Targeting semaphorins in MS as a treatment strategy to promote remyelination: A tale of mice, rats and men

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Keywords: Multiple sclerosis, neuroregeneration, semaphorin 7A, semaphorin 3A

Translating results generated in animal models or in vitro to the human paradigm is a key prerequisite for designing future therapies for patients. While sounding simple, this seemingly self-evident statement turns into a complicated issue when the disease in question affects a tissue that is notoriously difficult to procure: the human brain. Due to a plethora of ethical, logistical and monetary reasons, comparatively few research centres worldwide have access to human brain tissue. However, reproduction of data gathered from rodent experiments in human tissue is a sine qua non for the evaluation of molecular factors as future therapeutic targets. This is particularly relevant for diseases such as multiple sclerosis (MS), whose underlying aetiology is still unclear even 147 years after its first histopathological description by Jean Martin Charcot in 1868.

Despite this situation, the introduction of interferons and glatiramer acetate in the 1990s first allowed disease modification, and recent years have witnessed gratifying successes in the clinical development of newer drugs for MS. Therefore, we have moved past the era in which an MS diagnosis was automatically associated with becoming wheelchair-bound. What still remains, though, is the inconvenient realisation that the currently approved immunomodulatory medications for MS can at best achieve ‘no evidence of disease activity’ in about 50% of patients and ultimately ‘only’ slow disease progression and delay transition into secondary progressive MS.

For patients who have entered the stage of secondary progressive MS and those with primary progressive disease, on the other hand, few if any treatment options are available. The progressive disease stage features steady neurological decline, resulting from accumulating neurodegeneration mainly due to failure of remyelination and axonal damage and fallout. It is thus understandable that there is considerable interest in the development of new therapies aimed specifically at modifying the neurodegenerative aspects of MS. Endogenous remyelination delivered by oligodendrocytes, which are derived from oligodendrocyte precursor cells (OPCs), is considered a promising potential target for the treatment of all stages of MS. Moreover, the brain’s endogenous capacity for myelin repair diminishes over time, probably due to a failure of OPC differentiation and migration caused by numerous inhibitory factors.1,2

In this issue of MSJ, Costa and colleagues3 describe the results of a translational study in which the expression of such inhibitory molecules, semaphorin 3A and 7A and their respective receptors, were studied in MS lesions.

Semaphorins were originally described as axonal guidance molecules with both repellent and attractant properties in the context of central nervous system (CNS) development.4 However, they are also expressed in the adult CNS, where they can be found on resident cells as well as on infiltrating immune cells during neuroinflammation. Sema3A is a secreted molecule that inhibits regenerative axonal sprouting into the astrocytic glial scar.5 It also functions as a repulsive cue in MS lesions where it potentially counteracts the effect of its close relative Sema3F, which recruits OPCs into lesions. Here, Sema3A might function as a stop signal for this recruiting process, kicking in after a sufficient number of remyelinating OPCs have been attracted to the lesion.6 By stimulating microglial apoptosis, Sema3A might also help to control the ongoing inflammatory process, indirectly facilitating CNS repair.7 Finally, with regard to the immune system, it has been described as a mediator of T-cell immunosuppression and an inducer of dendritic cell migration into lymph nodes.8
Sema7A, on the other hand, a glycosphatidylinositol-anchored membrane protein that can also be cleaved and released as a soluble molecule, induces the maturation of the glial scar in spinal cord injuries. It has also been identified as a chemoattracting signal for monocytes and macrophages and evokes their production and release of proinflammatory cytokines. The role of Sema7A in neuroinflammation remains controversial, however, as it has been described in the literature as both detrimental and beneficial during the course of experimental autoimmune encephalomyelitis, one of the established animal models for MS.

In order to clarify further the potential roles of these two semaphorins in the human paradigm Costa and colleagues have now analysed their expression and the expression of the respective receptors in MS lesions. Although other researchers have already reported the presence of Sema3A in MS lesions, what significantly differentiates this work from previous investigations by other groups is the first-time description of Sema7A expression in MS lesions. Sema7A was predominantly localised to reactive astrocytes, similar to the previously described distribution in the injured spinal cord. This observation suggests that this molecule may be involved in glial scar formation and regeneration failure in the context of acute inflammation, as scar tissue is notorious for impeding OPC migration and subsequent remyelination. In accordance with this assumption, the authors report decreased Sema7A in chronic inactive MS lesions, which might indicate a resolving inflammatory process and a now-mature glial scar. Sema7A therefore represents an interesting potential target for future therapeutic approaches. Moreover, the pharmacological inhibition of Sema7A, possibly by small molecules, might simultaneously downregulate parenchymal monocye/macrophage-mediated proinflammatory activities while providing improved oligodendroglial cell access to lesions. Finally, Sema7A might even qualify as an MS disease course biomarker, as the same research group, in another paper, demonstrated that conversion from clinically isolated syndrome to MS disease course biomarker, as the same research group, in another paper, demonstrated that conversion from clinically isolated syndrome to multiple sclerosis? Brain 2011; 134: 1882–1900.


