From fish to man: understanding endogenous remyelination in central nervous system demyelinating diseases

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In the central nervous system (CNS) of man, evolutionary pressure has preserved some capability for remyelination while axonal regeneration is very limited. In contrast, two efficient programmes of regeneration exist in the adult fish CNS, neurite regrowth and remyelination. The rapidity of CNS remyelination is critical since it not only restores fast conduction of nerve impulses but also maintains axon integrity. If myelin repair fails, axons degenerate, leading to increased disability. In the human CNS demyelinating disease multiple sclerosis (MS), remyelination often takes place in the midst of inflammation. Here, we discuss recent studies that address the innate repair capabilities of the axon-glia unit from fish to man. We propose that expansion of this research field will help find ways to maintain or enhance spontaneous remyelination in man.

Keywords: multiple sclerosis; nodes of Ranvier; enhancing repair; animal models; transparent fish

Abbreviations: AMPA = amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF = brain-derived neurotrophic factor; BMB = 1,4-bis (p-aminostyryl)-2-methoxy benzene; CNS = central nervous system; CNTF = ciliary neurotrophic factor; CXCL = alpha chemokines; CXCLR = alpha chemokine receptor; DTI = diffusion tensor imaging; EAE = experimental autoimmune encephalitis; EB = ethidium bromide; EGF = epidermal growth factor; FGF-R = fibroblast growth factor receptor; GAG = glycosaminoglycan; IFN = interferon; LIF = leukemia inhibitory factor; LtBr = lymphotoxin beta receptor; MRI = magnetic resonance imaging; MS = multiple sclerosis; MTR = magnetisation transfer ratio; Nfasc = neurofascin; NMDA = N-methyl-D-aspartate; Nrg I = neuregulin I; OPC = oligodendrocyte precursor cells; PDGF A = platelet-derived growth factor A; PDGF-R = PDGF receptor; PET = positron emission tomography; PNS = peripheral nervous system; PSA-NCAM = polysialylated neural adhesion molecule; Sema = semaphorin; SVZ = subventricular zone; TGFbeta = transforming growth factor beta

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Introduction

Confronted with the urgency of combating the loss of function in multiple sclerosis (MS) patients, neuroscientists and neurologists have generated a wealth of new data on mechanisms of remyelination which restores rapid saltatory conduction along myelinated tracts and prevents axonal loss. These data come from gene expression analysis of MS neural tissues and experiments in a variety of animal models. Discoveries regarding the molecular basis of myelination and the biology of adult neural stem cells have also influenced views on myelin repair in the adult central nervous system (CNS) (reviewed in Dubois-Dalcq et al., 2005; Miller and Mi, 2007). Here, we present our viewpoint on these studies by apposing observations in man and human tissues to...
results obtained in experimental models. We particularly want to draw attention to the importance of restoring fast conduction in demyelinated axons by rapid remyelination in man and of developing strategies to enhance remyelination at the early stages of MS based on visualization of ongoing, recent demyelinating events by imaging.

Endogenous remyelination occurs in white and grey matter in MS and fully remyelinated areas are often referred to as ‘shadow plaques’ by neuropathologists (Patrikios et al., 2006; Albert et al., 2007; Patani et al., 2007 among others). Newly made myelin sheaths are indeed thinner than normal, have shorter internodes and variability in nodal length (Perier and Grégoire, 1965). These variations in myelin thickness and internode distance in shadow plaques might decrease the robustness of saltatory conduction along myelinated axons. Yet, in animal models, the conduction velocity increases during remyelination. For instance, grafting of embryonic glial cells into the dorsal columns of myelin-deficient rats resulted in a significant increase in conduction velocity compared to non-transplanted regions, provided a sufficient density of sodium channels is restored at the nodes of Ranvier (Utzschneider et al., 1994).

Unexpectedly, extensive remyelination has been observed not only in the early phase of MS, but also in patients with long-standing disease (Patrikios et al., 2006). An important question is whether genes modulating disease severity influence myelin repair. A case to study is HLA-G which is involved in materno-foetal tolerance and expressed in the CNS in inflammatory conditions. In women with relapsing-remitting MS, levels of expression of HLA-G in blood mononuclear cells and in serum during pregnancy and postpartum inversely correlate with disease activity (Airas et al., 2007). Discovery of genes modulating repair will expand our understanding of the physiological and molecular basis of endogenous CNS remyelination. It will likely provide clues as to how to develop strategies to enhance this spontaneous repair process that has been preserved by evolutionary pressure since the appearance of myelin in the first gnathostomes, the placoderms. This is a highly successful fish group that arose about 425 million years ago, and was a dominant organism in the ocean during the Devonian period (Zalc and Colman, 2000; Zalc, 2006; Zalc et al., 2008 in press).

An ancient neural regeneration programme, starting in fish

It is rather fascinating to browse through papers on fish CNS regeneration as they outline many of the processes occurring during axonal regeneration and remyelination in mammals. The process of axonal regeneration is also relevant to MS in view of the extensive axonal damage, including transection, which occurs in this disease. The optic nerve, a frequent site of the first clinical manifestation of MS, has been the focus of several early fish studies. Murray (1976) studied cytoskeletal and organelle changes during regeneration of goldfish retinal axons after optic nerve transection, reporting that ‘the regenerating axons gradually increase in diameter but do not reach preoperative sizes’ while ‘remyelination is delayed and proceeds slowly’. Wolburg’s study (1981) of goldfish optic nerve crush described that the regenerating axons acquired thinner myelin sheaths. The author proposed that ‘a neuron is capable of inducing a normally developed myelin sheath when its axon contacts an oligodendrocyte for the first time whereas a neuron whose axon contacts an oligodendrocyte the second time is not capable of forming a normal myelin sheath in the adult animal’. Nona et al. (2000) later found that, after optic nerve injury in fish, remyelination only occurred after the regenerating axons had reached the tectum where the axon terminals refine their map. Myelin repair was synchronous throughout the optic nerve and exacted by both Schwann cells and oligodendrocytes. Myelin protein zero, the major myelin protein in the mammalian peripheral nervous system (PNS), is present in zebrafish optic nerve and spinal cord where its expression increases during regeneration (Schweitzer et al., 2003). These fish studies therefore underline the requirement of connectivity of damaged CNS axons before axons can be remyelinated. This is in keeping with developmental studies in the mouse showing the crucial role of electrical activity along axons to induce myelination (Demerens et al., 1996; Stevens et al., 2002). It may also be important in MS where the maintenance or re-establishment of connectivity of demyelinated axons may be a prerequisite for remyelination.

In recent years, zebrafish mutant screens have identified genes essential to the development of myelinated axons (Kazakova et al., 2006; Pogoda et al., 2006). Most of these have homologues in higher vertebrates but, in some cases, new unexpected functions linked to myelination were discovered as in the case of NSF, a protein essential for vesicular fusion at synapses and ion channel clustering on axons (Woods et al., 2006). We advocate the use of fish models not only for studying neurite regeneration but also for remyelination in view of the rapid, convenient mutant analysis and the possibility to follow oligodendrocyte movement and activities in the living animal.

A see-through fish in lieu of a mouse?

The recognition of axons by migrating oligodendrocytes processes has been visualized in intact nearly transparent zebrafish larvae in which oligodendrocytes—and some axons—of the spinal cord expressed membrane-localized GFP under the control of the nks2.2 promoter (Kirby et al., 2006). A continuous process of oligodendrocyte extension and branching precedes the final positioning and wrapping of the axon by oligodendrocytes. When such oligodendrocytes were ablated by laser microsurgery, other oligodendrocytes compensated for the loss by rapidly extending new processes and migrating towards the region abandoned by the dying oligodendrocyte (Fig. 1). After all
oligodendrocytes were ablated in five hemi-segments of the spinal cord, oligodendrocyte precursor cells (OPCs) from the intact hemi-segments rapidly migrated toward the lesion site whilst dividing. The result was that 50% of oligodendrocytes had already been replaced on the lesion side at 1 day (ibidem).

Imaging such repair processes could be done in mutant medaka fish that are transparent throughout life (Wakamatsu et al., 2001). GFP-expressing transgenics of this fertile fish have been made, allowing non invasive studies of internal organs (ibidem). If nkx2.2-GFP transgenics could be obtained in medaka as in zebrafish, one could possibly succeed in performing multiple oligodendrocyte laser ablation in the spinal cord (a close equivalent to focal chemical lesions in rodent, discussed below) and imaging demyelination/remyelination in the living animal. As in demyelinated mammals, one would predict that fish-activated macrophages and lymphoid cells (Zapata et al., 2006) would be attracted to the lesion site. The transparent medaka fish stock of Nagoya University are available to interested scientists (Y. Wakamatsu, personal communication).

Whatever progress is made in fish, however, must be translated to mammals, which have an immune system that is more similar to that of humans.

Animal models of remyelination in mammals

A variety of rodent animal models has helped to elucidate some of the mechanisms involved in CNS remyelination. As there is no perfect model for MS, one particular animal model may be chosen to examine one specific aspect of MS to be investigated. These models include the induction of a focal demyelinated lesion by a toxin such as lysolecithin or ethidium bromide (Hall, 1972; Woodruff and Franklin, 1999). A cuprizone diet causes demyelination in major myelinated tracts such as the corpus callosum and cerebellar peduncles and is followed by myelin repair when the diet is stopped (Blakemore, 1973; Ludwin, 1978).

The value of viral-mediated and auto-immune demyelination lies mostly in their modelling of the immune cells in MS lesions. Some neurotropic strains of mouse corona virus induce demyelinating lesions mostly in the spinal cord followed by immune-mediated clearing of the virus, remyelination and recovery (Kristensson et al., 1986; Armstrong et al., 1990). Another viral model is the Theiler virus-induced murine encephalomyelitis whose chronic inflammation in gray and white matter mimics some aspects of MS and where natural IgM autoantibodies were shown to enhance remyelination (discussed in Arnett and Viney, 2007; Rodriguez, 2007).

Injection of a CNS-specific myelin protein such as myelin oligodendrocyte glycoprotein with adjuvants induces experimental autoimmune encephalitis (EAE) which mimics different clinical presentations of MS and its multifocal inflammatory lesions more closely. EAE has been extensively used to identify immunoregulators for preclinical trial in MS (reviewed in Gold et al., 2006) and also to assay remyelination as in a study on the role of Notch in repair (Seifert et al., 2007). Recently, cortical demyelination was induced by focal injection of pro-inflammatory cytokines in subclinically MOG-immunized rats, a model originally developed in the spinal cord (Kerschensteiner et al., 2004; Merkler et al., 2006). After cortical inflammation subsided, rapid remyelination occurred, mimicking extensive remyelination observed in MS cortical lesions (Albert et al., 2007). Mice deficient in neural and immune system genes have been used extensively in these models to study their impact on remyelination.
To understand how remyelination is initiated, a series of studies have characterized the precursors of remyelinating cells in rodent and man.

**Origin of remyelinating cells in the adult mammalian CNS**

The first event in myelin repair is the recruitment of OPCs to the demyelinated lesions (reviewed by Chandran *et al.*, 2008). In rodents, there are at least two known sources of remyelinating oligodendrocytes in the adult mammalian CNS: the first is the large pool of OPCs expressing the proteoglycan NG2 and/or PDGF-receptor alpha, the second comes from precursors in the adult subventricular zone (SVZ) (Menn *et al.*, 2006; reviewed in Zhao *et al.*, 2008). Both rodent and MS white matter OPCs express Olig 2, Nkx2.2 and Myt1 transcription factors when recruited to demyelinating lesions (Sim *et al.*, 2002; Fancy *et al.*, 2004; Nait-Oumesmar *et al.*, 2007; Vana *et al.*, 2007b). In mouse SVZ, some OPC markers such as NG2 and olig 2 are sometimes expressed in type C precursors which are derived from GFAP-expressing neural stem cells (Doetsch *et al.*, 2002; Aguirre *et al.*, 2004). The finding of OPC markers in some SVZ precursors may be due to the rapid commitment to an oligodendrocyte fate when precursors move out of the SVZ or a pre-commitment of these precursors to this fate within the SVZ (Delaunay *et al.*, 2008) as described also in the case of neurons (Kohwi *et al.*, 2007).

Of important relevance to CNS remyelination in man, OPCs have been isolated from normal appearing white matter obtained in the course of surgery for epilepsy and found to be multipotential *in vitro* (Nunes *et al.*, 2003). When grafted into dysmyelinating shiverer mice—which lack myelin basic protein—these human OPCs extensively migrate and remyelinate the mouse white matter (Windrem *et al.*, 2004). As remyelination occurs in MS, it is presumed that OPCs recruited from normal appearing white matter to lesions have similar remyelinating properties. The transcriptional profile of freshly sorted human OPCs was compared to that of the white matter from which they were isolated. The results indicate that adult human OPCs are responsive to local factors triggering distinct signaling pathways either regulating their self maintenance or inducing their differentiation (Sim *et al.*, 2006).

Another source of remyelinating cells in the CNS is Schwann cells. In some MS cases, Schwann cells were found in the spinal cord and hindbrain where they synthesize PNS myelin around demyelinated CNS axons (reviewed in Compston *et al.*, 2006). Importantly, the Schwann cells that migrate and remyelinate CNS lesions after experimental demyelination of rat dorsal columns by ethidium bromide (EB) restore fast conduction ‘within normal limits’ (Felts and Smith, 1992). Moreover, a normal pattern of sodium and potassium channels at the nodes of Ranvier was maintained 1 year after a similar EB lesion was made (Black *et al.*, 2006). Normal conduction velocity was also restored after grafting labelled cultured Schwann cells into EB-treated, glial free dorsal columns (Honmou *et al.*, 1996). These observations strongly suggest that PNS myelin made by remyelinating Schwann cells may restore conduction of CNS axons also in MS. Thus Schwann cell migration into the CNS is a remarkable natural repair mechanism. However, we do not know how extensive this is and what attract these repair cells to the CNS. Could it be the same factors that attract OPCs?

**Regulators of OPCs mitosis/migration may help remyelination**

Epidermal growth factor (EGF) and platelet-derived growth factor A (PDGFA) stimulate OPCs to divide and migrate during CNS development (reviewed in Rogister *et al.*, 1999). Experiments in transgenic mice have also revealed a role for these factors in remyelination. Indeed, mouse OPCs overexpressing human EGF-R showed increased mitotic and migratory activity toward a corpus callosum lesion and this resulted in acceleration of remyelination and functional recovery (Aguirre *et al.*, 2007). Transgenic mice overexpressing the human PDGF A gene and submitted to a cuprizone diet that caused chronic demyelination, showed enhanced remyelination and oligodendrocyte numbers after removal of the diet (Vana *et al.*, 2007a). The migration response of OPCs to PDGF is enhanced *in vitro* by the polysialylated form of the neural adhesion molecule (PSA-NCAM) (Zhang *et al.*, 2004). In response to a demyelinating event in the corpus callosum, some SVZ precursors expressing PDGFR alpha and PSA-NCAM divide, migrate away from the SVZ and generate OPCs in the lesion (Menn *et al.*, 2006). Accordingly, the SVZ of MS patients shows a significant increase in PSA-NCAM expressing precursors which also appear to migrate toward lesions (Nait-Oumesmar *et al.*, 2007). Interestingly, both OPCs and Schwann cells engineered to overexpress PSA on N-CAM show enhanced migratory properties in the rodent CNS (Lavdas *et al.*, 2006; Glaser *et al.*, 2007).

Semaphorins, a class of molecules providing guidance cues for developing neurons, have been shown to also regulate developing OPC migration. Semaphorins 3A and F are repulsive or attractive, respectively for embryonic OPCs (Spassky *et al.*, 2002). In MS, Sema3A and Sema3F expression is elevated in glial cells in and around active lesions and also in neurons whose axons have been demyelinated. There is a differential expression pattern, so that more Sema3F (attractive) expression is seen around and within those plaques which are very active with a dense inflammatory infiltrate, compared to more Sema3A (repulsive) expression around and within less active plaques (Williams *et al.*, 2007). These results suggest that repulsive or attractive properties of different semaphorins can influence OPC migration, a prerequisite for MS plaque remyelination. In addition, these observations are in good
agreement with several reports on the pro-remyelinating influence of inflammation.

**A link between inflammation and remyelination**

There have been several recent studies on MS tissues that argue convincingly for a link between components of the inflammatory milieu in and around the lesions and myelin repair, a concept that has been reinforced by animal studies of remyelination, including gain or loss of function experiments (discussed in Zhao *et al.*, 2005).

Nervous tissue inflammation generally implies the presence of T and/or B cells with macrophages/microglia showing signs of activation, leading to the local release of immune mediators. Abundance of T cells and activated macrophages/microglia are frequently observed in areas of active remyelination. Foamy macrophages and CD3 and CD8-positive T cells are often present in early MS lesions that at the same time show striking signs of remyelination (Fig. 2). Further evidence for a link between inflammation and remyelination comes from the presence of HLA-DR positive microglial cells close to areas of remyelination in MS shadow plaques (Patani *et al.*, 2007). Accordingly, loss of function experiments have shown that MHC type II antigens are necessary for efficient remyelination in mice (Arnett *et al.*, 2003).

The cause–effect relationship between myelin repair and macrophage activation/tissue invasion in MS was confirmed by experiments in rodent focal demyelination models showing that macrophage depletion impairs remyelination (Kotter *et al.*, 2005; reviewed in Zhao *et al.*, 2005). The clearing of myelin debris by macrophages may contribute to create an environment favourable to OPC recruitment for repair (ibidem). Moreover, induction of acute inflammation in chronically demyelinated tissue triggers remyelination in spinal cord (Foote and Blakemore, 2005) and acute inflammation also enhances myelination of retinal axons by OPCs grafted in the eye (Setzu *et al.*, 2006).

Could antibodies detected in lesions also have a role in myelin repair? The evidence that accumulation of B cells in submeningeal follicles is associated with extensive demyelination in some MS patients argues against this possibility (Magliozzi *et al.*, 2007). Unfortunately, the natural auto-antibodies that enhance remyelination in the mouse Theiler virus model (Rodriguez, 2007) have not been detected in MS tissues or correlated with remyelination in the human disease.

Many chemokines, which are potent mediators of immune cell migration, are released by lymphocytes and macrophages in MS tissues. Three alpha chemokine receptors CXCR1, CXCR2, CXCR3, expressed by OPCs and oligodendrocytes in the normal adult CNS, showed enhanced expression in MS but also in other CNS diseases. Yet, their respective ligands, chemokines CXCL8, 1 and 10, were specifically detected in reactive astrocytes at the edge of active MS lesions (Omari *et al.*, 2005). It was proposed that CXCL1 could stop OPC migration as it does during development (reviewed by Miller and Mi, 2007). CXCL12, which is essential to immune and nervous system development (Lazarini *et al.*, 2003), was detected in astrocytes around MS lesions as well as in the CSF of relapsing-remitting MS patients (Calderon *et al.*, 2006; Krumbholz *et al.*, 2006).
During mouse embryonic development, CXCL12 is an attractant for rodent neural precursors and OPCs expressing its CXCR4 receptor (Dziembowska et al., 2005). As CXCR4 is downregulated on mature oligodendrocytes and has not been described on adult rodent and human OPCs, the role of CXCL12 in MS lesions is presently unclear.

Two haemopoietic cytokines are released in MS inflammatory lesions. Leukemia inhibitory factor (LIF) is produced by myelin reactive T cells infiltrating demyelinating lesions (Vanderlocht et al., 2006). Interleukin 11 is expressed by astrocytes at lesion edges while its receptor is detected on nearby oligodendrocytes (Zhang et al., 2006). Both cytokines promote oligodendrocyte survival and myelination in vitro and LIF promotes remyelination in EAE (Butzkueven et al., 2002, 2006; Stankoff et al., 2002; Zhang et al., 2006). LIF has therefore emerged as a potential therapy to enhance remyelination.

Collectively, these human and experimental studies strengthen the proposal that some immune mediators, either membrane bound or secreted by T cells and macrophages, may positively influence endogenous remyelination in MS. Yet other components of the inflammatory cascade such as nitric oxide production and free radicals can damage axons, underlining the importance of protecting demyelinated axons from degeneration.

Neuroprotection: the first line of defence before remyelination

Even if remyelination is the best way to provide axon protection, this process takes place during which recently demyelinated axons risk exposure to nitric oxide, oxidative stress, glutamate-induced excitotoxicity as well as calcium influx and alterations of mitochondrial function (reviewed in Smith, 2006; Greenberg and Calabresi, 2008). Therefore, it would be beneficial to ‘protect’ axons at this time to enhance their survival, maintain axon connectivity and facilitate re-emergence of myelinating signals whilst OPCs are being recruited to the lesion site (reviewed in Scolding and Dubois-Dalcq, 2008). Some neurotrophic factors released either by immune cells or neurons may act locally to protect demyelinated axons in MS lesions. First, the synthesis of ciliary neurotrophic factor (CNTF) or brain-derived neurotrophic factor (BDNF) by immune cells is increased in MS patients treated with glatiramer acetate (a synthetic peptide mimicking MBP structure and inhibiting T cell peptide binding) or interferon (IFN) beta1a, the two major immunomodulators used to treat relapsing-remitting MS (Sarchielli et al., 2007). Thus these treatments are also potentially neuroprotective. Second, cortical neurons in MS showed increased expression of CNTF, its tripartite receptor complex composed of CNTR alpha, LIFR beta and gp130, and their phosphorylated downstream products (Dutta et al., 2007).

Towards discovery of specific mechanisms of remyelination

During demyelination in MS, it is thought that normal saltatory conduction is rapidly disturbed due to the loss of clustering of axonal sodium channels at the nodes of Ranvier (reviewed in Waxman, 2006). Yet, as observed in the visual system, partial restoration of current can occur in a continuous manner due to the presence of Nav1.2 channels along otherwise undamaged demyelinated axons. The paranode and juxtaparanode which surround the node are structures particularly vulnerable during demyelination (reviewed in Zawadzka and Franklin, 2007). The paranode, containing paranodin (Caspr) and the glial form of neurofascin (Nfasc155), is indeed dismantled in MS lesions, allowing Kv1.2 channels to diffuse to the node (Howell et al., 2006). This results in a diffuse distribution of Nav1.2 channels, paranodin and Kv1.2 channels on intact demyelinated fibres (Coman et al., 2006; Howell et al., 2006).

To begin understanding the process of remyelination, it seems appropriate to consider what has been learned from developmental myelination in rodents. A mouse postnatal transcriptome performed on oligodendrocytes and their precursors acutely isolated during the first postnatal month has revealed two waves of gene expression patterns during CNS myelination (Cahoy et al., 2008). The first wave of myelin gene up-regulation, concomitant with down-regulation of cytoskeleton maintenance-related genes, leads to ensheathment of nerve fibres. The second wave of up-regulation of intercellular junction genes may be linked to the assembly of the nodes of Ranvier.

How Ranvier nodes and paranodes form during rodent CNS development is not fully understood but apparently requires two steps (Kaplan et al., 2001; Dupree et al., 2005; Schafer et al., 2006). A complete, functional nodal region depends on each myelin loop maintaining a septate-like junction with the axon, while Kv1.2 channels are kept at bay in the juxtaparanode. A first event in node formation is the induction of axonal Nav1.2 channel clusters, possibly by an
as yet uncharacterized soluble factor made by oligodendrocytes (Kaplan et al., 1997, 2001). This process defines domains where oligodendrocytes position themselves along the axon to synthesize myelin internodes. Myelin excludes axonal Nav1.2 channels along the internode and promotes clustering of newly emerging Nav1.6 channels at the node while specific axon–glia interactions result in paranode/juxtanode formation. In the case of axon branching, collaterals dictate the position of the nodes of Ranvier. Since collaterals are branching before OPCs migrate towards axons, the position of branching points determines where the nodes of Ranvier will assemble. Thus, the putative oligodendroglial clustering factor can only regulate the distribution of nodes between two collaterals, therefore controlling the number (n) and the length (L) of the internode. The latter is calculated by the simple equation: \( L = Dc/n \), where \( Dc \) is the distance between two branch points (Lubetzki and Zalc, 2001).

Our knowledge of internodal axonal signals is also derived from developmental myelination studies in rodents. The adhesion molecule L1 positively regulates CNS and PNS myelination whereas Neuregulin 1 (Nrg1) type III is a major regulator of PNS myelination (Barbin et al., 2004; Coman et al., 2005; Nave and Salzer, 2006). Although Nrg1 is also expressed on CNS axons, its role in CNS myelination is not clear. Induction of Fyn kinase in OPCs by axons triggers oligodendrocyte process extension which is an essential event preceding myelin wrapping (Klein et al., 2002). Nrg1 and Laminin 2 on axons may strengthen axon recognition by OPC processes bearing their respective ErbB and alpha 6 beta1 integrin receptors. Laminin2 has a second receptor on OPCs called dystroglycan which regulates myelin membrane synthesis and the terminal stages of myelination (Colognato et al., 2007).

During the period preceding myelination in juvenile rats, unmyelinated axons of the corpus callosum release glutamate by exocytosis in response to electrical stimulation and groups of vesicles are detected at the axon contact sites with OPC processes (Kukley et al., 2007). Also, in optic nerve, small clusters of axonal vesicles are seen at ‘arbitrary’ sites of contact with OPCs, suggesting that axonal glutamate release mediates the recorded axo-glial currents at a premyelinating stage (ibidem). The concept emerging from these studies is that glutamate release by axons helps OPCs to find axons through an activity-dependent process, reinforcing the importance of electrical activity in OPC development and myelination (Barres and Raff, 1993; Demerens et al., 1996; Stevens et al., 2002; Karadottir and Attwell, 2007). Another important mediator liberated by firing axons is ATP which induces astrocytes to synthesize LIF. LIF in turn promotes myelination by cultured oligodendrocytes (Ishibashi et al., 2006).

Returning to the subject of remyelination in man, it appears that the first requirement is to reset the nodes by re-assembly of specific molecular complexes with adhesion molecules (Sasaki et al., 2006). The scenario for remyelination in MS is proposed as starting with the formation of several nodal-like clusters of Nav channels, often in partially remyelinated lesions as visualized on fibres that are still PLP-negative (Coman et al., 2006). In the rodent PNS, Nav channel clustering is promoted by gliomedin at the tips of Schwann cells and its cleavage product released in the node area (Eshed et al., 2007; Maertens et al., 2007). Gliomedin has been detected in the CNS but it is not yet fully characterized (Manuel Koch, personal communication). As CNS myelin synthesis progresses, Nav1.6 clusters are emerging and associate with the neuronal form of neurofascin (NFasc186), a signature of node restoration (Howell et al., 2006). Consolidation of node organisation may occur at the time when persisting currents with glutamate release sites along demyelinated axons may guide the correct positioning of adult OPCs processes before they enwrap axons to make myelin internodes. Intriguingly, this proposed sequence of repair events in MS is the reverse of the one predicted from the developmental waves of mouse oligodendrocyte gene expression discussed above where myelin internode synthesis starts first (Cahoy et al., 2008). If the nodes of Ranvier are reconfigured when internode synthesis is not yet occurring or is far from completion, could it result in node/internode abnormalities?

**Why is repaired and developmental myelin different?**

Is it true that a neuron whose axon is contacted for the second time by an oligodendrocyte is not able to trigger normal myelin sheath synthesis (Wolburg, 1981)? As mentioned above, a thin myelin sheath and increased nodal length are often observed during remyelination in vertebrates. Yet the association of remyelinating cells with naked axons in rodents closely resembles that in normal myelin (reviewed in Franklin and Hinks, 1999). These characteristics are observed whether remyelinating cells are endogenous or exogenenous and also in remyelination by Schwann cells. There is no substantial increase in axon diameter during remyelination whereas during development, as the animal grows and matures, the axons increase in length and diameter leading to an increase of myelin internode length and thickness. This suggests that axons may bear or release molecules that increase in density or production proportional to growth to control these parameters.

In developing peripheral nerves, myelin thickness is regulated by Nrg1 Type III isoform with the number of myelin wraps proportional to gene dosage (Michaelov et al., 2004). Despite recent data, a role for Nrg1 in CNS myelination is questionable (Taveggia et al., 2008). However, it is quite possible that another axonal surface molecule, yet to be discovered, control CNS myelin thickness. A decrease in concentration of this putative
axonal molecule in the adult would result in a thinner myelin sheath during remyelination.

Loss of function studies in mutant mice have revealed several other candidate molecules for the control of CNS myelin thickness such as the transmembrane aspartyl protease Bace (Hu et al., 2006). Deletion of the chemokine receptor CXCR2 in oligodendrocytes also results in thinner myelin (Padovani-Claudio et al., 2006) suggesting the possibility that CXCL1 (released by axons?) may enhance oligodendrocyte wrapping by signalling through the CXCR2 receptor on OPCs. In the case of the axonal adhesion protein Tag1, Tag1 defective adult mice show thinner myelin sheaths as well as increased numbers of nodes of Ranvier compared to controls (E. Chadzopollou and J.L. Thomas, personal communication).

A zebrafish mutant lacking alpha II spectrin shows abnormally long nodes (Voas et al., 2007). In wild type zebrafish, alpha II spectrin is normally enriched in nodes and paranodes during development and is essential to stabilize sodium channel clusters and the maturation of the nodes of Ranvier. This channel clustering is controlled by neurons, as wild-type neurons can rescue the mutant. It is presently unclear whether channel clustering at the nodes is also controlled by neurons in mammals and whether neuronal expression of alpha II spectrin is increased at nodes during repair in MS.

The presence of thinner and shorter myelin internodes does not appear to have a strong impact on physiological impulse conduction (Utzschneider et al., 1994; Honmou et al., 1996 among others). However, it is unclear whether this makes myelin more vulnerable to future injury (Smith, 2006). Funk and Faber (1984), who measured myelin sheath resistance, commented that ‘altering myelin thickness will be expected to have only minimal effects on the axon currents flowing in the axon’, whereas ‘minor changes in the paranodal junctions may have major consequences’. In that context, nature may have provided the best way to start remyelination by first securing the reconstruction of the nodes/paranodes. This brings us to the next question on how to enhance the endogenous remyelination program.

Remyelination enhancement strategies
Finding new targets
Transcriptome studies are powerful tools to unravel which neural and immune genes are differentially expressed in the course of human myelin repair. These studies are now considerably facilitated by the expansion of MS tissue banks where tissue integrity is optimized, providing access to a range of demyelinated lesions starting to be remyelinated and where remyelination is completed (shadow plaques). Such human studies may be guided by technologies already successfully applied to developmental myelination. A comparative transcriptome analysis from fish to man would consolidate the list of essential, conserved genes involved in signalling myelin repair and help the design of small compounds acting on their signalling pathways. As Olig 1 is a transcription factor essential for rodent remyelination (Arnett et al., 2004), ongoing gene profiling studies comparing remyelination in Olig1 deficient mice to wild-type mice is likely to yield interesting data on key regulators of remyelination downstream from Olig1 (S. Fancy, R. Franklin, and D. Rowitch, personal communication).

It would be a milestone if transcriptome data would reveal candidate neural or immune molecules or signalling pathways that could both decrease immune-mediated demyelination and enhance remyelination. For instance, TGF beta 2 is a potent inhibitor of inflammation but can also promote oligodendrocyte differentiation (Mc Kinnon et al., 1993), which may be useful when OPCs have arrived in demyelinating plaques. Unfortunately, TGF beta 2 is also nephrotoxic, but if this toxicity could be suppressed, it may down-regulate the immune response and reduce relapses in MS (discussed by Arnett and Viney, 2007). However, TGFbeta 2 may also down-regulate the promyelinating components of inflammation. This hypothetical double-edged sword highlights the importance of transcriptome/proteome studies to identify the exact pathways that favour myelin repair.

Testing pro-remyelinating therapies
To test potential pro-remyelinating therapies, we need suitable and appropriate animal models, and imaging correlates differentiating demyelination and remyelination. In spite of the fact that only a small proportion of biologics active in mouse EAE have reached the bed side, those that modulate successfully T-cell activation and their traffic to the brain were first identified in EAE models and proved beneficial to relapsing-remitting MS patients (Arnett and Viney, 2007). This is the case of Nataluzimab, an antibody to alpha 4 integrin, which decreases the number of relapses in relapsing-remitting MS. The anti-CD20 B-cell antibody rituximab, now in phase II clinical trials, has a rapid effect on acute disease activity and also reduces the number of clinical relapses. This antibody effect may result from an inhibition of B-cell antigen presentation to T cells as well as the re-emergence of naive B cells, leading to a reduction in the number of pathological antibodies (Mc Farland, 2008). The possibility that both of these treatments also promote or facilitate remyelination will have to be explored.

In considering translational aspects of pro-remyelinating strategies, a ‘sensible use’ of animal models is a key factor (Arnett and Viney, 2007). Using animal models of progressive complexity would seem appropriate. For candidate drugs for myelin repair, first compounds could be rapidly screened in a demyelination/remyelination fish model. Then rodent chemical demyelination models would be used. Finally, one could use focal EAE models in rodents for testing the selected candidate molecules.
Inhibitors and promoters of remyelination as targets

Promoters of remyelination and antagonists of myelination inhibitors are extremely interesting as therapeutic targets for MS. During developmental myelination, positive and negative regulators control the timing of myelination (Miller and Mi, 2007). In the adult-diseased CNS, some inhibitory immune mediators may contribute to the demise of oligodendrocytes.

Among developmental regulators of myelination, at least three may inhibit myelin repair. One is PSA-NCAM which is re-expressed on demyelinated axons in MS while axons in remyelinated plaques do not express PSA (Charles et al., 2002), which is consistent with the known down-regulation of axonal PSA preceding myelination. PSA re-emergence could also be related to axonal regrowth. In contrast to axonal PSA, PSA on glial precursors promotes rather than inhibits remyelination by stimulating differentiation (Zhang et al., 2004; Glasper et al., 2007). Therefore, inhibiting PSA-NCAM expression could be a double-edged sword.

FGF2 is a strong mitogen for postnatal rodent OPCs. This proliferative effect is later over-ridden by positive regulators of oligodendrocyte differentiation and by FGF receptor switching (reviewed by Register et al., 1999; Fortin et al., 2005). Furthermore siRNA to FGFR1, but not FGFR2 or 3, releases this FGF2-induced block of oligodendrocyte differentiation (Zhou et al., 2006). In adult mouse CNS demyelinated by corona virus infection or exposed for a long time to cuprizone, FGF2 increases in the lesions, leading to chronic demyelination whereas FGF2-deficient mouse OPCs repopulate the lesions and remyelinate completely (Armstrong et al., 2002, 2006). These results show that deletion of FGF creates a permissive environment for endogenous remyelination. Studies of FGF2 expression and its possible correlation with lack of remyelination of demyelinated lesions in MS are awaited.

Lingo-1 is a protein interacting with the Nogo-receptor complex (Nogo is one of the three or four major components of myelin that inhibit neurite regeneration (reviewed in Schwab et al., 2006)). Lingo-1 is made by oligodendrocytes and neurons, and inhibits oligodendrocyte differentiation and myelination (Mi et al., 2005; Lee et al., 2007). This inhibition is reversed by treatment with human soluble Lingo-1-Fc which increases Fyn kinase phosphorylation and myelination. When Lingo-1 antibody was delivered intrathecellarly by osmotic pump in rats with EAE, it enhanced remyelination and axonal integrity in the spinal cord (Mi et al., 2007). If Lingo-1 expression was found to be increased in MS demyelinating lesions, a Lingo-1 antagonist would be a candidate to promote endogenous remyelination (Miller and Mi, 2007).

Among immune mediators, IFN gamma has long been identified as an inhibitor of recovery/repair. It is present in active MS lesions and, when administered to MS patients, it aggravated clinical signs and this was attributed to an increase in immune activation (Panitch et al., 1987). In hindsight, this detrimental effect may have also been due partly to oligodendrocyte death and/or stress as both occur in mice overexpressing this cytokine. Such effects can be attenuated by Stat pathway inhibitors such as the ‘suppressor of cytokine signalling’ (Balabanov et al., 2006). The effect of IFN gamma at the lesion site—at concentrations close to those observed in vivo—was examined in mice by inducing cytokine release during recovery from EAE or cuprizone treatment (Lin et al., 2006). In both models, the induction of IFN gamma synthesis strongly inhibited lesion repopulation by OPCs, remyelination and clinical recovery (in the case of EAE). This was correlated with endoplasmic reticulum stress in remyelinating oligodendrocytes, suggesting that inhibitors of such stress responses may help repair in MS.

Lymphotoxin (Lt) beta receptor (LtBr) expressed on microglia in MS could be activated by its ligand Lt alpha/ beta made by astrocytes. Such activation might be detrimental and is also observed during demyelination in the cuprizone model. After stopping the cuprizone diet, repeated intraperitoneal injection of a fusion decoy, LtBr-Ig, dramatically enhanced spontaneous remyelination (Plant et al., 2007). Therefore, LtBr-Ig may be another candidate antagonist to enhance myelin repair.

Chondroitin sulfate proteoglycans such as NG2 and proteoglycans with glycosaminoglycan (GAG) chains can often accumulate in lesions and be inhibitory to repair (reviewed in Sherman and Back, 2008). OPC proliferation is inhibited by NG2 whose protein backbone can be degraded by metalloproteases MMP-9 which in turn facilitates remyelination (Larsen et al., 2003). The GAG hyaluronan is synthesized at the inner surface of cell membranes and composed of repeating units of glucuronic acid and N-acetyl glycosamine. It is made by reactive astrocytes, inhibits oligodendrocyte differentiation in vitro and accumulates in chronic lesions in MS and EAE (Back et al., 2005). These effects can be reversed by hyaluronidase, providing another avenue to enhance repair.

Among pro-myelinating molecules, the strongest candidate may be LIF which, as mentioned before, enhances oligodendrocyte survival and myelin repair in different experimental models while it also decreases demyelination (Marriott et al., 2008). In addition, OPC promigratory factors such as PDGF, EGF and Semaphorin 3F, discussed above, are promising, also in view of the possible use of synthetic peptides stimulating their downstream signalling pathway. Experimental models should be used to determine whether a local vector delivery or placement of a delivery pump nearby a large demyelinated lesion is a feasible and safe approach. Ongoing studies are also exploring the possible effects on neuroprotection and remyelination of progesterone and thyroid hormone (Schumacher et al., 2007; M. Schumacher and S. Ghandour, personal communication).
In the long term, it should become possible to combine neuroprotective and remyelination strategies with the most efficient immunomodulators tailored to each type of MS presentation. Most importantly, appraisal of any clinical trial in this field will rely on the ability to detect the status of the demyelinating lesions by imaging.

**Imaging remyelination**

Before embarking on any clinical trial to promote endogenous remyelination, the functional benefits of remyelination need to be solidly established in primates (including man) and good imaging correlates of remyelination should be available. There are many as yet unanswered questions. How many axons need to be remyelinated to restore function in a particular fibre tract and how tightly is remyelination correlated with clinical recovery? Thus an essential milestone before testing pro-remyelinating therapies in man is to image newly demyelinated axons and endogenous remyelination in vivo while measuring its effect on functional recovery.

The most frequently used imaging technology in this regard is currently MRI. Conventional T1 hypointense lesions likely indicate irreversible demyelination and axonal loss while T2 hyperintense lesions may reflect inflammation or persisting damage (reviewed in Neema et al., 2007). However both measures lack specificity to assess myelin loss and repair. The use of newer technologies such as magnetisation transfer imaging, myelin water imaging, diffusion tensor imaging, and high field MRI strongly enhance the specificity of myelinated white matter imaging (Zivadinov, 2007).

Magnetisation transfer imaging is based on the interaction and exchange of unbound protons in free water with protons bound to macromolecules such as those present in myelin. A decrease of exchange of these protons occurring in injured CNS structures can result in a decreased magnetisation transfer ratio (MTR). A reduced MTR likely reflects loss of myelin whereas an MTR increase may indicate remyelination (Doloire-Grassin et al., 2000; Barkhof et al., 2003; Chen et al., 2005). Importantly, the persistent loss of MTR in lesions is linked with disability and disease modifying treatments may cause an increase in MTR measures (Neema et al., 2007). Moreover, in optic neuritis, MTR correlates with function as assayed by visual evoked potential latency and optical coherence tomography, a measure of retinal neuroaxonal loss (Tripp et al., 2007). The measure of myelin water fraction, which probably corresponds to water trapped within the myelin bilayer, has been shown to correlate with MTR measures on MRI of MS lesions and to luxol fast blue staining of myelin on histopathology (Tozer et al., 2005; Laule et al., 2006).

Diffusion tensor imaging (DTI), a measure of diffusion of water molecules and anisotropy, has provided details of tissue microstructure and has allowed fibre tractography which reveals brain anatomy in the living (Le Bihan et al., 2001; reviewed by Nucifora et al., 2007). Studies of animal models indicate that a decrease in water axial diffusivity is associated with axonal degeneration, whereas increased radial diffusivity reflects demyelination in corpus callosum (Song et al., 2002, 2005). Accordingly radial diffusivity decreases during remyelination, indicating the importance of applications of DTI to measure repair in man. A DTI-fibre tracking study using 7 Tesla field MRI on marmosets has accurately traced damage in the cortico-spinal tract after spinal cord hemisection (Fujiyoshi et al., 2007). Experiments are ongoing to improve this technology in order to visualize regenerating fibres, information also of relevance to MS.

Seven Tesla high-field MRI can be combined with a multi-channel detector of increased sensitivity to reveal the heterogeneity of white matter intensity (Li et al., 2006) as well as its relation to vasculature (Bagnato et al., 2005). This method produced T2-weighted images with increased spatial resolution, revealing differences between fibre tracts and details of the brain cortical substructure (Duyn et al., 2007). Such structural aspects revealed by high-field MRI are presently being analysed in MS patients, and this should allow characterization of myelin changes during different phases of the disease (Bagnato et al., 2007).

In addition to these major advances in MRI techniques, it would be useful to develop a molecular imaging technique specific for myelin that would quantify CNS remyelination and further validate the MRI approaches. This could be achieved using positron emission tomography (PET). Of great interest is the recent identification of a newly synthesized fluorescent Congo red derivative, 1,4-bis-(p-aminostyril)-2-methoxy benzene, also named BMB, that selectively binds to myelin ex vivo and in vivo (Fig. 3A; Stankoff et al., 2006). This compound allowed the detection of dysmyelination in myelin mutants and of demyelinated lesions in EAE. In MS brain samples, levels of BMB staining can differentiate remyelination in shadow plaques from either demyelinated lesions or normal appearing white matter (Fig. 3B), suggesting that this biomarker could be used to quantify myelin loss and repair. BMB was shown to cross the blood brain barrier and, when radiolabelled with carbon-11, imaging of CNS myelin was obtained by PET in non-human primates (Fig. 3C). Interestingly, a similar affinity for CNS myelin was reported for several other Congo red derivatives (Xiang et al., 2005; Wu et al., 2006). As Congo red derivatives were previously known to be amyloid markers, these findings suggest the existence of a molecular target common to amyloid plaques and CNS myelin. In favour of this proposal is the observation that other amyloid markers, related to thioflavinT, could also stain myelin and be used as a PET radiotracer for myelin (Stankoff et al., unpublished data).

**Conclusion**

Where do we go from here? Ideally, the best way to promote remyelination and therefore protect demyelinated...
axons is to promote efficient endogenous remyelination by native cells rather than surgically introducing exogenous cells. As the advantages and risks of transplantation approaches in MS have been reviewed elsewhere (Lubetzki et al., 2005; Zuovic et al., 2007; Chandran et al., 2008; Scolding and Dubois-Dalcq, in press), we have chosen here to discuss spontaneous remyelination in the CNS because expansion of this field of research might bring promyelinating therapies to the bedside. To do this, we must continue to learn more about the normal repair process in all animal models, including fish. We also must be able to consistently visualise remyelination in living mammals and correlate this to functional recovery, otherwise in vivo testing of putative remyelination enhancers will be slow and uncertain. Concomitantly, the postulated impact of remyelination on the clinical course of MS should become measurable with increasingly myelin-specific imaging technologies.

We may be able to learn from research into spinal cord injury, where there is great interplay between damaged axons and myelin-forming cells and where stimulation of remyelination plays an important role in functional recovery (Pearse et al., 2007). Promoters of neurite outgrowth may also be important in MS as transected and damaged axons cannot be effectively remyelinated. The characterization of the NOGO receptor complex, its interaction with myelin inhibitors (reviewed by Schwab et al., 2006) and the demonstration that intracellular cAMP and its downstream targets may promote axonal regeneration (reviewed by Hannila and Filbin, 2008), have led to new clinical approaches in attempting to treat spinal cord injury (Rossignol et al., 2007). If patients with spinal cord injury show motor improvement in clinical trials, it might also be of benefit in some MS patients with acute axonal damage.

Bearing in mind that remyelination was only described in the CNS in 1961 (Bunge et al., 1961) and in MS in 1965 (Perier and Gregoire, 1965), we have made great progress, but effective clinical promotion of remyelination is still not quite within our reach. However, as discussed here and before (Lubetzki et al., 2005), there are a number of promising avenues being explored that might reach the bedside in the next few years provided that research in basic and clinical science keeps its momentum.

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