillary acidic protein gene promoter in astrocytes *in vitro* and *in vivo* (Diniz et al., 2019). Therefore, it is likely that increased levels of TGF-β1 would be able to increase glial fibrillary acidic protein expression promoting astrogliosis, a hallmark of MS lesions. Additionally, TGF-β signaling could also undermine the ability of microglia to promote OPC maturation in demyelinating lesions, as it was shown in an *in vivo* toxin-induced demyelination model of MS (Baror et al., 2019).

TGF-β1 as a protective/pro-regenerative signal in MS: Genetic analysis of demyelinated tissue of MS patients suggests that TGF-β1 expression in astrocytes might reduce the neuroinflammatory microenvironment by decreasing the expression of interleukins-17D, -12A, and -33 (Nataf et al., 2017). Importantly, a recent study showed that by manipulating the plasmatic levels of TGF-β1 and their signaling pathways (i.e., TGF-βRI inhibition) in the cuprizone- and lysolecithin-induced demyelination MS models and the EAE mice, this cytokine promotes *in vivo* spinal cord remyelination through TGF-β1RI activation, as well as OL maturation in culture (Hamaguchi et al., 2019).

Considering these results, it is possible to propose that during the remyelination process, astrocytic TGF-β1 might promote the differentiation of OPCs into mature OLs, which, in turn, would synthesize new myelin in the injured region (**Figure 1**). Discussion on intracellular mechanisms which might account for the expected switch from detrimental to beneficial astrocyte is beyond the scope of this proposal. However, a likely candidate is the JAK/STAT3 pathway, which has been pointed out to play a pivotal role in determining the final outcome of astrocyte activity under inflammatory conditions (Ceyzeriat et al., 2016).

Concluding remarks: It is well established that TGF-β1 is involved in fundamental processes in the CNS. This signaling pathway has been largely associated with glial activation and neuroinflammation in different experimental paradigms and clinical studies. Moreover, it has been recently reported that this cytokine is involved in the progression of demyelination in both MS patients and animal MS models. Then, we hereby propose that glial-released TGF-β1 might play a central role as a mediator of glial cell-dependent mechanisms on MS, likely by modifying both the inflammatory response and oligodendroglia maturation, hence representing a putative therapeutic target to promote remyelination.

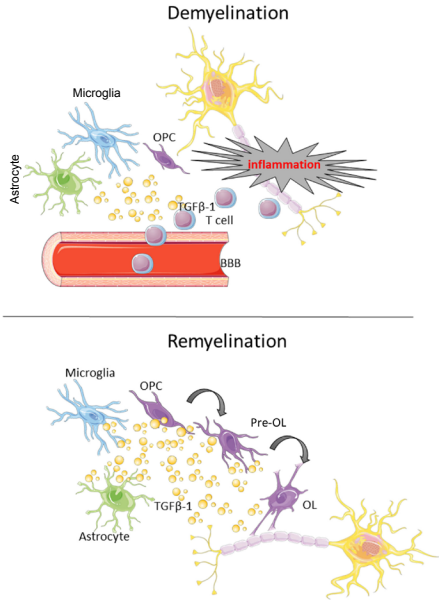

Figure 1 | **Possible role of transforming growth factor β1 (TGF-β1) in multiple sclerosis neuroinflammation and oligodendroglia maturation.**
In an early demyelinating environment, glial TGF-β1 (yellow circles) might increase the blood-brain barrier (BBB) permeability, favoring the passage of peripheral immune cells, such as T cells, and promoting myelin damage and neuroinflammation. However, during the remyelination process, glial TGF-β1 could favor the differentiation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes (OL), which in turn will promote myelin regeneration. This figure was prepared based on the free online Servier Medical Art repository images (https://smart.servier.com/).

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