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TARGETING OLIGODENDROCYTE PROTECTION AND REMYELINATION IN MULTIPLE SCLEROSIS

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Abstract

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the brain and spinal cord with a presumed autoimmune etiology. Conduction block in demyelinated axons underlies early neurological symptoms, whereas axonal transection is believed responsible for more permanent later deficits. Approved treatments for the disease are immunoregulatory, and reduce the rate of lesion formation and clinical exacerbation, but are only partially effective in preventing the onset of disability in MS patients. Approaches that directly protect myelin-producing oligodendrocytes and enhance remyelination may improve long-term outcomes and reduce the rate of axonal transection. Studies in genetically modified animals have improved our understanding of mechanisms underlying CNS pathology in MS models, and have identified pathways that regulate oligodendrocyte viability and myelin repair. However, although clinical trials are ongoing, many have been unsuccessful and no treatments are yet approved that target these areas in MS. In this review, we examine avenues for oligodendrocyte protection and endogenous myelin repair in animal models of de- and remyelination, and their relevance as therapeutics in human patients.

Keywords

multiple sclerosis; ms; oligodendrocyte; neuroprotection; remyelination; repair

The initial presentation of multiple sclerosis (MS) occurs most commonly in young adults, and conduction block in demyelinated axons is believed to underlie early neurological deficits [1], whereas axonal transection is responsible for more permanent later disability [2]. Remyelination is known to occur in early lesions and is associated with recovery of conduction and return of function [3,4], but fails with disease progression [5,6]. Evidence supports a cellular model of CNS remyelination that involves the presence of progenitors in or recruitment into demyelinated areas, and subsequent differentiation and myelin formation [7–9], and committed oligodendrocyte progenitors (OPCs) have been detected in developing brain, normal adult human brain, MS lesions and animal models [5,10–12]. Approaches that directly protect oligodendrocytes and enhance remyelination may improve long-term outcomes and reduce the rate of axonal transection, and moreover such approaches could be employed in combination with currently available immunoregulatory treatments, for additive or perhaps synergistic effects [13]. However, all currently-approved therapies for the disease are immunoregulatory, and no existing treatments directly address oligodendrocyte protection and myelin repair. As a result, these areas are now the subject of

intense research focus, and the race is on to develop the first neuroprotectant approved for use in MS.

[Callout] Currently approved treatments for multiple sclerosis (MS) are all immunoregulatory. These treatments reduce the rate of lesion formation and clinical exacerbation, but are only partially effective in preventing the onset of disability. Long-term outcomes may be improved and the rate of axonal transaction reduced by approaches that directly protect myelin-producing oligodendrocytes and enhance remyelination.

Studies in genetically modified animals have improved our understanding of mechanisms underlying CNS pathology in MS models, and have identified pathways that regulate oligodendrocyte viability and remyelination [14]. Mediators implicated in oligodendrocyte protection or regeneration include the neurotrophins and members of the gp130 neurotrophic cytokine family, and insulin-like growth factor-1 (IGF-1), while pathways suggested as restricting repair have included LINGO-1 and canonical Wnt and Notch signaling [13–15]. However, although clinical trials are ongoing, no treatments are yet approved that target these areas in patients with MS.

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Here, we examine potential avenues for oligodendrocyte protection and endogenous myelin repair in MS and its animal models. While some such as neuregulin 1 type III or canonical Notch signaling rely on contact-mediated interactions, others depend on soluble factor binding of surface receptors on oligodendrocytes or their progenitors. Interestingly, a current theme in the biology of repair is whether regeneration of adult tissues involves reactivation of developmental pathways in a different context and timescale, or whether repair and development are unrelated. Where appropriate, in this review we will also examine data on both sides of this discussion for the relevant pathways.

PATHWAYS PROMOTING OLIGODENDROCYTE VIABILITY, MATURATION AND MYELINATION

Neurotrophins

Neurotrophins (NTs) comprise a family of soluble mediators including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) [16]. Neurotrophins interact with two classes of transmembrane receptors: the receptor tyrosine kinase tropomyosin-related kinase (Trk) and the TNF- α receptor superfamily p75 neurotrophin receptor p75NTR [17]. All neurotrophins bind to p75NTR, and also exhibit a selective and higher affinity interaction with Trk receptors, with NGF binding to TrkA, BDNF and NT-4/5 to Trk-B and NT-3 to Trk-C. The precursor form of NT known as proneurotrophin is also found in abundance in the brain, and is believed to be biologically active [18,19].

While NTs were originally characterized as playing important roles in the development and maturation of specific neuronal populations within the CNS [17], they have also been found to exert strong effects on myelinating glia, and relevant effects on earlier uncommitted progenitors.

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Neurotrophins and Myelin Formation—NGF has been shown to regulate myelination of TrkA-expressing dorsal root ganglion (DRG) neurons by both Schwann cells and oligodendrocytes *in vitro*, with this effect mediated via direct interaction between NGF and neuronal TrkA receptors [20]. Interestingly, the interaction between NGF and TrkA leads to differential outcomes, promoting myelination by Schwann cells but inhibiting myelin formation by oligodendrocytes [20]. Thus, the impact of NGF on myelin formation is believed to include effects on neurons. However, additional work has shown that NGF also enhances oligodendrocyte survival, but does not promote the proliferation of oligodendrocyte progenitor cells (OPCs) unless coadministered with the mitogen fibroblast growth factor [21].

Conversely, the impact of NT-3 on myelin formation is believed to encompass potent glial effects, and a promyelinating role is supported by examination of NT-3 or TrkC-deficient mice. NT-3 is essential for normal cardiac development and so most NT3^{-/-} mice die within 3 weeks of birth [22], but at postnatal day 0 (P0) they exhibit a 35% reduction in the number of OPCs in ventral spinal cord [23]. In addition, quantification of more mature cells in the oligodendrocyte lineage reveals significant reductions in the number of more mature GalC⁺ cells (28% reduction) and myelin basic protein (MBP) mRNA⁺ (27% reduction) oligodendrocytes in spinal cords of NT-3^{-/-} mice [23]. TrkC^{-/-} mice display comparable findings [23]. Studies *in vitro* have also documented the effects of NT-3 on oligodendrocyte survival and proliferation, in addition to promoting the clonal expansion of oligodendrocyte progenitor cells when combined with the mitogen platelet-derived growth factor [24,25]. While NT-3 promotes the survival and proliferation of OPC monocultures, in the presence of neurons it has also been shown to enhance myelination by inducing OPC differentiation [26]. NT-3-transfected OPCs also show increased MBP and enhanced myelination of hippocampal neurons [27]. In the optic nerve, neutralization of NT-3 *in vivo* by injection of hybridoma cells secreting anti-NT-3 antibody severely abrogates the proliferation of OPCs and depletes the population of mature oligodendrocytes [25].

Interestingly, while BDNF, NGF and NT-3 have all been shown to promote differentiation of basal forebrain oligodendrocytes, in cortical oligodendrocytes only NGF and NT-3 promote maturation, without any effect from BDNF [28]. Whereas studies *in vivo* suggest relevance of BDNF in regulating myelination, the underlying mechanism remains incompletely characterized. BDNF^{-/-} mice usually show perinatal lethality but may live for up to 21 days [29], and at postnatal day 13 the number of retinal ganglion cells and the thickness of the retina is normal in these mice but the proportion of myelinated axons in the optic nerve is reduced by approximately 50% compared to littermate controls. This reduction is also present at P21, but is also accompanied by a significant reduction in optic nerve axon diameter, suggesting that BDNF^{-/-} mice develop with a greater number of small unmyelinated axons. In addition, the hippocampus and cortex of BDNF^{-/-} mice display reduced levels of the myelin components myelin basic protein (MBP) and proteolipid protein (PLP) mRNA [30]. Since this phenotype combines alterations in both neuronal and glial compartments, it is not yet clear whether these events are mediated by BDNF acting directly on oligodendrocytes, or via effects on neuronally expressed receptors.

Neurotrophins, Remyelination, and Functional Recovery—Recent work has also suggested the potential of neurotrophins to establish functional recovery following nerve injury and demyelination. For example, transplantation of fibroblasts expressing either BDNF or NT-3 has been shown to enhance axonal growth, OPC proliferation and myelination in adult rat spinal cords after injury [31]. Moreover, transplantation of BDNF or

NT-3-expressing Schwann cells into demyelinated mouse spinal cords leads to increased OPC proliferation and differentiation, remyelination and locomotor recovery [32]. Interestingly, studies in the MS model experimental autoimmune encephalomyelitis (EAE) imply a functional role of BDNF in mediating axon protection in autoimmune demyelination [33]. Remyelination and functional recovery have also been reported following transplantation of glial-restricted precursor cells (GRPs) expressing a multi-neurotrophin of BDNF and NT-3 into the CNS of rats subjected to spinal cord injury [34]. However, while these studies provide evidence that neurotrophins are effective at promoting regeneration of the injured spinal cord, the relative contributions to these outcomes of effects on neurons versus glia remain to be fully defined.

Insulin-like Growth Factors

IGFs are neuroprotective trophic factors for cells of the oligodendrocyte lineage [35]. The IGF system includes IGF-1, IGF-2 and modulating IGF-binding proteins (IGFBPs). IGF-1 and IGF-2 signal through the IGF-1 receptor (IGF-1R) and IGF-2 receptor (IGF-2R) respectively. IGF-1 is expressed at high level in neuron-rich areas of the brain, whereas IGF-2 which is the most abundant IGF in the CNS is found at high levels in myelinated tracts [36].

IGF-1^{-/-} mice display reduced brain size, hypomyelination, reduced numbers of oligodendrocytes and severe loss of neurons [37]. *In vitro*, IGF-1 exerts neurotrophic and neuroprotective effect, and enhances neuronal survival and differentiation. By comparison, the brains of transgenic mice overexpressing IGF-1 are 55% larger than controls, and show increased cell number and size, while myelin content in these animals is increased by 130% [38]. Moreover, in transgenic mice overexpressing the IGF binding protein IGFBP-1, the percentage of myelinated axons and myelin thickness are reduced [39]. *In vitro*, IGF-1 enhances oligodendrocyte survival and supports differentiation, which is accompanied by enhanced process branching and increased myelin production [35,40].

With regard to de- and remyelination, injection of IGF-1 into Lewis rats with EAE has been shown to reduce the numbers and area of demyelinating lesions [41]. IGF-1 treatment also increased the number of axons containing regenerating myelin segments, reduced permeability of the blood spinal cord barrier, and enhanced expression of myelin genes, and was associated with rapid clinical and pathological recovery in the treated animals. However, while a subsequent study in chronic relapsing EAE revealed transient clinical amelioration and low-level remyelination after IGF-1 administration during the acute phase of disease, samples from acute phase-treated animals at chronic time points did not show potentiated remyelination [42].

In MS patients, the translational potential of IGF-1 remains unfulfilled. Although no change in circulating IGF levels was found in MS patients, in active MS lesions IGF-1 is detected in reactive astrocytes while IGF-2 is found in foamy microglia [43]. However, a clinical trial testing the effects of recombinant IGF-1 in MS patients failed to produce significant results [44]. The extent to which this failure was attributable to the inability of IGF-1 to cross the BBB is not clear [44], and restrictions in CNS access and issues with cell type specificity represent a recurring confound in clinical trial design and interpretation for potential neuroprotectants and regenerative therapies.

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Gp130 family of Neurotrophic Cytokines

Gp130 was initially identified as a signal transducing receptor component that associates with the interleukin 6 receptor (IL-6R) upon interleukin 6 (IL-6) binding [45]. It is a shared receptor that defines a large and pleiotropic family of cytokines including IL-6, IL-11, oncostatin M (OSM), leukemia inhibitory factor (LIF), cardiotrophin 1 (CT-1), and ciliary neurotrophic factor (CNTF) [46]. All receptor complexes of the family contain gp130. IL-6R and IL-11R α induce its homodimerization [47], whereas LIF, CNTF, oncostatin M and CT-1 binding lead to heterodimerization of gp130 with the LIF receptor (LIFR) [48]. Homo- or heterodimerization of gp130 triggers the activation of JAK family of cytoplasmic tyrosine kinases [49,50] leading to cytokine- and cell type-specific phosphorylation and nuclear translocation of Stat transcription factors [51]. Stat-independent signaling has also been described [51].

Gp130 cytokine family members have functions in the hematopoietic, immune, reproductive and cardiovascular systems as well as in the CNS [51]. IL-6 is immunoregulatory [52], and acts with TGF β 1 in differentiation of Th17 effector cells [53]. IL-27 also exerts Th1-enhancing activity, but has additional anti-inflammatory functions [54]. IL-6 and LIF regulate hematopoiesis, and numbers of hematopoietic progenitors are reduced in IL-6 $^{-/-}$ and LIF $^{-/-}$ mice [55,56], while LIF and IL-11 are also both important in pregnancy, and decidualization or implantation are defective in IL-11R α $^{-/-}$ or LIF $^{-/-}$ mice [57,58].

Mice deficient in CNTF or CNTFR, and CT-1 $^{-/-}$ mice, also show loss of motoneurons [59,60], and CNTF is protective in neurodegenerative primate models [61]. These reports of neuroprotection have stimulated research focus on the translational relevance of gp130 mediators within the CNS, and the mechanisms responsible for their effects. These reports have encompassed effects of several family members, but effects on oligodendrocytes have focused primarily on CNTF, LIF and IL-11, and these will be reviewed here.

Protective Effects of Ciliary Neurotrophic Factor and Leukemia Inhibitory Factor—

CNTF has been shown to act on oligodendrocytes by promoting their final maturation, and this effect is mediated through the gp130 signaling receptor and Janus kinase pathway [62] and activation of STAT-1 and STAT-3 [63]. Soluble interleukin-6 (IL-6) receptor/IL-6 fusion protein also induces STAT1/3 phosphorylation and enhances differentiation of purified rat oligodendroglial lineage cells *in vitro*, although the IL-6 receptor has been reported as not expressed on oligodendrocyte lineage cells [64]. CNTF and LIF also promote oligodendrocyte viability [24,65], and CNTF $^{-/-}$ or LIFR $^{+/-}$ gp130 $^{+/-}$ mice with EAE display exacerbated disease and oligodendrocyte apoptosis, although LIF $^{-/-}$ mice also show an attenuated late phase of the disease [66–68]. Interestingly, however, CNTF administration *in vivo* is not sufficient to promote oligodendrocyte remyelination in demyelinating lesions induced via microinjection of ethidium bromide [69], although transplantation of CNTF-expressing adult oligodendrocyte precursor cells has recently been reported to promote remyelination and functional recovery after spinal cord injury [70]. Administration of CNTF does protect mice from inflammatory pathology in EAE for the duration of treatment [71]. Endogenous LIF not only protects mature oligodendrocytes from demyelination but also enhances remyelination, while exogenous LIF also has therapeutic potential in limiting the consequences of oligodendrocyte damage. [72,73].

Collectively, these data suggest CNTF and LIF signaling as a potential neuroprotective and pro-regenerative approach for therapy of demyelinating disease. However, enthusiasm for

clinical trials has been dampened by failures of CNTF in clinical trials in neurodegenerative conditions. For example, although CNTF is effective in treating animal models of neurodegeneration [61,74], it was not successful in clinical trials in human patients [75,76].

[Callout] Animal models suggest that signaling by ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF) has a potential neuroprotective and pro-regenerative effect on demyelinating disease. For example, the administration of CNTF to mice with experimental autoimmune encephalitis (EAE) protects them from inflammatory pathology for the duration of treatment. Similarly, endogenous LIF protects mature oligodendrocytes from demyelination and enhances remyelination.

Interleukin-11: Neuroprotection and Immunoregulation

The chromosomal region containing the IL-11 gene (19q13) has been linked to MS by genetic studies [77], and the results of functional studies in primary human cultures have shown that IL-11 enhances oligodendrocyte survival and maturation, and that these effects may be more potent than those of LIF. IL-11 treatment was also associated with increased myelin formation in rodent CNS cocultures [78]. Interestingly, in contrast to the predominantly neuroprotective effects of CNTF and LIF, IL-11 also appears to display significant immunoregulatory actions. *In vivo* studies have shown that IL-11 decreases the clinical course and neuropathology of EAE, whereas IL-11R $\alpha^{-/-}$ mice display exacerbated demyelination and oligodendrocyte loss, accompanied by potentiation of CNS inflammation [79]. While IL-11 directly increases the viability of oligodendrocyte lineage cells, its immunoregulatory properties appear to depend on downregulation of the functions of antigen-presenting dendritic cells [79]. The extent to which both mechanisms determine the net outcome in terms of clinical signs and pathology in EAE will depend on subsequent studies using cell type-specific mutants.

Neuregulin 1 type III

In the years following their discovery, members of the neuregulin 1 (NRG1) family have been shown to be important in CNS and PNS development and maintenance [80]. They are ligands for Erb receptor tyrosine kinases located on glial cells. Over 16 NRG1 isoforms are encoded through multiple promoter utilization and alternative splicing [80,81], including neu differentiation factor (NDF), heregulin, acetylcholine receptor inducing activity (ARIA), and glial growth factor (GGF). The NRG family all share a unique epidermal growth factor (EGF)-like domain required for receptor activation.

The best understood function of NRG1 is the control of myelination in the peripheral nervous system (PNS), where axonal NRG1 is essential for glial and neuronal survival and Schwann cell proliferation and differentiation [82].

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In the developing PNS, a threshold level of axonal NRG1 type III is required to induce Schwann cell ensheathment [83], and both Schwann cell proliferation and myelination are known to require glial ErbB2 receptors [84]. Subsequently, the amount of NRG1 type III expressed on myelinated axons determines myelin sheath thickness [85]. Interestingly, expression of another neuregulin isoform, Nrg1 type I, has no effect [85].

In the CNS, NRG1/ErbB signaling has been implicated in neuronal migration and in synaptic function [86]. NRG1 signaling also affects oligodendrocyte specification, differentiation, myelination, and survival *in vitro* [87–89], and heterozygous NRG1 type III mutants are hypomyelinated [90]. Oligodendrocytes and their progenitors express ErbB2 and ErbB4 but not ErbB3, and these two receptors have been suggested to control CNS myelination *in vivo*, [88]. However, analysis of mice with conditional null mutants that lack NRG1 beginning at different stages of neural development show that these animals produce normal CNS myelin [91]. Moreover, disruption of ErbB signaling produces similar results. While oligodendrocytes express ErbB2 and ErbB4 homo/heterodimers, ErbB2 lacks ligand-binding activity thus double-mutants lacking oligodendroglial ErbB3 and ErbB4 should lack oligodendroglial neuregulin signaling. However, mice conditionally null for both receptors myelinate normally in the absence of neuregulin stimulation [91]. In contrast, a significant hypermyelination is achieved by transgenic overexpression of NRG1 type I or NRG1 type III [91]. Thus, collectively these data suggest that axonal NRG1/ErbB signaling may play different roles in myelin formation in the PNS versus the CNS. Although neuregulin signaling regulates oligodendrocyte development and CNS myelin formation, control of oligodendrocyte myelination is significantly NRG/ErbB-independent. These recent findings significantly impact the potential for this pathway as a therapeutic avenue in MS.

INHIBITORS OF MATURATION AND MYELINATION

Although myelin repair has been demonstrated in early lesions in MS, and is associated with recovery of conduction and return of function [3,4], remyelination is known to gradually fail with disease progression [5,6]. While committed oligodendrocyte progenitors (OPCs) have been detected in adult human brain and in MS lesions [5,10–12], the capacity of CNS precursors for regeneration appears limited [92]. The mechanisms underlying this failure of repair are incompletely characterized [93,94].

Interestingly, while committed OPCs are known to mature into remyelinating oligodendrocytes in the adult CNS [5,10–12], recent studies have suggested that remyelinating cells may also arise from the proliferation and differentiation into mature oligodendrocytes of neural progenitor cells (NPCs) from germinative areas of the telencephalon such as the subventricular zone (SVZ) [95,96]. NPCs may therefore be another source of remyelinating cells in MS. Like all immature progenitor cells, OPCs and NPC are normally submitted to precisely coordinated intrinsic and extrinsic signals that provide highly regulated control of the balance between proliferation and differentiation. In the scope of regeneration and repair therapies for MS, it is critical to identify those signals, which could be manipulated to enhance the differentiation of OPCs and NPCs towards myelinating cells.

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Canonical Notch Signaling

The Notch signaling pathway plays a significant role in regulating the balance between OPC proliferation and differentiation and myelination in the developing CNS [97,98]. The Notch family includes four cell surface receptors (Notch1–Notch4). Following direct contact between the receptor and its ligand, two successive cleavages mediated by an ADAM

metalloprotease and a γ -secretase complex, release the Notch intracellular domain (NICD) from the cell membrane, and it then translocates to the nucleus where it activates the transcription of target genes [99]. Depending upon the type of ligand that binds the Notch receptor, this may either inhibit or promote differentiation and maturation of OPCs, via canonical or non canonical signaling respectively [100]. Contact-mediated activation of canonical signaling by ligands including Jagged1 and Delta1 restricts OPC differentiation and is permissive for proliferation, whereas the non-canonical Notch signaling pathway in OPC is triggered by axonal ligands including F3/contactin and is implicated in instructive effects on maturation [101]. Interestingly, studies have also implicated Notch signaling in maintenance of the size of the pool of neural stem cells in the subventricular zone [102–104], suggesting the relevance of the pathway to both populations of progenitors that may potentially generate remyelinating cells.

Interestingly, EAE and MS lesions have been shown to display high amounts of the Notch1 receptor and its canonical ligand Jagged1, and further characterization of this phenomenon has revealed that Jagged-1 is expressed by reactive astrocytes under inflammatory conditions while Notch-1 and its downstream effector Hes5 localize to OPC [105]. Notch signaling in demyelinating conditions may therefore act as a regulator of the balance between differentiation and maintenance of the pool of progenitor cells. However, studies examining myelin repair *in vivo* have reported contrasting findings. Initial experiments using *PLPCreERT2:Notch1^{fl/fl}* animals did not report strong effects on remyelination [106], whereas subsequent studies of lysolecithin-induced demyelinating lesions in *Olig1Cre:Notch1^{12f/12f}* mice revealed mildly potentiated OPC differentiation and accelerated remyelination [107]. Interestingly, it has also been proposed that the effects of canonical Notch signaling in oligodendrocytes may be countered by the noncanonical Notch pathway within chronic silent lesions in MS [108].

Canonical Wingless Pathway

In addition to environmental cues within the lesions, regulation of progenitor differentiation may also result from intrinsic signals occurring inside OPCs themselves. In order to initiate myelination, the immature proliferating OPC must exit the cell cycle and differentiate [109], and it has become clear that this transition involves factors that induce epigenetic regulation, which can control cell type-specific transcriptional states. How these factors participate to OPC maturation and remyelination in the lesioned CNS remains only partially elucidated but several studies have reported the implication of histone deacetylases (HDAC) in these processes [110,111]. HDAC are a class of enzymes that antagonize the actions of histone acetyltransferases (HAT). Acetylation and deacetylation oppose each other, as acetylation is functionally associated with active and open chromatin, while deacetylation is functionally correlated with inactive and often closed chromatin [112]. Interestingly, in a recent report Ye et al. demonstrated an interaction between HDAC and *Wingless* (Wnt) signaling, in which the inhibitory effect of the canonical Wnt pathway on oligodendrocyte differentiation was reversed by HDAC1 and 2 [113]. This molecular communication within OPC appears to be important for the control of oligodendrocyte lineage commitment and maturation [114].

One of the molecules implicated in controlling the exit of OPCs from the cell cycle is the transcription factor YY1 (Yin-Yang 1) [115], which can act either as a repressor or activator of transcription. Interestingly, recent work has shown that conditional ablation of YY1 in oligodendrocytes results in impairment of CNS myelination, accompanied by arrest of OPC differentiation following cell cycle exit [115]. This block has been linked to loss of recruitment of YY1 and inhibitory HDACs to the promoters of inhibitors such as the Wnt pathway transcription factor 4 (Tcf4), and the helix-loop-helix factor Id4, resulting in potent restriction of OPC differentiation.

Potential relevance of these mechanisms to myelin repair has been suggested by the recent demonstration that Wnt–catenin β 1 signaling is active in oligodendrocyte lineage cells surrounding MS lesions, and that dysregulation of Wnt signaling in OPCs results in delayed myelination and remyelination [116,117]. However, unexpectedly, Tcf4-null mice display reduced rather than potentiated expression of oligodendrocyte terminal differentiation genes [118], thus additional work will be required to fully characterize the role of Wnt signaling in this myelination and remyelination, and its potential as a novel therapeutic avenue.

Bone Morphogenetic Proteins

Role of Bone Morphogenetic Proteins in Oligodendrocyte Development—Bone morphogenetic proteins (BMPs) comprise a group of soluble proteins with more than 20 members that represents one of the largest subclasses of the transforming growth factor- β (TGF β) superfamily. They are classified into five major subgroups based on structural and evolutionary considerations [119]. BMP ligands bind to a complex of the BMP receptor type 2 and Type 1 (a or b), leading to phosphorylation of R-Smads1, 5 and 8 and translocation with the co-Smad, Smad4 to the nucleus, where they acts as transcriptional enhancers [120].

BMPs play pivotal roles in morphogenesis from gastrulation onwards [121]. In the developing spinal cord, development of neuronal populations is known to depend on the relative gradients of roof plate-derived dorsal BMPs, versus the ventralizing morphogen Sonic hedgehog (Shh) expressed by the notochord and floor plate [122,123]. Interestingly, the same cues later control oligodendrocyte specification and maturation. Generation of oligodendrocyte progenitor cells (OPCs) in the spinal cord is believed to occur in two phases [124]. The first occurs ventrally, with OPCs first observed within the ventricular zone of the motor neuron progenitor (pMN) domain of neuroepithelium [125]. This requires Nkx6-regulated expression of the bHLH transcription factor Olig2 and occurs under the influence of Shh [126]. Conversely, the second phase of oligodendrogenesis occurs dorsally [127,128], and is dependent on inhibition of roof plate-derived BMPs by the specific inhibitor Noggin [129,130]. BMPs are known to restrict Shh-induced oligodendrocyte specification [129,131] and subsequently differentiation of specified cells [130,132], and blockade of BMP signaling induces oligodendrocyte generation *in vitro* and *in vivo* [132,133].

Upregulation of Bone Morphogenetic Proteins following Demyelination—BMPs are also known to be upregulated in the CNS following injury or inflammation, and have been linked to induction and maintenance of reactive astrogliosis and glial scar formation [134–136]. Importantly, BMPs are also significantly upregulated in models of disease that result in demyelination, suggesting potential relevance to oligodendrocyte development and myelin repair in the adult CNS [132].

[Callout] Bone morphogenetic proteins are significantly upregulated in models of disease that result in demyelination, suggesting potential relevance to oligodendrocyte development and myelin repair in the adult CNS.

For example, recent studies show that both lysolethycin-induced demyelination in the spinal cord and ethidium bromide injection into the caudal cerebellar peduncle lead to upregulation of BMP4 [137,138]. Furthermore, in EAE BMPs 4, 6 and 7 are significantly increased in the spinal cord, correlating with disease severity [139]. Additionally, BMP4 and 5 are both detected in MS lesions in human post mortem brain tissue [140]. Inhibition of BMP signaling has therefore been suggested as a route to potentiating myelin repair [132], and such a strategy may represent a potent future avenue for understanding and manipulating glial responses in MS, although it is still early in its translational evolution.

[Callout] Despite impressive results in animal models of MS, strategies for neural protection and repair have yet to meet with major breakthroughs in human trials, a lack of effective translation that is not yet fully understood.

CONCLUSION

Approaches directly targeting oligodendrocytes and their progenitors in MS have the potential to bring about improved long-term outcomes and delay the accumulation of chronic demyelination and axonal loss. They could also be used in combination with current immunoregulatory treatments for additive or synergistic results. However, despite impressive results in animal models, strategies for neural protection and repair have yet to meet with major breakthroughs in human trials, and this lack of effective translation is not fully understood. Potential confounds include incomplete access to the CNS through the blood-brain barrier, actions on bystander cell lineages, and/or species differences. Notwithstanding these difficulties, neuroprotective and regenerative approaches represent a major and increasingly important focus for translational research. These treatments are likely to define a major shift in our approach to MS and may result in significant improvements in human health, and their successful development is a critical goal in the coming decade.

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Figure 1. Factors regulating oligodendrocyte lineage proliferation, maturation and death

This schematic outlines the progression of oligodendrocyte maturation, from unspecified neural progenitors (top), through specified oligodendrocyte progenitors, to mature postmitotic cells that enter the myelination program (bottom). Illustrated are the mechanisms of action within this system of factors that increase (right side of panel) or decrease (left side) the numbers of mature myelinating oligodendrocytes. The neurotrophin NT-3, the gp130 cytokines CNTF, IL-11 and LIF, and the insulin-like growth factor IGF-1 (right side of panel) all increase the viability of mature oligodendrocytes or their precursors. Additionally, NT-3 potentiates precursor proliferation, whereas gp130 cytokines promote differentiation. Neuregulin 1 type III-ErbB signaling facilitates axonal ensheathment and myelin wrapping. Conversely, bone morphogenetic proteins (left side of panel) inhibit oligodendrocyte lineage specification and subsequent progenitor differentiation. Canonical Notch and Wnt signaling restrict oligodendrocyte maturation and maintain the size of the progenitor pool.