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Enhancing Central Nervous System Remyelination in Multiple Sclerosis

Minireview

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Recent studies on adult neural stem cells and the developmental biology of myelination have generated the expectation that neural precursors can repair the damaged central nervous system of multiple sclerosis patients where the endogenous remyelination process has failed. As a result, many laboratories are engaged in translational studies in which the goal is to design ways to promote remyelination and repair. Here we raise issues highlighted by prior experimental and human work that should be considered lest these studies become "lost in translation."

Myelination of nerve fibers is a remarkable evolutionary acquisition of vertebrates, with the confinement of voltage-dependent sodium channels to the small gap—the node of Ranvier—between myelin internodes allowing fast "saltatory" conduction of action potentials. The most common disease of myelin, multiple sclerosis (MS), is an inflammatory demyelinating disease that often starts in young adults and can over subsequent decades follow a chronic progressive course associated with major disability. While therapies designed to reduce inflammation can decrease the disease burden, they do not directly address the question of myelin repair in chronic disease. Recent advances in the stem cell field, and in particular the biology of adult neural precursor cells, have raised hopes that remyelinating therapies may soon be developed, as these cells enable the turnover or addition of differentiated cells in specific regions of the brain. The premise of this minireview is that ongoing translational studies designed to promote repair by harnessing or replacing these cells, while timely, need to consider a series of questions raised by recent work if they are to be successful in their goal of leading to novel therapies for MS.

Historically, the case for promoting remyelination rested on the improvement in conduction efficiency conferred by the switch from nonsaltatory conduction along demyelinated axons to saltatory conduction along a remyelinated axon. However, the more recent appreciation of axon loss as the major pathological correlate of progressive functional deterioration in MS has created an even more compelling case. Axons can be damaged in the acute inflammatory phase of the disease or as a result of being chronically demyelinated (Figure 1). The evidence for the crucial role of the myelin sheath in long-term axon survival comes from knockout mice lacking oligodendrocyte-specific genes. For example, mice defective in the myelin protein gene proteolipid protein have progressive axonal degeneration associated with impaired fast axonal transport, even though the axons are surrounded by loosely compacted myelin (Edgar et al., 2004). More surprising is the phenotype of mice deficient in cyclic nucleotide phosphodiesterase (CNP). This gene is expressed in oligodendrocytes. However, the phenotypic consequences are not in these cells, which form normal-looking myelin, but are instead in the underlying axons that undergo severe degeneration, accumulate amyloid precursor protein, and lead to a motor deficit at 7 months (Lappe-Siefke et al., 2003). It is clear from studies such as these that axons in myelinated tracts are dependent on molecularly "fit" oligodendrocytes to maintain their integrity. Elucidating the precise molecular mechanisms is a critical issue to be resolved and will in all likelihood involve the points of contact between the myelin sheath and the axons that occur at the paranode.

An important implication of this work is that long-term axon protection needs to be considered a primary goal of remyelination. How much remyelination is required to achieve this goal remains unknown. It is reasonable to assume that the number of internodes lost and the length of time the axon remains demyelinated will determine the vulnerability of that axon to degeneration. Therefore, efficient remyelination will reduce chronic axonal loss, a view supported by the relative sparing of axons in areas of remyelination compared to areas of demyelination (Kornek et al., 2000). A characteristic feature of endogenous remyelination is that the new myelin sheaths are invariably thinner and shorter than the original myelin sheath. The reasons for this are unclear, but the composition of the myelinated and remyelinated myelin sheath do not appear to be fundamentally different, and its smaller dimensions have only minor consequences for the conduction properties of the axon. However, it remains unknown whether a myelin sheath of reduced volume has consequences for an axon's vulnerability to degeneration. If this is so then recent intriguing data on the role of neuregulins in determining myelin sheath thickness in the PNS (Michailov et al., 2004) will have important implications for similar mechanisms in the CNS.

What Animal Models of MS Should We Use?

There are at least two ways in which animal models can be used to study regenerative processes in MS. The most immediately relevant are models that in the absence of a naturally occurring animal disease akin to MS provide a facsimile of the human disease. The most widely used is experimental allergic encephalitis (EAE), induced by immunization against a specific myelin anti-

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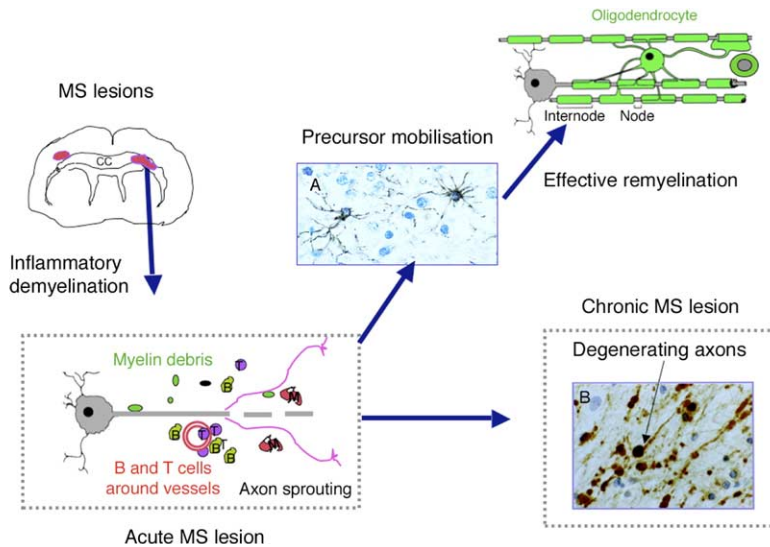

Figure 1. Some Key Steps in the Pathogenesis and Repair of Multiple Sclerosis Lesions

In the normal adult CNS, oligodendrocytes sustain multiple myelin internodes around different axons (upper right). These play a necessary role in the maintenance of the axon. In the majority of multiple sclerosis lesions, acute inflammatory demyelination (lower left) results in destruction of the myelin sheath, with demyelinated axons surrounded by myelin debris (in green), macrophages (M), and T and/or B lymphocytes. There are two possible outcomes: either demyelination persists, leading to irreversible axonal degeneration and chronic progressive disease (B), or the lesion is remyelinated by oligodendrocyte precursors that move into the demyelinated area (panel [A]), reducing or preventing axonal degeneration. A key therapeutic goal alongside suppression of the inflammatory process is therefore to remyelinate naked axons rapidly and prevent or slow the chronic progressive disability associated with the disease. This might be achieved either by transplantation of exogenous precursor cells or the recruitment into the repair process of those already present in and around many MS lesions (A). (A) An MS lesion contains oligodendrocyte precursors immunostained for the chondroitin sulfate proteoglycan NG2 (courtesy of Ansi Chang and Bruce Trapp). (B) Another MS lesion contains degenerating axons stained for amyloid precursor protein. Reprinted with permission of Hans Lassmann and the American Journal of Pathology (Kornek et al., 2000).

gen, even though there is no evidence that MS is triggered by a similar mechanism. Such "disease models" are clearly necessary as part of the final preclinical testing of proremyelination interventions. However, faced with a complex and diverse disease, an initial, more reductionist type of model is required that permits the detailed dissection of specific disease mechanisms. Such "mechanism models" are especially useful for understanding the cell and molecular biology of remyelination, as illustrated by the extensive use of models based on direct injection of lysolecithin or ethidium bromide into white matter to kill myelin-forming glia. In these models, the acute process of demyelination has a clear temporal separation from the subsequent repair process allowing the specific roles played by individual molecules in repair to be studied. By contrast, in EAE the two processes occur simultaneously in the CNS, making it difficult to separate an effect that renders the environment less hostile to remyelination, allowing it to proceed unhindered, from an effect that truly makes remyelination more effective. Diverse though these models are, they do not cover the full spectrum of pathological manifestations of MS. Within the category of mechanism models, the need for a model of oligodendrocyte apoptosis is highlighted by the recognition that this can be an important cause of pathology in some subgroups of MS (Barnett and Prineas, 2004). To some extent, this form of demyelination is mimicked by the use of the demyelinating toxins. An alternative and perhaps highly relevant inducer of oligodendrocyte death when injected in corpus callosum is recombinant syncitin, a human endogenous retrovirus HERV glycoprotein that was recently detected in MS lesions (Antony et al., 2004). Anatomically targeted oligodendrocyte death can also be induced by recombination in transgenic mice carrying a floxed Cholera toxin (fragment A) gene under the CNP promoter following stereotaxic injection of a Cre-expressing virus (Brockschnieder et al., 2004), and such newly developed genetic strategies may also prove useful in generating models of the neuronal apoptosis also seen in cortical MS lesions (Peterson et al., 2001).

There is also a critical need for new models that better bridge the gap between disease pathology and the clinical assessments used in MS. A logical choice would be optic neuritis, which is often the first clinical presentation in MS and can be associated with lesions detected by Gadolinium-enhanced magnetic resonance imaging that reflect inflammation. Anatomically localized EAE models (Kerschensteiner et al., 2004) are also potentially valuable, especially if they can be used in primates. The application of imaging techniques such as serial magnetization transfer, able to provide details on demyelination, axonal loss, and/or nerve atrophy in MS, and diffusion tensor imaging that can distinguish axon loss from myelin damage to these rodent and primate models would provide an excellent translational system for the analysis of both drug- and cell-based proremyelination therapies.

Do Cell-Based Therapies Have a Role in MS?

The transplantation of myelinogenic cells was pioneered by Bill Blakemore and Madeleine Gumpel over 20 years ago and has been followed by numerous studies that use oligodendrocyte precursor cells (OPC), Schwann cells, olfactory ensheathing cells, and neural stem cells. From this extensive work, it is clear that this approach provides an excellent experimental tool with which to study the biology of remyelination. The widespread myelination that can result in animal models has encouraged the idea that cell transplantation also provides a potential therapeutic approach to remyelination in MS (Archer et al., 1997). This idea has received added impetus from two recent studies. First, the demonstration that cells closely resembling rodent OPCs are numer-

ous in the adult human brain, can be isolated during neurosurgical procedures, and myelinate *shiverer* axons extensively after grafting (Windrem et al., 2004). Second, the remyelination of a focal demyelinated lesion achieved in the spinal cord of rhesus monkeys by grafting autologous Schwann cells (Bachelin et al., 2005). There are, however, some obvious problems with this approach. First, how will cells be delivered? Multiple injection sites (each requiring an expensive neurosurgical procedure and with a small but definite risk of intracerebral hemorrage) will be required in a multifocal disease unless transplanted cells can migrate long distances within the CNS. While the entry of neurosphere-derived neural precursors into the CNS from the bloodstream seen in mouse EAE provides a potential solution (Pluchino et al., 2005), the extent to which the cells migrate away from their entry points remains to be addressed. Second, what will be the benefit of transplanting new myelin-forming precursors into an environment where OPCs are already abundant and apparently unable to contribute to repair? It might be possible to engineer ES cell-derived OPCs (Glaser et al., 2005) to overcome putative inhibitory cues, but will such engineered cells then be safe over the subsequent years? Short-acting and self-limiting treatments, such as polysialic acid (PSA) mimetic peptides shown to promote migration (Torregrossa et al., 2004), might be a safer method of manipulating cells prior to transplantation, but the optimum strategy would then be to use these small molecules to alter the behavior of endogenous cell populations. Further concerns over safety would also be raised if neural cell grafting requires immunosuppression, as this may release the inhibition of a dormant virus. Thus, cell therapies alone seem unlikely to contribute to remyelination on the scale required in MS, although their use to induce temporary immunoregulation and exert a neuroprotective effect as observed in chronic EAE (Pluchino et al., 2005) or as a means of delivering therapeutic factors into the CNS holds considerable potential.

Promoting Endogenous Remyelination—What Are Appropriate Targets?

The broad philosophy behind the quest for proremyelination therapies is the belief that by studying the mechanisms of myelination and remyelination it will be possible to identify key factors whose activation or inhibition will lead to the process proceeding more efficiently. Remyelination requires the recruitment of precursor cells, their differentiation into myelin- forming oligodendrocytes, and the axo-glial interactions that create the sheath. This process is regulated by a complex network of factors derived from neural and immune cells and occurs in response to the unpredictable pathological process of demyelination (Figure 1). It therefore differs from the tight spatial and temporal genetic program characteristic of myelination. It would make biological sense for the degree of redundancy to be greater in remyelination than myelination, as it would provide a more secure system if several alternative pathways can achieve repair. This concept has important implications for remyelination therapies. First, remyelination failure is unlikely to be the fault of a single factor but instead arises because of disturbances in the controlled regulation of the many factors required to orchestrate remyelination—this is the “dysregulation hypothesis” of remyelination failure (Franklin, 2002). Second, while a strategy designed to activate a single redundant pathway could still have an effect on repair, inhibiting a single signaling pathway within a redundant network may be inefficient. Therefore the most effective strategies will be those that target the least redundant pathways.

In the search for these targets, much previous attention has focused on molecules on the cell surface or the extracellular environment. Developmental studies have told us a great deal about how these factors control precursor proliferation, migration, and differentiation, and in the considerably smaller number of studies on remyelination, a few individual molecules have been shown to play a role in both development and repair. So, for example, integrins regulate oligodendrocyte apoptosis during myelination and remyelination in focal lesions and, as a consequence of their wide-ranging effects on oligodendrocyte lineage cells and their ability to significantly modify the function of other signaling molecules such as growth factors, may have the nonredundant properties that make them attractive therapeutic targets (Colognato et al., 2002). Platelet-derived growth factor has also emerged as a potent regulator of OPC numbers following demyelination as well as during development and may therefore be effective therapeutically in circumstances where inadequate provision of OPCs constitute a primary reason for remyelination failure (Woodruff et al., 2004). In other cases, however, genetic approaches to the identification of candidate drug targets for precursor recruitment and/or remyelination in rodents have not supported hypotheses based on developmental studies. So, for example, targeted ablation of Notch 1, a regulator of OPC differentiation that was proposed to inhibit remyelination in MS (John et al., 2002), does not induce enhanced remyelination in experimental studies (Stidworthy et al., 2004). The role of many other candidates in remyelination remains to be explored. The demonstration that peripheral delivery of a sonic hedgehog agonist induces mitosis of precursor cells in the adult subventricular zone (SVZ) (Machold et al., 2003) and that these SVZ cells can migrate toward the white matter in EAE (Picard-Riera et al., 2002) points to a therapeutic potential. However, the great majority of clinically eloquent MS lesions (such as those in optic nerve or spinal cord) are likely to be too remote from the SVZ for this to be an effective approach throughout the CNS. PSA-NCAM, expressed on demyelinated axons within MS plaques and suggested to inhibit axonal contact (Charles et al., 2002), could also be a target for drugs designed to generate “permissive” axonal signaling for remyelination, and ongoing cDNA and protein array studies on demyelinating and remyelinating lesions will doubtless lead to the identification of other important drug targets.

In the search for nonredundant mediators of remyelination, one alternative is to explore empirical approaches for which the biological basis remains unclear, such as human monoclonal antibodies where binding to the oligodendrocyte surface enhances remyelination in a viral-induced model (Pirko et al., 2004). Another is to bypass extrinsic signaling events and target transcription factor genes critical for the develop-

mental differentiation of multipotent precursors into oligodendrocytes. An example is the Olig1 gene, whose nonredundant role in precursor cell differentiation during remyelination has been recently shown (Arnett et al., 2004). The development of small molecule agonists and antagonists of transcription factors, or their delivery into the human CNS by viral vectors or nanoparticles, therefore represents a therapeutic approach that, although very challenging, has great potential.

Conclusions

Axons can be damaged in MS during the acute inflammatory phase of the disease or as a result of being chronically demyelinated. Remyelination in MS has the capacity to reduce the latter damage and so alleviate the chronic progressive nature of the disease and as anti-inflammatory treatments become more effective in controlling the acute disease it will become a therapeutic priority. With appropriate use of different animal models, careful consideration of the practicalities and potential benefits of cell therapies, and exploration of multiple targets for drug therapies, we believe that remyelinating therapies will emerge (Figure 1). However, they remain an extremely challenging objective, and a realistic appraisal of the timescale required for their development is an important message for myelin biologists to make to the MS community.

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