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TGF-beta 1 and the spinal cord-specific outcome of multiple sclerosis active plaques

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Abstract:

We recently reported that in the spinal cord of PPMS or SPMS patients, large areas of periplaque demyelinating lesions extend distance away from plaque borders. Such lesions are characterized by a progliotic TGF-beta 1 signature accompanied by: i) a low-grade inflammatory reaction, ii) an extensive astrocytosis and iii) a process of incomplete demyelination. It was proposed that, while efficiently dampening inflammation in MS spinal cords, TGF-beta 1 could promote astrocytosis, prevent remyelination and possibly trigger alterations of myelin synthesis. In light of these findings, a re-interpretation of two large neuropathological studies performed on MS brains and spinal cords is provided here. While results from these studies clearly showed that active plaques do not display any region-specific distribution, an important point was apparently overlooked and not discussed by the authors: a significantly higher percentage of inactive plaques was found in MS spinal cords as compared to brains and, conversely, the percentage of slowly-expanding (or smoldering) lesions was significantly lower in the spinal cord as compared to the brain. These data indicate that the spinal cord environment may be more favorable to the resolution of inflammation. Downstream of the autoimmune process leading to plaque formation, region-specific mechanisms may thus drive the outcome of active plaques. While inflammation triggers tissue destruction, inflammation may also be needed for effective tissue repair and an inappropriate dampening of inflammatory events may possibly translate into a poor level of remyelination in MS spinal cords. It is proposed here that TGF-beta 1 is involved in such a brain-spinal cord dissociation of active plaques outcome.

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A high frequency of inactive plaques is observed in the spinal cord of multiple sclerosis patients

The current picture of multiple sclerosis (MS) neuropathology is essentially based on the analysis of brain tissue samples. A relatively poor number of works investigated MS spinal cords and only few concurrently assessed brains and spinal cords from MS patients. In this context, a recent paper reported on an extensive and systematic analysis of plaque activity on brains and spinal cords derived from a large cohort of MS patients[1]. While the main conclusion of this work related with the role of smoldering plaques (i.e slowly-expanding lesions) in MS progression, an important finding was unraveled but somehow neglected and not discussed. Indeed, when assessing the impact of localization on the percentage of active vs inactive plaques, the authors found that, irrespective of age and disease duration, significant differences were observed when comparing the spinal cord to the brain: "*Lesions in the spinal cord were more likely to be inactive ($p < 0.001$, $p=0.002$) compared to supratentorial and infratentorial lesions.* In addition *"Lesions in the spinal cord were less likely to be smoldering ($p=0.02$) compared to supratentorial lesions*"[1]. Finally, "*no/ few smoldering plaques were found in the spinal cord or optic nerve*" while "*smoldering and inactive plaques were both equally distributed between the supratentorial and the infratentorial white matter*"[1]. Importantly, the authors also reported that active plaques did not display any region-specific distribution even when specifically assessing early active or late active plaque[1]. It appears thus that, downstream of the triggering autoimmune mechanisms leading to the formation of active plaques, a spinal cord-specific process is responsible for a dampening of plaque-associated inflammation. It is worth noting that a previous work based on the coupled brain/spinal cord neuropathological analysis of SPMS or PPMS patients similarly concluded to a dissociation between brain and spinal cord with regard to: i) the percentage of inactive plaques (89% of inactive plaques in the spinal cord as compared to 54% in the brain) and ii) the percentage of slowly-expanding plaques (5% of slowly-expanding plaques in the spinal cord as compared to 18% in the brain)[2]. Altogether these data indicate that region-specific parameters may play a major role in the outcome of plaque activity in MS. The inflammation-

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resolving phase of plaque evolution, a process known to be coupled to tissue repair, might differ between brain and spinal cord.

Anatomical and glial specificities shape the neuroimmune status of MS spinal cords

To explain such brain-spinal cord dissociation with regard to the kinetics of plaques, the first important point that has to be taken into account is the particular anatomical organization of the spinal cord: white matter areas surround the grey matter while in both brain and cerebellum the cortical gray matter surround white matter tracts. Of note, optic nerves, which roughly share the same inside out anatomy than the spinal cord, were also shown to display a high % of inactive plaques and no smoldering lesions[1]. There is yet no clear evidence on how spinal cord anatomical specificities may impact on plaque evolution. However, it is worth noting that although clearly demonstrated in the cortical meninges of MS brains, to our knowledge, B-cell follicles were not observed in the spinal cord meninges of MS patients[3]. One may propose that the microenvironment of cortical meninges, in part determined by the sub-pial grey matter, is uniquely favorable to the formation of meningeal B-cell follicles. In turn, B-cell infiltration in brain meninges may support the perpetuation of plaque activity in brains but not spinal cords. Finally, the region-specific functional heterogeneity of astrocytes and oligodendrocytes is just starting to be robustly documented[4] and may account for the existence of spinal cord-specific properties of glial cells.

TGF-beta 1 dampens inflammation and drives astrocytosis in spinal cord periplaques

We recently demonstrated that in the spinal cord of MS patients with a progressive form of the disease, areas of incomplete demyelination extend distance away from plaque borders and cover up to 40 % of the spinal cord surface on transverse section[5]. The whole genome transcriptomic analysis of such periplaque demyelinating lesions essentially demonstrated a progliotic TGF-beta 1 (*TGFB1*) genomic signature in which genes of the TGFB1 signaling pathway co-expressed with *GJA1* (also known as Connexin 43), *GFAP* and multiple astrocyte-related extra-cellular matrix (ECM) genes[5,6]. Of note, previous works demonstrated that TGFB1 strongly induces the astrocytic expression of ECM genes that were shown to inhibit myelin repair[7]. Finally, based on the identification of periplaque-

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associated gene co-expression modules, we proposed that TGFB1 along with PDGFC (Platelet derived growth factor C) could be responsible for an altered translation/elongation of myelin genes in spinal cord periplaques[6].

Incomplete demyelination in spinal cord periplaques: the cost of an effective endogenous immune regulatory mechanism?

The functional scheme (Figure 1) that emerges from the above-mentioned observations is that a TGFB1-mediated regulation of inflammation operates in the spinal cord of MS patients. In the brain, owing in part to chronic meningeal inflammation, such an endogenous process may allow only a delayed or partial control of plaque-associated inflammation. However, while dampening inflammation in MS spinal cords, TGFB1 might be concurrently responsible for: i) the development of an astrocytosis process that progressively extends from plaque borders to the normal-appearing white matter, ii) the synthesis by astrocytes of extra-cellular matrix (ECM) molecules that prevent effective remyelination and iii) a direct inhibitory effect on the myelinating functions of oligodendrocytes. An important unanswered question in this pathophysiological scheme would be the cellular origin(s) of TGFB1. In this regard, multiple potential sources of TGFB1 have been described in the chronically inflamed CNS including reactive astrocytes but also regulatory populations of microglia and T-cells. In any case, TGFB1-targetting molecules currently used for the treatment of another “sclerosis disease”, namely systemic sclerosis, alone or in combination with anti-inflammatory agents, should be considered as a therapeutic option for MS patients with a progressive form of the disease.

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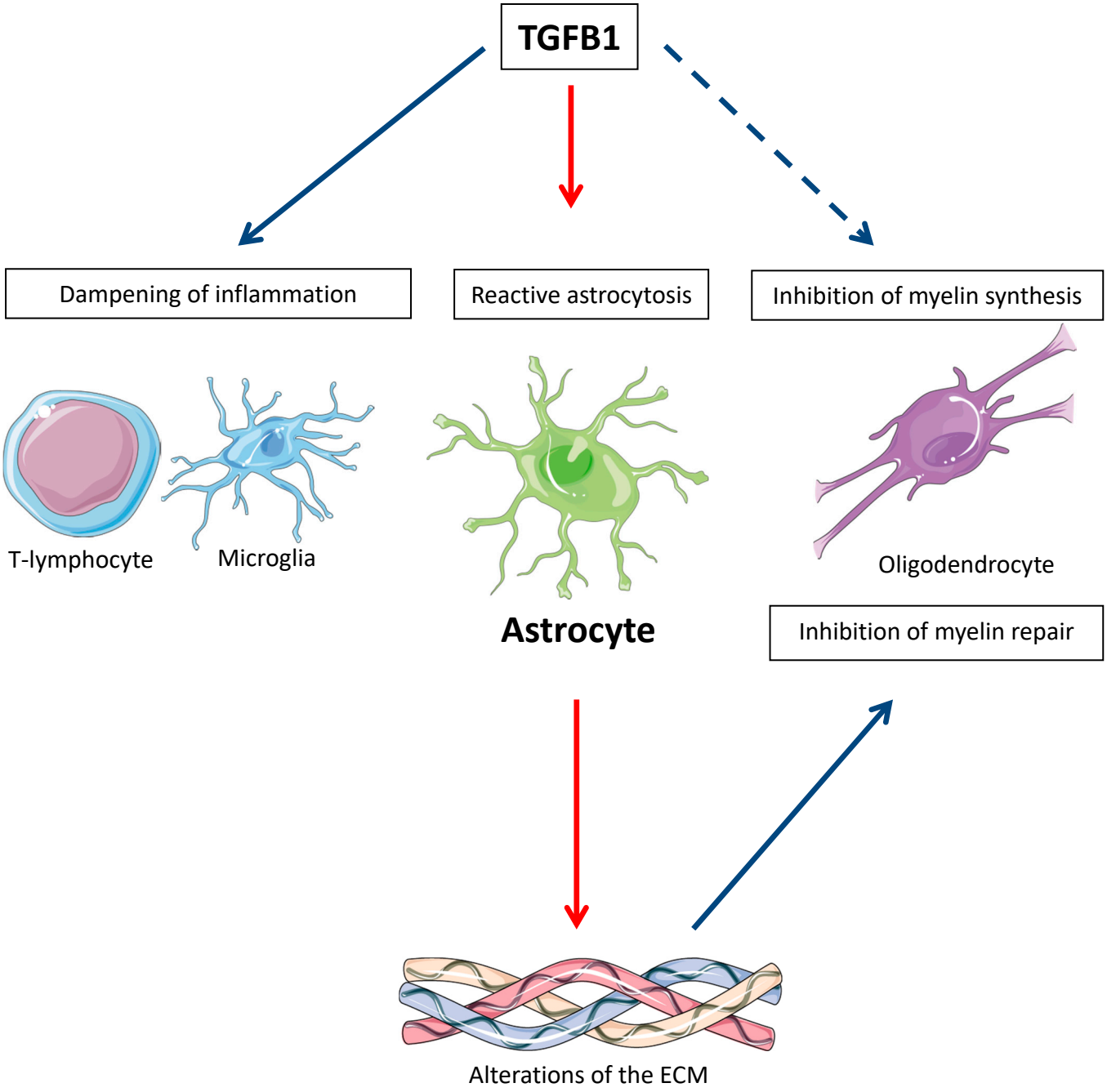

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Figure legend: In multiple sclerosis (MS) spinal cords, transforming growth factor-beta 1 (TGFB1) may be responsible for the following direct effects: i) dampening of microglia- and T cell-mediated inflammation, ii) promotion of a chronic, slowly expanding reactive astrocytosis and iii) inhibition of oligodendrocyte myelinating functions. Indirectly, TGFB1 may also inhibit myelin repair processes via an astrocyte-mediated alteration of the extra-cellular matrix (ECM) molecular composition. Plain lines: mechanisms previously demonstrated by experimental data; dashed line: putative mechanism inferred from bioinformatics analyses. Red lines and blue lines indicate stimulating and inhibitory mechanisms respectively. Images were obtained from the "Smart Servier Medical Art" website (http://smart.servier.com) under the terms of use defined by Creative Common License.