

Editorial

## Interactions between Axon Cytoskeleton Proteins and Oligodendrocytes during Remyelination

Catherine Fressinaud<sup>1\*</sup>

<sup>1</sup> LUNAM, Neurology Department, University Hospital, 4 rue Larrey, 49933 Angers Cedex 9, France

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In the central nervous system (CNS) oligodendrocytes (OL) synthesize myelin sheaths around large diameter axons. This allows the saltatory conduction of action potentials, and increases considerably the velocity of neural conduction. These cellular structures are altered during Multiple Sclerosis (MS), the most frequent demyelinating disease of the CNS. Actually its lesions are characterized by inflammation, demyelination and death of some OL, as well as by axonal damage. Experimentally, saltatory conduction is restored by axon remyelination [1], whereas remyelination fails in MS for partially unknown reasons. Four main factors might be involved in the repair defect in MS: I) astrocytic gliosis [2], II) axon degeneration [3, 4], III) and/or OL alterations [5], IV) and finally the coexistence of these parameters with inflammatory cells and molecules in the lesions [6] which renders the clarification of their respective involvement in the persistency of lesions difficult.

Similarly the origin of axonal lesions is equivocal, either secondary to the inflammatory process, or to demyelination itself [7]. Occurring early in the course of the disease, they probably account for patient's disability, and for atrophy of the CNS [8]. Axon-OL interactions are subtle, and relies on complex bidirectional interactions, including trophic and regulatory interactions [9, 10], as well as metabolic exchanges. For example, axon-derived neuregulins (NRG) promote OL survival, and NRG-1 increases myelination [11]. Although OL are able to synthesize myelin-like membranes *in vitro* in the absence of neurons [12], neurons in cocultures increase myelination [13]. Furthermore, axotomy decreases the number of OL progenitors in the optic nerve of rodents [14], now numerous axon sections have been observed in MS lesions [15, 16]. Thus, axon lesions could, at least partly, be involved in the remyelination defect during MS. Since the integrity of both axon and OL is required for proper CNS function, the putative consequences on remyelination of changes in these axon proteins have to be precised.

In fact the regulation of (re)myelination in the CNS is not fully elucidated. Since myelination depends on axon diameter (only large diameter axons are myelinated), these interactions could also involve, at least indirectly, neurofilaments (NF) which modulate axon calibre, as well as microtubules responsible for axonal transport [17]. In an interesting way, some axonal proteins known to be

involved in myelination are altered in MS lesions: the expression of paranodin, which localizes to paranode when myelination begins, is repressed [18], and PSA-NCAM, which inhibits myelination, is expressed by some axons in plaques [19]. Finally, as numerous OL at a premyelinating stage have been observed in contact with dystrophic axons, it has been hypothesized that axons might be improper for remyelination [20].

In addition, axon cytoskeleton alterations, especially abnormal phosphorylated forms of NF (e. g. [15, 20]), and decrease in NF and  $\beta$  tubulin expression [21] are present in MS lesions. Apart from this decreased expression and abnormal phosphorylation, the fate of axonal NF in these lesions has not been clarified. They have been detected by immunocytochemistry into macrophages in the plaques [22]. Moreover NF are released in the cerebrospinal fluid (CSF), and appear as potential biological markers in MS, as their concentration is correlated with the relapse rate and the disability [23, 24].

These observations do not completely unravel the role of axon molecules in the regulation of remyelination. In order to identify the putative role of axon proteins in remyelination, we have studied their effects in OL pure cultures. We have observed that NF, as well as some other axon cytoskeleton proteins; up regulate dramatically OL growth *in vitro*. They increase the proliferation of OL progenitors, and/or the morphological differentiation and maturation of OL (characterized by the expression of myelin basic protein). They also protect significantly the cells from toxic demyelinating chemicals *in vitro*. These properties are shared by a synthetic peptide corresponding to the tubulin-binding sequence of the low molecular unit of NF (NFL) [25]. *In vitro* these molecules (NF and synthetic peptide) are up taken by OL through an endocytic

**\*Corresponding author:** Catherine Fressinaud, Neurology Department, University Hospital, 4 rue Larrey, 49933 Angers Cedex 9, France, Email : catherine.fressinaud@univ-angers.fr

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process. Thus it appears possible that, similarly *in vivo*, NF could participate in lesion restoration. NF released during MS relapses could be taken up by OL present in the vicinity, and up regulate OL growth, promoting thereby myelin repair [26-29]. We hypothesize that a first demyelinating event *in vivo* might be associated with the release of unaltered NF forms, which could increase remyelination. On the contrary altered NF, lacking proremyelinating properties, could be released after several relapses; in that case demyelination and axon damage could become irreversible. This hypothesis will have to be tested experimentally *in vivo*.

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