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Invited Review

Growth factors and remyelination in the CNS

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Summary. It is now well established that there is an inherent capacity within the central nervous system (CNS) to remyelinate areas of white matter that have undergone demyelination. However this repair process is not universally consistent or sustained, and persistent demyelination occurs in a number of situations, most notably in the chronic multiple sclerosis (MS) plaque. Thus there is a need to investigate ways in which myelin deficits within the CNS may be restored. One approach to this problem is to investigate ways in which the inherent remyelinating capacity of the CNS may be stimulated to remyelinate areas of long-term demyelination. The expression of growth factors, which are known to be involved in developmental myelinogenesis, in areas of demyelination strongly suggests that they are involved in spontaneous remyelination. Therefore delivery of exogenous growth factors into areas of persistent demyelination is a potential therapeutic strategy for stimulating remyelination. This review will discuss the evidence that growth factors may have a role in promoting CNS remyelination by enhancing the survival and stimulating the proliferation and recruitment of remyelinating oligodendrocytes.

Key words: Remyelination, Oligodendrocyte, Oligodendrocyte Progenitor, Growth Factors, CNS

Introduction

Most central nervous system (CNS) axons are enwrapped by myelin sheaths, which are synthesised and maintained by oligodendrocytes. Loss of myelin sheaths, or demyelination, results in impaired impulse conduction and neurological dysfunction (reviewed by Smith, 1994). There is, however, an inherent capacity within the CNS to remyelinate denuded axons. This repair process, which may be extensive, occurs in a number of experimental situations (reviewed by Ludwin, 1987a,b), including the gliotoxic models (reviewed by Blakemore et al., 1983) and in naturally-occurring diseases such as multiple sclerosis (MS) (Prineas and Connell, 1979; Prineas et al., 1989, 1993; Raine and Wu, 1993). However, remyelination is not universally consistent or sustained, and incomplete remyelination has been reported in gliotoxic lesions of old animals (Gilson and Blakemore, 1993), in certain forms of experimental allergic encephalitis (EAE) (Raine et al., 1974), and is a hall-mark feature of the chronic MS plaque. Thus, there is considerable interest in developing ways in which persistently demyelinated axons may be reinvested with myelin sheaths in order to restore secure conduction of impulses. Efforts to address this problem have focussed mainly on the use of glial cell transplantation techniques to deliver exogenous glial cells into the CNS of hypomyelinating myelin mutants (Lachapelle et al., 1984; Duncan et al., 1988, reviewed by Gumpel et al., 1989; Duncan, 1996) and into gliotoxic lesions (Blakemore and Crang, 1988; Groves et al., 1993) and thereby replace myelin deficits (reviewed by Franklin, 1993). An alternative approach to transplantation is to investigate ways in which the endogenous remyelinating capacity of the CNS may be enhanced in situations where spontaneous remyelination has failed, such as the chronic MS plaque (Grinspan et al., 1994). Evidently, this requires a detailed understanding of the cellular and molecular mechanisms that are involved in remyelination in order to identify logical strategies for therapeutic intervention. This review will discuss current views on the mechanisms of remyelination by oligodendrocytes and the evidence that growth factors may be potentially useful agents for augmenting the inherent remyelinating response.

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The oligodendrocyte lineage in development

An understanding of the oligodendrocyte lineage is important since remyelination shows many similarities to developmental myelinogenesis and, furthermore, growth factors have a variety of effects on different stages of the oligodendrocyte lineage. During development oligodendrocyte progenitors are generated within germinal zones, such as the subventricular zone (Curtis et al., 1988; Levine and Goldman, 1988; Levison and Goldman, 1993) and ventral spinal cord (Warf et al., 1991; Yu et al., 1994), from where they migrate into

both white and grey matter to reach their final destinations in the CNS. Oligodendrocyte progenitors are small, round process-bearing cells that may be identified in vivo by a number of specific markers, including NG2 proteoglycan (Levine et al., 1993; Nishiyama et al., 1996b), platelet-derived growth factor (PDGF) α-receptor (Pringle et al., 1992; Ellison and de Vellis, 1994), DM-20 (Timsit et al., 1995), and quisqualate-stimulated uptake of cobalt (Fulton et al., 1992). Historically, they are referred to in the literature as O-2A progenitors on the basis of their bipotentiality in vitro (Raff et al., 1983; Behar et al., 1988; Levi et al., 1988). Although they constitutively differentiate into oligodendrocytes, they may be induced to differentiate into $A2B5^+$ $GFAP^+$ type-2 astrocytes in the presence of 10% fetal calf serum (Raff et al., 1983), ciliary neurotrophic factor (CNTF) (Hughes et al., 1988; Lillien et al., 1988; Kahn and De Vellis, 1994), leukaemia inhibitory factor (LIF) (Kahn and De Vellis, 1994; Gard et al., 1995) and oncostatin M (Gard et al., 1995). However this nomenclature is slightly misleading since it does not appear that type-2 astrocytes are generated during normal development in vivo (Skoff, 1990; Fulton et al. 1992), or if they do occur it is only rarely (Levison and Goldman, 1993), although they may occur in certain pathological conditions (Barnett et al., 1993; Franklin et al., 1995; reviewed by Franklin and Blakemore, 1995). The perinatal oligodendrocyte progenitor gives rise to a population of oligodendrocyte progenitors that is present in the adult CNS (ffrench-Constant and Raff, 1986; Wolswijk and Noble, 1989; Wren et al., 1992; Scolding et al., 1995). Adult oligodendrocyte progenitors show bipotentiality in vitro, but have a longer cell cycle time and slower migratory rate than their perinatal forebears and have a slightly different antigenic phenotype. It is widely believed that newly-generated oligodendrocytes in remyelination are derived from this pool of cells in response to demyelination.

The next stage in the oligodendrocyte lineage is an intermediate stage known as the pro-oligodendrocyte that has a multipolar morphology and expresses the surface antigens pro-oligodendroblast antigen (POA) (Bansal et al., 1992) and sulfatide (Bansal et al., 1989) recognised by the monoclonal antibody O4 (Sommer and Schachner, 1982). Differentiation into oligodendrocytes is characterised by the development of a complex morphology, the expression of galactocerebroside (Gal C) (Raff et al., 1978), and the cessation of cell division. The final stage of oligodendrocyte maturation involves the orderly expression of the myelin proteins 2',3'-cyclic nucleotide 3'-phosphorylase (CNP), myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated glycoprotein (MAG) (Monge et al. 1986), myelin oligodendrocyte glycoprotein (MOG) (Mattieu and Amiguet, 1990), and, in vivo, myelin-associated/oligodendrocytic basic protein (MOBP) (Holz et al., 1996), and the elaboration of myelin sheaths (reviewed by Pfeiffer et al., 1993) (see Fig. 1).

Current hypotheses on oligodendrocyte remyelination in the central nervous system

Remyelination was first described over thirty years ago in the adult cat spinal cord following CSF barbotage (Bunge et al., 1961). Despite vigorous investigation, the precise mechanisms of remyelination are still incompletely understood at present. In general, it is widely accepted that the remyelinating oligodendrocyte is a proliferative cell of immature phenotype.

The first evidence that remyelination is associated with the proliferation of cells of immature phenotype was described in early studies on cuprizone-induced demyelination (Blakemore, 1973; Ludwin, 1979b). These observations are supported by other studies using JHM virus-induced demyelination showing that remyelination involves proliferation of cells of the oligodendrocyte lineage (Herndon et al., 1977). However, the long interval between administration of $[^3H]$-thymidine and perfusion prevented identification of the phenotype of the dividing cells. More recently, similar findings have been described in a model of focal experimentally-induced demyelination in the cat optic nerve (Carroll and Jennings, 1994). These morphological observations have been supported by immunocytochemical studies which have identified an early increase in the number of oligodendrocyte progenitors expressing O4, (Godfraind et al., 1989) and GD3 (Reynolds and Wilkin, 1993) in demyelinating lesions. Furthermore spontaneous remyelination of gliotoxic lesions is inhibited following exposure to doses of x-irradiation that kill mitotic cells (Blakemore and Patterson, 1978), providing further evidence that cell division is necessary for remyelination. On the basis of the evidence described above, it may be postulated that immature oligodendrocytes are generated in the vicinity of areas of demyelination by mitosis, before migrating into these areas where they engage axons and synthesise myelin sheaths in a similar fashion to developmental myelinogenesis. The highly proliferative and migratory behaviour of perinatal oligodendrocyte progenitors both in vitro (Small et al., 1987; Wolswijk and Noble, 1989) and during development (Curtis et al., 1988; Levine and Goldman, 1988; Hardy and Reynolds, 1991; Reynolds and Wilkin, 1991) is consistent with this view. One of the criticisms of this hypothesis is that the adult oligodendrocyte progenitor has a markedly increased cell cycle time and reduced migration rate in vitro compared to its perinatal forebear (Wolswijk and Noble, 1989), which has lead to suggestions that the proliferative and migratory capacity of the adult oligodendrocyte progenitor in vivo may be insuf ficient to account for the extent of myelin formation during remyelination. However, when adult oligodendrocyte progenitors are exposed to platelet-derived growth factor (PDGF) and fibroblast growth factor-2 (FGF-2) in vitro their proliferation and migration rate are significantly increased (Wolswijk and Noble, 1992), suggesting that such phenotypic alterations may occur in vivo in the

presence of appropriate environmental cues.

Whether newly-generated cells in remyelination are derived from adult oligodendrocyte progenitors, perineuronal satellite oligodendrocytes (Ludwin, 1979a) or mature oligodendrocytes that have de-differentiated remains somewhat controversial. Since it is implicit in this model that the events of remyelination are essentially similar to developmental myelinogenesis, it would seem logical to suggest that remyelinating oligodendrocytes are recruited from the pool of oligodendrocyte precursors that is known to be present within the CNS (ffrench-Constant and Raff, 1986; Wolswijk and Noble, 1989; Scolding et al, 1995). However, an alternative view is that remyelinating oligodendrocytes are generated from mature oligodendrocytes (reviewed by Wood and Bunge, 1991; reviewed by Wood and Mora, 1993), implying that mature oligodendrocytes have the capacity to de-differentiate and re-enter the cell cycle. In vitro studies have shown that oligodendrocytes expressing GalC proliferate (Wood and Bunge, 1986) and may de-differentiate (Wood and Bunge, 1991) following exposure to naked axons, although it is possible that the increased numbers of pro-oligodendrocytes observed may have arisen from contaminating oligodendrocyte progenitors rather than GalC$^+$ oligodendrocytes. It has been assumed in these studies that expression of GalC denotes a fully differentiated phenotype, although cells expressing this marker in vitro may be very different in their behaviour from the myelinating oligodendrocyte of adult white matter. The evidence that mature oligodendrocytes are able to divide in vivo is equivocal. Uptake of [^{3}H]-thymidine has been observed in oligodendrocytes attached to myelin sheaths (Ludwin and Bakker, 1988), but this is not a wholly convincing indicator of mitosis since [^{3}H]-thymidine uptake also occurs following DNA damage. Furthermore, it is questionable whether the proliferative capacity of these cells, if they proliferate at all, is sufficient to bring about extensive remyelination (reviewed by Ludwin, 1987a). Finally, in the x-irradiation paradigm one would predict that, if remyelinating oligodendrocytes were generated from mature oligodendrocytes, the lesion would get progressively larger as oligodendrocytes adjacent to the area of demyelination would die as a result of attempting to divide in response to remyelination signals within the lesion. The fact that this does not occur argues against significant proliferation of mature oligodendrocytes in response to demyelination.

The essential feature of the models of remyelination described above is that remyelinating oligodendrocytes are a population of cells generated de novo by mitosis in response to the demyelinating insult. A wholly different concept of remyelination is that it is brought about by

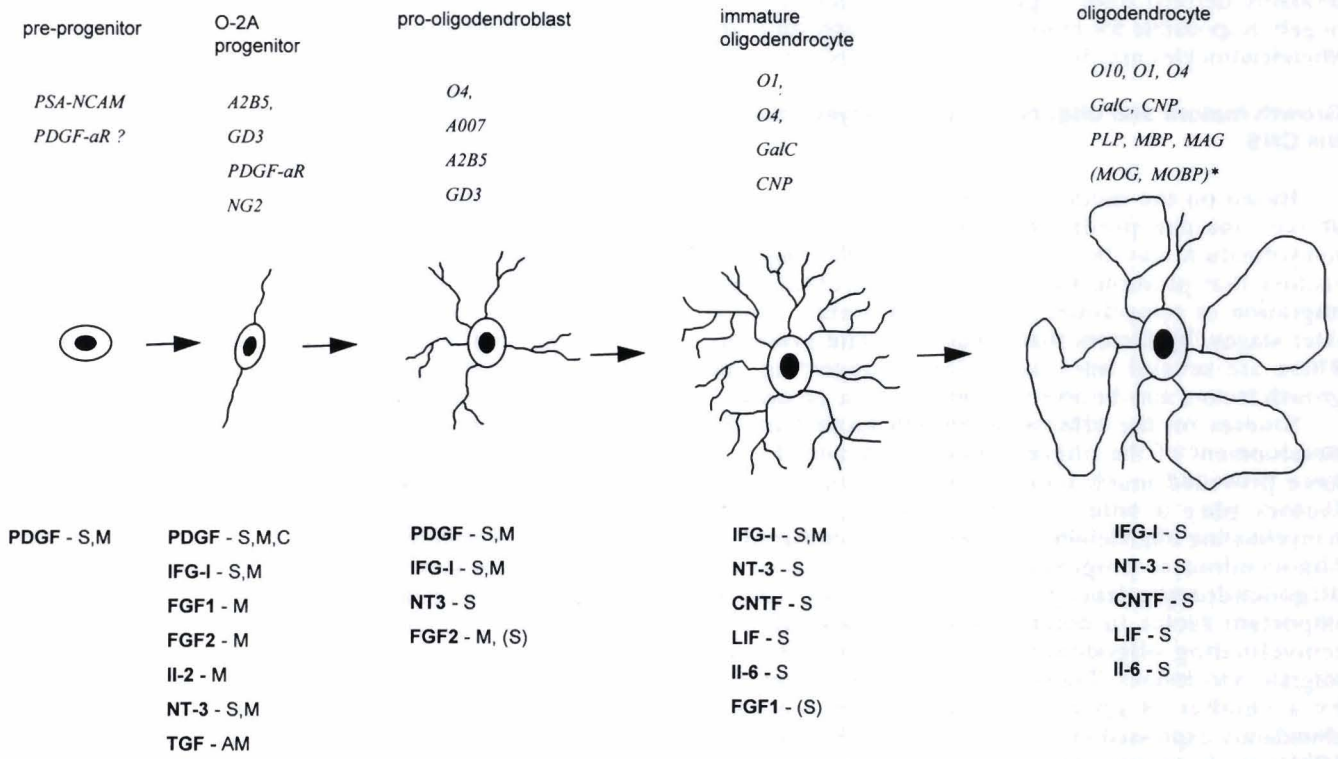

Fig. 1. Effects of growth factors on proliferation, motility and survival in the oligodendrocyte lineage. C: chemoattractant; M: mitogen; AM: anti-mitotic effect; S: survival factor. Recognised markers for stages in the lineage are in italics. (): effects for which equivocal data exists. *: markers associated with myelinating cell in vivo.

oligodendrocytes that survive within areas of demyelination and regenerate new myelin sheaths. This raises the question whether mature oligodendrocytes are able to re-initiate the myelination programme without undergoing cell division. Studies modelling demyelination in vitro have indicated that oligodendrocytes are able to regenerate myelin-like membranes (Fressinaud and Vallat, 1994), which suggests that surviving oligodendrocytes may be able to remyelinate in vivo. Evidently, this prediction is dependent on the demonstration of oligodendrocyte survival within areas of demyelination and of a correlation between the degree of oligodendrocyte survival and the potential to undergo remyelination. MOG has proved to be a useful oligodendrocyte marker in this regard, since it is expressed on the surface of oligodendrocytes that have survived destruction of their myelin sheaths (Ludwin, 1990) and thus can be used to identify surviving oligodendrocytes. Evidence in support of this view comes from studies that have identified mature oligodendrocytes within lesions formed during the early course of multiple sclerosis (Brück et al., 1994; Ozawa et al., 1994). In contrast to this, another study reported that oligodendrocytes were almost completely absent from fresh multiple sclerosis lesions (Prineas et al., 1993), implying that there is considerable heterogeneity in MS lesions.

In summary, the balance of evidence tends to suggest that immature oligodendrocytes, that are probably derived from oligodendrocyte precursors, are largely responsible for remyelination, although surviving oligodendrocytes may be involved to a limited extent.

Growth factors and oligodendrocyte remyelination in the CNS

Based on the models of remyelination described above, one can predict that that the efficiency of remyelination may be enhanced in its early stages by factors that promote the survival, proliferation and migration of remyelinating oligodendrocytes, and, at later stages, by factors that enhance myelin synthesis. There are several lines of evidence suggesting that growth factors may be able to influence these processes.

Studies on the effects of growth factors on the development of the oligodendrocyte lineage (Fig. 1) have provided much indirect evidence that growth factors play a role in remyelination, since the remyelinating oligodendrocyte seems to be similar to the oligodendrocyte progenitor. Survival of cells of the oligodendrocyte lineage, which is likely to be an important factor in determining the availability of remyelinating oligodendrocytes and their ability to migrate into lesions (Franklin et al., 1996), is regulated by a number of growth factors. PDGF, which is abundantly expressed in the developing CNS (Yeh et al., 1991) and is secreted by astrocytes (Richardson et al., 1988), promotes the survival of cells of the oligodendrocyte lineage from the pre-progenitor stage (Grinspan and Franceschini, 1995) until the pro-oligodendrocyte stage at which point PDGFα-receptor expression is lost (Barres et al., 1992; Ellison and de Vellis, 1994), whilst insulin-like growth factors (IGFs) increase the survival of both oligodendrocyte progenitors and oligodendrocytes (Barres et al., 1992). In addition to IGFs, neurotrophin-3 (NT-3), ciliary-neurotrophic factor (CNTF), LIF and interleukin-6 (IL-6) are survival factors for oligodendrocytes (Barres et al., 1993; Louis et al., 1993). Furthermore, CNTF is able to protect oligodendrocytes from the toxic effects of tumour necrosis factor (Louis et al., 1993; D'Souza et al., 1996).

A variety of growth factors are potent mitogens for oligodendrocyte progenitors, and therefore may act during remyelination to stimulate the proliferation of remyelinating oligodendrocytes. PDGF is a potent mitogen for oligodendrocyte progenitors isolated from the perinatal (Noble et al., 1988; Richardson et al., 1988) and adult CNS (Wolswijk et al., 1991), and prevents their premature differentiation into oligodendrocytes (Noble et al., 1988; Richardson et al., 1988). Loss of responsiveness to the mitogenic effects of PDGF occurs prior to the loss of cell surface PDGFα-receptors from newly differentiated oligodendrocytes (Hart et al., 1992) possibly due to changes in signal transduction mechanisms or changes in the expression of NG2 proteoglycan (Nishiyama et al., 1996a). Finally, the chemoattractive effect of PDGF on oligodendrocyte progenitors in vitro (Armstrong et al., 1990) suggests that it may play a role in directing the migration of remyelinating oligodendrocytes towards areas of demyelination.

Fibroblast growth factor-2 (FGF-2) is a potent mitogen for both oligodendrocyte progenitors (McKinnon et al., 1990, Fressinaud and Vallat, 1994) and oligodendrocytes (Besnard et al., 1989; Grinspan et al., 1993), and exerts an inhibitory effect on their differentiation (McKinnon et al., 1990). Indeed it has been reported that FGF-2 treatment induces mature oligodendrocytes to de-differentiate in vitro (Grinspan et al., 1993), an observation which lends support to the hypothesis that remyelinating oligodendrocytes may be generated from mature stages of the oligodendrocyte lineage. However, these results must be interpreted with some caution as it is possible that contaminating pre-progenitors may have given rise to the increased numbers of oligodendrocyte progenitors observed, and that FGF-2 may actually induce oligodendrocyte death in some circumstances (Scolding and Compston, 1995; Muir and Compston 1996). IGF-I and interleukin 2 (IL-2) have been reported to stimulate proliferation of oligodendrocyte progenitors and promote their maturation (Benveniste and Merrill, 1986; McMorris and Dubois-Dalq; 1988, McMorris et al., 1993). However, other studies were unable to show a clear mitogenic effect of IGF-I on oligodendrocyte progenitors (Barres et al., 1992). In the pig, nerve growth factor (NGF) stimulates proliferation of $GalC^+$ oligodendrocytes in vitro (Althaus et al., 1992), but the growth factors that are mitogens for rodents have no effect. On a cautionary

note, no mitogens for proliferating stages of the human oligodendrocyte lineage have been identified to date (Scolding et al., 1995).

In addition to their individual actions described above, combinations of growth factors have been shown to exert co-operative effects on oligodendrocyte progenitors. When perinatal oligodendrocytes are treated with a combination of PDGF and FGF-2 they are prevented from differentiating and undergo sustained proliferation (Bögler et al., 1990). This is believed to be due to an upregulation of PDGFα-receptors by FGF-2 (McKinnon et al., 1990; Nishiyama et al., 1996a). Treatment of adult oligodendrocyte progenitors with the same combination of growth factors results in a similar inhibition of differentiation and causes a marked increase in their rate of division and migration (Wolswijk and Noble, 1992; Engel and Woswijk, 1996), which is a potential mechanism whereby large pools of remyelinating oligodendrocytes may be generated in vivo. Similarly NT-3, which exerts a modest proliferative effects on its own, acts co-operatively with PDGF to promote clonal expansion of oligodendrocyte pro-genitors derived from the neonatal optic nerve (Barres et al., 1994), although no mitogenic effect is observed on oligodendrocyte progenitors isolated from the adult spinal cord (Engel and Wolswijk, 1996).

As well as their various effects on the early stages of the oligodendrocyte lineage, a number of studies have indicated that growth factors are able to influence myelin synthesis during development, suggesting that they may have similar effects during remyelination. Transgenic mice that overexpress IGF-I in the CNS show increased myelin content that is not simply due to increased brain size (Carson et al., 1993), increased myelin sheath thickness relative to axon diameter and increased levels of MBP and PLP mRNA (Ye et al., 1995). Overexpression of IGF binding protein 1 (IGFBP-1), which inhibits the actions of IGF-I by reducing its bioavailability, causes a corresponding reduction in these parameters. Moreover, PDGF (Fressinaud et al., 1996) and FGF-2 (Fressinaud and Vallat, 1994, Fressinaud et al., 1995) promote the recovery of myelin-like membranes in vitro following membrane disruption by lysolecithin, although FGF-2 reduces myelin gene expression and myelin compaction. Finally in the pig, NGF promotes regeneration of processes by mature oligodendrocytes in vitro (Althaus et al., 1992).

More direct evidence of growth factor involvement in remyelination comes from studies on their expression in demyelinating lesions, although this area has not been widely researched. Expression of IGF-I and its receptor (IGFR-I) by astrocytes and oligodendrocytes respectively is induced during demyelination by cuprizone (Komoly et al., 1992), and in EAE (Liu et al., 1994), which suggests that IGF-I may be involved in remyelination, especially considering the effects of IGF-I on the oligodendrocyte development described above. Moreover, activated microglia and macrophages express FGF-2 in EAE, whilst its receptor is expressed by the same cells and also by astrocytes (Gehrmann et al., 1996). In lysolecithin-induced demyelination in the rat spinal cord, there is increased expression of PDGF during the period when recruitment of remyelinating oligodendrocytes is believed to occur, and the putative PDGF antagonist trapidil inhibits the spontaneous remyelination of these lesions, observations which are highly suggestive that PDGF does indeed play a role in remyelination (McKay et al., 1997). Furthermore, astrocytes that are similar to those that have been shown to produce PDGF in vitro, promote remyelination by host oligodendrocytes when transplanted into ethidium bromide-induced lesions in the adult rat spinal cord (Franklin et al., 1990). Finally, the precedent of using exogenous growth factors to alter recovery has been established in an EAE model in which treatment with IGF-I reduces clinical severity and lesion size, and increases MBP mRNA expression (Yao et al., 1995, 1996). However the improvement may be due to anti-inflammatory effects of IGF-I rather than a direct effect on oligodendrocytes to promote remyelination.

Conclusion

The effects of growth factors on the developing oligodendrocyte lineage are suggestive of a number of ways in which they may potentially promote remyelination, especially in the context of the model of remyelination considered above. The events that may potentially be modulated by growth factors during remyelination are the generation of immature oligodendrocytes by mitosis and their survival, the migration of remyelinating oligodendrocytes into areas of demyelination, the regeneration of oligodendrocyte processes and the expression of myelin protein genes. The expression of growth factors in demyelinating lesions strongly suggests that they are involved in spontaneous remyelination, and therefore delivery of exogenous growth factors to poorly-repairing demyelination may be a viable strategy to promote remyelination in the CNS.

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