Trends in Neurosciences

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Review

Pushing Forward: Remyelination as the New Frontier in CNS Diseases

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The evolutionary acquisition of myelin sheaths around large caliber axons in the central nervous system (CNS) represented a milestone in the development of vertebrate higher brain function. Myelin ensheathment of axons enabled saltatory conduction and thus accelerated information processing. However, a number of CNS diseases harm or destroy myelin and oligodendrocytes (myelin-producing cells), ultimately resulting in demyelination. In the adult CNS, new oligodendrocytes can be generated from a quiescent pool of precursor cells, which – upon differentiation – can replace lost myelin sheaths. The efficiency of this spontaneous regeneration is limited, which leads to incomplete remyelination and residual clinical symptoms. Here, we discuss CNS pathologies characterized by white matter degeneration and regeneration and highlight drugs that could potentially serve as remyelination therapies.

Myelin: A Specialized Cellular Structure and a Prime Target in CNS Diseases

Myelin – together with axons and astrocytes – is a major component of the white matter of the vertebrate brain and spinal cord. It is a lipid-rich structure organized in multilayered sheaths around the conductive parts of neurons, the axons. Myelin sheaths represent an evolutionary acquired product of nature formed by oligodendroglial cells of the central nervous system (CNS) and by Schwann cells of the peripheral nervous system (PNS). These structures are a prerequisite for higher brain function as axonal ensheathment assures long-term axonal integrity and health by means of trophic and metabolic support. Furthermore, it allows for nerve conduction under minimal energy and space consumption [1,2]. In recent years, the impact of myelin dysfunction and white matter deficits has received more and more attention and is now thought to be a major contributing factor for neurodegenerative diseases of the CNS [3]. Given that approximately 40% of the human brain consists of white matter, of which besides compact fibers, myelin constitutes the main component, it is not surprising that its structural integrity is of vital importance for CNS function and restoration [4].

Myelin Composition and Developmental Oligodendrogenesis

Myelin sheaths, as extensions of the oligodendroglial plasma membrane, are separated into distinct domains, that is, compact myelin, composed of specialized plasma membrane spirals, and non-compacted myelin-forming loops that retain small amounts of cytoplasm near the nodes. These structures are important for protection and electrical insulation of axons and represent a key determinant for saltatory nerve conduction in which neuronal action potentials are restricted to nodes of Ranvier increasing conduction speed 20–100-fold as compared with non-myelinated axons [5] (Figure 1). While the early postnatal human brain is mostly non-myelinated, CNS myelination progressively increases in a defined topographic and temporal

Trends

In light of the current clinical success of immunomodulatory treatments in multiple sclerosis, the development of neuro- and glioprotective treatment options has received increased attention.

Several other neurological diseases are also characterized by loss of oligodendrocytes and myelin damage.

Myelin sheaths are generated by oligodendrocytes and represent key structures for saltatory signal propagation and trophic support of axons.

Remyelination, as one of the few spontaneous repair processes in the CNS, can provide a certain degree of myelin reconstitution but remains overall inefficient.

Migration, survival, proliferation, and differentiation have been recognized as key processes for successful myelin regeneration by resident oligodendroglial precursor cells.

Recently, multiple pharmacological compounds have emerged that exert beneficial effects on oligodendroglial precursor cells, thus representing potential candidates for the development of future myelin repair therapies.

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sequence within the first two decades of life [6]. Oligodendroglial precursor cells (OPCs) are considered the main source for generating mature oligodendrocytes and myelin during development. They are generated in sequential waves within specific regions of the ventral and the dorsal neuroepithelium of the spinal cord and brain before they migrate and disperse into the CNS [7]. While the vast majority of OPCs differentiate into myelinating oligodendrocytes, a proportion of OPCs characterized by the surface expression of neural/glial antigen 2 (NG2) and platelet-derived growth factor receptor α (PDGFRα) remains undifferentiated and persists as quiescent cells within the adult CNS (Figure 1). They comprise 5–8% of the total cell population and are distributed throughout gray and white matter [8–10]. Adult OPCs also known as adult NG2 cells, polydendrocytes, or synantocytes are primarily thought to contribute to myelin restoration in the injured or diseased CNS, but an involvement in synaptic transmission has also been demonstrated [11]. Both during development and under pathophysiological conditions, differentiation into mature oligodendrocytes requires a complex and precisely timed program including axonal selection and contact, cell cycle exit, expression of myelin-associated regulatory and structural genes and proteins, and the subsequent wrapping process generating internodes (Figure 1) [1].

Remyelination

Independent of underlying mechanisms and causes, neurodegenerative diseases generally result in permanent damage, functional loss, and persisting disabilities, since the adult CNS has only a limited capacity to repair damaged tissue. This restriction not only relates to neurons and their axons but also to mature oligodendrocytes that are unable to compensate for myelin loss as they usually degenerate [12,13]. Such demyelination, however, often triggers a spontaneous myelin repair process, also known as remyelination [14]. Remyelination results in myelin reconstitution and functional recovery via recruitment and activation of resident OPCs that can differentiate and replace lost oligodendrocytes [15]. In many ways this process recapitulates developmental myelination [16]; however, myelin sheaths generated in the adult brain exhibit decreased myelin thickness and shorter internodes as compared with their developmental counterparts. In multiple sclerosis (MS; see Glossary), the most frequent demyelinating disease of the adult CNS, so-called shadow plaques, partly remyelinated lesions characterized by their intermediate levels of myelin, can be observed as a neuropathological criterion for repair activity [17]. Remyelination-related steps such as OPC activation, recruitment, differentiation, and myelination [14,18] are tightly regulated by a number of extrinsic and intrinsic factors that act either as inhibitors or activators [19,20]. While remyelination can be very efficient in experimental *in vivo* models (Box 1), it varies between MS patients, lesions, and disease stages [21], and the efficiency of this endogenous repair process remains generally low, leading to permanent deficits and dysfunctions. To a certain extent, this decline is due to failure of OPCs to successfully generate new myelinating cells. Although the underlying reasons are not yet fully understood, several lines of evidence point to a variety of factors such as gender (sex), genetic background, age [22–24], as well as the presence of multiple differentiation inhibitors that specifically restrict the glial regeneration potential [20,25–27] (see also Box 2 for further information).

Myelin Damage in Multiple Sclerosis and Beyond

Myelin sheaths and oligodendrocytes are destroyed by inflammatory attacks during MS relapses (Figure 2). As a result, saltatory signal conduction is impaired and axonal damage occurs that manifests itself in clinical symptoms such as, for instance, optic neuritis, paraesthesias, motor weakness, or cognitive impairment. Inflammatory lesions occur throughout the brain and spinal cord and can be located in white as well as gray matter [28]. The enormous scientific effort invested into the accurate description of these processes in the past 50 years and its high prevalence of 1:1000 in Europe and North America have established MS as the lead disease featuring demyelination. However, there is ever-increasing evidence that myelin and oligodendrocyte loss are also relevant for many other CNS pathologies that are classically viewed as

Glossary

Alzheimer's disease (AD): is the most common form of dementia. AD has predominantly been associated with neuronal death due to the accumulation of extracellular β-amyloid (Aβ) plaques and intracellular tau-protein neurofibrillary tangles [135]. Prior to the appearance of typical Aβ plaques and tangles, myelin abnormalities occur in the AD brain and Aβ itself was reported to lead to increased oligodendroglial apoptosis [41,42]. In addition, myelin breakdown releases toxic iron promoting Aβ formation [44].

Amyotrophic lateral sclerosis (ALS): this neurodegenerative disease features progressive loss of bulbar and limb functions due to the degeneration of both upper and lower motor neurons [136]. The underlying cause for neurodegeneration is still largely unknown but several lines of evidence point to the importance of oxidative stress [137]. Particularly, the so-called Cu–Zn superoxide dismutase (SOD1) has been the focus of attention with approximately 20% of familial ALS cases being associated with mutations in this gene [138]. In early ALS, OPCs proliferate but seem to be blocked in their capacity to mature [38]. In general, expression of lactate transporters is decreased in ALS brains affecting energy supply for neurons and oligodendrocytes themselves [29], which might explain why spinal cord mature oligodendrocytes degenerate in ALS even prior to the development of clinical symptoms.

Cerebral ischemia: or stroke is the most common acute CNS disease and a major cause of mortality and morbidity throughout the world [139]. Besides hypoxic neuronal death as a result of disrupted cerebral blood flow, myelin loss seems to play a decisive role in the long-term clinical outcome [140]. Oligodendrocytes are highly sensitive to ischemic injury due to their high lipid content (myelin sheaths) and high iron content (as pointed out earlier in the context of AD). Resident OPCs in ischemia suffer from oxidative stress leading to substantial cell death and mature oligodendrocytes are harmed by glutamate-mediated excitotoxicity [57]. Increasing OPC numbers initiating differentiation were observed

primarily neuronal diseases. While the overall clinical relevance of myelin loss in these diseases remains to be elucidated in greater detail, white matter features should not be neglected – not least because for most of these pathological entities causal treatments or effective symptomatic therapies do not exist.

In recent years, a growing number of studies revealed that the function of oligodendroglial cells exceeds the formation and maintenance of myelin sheaths and also involves trophic support of axons [29]. Beyond demyelination – a result of oligodendroglial injury – it has become evident that without sufficient energy supply with substrates such as pyruvate, ketone bodies, and lactate via oligodendroglial monocarboxylate transporters (MCTs), neurons degenerate and ultimately die [2]. It is therefore essential to re-evaluate the role of oligodendroglia and their replacement in neurological diseases predominantly characterized by neuronal cell loss as it occurs, for instance, in **multiple system atrophy (MSA)**, **amyotrophic lateral sclerosis (ALS)**, **Alzheimer's diseases (AD)**, **schizophrenia (SZ)**, **cerebral ischemia**, and spinal cord injury (SCI) (Figure 2). Regeneration of functional oligodendrocytes that can provide trophic support and protection for neuronal structures might therefore also hold promise for the future treatment of such diseases. Of note, in this review we have not included diseases in which myelin degeneration occurs due to metabolic cell-intrinsic defects based on specific mutations as found in most of the so-called leukodystrophies (e.g., Krabbe disease, metachromatic leukodystrophy, or X-linked adrenoleukodystrophy). As opposed to these diseases in which myelin loss is intrinsically anticipated and occurs relatively early in life, we decided to focus on pathomechanisms that lead to the destruction of established mature myelin.

Although historically considered a relative of the α-synucleinopathy Parkinson's disease (PD), accumulation of misfolded α-synuclein in MSA occurs predominantly in oligodendrocytes and not in neurons. Recent studies unveiled a dysregulated myelin basic protein (MBP) metabolism in affected tissue even before synuclein deposits are observed, which suggest that MSA could be a primary oligodendrogliopathy [30]. Regarding the neurodegenerative feature of the disease, there is evidence pointing to a neuron-to-oligodendrocyte transfer of α-synuclein similar to the pathological processes observed in prion diseases [31]. Histopathologically, mature oligodendrocytes accumulate α-synuclein in the form of cytoplasmic inclusions, the so-called Papp–Lantos bodies (glial cytoplasmic inclusions, GCI) [32], leading to cell death (Figure 2). Accordingly, active immunization against α-synuclein was found to ameliorate degeneration and demyelination in respective transgenic animal models [33]. With regard to the impact of MSA on the resident OPC population, *in vitro* studies demonstrated that extracellular as well as endogenously produced α-synuclein inhibits glial differentiation resulting in elevated numbers of immature OPCs in MSA brain tissue [34]. However, in how far this observation is relevant for MSA is currently debated as there are contradicting results regarding the accumulation of α-synuclein in OPCs in postmortem patient tissue [35,36].

Growing evidence suggests that oligodendroglial cells might also play a relevant role in the pathology of ALS as, for example, myelin abnormalities were reported in SOD1 rats even before the onset of clinical signs [37]. Moreover, MCT1 expression levels were found to be substantially decreased in ALS brains affecting lactate transport from oligodendrocytes to neurons as well as energy supply for oligodendrocytes themselves [29]. Under such homeostatic disbalance, oligodendrocytes are more likely to become vulnerable to additional SOD1-associated increased oxidative stress by reactive oxygen species (ROS), which might explain why in the ALS spinal cord mature oligodendrocytes degenerate even prior to the development of symptoms [38,39]. OPCs, by contrast, were shown to enhance their proliferation rate, possibly to compensate for oligodendrocyte loss but were found to be inhibited in their capacity to differentiate [38].

in the ischemic penumbra of rats [58] so that exogenous stimulation of myelin repair could potentially contribute to recovery from ischemia. Specific blockade of proton-gated Ca^{2+}-permeable transient receptor potential (TRP) channels could be an alternative therapeutic approach as they were recently shown to damage myelin in white matter ischemia [141].

Multiple sclerosis (MS): based on the clinical disease course, different subtypes of MS can be distinguished [142]. Relapsing remitting MS (RRMS), the most common type (80–90% of patients), is characterized by acute disease exacerbations featuring demyelination followed by total or partial recovery of previously worsened functions. RRMS may transform into secondary progressive MS (SPMS), a disease form with or without eventual relapses and minor remissions that ultimately occurs in approximately 40% of all relapsing remitting courses. Thirdly, primary progressive MS (PPMS; approximately 15% of all patients) shows a steady worsening of symptoms without relapses or remissions and is most common among patients with a late disease onset. In both progressive disease forms, neurodegeneration outweighs inflammatory activity and damage steadily accumulates, whereas during early disease stages demyelinated lesions can regenerate that translates to transient functional improvement and clinical remission. Regeneration and remyelination in all MS types depend on the recruitment of resident OPCs that can replace lost oligodendrocytes. The remyelination process is tightly regulated by numerous extrinsic and intrinsic factors and its efficiency is overall low, decreasing further as the disease progresses.

Multiple system atrophy (MSA): is one of the most intriguing CNS diseases characterized by oligodendroglial cell death – a neurodegenerative disorder featuring myelin and axonal loss and subsequent gliosis [35]. Clinically, MSA occurs in different subtypes including a parkinsonian type (MSA-P) presenting with rigidity, bradykinesia, tremor, and postural instability and a cerebellar type (MSA-C) in which ataxia and dysarthria predominate. Accumulation of misfolded α-synuclein in MSA occurs predominantly in oligodendrocytes

There is also increasing evidence that oligodendrocytes and myelin might be relevant factors in AD pathology. Besides neuronal loss, myelin disruption can be observed particularly in late-onset AD brains [40] and it could be shown that even prior to the appearance of plaques and tangles myelin abnormalities occur in the brain [41]. Furthermore, Aβ stimulation of oligodendroglia was reported to lead to increased apoptosis [42]. Other lines of evidence suggest that rather than being merely the target of pathological processes, oligodendroglia and myelin might also actively participate in primary AD pathogenesis. It is hypothesized that age-related myelin breakdown in late-myelinating brain regions – those regions that are first affected by AD [43] – releases toxic iron that, in turn, promotes Aβ formation in neuritic plaques [44]. Even though as of now it remains unclear if myelin damage and oligodendroglial death are rather a cause or a consequence of AD (or both), it becomes increasingly clear that future therapeutic approaches should include strategies to protect and restore oligodendroglial functionality.

A number of studies suggested that oligodendrocytes and myelin dysfunction could also contribute to the development of SZ [45,46], as diseased brains showed a downregulation of key oligodendroglial and myelination genes [47]. Moreover, MRI imaging revealed white matter changes [45] with a decreased myelin water fraction indicating disturbed myelin maturation [48]. All this falls in line with genetic linkage studies that have shown that among others one particular gene, disrupted-in-Schizophrenia-1 (DISC1), is involved in the development of SZ. DISC1 and the DISC1-binding zinc finger (DBZ) are of interest since they have been shown to inhibit oligodendroglial differentiation [49–51]. It is therefore conceivable that DISC1 dysfunction contributes to SZ pathophysiology by improper myelination leading to detrimental changes in synapse formation and thus to a dysfunctional neurocircuitry. Finally, reported beneficial effects of the antipsychotic drug quetiapine on oligodendroglial maturation provide additional evidence for an oligodendroglial role in disease development [52–54].

Oligodendrocytes are extremely sensitive to ischemic injury due to their high lipid content (myelin sheaths), high iron content (as pointed out earlier in the context of AD), and comparatively limited reservoir of intracellular antioxidants such as glutathione [55]. These are the major mechanisms that seem to account for demyelination and oligodendroglial injury in cerebral ischemia. Whereas resident OPCs suffer from oxidative stress leading to substantial cell death [56], mature oligodendrocytes are more resilient but are nonetheless harmed by glutamate-mediated excitotoxicity [57]. It is important to note that myelin repair activities seem to kick in early following ischemia as increasing OPC numbers initiating differentiation were observed in the ischemic penumbra of rats [58]. It is therefore tempting to speculate that therapeutic approaches promoting myelin repair and protecting OPCs could also enhance recovery from ischemia.

Finally, research in the past decades focused on understanding the role of the so-called glial scar formed by reactive astrocytes following SCI that prevents injured axons from regenerating beyond lesions [59]. The question of oligodendroglial and myelin damage in SCI has recently received increasing attention as it harms oligodendrocytes acutely via mechanical stress, oxygen deprivation, and hemorrhage, but also entails protracted oligodendroglial apoptosis resulting in demyelination and diminished axonal functionality (reviewed in [60]; Figure 2). In injured rodents, oligodendroglial loss even continues for approximately 3 weeks in the lesion [61] until NG2-positive cells partly replace lost oligodendrocytes [62] – a process that is, however, weakened by the fact that NG2 cells may also generate astrocytes [63]. Reactivation of Notch signaling was reported to occur in the harmed spinal cord [64] and may thus contribute to OPC differentiation failure and the promotion of astrogliosis [65,66]. Furthermore, polysialylated neuronal cell adhesion molecule (PSA-NCAM), known to exert a detrimental effect on remyelination when expressed on the surface of demyelinated axons in MS, can also be found on reactive astrocytes in SCI [67]. Finally, neutralization of LINGO-1, a component of the Nogo-66 receptor/p75 signaling complex, was found to lead to improved functional recovery and axonal sprouting

and myelin basic protein (MBP) metabolism was found to be dysregulated even prior to synuclein deposition. There is evidence that oligodendrocytes actively participate in the disease process by transferring toxic α-synuclein to neurons leading to cell death (see also [31] for an overview on this disease). In addition, extracellular as well as endogenously produced α-synuclein inhibits glial differentiation resulting in elevated numbers of immature OPCs in MSA brain tissue [34,36].

Schizophrenia (SZ): a psychiatric disorder of largely unknown etiology manifesting itself with so-called 'positive' symptoms such as delusions, hallucinations, thought disorganization, and 'negative' symptoms such as depression and social withdrawal [143]. Myelin-forming oligodendrocytes are currently thought to contribute to psychiatric diseases in many ways, via hypomyelination, hypermyelination, as well as metabolic support [144]. In the SZ brain, key oligodendroglial and myelination genes are downregulated and white matter changes indicating disturbed myelin maturation can be detected [47]. Disrupted-in-schizophrenia-1 (DISC1), one of the most relevant genes for the development of SZ, was shown to inhibit oligodendroglial differentiation [49].

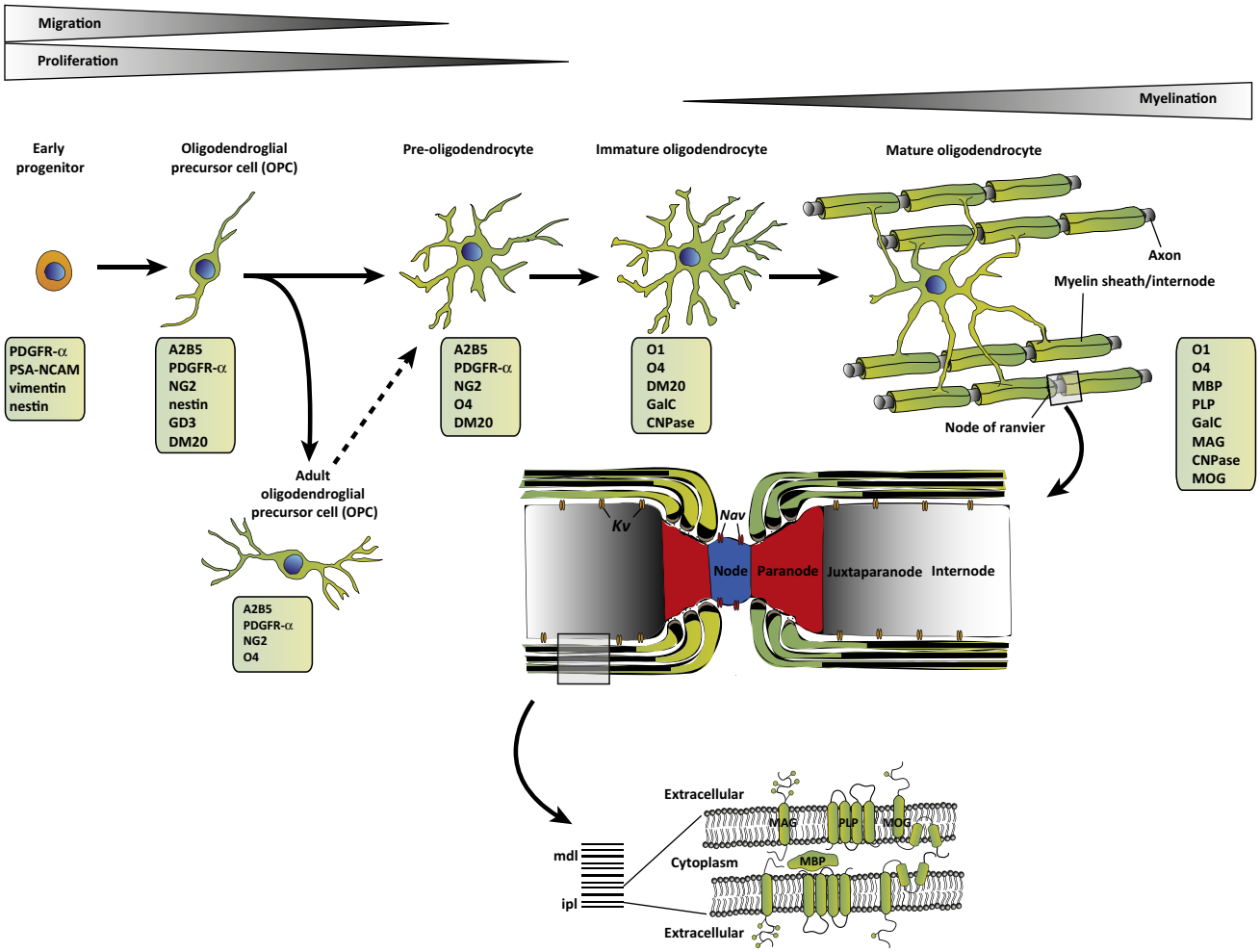

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Figure 1. Oligodendrogenesis, Cellular Stages, and Markers. During development, early (glial) progenitor cells give rise to oligodendroglial precursor cells (OPCs) that eventually transform into premature and immature oligodendrocytes. Cellular differentiation is accompanied by morphological conversion from bipolar precursor to mature cells with multiple processes forming a large network. These processes make contact with up to 40 segments of different axons to generate a multilayered myelin sheath that spirally covers the axon. Such internodes are separated by regions of exposed axonal membrane, the so-called nodes of Ranvier. Cells at different stages of maturation are characterized by specific combinations of marker proteins while their migratory activity and proliferation rates cease during the differentiation process. In the adult central nervous system (CNS), a fraction of immature oligodendroglial precursor cells (adult OPCs) persists. These cells are also referred to as adult NG2 cells, synantocytes, or polydendrocytes and are involved in synaptic signaling. Under pathophysiological conditions, they are recruited to generate new oligodendrocytes and myelin sheaths. In myelinated axons, voltage-gated sodium channels (Nav) are concentrated within central aspects of nodes, whereas voltage-gated potassium channels (Kv) are located in juxtaparanodes. Insulating properties of internodes can be attributed to compact myelin that consists of approximately 30% proteins and 70% lipids. Structural proteins such as proteolipid protein (PLP) and myelin basic protein (MBP) are fundamental to the compaction process, resulting in the typical appearance of alliterating concentric major dense lines (mdl) and light layers (intraperiod lines, ipl). Myelin-associated glycoprotein (MAG) is located in non-compacted periaxonal regions mediating cell–cell interactions between glial and axonal membranes. Myelin oligodendrocyte glycoprotein (MOG) is important for the glial–axonal junction at the paranode.

in SCI [68]. This is of significance as LINGO-1 inhibition has recently received considerable attention in the context of MS with clinical trials assessing its efficacy to enhance remyelination being currently underway (Table 1). These observations suggest that oligodendroglial inhibitory factors identified in the context of remyelination in MS [20] might similarly act in the injured CNS.

In general, with regard to inhibitory processes involved in failing or inefficient CNS repair in many diseases, the past years have seen mounting interest in the role of the so-called glial scar.

Box 1. Experimental Demyelination and Remyelination Models

Given that MS brain and spinal cord tissues are difficult to procure, a number of animal models were created to gain new insights into disease mechanisms and to test putative therapeutic agents. However, animal models only partly mimic the complex pathomechanisms of MS. For the induction of experimental demyelination, three general categories can be distinguished: (i) toxin-induced demyelination that is typically used to investigate demyelination and remyelination; (ii) autoimmune-induced models that have been used to study neuroinflammation and subsequent demyelination; and (iii) viral models. Toxin-induced demyelination models make use of lysolecithin (LPC), ethidium bromide (EtBr), or cuprizone to induce local oligodendroglial damage resulting in primary demyelination. In these models, demyelination is accompanied by a reproducibly timed spontaneous remyelination and both processes can be studied under non-inflammatory conditions. EAE, by contrast, recapitulates many features of MS, including demyelination, inflammation (myelin-reactive T cells), and neurodegeneration. This experimental disease is elicited by immunization of susceptible animals with CNS antigens such as whole white matter, myelin proteins or immunodominant peptides, or via adoptive transfer using activated, myelin antigen-specific T cells. Lastly, Theiler's murine encephalomyelitis virus (TMEV) and murine hepatitis virus (MHV) are used as infectious models that closely mimic certain aspects of MS pathology. Intracerebral infection of susceptible animals with certain TMEV or MHV strains results in a biphasic disease progression, comprising an early acute disease, followed by a late chronic phase featuring demyelination and remyelination, as well as axonal damage.

Historically, the glial scar formed by reactive astrocytes invading lesion sites upon injury has been viewed as a detrimental factor mainly for axonal regeneration. This is particularly the case in SCI where, probably via integrin disruption, the accumulation of chondroitin sulfate proteoglycans (CSPGs) inhibits axonal sprouting and growth (reviewed in [69]) or in MS where CSPGs interfere with OPC differentiation creating an unfavorable environment for remyelination [70]. More recent research, however, has led to a more balanced assessment of the role of the glial scar (reviewed in [71]). In SCI, it was shown to 'wall off' the lesion area restricting infiltration of activated inflammatory cells into surrounding tissue and it could be demonstrated that loss of reactive astrocytes in lesions leads to enhanced intralesional cell death potentially via increased glutamate levels [72]. However, one of the most relevant aspects when discussing neurorepair remains whether or not the glial scar is permissive to cellular transmigration allowing intralesional OPC recruitment and subsequent remyelination. In this regard, chemoattractive or repellent molecules play a decisive role. Two of the most intriguing candidates in this context that can be traced back to reactive astrocytes are the semaphorins 3A and 3F that can attract OPCs to lesions (3F) or repel them (3A; [73–75]). Further examples are netrin-1, which is also upregulated by reactive astrocytes in demyelinated lesions in MS and which has been shown to act as a chemorepellent for OPCs [76], and ephrinB3, initially described among axonal growth inhibitors, now revealed to be a potent blocker of oligodendrogenesis [77]. In summary, against the backdrop of the earlier-discussed contrasting roles of the glial scar in neuroregeneration, a definite assessment of its modulation as a future therapeutic tool remains, at present, difficult.

Therapeutic Approaches

Given the recent encouraging growth of the immunomodulatory treatment repertoire in MS, the current therapeutic research focus in MS has shifted from the prevention of new damage to the

Box 2. Remyelination

The adult mammalian CNS is generally regarded as a regeneration incompetent organ, as opposed to the PNS, where axonal connections and myelin sheaths can be restored more easily. Remyelination refers to the generation of new myelin sheaths around demyelinated axons as it occurs in a number of neurological conditions such as MS, peripheral neuropathies, and upon traumatic injuries. The aim of this process is to restore saltatory signal transduction, axonal stability, and trophic support. New myelin sheaths are shorter and thinner as the ones established during brain development. Myelin repair in the adult CNS is dependent on activation and recruitment of either resident OPCs or adult neural stem cells (aNSCs). Until recently, the contribution of aNSCs to myelin repair was considered to be minor, an assumption that is currently re-evaluated based on new observations in rodent demyelination models. Nevertheless, as one of the few regeneration processes that occur in the CNS, remyelination remains overall inefficient with an increasingly diminished myelin repair capacity during disease progression. By contrast, in the more regenerative adult PNS, remyelination is primarily dependent on Schwann cells. These peripheral myelinating glial cells can dedifferentiate and redifferentiate in response to lesion and disease. By doing so, they adopt a repair-mediating cellular phenotype, interact with immune cells, promote axonal regeneration, and finally myelinate regrown axons.

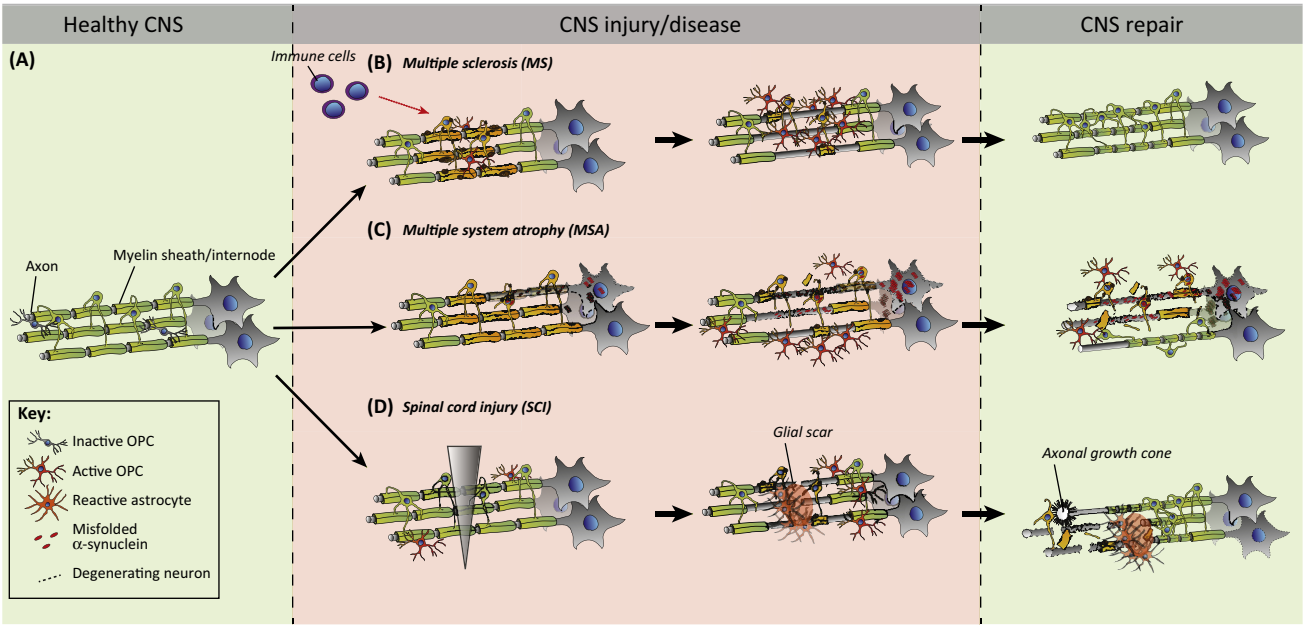

Figure 2. Roads to Demyelination. (A) Myelinated axons in the healthy central nervous system (CNS) can degenerate by various ways (B–D). (B) In multiple sclerosis (MS), immune cells attack myelin sheaths and oligodendrocytes. Upon demyelination, resident oligodendroglial precursor cells (OPCs) can be recruited to form new myelin sheaths around naked axons. Although this is one of the few possible spontaneous regeneration processes occurring in the CNS, the efficiency of myelin repair remains limited and many lesions/axons remain demyelinated. (C) Pathogenic mechanisms underlying selective degeneration in MSA. Mature oligodendrocytes accumulate cytoplasmic α-synuclein and intranuclear α-synuclein inclusions (red). α-Synuclein is transferred to neurons resulting in progressive neuronal dysfunction, axonal degeneration, and ultimately loss of oligodendrocytes and neurons. Remyelination of spared axons is thought to be impaired as extracellular as well as endogenously produced α-synuclein was found to interfere with oligodendroglial differentiation resulting in elevated numbers of immature OPCs in multiple system atrophy (MSA) brains. (D) Traumatic lesions such as in spinal cord injury result in axonal degeneration and neuronal loss. Directly injured oligodendrocytes or cells upon loss of axons also degenerate. Moreover, local inflammation, excitotoxic, and oxidative stress can affect spared axons and oligodendrocytes leading to secondary demyelination. Regeneration of injured axons and neuronal cell survival are limited by glial scar formation. Spared, regenerating, or new axons (plasticity) can eventually be myelinated by successfully recruited OPCs, given that they can access the lesion area through the surrounding glial scar.

repair of existing lesions. However, as outlined earlier, remyelination might also hold promise for a multitude of other neurological diseases so that future therapeutic compounds could have multiple clinical applications. In this context, MS may serve as a pioneering exemplary paradigm providing insight into potential new treatments for other diseases including demyelinating components. Even though the pathology and underlying molecular causes of remyelination failure in these diseases may differ from what is observed in the inflamed CNS, it is conceivable that knowledge about remyelination mechanisms in MS could, at least to a certain extent, be translated to these pathological entities. This concept is supported by the fact that many of the diseases discussed here share similar pathways and molecular cascades with MS such as, for instance, reactivation of Notch signaling in SCI [64] or the still unclear OPC differentiation block in ALS where, in early disease stages, OPCs have been observed to proliferate without subsequent maturation [38].

In the case of MS, neurorepair, as it occurs naturally and spontaneously in the CNS, is an overall inefficient process that fails to successfully counteract the accumulation of lasting axonal damage [78], increasing brain atrophy [79] and resulting motor and neuropsychological disabilities. As OPCs have been detected in chronic MS lesions even after years of disease progression [26], other determinants such as factors affecting migration and differentiation must be responsible for repair failure. As summarized in a recent overview [20], a plethora of inhibitory molecules ranging from transcription factors to extracellular matrix (ECM) proteins

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Table 1. Currently Evaluated Drugs Related to the Development of Myelin Repair Therapies

Drug	General Mode of Action	Relevance for Remyelination	Clinical Status	Current Trials	Refs
Drugs in Use					
Fingolimod	Blocks lymphocytic egress from lymph nodes by downregulation of lymphocytic S1P1 receptors.	Modulates process outgrowth in immature oligodendrocytes, enhances remyelination in experimental MS models, and reduces brain atrophy in RRMS patients.	Approved for the treatment of RRMS by the FDA in 2010 and the EMA in 2011.	Failed to improve the neurodegenerative processes in PPMS (INFORMS study).	[98–102]
Benztropine	Anticholinergic molecule inhibiting parasympathetic nerve activation.	Increases remyelination in toxic demyelination and decreases the clinical severity of EAE via muscarinic receptors; possibly also stimulates OPC differentiation by blocking Notch signaling.	Approved for treatment of Parkinson's disease and dystonia.	Currently the initiation of a clinical trial for efficacy in MS is being considered.	[103]
Quetiapine fumarate	Antagonist at the D2, 5-HT2A, H1, alpha 1, and 5-HT1A receptors exerting an antipsychotic effect.	May stimulate proliferation and maturation of oligodendrocytes; increases antioxidant defense.	Approved for use in schizophrenia, bipolar disorder, and as an add-on antidepressant medication.	Phase I study to determine safety and tolerability in MS patients (ClinicalTrials.gov: NCT02087631).	[52–54]
Simvastatin	3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor.	Reduces brain atrophy in SPMS via a so-far unknown mechanism but has no significant effect on relapse frequency or lesion load; was reported to have a detrimental effect on remyelination in the toxic cuprizone model.	Approved for the treatment of hypercholesterolemia.	Phase II trial (NCT00647348) in SPMS completed with a phase III trial currently in preparation.	[95,106, 107]
Indomethacin	Non-steroidal anti-inflammatory drug (NSAID) inhibiting cyclooxygenase.	Increases activation of the β-catenin destruction complex that phosphorylates β-catenin leading to its degradation. Loss of β-catenin promotes OPC differentiation and remyelination upon cuprizone-induced demyelination.	Approved as an OTC pain medication.	So far no clinical studies investigating efficacy in MS are underway.	[108]
Miconazole	Antifungal agent that weakens the formation of cell membranes by interfering with ergosterol synthesis.	Induces OPC differentiation probably via phosphorylation and activation of ERK1/2.	Approved for local antifungal treatment.	So far no clinical studies investigating efficacy in MS are underway.	[109]
Clobetasol	Derivate of the corticosteroid betamethasone suppressing inflammation.	Enhances OPC differentiation probably via an activation of the glucocorticoid receptor signaling axis.	Approved for local treatment of non-bacterial skin infections	So far no clinical studies investigating efficacy in MS are underway.	[109]

Table 1. (continued)

Drug	General Mode of Action	Relevance for Remyelination	Clinical Status	Current Trials	Refs
CDP-choline	Relevant metabolite in the synthesis of the membranous phospholipid phosphatidylcholine.	Increases OPC proliferation and facilitates remyelination by enhanced synthesis of phosphatidylcholine as an integral part of myelin.	Available as a supplement.	So far no clinical studies investigating efficacy in MS are underway. Failed in studies investigating cerebral ischemia.	[110]
Drugs in Trials					
BIIB033	Antibody against LINGO-1 modulating RhoA signaling.	Neutralization of LINGO-1 enhances oligodendroglial maturation, myelin sheath formation, and reduces severity of EAE.	Not approved yet.	Phase II study for efficacy in MS as an add-on therapy for interferon β-1a (NCT01864148). A study in optic neuritis (NCT01721161) has not reached its primary endpoint.	[111]
rHigM22	Recombinant human antibody binding to vitronectin/fibronectin receptor αvβ3.	Promotes the synthesis of new myelin in animal models by reduction of oligodendroglial apoptosis.	Not approved yet.	A phase I study in MS patients shows that rHigM22 is well-tolerated and can be found in the cerebrospinal fluid (CSF) (NCT01803867).	[112]
GNbAC1	Humanized antibody GNbAC1, directed against the proinflammatory envelope protein (ENV) of multiple sclerosis-associated retrovirus (MSRV).	GNbAC1 targets ENV to protect OPC differentiation by reduction of nitrosative stress.	Not approved yet.	Phase IIa study was successfully concluded (NCT01639300); a proof-of-concept Phase IIb study is currently being prepared.	[115,116]
Olesoxime	Cholesterol-like small molecule compound binding to two components of the mitochondrial permeability transition pore (PTP).	Increases the number of mature rodent oligodendroglial cells in animal models.	Not approved yet.	Phase I clinical trial evaluating olesoxime as an add-on therapy for interferon-β in patients with stable RRMS (NCT01808885).	[118]
GSK239512	Histamine H3 receptor antagonist so far studied in the context of Alzheimer's disease and in the hypomyelinated mouse model where it boosts oligodendroglial differentiation of transplanted OPCs.	H3 receptor antagonist enhances remyelination in the cuprizone model and increases the differentiation of human oligodendroglial precursor cells transplanted into the hypomyelinated mouse model.	Not approved yet.	Phase II study assessing whether GSK239512 can promote remyelination as an add-on therapy in patients receiving glatiramer acetate or interferon β-1a has been completed, results are not yet available (NCT01772199).	[119,120]

Table 1. (continued)

Drug	General Mode of Action	Relevance for Remyelination	Clinical Status	Current Trials	Refs
Clemastine	Antihistamine/anticholinergic compound blocking histamine H1 receptor.	Acts as an enhancer of OPC differentiation.	Not approved yet.	Phase II study investigating the potential of clemastine as a remyelinating agent in RRMS patients (NCT02040298).	[121]
VX15/2503	Humanized IgG4 anti-semaphorin 4D (SEMA4D) antibody interfering with SEMA4D/plexin B1 interactions.	Blockade of this pathway ameliorates EAE, increases OPC differentiation, and restores BBB breakdown.	Not approved yet.	Phase I study investigating the safety of VX15/2503 demonstrated that it is well tolerated by MS patients without major adverse effects (NCT01764737).	[123–126]
Experimental Compounds					
Quercetin	Flavonoid molecule acting as: (i) inhibitor of intramembranous γ-secretase and (ii) disruptor of β-catenin binding to transcription factor 4 (TCF4).	(i) γ-Secretase inhibitors interfere with canonical Notch signaling, which leads to enhanced remyelination. (ii) Binding of β-catenin to TCF4 was shown to delay myelin repair.	Not approved yet.	None of the γ-secretase compounds have yet been evaluated in CNS remyelination.	[128,129]
XAV939	Small molecule inhibiting the poly-ADP-ribosylating enzymes tankyrase 1 and 2.	Stabilizes Axin2 in OPCs, thereby improving remyelination by inhibition of Wnt signaling.	Not approved yet.	So far no clinical studies investigating efficacy in MS are underway.	[131]
Indazole chloride	Selective estrogen receptor–β agonist.	Improves remyelination in the cuprizone model.	Not approved yet.	So far no clinical studies investigating efficacy in MS are underway.	[133]
IRX4204	Small molecule IRX4204 activates retinoic acid receptor γ (RXR-γ), which is involved in remyelination.	Enhances oligodendroglial differentiation.	Not approved yet.	Clinical trials for MS are currently in the planning stage.	[132]
GANT61	Small molecule blocking Gli1 transcription factor.	Promotes the generation of oligodendrocytes from adult neural stem cells.	Not approved yet.	So far no clinical studies investigating efficacy in MS are underway.	[89]
Solifenacin	Blocks CHRM3, an M3R muscarinic acetylcholine receptor.	Increased differentiation of transplanted human OPCs in hypomyelinated shiverer/rag2 mice.	FDA-approved for treating contraction of overactive bladder.	So far no clinical studies investigating efficacy in MS are underway.	[85]
BQ788	Endothelin (ET) receptor antagonists.	Blocks endothelin-B receptor activation on astrocytes and thereby rescues oligodendrogenesis in remyelination.	Used in research but has not yet reached the clinical trial stage.	So far no clinical studies investigating efficacy in MS are underway.	[88]

were observed to interfere with proper differentiation of OPCs. While it still remains to be shown to what extent all these factors affect alone or in combination glial responses, additional negative regulators emerged in the meantime such as death receptor 6 (DR6; [80]), GSK3β [81], NFIA [82], galectin-4 [83], DISC1 [49], non-muscle myosin IIB [84], the CHRM3 muscarinic acetylcholine receptor [85], TROY [86], endothelin-1 (ET-1; [87,88]), Gli1 [89], the protease-activated receptor 1 [90], and the transmembrane signaling protein ephrinB3 [77]. In light of the apparently overwhelming negative input immature oligodendroglial cells are confronted with, there is a need to address how we can target those factors to support and disinhibit the endogenous repair capacity of the brain or whether among them master regulators can be identified. Among those recently discovered negative regulators, extracellular or cell surface components such as DR6, galectin-4, CHCRM3, TROY, and ephrinB3 are most likely the targets with the highest translational potential given their accessibility and some reports on successful neutralization using specific antibodies or antagonists. But even for transcriptional regulators such as Gli1 or secreted intercellular signaling molecules such as endothelin-1, suitable pharmacological compounds can be identified, as exemplified by the small molecule inhibitor GANT61 [89] as well as the ET receptor antagonists PD142,893 or BQ788 [87,88], and thus lead towards therapeutic application.

However, stimulating remyelination will only be one part of future therapeutic strategies that must, in a two-pronged approach, also provide neuroprotection for vulnerable axons in demyelinated tissue. Prior to remyelination, demyelinated 'naked' axons are exposed to increased pH and ionic disbalances leading to cell swelling, mitochondrial failure, oxidative stress (reviewed in [91]), and ultimately axonal transection (reviewed in [92]). Supporting neuronal survival and viability is therefore a vital prerequisite for successful remyelination. Several neuroprotective substances have emerged in the past decade targeting the pathological features described earlier. Sodium channel blockers clinically used as antiepileptic drugs, such as phenytoin [93] or lamotrigine [94], seem to have a beneficial effect on neuronal integrity. Other medications that might protect axons include the HMG-CoA reductase inhibitor simvastatin that was found to reduce brain atrophy in MS patients [95] and erythropoietin that showed promising effects in optic neuritis [96]. To provide an environment susceptible for repair such drugs will have to be combined with agents specifically enhancing remyelination.

Fortunately, the past years have seen the emergence of multiple pharmacological agents and compounds exerting beneficial effects on the remyelinating cell repertoire acting via a host of different molecular pathways, thus representing potential candidates for the development of novel therapies. These agents can be generally divided into three distinct subgroups: (i) medications that are FDA- and EMA-approved for other diseases but have a proposed role in regeneration; (ii) regenerative treatments under investigation in clinical trials; and (iii) promising experimental compounds aiming specifically at facilitating endogenous repair (Table 1).

Currently Evaluated Drugs Related to the Development of Myelin Repair Therapies

Fingolimod/Gilenya that was approved as the first oral immunomodulatory MS drug in 2010 is a first-in-class sphingosine-1-phosphate (S1P) receptor modulator that controls lymphocyte trafficking [97]. However, it was also found to modulate resident oligodendroglial cells and to increase remyelination efficiency [98–100]. To what extent this holds true for demyelination in inflammatory paradigms and whether Fingolimod acting on all S1P receptors expressed by oligodendroglial cells (i.e., S1P1, S1P3, S1P5) is beneficial to the regeneration process has not yet been completely clarified. It is therefore conceivable that the slowing of brain atrophy in Relapsing remitting MS (RRMS) patients treated with Fingolimod as measured by MRI [101] is a direct result of its regenerative potential. However, a recent Phase III trial in primary progressive MS failed to show a therapeutic effect [102]. Benztropine, an anticholinergic drug used to treat

PD was identified in a large-scale compound screening and was demonstrated to affect remyelination [103] (Figure 3). Probably via muscarinic receptors it blocks Notch signaling, a known inhibitory pathway for oligodendroglial differentiation [20]. Quetiapine fumarate, by contrast, is a medication commonly used to treat psychosis (see paragraph on schizophrenia earlier) and acts on several different receptors (Table 1). It was found to stimulate oligodendroglial

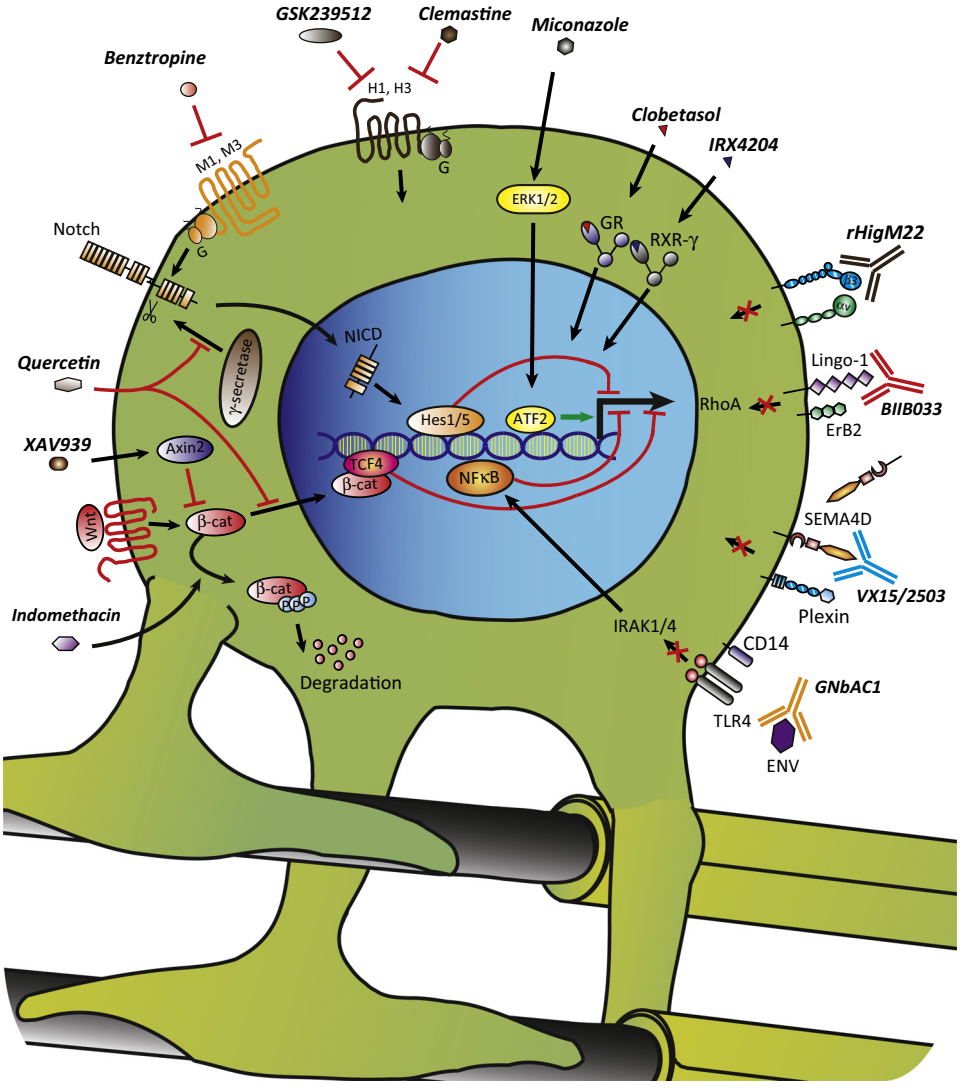

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Figure 3. Oligodendroglial Precursor Cell (OPC) Differentiation Promoting Processes. For an improved myelin repair, OPC recruitment, survival, and differentiation were found to be promoted by a number of agents: antibodies such as BIIB033, GNbAC1, VX15/2503, and rHigM22 can be applied to neutralize negative regulatory factors such as Lingo-1, Herv-W envelope (ENV), and SEMA4D or to enhance cell survival and proliferation rates, respectively. Modulated nuclear receptor signaling via clobetasol and IRX4204 acting on glucocorticoid and retinoic acid receptors, respectively, and miconazole acting on ERK1/2 signaling could also contribute to improved OPC maturation. Moreover, histamine receptor blockers such as GSK239512 and clemastine, molecules influencing Notch and Wnt signaling cascades such as quercetin, XAV939, indomethacin, and benztropine were also reported to stimulate oligodendroglial differentiation and thus represent putative drugs suitable for the promotion of myelin repair activities. Some of these signaling pathways act on transcription factors such as TCF4, Hes1/5, ATF, NFκB, or Notch receptor intracellular domain (NICD). Abbreviations: β-cat, β-catenin; G, G protein; M1, M3, M1 and M3 muscarinic receptors; H1, H3, H1 and H3 histamine receptors; GR, glucocorticoid receptor; RXR-γ, retinoic acid receptor γ.

differentiation [52–54] and a Phase I clinical trial is currently recruiting patients (ClinicalTrials.gov: NCT02087631). It is, however, conceivable that the pro-oligodendroglial effect could also be attributed to its fumarate portion as dimethyl fumarate (DMF) was shown to exert neuroprotective effects in the inflamed CNS and to directly protect oligodendroglial cells from oxidative stress in culture [104,105]. Simvastatin, one of the most frequently used medications for hypercholesterinemia, has been the subject of controversial scientific discussions regarding its impact on neurorepair. While one study demonstrated that statins can induce peroxisome proliferator-activated receptor (PPAR)γ-mediated oligodendroglial differentiation [106], later results suggested that it may even be counterproductive by inhibiting remyelination in an animal model [107]. Of note, a clinical study demonstrated that statins reduce the development of brain atrophy in secondary progressive MS (SPMS) while lacking an effect on relapse frequency or lesion load [95]. Indomethacin, a widely used non-steroidal anti-inflammatory drug (NSAID) was recently shown to diminish β-catenin activity that, in turn, promotes OPC differentiation and remyelination in animal models [108] (Figure 3). Further drugs of interest in the context of myelin restoration are miconazole, an approved antifungal agent, and clobetasol, a betamethasone derivate approved for treating non-bacterial skin infections. Both substances were identified in a large-scale screening and found to stimulate oligodendroglial differentiation via ERK1/2 signaling and through glucocorticoid receptor activation, respectively [109] (Figure 3). CDP-choline, an important metabolite for plasma membrane synthesis, notably available as an over-the-counter (OTC) food supplement, was recently described to facilitate CNS remyelination [110]. Although unproven, this effect is probably a consequence of enhanced phosphatidylcholine synthesis that constitutes an integral part of myelin.

BIIB033, a monoclonal antibody, developed to neutralize LINGO-1, which is known to inhibit remyelination via activation of Rho-A, is currently tested for its efficiency as a remyelinating drug. Neutralization of LINGO-1 promoted remyelination in a number of animal paradigms (reviewed in [111]; Figure 3) that fueled very high expectations regarding its potential effect in MS. While a study investigating the effect of BIIB033 in optic neuritis (ClinicalTrials.gov: NCT01721161) has unfortunately not reached its primary endpoint (retinal nerve fiber thickness preservation) while improving nerve conduction velocity as measured by visually evoked potentials (VEPs; a secondary outcome and fingerprint of functional remyelination), a Phase II study in RRMS is still underway (ClinicalTrials.gov: NCT01864148). rHigM22, a recombinant human IgM antibody targeting the oligodendroglial vitronectin/fibronectin receptor αvβ3 (Figure 3), was shown to decrease OPC apoptosis and to simultaneously elevate oligodendroglial proliferation rates by lowering the threshold for PDGF stimulation [112]. A Phase I trial using this antibody has recently been completed (ClinicalTrials.gov: NCT01803867). The IgG4 antibody GNbAC1 directed against the envelope protein (ENV) of multiple sclerosis-associated retrovirus (MSRV), a member of the HERV-W family of endogenous retroviruses, constitutes yet another compound that could enhance remyelination (Figure 3). Reactivated MSRV particles and ENV protein can be detected in the serum and the cerebrospinal fluid of MS patients [113]. The ENV protein was then found to act as a proinflammatory factor [114] and recently it was shown that it also interferes with OPC differentiation via nitrosative stress induction [115]. GNbAC1, by contrast, can neutralize this effect and rescue myelin expression in OPCs [116]. Of note, in a recent Phase IIa study GNbAC1 was well tolerated by MS patients [117]. Olesoxime, a cholesterol-like small molecule, binds to two components of the mitochondrial permeability transition pore (PTP) in oligodendrocytes and thereby exerts a primarily glioprotective effect [118]. While a study in ALS investigating motoneuron survival under olesoxime treatment failed to show a clinical benefit, a Phase I study in RRMS was conducted in 2014 with no results posted to date (ClinicalTrials.gov: NCT01808885). Histamine receptor blockers represent another forthcoming group of pro-oligodendroglial agents (Figure 3). GSK239512 was initially identified as a stimulator of oligodendroglial differentiation in a compound screening based on MBP expression analysis [119]. Corresponding histamine receptors can be detected in MS lesions and their depletion increased

rodent experimental autoimmune encephalomyelitis (EAE) resistance [120]. While a Phase II study to assess whether GSK239512 can remyelinate lesions in RRMS patients has been completed (ClinicalTrials.gov: NCT01772199), a phase II study on the role of clemastine fumarate as a remyelinating agent [121] is currently recruiting patients (ClinicalTrials.gov: NCT02040298). This compound might even be of broader interest as it could recently be demonstrated that clemastine boosts myelination in prefrontal cortex of socially isolated mice, thereby rescuing behavioral changes [122]. Modulation of semaphorin signaling could also be a functional base for future remyelination approaches. Semaphorin 4D (SEMA4D) was shown to inhibit OPC differentiation [123], to induce oligodendroglial process collapse [124], and to worsen EAE probably via blood–brain barrier (BBB) breakdown induction [125]. Accordingly, the humanized IgG4 anti-SEMA4D antibody VX15/2503 that interferes with SEMA4D/plexin B1 interactions was shown to improve OPC differentiation and EAE ([126]; Figure 3). A Phase I study investigating the safety of VX15/2503 demonstrated that the drug is well tolerated by MS patients (ClinicalTrials.gov: NCT01764737). Of note, it was recently demonstrated that another member of the semaphorin family, SEMA7A, can serve as a molecular parameter for disease progression in MS as elevated titers of this molecule could be detected in worsening disease courses. Functionally, SEMA7A is thought to modulate oligodendroglial migration into demyelinated lesions [127].

Finally, there are several agents that have shown promising effects *in vitro* and/or in the animal model but have so far not progressed to clinical trials. As described further above in the context of benztropine, inhibiting oligodendroglial Notch signaling may exert beneficial effects on oligodendroglial differentiation. Quercetin, a flavonoid molecule, acts as an inhibitor of intramembranous γ-secretase, thereby reducing the cleavage of the Notch receptor intracellular domain (NICD). This, in turn, was found to enhance remyelination in the demyelinated hypoxic animal model [128,129] (Figure 3). Quercetin also modulates the Wnt signaling pathway by disrupting β-catenin/transcription factor TCF4 interactions known to delay myelin repair [130]. Of note, XAV939, a small molecule inhibiting the poly-ADP-ribosylating enzymes tankyrase 1 and 2 exerts an inhibitory effect on Wnt signaling [131] (Figure 3) and is therefore yet another agent with remyelination potential. Further factors that could be beneficial in the context of white matter repair are, for example, IRX4204, a small molecule that activates retinoic acid receptor γ (RXR-γ; [132]) (Figure 3), and indazole chloride, a selective estrogen receptor–β agonist that has been shown to be effective upon cuprizone-mediated demyelination and in EAE [133]. This might at least partly reflect the clinical observation that pregnant MS patients are often free of relapses during their third trimenon – a phenomenon still not entirely understood. Finally, high-dose biotin might also be considered for the future treatment of myelin loss as it has been described to activate myelin formation in oligodendrocytes through its role as a cofactor for acetyl-CoA carboxylase and given that high-dose biotin treatments were recently shown to exert a therapeutic effect in patients with progressive MS [134].

Concluding Remarks

The main limitation of current treatments for most neurological diseases consists in the fact that they do not reduce existing deficits but rather aim at preventing new damage. Long-term goals such as averting neurodegeneration as it occurs in SPMS by means of restoring functional axon/glia interactions can currently not be achieved. Nevertheless, in the past decade the process of myelin repair in the adult CNS has received increasing attention, both among scientists as well as clinicians. This has promoted the identification of regulatory processes and substances that might pave the way towards the development of therapeutic agents. Since some drugs with a putative regenerative potential are already approved for other diseases, translation to MS could be accelerated. More specific compounds identified through basic and preclinical research will most likely only emerge in a few years, upon successful completion of specific clinical studies. Given the plethora of regulatory processes found to interfere with oligodendrogenesis as well as

Outstanding Questions

Can oligodendroglial precursor cells in the CNS parenchyma be reached by remyelination-mediating drugs? What are the BBB penetration and diffusion properties of antibodies versus small molecules?

What are appropriate windows of opportunity for the treatment of different neurological diseases?

Can appropriate assessment tools be defined to measure neuroregeneration and myelin repair in patients? Can suitable biomarkers be identified? Are the currently used clinical and paraclinical readouts such as MRI imaging and Expanded Disability Status Scale (EDSS) scoring sensitive enough to measure remyelination?

Can all neurological diseases with white matter injuries be treated using the same myelin repair drugs?

Can we identify master negative regulatory switches influencing OPC migration and/or differentiation?

the significant number of different pathologies featuring white matter injury, it will most likely be necessary to address myelin repair with the simultaneous use of different compounds. Moreover, limitations of currently used imaging techniques should be complemented by other readouts such as newly identified biomarkers (see Outstanding Questions).

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References

1. Mitew, S. *et al.* (2014) Mechanisms regulating the development of oligodendrocytes and central nervous system myelin. *Neuroscience* 276, 29–47
2. Morrison, B.M. *et al.* (2013) Oligodendroglia: metabolic supporters of axons. *Trends Cell Biol.* 23, 644–651
3. Bercury, K.K. and Macklin, W.B. (2015) Dynamics and mechanisms of CNS myelination. *Dev. Cell* 32, 447–458
4. Snaidero, N. and Simons, M. (2014) Myelination at a glance. *J. Cell Sci.* 127, 2999–3004
5. Nave, K.A. and Werner, H.B. (2014) Myelination of the nervous system: mechanisms and functions. *Annu. Rev. Cell Dev. Biol.* 30, 503–533
6. Yeung, M.S. *et al.* (2014) Dynamics of oligodendrocyte generation and myelination in the human brain. *Cell* 159, 766–774
7. Crawford, A.H. *et al.* (2014) Oligodendrocyte progenitors: adult stem cells of the central nervous system? *Exp. Neurol.* 260, 50–55
8. Nishiyama, A. *et al.* (2009) Polydendrocytes (NG2 cells): multifunctional cells with lineage plasticity. *Nat. Rev. Neurosci.* 10, 9–22
9. Levine, J.M. *et al.* (2001) The oligodendrocyte precursor cell in health and disease. *Trends Neurosci.* 24, 39–47
10. Chang, A. *et al.* (2000) NG2-positive oligodendrocyte progenitor cells in adult human brain and multiple sclerosis lesions. *J. Neurosci.* 20, 6404–6412
11. Dimou, L. and Gallo, V. (2015) NG2-glia and their functions in the central nervous system. *Glia* 63, 1429–1451
12. Pomeroy, I.M. *et al.* (2010) Focal and diffuse cortical degenerative changes in a marmoset model of multiple sclerosis. *Mult. Scler.* 16, 537–548
13. Wegner, C. *et al.* (2006) Neocortical neuronal, synaptic, and glial loss in multiple sclerosis. *Neurology* 67, 960–967
14. Franklin, R.J. and Ffrench-Constant, C. (2008) Remyelination in the CNS: from biology to therapy. *Nat. Rev. Neurosci.* 9, 839–855
15. El Waly, B. *et al.* (2014) Oligodendrogenesis in the normal and pathological central nervous system. *Front. Neurosci.* 8, 145
16. Franklin, R.J. and Hinks, G.L. (1999) Understanding CNS remyelination: clues from developmental and regeneration biology. *J. Neurosci. Res.* 58, 207–213
17. Miron, V.E. *et al.* (2011) Cells of the oligodendroglial lineage, myelination, and remyelination. *Biochim. Biophys. Acta* 1812, 184–193
18. Bruce, C.C. *et al.* (2010) Remyelination – an effective means of neuroprotection. *Horm. Behav.* 57, 56–62
19. Rivera, F.J. *et al.* (2010) Deciphering the oligodendrogenic program of neural progenitors: cell intrinsic and extrinsic regulators. *Stem Cells Dev.* 19, 595–606
20. Kremer, D. *et al.* (2011) The complex world of oligodendroglial differentiation inhibitors. *Ann. Neurol.* 69, 602–618
21. Louapre, C. *et al.* (2015) Beyond focal cortical lesions in MS: an in vivo quantitative and spatial imaging study at 7T. *Neurology* 85, 1702–1709
22. Li, W.W. *et al.* (2006) Females remyelinate more efficiently than males following demyelination in the aged but not young adult CNS. *Exp. Neurol.* 202, 250–254
23. Bieber, A.J. *et al.* (2005) Genetically dominant spinal cord repair in a murine model of chronic progressive multiple sclerosis. *J. Neuropathol. Exp. Neurol.* 64, 46–57
24. Shields, S.A. *et al.* (1999) Remyelination occurs as extensively but more slowly in old rats compared to young rats following gliotoxin-induced CNS demyelination. *Glia* 28, 77–83
25. Kuhlmann, T. *et al.* (2008) Differentiation block of oligodendroglial progenitor cells as a cause for remyelination failure in chronic multiple sclerosis. *Brain* 131, 1749–1758
26. Chang, A. *et al.* (2002) Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. *N. Engl. J. Med.* 346, 165–173
27. Wolswijk, G. (1998) Chronic stage multiple sclerosis lesions contain a relatively quiescent population of oligodendrocyte precursor cells. *J. Neurosci.* 18, 601–609
28. Chang, A. *et al.* (2012) Cortical remyelination: a new target for repair therapies in multiple sclerosis. *Ann. Neurol.* 72, 918–926
29. Lee, Y. *et al.* (2012) Oligodendroglia metabolically support axons and contribute to neurodegeneration. *Nature* 487, 443–448
30. Wenning, G.K. *et al.* (2008) Multiple system atrophy: a primary oligodendrogliopathy. *Ann. Neurol.* 64, 239–246
31. Jellinger, K.A. (2014) Neuropathology of multiple system atrophy: new thoughts about pathogenesis. *Mov. Disord.* 29, 1720–1741
32. Papp, M.I. *et al.* (1989) Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy–Drager syndrome). *J. Neurol. Sci.* 94, 79–100
33. Mandler, M. *et al.* (2015) Active immunization against alpha-synuclein ameliorates the degenerative pathology and prevents demyelination in a model of multiple system atrophy. *Mol. Neurodegener.* 10, 10
34. Ettle, B. *et al.* (2014) Intracellular alpha-synuclein affects early maturation of primary oligodendrocyte progenitor cells. *Mol. Cell. Neurosci.* 62, 68–78

35. Ahmed, Z. *et al.* (2013) Identification and quantification of oligodendrocyte precursor cells in multiple system atrophy, progressive supranuclear palsy and Parkinson's disease. *Brain Pathol.* 23, 263–273
36. May, V.E. *et al.* (2014) alpha-Synuclein impairs oligodendrocyte progenitor maturation in multiple system atrophy. *Neurobiol. Aging* 35, 2357–2368
37. Niebroj-Dobosz, I. *et al.* (2007) Myelin composition of spinal cord in a model of amyotrophic lateral sclerosis (ALS) in SOD1G93A transgenic rats. *Folia Neuropathol.* 45, 236–241
38. Kang, S.H. *et al.* (2013) Degeneration and impaired regeneration of gray matter oligodendrocytes in amyotrophic lateral sclerosis. *Nat. Neurosci.* 16, 571–579
39. Philips, T. *et al.* (2013) Oligodendrocyte dysfunction in the pathogenesis of amyotrophic lateral sclerosis. *Brain* 136, 471–482
40. Zhan, X. *et al.* (2014) Myelin injury and degraded myelin vesicles in Alzheimer's disease. *Curr. Alzheim. Res.* 11, 232–238
41. Desai, M.K. *et al.* (2009) Triple-transgenic Alzheimer's disease mice exhibit region-specific abnormalities in brain myelination patterns prior to appearance of amyloid and tau pathology. *Glia* 57, 54–65
42. Roth, A.D. *et al.* (2005) Oligodendrocytes damage in Alzheimer's disease: beta amyloid toxicity and inflammation. *Biol. Res.* 38, 381–387
43. Braak, H. and Braak, E. (1998) Evolution of neuronal changes in the course of Alzheimer's disease. *J. Neural Transm. Suppl.* 53, 127–140
44. Bartzokis, G. *et al.* (2007) Human brain myelination and amyloid beta deposition in Alzheimer's disease. *Alzheim. Dement.* 3, 122–125
45. Davis, K.L. and Haroutunian, V. (2003) Global expression-profiling studies and oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* 362, 758
46. Walterfang, M. *et al.* (2005) Diseases of white matter and schizophrenia-like psychosis. *Aust. N. Z. J. Psychiatry* 39, 746–756
47. Tkachev, D. *et al.* (2003) Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* 362, 798–805
48. Flynn, S.W. *et al.* (2003) Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem with analysis of oligodendrocyte proteins. *Mol. Psychiatry* 8, 811–820
49. Hattori, T. *et al.* (2014) DISC1 (disrupted-in-schizophrenia-1) regulates differentiation of oligodendrocytes. *PLoS ONE* 9, e88506
50. Katsel, P. *et al.* (2011) Expression of mutant human DISC1 in mice supports abnormalities in differentiation of oligodendrocytes. *Schizophr. Res.* 130, 238–249
51. Shimizu, S. *et al.* (2014) DBZ, a CNS-specific DISC1 binding protein, positively regulates oligodendrocyte differentiation. *Glia* 62, 709–724
52. Bi, X. *et al.* (2012) Quetiapine prevents oligodendrocyte and myelin loss and promotes maturation of oligodendrocyte progenitors in the hippocampus of global cerebral ischemia mice. *J. Neurochem.* 123, 14–20
53. Xiao, L. *et al.* (2008) Quetiapine facilitates oligodendrocyte development and prevents mice from myelin breakdown and behavioral changes. *Mol. Psychiatry* 13, 697–708
54. Zhang, Y. *et al.* (2012) Quetiapine enhances oligodendrocyte regeneration and myelin repair after cuprizone-induced demyelination. *Schizophr. Res.* 138, 8–17
55. Dewar, D. *et al.* (2003) Oligodendrocytes and ischemic brain injury. *J. Cereb. Blood Flow Metab.* 23, 263–274
56. Skoff, R.P. *et al.* (2001) Hypoxic–ischemic injury results in acute disruption of myelin gene expression and death of oligodendroglial precursors in neonatal mice. *Int. J. Dev. Neurosci.* 19, 197–208
57. Matute, C. *et al.* (2007) Excitotoxic damage to white matter. *J. Anat.* 210, 693–702
58. Ohta, K. *et al.* (2003) Dissociative increase of oligodendrocyte progenitor cells between young and aged rats after transient cerebral ischemia. *Neurosci. Lett.* 335, 159–162
59. Silver, J. and Miller, J.H. (2004) Regeneration beyond the glial scar. *Nat. Rev. Neurosci.* 5, 146–156
60. McTigue, D.M. and Sahinkaya, F.R. (2011) The fate of proliferating cells in the injured adult spinal cord. *Stem Cell Res. Ther.* 2, 7
61. Warden, P. *et al.* (2001) Delayed glial cell death following wallerian degeneration in white matter tracts after spinal cord dorsal column cordotomy in adult rats. *Exp. Neurol.* 168, 213–224
62. Lytle, J.M. *et al.* (2009) NG2 cell response in the CNP–EGFP mouse after contusive spinal cord injury. *Glia* 57, 270–285
63. Sellers, D.L. *et al.* (2009) Postinjury niches induce temporal shifts in progenitor fates to direct lesion repair after spinal cord injury. *J. Neurosci.* 29, 6722–6733
64. Yamamoto, S. *et al.* (2001) Transcription factor expression and Notch-dependent regulation of neural progenitors in the adult rat spinal cord. *J. Neurosci.* 21, 9814–9823
65. Kamei, N. *et al.* (2012) Endothelial progenitor cells promote astrogliosis following spinal cord injury through Jagged1-dependent Notch signaling. *J. Neurotrauma* 29, 1758–1769
66. Wang, S. *et al.* (1998) Notch receptor activation inhibits oligodendrocyte differentiation. *Neuron* 21, 63–75
67. Camand, E. *et al.* (2004) Long-term changes in the molecular composition of the glial scar and progressive increase of serotoninergic fibre sprouting after hemisection of the mouse spinal cord. *Eur. J. Neurosci.* 20, 1161–1176
68. Ji, B. *et al.* (2006) LINGO-1 antagonist promotes functional recovery and axonal sprouting after spinal cord injury. *Mol. Cell. Neurosci.* 33, 311–320
69. Lemons, M.L. and Condic, M.L. (2008) Integrin signaling is integral to regeneration. *Exp. Neurol.* 209, 343–352
70. Lau, L.W. *et al.* (2012) Chondroitin sulfate proteoglycans in demyelinated lesions impair remyelination. *Ann. Neurol.* 72, 419–432
71. Raposo, C. and Schwartz, M. (2014) Glial scar and immune cell involvement in tissue remodeling and repair following acute CNS injuries. *Glia* 62, 1895–1904
72. Faulkner, J.R. *et al.* (2004) Reactive astrocytes protect tissue and preserve function after spinal cord injury. *J. Neurosci.* 24, 2143–2155
73. Piaton, G. *et al.* (2011) Class 3 semaphorins influence oligodendrocyte precursor recruitment and remyelination in adult central nervous system. *Brain* 134, 1156–1167
74. Moreau-Fauvarque, C. *et al.* (2003) The transmembrane semaphorin Sema4D/CD100, an inhibitor of axonal growth, is expressed on oligodendrocytes and upregulated after CNS lesion. *J. Neurosci.* 23, 9229–9239
75. Williams, A. *et al.* (2007) Semaphorin 3A and 3F: key players in myelin repair in multiple sclerosis? *Brain* 130, 2554–2565
76. Tepavcevic, V. *et al.* (2014) Early netrin-1 expression impairs central nervous system remyelination. *Ann. Neurol.* 76, 252–268
77. Syed, Y.A. *et al.* (2016) Antibody-mediated neutralization of myelin-associated EphrinB3 accelerates CNS remyelination. *Acta Neuropathol.* 131, 281–298
78. Trapp, B.D. *et al.* (1998) Axonal transection in the lesions of multiple sclerosis. *N. Engl. J. Med.* 338, 278–285
79. Chard, D.T. *et al.* (2002) Brain atrophy in clinically early relapsing-remitting multiple sclerosis. *Brain* 125, 327–337
80. Mi, S. *et al.* (2011) Death receptor 6 negatively regulates oligodendrocyte survival, maturation and myelination. *Nat. Med.* 17, 816–821
81. Azim, K. and Butt, A.M. (2011) GSK3beta negatively regulates oligodendrocyte differentiation and myelination in vivo. *Glia* 59, 540–553
82. Fancy, S.P. *et al.* (2012) Evidence that nuclear factor IA inhibits repair after white matter injury. *Ann. Neurol.* 72, 224–233
83. Stancic, M. *et al.* (2012) Galectin-4, a novel neuronal regulator of myelination. *Glia* 60, 919–935
84. Rusielewicz, T. *et al.* (2014) Accelerated repair of demyelinated CNS lesions in the absence of non-muscle myosin IIB. *Glia* 62, 580–591
85. Abiraman, K. *et al.* (2015) Anti-muscarinic adjunct therapy accelerates functional human oligodendrocyte repair. *J. Neurosci.* 35, 3676–3688

86. Sun, L. *et al.* (2014) Inhibition of TROY promotes OPC differentiation and increases therapeutic efficacy of OPC graft for spinal cord injury. *Stem Cells Dev.* 23, 2104–2118
87. Hammond, T.R. *et al.* (2014) Astrocyte-derived endothelin-1 inhibits remyelination through notch activation. *Neuron* 81, 588–602
88. Hammond, T.R. *et al.* (2015) Endothelin-B receptor activation in astrocytes regulates the rate of oligodendrocyte regeneration during remyelination. *Cell Rep.* 13, 2090–2097
89. Samanta, J. *et al.* (2015) Inhibition of Gli1 mobilizes endogenous neural stem cells for remyelination. *Nature* 526, 448–452
90. Yoon, H. *et al.* (2015) The thrombin receptor is a critical extracellular switch controlling myelination. *Glia* 63, 846–859
91. Dendrou, C.A. *et al.* (2015) Immunopathology of multiple sclerosis. *Nat. Rev. Immunol.* 15, 545–558
92. Dutta, R. and Trapp, B.D. (2007) Pathogenesis of axonal and neuronal damage in multiple sclerosis. *Neurology* 68, S22–S31 discussion S43–S54
93. Black, J.A. and Waxman, S.G. (2008) Phenytoin protects central axons in experimental autoimmune encephalomyelitis. *J. Neurol. Sci.* 274, 57–63
94. Kapoor, R. *et al.* (2010) Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Neurol.* 9, 681–688
95. Chataway, J. *et al.* (2014) Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. *Lancet* 383, 2213–2221
96. Suhs, K.W. *et al.* (2012) A randomized, double-blind, phase 2 study of erythropoietin in optic neuritis. *Ann. Neurol.* 72, 199–210
97. Ingwersen, J. *et al.* (2012) Fingolimod in multiple sclerosis: mechanisms of action and clinical efficacy. *Clin. Immunol.* 142, 15–24
98. Choi, J.W. *et al.* (2011) FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. *Proc. Natl. Acad. Sci. U.S.A.* 108, 751–756
99. Miron, V.E. *et al.* (2008) FTY720 modulates human oligodendrocyte progenitor process extension and survival. *Ann. Neurol.* 63, 61–71
100. Miron, V.E. *et al.* (2010) Fingolimod (FTY720) enhances remyelination following demyelination of organotypic cerebellar slices. *Am. J. Pathol.* 176, 2682–2694
101. Barkhof, F. *et al.* (2014) The influence of patient demographics, disease characteristics and treatment on brain volume loss in Trial Assessing Injectable Interferon vs FTY720 Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS), a phase 3 study of fingolimod in multiple sclerosis. *Mult. Scler.* 20, 1704–1713
102. Lublin, F.D. *et al.* (2016) Oral fingolimod versus placebo in primary progressive multiple sclerosis: results of INFORMS, a large phase III, randomised, double-blind, placebo-controlled trial. *Lancet* Published online 27 January, 2016. http://dx.doi.org/10.1016/S0140-6736(15)01314-8
103. Deshmukh, V.A. *et al.* (2013) A regenerative approach to the treatment of multiple sclerosis. *Nature* 502, 327–332
104. Huang, H. *et al.* (2015) Dimethyl fumarate modulates antioxidant and lipid metabolism in oligodendrocytes. *Redox Biol.* 5, 169–175
105. Linker, R.A. *et al.* (2011) Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. *Brain* 134, 678–692
106. Miron, V.E. *et al.* (2007) Simvastatin regulates oligodendroglial process dynamics and survival. *Glia* 55, 130–143
107. Miron, V.E. *et al.* (2009) Statin therapy inhibits remyelination in the central nervous system. *Am. J. Pathol.* 174, 1880–1890
108. Preisner, A. *et al.* (2015) Non-steroidal anti-inflammatory drug indometacin enhances endogenous remyelination. *Acta Neuropathol.* 130, 247–261
109. Najm, F.J. *et al.* (2015) Drug-based modulation of endogenous stem cells promotes functional remyelination in vivo. *Nature* 522, 216–220
110. Skripuletz, T. *et al.* (2015) Pivotal role of choline metabolites in remyelination. *Brain* 138, 398–413
111. Mi, S. *et al.* (2013) Blocking LINGO-1 as a therapy to promote CNS repair: from concept to the clinic. *CNS Drugs* 27, 493–503
112. Watzlawik, J.O. *et al.* (2013) PDGF is required for remyelination-promoting IgM stimulation of oligodendrocyte progenitor cell proliferation. *PLoS ONE* 8, e55149
113. Perron, H. *et al.* (2012) Human endogenous retrovirus type W envelope expression in blood and brain cells provides new insights into multiple sclerosis disease. *Mult. Scler.* 18, 1721–1736
114. Rolland, A. *et al.* (2006) The envelope protein of a human endogenous retrovirus-W family activates innate immunity through CD14/TLR4 and promotes Th1-like responses. *J. Immunol.* 176, 7636–7644
115. Kremer, D. *et al.* (2013) Human endogenous retrovirus type W envelope protein inhibits oligodendroglial precursor cell differentiation. *Ann. Neurol.* 74, 721–732
116. Kremer, D. *et al.* (2015) The neutralizing antibody GNbAC1 abrogates HERV-W envelope protein-mediated oligodendroglial maturation blockade. *Mult. Scler.* 21, 1200–1203
117. Derfuss, T. *et al.* (2015) A phase IIa randomised clinical study of GNbAC1, a humanised monoclonal antibody against the envelope protein of multiple sclerosis-associated endogenous retrovirus in multiple sclerosis patients. *Mult. Scler.* 21, 885–893
118. Magalon, K. *et al.* (2012) Olesoxime accelerates myelination and promotes repair in models of demyelination. *Ann. Neurol.* 71, 213–226
119. Wang, R.R. *et al.* (2014) Histamine H3 receptor negatively regulates oligodendrocyte differentiation and myelination. In *Joint ACTRIMS-ECTRIMS Meeting MSBoston*. 2014, Poster 621
120. Saligrama, N. *et al.* (2013) Systemic lack of canonical histamine receptor signaling results in increased resistance to autoimmune encephalomyelitis. *J. Immunol.* 191, 614–622
121. Mei, F. *et al.* (2014) Micropillar arrays as a high-throughput screening platform for therapeutics in multiple sclerosis. *Nat. Med.* 20, 954–960
122. Liu, J. *et al.* (2016) Clemastine enhances myelination in the prefrontal cortex and rescues behavioral changes in socially isolated mice. *J. Neurosci.* 36, 957–962
123. Yamaguchi, W. *et al.* (2012) Sema4D as an inhibitory regulator in oligodendrocyte development. *Mol. Cell. Neurosci.* 49, 290–299
124. Giraudon, P. *et al.* (2004) Semaphorin CD100 from activated T lymphocytes induces process extension collapse in oligodendrocytes and death of immature neural cells. *J. Immunol.* 172, 1246–1255
125. Treps, L. *et al.* (2013) Emerging roles of Semaphorins in the regulation of epithelial and endothelial junctions. *Tissue Barriers* 1, e23272
126. Smith, E.S. *et al.* (2015) SEMA4D compromises blood–brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease. *Neurobiol. Dis.* 73, 254–268
127. Costa, C. *et al.* (2015) Expression of semaphorin 3A, semaphorin 7A and their receptors in multiple sclerosis lesions. *Mult. Scler.* 21, 1632–1643
128. Jurynczyk, M. *et al.* (2005) Inhibition of Notch signaling enhances tissue repair in an animal model of multiple sclerosis. *J. Neuroimmunol.* 170, 3–10
129. Wu, X. *et al.* (2014) Quercetin promotes proliferation and differentiation of oligodendrocyte precursor cells after oxygen/glucose deprivation-induced injury. *Cell. Mol. Neurobiol.* 34, 463–471
130. Fancy, S.P. *et al.* (2009) Dysregulation of the Wnt pathway inhibits timely myelination and remyelination in the mammalian CNS. *Genes Dev.* 23, 1571–1585
131. Fancy, S.P. *et al.* (2011) Axin2 as regulatory and therapeutic target in newborn brain injury and remyelination. *Nat. Neurosci.* 14, 1009–1016
132. Huang, J.K. *et al.* (2011) Retinoid X receptor gamma signaling accelerates CNS remyelination. *Nat. Neurosci.* 14, 45–53
133. Moore, S.M. *et al.* (2014) Multiple functional therapeutic effects of the estrogen receptor beta agonist indazole-Cl in

a mouse model of multiple sclerosis. *Proc. Natl. Acad. Sci. U. S.A.* 111, 18061–18066

134. Sedel, F. *et al.* (2015) Targeting demyelination and virtual hypoxia with high-dose biotin as a treatment for progressive multiple sclerosis. *Neuropharmacology* Published online September 5, 2015. http://dx.doi.org/10.1016/j.neuropharm.2015.08.028
135. Kumar, A. *et al.* (2015) A review on Alzheimer's disease pathophysiology and its management: an update. *Pharmacol. Rep.* 67, 195–203
136. Kuhnlein, P. *et al.* (2008) Diagnosis and treatment of bulbar symptoms in amyotrophic lateral sclerosis. *Nat. Clin. Pract. Neurol.* 4, 366–374
137. Barber, S.C. and Shaw, P.J. (2010) Oxidative stress in ALS: key role in motor neuron injury and therapeutic target. *Free Radic. Biol. Med.* 48, 629–641
138. Ivanova, M.I. *et al.* (2014) Aggregation-triggering segments of SOD1 fibril formation support a common pathway for familial and sporadic ALS. *Proc. Natl. Acad. Sci. U.S.A.* 111, 197–201
139. Prabhakaran, S. *et al.* (2015) Acute stroke intervention: a systematic review. *JAMA* 313, 1451–1462
140. Zhou, J. *et al.* (2013) Long-term post-stroke changes include myelin loss, specific deficits in sensory and motor behaviors and complex cognitive impairment detected using active place avoidance. *PLoS ONE* 8, e57503
141. Hamilton, N.B. *et al.* (2016) Proton-gated Ca-permeable TRP channels damage myelin in conditions mimicking ischaemia. *Nature* 529, 523–527
142. Polman, C.H. *et al.* (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann. Neurol.* 69, 292–302
143. Andreasen, N.C. (1995) Symptoms, signs, and diagnosis of schizophrenia. *Lancet* 346, 477–481
144. Nave, K.A. and Ehrenreich, H. (2014) Myelination and oligodendrocyte functions in psychiatric diseases. *JAMA Psychiatry* 71, 582–584