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Oligodendrocyte regeneration: its significance in myelin replacement and neuroprotection in multiple sclerosis

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Abstract

Oligodendrocytes readily regenerate and replace myelin membranes around axons in the adult mammalian central nervous system (CNS) following injury. The ability to regenerate oligodendrocytes depends on the availability of neural progenitors called oligodendrocyte precursor cells (OPCs) in the adult CNS that respond to injury-associated signals to induce OPC expansion followed by oligodendrocyte differentiation, axonal contact and myelin regeneration (remyelination). Remyelination ensures the maintenance of axonal conduction, and the oligodendrocytes themselves provide metabolic factors that are necessary to maintain neuronal integrity. Recent advances in oligodendrocyte regeneration research are beginning to shed light on critical intrinsic signals, as well as extrinsic, environmental factors that regulate the distinct steps of oligodendrocyte lineage progression and myelin replacement under CNS injury. These studies may offer novel pharmacological targets for regenerative medicine in inflammatory demyelinating disorders in the CNS such as multiple sclerosis.

1. Introduction

Oligodendrocytes are glial cells that extend myelin membranes around axons in the central nervous system (CNS). In between myelin segments are unmyelinated axonal regions termed nodes of Ranvier, where sodium channels involved in action potential generation are clustered. This exquisite organization defines the typical vertebrate nerve fiber and is crucial for saltatory propagation of electrical impulses down the axon, enabling rapid communication between networks of nerve cells in the CNS (Bhatt et al., 2014; Frankenhaeuser, 1952; Hartline and Colman, 2007). In addition to increasing axonal conduction speed through generating myelin, oligodendrocytes secrete metabolic factors that maintain the integrity and survival of CNS neurons (Edgar et al., 2009; Fünfschilling et al., 2012; Griffiths et al., 1998; Lee et al., 2012; Oluich et al., 2012). Disturbances to oligodendrocyte function or myelination in the developing or injured brain impairs axonal

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conduction (Waxman, 2006) and is associated with neuronal degeneration (Haines et al., 2009), highlighting the importance of oligodendrocytes in maintaining CNS function.

One of the most intriguing features of the adult CNS is its ability to spontaneously regenerate oligodendrocytes and replace myelin (remyelination) following acute demyelination (Franklin and Ffrench-Constant, 2008). Oligodendrocyte regeneration is possible because of an abundantly distributed source of oligodendrocyte precursor cells (OPCs) in the adult CNS (Dawson et al., 2003; Horner et al., 2002; Pringle et al., 1992; van Wijngaarden and Franklin, 2013). Following demyelination, neighboring OPCs rapidly migrate to the site of injury where they differentiate into oligodendrocytes to remyelinate recently denuded axons. This spontaneous regenerative response restores saltatory conduction (Smith et al., 1979) and has been suggested to protect axons from degeneration (Irvine and Blakemore, 2008; Jeffery and Blakemore, 1997; Kornek et al., 2000). Failure to regenerate oligodendrocytes and replace myelin exacerbates axonal dysfunction from myelin loss, leading to a cascade of pathological events that ultimately concludes with neurodegeneration (Trapp and Stys, 2009). Clinical manifestations of acute CNS demyelination followed by spontaneous remyelination, as well as the progressive neurodegeneration associated with remyelination failure, are most evident in the chronically demyelinating disorder, multiple sclerosis (MS).

MS is an immune-mediated neurological disease affecting more than 2.3 million people worldwide (Milo and Kahana, 2010; Compston and Coles, 2011). For reasons that remain poorly understood, myelin membranes and oligodendrocytes are destroyed through chronic inflammation in the CNS. Although efficient oligodendrocyte regeneration and remyelination occurs in the early stages of MS, remyelination becomes inefficient and ultimately fails with disease progression (Franklin, 2008). The mechanism of remyelination failure remains unclear, however it has been hypothesized that OPCs become “stalled” and may fail to differentiate into mature oligodendrocytes at sites of lesions (for review see Franklin, 2002). Since remyelination restores axonal conduction and protects against axonal damage in rodent models of MS (Irvine and Blakemore, 2008; Jeffery and Blakemore, 1997; Kornek et al., 2000), it is hypothesized that pro-remyelination therapies may be beneficial for patients with MS. In order to understand the biology of remyelination and to develop therapies to enhance this process in MS, several models of experimental demyelination are used. We have provided an abbreviated description of the most widely used model systems in Table 1. More thorough reviews have been published elsewhere (Blakemore and Franklin, 2008; Pachner, 2011; Rodriguez, 2007; Tanaka and Yoshida, 2014). In this review we discuss the neuroprotective functions of oligodendrocytes, molecular pathways involved in regulating their regeneration, and possible therapeutic targets for promoting remyelination in the CNS.

2. Role of oligodendrocytes in myelination and neuroprotection

Oligodendrocytes extend myelin sheaths around axons in a stereotyped fashion, leaving intermittent gaps of unmyelinated axon, termed nodes of Ranvier, between adjacent myelinated segments or internodes. This precise organization enables the restriction of voltage gated sodium channels to nodes of Ranvier and voltage gated potassium channels to

areas called juxtaparanodes (Pedraza et al., 2001; Rasband, 2010, 2008). Demyelination disrupts ion channel segregation (Coman et al., 2006; Wolswijk and Balesar, 2003), such that sodium and potassium channels redistribute along the axon, causing overlap of paranodal and juxtaparanodal protein domains (Craner et al., 2004; England et al., 1990; Podbielska et al., 2013; Scherer and Arroyo, 2002). The diffusion of ion channels and increased membrane capacitance from myelin loss produce an impedance mismatch in demyelinated axons, which causes inefficient conduction (Waxman, 2006). In MS, the manifestation of impaired impulse conduction is frequently associated with functional and/or cognitive disabilities, highlighting the importance of intact myelin around CNS axons for mediating efficient communication between neural networks (Charil et al., 2003).

In addition to their role in myelination, recent studies have found that oligodendrocytes play a critical role in maintaining axonal integrity (Edgar et al., 2009; Griffiths et al., 1998; Lappe-Siefke et al., 2003; Nave and Trapp, 2008; Nave, 2010; Saab et al., 2013). For example, mice deficient in proteolipid protein (PLP1) or CNP, major oligodendrocyte proteins found in myelin, do not display obvious structural abnormalities in myelin, but display impaired axonal transport (Edgar et al., 2010, 2009). Moreover, targeted ablation of oligodendrocytes in mice resulted in axonal pathology (Oluich et al., 2012; Traka et al., 2010). Exactly how oligodendrocytes maintain axonal integrity remains unclear. Several studies have observed that mitochondrial density in axons increases significantly in demyelinated lesions in MS and after experimental demyelination in mice, suggesting that the presence of myelin or oligodendrocytes may be important in regulating axonal energy metabolism (Campbell et al., 2012; Kiryu-Seo et al., 2010; Mutsaers and Carroll, 1998; Traka et al., 2010; Zambonin et al., 2011). It is possible that oligodendrocytes provide metabolic factors to the axon in order to meet its high energetic demand, and that the absence of oligodendrocyte support may render neurons vulnerable to oxidative damage and cell death (Nave, 2010). Indeed, recent studies have found that lactate transport to neurons is crucial for maintaining neuronal health and survival (Fünfschilling et al., 2012; Lee et al., 2012). The downregulation of the lactate transporter MCT1 in oligodendrocytes has recently been shown to result in impaired lactate transport, leading to neuronal dysfunction and degeneration (Lee et al., 2012).

In addition to supporting axonal energy metabolism, oligodendrocytes may also regulate neuronal survival through the production of neurotrophic factors. Several previous studies have suggested that oligodendrocytes express brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3) mRNA (Byravan et al., 1994; Dai et al., 2003; Dougherty et al., 2000; Gonzalez et al., 1990; Zhang et al., 2014). Moreover, BDNF and NT-3 secretion from oligodendrocytes have been shown to enhance the function of basal forebrain neurons *in vitro*, by increasing the expression choline acetyltransferase (ChAT) (Dai et al., 2003). Moreover, oligodendrocytes may also express glial cell line-derived neurotrophic factor (GDNF) and insulin-like growth factor type-1 (IGF1), and both factors have been shown to enhance cortical neuron survival (Wilkins et al., 2003; Zhang et al., 2014; Wilkins et al., 2001; Zhang et al., 2014; Wilkins and Compston, 2005; Wilkins et al., 2001). However, most of these studies were performed *in vitro*, so further studies are needed to understand the role of neurotrophic factors and IGF1 in oligodendrocyte-mediated neuronal survival *in vivo*.

3. Drivers of disease progression: axon damage and neurodegeneration

Considering the many roles of oligodendrocytes in supporting neuronal health, it may not be surprising that remyelination failure in progressive MS is accompanied by neurodegeneration (Compston and Coles, 2008; Dutta and Trapp, 2011; Haines et al., 2009; Nave and Trapp, 2008). It is hypothesized that the degeneration of axons in the chronically demyelinated CNS is a cause of irreversible disability (Mahad et al., 2015; Wegner et al., 2006). The evidence for axonal damage in MS is robust and comes from clinical, histopathological, biochemical, and imaging studies (for review see Haines et al., 2011; Trapp and Nave, 2008). Notably, although current immunosuppressive therapies reduce the number of relapses, they do not prevent patients from progressing (Carrithers, 2014; Rice CM, 2014) or developing significant cortical atrophy (Sailer et al., 2003). In fact, early in the disease, brain atrophy positively correlates with subsequent disability progression (Fisher et al., 2002; Rudick et al., 1999). MS patients with permanent paralysis are estimated to have between 60-70% axonal loss (Bjartmar et al., 2000; Mews et al., 1998) and this finding is closely recapitulated in the chronic EAE model, in which mice with permanent paralysis exhibit 59% and 43% axonal loss in the cervical and lumbar spinal cord, respectively (Wujek et al., 2002). Histologically, acute axon damage is characterized by the presence of varicosities and spheroid structures (Saxena and Caroni, 2007), which reflect impaired organelle transport in the axon (Williamson and Cleveland, 1999). This impairment results in the accumulation of proteins, including amyloid precursor protein (APP), along the damaged axon. APP accumulation is present in active, remyelinating, and inactive MS lesions (Bitsch et al., 2000; Ferguson et al., 1997). A second marker of neurodegeneration, non-phosphorylated neurofilament heavy chain (NFH), also accumulates in neurons in MS lesions (Dziedzic et al., 2010; Gray et al., 2012; Petzold et al., 2008; Schirmer et al., 2011).

Axon damage occurs in both acute demyelinating lesions and in chronically demyelinated lesions (Ciccarelli et al., 2014; Ferguson et al., 1997; Trapp et al., 1998), however it remains unknown whether this is a consequence of direct inflammatory attack, secreted inflammatory mediators, or is a secondary effect of demyelination (Haines et al., 2011; Trapp et al., 1998). Observations of neuronal loss and dendritic atrophy in normal appearing white matter (NAWM) (Bjartmar et al., 2000; Trapp et al., 1998; Wood et al., 2012), and in normal appearing gray matter (NAGM) (Klaver et al., 2015) suggest an early pathogenic mechanism. A growing body of evidence suggests that energetic failure and oxidative stress may be a driving factor of neurodegeneration (Trapp and Stys, 2009), as abnormalities in mitochondria density, morphology, and activity are consistently found in models of MS (Campbell et al., 2014; Fischer et al., 2012; Joshi et al., 2015; Kiryu-Seo et al., 2010; Mahad et al., 2008, 2009; Qi et al., 2006; Witte et al., 2014, 2010, 2009). The exact cause of neurodegeneration in MS remains to be seen, however the demonstration that early axonal damage can be reversed with remyelination (Bjartmar et al., 2003; Nikić et al., 2011) strengthens the rationale that pro-remyelination therapies could be beneficial for the treatment of MS.

4. Restoring function: mediators of oligodendrocyte regeneration and remyelination

Remyelination is remarkably prolific in the early stages of MS (Franklin 2002, Goldschmidt et al., 2009; Patrikios et al., 2006), but becomes less efficient with disease progression for unknown reasons (Goldschmidt et al., 2009; Franklin 2002). While OPCs continue to be recruited to demyelinated regions in approximately 70% of lesions (Chang et al., 2002; Lucchinetti et al., 1999), their differentiation into re-myelinating cells is halted (Back et al., 2005; Charles et al., 2002, 2000; Fancy et al., 2010; Mi et al., 2005). Thus, it was hypothesized that impairment of OPC differentiation contributes to remyelination failure (Chang et al., 2002; Huang and Franklin, 2011; Kuhlmann et al., 2008; Wolswijk, 1998). Here, we will describe the role of intrinsic signaling pathways known to regulate OPC differentiation and how this process is influenced by extrinsic signals from the surrounding inflammatory milieu (Figure 1).

4a. Intrinsic mediators of OPC differentiation

Several molecular pathways have been implicated in the inhibition of OPC differentiation. It is likely that transcriptional repression of these inhibitory pathways, combined with transcriptional activation of myelin genes, regulates OPC differentiation (Li et al., 2009). Here, we discuss the most widely studied inhibitory pathways including LINGO-1, canonical Notch, canonical wingless (Wnt), and semaphorin signaling. In addition, we discuss the few signaling cascades known to stimulate endogenous oligodendrocyte regeneration, including RXR and muscarinic receptor signaling pathways.

LINGO-1 Signaling—LINGO-1 (leucine-rich repeat and immunoglobulin-like domain-containing nogo receptor-interacting protein 1), a membrane protein expressed in neurons and oligodendrocytes, negatively regulates oligodendrocyte differentiation in rodent (Ji et al., 2006; Lee et al., 2007; Mi et al., 2005) and zebrafish (Yin and Hu, 2014). LINGO-1 knockout mice exhibit enhanced myelin sheath formation and recovery from EAE (Mi et al., 2007, 2005). Similarly, treatment with a LINGO-1 antagonist results in increased OPC differentiation and enhanced remyelination following EAE and lysolecithin-mediated demyelination (Mi et al., 2009), suggesting that LINGO-1 inhibition may be a useful therapeutic approach. Indeed, anti-LINGO-1 antibody promotes remyelination following lysolecithin-mediated demyelination (Zhang et al., 2015) and excitingly, has proven safe and well tolerated in patients (Tran et al., 2014). Now in a Phase II randomized clinical trial, LINGO-1 antibody may become the first available MS drug for promoting remyelination (Rudick et al., 2008). Precisely how LINGO-1 exerts its pro-regenerative effect in models of MS remains to be seen. A recent study demonstrated that LINGO-1 inhibition of oligodendrocyte differentiation may be due to decreased lipid raft translocation of the tyrosine kinase receptor ErbB2 (Lee et al., 2014). The ErbB receptor family, which also includes epidermal growth factor receptor (EGFR) and the neuregulin receptors, ErbB3 and ErbB4, has been implicated in the modulation of oligodendrocyte differentiation and myelination, albeit in a convoluted manner. ErbB2 deficiency halts oligodendrocyte lineage cells in an early stage leading to reductions in terminally differentiated oligodendrocytes (Kim et al., 2003; Park et al., 2001). While ErbB3 and ErbB4 are not required for

oligodendrocyte differentiation (Brinkmann et al., 2008; Stolt et al., 2002; Sussman et al., 2005), ErbB3 may mediate experience-dependent myelination (Makinodan et al., 2012). At this point, it remains unclear whether targeting ErbB receptors would improve outcome in models of MS. Results from the anti-LINGO-1 clinical trial should inform the future direction of research in this area.

Canonical Notch Signaling—The Notch receptors are a family of transmembrane proteins that are cleaved when activated to modulate gene expression (Brosnan and John, 2009; D'Souza et al., 2008). It is generally established that canonical Notch signaling, which occurs through ligands such as Jagged, inhibits OPC differentiation during development. Activation of Notch1 receptors on OPCs inhibits their differentiation *in vitro* (Wang et al., 1998) and inhibition of Notch1 in OPCs disrupts the spatial and temporal regulation of oligodendrocyte differentiation in the spinal cord (Genoud et al., 2002). Further, mice heterozygous for the null allele of Notch1 exhibit premature oligodendrocyte differentiation and increased myelination (Givogri et al., 2002). Genetic inactivation of Notch1 in OPCs produces a similar phenotype characterized by premature OPC differentiation (Zhang et al., 2009). Although these studies suggest that Notch1 controls the time-course of OPC differentiation during development, its role in CNS remyelination appears more convoluted. Mice undergo complete spontaneous remyelination (Stidworthy et al., 2004) despite re-expression of Notch1 and Jagged1 in demyelinated lesions (John et al., 2002; Seifert et al., 2007; Stidworthy et al., 2004), bringing into question the role of this signaling pathway in remyelination. Genetic inactivation of Notch1 in OPCs has yielded conflicting results (Stidworthy et al., 2004; Zhang et al., 2009), however Hammond et al. recently demonstrated that OPC differentiation following lysolecithin demyelination is inhibited by Jagged1-expressing astrocytes, which directly bind to Notch1 on OPCs (Hammond et al., 2014). Reactive astrocytes express Jagged1 in MS plaques (John et al., 2002) and this expression appears to be regulated by the secreted protein endothelin-1 (ET-1) (Hammond et al., 2014), which is upregulated following lysolecithin-mediated demyelination (Gadea et al., 2008) and inhibits oligodendrocyte differentiation during development (Gadea et al., 2009). Although ET-1 directly inhibits OPC differentiation and migration *in vitro* (Gadea et al., 2009), it is the indirect regulation of Jagged1 expression on reactive astrocytes that is proposed to inhibit OPC differentiation following demyelination (Hammond et al., 2014). ET-2 is also implicated in the regulation of CNS remyelination, as it has been shown to promote OPC differentiation and remyelination in a model of innate immunity (Yuen et al., 2013). However, a link between ET-2 and Notch signaling has not been identified to our knowledge. Although more work is needed to identify the precise function of Notch signaling in mediating the progression of oligodendrocyte lineage cells, the majority of findings implicate this pathway in the inhibition of OPC differentiation.

Wnt Signaling—Wnt proteins are secreted ligands that play numerous roles in regulating development, including oligodendrocyte genesis (Azim and Butt, 2011; Fancy et al., 2009; Ortega et al., 2013; Shimizu et al., 2005; Ye et al., 2009). The canonical Wnt pathway is activated when extracellular Wnt binds to Frizzled membrane receptors, resulting in the stabilization of intracellular β-catenin, which enters the nucleus to promote Wnt gene transcription (Xie et al., 2014). Shimizu et al. (2005) showed that OPC differentiation in the

spinal cord is inhibited by Wnt signaling through the canonical β-catenin pathway (Shimizu et al., 2005). Similarly, upregulating Wnt signaling decreases the number of proteolipid protein (PLP)-positive oligodendrocytes (Azim and Butt, 2011; Fancy et al., 2009). Interestingly, a recent study demonstrated that clustering of Frizzled receptors and the subsequent transduction of Wnt signals is modulated by Daam2-PIP5K (Lee et al., 2015). Daam2 may be a potential upstream target of Wnt as its activation inhibits OPC differentiation in development and white matter injury (WMI) (Lee et al., 2015). Although there is a general consensus that canonical Wnt signaling inhibits OPC differentiation, conflicting findings have been reported (Xie et al., 2014). Wnt/β-catenin signaling pathway is essential for myelin protein expression and myelin sheath compaction in zebrafish (Tawk et al., 2011). In addition, decreased MBP and PLP are found in mice lacking T-cell factor 4 (Fu et al., 2009), a transcription factor downstream of β-catenin that is expressed by OPCs during development and remyelination (Fancy et al., 2009). These studies suggest that Wnt/β-catenin signaling serves distinct functions in oligodendrocyte specification, differentiation, and myelination depending on timing and dosage (Xie et al., 2014). In support of this hypothesis, Wnt pathway activation was found to affect oligodendrocyte lineage cells in a dose-dependent fashion; low Wnt tone allows OPCs to differentiate and high Wnt tone after injury is associated with permanent WMI (Fancy et al., 2014). Importantly, most studies demonstrate an inhibitory role for Wnt signaling in remyelination. Mice lacking one copy of APC, a β-catenin antagonist, exhibit severely diminished PLP+ oligodendrocytes and remyelination (Fancy et al., 2009; Lang et al., 2013). Moreover, mice lacking *Axin2*, a Wnt target gene that promotes the degradation of β-catenin (Behrens et al., 1998; Jho et al., 2002), exhibit impaired OPC differentiation and delayed remyelination (Fancy et al., 2011b). Axin2 is expressed in OPCs in active MS lesions and in human hypoxic-ischemic white matter lesions (Fancy et al., 2011b), suggesting it may be a viable therapeutic target. More work is needed to elucidate the mechanisms by which Wnt signaling regulates oligodendrocyte lineage cells embryonically, postnatally, and following injury (Azim et al., 2014; Dai et al., 2014; Rodriguez et al., 2014) in order to resolve the ongoing debate about how and when to modulate Wnt signaling to effectively stimulate remyelination (Guo et al., 2015). Several Wnt inhibitory compounds have been identified as potential anti-cancer therapies (Le et al., 2014). Thus, inhibiting Wnt pathways as a pro-remyelination strategy may be feasible in the near future (Fancy et al., 2011a; Huang and Franklin, 2011).

Semaphorin Signaling—Failure of OPCs to migrate into demyelinated lesions may contribute to failed remyelination in approximately 30% of MS lesions which exhibit reduced OPC numbers (Chang et al., 2002; Lucchinetti et al., 1999). Semaphorins are a family of secreted and membrane proteins that have been implicated in this context. Semaphorins regulate neural development primarily by forming migratory cues through extracellular matrix binding to plexin and neuropillin receptors (for review see Jongbloets and Pasterkamp, 2014). Several members of the semaphorin family have been implicated in regulating OPC migration and differentiation, including semaphorin 3A (SEMA3A), 3F (SEMA3F), and 4D (SEMA4D). Interestingly, SEMA3A and SEMA3F play opposing roles in regulating OPC migration during development. SEMA3A serves as an inhibitory migratory cue whereas SEMA3F serves as an attractive migratory cue (Spassky et al., 2002; Sugimoto et al., 2001). While these proteins are down-regulated in the adult, SEMA3A and

SEMA3F are re-expressed in active demyelinating lesions (Williams et al., 2007) where they inhibit and promote OPC migration, respectively (Piaton et al., 2011). Knockdown of SEMA3A promotes *in vivo* remyelination following focal demyelination of corpus callosum (Boyd et al., 2013). This effect was due to increased OPC migration into the lesion, whereas OPC proliferation, differentiation, and apoptosis were unaffected (Boyd et al., 2013). In contrast, another study found that SEMA3A directly inhibits OPC differentiation *in vitro* (Syed et al., 2011). While this discrepancy may be explained by different doses of SEMA3A or the use of different species, both groups show that the downstream effect of SEMA3A signaling is failed remyelination (Boyd et al., 2013; Syed et al., 2011). SEMA4D is also inhibitory, as it induces collapse of oligodendrocyte cell processes (Giraudon et al., 2004) and inhibits both OPC survival and differentiation (Smith et al., 2015). Blocking SEMA4D with a monoclonal antibody promotes OPC migration to lesions and improves myelin status following focal demyelination (Smith et al., 2015). Because diminished OPC migration likely contributes to failed remyelination in some MS lesions (Chang et al., 2002; Lucchinetti et al., 1999), inhibiting SEMA4D could be beneficial for MS. While these studies suggest that targeting semaphorins may be beneficial for promoting remyelination, further validation and human trials are needed to thoroughly assess the efficacy of this approach.

RXR Signaling—To date, only a few signaling cascades have been identified for stimulating oligodendrocyte regeneration. Among them is the nuclear retinoid X receptor (RXR) pathway, which plays an important role in cell proliferation and development (for review see Mark et al., 2009). RXRs couple with several other nuclear receptors including retinoic acid receptor, vitamin D receptor, thyroid receptor, and peroxisome proliferator-activated receptor to induce gene transcription (Rastinejad, 2001). The RXR-γ isoform is the first identified nuclear receptor to play a role in promoting remyelination. Huang et al. (2011) found that RXR-γ is differentially upregulated during remyelination in rodent and in active and remyelinated MS lesions (Huang et al., 2011). Further, knockdown of RXR-γ receptor by RNA interference/RXR-specific antagonists dramatically reduces OPC differentiation *in vitro* and RXR-γ knockout mice exhibit significantly less mature oligodendrocytes following demyelination (Huang et al., 2011). These studies suggest that RXR-γ signaling may regulate oligodendrocyte differentiation and open new doors for pharmacological targeting using RXR ligands, many of which are under study or already approved for the treatment of certain cancers (Ballanger et al., 2010).

Muscarinic Signaling—Acetylcholine muscarinic receptors (mAChR) have been widely studied as potential drug targets for Alzheimer's disease, Parkinson's disease, and schizophrenia (Langmead et al., 2008). A recent study using high-throughput screening for MBP expression in primary rat progenitor cells identified Benztropine, a selective M1 mAChR antagonist used for treating Parkinson's Disease, as an enhancer of OPC differentiation *in vitro* (Deshmukh et al., 2013). Benztropine also promoted OPC differentiation in the EAE and cuprizone models of demyelination (Deshmukh et al., 2013). The beneficial effect of Benztropine is thought to result from direct anticholingeric activity on OPCs (Deshmukh et al., 2013; Eshleman et al., 1994). However, because Benztropine also has anti-histaminic activity (McKearney, 1982) and can inhibit dopamine uptake

(Agoston et al., 1997), more work is needed to confirm the mechanism of action. Further, although Benztropine is still used in the clinical treatment of Parkinson's disease (Katzenschlager et al., 2003), it is associated with severe side effects such as impaired cognition, urinary retention, nausea, and constipation (Lang and Lees, 2002; Lees, 2005). Recently, Mei et al. (2014) discovered a cluster of eight FDA-approved antimuscarinic compounds that enhance OPC differentiation and myelination using a novel micropillar assay for high-throughput screening. One drug in particular, Clemastine, readily passes the BBB and was highly effective in promoting OPC differentiation and myelination in their assay (Mei et al., 2014). Although more *in vivo* validation is needed, muscarinic receptors seem to be an exciting new target for the development of MS therapeutics.

4b. Influence of extrinsic inflammatory cues on OPC differentiation

Both microglia, the resident immune cells of the CNS, and peripherally derived macrophages play critical roles in neuroinflammatory disorders. Although they have different developmental origin and localization under physiological conditions, both macrophages and microglia can be polarized to acquire distinct phenotypes and functions (Colton, 2009). We will discuss the generalized activation states of macrophages/microglia as classically-activated macrophages/microglia (CAM) and alternatively-activated macrophages/microglia (AAM) because these are the most widely studied in the context of neuroinflammatory disorders. It is important to note that the distinction between CAM and AAM is not always clear, as microglia and macrophages are plastic and respond rapidly to changes in their environment and can acquire a diverse range of activation programs depending on the stimuli received (Katsumoto et al., 2014).

CAM are the first to respond to an injury or infection by secreting pro-inflammatory cytokines, reactive oxygen species (ROS), and nitrogen species to create an unfavorable (inflammatory) environment for the survival of pathogens (Cao et al., 2013, Mandovani *et al.*, 2013). Additionally, CAM have an increased capacity for antigen-presentation. In the context of MS, this leads to widespread primary demyelination by promoting the phagocytosis of myelin fragments and dying oligodendrocytes by macrophages/microglia and reactive astrocytes (Lassmann, 2014; Sosa et al., 2013; Wu and Raine, 1992). Conversely, AAM are generally thought to suppress inflammation by promoting debris removal, angiogenesis, tissue remodeling, and wound healing (Cao et al., 2013, Mandovani *et al.*, 2013).

Although inflammation leads to oligodendrocyte death and demyelination, depletion of immune cells including macrophages, microglia, and T cells or removal of pro-inflammatory factors including TNFα, IL-1β, and MHCII paradoxically impairs the remyelination process (Arnett et al., 2001; Bieber et al., 2003; Kotter et al., 2005; Mason et al., 2001). Interestingly, remyelination of aged mice, which exhibit impaired OPC recruitment and differentiation (Sim et al., 2002), is enhanced when blood circulation is shared with young mice via parabiosis (Miron et al., 2013; Ruckh et al., 2012). Shared circulation stimulated differentiation and remyelination of endogenous, aged OPCs in old animals following demyelination, an effect that may be partially mediated by the recruitment of young macrophages (Kotter et al., 2006; Miron et al., 2013; Ruckh et al., 2012; Shechter and

Schwartz, 2013). More work is needed to elucidate the contribution of potentially additive cell types or other circulating factors to the pro-regenerative effect of young/old parabiosis, however these experiments strongly suggest that the inflammatory environment can be modulated to promote remyelination.

Activated macrophages/microglia might promote remyelination by phagocytosing myelin debris, which is known to inhibit regeneration (Copelman et al., 2001; Ousman and David, 2000; Robinson and Miller, 1999), or by secreting pro-remyelination cytokines and growth factors (Arnett et al., 2001; Hinks and Franklin, 1999; Kotter et al., 2005; Mason et al., 2001; Vela et al., 2002). AAM seem to be particularly important for the beneficial effect of inflammation on remyelination as their depletion leads to delayed oligodendrocyte differentiation following demyelination (Miron et al., 2013). Further, increasing the number of AAM attenuates symptoms in EAE mice (Denney et al., 2012; Mikita et al., 2011). The paradoxical effects of inflammation in MS suggest that it may be the balance of CAM and AAM that sets the tone for remyelination. In support of this hypothesis, Mikita et al. (2011) found that while CAM and AAM are relatively balanced after the first clinical attack following EAE induction, the CAM population significantly outnumbers the AAM population during relapse (Mikita et al., 2011). This work suggests that therapeutically manipulating the balance of CAM/AAM may be beneficial for promoting remyelination in chronic lesions. Significantly more work is needed to elucidate how CAM/AAM balance is regulated and how this balance changes with disease progression in order to test this hypothesis.

Contribution of reactive astrocytes—Astrocytes, the most abundant cells in the CNS, play numerous roles in the healthy brain as well as in disease (Mayo et al., 2014). In a process known as astrogliosis, they rapidly respond to injury by becoming ‘activated,” a phenotype characterized by altered protein expression, cell morphology remodeling, and the upregulation of proinflammatory cytokines (eg. IL6, iNOS, TNFalpha) and growth factors (eg. LIF, IGF1, PDGFalpha, CNTF) (Sofroniew, 2009). Reactive astrocytes are also characterized by increased proliferation, cellular hypertrophy, and process extension, which are thought to contribute to glial scar formation. While glial scar formation restricts infection and cell necrosis to avoid damaging adjacent tissue (Sofroniew, 2009), it can also be detrimental by contributing to chronic inflammation and blockage of oligodendrocyte lineage cell migration into the lesion (Bannerman et al., 2007; Mayo et al., 2014).

Reactive astrocytes appear to have direct and indirect effects on oligodendrocyte lineage cells. For example, expression of Jagged1 receptors on astrocytes directly inhibits OPC differentiation via Notch signaling (Hammond et al., 2014; Stidworthy et al., 2004; Zhang et al., 2009) as described in section 4a. Activated astrocytes play additional, indirect roles in regulating OPC differentiation by affecting macrophages/microglia and infiltrating T-cells. Mice lacking astrocytic NF-kB, a transcription factor that alters production of pro-inflammatory cytokines, have reduced infiltration of inflammatory cells in the spinal cord and less cytokine secretion by T cells following EAE induction (Brambilla et al., 2014, 2009). Similarly, the astrocyte-derived enzyme B4GALT6 (β-1,4-galactosyltransferase 6), has recently been identified as a driver of neuroinflammation and of microglia/macrophage activation and recruitment in chronic EAE (Mayo et al., 2014). Reactive astrocytes also

indirectly affect OPC differentiation by contributing to increased BBB permeability via secretion of thymidine phosphorylase (TYMP) and vascular endothelial growth factor A (VEGF-A) (Argaw et al., 2012; Chapouly et al., 2015). Deletion of VEGF-A specifically in astrocytes improves outcome in the lysolecithin and EAE models of MS, likely by reducing the infiltration of monocytes into the CNS (Argaw et al., 2012). While it is clear that astrocytes contribute to the pathology of MS, future work should focus on identifying the mechanisms by which astrocytic signals directly affect OPC differentiation as well as regulate the inflammatory environment.

5. Conclusion

In lieu of a cure, oligodendrocyte regeneration may be a useful therapeutic approach for the treatment of MS. Remyelination restores the physiological interaction between oligodendrocyte and axon, and is hypothesized to restore the necessary structural and secreted support for axonal maintenance and efficient impulse conduction. Here we discussed several molecular pathways that regulate differentiation of OPCs into mature, myelinating oligodendrocytes that should be carefully considered as possible therapeutic targets. In conjunction, the state of inflammation must be carefully weighed. As it is now appreciated that inflammation is both damaging to myelin and necessary for myelin regeneration, combination therapies may be needed to promote remyelination across a changing inflammatory background.

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Highlights

- Oligodendrocytes regenerate and remyelinate axons following injury
- Remyelination is important in maintaining axonal conduction and integrity
- Understanding the intrinsic and environmental signals involved in remyelination allows the identification of therapeutic targets for improving remyelination in multiple sclerosis

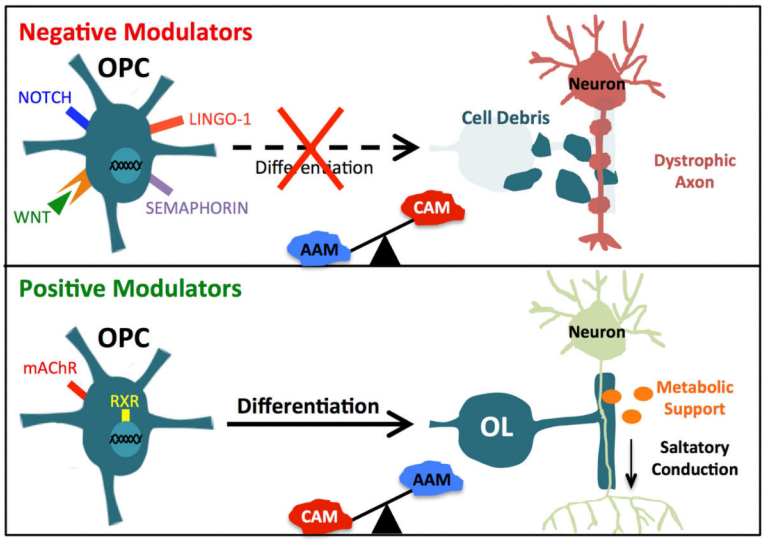

Figure 1.

Negative modulators of remyelination include Notch, Wnt, Lingo, and Semaphorin signaling as well as extracellular debris. Positive modulators of remyelination include muscarinic acetylcholine receptor (mAChR) and retinoid X receptor (RXR) signaling. Remyelination efficiency is also dependent on extrinsic factors, including those secreted by classically activated (CAM) and alternatively activated (AAM) macrophages/microglia, and a balance between CAM and AAM appears to modulate the regenerative process. Since myelin is necessary for saltatory conduction and oligodendrocytes provide metabolic support to neurons, chronic demyelination and oligodendrocyte loss in MS are likely to contribute to axonal dystrophy and progressive neurodegeneration.

Table 1

Animal Models of Experimental Demyelination

Model	Mechanism	Aspect(s) of MS Modeled	Pros	Cons
Autoimmune experimental autoimmune/ allergic encephalomy-elitis (EAE)	Co-injection of pertussis toxin and a specific myelin protein (MOG,MBP, or PLP) causes myelin destruction mediated primarily by invasion of peripheral antigen-specific T cells.	• myelin destruction • systemic inflammation • immune surveillance • Immune-mediated tissue destruction	• Led to the development of 3 FDA-approved therapies[1] • Closely models post-vaccinal encephalitis[2]	• Poor model for remyelination due to stochastic lesion location and occurrence[3] • Many approaches developed in EAE fail in human trials[4] • Lacks classic features of auto-immunity[1] • EAE lesions are dominated by CD4+ T-cells, compared to CD8+ T-cells in human lesions[1]
Theiler's murine encephalomy elitis virus (TMEV)	Intracerebral infection with TMEV in susceptible mouse strains leads to chronic demyelination primarily in the spinal cord.	• chronic progressive demyelination • autoimmune response triggered by viral infection	• demyelination is immunemediated[1] • chronic demyelination persists throughout lifespan[1] • recapitulates several MS features by small animal MRI and MRS[1]	• Mechanism of demyelination is unknown • Primarily models the contribution of viruses
Toxin Induced Models:				
Lysolecithin	Focal injection of 1% lysolecithin, an activator of phospholipase A_2, into the spinal cord produces local demyelination.	• myelin destruction • remyelination	• Useful for identifying proremyelination therapies[3] • spatiotemporal predictability fosters the study of discrete mechanisms mediating the demyelination and remyelination processes[3]	• Demyelination is not immune-mediated1 • Absence of ongoing immune activity3 • mechanism of lysolecithin toxicity is unknown

Model	Mechanism	Aspect(s) of MS Modeled	Pros	Cons
Cuprizone	Administration of 0.2% cuprizone, a copper chelator, in the chow leads to mitochondrial complex IV dysfunction and oligodendrocyte toxicity, leading to demyelination in the corpus callosum and hippocampus.	• oligodendrocyte death • myelin destruction • remyelination	• Can be used to model chronic demyelination with continued feeding • Useful for identifying pro-remyelination therapies[3] • Lesions resemble pattern III human MS lesions[3] • Lesion development closely mimics that of human MS lesions, with demyelination and remyelination coinciding[3]	• Overlap of demyelination and remyelination can confound interpretation[3]

[1](Denic et al., 2011),

[2](Baxter, 2007),

[3](Ransohoff, 2012),

[4](Sriram and Steiner, 2005)