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## Accepted Manuscript

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**CHAPTER 5:** For “Molecular Basis of Multiple Sclerosis”, BBA

Editor: Alexandre Prat

**Title:** Cells of the oligodendroglial lineage, myelination, and remyelination

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Summary:

Myelin is critical in maintaining electrical impulse conduction in the central nervous system. The oligodendrocyte is the cell type responsible for myelin production within this compartment. The mutual supply of trophic support between oligodendrocytes and the underlying axons may indicate why demyelinated axons undergo degeneration more readily; the latter contributes to the neural decline in multiple sclerosis (MS). Myelin repair, termed remyelination, occurs in acute inflammatory lesions in MS and is associated with functional recovery and clinical remissions. Animal models have demonstrated that remyelination is mediated by oligodendrocyte progenitor cells (OPCs) which have responded to chemotactic cues, migrated into the lesion, proliferated, differentiated into mature oligodendrocytes, and ensheathed demyelinated axons. The limited remyelination observed in more chronic MS lesions may reflect intrinsic properties of neural cells or extrinsic deterrents. Therapeutic strategies currently under development include transplantation of exogenous OPCs and promoting remyelination by endogenous OPCs. All currently approved MS therapies are aimed at dampening the immune response and are not directly targeting neural processes.

## 5.1 Myelin

The rapid transduction of electrical impulses, termed action potentials, is required for the efficient function of the vertebrate nervous system. The conduction velocity of these impulses is maximized by the presence of an insulating layer surrounding the axon referred to as the myelin sheath [1-3]. In the central nervous system (CNS), the oligodendrocyte is the resident cell type responsible for the production of myelin that consists of oligodendroglial plasma membrane loops tightly wound concentrically around the axon. Oligodendrocyte progenitor cells (OPCs) are generated in the ventral neuroepithelium of the neural tube in early embryonic life, more specifically from the motor neuron progenitor (pMN) domain [4-5], and in the dorsal spinal cord and hindbrain / telencephalon of the brain in late embryonic development and early post-natal life [6-9]. These proliferative cells migrate into the developing white matter [10-12], exit the cell cycle, undergo differentiation into mature oligodendrocytes, and begin to express a subset of myelin-associated proteins [13-14]. Following the extension of flat oligodendroglial membrane sheets, there is recognition and adhesion to axonal targets [15]. Myelin components are then synthesized and transported to the appropriate location within the sheath, axons are wrapped, and the myelin membrane is compacted such that the cytoplasmic myelin leaflets are practically fused and almost devoid of cytoplasm [16-18]. In the CNS, one oligodendrocyte can produce up to 40 myelin segments on multiple axons. Consequently, myelinating oligodendrocytes produce as much as  $5-50 \times 10^3 \mu\text{m}^2$  of membrane a day [19]. Maintenance of this myelin membrane occurs throughout adulthood and comprises of a continual turnover of myelin correlated with a high level of expression of myelin genes long after the completion of the myelination process [20-21].

Signals derived from electrically active neurons (such as growth factors, neurotrophic factors, and electrical activity) regulate cellular events involved in myelination and myelin gene expression in oligodendrocytes [22-25]. Oligodendrocytes also reciprocate signals for neurons, by producing growth factors and by inducing the organization of the axon into specific sub-domains by controlling the distribution of various axonal proteins [26-27]. Gaps of myelin cause the formation of the 'Nodes of Ranvier', which are axonal segments where the sodium channels that regulate electrical impulse conduction are aggregated (Figure 1A). Experimental models of demyelination have indicated that the myelin sheath is crucial in maintaining these nodal domains over the long term [28]. Myelin also forms the flanking membrane loops, termed the paranodes, which serve to separate the nodal sodium channels from the potassium channels concentrated in the adjacent juxtaparanodal regions (Figure 1A). Together, the paranodes and juxtaparanodes form the myelin segments called the internodes. The importance of reciprocal communication between axons and oligodendrocytes is apparent in neurological diseases where oligodendrocyte loss and demyelination is associated with a considerable degeneration of axons. For instance, in multiple sclerosis (MS), oligodendrocyte loss and demyelination are associated with progressive axonal degeneration and neurological decline [29-31]. Recovery from relapses in MS (remissions) can reflect a number of mechanisms, including the resolution of the exaggerated inflammation response and consequent sparing of neural cells, the functional reorganization of nodal components, and myelin repair (remyelination).

### 5.2 Role of Remyelination in Functional Neural Recovery

Remyelination is the default spontaneous process by which demyelinated axons undergo ensheathment with new myelin sheaths leading to functional recovery [32-33]. Remyelination of demyelinated lesions has been documented to occur in MS by neuropathologic criteria, where

completely remyelinated MS lesions are called shadow plaques due to the intermediate levels of myelin staining intensity [34-35]. This likely reflects the relative decrease in myelin thickness and internodal length in the new myelin sheaths relative to the original parameters of the sheath [36]. Remyelination is not only found in inactive lesions but can also be observed in lesions with ongoing demyelinating activity [35-37]. Remyelination in MS has also been evidenced by magnetic resonance imaging-based criteria of changes in magnetization transfer ratio within lesions [38]. The new myelin sheath may either act as a protective physical barrier to damaging inflammatory molecules [39], or may restore trophic support to the axon [40-42]. However, some patients demonstrate extensive remyelination and yet clinical deterioration proceeds [43], suggesting that remyelination alone is not always sufficient in restoring function.

Demyelination in MS has been associated with a disruption of the paranodal region, resulting in altered expression and distribution of proteins such as neurofascin 155, contactin-associated protein (Caspr), and paranodin, as well as ion channels [44-46]. Consequently, nodal sodium channels are then directly adjacent to juxtaparanodal potassium channels, leading to impaired saltatory conduction of action potentials (Figure 1B). The remyelination process is associated with a correct re-distribution of paranodal proteins comparable to the developmental sequence of nodal assembly [28] (Figure 1C). Studies have demonstrated that sodium channel re-aggregation at the nodes of Ranvier is an early event in remyelination that occurs prior to new myelin sheath formation [45]. However, this aggregation of sodium channels on a demyelinated axon just prior to remyelination may render it more susceptible to injury [33].

### 5.3 Role of oligodendrocyte progenitor cells in remyelination

Animal models of toxin-induced demyelination have designated the remyelination process as being mediated by newly infiltrated proliferative OPCs that have differentiated into mature

myelinating phenotypes, rather than previously myelinating post-mitotic mature oligodendrocytes within the lesion. More specifically, retroviral tracing has indicated that proliferative cells eventually give rise to remyelinating oligodendrocytes [47]. OPCs also remyelinate efficiently upon transplantation into focal demyelinated lesions [48-50]. Additionally, lesions in which there is widespread oligodendrocyte death are characterized by a repopulation of OPCs prior to new oligodendrocyte formation [51-53]. The role of OPCs in protecting axonal integrity has also been highlighted in an animal model of demyelination where depletion of these cells via X-ray irradiation results in increased axonal swellings and decreased axonal numbers in white matter tracts that would normally undergo remyelination [54].

The OPCs with remyelinating potential are believed to be randomly distributed within the CNS. However, areas that are distal from progenitor germinal zones, such as the optic nerves, are the first to demonstrate impairments in the remyelination process [55]. OPCs have been termed as stem cells of sort due to their multi-potentiality, self-renewal potential, and rapid proliferative response to injury. OPCs are highly proliferative, motile, bipolar cells expressing high levels of the GT3 ganglioside A2B5, PDGF receptor alpha (PDGF $\alpha$ R), and the CSPG NG2 [19]. The expression of these molecules and hence OPC specification are regulated by the basic helix-loop-helix (bHLH) transcription factors Olig1, Olig2, Mammalian achaete scute Homolog 1 (Mash1), and the zinc finger transcription factor Myelin transcription factor 1 (MyT1) [52, 56, 57]. OPCs are also very responsive to agents that promote their differentiation along the oligodendroglial lineage, such as insulin-like growth factor (IGF)-1, ciliary neurotrophic factor (CNTF), and thyroid hormone (T3) [58, 59]. Differentiation requires the function of Olig1, Olig2, Nkx2.2, Nkx2.6, MyT1, and sex determining region Y box (Sox)-10 [50, 56, 57, 60], likely due to interaction of these transcription factors with the promoters of myelin genes [61-63] (Figure 1D).



The directed migration of these cells to presumptive white matter has been suggested to be mediated by the chemo-attractant PDGF and semaphorin 3F, the chemo-repellents netrin-1, semaphorin 3A, and the ephrins, as well as the stop-signals CXCL1 and tenascin C [64-68]. OPCs can be identified in the adult human brain, consisting of 5-8% of total glial cells [59]. Interestingly, adult OPCs demonstrate slower motility, a prolonged cell cycle, and poorer survival relative to developmental OPCs [70-72]. The restriction of these cells to the oligodendroglial lineage *in vivo* is unlikely: these cells were originally termed O-2A cells due to their potential to generate both oligodendrocytes and astrocytes *in vitro*. In addition, they can develop into neurons within neurogenic domains of the CNS (i.e. hippocampus) and have the capacity to generate Schwann cells following immune-mediated white matter injury [73]. The generation of OPCs from differing developmental pathways likely contributes to the heterogeneous population of OPCs observed in development [73-75]; whether this heterogeneity exists in adulthood is unknown. Subsets of precursors expressing varying levels and combinations of markers do exist in adult white matter [76]. Precursors with differential responses to growth factors can also be isolated from the adult rat forebrain [77]. These precursor subsets may differentially contribute to remyelination and may be under the control of distinct regulatory mechanisms. OPCs can mature into pre-oligodendrocytes, expressing an unidentified sulfatide recognized by the O4 antibody [78]. Although still proliferative, these cells are non-motile likely due to the adoption of a multi-processed complex morphology. Once these cells have then progressed to differentiation into immature oligodendrocytes, they have undergone cell cycle-arrest. They can still be identified by the O4 antibody, yet expression of OPC markers such as A2B5 and PDGF $\alpha$ R is repressed (Figure 1D). Arborizations are elaborated and maturity-associated markers are acquired (galactocerebroside (GalC)) without the formation of myelin

(Figure 1D). The subsequent final stage of differentiation into mature oligodendrocytes comprises of the acquisition of myelin proteins and axonal contact (Figure 1D). Interestingly, factors that promote survival and differentiation, such as CNTF, are not necessarily sufficient in causing myelin formation to occur *in vivo* [79].

Whether mature oligodendrocytes can themselves contribute to remyelination has been a topic of great debate. This has been negated by the findings that these cells are post-mitotic, non-migratory, and unable to remyelinate upon transplantation into lesions [80, 81]. Mature oligodendrocytes do re-extend processes following sub-lethal injury; however these processes are intercalated between axons and do not ensheath them [82].

#### 5.4 Requirements for remyelination: inflammation-dependent OPC activation

The ‘activation’ of OPCs is thought to be required for remyelination to occur. This involves the adoption of a hypertrophic morphology, increased expression of genes associated with oligodendroglial differentiation (such as the transcription factors Olig2 and NK2 transcription factor related locus 2 (Nkx2.2)), and responsiveness to mitogens and chemoattractants that are released from glia in the injured tissue [56, 83]. This activation process may be required to prevent OPC differentiation in the normal intact white matter [84]. This activation response is proportional to the inflammatory reaction that succeeds demyelination and is required for successful remyelination to occur in animal model systems [85, 86]. Myelin debris has been shown to be inhibitory to OPC differentiation and is phagocytosed by reactive macrophages that have entered the lesion area [87]. Furthermore, chemokines and cytokines such as tumor necrosis factor (TNF)  $\alpha$ , interleukin (IL)-1 $\beta$ , IL-11, and Chemokine C-X-C motif ligand (CXCL)-2 can promote OPC proliferation, differentiation, and remyelination [88-91]. Inflammatory cells and reactive astrocytes, which can both be found within MS lesions, can release growth factors that

can affect the remyelination process [92-95]. Accordingly, the migration and differentiation of transplanted progenitors in the commonly used inflammatory model of MS, experimental autoimmune encephalomyelitis (EAE) corresponds to the peak of inflammation [96]. The pro-inflammatory cytokines IL-1 $\beta$  and TNF $\alpha$  synergistically enhance OPC migration to FGF [97].

### 5.5 Animal models to study remyelination

Various animal model systems have been developed to study different aspects of remyelination.

#### 5.4.1 Lysolecithin and Ethidium Bromide focal injections

A common model used to study the remyelination process in the absence of concomitant demyelination and exaggerated inflammation involves focal injections of toxins such as ethidium bromide or lysolecithin either into the spinal cord or white matter tracts of the brain. This induces a reproducible demyelination in predefined areas of the central nervous system (CNS) by inducing cell death of oligodendrocytes (using ethidium bromide) and myelin membrane solubilization (using lysolecithin) at the site of injection [98-100]. These models are attractive in their succinct temporal separation between de- and remyelination processes and the spontaneous OPC-mediated remyelination that occurs within 4 weeks post-injection. There are, however, confounding issues of toxin-induced axonal damage, BBB breakdown, and moderate traumatic injury with consequent immune cell infiltration at the injection site [101-103].

#### 5.4.2 Oral Cuprizone administration

Another commonly used model involves oral administration of the toxin cuprizone (oxalic acid bis (cyclohexylidene hydrazide)) that induces oligodendrocyte cell death, myelin membrane vacuolization, and demyelination in specific white matter tracts of the brain (i.e. cerebellar

peduncles, corpus callosum, and anterior commissure) [104]. Although the mechanism of demyelination of cuprizone is unknown, its copper chelation functions have implicated the deregulation of copper-dependent mitochondrial functions and resultant impairment in energy production in oligodendrocytes [105]. Interestingly, some areas of white matter are spared from cuprizone toxicity (i.e. spinal cord, optic nerve) suggesting regional differences in oligodendroglial / myelin energy requirements. Following cessation of cuprizone treatment, demyelinated lesions demonstrate robust spontaneous remyelination [106]. OPC proliferation and recruitment to lesion areas is initiated during the period of cuprizone-induced demyelination, causing an overlap in demyelination and repair processes [107]. This model is characterized by a significant lesional infiltration and reactivity of microglia and astrocytes that likely contribute to the secretion of remyelination-promoting factors; there is no evidence of T lymphocyte involvement or of BBB breakdown [108].

#### 5.4.3 Inflammatory models

As previously mentioned, the inflammatory process is critical in inducing OPC activation and subsequent remyelination. Several models of inflammation-induced demyelination show spontaneous remyelination even in the presence of an exaggerated immune response. For instance, the EAE model in which animals are immunized against the myelin-oligodendrocyte glycoprotein (MOG) antigen is characterized by a relapse-remitting phenotype, however remyelination is not very extensive perhaps due to the dense infiltration of macrophages and microglia in the lesion over prolonged periods of time. The only indication of impressive levels of remyelination in EAE is observed in focal models of cortical demyelination involving immunization with subclinical doses of MOG and injection of pro-inflammatory mediators

[109]. Another model, Theiler's murine encephalomyelitis (TME), consists of injection of a single-stranded ribonucleic acid (RNA) picovirus into the CNS to induce immune-mediated oligodendroglial cell death, axonal damage, and demyelination in the gray and white matter of the CNS [110]. This model can be characterized by varying levels of remyelination which renders it appropriate for testing of agents that can potentially inhibit or enhance the myelin repair process [111]. Both these models have been used as standards for the development and testing of therapeutic strategies for autoimmune diseases.

#### 5.6 Postulates for failure of remyelination in MS

Although a limited number of MS patients have extensive spontaneous remyelination in up to 96% of lesions [112], most patients eventually demonstrate impaired or insufficient remyelination as the disease progresses [112, 113]. OPCs are increased in numbers in actively demyelinating MS plaques, yet are depleted over time [114-117]. Failure in remyelination would imply that chronically demyelinated axons are rendered more susceptible to degeneration and immune-attack. Indeed, chronically demyelinated plaques are comprised of severely injured axons that are progressively cleared over time [118, 119]. Axons that have been chronically demyelinated for long periods of time, however, can still be remyelinated under acute inflammation [120]. There are a multitude of hypotheses as to why remyelination fails in MS, which may reflect either changes in environmental inputs or intrinsic pathways regulating OPC function [121, 122].

### 5.6.1 Immune-mediated injury to OPCs and new myelin sheath

A postulate that supports that former hypothesis proposes that the new myelin sheath and OPCs are subject to immune-mediated injury to the same degree as the initial insult to the oligodendrocytes and myelin [122]. Post-mortem analysis of MS plaques indicates that remyelination may be interrupted by inflammation [123]. In acute demyelinating animal models with a single insult and no continuing injury to myelin, the ensuing remyelinating is complete [124]. Antibodies recognizing progenitor cell-specific antigen (AN2) have been identified in the CSF of relapse-remitting MS patients and could induce OPC lysis [125].

### 5.6.2 Exhaustion of OPC source

Another proposal is that repeated demyelinating insults, as observed in the relapse-remitting form of MS, causes an exhaustion of the OPC source. Accordingly, recurrent demyelinating insults to the corpus callosum with oral administration of the oligodendrocyte toxin, cuprizone, resulted in accumulative failure in remyelination and progressive diminishment in repopulation of mature oligodendrocytes [126]. However, successive demyelination of the brain stem with ethidium-bromide does not affect the efficiency of remyelination nor progenitor numbers [127]. This suggests that remyelination failure may be regionally defined due to exhaustion of distinct progenitor pools. Proliferating OPCs are rare in MS lesions suggesting that depletion of progenitors is conceivable following repeated episodes or extended periods of demyelination and recurrent episodes of remyelination [117, 127, 128, 129].

### 5.6.3 Glial Scar in lesion

The glial scar formed within the lesion, comprised of hypertrophic reactive astrocytes and meningeal fibroblasts, likely serves to form a barrier between inflamed damaged tissue and normal brain but is also thought to secrete factors that may inhibit OPC migration into the scar and subsequent differentiation. For example, some plaques with a reactive astrocytic core have high levels of CXCL-1 and ephrins at their perimeter that may impede OPC migration into the lesion [130, 131]. Also, the presence of myelin-associated debris in the glial scar, including myelin associated glycoprotein (MAG), oligodendrocyte-myelin glycoprotein (OMgp), and NogoA, can prevent axonal regeneration and inhibit OPC differentiation [134]. OPCs grown on myelin substrates *in vitro* show impairments in maturation [132]. Additionally, the injection of myelin debris into a focal demyelinated lesion prevents the remyelination that normally succeeds [87]. The scar is also hypothesized to have upregulated levels of other molecules inhibitory to axonal regeneration and may render the axon unsuitable for remyelination, such as chondroitin sulfate proteoglycans (CSPGs) and semaphorins [133]. The presence of astrocytes within the lesion has been previously hypothesized to be sufficient to dampen the rate of remyelination via inhibition of OPC process extension and migration [97]. Nonetheless, transplanted OPCs are able to repopulate astrocytic lesions and endogenous remyelination does not occur in the adult when astrocytes are depleted [134]. LIF released from astrocytes can indeed promote myelin formation [25]. Some have argued that the glial scar is not a cause of failed remyelination but rather a consequence of it [83].

#### 5.6.4 Upregulation of developmental regulators of myelination

An additional hypothesis for the failure in remyelination in MS proposes that re-expression of developmental regulators of myelination, such as Leucine rich repeat and Ig domain-containing (LINGO)-1 and polysialic acid-neural cell adhesion molecule (PSA-NCAM), may be re-expressed on stressed axons within the lesion and repel OPCs [135]. This is supported by the finding that non-differentiated and non-myelinating OPCs are closely associated to the axon in some MS lesions [136]. In addition, reactivation of the Wnt signaling pathway in MS lesions suggests that dysregulation of this pathway may contribute to inefficient myelin repair; indeed, dysregulation of this pathway in an experimental model of demyelination interfered with remyelination [137].

#### 5.6.5 Aging-related deficits in inflammation and OPC differentiation

The remyelination process has also been shown to decline with age in experimental animal models; this is relevant in the context of MS that runs over several decades of life [138, 139]. One explanation could relate to prolonged exposure to inflammatory mediators that induce an accumulation of neural damage over time [108]. This age-related failure in remyelination has also been attributed to delayed clearance of myelin debris by phagocytic macrophages, consequently impairing OPC differentiation [124]. This is supported by studies of MS lesions in which early lesions and periplaque white matter (PPWM) have an increased number of OPCs (Olig2+) co-expressing a mature oligodendrocyte marker NogoA, thereby suggesting a differentiation block as a potential cause for remyelination failure [117]. The aforementioned importance of inflammation in inducing the activation of OPCs and resultant remyelination would also suggest that OPCs in un-remyelinated MS lesions may still be functional yet are not



immersed in the appropriate inflammatory environment that would induce differentiation [136, 140]. Furthermore, studies have demonstrated that remyelination efficiency is regulated by age-dependent epigenetic control of gene expression, and dysregulation of this process may contribute to the decline in remyelination with age [141].

#### 5.6.6 Temporal discordance of remyelination with inflammation

The slow rate of OPC repopulation of demyelinated lesions observed in animal systems has led to the hypothesis that remyelination may be unsuccessful in MS due to a temporal discordance between OPC migration into the lesion and the inflammation required for OPC activation that is generated from myelin breakdown [83]. Delaying OPC infiltration into lesions by their transplantation at a site distal from the demyelinated area results in impaired remyelination [122]. However, increasing progenitor recruitment to demyelinated lesions in aged animals via PDGF upregulation in astrocytes is not sufficient in rescuing the failed remyelination process [142]. This suggests that deficits in OPC migration cannot explain the deficiency in remyelination with aging.

#### 5.7 Therapeutic strategies to promote remyelination

Current studies using experimental animal models of demyelination are aimed at discovering therapeutic strategies to overcome these obstacles and to replace myelin under circumstances in which endogenous remyelination is unsuccessful. Remyelination efficiency may be improved either by supplementing the CNS with an exogenous source of OPCs or promoting the endogenous repair process.

### 5.7.1 Transplantation of exogenous cells with myelinating potential

Exogenous cells (such as neural stem cells, schwann cells, olfactory ensheathing cells, mesenchymal stem cells, and OPCs) have been transplanted into focal demyelinated lesions to promote remyelination. Using this therapeutic approach in the demyelinated brain, however, is confounded by the limited migration of transplanted cells in the adult CNS, the availability of source material, potential tumorigenesis, immunological incompatibility/ immune-mediated targeting of these cells, and the putative exhaustion of transplanted cells with recurrent demyelination. The route of administration also represents an additional dilemma; for instance, direct parenchymal injections would be complex given the presence of multi-focal randomly distributed lesions in MS. Other methods of administration, such as intravenous and intra-arterial injections, trigger functional improvement but raise the issue of tissue targeting and distribution [143].

Nevertheless, transplantation of human OPCs has proven effective in initiating myelin formation in dysmyelinated mutants [144, 145]. Interestingly, adult CNS-derived progenitors can myelinate dysmyelinated CNS at a relatively quicker rate than their embryonic counterparts [146].

Transplantation of human OPCs into a leukodystrophy animal model has demonstrated the capacity of these cells to integrate into white matter, contribute to myelination, and survive for prolonged periods of time in the host. Additionally, transplantation of bone marrow cells and embryonic neurospheres results in amelioration of EAE pathology and clinical symptoms [147, 148]. Moreover, transplanted neurospheres can promote remyelination mediated by cells of both endogenous and exogenous origins in EAE-afflicted animals [149].

Transplantation may prove effective if the exogenous cells functionally substituted for or stimulated endogenous remyelination by OPCs that have intrinsic defects in remyelination-

associated processes, such as migration and differentiation. Accordingly, following an acute demyelinating insult, transplanted cells remyelinate lesions at a faster rate than endogenous progenitors [85, 150].

Notably, repopulation of a demyelinated lesion with OPCs is not sufficient to induce remyelination [150]. Contrary to the ability of axonal signals to induce OPC differentiation during developmental myelination, chronically demyelinated axons in adult CNS lesions do not promote OPC differentiation and remyelination even under prolonged co-existence with these OPCs [150, 151]. Interestingly, the cell transplantation approach may prove more effective as an anti-inflammatory therapy given that systemic administration of CNS-derived progenitors promotes endogenous repair via peripheral immuno-modulation rather than through new myelin formation [152]. Systemically applied neural stem cells distribute to the lymphoid organs and reduce pro-inflammatory cytokine production and auto-reactive cytotoxic T cell responses. Transplanted cells also have neuroprotective properties via release of trophic factors [153].

#### 5.7.2 Promoting endogenous remyelination

A parallel approach to enhance remyelination is to attempt to promote endogenous repair. One area of interest involves the application of growth factors that stimulate OPC responses relevant for remyelination, such as proliferation, migration, differentiation, and survival. In fact, the upregulation of growth factors in many instances of trauma, including ischemia and spinal cord injury, indicates the importance of these factors in initiating a repair process [154, 155].

Promoting oligodendroglial survival via treatment with neurotrophic factors such as CNTF, IGF-1, and glia growth factor (GGF)-2 has been successful in attenuating EAE pathology [156-158].

However, the repair-promoting characteristics of these factors are lost upon targeted delivery to the CNS, suggesting peripheral mechanisms of action [159, 160]. In light of this, systemic growth factor treatment raises the issue of non-specific effects on the immune system. Moreover, the efficiency of growth factors in attenuating EAE does not necessarily translate into successful treatment of MS patients, as evidenced by the failed clinical trial with IGF-1[161].

An initial counter-intuitive observation that immunization of animals with spinal cord homogenates can induce extensive remyelination has revealed that myelin- and oligodendrocyte-reactive Immunoglobulin M (IgM) autoantibodies can promote endogenous myelin repair in models of viral- or toxin-based demyelination [162, 163]. Although these antibodies bind oligodendrocytes and white matter tracts, the mechanism of action through which repair is enhanced is unknown. Hypotheses include antibody-dependent cross-linking of molecules on the surface of oligodendrocytes that initiate signaling cascades relevant for the remyelination process.

Recent studies have focused on hormonal therapy as a means of enhancing endogenous repair mechanisms in the CNS. The observations that MS is more prevalent in females, that remission occurs during the course of pregnancy, and that relapses increase post-partum [164] have highlighted the importance of sex-specific factors in regulating immune responses and repair. Pregnant murine females have increased numbers of newly generated oligodendrocytes, OPCs, and myelinated axons, and demonstrate enhanced remyelination following lysolecithin-induced demyelination of the spinal cord [139, 165]. Endogenous hormone production occurs both in the adrenal glands and in the CNS in a cholesterol-dependent manner [166], and is hypothesized to not be sufficient enough in males to protect them from brain injury [167]. Hormones can readily penetrate the blood-brain barrier and have neuroprotective properties. Additionally, hormones

have been implicated in regulating the survival of oligodendrocytes and myelination [168-170]. Even though hormone receptor expression is modulated in a sex- and hormone status-dependent manner, both males and female rats are responsive to the neuroprotective effects of hormonal therapy [180]. Administration of the hormone prolactin to virgin mice is sufficient in reproducing the superior remyelination observed in pregnant females [165]. Other hormonal therapies such as the synthetic analogues estradiol and progestin bestow neuroprotection in various CNS injury systems including EAE [170]. Clinical trials in which non-pregnant and post-partum relapse-remitting MS patients were treated with these hormones demonstrated their potential application for autoimmune disease therapy [171]. The use of hormonal therapies for MS is confounded by their potential pro-inflammatory properties [172], the risk of development of hormone-responsive cancers [167], and putative excitotoxicity due to their actions on neurotransmitter receptors [173].

We are entering a new era of MS-directed immunomodulatory therapies that can not only modulate peripheral immune responses, but can access the CNS by virtue of their lipophilicity and may therefore directly impact cells of the oligodendroglial lineage and remyelination. A newly emerging sphingosine-1-phosphate analogue, FTY720 (fingolimod), was initially propelled into MS clinical trials due to observations of its anti-inflammatory properties in EAE [174-176]. FTY720 can cross the BBB and enter the brain parenchyma [177]. Microarray profiling has revealed that FTY720 treatment of EAE animals results in an increase in transcript levels of myelin-related genes and normalization of electrophysiological responses [178,179]. The efficacy of FTY720 in relieving clinical disability in the later stages of EAE where inflammation has subsided suggests a neuroprotective effect [174, 175, 179].

Autoradiographical and microscopic analysis of rodents that were orally administered C<sup>14</sup>-

labelled FTY720 (7.5mg/kg) for 1 week demonstrated that the drug is concentrated in myelin sheaths [179]. Both rodent and human OPCs and mature oligodendrocytes have been shown to express the sphingosine-1-phosphate (S1P) receptor isoforms that can bind the active phosphorylated form of FTY720 [180-184]. Studies where FTY720 was directly applied to dissociated cultures of human and rodent OPCs and mature oligodendrocytes demonstrate the capacity of these cells to respond to this drug in a dose- and treatment duration-dependent manner [183-186]. FTY720 was able to modulate process extension, differentiation, migration, and survival in these cells. Application of physiological doses of the active form of the drug to demyelinated organotypic cerebellar slice cultures resulted in enhanced remyelination with an accompanying increase in OPC and mature oligodendrocyte process extension and astrocytic/microglial response [187]. Fumaric acid esters (FAE), including BG12, are intermediate products of the citric acid cycle that are currently being evaluated in MS clinical trials due to their immunomodulatory properties [188]. Recent studies have suggested that FAEs may have neuroprotective properties by affecting anti-oxidative pathways in oligodendrocytes and other glia, which may conceivably protect neural cells from metabolic and inflammatory stress [189]. FAEs have been shown to protect myelin from immunological damage in EAE [190], yet not from cuprizone-induced demyelination [191]. FAEs have, however, been associated with a slight enhancement in remyelination *in vivo* [191]. In addition, neurotrophic cytokines (neurokines), such as leukemia inhibitory factor (LIF), CNTF, IL-6, oncostatin-M and IL-11, are cytokines which can regulate neural cell function. CNTF, LIF, and oncostatin-M were identified in a screen as being associated with enhanced myelin production [192]. Oligodendrocyte survival is enhanced by exposure to exogenous LIF *in vitro* [193] and *in vivo* in both chronic and relapse-remitting forms of EAE [194]. Additionally, IL-11 is able to potentiate

the survival, maturation, and myelination potential of oligodendrocytes [91]. The production of neurotrophic cytokines within the CNS and their accessibility to this compartment when exogenously applied [194] highlights them as candidates for multiple sclerosis therapy. Neurotrophins such as CNTF have been detected in the cerebral spinal fluid of multiple sclerosis patients [195]; however, CNTF therapy worsened clinical conditions of treated patients [196].

### 5.8 Conclusions:

Experimental animal systems have revealed the importance of OPCs and remyelination in reconstitution of the myelin sheath and subsequent recovery of neural function. Analyses of MS lesions by neuropathologic and magnetic resonance based criteria have demonstrated that remyelination does occur in acute inflammatory lesions yet is limited in more chronic lesions, perhaps reflecting a plethora of biological indices. All currently approved therapies for MS are aimed at dampening the exaggerated immune response, are only moderately effective at reducing the frequency of clinical relapses, do not slow the progression of the disease, and do not directly influence myelin and remyelination in the central nervous system. As such, the identification of new therapeutic factors that can protect neural cells from injury, directly promote myelin repair, and hinder disease progression has profound implications for the treatment of MS.

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ACCEPTED MANUSCRIPT



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**Figure Legend:**

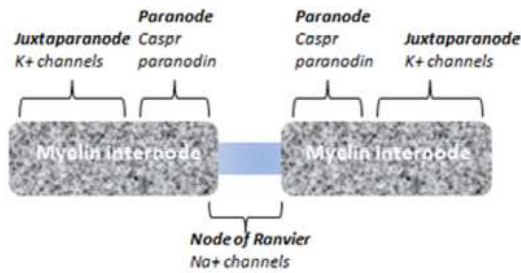
Figure 1. Myelin characteristics, Demyelination, and Remyelination.

- A. Schematic of Node of Ranvier organization. Nodes of Ranvier are axonal regions of concentrated sodium channels devoid of myelin, formed between two internodes of myelin. The area adjacent to the node is termed the paranode, characterized by Caspr and paranodin expression. The area adjacent to the paranode is termed the juxtaparanode, where the potassium channels reside.
- B. Upon demyelination, there is destruction of the paranode and lateral migration of sodium channels from the nodal region.
- C. Remyelination is initiated by activation of OPCs, likely by inflammation-associated factors (i.e. IL-1 $\beta$ , TNF $\alpha$ , LIF), and chemotactic migration towards the lesion (i.e. PDGF, bFGF, CXCL1). Differentiation into mature oligodendrocytes and remyelination is associated with an upregulation of Olig2 and Nkx2.2, and requires both removal of myelin debris and inflammatory factors (i.e. IL-1 $\beta$ , TNF $\alpha$ , CXCL-2). The new myelin sheath has shorter internodes, thinner myelin loops, and may act as a physical barrier to protect from injurious inflammatory molecules, or provide trophic support anew to the axon.
- D. Multi-potent neural stem cells (nestin<sup>+</sup>) are specified into oligodendrocyte progenitor cells (OPCs; A2B5<sup>+</sup>, PDGF $\alpha$ R<sup>+</sup>, NG2<sup>+</sup>) by exposure to sonic hedgehog (SHH) and fibroblast growth factor (FGF), whereas bone morphogenic proteins (BMPs) inhibit this specification. This specification involves the transcription factors Olig2, Nkx2.2, Mash1, MyT1, Nkx2.6, Gli2, and Sox 8/9/10. OPCs can differentiate into multiple cell types

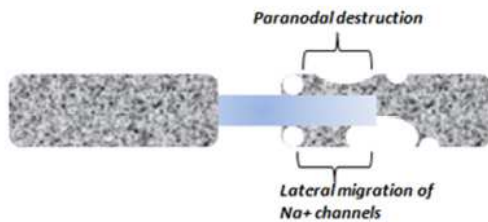
including astrocytes, neurons, and Schwann cells. Differentiation along the oligodendroglial lineage to pre-oligodendrocytes/ immature oligodendrocytes (O4+/GalC+) is potentiated by the growth factor IGF-1, the cytokine CNTF, and the thyroid hormone T3, and requires the transcription factors Olig1/2, Sox10, Nkx2.2/ 2.6. Conversely, BMPs and transcription factors Sox5/6 prevent this differentiation. Differentiation into mature oligodendrocytes is associated with acquisition of myelin-related proteins, such as myelin basic protein (MBP), myelin associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte myelin glycoprotein (OMgp), and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase).

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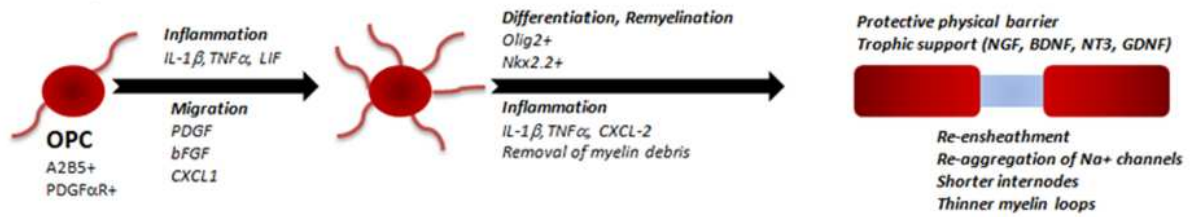
### A. Non-pathologic conditions



### B. Demyelination



### C. Remyelination



### D. Oligodendrocyte Specification & Differentiation

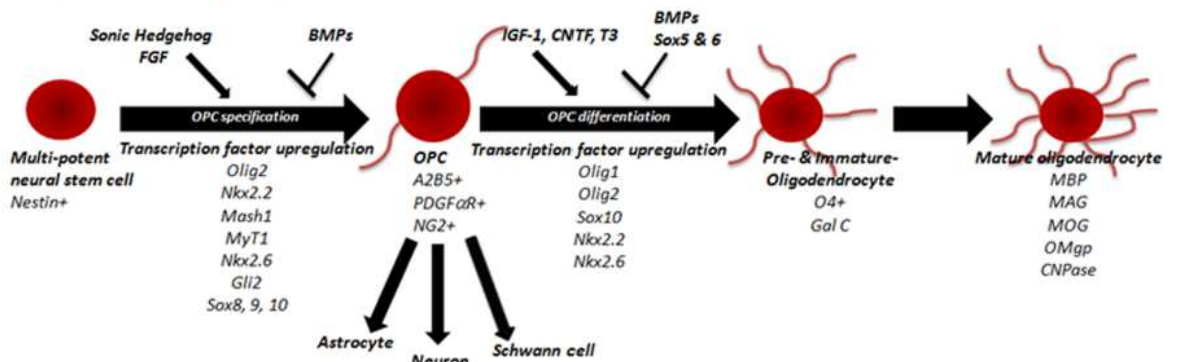


Fig. 1