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Extracellular Cues Influencing Oligodendrocyte Differentiation and (Re)myelination

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Abstract

There is an increasing number of neurologic disorders found to be associated with loss and/or dysfunction of the CNS myelin sheath, ranging from the classic demyelinating disease, Multiple Sclerosis, through CNS injury, to neuropsychiatric diseases. The disabling burden of these diseases has sparked a growing interest in gaining a better understanding of the molecular mechanisms regulating the differentiation of the myelinating cells of the CNS, oligodendrocytes (OLGs), and the process of (re)myelination. In this context, the importance of the extracellular milieu is becoming increasingly recognized. Under pathological conditions, changes in inhibitory as well as permissive/promotional cues are thought to lead to an overall extracellular environment that is obstructive for the regeneration of the myelin sheath. Given the general view that remyelination is, even though limited in human, a natural response to demyelination, targeting pathologically 'dysregulated' extracellular cues and their downstream pathways is regarded as a promising approach toward the enhancement of remyelination by endogenous (or if necessary transplanted) OLG progenitor cells. In this review, we will introduce the extracellular cues that have been implicated in the modulation of (re)myelination. These cues can be soluble, part of the extracellular matrix (ECM) or mediators of cell-cell interactions. Their inhibitory and permissive/promotional roles with regard to remyelination as well as their potential for therapeutic intervention will be discussed.

Keywords

Myelin; oligodendrocyte; remyelination; regeneration; extracellular; signaling; multiple sclerosis; CNS injury; neuropsychiatric diseases

Introduction

Myelination in the central nervous system (CNS) is carried out by specialized glia cells, oligodendrocytes (OLGs), to enable rapid saltatory conduction of action potentials and to

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maintain axonal integrity and function (Hirrlinger and Nave, 2014; Saab et al., 2013; Simons and Nave, 2015; Trapp and Nave, 2008). The critical importance of the myelin sheath becomes evident in diseases in which this structure is damaged or its growth or maintenance is impaired. Classic examples for such pathological conditions are the major human demyelinating disease, Multiple Sclerosis (MS), and the dysmyelinating genetic disorders grouped under the term leukodystrophies (Griffin and Lassman, 2004). More recently, myelin dysfunction and/or damage has also been associated with ischemic and traumatic brain injury (Armstrong et al., 2015; Back and Rosenberg, 2014; Rosenzweig and Carmichael, 2015), perinatal white matter injury/periventricular leukomalacia (Back, 2015; Folkerth, 2006; Haynes et al., 2003; Volpe, 2009), as well as neuropsychiatric diseases (Haroutunian et al., 2014; Miguel-Hidalgo, 2013; Nave and Ehrenreich, 2014). In light of the disabling burden of all of the above mentioned neurologic disorders, there is the hope that our progressive biological understanding of the OLG and the regulation of CNS myelination will lead to therapeutic approaches aimed at the regeneration of the myelin sheath as a critical step toward curative treatments.

It has been well-recognized that re-establishment of the myelin sheath can occur in response to CNS injury and demyelination (Blakemore and Franklin, 2008; Patani et al., 2007; Patrikios et al., 2006; Powers et al., 2013), and that remyelination, at least in animal models, can restore function and provide axonal protection (Duncan et al., 2009; Irvine and Blakemore, 2006; Jeffery and Blakemore, 1997; Liebetanz and Merkler, 2006; Smith et al., 1979). However, this regenerative process is, in particular with progression of disease and/or age, often limited and only partially able to fully restore axonal conduction velocity and the neuroprotective functions of the myelin sheath (Franklin and Gallo, 2014; Goldschmidt et al., 2009; Piaton et al., 2009). Thus, enhancing remyelination is considered a promising strategy toward the regenerative/protective treatment of diseases in which the myelin sheath is lost (Franklin and Goldman, 2015; Hagemeier et al., 2012; Lubetzki and Stankoff, 2014).

Remyelination at large requires the activation, recruitment and maturation of adult OLG progenitor cells (OPCs) present throughout the CNS and/or derived from stem/progenitor cells located within the subventricular zone (SVZ) (Brousse et al., 2015; Chari and Blakemore, 2002; Hesp et al., 2015; Mecha et al., 2013; Moyon et al., 2015a; Reynolds et al., 2002; Sullivan et al., 2013; Xing et al., 2014). Impairment of myelin regeneration under pathological conditions has been attributed to a decrease in both OPC recruitment and differentiation, whereby the latter is currently considered to play a more prominent role in determining the rate of remyelination (Franklin and Goldman, 2015). While the exact reasons for impaired remyelination are not fully understood, there is increasing evidence for a critical role of the extracellular environment (Berezin et al., 2014; Hinks and Franklin, 2000; Satoh et al., 2009; van Horssen et al., 2006), which likely acts upstream of transcriptional and epigenetic mechanisms regulating OLG differentiation (Emery and Lu, 2015; Hernandez and Casaccia, 2015; Moyon et al., 2015b; Svaren, 2014). Importantly, OLG lineage cells, even in the aged CNS, retain their competence for efficient repair (Ruckh et al., 2012), thus supporting enhancement of endogenous processes as a viable strategy toward myelin regeneration.

Extracellular cues are increasingly recognized to mediate communication between cells in the CNS. Such extracellular cues can be soluble factors, such as growth factors and chemokines, cell-cell adhesion molecules or represent extracellular matrix (ECM) molecules, whereby the latter become progressively known to function as important molecular signals not only outside of, but also within the CNS. In this context, it is of note that in the CNS ECM, organized in a traditional basal lamina, is only found lining endothelial cells and the pial surface; in the parenchyma, ECM components are found primarily in the form of dense networks (Rauch, 2007). During development, as well as under pathological conditions, this extracellular milieu undergoes dynamic changes and thereby influences the behavior and function of CNS cells, including OLGs (Colognato and Tzvetanova, 2011). In the following, we will focus on the review of extracellular signals that are known to influence OLGs and their progenitors at stages beyond their initial specification and that have been implicated in the regulation of CNS remyelination by functioning as inhibitory and/or permissive/promotional cues (for a schematic diagram see Fig. 1).

1. Secreted signaling molecules

1.1. Inhitbitory effects on OLG differentiation and (re)myelination

1.1.1. Bone Morphogenetic Proteins (BMPs): BMPs are secreted ECM-associated proteins of the TGFβ family of signaling molecules that have been recognized as key players in regulating a variety of developmental processes including OLG differentiation and myelination (Grinspan, 2015). To date, 22 members of the BMP family have been identified to activate, in the form of mature dimers, a signaling pathway that is initiated by binding to two copies of BMP type I (BMPR1) and type II (BMPR2) receptors (Brazil et al., 2015). Activation of this complex leads to downstream phosphorylation of a set of Smad proteins (R-Smad1/5/8), which, in turn, bind to the nuclear Smad4 protein and thereby mediate BMP-dependent gene expression. At each step, this pathway is tightly regulated, such as intracellularly by the inhibitory Smads Smad6 and Smad7 and extracellularly by antagonists such as Noggin and the Follistatin-Activin complex.

The first experiments demonstrating the inhibitory effect of an excess of BMPs on OLG differentiation were done in culture where treatment of OPCs with BMP2 or BMP4 inhibited the generation of mature OLGs and, at the same time, promoted the appearance of astrocyte-like cells (Grinspan et al., 2000; Mabie et al., 1997). This effect was found to be restricted to very early stages of the OLG lineage as treatment of immature OLGs with BMPs inhibited myelin gene expression without significantly affecting cell fate (See et al., 2004). Both inhibitory effects have been validated using developmental animal models in which BMP signaling was increased (Gomes et al., 2003; Miller et al., 2004; See et al., 2004). More specifically, the inhibitory effect on early stages of the lineage was found to be mediated by an increase in the expression of the transcriptional inhibitor Id4 and a decrease in the expression of the OLG-associated transcription factors Olig1 and Olig2, as well as complex formation between ID4 and both OLIG proteins (Cheng et al., 2007; Samanta and Kessler, 2004).

While BMPs can inhibit OLG differentiation, the overall picture of their developmental role in regulating cells of the OLG lineage is not perfectly clear. Experiments using Noggin to negatively regulate BMP signaling revealed confirmatory data for an inhibitory role of BMPs on the differentiation/specification of very early stages of the lineage (Kondo and Raff, 2004; Mekki-Dauriac et al., 2002). Results obtained from mice, in which BMP receptors were genetically deleted, however, favor an interpretation in which BMPs play, if at all, a minor developmental role in regulating early stage OLG lineage cells (Samanta et al., 2007; See et al., 2007). With regard to later stages of the lineage, deletion of both *Bmpr1a* (conditional in cells of the neural tube) and *Bmpr1b* (constitutive) led to a decrease in the number of mature OLGs (See et al., 2007), while deletion of only *Bmpr1a* (conditional in *Olig1* expressing cells) resulted in increased numbers of OLGs (Samanta et al., 2007). Notably, during development of the rat spinal cord, BMP levels were found significantly decreased around birth (Miller et al., 2004), and it has thus been proposed that once BMP levels are below a critical threshold OLGs can differentiate into mature myelinating cells. In this context, TCF4/TCF7l2 has recently been suggested to promote OLG differentiation, not by functioning downstream of the canonical Wnt signaling pathway but by repressing BMP signaling in neonatal and postnatal OLG lineage cells (Hammond et al., 2015).

BMP levels have been found increased in a number of different CNS injury models, including spinal cord (Chen et al., 2005; Park et al., 2013; Setoguchi et al., 2001a; Xiao et al., 2010), demyelinating (Ara et al., 2008; Cate et al., 2010; Fuller et al., 2007) and hypoxic/ischemic injury (Dizon et al., 2011; Dummula et al., 2011; Martinez et al., 2001). In addition, elevated levels of BMPs have been observed in CNS lesions of MS patients (Deininger et al., 1995; Mausner-Fainberg et al., 2013). In light of the reported inhibitory effects of BMPs on cells of the OLG lineage, it is not surprising that inhibition of BMP signaling has been proposed as a promising strategy toward enhancing remyelination. In support of this idea, infusion of Noggin or Chordin, known antagonists of BMP signaling, in experimental models of demyelination stimulated the regeneration of mature OLGs and promoted remyelination (Cate et al., 2010; Jablonska et al., 2010; Sabo et al., 2011). Blocking or decreasing BMP signaling in spinal cord injury models similarly increased OLG regeneration and remyelination (Park et al., 2013; Setoguchi et al., 2001b). In addition, Noggin infusion or overexpression in models of neonatal hypoxic/ischemic injury was found to improve clinical outcome and increase myelin gene expression and/or the number of mature OLGs (Dizon et al., 2011; Dummula et al., 2011). An interesting additional outcome from these studies is that BMP4 emerges as the primary BMP mediating an inhibition of OLG regeneration and remyelination in the context of pathological conditions associated with de- or dysmyelination (Grinspan, 2015). Further notable is the fact that all of these pathologies are associated with astrogliosis, which has been found decreased upon inhibition of BMP signaling (Cate et al., 2010; Dummula et al., 2011). Thus, myelination/ remyelination could be affected by BMPs under these pathological conditions, either via direct effects on OLGs, or indirect effects on astrocytes or both (Grinspan, 2015). In either case, inhibition of BMP signaling may offer a promising approach toward enhancing remyelination, with the cautionary note, however, that such a strategy may be complicated by potential beneficial roles of BMPs (Grinspan, 2015).

1.2. Permissive/promotional effects on OLG differentiation and (re)myelination

1.2.1. Autotaxin (ATX): ATX, also known as ENPP2, phosphodiesterase-Iα/ATX or lysophospholipase D (lysoPLD), is an extracellular factor that has been shown to promote OLG differentiation at two steps along the progression of the lineage via the action of two distinct functionally active domains (Wheeler et al., 2015; Yuelling and Fuss, 2008). The functional activity for which ATX is best known is its enzymatic lysoPLD activity, which generates the bioactive lipid signaling molecule lysophosphatidic acid (LPA) (Nakanaga et al., 2010; Tokumura et al., 2002; Umezu-Goto et al., 2002; van Meeteren and Moolenaar, 2007). LPA exerts its actions through a family of G protein-coupled receptors, the so-called LPA receptors (LPARs) (Fukushima et al., 2015; Kihara et al., 2014). In mammals, there are currently six bona-fide LPARs, all of which are, at least to some extent, expressed by cells of the OLG lineage (Nogaroli et al., 2009; Stankoff et al., 2002; Weiner et al., 1998; Yu et al., 2004; Y. Zhang et al., 2014). Activation of one or more of these receptors via ATX's lysoPLD activity has been implicated in stimulating gene expression changes associated with OLG differentiation (Nogaroli et al., 2009; Wheeler et al., 2015). More specifically, studies assessing ATX's functions *in vivo* in the developing zebrafish revealed that ATX's lysoPLD activity promotes early stage lineage progression by increasing HDAC activity and thereby repressing transcription factors known to inhibit OLG differentiation (Wheeler et al., 2015). ATX's second functionally active domain, the Modulator of Oligodendrocyte Remodeling and Focal Adhesion Organization (MORFO) domain, has been shown to regulate primarily the morphological aspects of OLG differentiation, i.e. process outgrowth and branching (Dennis et al., 2012, 2008; Fox et al., 2003). These effects of ATX's MORFO domain have been shown to require the presence of the purinergic receptor P2YR12 (Dennis et al., 2012). Taken together, these findings suggest that ATX coordinates gene expression and morphological changes as they occur during differentiation along the OLG lineage.

In MS, the expression levels of ATX (*ENPP2*) appear reduced in the brain parenchyma (Comabella and Martin, 2007; Lindberg et al., 2004; Raddatz et al., 2014). Consistent with ATX's role in regulating HDAC activity, it has also been shown that histone deacetylation is decreased in the MS brain (Pedre et al., 2011). Thus, ATX likely represents a permissive/promotional cue that is limited in the CNS parenchyma under pathological conditions of inefficient myelin regeneration. It is of note, however, that contrary to the CNS parenchyma, ATX protein levels in the cerebrospinal fluid of relapsing-remitting MS patients appear increased likely due to functional roles related to the pro-inflammatory environment (Hammack et al., 2004; Zahednasab et al., 2014). Toward the development of promising therapeutic approaches enhancing remyelination, it seems thus necessary to design strategies specifically targeting the signaling axis that is initiated by ATX in the CNS parenchyma and directed at cells of the OLG lineage.

1.2.2. Insulin Growth Factor (IGF-1): IGF-1 is a peptide closely related to insulin that is expressed by resident CNS cells, and it is one of the ligands of the type 1 IGF-1 receptor (IGF-1R) (Binoux et al., 1985; Dorn et al., 1984; Russo et al., 2005). IGFs, including IGF-1, are present almost entirely bound to members of a family of high-affinity IGF-binding proteins (IGFBPs), which coordinate and regulate the biological activities of IGFs. More specifically, IGFBPs act as transport carrier proteins, stabilize IGFs, determine tissue and

cell-type-specific localization, and directly stimulate or inhibit the interactions of IGFs with their receptors (Jones and Clemmons, 1995). Binding of IGF-1 to its receptor stimulates a complex network of intracellular signaling cascades, which ultimately leads to the regulation of a variety of cellular processes including proliferation, survival and differentiation (Chesik et al., 2008). Two main signaling pathways are known to be initiated by IGF-1. The first pathway involves the activation of PI3 kinase and subsequent Akt pathways, which are often associated with survival and inhibition of apoptosis. The second pathway involves the extracellular signal-related kinases, ERK-1 and ERK-2 (MAP kinases), which are translocated to the nucleus where they phosphorylate a variety of transcription factors involved in cellular growth and mitogenesis.

With regard to OLGs, IGF-1 is considered an indispensable factor for proper differentiation and accompanying myelin production (Bibollet-Bahena and Almazan, 2009; Chesik et al., 2008). First evidence for a role of IGF-1 in regulating OLGs came from cell culture studies demonstrating that IGF-1 induces OLG development and proliferation, and that it mimics the stimulating effect of insulin on sulfolipid synthesis (McMorris et al., 1986; McMorris and Dubois-Dalcq, 1988; van der Pal et al., 1988). Consistent with a critical role of IGF-1 in directly regulating OLGs *in vivo*, genetic deletion of the IGF-1R receptor (*Igfr1*) in cells of the OLG lineage reduces the number of OPCs and more mature OLGs, an effect thought to be due to a decrease in proliferation and an increase in apoptosis, rather than a decrease in differentiation (Zeger et al., 2007). In addition, constitutive deletion of IGF-1 (*Igf1*) decreases the number of OLGs and myelinated axons (Beck et al., 1995; Ye et al., 2002) and overexpression of the IGF inhibitory protein IGFBP-1 decreases the percentage of myelinated axons and reduces the thickness of the myelin sheath (Ye et al., 1995). Conversely, transgenic mice, in which *Igf1* is overexpressed, have 55% larger brains with increased myelin content and cell numbers (Carson et al., 1993), and myelination is increased upon intraventricular injection of IGF-1 (Goddard et al., 1999).

As already indicated above and confirmed in subsequent studies, IGF-1 regulates OLGs at different levels. First and in line with the initial observations, IGF-1 enhances OPC proliferation by pathways that involve the stimulation of both MAPK and Akt (Cui and Almazan, 2007). In addition, IGF-1 has been shown to cooperate with FGF-2 to synergistically enhance OPC proliferation (Jiang et al., 2001), whereby FGF-2 promotes cyclin D1 expression via stimulation of the MAPK pathway while IGF-1 inhibits cyclin D1 degradation via activation of the PI3K pathway (Frederick et al., 2007; Frederick and Wood, 2004). Complementary to its functions in stimulating OPC proliferation, IGF-1 has been shown to enhance survival of OLG lineage cells in the presence of a number of toxic insults, including glutamate-induced toxicity (Ness et al., 2004; Wood et al., 2007), hypoxic-ischemic injury (Wood et al., 2007), toxin-induced demyelination (Mason et al., 2000) as well as TNFα-induced injury (Pang et al., 2007; Ye et al., 2007). These data suggest that administration of IGF-1 may protect OLGs from injurious insults and thereby promote myelination and remyelination. In addition to the above, IGF-1 has been well-established to directly drive OLG differentiation and myelination (Goddard et al., 1999; McMorris and Dubois-Dalcq, 1988; Mozell and McMorris, 1991; Wilson et al., 2003; Ye et al., 1995).

Overall, the above described effects of IGF-1 on cells of the OLG lineage suggest IGF-1 as an attractive candidate for therapeutic intervention toward enhancing remyelination. In this context, it is of note that an upregulation of IGF binding protein expression has been observed in MS lesions, thus potentially indicating an overall downregulation of IGF signaling (Chesik et al., 2007, 2006; Gveric et al., 1999; Wilczak et al., 2008). Importantly, IGF-1 receptor densities and binding characteristics appear unchanged in the MS brain (Wilczak and De Keyser, 1997). In light of the potential promise of IGF-1 treatment, the approach has been tested in preclinical animal models. In EAE, subcutaneous or intravenous IGF-1 application has been shown to reduce the disruption of the blood–brain barrier, decrease immune cell infiltration and enhance remyelination (Li et al., 1998; Yao et al., 1995). The importance of IGF signaling for remyelination has been further supported by the observation that remyelination, subsequent to cuprizone-induced demyelination, is diminished in the absence of *Igf1r* expression in the brain (Mason et al., 2003). In other studies, however, little to no improvement in clinical outcome and remyelination were observed, despite the fact that in some cases OLG numbers were found increased (Cannella et al., 2000; Genoud et al., 2005; O'Leary et al., 2002; Sabo et al., 2013). Consistent with the latter, IGF-1 treatment in a small pilot study of seven MS patients did not reveal any significant change in clinical outcome measures, even though the treatment was well-tolerated (Frank et al., 2002). Thus, while targeting overall IGF-1 signaling is unlikely to achieve an enhancement in remyelination under the conditions as seen in MS, it may still hold promise if directed at more specific aspects of the pathway (Chesik et al., 2007) and/or employed as therapeutic strategy for neurologic disorders accompanied by OLG and/or myelin defects other than MS (Bou Khalil, 2011; Chen et al., 2014; Wood et al., 2007).

1.2.3. Platelet-derived growth factor-(PDGF-A): Platelet-derived growth factor-A (PDGF-A), which is secreted by neurons and astrocytes, exerts its function through signaling via its cognate tyrosine kinase receptor, the PDGFRα (Fredriksson et al., 2004) and is likely the most prominent factor known to promote OPC proliferation and survival in development and post-demyelination (Fruttiger et al., 1999; Murtie et al., 2005; Noble et al., 1988; Redwine and Armstrong, 1998; Richardson et al., 1988). In addition, PDGF-A has been implicated as a signal crucial for the establishment of a motile OPC state, a prerequisite for OPC migration and recruitment (Armstrong et al., 1991; Frost et al., 2009; McKinnon et al., 1993). Consistently, human PDGFRα-positive OPCs were found to be highly migratory and myelination competent when transplanted into a hypomeylinated shiverer mouse brain (Goldman et al., 2012; Sim et al., 2011) or upon spinal cord injury (Plemel et al., 2011). In addition, experimentally increasing PDGF-A levels in mouse models of demyelination has been found to promote OPC recruitment and survival (Kumar et al., 2007; Vana et al., 2007; Woodruff et al., 2004). What remains, however, not fully clear from these studies, is the extent to which the availability of OPCs may be rate-limiting for remyelination. Consequently, PDGF-A-PDGFRα signaling is considered essential for the generation of sufficient numbers of OPCs during development and it could potentially represent a promising target toward promoting the generation and recruitment of OPCs destined for remyelination.

1.3. Diverse/pleiotropic effects on OLG differentiation and (re)myelination

1.3.1. Fibroblast Growth Factor (FGF): The family of fibroblast growth factors (FGFs) has been shown to exert distinct roles in cells of the OLG lineage via the activation of three of the four known tyrosine kinase FGFRs, FGFR1, 2 and 3 (Bansal, 2002). Out of the at least 23 members of the FGF family, 10 have been described to be expressed in the CNS (Ford-Perriss et al., 2001), and FGF-2, the prototypic member of the family, has long been known to stimulate OPC proliferation while at the same time inhibiting OLG differentiation (Gard and Pfeiffer, 1993; McKinnon et al., 1993). FGF-2 facilitated stimulation of OPC proliferation is thought to be mediated by the activation of FGFR1, while inhibition of OLG differentiation may involve both FGFR1 and FGFR3 (Fortin et al., 2005; Zhou et al., 2006). In addition to the above described direct effects on OLGs, FGF-2 signaling can, at least *in vitro*, maintain high expression levels for PDGFRα and thereby allow cross-talk between FGF and PDGF signaling to enhance proliferation in the presence of both growth factors (Baron et al., 2000; Bögler et al., 1990; McKinnon et al., 1990; Wolswijk and Noble, 1992). Furthermore, FGF-2 has been implicated to function as a motogenic factor for OPCs and to mediate OPC migration via the activation of FGFR1 and its counteracting ECM glycoprotein anosmin-1 (Bribián et al., 2006; Milner et al., 1997; Murcia-Belmonte et al., 2014; Osterhout et al., 1997). Effects described for FGF-2 on terminally differentiated OLGs include a downregulation of myelin gene expression, re-entry into the cell cycle and a loss of membrane sheath formation mediated by FGFR1, as well as a stimulation of process elongation via FGFR3 (Bansal and Pfeiffer, 1997; Fortin et al., 2005; Fressinaud et al., 1995, 1993; Grinspan et al., 1993, 1996; Hoffman and Duncan, 1995; Muir and Compston, 1996; Wang et al., 2007; Zhou et al., 2006). Interestingly, the OLG differentiation inhibitory effects of FGF-2 signaling have been proposed to include an interaction with downstream targets of the Notch pathway, including an upregulation of Hes5 expression (Zhou and Armstrong, 2007). Consistent with the above *in vitro* described effects of FGF-2 on OLG differentiation, transgenic mice expressing a dominant-negative FGFR1, under the control of the myelin basic protein (MBP) promoter, showed an increase in myelin thickness (Harari et al., 1997). On the contrary, however, knockout of FGFR3 resulted in a transient delay in OLG differentiation, suggesting that FGF-2 signaling via FGFR3 regulates the timing of OLG differentiation, an effect that may be mediated by direct effects on OLGs or indirectly by influencing astrocytes (Oh et al., 2003).

The involvement of FGFR signaling is complicated due to the existence of a set of distinct receptors and the expression of a diverse number of ligands with different degrees of selectivity for specific FGFRs. For example, FGF-9, which is expressed constitutively by many adult neurons, similarly to FGF-2, has been shown to suppress the expression of myelin protein genes (Cohen and Chandross, 2000). As FGFR expression profiles, as well as the availability of their ligands, change when OLGs progress through the developmental stages of their lineage, it has, based *on vitro* data, been proposed that FGF-2, FGF-8, FGF-17, and FGF-18 may be important during early development of OPCs acting via FGFR1 and FGFR3, while FGF-9 may be more important during myelination acting via FGFR2 (Fortin et al., 2005). Despite the above demonstrated diverse effects of FGF signaling on cells of the OLG lineage, genetic deletion of both FGFR1 and FGFR2 was found to not affect OPC proliferation and OLG differentiation during *in vivo* development,

but to inhibit the establishment of a myelin sheath of proper thickness (Furusho et al., 2012, 2011).

In addition to the complex developmental roles described above, activation of FGFR signaling in OLGs has been proposed to play important roles under pathological conditions by potentially promoting the recruitment and expansion of OPCs, but at the same time to also lead to detrimental effects. In support of a positive role, FGF-2 and FGFR1 levels have been found increased under demyelinating conditions under which OPCs are being recruited and remyelination may occur to some extent, including active MS lesions (Armstrong et al., 2006; Clemente et al., 2011; Hinks and Franklin, 1999; Messersmith et al., 2000; Tourbah et al., 1992). With regard to potential detrimental roles, injection of FGF-2 into the lateral ventricles of postnatal mice was found to delay myelination and lead to myelin breakdown (Goddard et al., 2001, 1999), and genetic deletion of *Fgf2* or FGFR1 resulted in improved remyelination following experimental demyelination (Mierzwa et al., 2013; Tobin et al., 2011; Zhou et al., 2012). Conversely, however, FGF signaling has also been associated with successful remyelination (Mohan et al., 2014) and been described to potentiate myelin repair (Dehghan et al., 2012), provide neuroprotection (Rottlaender et al., 2011) and ameliorate clinical signs in a chronic EAE model (Ruffini et al., 2001). Recent data revealed that conditional deletion of both FGFR1 and FGFR2 in cells of the OLG lineage does not affect remyelination following acute myelination, but impairs OLG differentiation and/or survival in chronically demyelinated lesion, suggesting that cell-autonomous FGF signaling in OLGs is redundant during recovery of acute demyelinated lesions, but may facilitate regenerative processes in chronic demyelination (Furusho et al., 2015).

The present conflicting results related to the ascribed functional roles of FGF signaling in OLG differentiation, myelination and remyelination may be reflective of the multitude of responses exerted in, not only cells of the OLG lineage, but also for instance reactive astrocytes and microglia. For example, inhibition of myelination and remyelination by FGF-9 has been attributed to an increased expression and secretion of various factors by astrocytes (Lindner et al., 2015). Thus, it is at this point difficult to assess whether the outcome of FGF perturbation on OLG differentiation and myelin recovery is due to direct or indirect effects and/or diverse and potentially opposing effects of the activation of different FGFR types by the same or different FGF family member(s).

1.3.2. G-protein coupled receptor 17 (GPR17) and its extracellular ligands: G protein (heterotrimeric guanine nucleotide–binding protein)–coupled receptors (GPCRs) are the largest class of cell surface receptors, and they have been proven as attractive drug targets (Jacobson, 2015; Kumari et al., 2015; Overington et al., 2006; Rask-Andersen et al., 2011). With regard to CNS myelination and remyelination, we are only at the beginning of a better understanding of the role of GPRCs and their ligands. In particular, the lysophospholipid receptors, adhesion GPCRs and purinergic receptors are increasingly recognized to regulate OLG differentiation and myelination (Fumagalli et al., 2015b; Groves et al., 2013; Liebscher et al., 2014; Yung et al., 2015). Here we will focus on GPR17 and its extracellular ligands as they have been implicated to contribute to the pathology seen upon CNS injury (see below).

In the CNS, GPR17 is under physiological conditions expressed predominantly by cells of the OLG lineage and in particular by newly formed OLGs (Boda et al., 2011; Chen et al., 2009; Fumagalli et al., 2011; Lecca et al., 2008; Y. Zhang et al., 2014). Structurally and phylogenetically, GPR17 is located at an intermediate position between two distinct receptor families: the P2Y and CysLT receptors for extracellular nucleotides and cysteinyl-LTs, respectively (Abbracchio et al., 2006; Parravicini et al., 2008). Thus, it does not seem surprising that GPR17 has been described to respond to both extracellular nucleotides (UDP, UDP-glucose) and cysteinyl-leukotrienes (CysLT) (Benned-Jensen and Rosenkilde, 2010; Ciana et al., 2006; Daniele et al., 2011; Lecca et al., 2008). On the other hand, however, it has been suggested that UDP, UDP-glucose, UDP-galactose, and cysteinyl leukotriene C4 (LTC4) may not represent cognate ligands for GPR17 and that instead the receptor functions as a negative regulator of cysteinyl leukotriene receptor 1 (CysLTR1) responses (Maekawa et al., 2009; Qi et al., 2013). The reasons for these controversies related to the functional ligand(s) of GPR17 are currently unclear and require further investigation.

Functionally, it has been proposed that activation of GPR17, at early stages of the OLG lineage, promotes OLG differentiation (Ceruti et al., 2011; Coppi et al., 2013; Fumagalli et al., 2011; Lecca et al., 2008). Consistent with this idea, treatment with UDP-glucose was reported to increase OLG differentiation in neonatal rats with ischemia-induced periventricular leukomalacia (Li et al., 2015). At later stages of the lineage, however, downregulation of GPR17 appears necessary for full maturation of OLGs and efficient myelination to occur, as well evidenced by the observation that sustained expression of GPR17 inhibits OLG maturation and CNS myelination (Chen et al., 2009; Fumagalli et al., 2015a). The proposed endogenous agonists of GPR17 are released at sites of CNS injury (Buffo et al., 2010; Ciceri et al., 2001; Cieślak et al., 2011; Whitney et al., 2001), and the expression of GPR17 itself has been found upregulated upon CNS injury (Boda et al., 2011; Franke et al., 2013; Lecca et al., 2008) and in demyelinating lesions (Chen et al., 2009). Thus, it has been hypothesized that under pathological conditions, GPR17 is initially induced to promote remyelination and repair, while at later stages the inhibitory function of sustained GPR17 expression limits myelin regeneration (Fumagalli et al., 2015b).

1.3.3. Netrin-1: Netrin-1, secreted by cells of the floorplate, has been well-characterized to function as an axonal guidance cue for commissural axons (Kennedy et al., 1994). The functions of netrin-1 are mediated primarily through receptors of the DCC (deleted in colorectal cancer) and UNC5 (unccordinated 5) families, whereby, in general, DCC mediates axon attraction (Fazeli et al., 1997), while Unc5 homodimers and UNC5-DCC heterodimers mediate axon repulsion (Hong et al., 1999). Similarly, netrin-1 has been found to act as a bifunctional guidance cue for OPCs. For example, during development of the optic nerve, netrin-1 (via DCC) functions early on as a chemoattractant for OPC entry into the nerve, while at later stages it functions as a repellent (via DCC-UNC5A), likely to stop migration and prevent entry of OPCs into the retinal end of the nerve (Spassky et al., 2002; Sugimoto et al., 2001; Tsai and Miller, 2002). In the developing spinal cord, however, ventrally secreted netrin-1 (via DCC and/or DCC-UNC5A) functions apparently purely as a chemorepellent to mediate dispersal of OPCs (Jarjour et al., 2003; Tsai et al., 2006, 2003). At later stages of the OLG lineage, a switch in the functional role of netrin-1 toward a signal

promoting process branching has been observed (Rajasekharan et al., 2010; Tepavčević et al., 2014). This switch has been proposed to involve an increased association of DCC with the src family tyrosine kinase Fyn (Rajasekharan et al., 2010, 2009).

In the context of remyelination, full length and fragmented netrin-1 were detected in human samples of control white matter as well as MS lesions. Importantly, MS lesions displayed an increased level of diffuse netrin-1 immunoreactivity, likely due to an upregulation of netrin-1 expression in astrocytes early during demyelination (Bin et al., 2013; Tepavčević et al., 2014). These findings suggest that netrin-1 may limit recruitment of OPCs to demyelinated MS lesions. Indeed, injection of netrin-1 blocking antibodies into lysolecithin-induced demyelinated lesions led to an increase in the number of OPCs. However, there was also a decrease in the number of more mature stages of the OLG lineage (Tepavčević et al., 2014). From these data it was concluded that early presence of netrin-1 in MS lesions likely impairs OPC recruitment and remyelination, while later expression may act to promote OLG differentiation. It therefore seems that the timing of netrin-1 expression within areas of demyelination may be an important determinant of myelin repair (Tepavčević et al., 2014).

1.3.4. Semaphorins: Semaphorins comprise a large family of secreted and transmembrane proteins and their principal receptors are plexins (Jongbloets and Pasterkamp, 2014). While most semaphorins interact directly with plexins, the binding of secreted class 3 semaphorins (except Sema3E) to plexin is facilitated by neuropilins. Cells of the OLG lineage have been found to express both semaphorins and their receptors (Cohen et al., 2003; Zhang et al., 2014). Functionally, the transmembrane semaphorin Sema6A, which is expressed by OLGs, has been proposed to positively modulate OLG differentiation by a cell-autonomous mechanism (Bernard et al., 2012), and Sema4D has been implicated in limiting remyelination through a number of mechanisms, including direct effects on OLG lineage, as well as immune, cells (Giraudon et al., 2004; Smith et al., 2015; Taniguchi et al., 2009; Zhang et al., 2014). With regard to remyelination, it is the class 3 semaphorins that have received most attention as the expression of Sema3A and Sema3F was found upregulated in MS brains and in response to experimental demyelination (Williams et al., 2007). Originally characterized as axon guidance cues exerting, similar to netrins, repulsive as well as attractive functions (Chisholm and Tessier-Lavigne, 1999), Sema3A and Sema3F have also been described to regulate developmental OPC migration in an antagonistic fashion, whereby Sema3A was defined as a repulsive signal, while Sema3F was found to act as an attractive cue (Ricard et al., 2001, 2000; Spassky et al., 2002; Sugimoto et al., 2001; Tsai and Miller, 2002). These developmental observations apparently also apply to remyelination as in a toxin-induced demyelination model Sema3A impaired OPC recruitment, while Sema3F accelerated recruitment and remyelination (Piaton et al., 2011). Interestingly, in MS, a higher number of cells expressing Sema3F (compared to Sema3A) was seen around and within most inflammatory lesions, while around and within less inflammatory lesions, there was a predominance of cells expressing Sema3A (Williams et al., 2007). These findings are consistent with the idea that inflammatory lesions are more favorable for myelin regeneration, while it may be, in particular, the less inflammatory chronic lesions in which there is a shifted balance toward the presence of inhibitory cues (Foote and Blakemore, 2005; Kuhlmann et al., 2008; Li et al., 2005; Miron et al., 2013). It is worth mentioning that

at least under experimental demyelinating conditions, Sema3A can additionally function as an inhibitor of OLG differentiation and thereby inhibit remyelination (Syed et al., 2011). Due to its apparent overall role as an inhibitory cue, Sema3A signaling represents a relevant therapeutic target to be further explored in the context of enhancing remyelination under pathological conditions.

1.3.5. Sphingosine-1-Phosphate (S1P): The lipid signaling molecule sphingosin-1-phosphate (S1P) has received increasing attention since the discovery and approval of its non-selective S1P receptor modulator FTY720 (also known as Fingolimod) as the first oral disease-modifying medication for relapsing-remitting MS (Brinkmann et al., 2010; Cohen et al., 2010; Kappos et al., 2010; O'Connor et al., 2009). The naturally occurring lipid mediator S1P is generated intracellularly from sphingolipids present in the cell membrane via the actions of metabolic enzymes including the two sphingosine kinases SPHK1 and SPHK2. It exerts its biological functions mostly as an extracellular signaling molecule that upon extracellular release, via transmembrane transport, can activate five different high-affinity G protein-coupled S1P receptors, termed $S1P_1$–$S1P_5$ (Kihara et al., 2014; Maceyka et al., 2012; Proia and Hla, 2015). In the context of S1P signaling in MS, FTY720 was, similar to sphingosine, found to be phosphorylated by SPHKs (primarily SHK2), thereby yielding a structural analog of S1P, namely FTY720-phosphate (Zemann et al., 2006). FTY720-phosphate represents a potent and acute agonist for $S1P_1$, $S1P_3$, $S1P_4$, and $S1P_5$. Upon chronic exposure, however, FTY720-phosphate can inhibit signaling through the S1P receptors by mediating irreversible internalization and acting as a so-called "functional antagonist" (Brinkmann et al., 2002; Gräler and Goetzl, 2004; Mullershausen et al., 2009). In its antagonist function, FTY720 was found to induce lymphopenia by inhibiting $S1P_1$ signaling-dependent lymphocyte egress from secondary lymphoid organs and to thereby attenuate inflammation, demyelination, and axonal loss in EAE (Brinkmann et al., 2002; Chiba et al., 2011; Fujino et al., 2003; Kataoka et al., 2005; Mandala et al., 2002; Matloubian et al., 2004; Papadopoulos et al., 2010; Webb et al., 2004).

In addition to the above immune-modulatory effects, S1P and FTY720 have also been shown to directly affect cells of the CNS, including OLG lineage cells (Coelho et al., 2010; Groves et al., 2013; Miron et al., 2008b). In early studies, expression of the $S1P_5$ receptor (*S1pr5*) was discovered to be associated with CNS white matter tracts (Im et al., 2000) and its expression in the CNS was then found to occur preferentially in cells of the OLG lineage (Jaillard et al., 2005; Terai et al., 2003). In addition to $S1P_5$, OLGs express the S1P receptors $S1P_1$ (*S1pr1*), $S1P_3$ (*S1pr3*) and $S1P_2$ (*S1pr2*) (Novgorodov et al., 2007; Yu et al., 2004). Functionally and based on cell culture studies, S1P signaling through $S1P_5$ modulates several processes, including survival, migration and differentiation, depending on the developmental stage of the cell (Jaillard et al., 2005; Jung et al., 2007; Miron et al., 2008a; Novgorodov et al., 2007). Under non-pathological conditions, however, mice deficient in *S1pr5* do not show impaired myelination, suggesting that there is functional redundancy among S1P receptor subtypes expressed by OLGs (Groves et al., 2013).

As S1P signaling is altered in MS (Fischer et al., 2011; Kułakowska et al., 2010; Van Doorn et al., 2010; Wheeler et al., 2008), direct functional roles of FTY720 on cells of the CNS and their potential contribution to the therapeutic outcomes in MS have gained an increasing

interest. In this context, direct effects on astrocytes and microglia have been implicated to contribute to the efficacy of FTY720 treatment in experimental models of demyelination (Choi et al., 2011; Jackson et al., 2011). With regard to OLGs, cell culture studies revealed effects similar to those seen for S1P (Groves et al., 2013; Miron et al., 2008b). Importantly, FTY720 was shown to have direct cytoprotective effects and to promote OLG differentiation at low concentrations or when given daily in the absence of PDGF-A (Coelho et al., 2007; Cui et al., 2014; Jung et al., 2007). FTY720 was, however, also found to exert negative effects by inhibiting OLG differentiation at high concentrations and by impeding OPC migration (Coelho et al., 2007; Jung et al., 2007; Miron et al., 2008a; Novgorodov et al., 2007). To better assess the direct effects of FTY720 treatment on remyelination, studies were undertaken in toxin-induced models of demyelination that are characterized by a minimal immunological component and thereby avoid a predominance of FTY720's immune-modulatory effects as seen in EAE. Consistent with a lack of reliable pro-myelinating effects on OLGs, FTY720 treatment in toxin-induced models of demyelination, with a minimal immunological component (to avoid a predominance of immune-modulatory effects as seen in EAE), failed to demonstrate a direct promotion of remyelination; FTY720 treatment was, however, associated with direct protective effects toward OLGs (Hu et al., 2011; Kim et al., 2011). Somewhat puzzling in this context is the finding obtained in an organotypic cerebellar slice culture system in which application of FTY720 was reported to increase remyelination (Miron et al., 2010). Nevertheless, from the studies so far, it appears that the positive outcomes of FTY720, with regard to remyelination, are mediated to a large extent through its immune-modulatory properties, but are complemented by direct effects on cells of the CNS, including direct protection of OLG lineage cells. Interestingly, such direct cytoprotective effects of FTY720 on OLGs have recently been reported to also contribute to the beneficial effects of FTY720 treatment in neonatal oxygen-induced brain injury (Serdar et al., 2015). Despite these positive effects, however, in light of the limited experimental support for a direct role of FTY720 in promoting remyelination, therapeutic use of FTY720 may require add-on therapies to enhance myelin regeneration for achieving long-term functional restoration of the CNS under pathological conditions that are associated with persistent demyelination (Hu et al., 2011).

1.3.6. Wnt Signaling: The canonical Wnt/β-catenin signaling pathway has attracted much attention as a signaling mechanism implicated in inhibiting OLG differentiation as well as restricting remyelination in MS and myelination in periventricular leukomalacia (Fancy et al., 2009; Feigenson et al., 2009; Guo et al., 2015; Shimizu et al., 2005; Ye et al., 2009). The canonical Wnt/β-catenin pathway is initiated by binding of one of the 19 (in mammals) Wnt ligands to one of their 10 (in mammals) plasma membrane Frizzled receptors and one of the co-receptors Lrp5/6. In the absence of Wnt ligands, and thus the OFF state of the pathway, cytosolic β-catenin is targeted for degradation by a complex composed of the scaffolding protein Axin, adenomatous polyposis coli (APC), and the two serine/threonine kinases, glycogen synthase kinase 3β (GSK3β) and casein kinase 1 (CK1) (Clevers and Nusse, 2012; MacDonald et al., 2009; MacDonald and He, 2012). Upon activation, and thus in the ON state of the pathway, β-catenin is stabilized through recruitment of Dishevelled and Axin by the activated receptor complex, thereby preventing constitutive β-catenin degradation. The stabilized β-catenin can then either become bound to the plasma membrane or translocate to

the nucleus where it interacts with TCF/LEF (T cell factor/lymphoid enhancer factor) transcription factors to initiate gene expression (Daniels and Weis, 2005).

During development and remyelination, one of the canonical Wnt/β-catenin target transcription factors, Tcf4/Tcf7l2, is expressed specifically and transiently by differentiating OLGs (Fancy et al., 2009; Fu et al., 2009; Ye et al., 2009; Y. Zhang et al., 2014), suggesting an important regulatory role of the canonical Wnt/β-catenin signaling pathway in OLG differentiation. In experimental paradigms of sustained activation of the canonical Wnt/β-catenin pathway, via conditional expression of dominant-active β-catenin or deletion of one functional copy of the Wnt pathway inhibitor APC, developmental myelination as well as remyelination were inhibited and/or delayed (Fancy et al., 2009; Feigenson et al., 2009). Since under pathological conditions, as seen in MS and one of its animal models, EAE, the expression of several Wnt ligands and Frizzled receptors were found upregulated (Fancy et al., 2009; Han et al., 2008; Lock et al., 2002; Yuan et al., 2012), the concept emerged that dysregulation of the canonical Wnt/β-catenin signaling pathway contributes to inefficient myelin regeneration. Pharmacological *in vivo* modulation of the pathway via the use of the small tankyrase inhibitor XAV939 (to stabilize Axin and promote β-catenin degradation) supported this idea (Fancy et al., 2011). However, modulation of the pathway via the use of GSK3β inhibitors (to activate Wnt/β-catenin signaling) provided controversial findings, which may be explained by these pharmacological agents affecting more than one signaling pathway and/or by cross-talk between different signaling cascades (Azim and Butt, 2011). In a more recent study, a high Wnt tone in OPCs was described to lead to an induction of Lef1 expression, a switch from a Tcf4/Tcf7l2- β-catenin to a Lef1- β-catenin complex formation and a block of OLG differentiation (Fancy et al., 2014). Characteristics of a high pathological Wnt tone was also seen in OPCs in human neonatal subcortical white matter affected by hypoxic ischemic encephalopathy. These findings suggested a model in which pathological high Wnt signaling inhibits OLG differentiation while low to moderate activity of the pathway may promote developmental OLG differentiation and remyelination, thereby resolving some of the controversial findings related to the role of the canonical Wnt/β-catenin signaling in OLGs (see below).

As indicated above, in addition to an inhibitory role, the canonical Wnt/β-catenin signaling pathway has been proposed to promote OLG differentiation and myelination/remyelination (Guo et al., 2015; Xie et al., 2014). For example, Wnt1 and Wnt3a have been described as drivers of myelin gene expression (Tawk et al., 2011) and genetic deletion of Tcf4/Tcf7l2 was found to inhibit developmental OLG differentiation (Fu et al., 2009; Ye et al., 2009). To reconcile the controversies, it was proposed that HDAC1/2 competes with β-catenin for binding to Tcf4/Tcf7l2 and thereby promotes OLG differentiation. More recent data, however, point toward an alternate model in which Tcf4/Tcf7l2 promotes OLG differentiation via a Wnt/β-catenin-independent pathway (Hammond et al., 2015). Such a pathway could explain the inhibition of OLG differentiation seen upon genetic ablation of the canonical Wnt signaling negative regulators, APC and Axin2, as in both cases the expression of Tcf4/Tcf7l2 was found reduced (Dai et al., 2014; Guo et al., 2015; Lang et al., 2013). Interestingly, a Wnt/β-catenin independent role of Tcf4/Tcf7l2 opens the door for re-interpretation of the observed upregulation of Tcf4/Tcf7l2 in active demyelinating lesions

(Fancy et al., 2009), as this could reflect an indication of spontaneous remyelination rather than an inhibition of myelin regeneration.

Further complicating the role of Wnt/β-catenin signaling is the emerging picture that this pathway has varying effects on cells of the OLG lineage depending on the developmental stage of these cells. Based on existing data, the following multistage model has been recently developed (Guo et al., 2015): Low level Wnt/β-catenin signaling mediated by Tcf4/Tcf7l2 promotes the transition from OPC to immature OLG, while under pathological high Wnt tone this transition is inhibited. Wnt/β-catenin signaling is dispensable for the transition from immature to mature OLG, which is promoted by Tcf4/Tcf7l2 in a Wnt/β-catenin-independent fashion. Still unclear are conceivable, but not yet fully defined, roles of non-canonical Wnt signaling pathways (Yuan et al., 2012) and the effects of Wnt/β-catenin signaling on the final process of myelination.

2. Cell-adhesion and extracellular matrix (ECM) molecules

2.1. Inhitbitory effects on OLG differentiation and (re)myelination

2.1.1. Glycosaminoglycans: Glycosaminoglycans are a family of linear polymers of repeated disaccharide units, which represent a major component of the CNS ECM. Two family members, hyaluronan and chondroitin sulfate proteoglycans, have been implicated in limiting myelin regeneration under pathological conditions. Studies on a potential role of hyaluronan were initially driven by the known accumulation of this glycosaminoglycan in inflammatory lesions outside of the CNS (Toole, 2004) and after spinal cord injury (Struve et al., 2005). These initial studies revealed an increased synthesis of high molecular weight hyaluronan by astrocytes in demyelinated lesions in MS and experimental autoimmune encephalomyelitis (EAE), an animal model for immune-mediated demyelination (Back et al., 2005). The pericellular accumulation of hyaluronan around astrocytes and OLGs in these lesions could be attributed to an increased expression of the hyaluronan-binding transmembrane protein CD44. Importantly, these studies provided convincing evidence that accumulation of hyaluronan inhibits OLG differentiation and remyelination by a mechanism that is reversible (Back et al., 2005). Notably, accumulation of hyaluronan has also been implicated in OLG maturation arrest in diffuse whiter matter injury and vanishing white matter disease (Bugiani et al., 2013; Buser et al., 2012). The mechanism leading to OLG maturation arrest was later found to involve degradation of hyaluronan by the OLG-expressed hyaluronidases PH20 and interaction of the degradation products with the Toll-like receptor 2 (TLR2) expressed on the surface of OLGs (Preston et al., 2013; Sloane et al., 2010). Of note, TLR2 expression is also upregulated in MS lesions (Sloane et al., 2010). These findings suggest that small-molecular-weight compounds interfering with the hyaluronan-TLR2 signal as well as pharmacological inhibition of PH20 may represent effective ways to promote remyelination in MS and related conditions.

High levels of chondroitin sulfate proteoglycans (CSPGs) have extensively been characterized to inhibit the regeneration of axons especially after spinal cord injury (Baldwin and Giger, 2015; Cregg et al., 2014). Similar increases, however, have also been reported for CNS injuries known to affect myelin and OLGs, such as stroke (Carmichael et al., 2005), perinatal white matter injury (Deng et al., 2015) and MS (Sobel and Ahmed, 2001; van

Horssen et al., 2006). Notably, chondroitin sulfate proteoglycans have been shown to also impair OLG process outgrowth and remyelination (Lau et al., 2012; Siebert et al., 2011; Siebert and Osterhout, 2011). Reducing CSPG levels in animal models via the use of chondroitinase ABC (cABC), which cleaves the glycosaminoglycan chains from the central core protein of CSPGs, has been shown to promote remyelination, thereby providing support for the reversibility of the effects mediated by CSPGs (Lau et al., 2012; Pendleton et al., 2013; Siebert et al., 2011; Zuo et al., 1998). From a mechanistic point of view, it has been proposed that the CSPG mediated impairment in remyelination is, at least in part, triggered by signaling through the protein tyrosine phosphatase sigma (PTPσ) receptor, which has been similarly implicated in the inhibition of axonal growth and neuronal regeneration (Coles et al., 2011; Harlow and Macklin, 2014; Pendleton et al., 2013; Shen et al., 2009). Thus, targeting PTPσ via the use of small molecule inhibitors may provide a viable therapeutic strategy for enhancing not only neuronal regeneration but also remyelination (Harlow and Macklin, 2014; Martin et al., 2014, 2012; Pendleton et al., 2013).

2.1.2. LINGO-1: OLG differentiation is considered a major checkpoint in the process of remyelination (Franklin and Goldman, 2015) and LINGO-1 (leucine-rich repeat and Ig domain-containing, Nogo receptor-interacting protein) is clinically probably the most advanced of the therapeutic targets implicated in this process. LINGO-1 is a CNS-specific transmembrane protein expressed by neurons and OLGs that functions as an extracellular adhesion (or recognition) molecule. LINGO-1 was originally characterized to participate in the inhibition of axon outgrowth in response to myelin components, such as myelin associate glycoprotein (MAG), OLG myelin glycoprotein (OMgp) and Nogo, via the formation of a three-component receptor complex with the Nogo-66 receptor (NgR1) and either the p75 neurotrophin receptor or the TNF receptor family member TAJ/TROY (Mi et al., 2004; Park et al., 2005; Shao et al., 2005). LINGO-1 was later found to also negatively regulate OLG differentiation and myelination (Lee et al., 2007; Mi et al., 2005). The effect of LINGO-1 on OLGs has been proposed to occur primarily via its actions as both ligand and receptor, i.e. by mediating signaling via homophilic extracellular interactions (Jepson et al., 2012a; Kwon et al., 2014). In addition, LINGO-1 has been found to negatively regulate OLG differentiation by blocking the translocation and activation of the positive regulator of OLG differentiation ErbB2 (Lee et al., 2014).

During CNS development, LINGO-1 expression is downregulated coinciding with the onset of OLG differentiation, and thought to thereby allow differentiation to proceed (Jepson et al., 2012b; Pernet et al., 2008). Consistently, myelination is initiated earlier in *Lingo-1* knockout mice (Mi et al., 2005) and continued axonal expression of LINGO-1 inhibits OLG differentiation and myelination (Lee et al., 2007). An additional LINGO-1-related mechanism allowing developmental OLG differentiation, at least in the optic nerve, may be the release of myocilin by astrocytes. Myocilin has been reported to bind to LINGO-1 and to thereby inhibit homophilic LINGO-1 interactions and lead to a release of the inhibitory effects on OLG differentiation (Kwon et al., 2014). Interestingly, the NgR1 ligand Nogo-A has been implicated in the stimulation of OLG maturation, an effect that may, however, be independent of NgR1 signaling (Pernet et al., 2008).

In contrast to its developmental regulation, the expression of LINGO-1 was found upregulated upon CNS injury as shown in spinal cord injury and human MS (Mi et al., 2004; Mohan et al., 2014; Satoh et al., 2007). There seems to be, however, some controversy on whether this upregulation occurs primarily on cells of the OLG lineage or in subpopulations of reactive astrocytes, macrophages/microglia and neurons (Satoh et al., 2007). Nevertheless, and due to the restricted expression of LINGO-1 in the CNS, the potential of LINGO-1 as a therapeutic target for stimulating remyelination has been extensively studied. First, *in vitro* studies using small interfering RNAs (siRNAs), dominant-negative LINGO-1, or soluble LINGO-1 (LINGO1-Fc) revealed that reducing LINGO-1 expression or inhibiting its function can increase OLG differentiation (Mi et al., 2005). Follow-up *in vivo* studies uncovered an increase in remyelination and an improvement in functional recovery in EAE when LINGO-1 expression was reduced (Mi et al., 2007; Wang et al., 2014). Even though direct effects on cells of the OLG lineage were not demonstrated in these studies, antibody antagonists of LINGO-1 were developed as the next step toward clinical intervention, and their use in preclinical animal studies provided great promise for promoting remyelination by antagonizing LINGO-1 function (Mi et al., 2009, 2007; Rudick et al., 2008; Sun et al., 2015; Zhang et al., 2015). These encouraging results led to the development of a fully human IgG1 monoclonal antibody (BIIB033/Li81) that binds human LINGO-1 with high affinity and specificity (Mi et al., 2013; Pepinsky et al., 2014, 2011). Results from phase I safety trials indicated that administration of BIIB033 is safe for use in humans and is well tolerated (Brugarolas and Popko, 2014; Tran et al., 2014). A first phase II clinical trial of BIIB033 in 82 patients with optic neuritis revealed an improvement in recovery of optic nerve conduction latency but no overall improvement in visual function (Ledford, 2015). A second phase II trial in patients with active relapsing MS is currently ongoing, and it will be such current and future clinical trials that will reveal the impact of antagonizing LINGO-1 function in promoting remyelination in a clinical setting.

2.2. Permissive/promotional effects on OLG differentiation and (re)myelination

2.2.1. Laminin-2: The ECM molecule Laminin-2 (also called merosin) represents an isoform of laminin comprised of the α2, β1 and γ1 chains (Ehrig et al., 1990). As with all other laminins, it forms a cross-shaped heterotrimeric complex that mediates its functions primarily by binding to cell surface receptors, including the integrin receptor α6β1 and the non-integrin ECM receptor dystroglycan (Colognato and Yurchenco, 2000; Schéele et al., 2007).

Laminin-2 began attracting much attention when it was discovered that a mutation in the gene encoding the laminin α2 chain (*LAMA2*) causes a form of congenital muscular dystrophy (CMD), merosin-deficient CMD (MDC1A), which is characterized by alterations in skeletal muscle and peripheral nerves, and is associated with white matter abnormalities (Miyagoe-Suzuki et al., 2000; Wewer and Engvall, 1996). Laminin-2 is found in the CNS as part of the traditional ECM-rich vascular and pial basement membrane as well as in the form of non-basal lamina-associated ECM, and it is the latter that most likely affects cells of the OLG lineage (Colognato et al., 2005).

In early cell culture studies, laminin-2 was found to enhance OLG myelin membrane formation via signaling through the integrin receptor α6β1 (Buttery and ffrench-Constant, 1999; Chun et al., 2003). The exact *in vivo* role of laminin-2-β1 integrin signaling in myelination, however, is still a matter of debate due to the existence of inconclusive findings (Barros et al., 2009; Benninger et al., 2006; Câmara et al., 2009; Colognato et al., 2002). In an attempt to reconcile the differences, it was proposed that some approaches, as for example the expression of a β1 integrin mutant form lacking the C-terminal tail (DeltaC) (Lee et al., 2006), may not only disturbe laminin-2 signaling through α6β1 integrin, but also through other laminin-binding receptors (Câmara et al., 2009). In this context, while the non-β1 laminin-binding receptor α6β4 is not expressed by OLGs (Milner and ffrench-Constant, 1994), dystroglycan has been characterized, at least *in vitro*, as a significant laminin-2 receptor involved in the regulation of OLG process outgrowth and differentiation-associated gene expression (Colognato et al., 2007; Eyermann et al., 2012).

The role of laminn-2 on cells of the OLG lineage is accompanied by further complexity as laminn-2 has also been implicated in the regulation of OLG survival. More specifically, laminin-2, via an interaction with the integrin receptor α6β1, was found to enhance the survival of newly formed OLGs by amplifying trophic signaling from PDGF-A and neuregulins (Baron et al., 2005; Colognato et al., 2002; Frost et al., 1999; Laursen et al., 2009). Importantly, and different from the regulation of myelination, survival signaling via laminin-2-α6β1 integrin appears dependent on the cytoplasmic domain of the α6 subunit (Colognato et al., 2002). *In vivo*, however, it appears that there are redundant signaling pathways that control OLG survival, as loss of the laminin-2-α6β1 integrin survival pathway in *Itgβ1* knockout mice can apparently be well-compensated for during development (Benninger et al., 2006; Colognato et al., 2002). In addition to the regulation of OPC survival, laminin-2 has recently been reported to regulate OPC proliferation via the stimulation of metalloproteinase-mediated dystroglycan cleavage (Leiton et al., 2015).

With regard to remyelinaton, it is of note that increased levels of laminin-2 expression were seen on axonal tracts during the formation of new myelin sheaths following toxin-induced demyelination (Zhao et al., 2009). In addition, β1 integrin signaling has been reported to be important for successful remyelination (Lee et al., 2006; Relvas et al., 2001). These observations may suggest a lack of laminin-2 signaling as a contributing factor for the limitations in remyelination seen under pathological conditions.

2.3. Diverse/pleitropic effects on OLG differentiation and (re)myelination

2.3.1. Fibronectin: Fibronectin is an ECM protein well-known to regulate early developmental processes (George et al., 1993). In general, fibronectin is thought to exert its functions by binding to and activating receptors belonging to the integrin family (Hynes, 2002). Fibronectin is typically absent in the adult CNS, but has been found upregulated upon CNS injury, including demyelination (Hibbits et al., 2012; Satoh et al., 2009; Sobel and Mitchell, 1989; Stoffels et al., 2013; van Horssen et al., 2006). First evidence for a role of fibronectin in OLG biology came from tissue culture studies in which fibronectin stimulated the migration and proliferation of OPCs at low growth factor levels via interaction with integrin receptors αvβ1 and αvβ3, respectively (Blaschuk et al., 2000; Milner et al., 1996).

Subsequent studies revealed an important role of a crosstalk between fibronectin and growth factor signaling by demonstrating that activation of the αvβ3 integrin receptor via fibronectin (or vitronectin) binding can potentiate the proliferative response elicited by the mitogenic growth factor PDGF-A (Baron et al., 2005, 2003, 2002; Decker et al., 2004). Given fibronectin's role in OPC proliferation and migration, the observation that fibronectin expression is upregulated upon CNS injury and demyelination led to the idea that fibronectin functions as a positive regulator of remyelination by promoting OPC recruitment. Consistent with this idea, the expression of αv integrins and their ligands, including fibronectin, were seen transiently upregulated during successful remyelination (Stoffels et al., 2013; Zhao et al., 2009). Upon CNS injury, two forms of fibronectin, which differ in cellular source and the presence/absence of alternatively spliced domains, can be found: plasma fibronectin leaking through a damaged blood-brain-barrier and cellular fibronectin released by predominantly astrocytes (Stoffels et al., 2013). Genetic ablation of plasma and/or astrocyte fibronectin (*Fn*) in a model of lysolecithin-induced demyelination revealed a role of predominantly astrocyte fibronectin on OPC proliferation, but not migration (Stoffels et al., 2015). The apparent redundancy of plasma fibronectin, despite its well-documented ability to promote OPC proliferation *in vitro*, was accounted for by the limited blood-brain barrier break-down in the employed model. Importantly, the deletion of both plasma and astrocyte *Fn* did not affect the overall extent of OLG differentiation and remyelination (Stoffels et al., 2015), an observation that is consistent with the notion that recruitment of OPCs may not always be the rate-determining factor for remyelination (Franklin and Goldman, 2015).

In contrast to fibronectin's positive regulatory role in OPC proliferation and migration and despite the proposed role of the fibronectin receptor αvβ5 integrin in promoting OLG differentiation (Blaschuk et al., 2000), more recent studies point toward an OLG differentiation and remyelination inhibitory role of in particular astrocyte-derived fibronectin aggregates, which are formed under pathological conditions, and are likely mediated by inflammatory factors (Lafrenaye and Fuss, 2010; Maier et al., 2005; Sisková et al., 2009, 2006; Stoffels et al., 2013). Notably, intralesional injection of fibronectin aggregates into remyelinating lesions inhibited OLG differentiation and myelin regeneration, and levels of aggregated fibronectin were found to be high in demyelinated, but not remyelinated MS lesions (Stoffels et al., 2013). Hence, the inhibitory signals induced by fibronectin aggregates or factors that affect fibronectin aggregation could represent potential therapeutic targets for promoting remyelination (Stoffels et al., 2013).

2.3.2. Notch signaling: Notch signaling is an evolutionarily conserved cell-cell recognition mechanism considered to play fundamental roles during development and in the adult (Artavanis-Tsakonas et al., 1999; Lathia et al., 2008). In vertebrates, there are four members of the Notch receptor family, Notch1-4, which can mediate cell-cell interactions by binding to one of their five canonical ligands, Jagged1,2 or Delta1,2,3 (D'Souza et al., 2010; Lathia et al., 2008). Of the Notch receptors, Notch1 has been most widely investigated and is often referred to as simply Notch. Activation of the pathway through receptor-ligand interaction leads to proteolytic cleavage of Notch via the activity of presenilin-1/γ-secretase and release of the Notch intracellular domain (NICD). The NICD then translocates to the nucleus where

it associates with DNA-binding proteins to regulate transcription and gene expression (Kopan, 2002).

In OLGs, Notch1 has been characterized as a negative regulator of OLG differentiation that upon interaction with Jagged1, which is expressed on axonal surfaces prior to myelination, or Delta1 mediates an upregulated expression of the transcription factor *Hes5*, a well-characterized repressor of OLG differentiation (Kondo and Raff, 2000; Liu et al., 2006; Wang et al., 1998). In further support of an inhibitory role of Notch1 in OLG differentiation, myelination in heterozygous *Notch1* knockout mice is accelerated (Givogri et al., 2002) and OLG differentiation occurs precociously in conditional *Notch1* knockout mice (Genoud et al., 2002; Zhang et al., 2009). These findings prompted the idea that the high levels of Notch canonical signaling pathway components seen in chronic active MS lesions (John et al., 2002), may contribute to inefficient myelin regeneration under pathological conditions. Animal studies addressing this idea have so far provided ambiguous findings. Intraventricular administration of a γ-secretase inhibitor in a model of EAE promoted remyelination (Jurynczyk et al., 2008), an effect, however, that may be due to modulation of Notch signaling in cells of the immune system (Juryńczyk and Selmaj, 2010). In the lysolecithin model of focal demyelination, conditional deletion of *Notch1* accelerated remyelination (Zhang et al., 2009). Similarly, pharmacological inhibition of signaling activated by the secreted peptide endothelin-1 (ET-1), accelerated remyelination by preventing an upregulation of *Jagged1* expression in astrocytes and subsequent activation of canonical Notch signaling in OLGs (Hammond et al., 2014). In addition, however, endothelins have been reported to directly stimulate OPC migration and to possibly also directly regulate OLG differentiation (Gadea et al., 2009; Jung et al., 2011; Yuen et al., 2013). Of note, in chronic active MS lesions levels of ET-1 have been, similar to those of canonical Notch signaling pathway components, found increased, thus further supporting the idea of a clinically relevant inhibitory effect of canonical Notch signaling on OLG differentiation and remyelination (Hammond et al., 2014). Different from the above findings, OLG-targeted Notch1 ablation in cuprizone-treated *Plp-creER:Notch1*$^{flox/flox}$ mice yielded no significant differences in remyelination (Stidworthy et al., 2004). The lack of effect in the latter study has been discussed to potentially be due to the timing of *Notch1* ablation (Brosnan and John, 2009).

Further complicating is the fact that Notch signaling via a non-canonical pathway has been implicated in positively regulating OLG differentiation. More specifically, interaction between Notch1 on OLGs and F3/contactin on axons has been shown to initiate a Notch/Deltex1 signaling pathway that promotes OLG maturation and myelination (Hu et al., 2003). In an attempt to demonstrate that inefficient remyelination in MS may be due to a lack of axonal F3/contactin, Nakahara et al. (2009) discovered that, to the contrary, F3/contactin was saturated on demyelinated axons in chronic silent MS lesions. In addition, the Notch1 receptor was engaged in OPCs, as evidenced by the presence of the NICD. However, nuclear transport of the NICD was blocked in OPCs due to pathologically increased expression of TAT-interacting protein 30 kDa (TIP30, also known as CC3) and complex formation with Importin β (Nakahara et al., 2009). Comparing these findings with those reported earlier and describing an upregulation of the canonical, rather than an interference with the non canonical, Notch pathway in chronic active MS lesions (John et al., 2002), might suggest

that mechanistically the main reason for inefficient myelin regeneration may differ depending on the type of lesion (chronic active versus chronic silent). These observations highlight the complexity and potential heterogeneity of the regulation of remyelination under pathological conditions (Brosnan and John, 2009).

2.3.3. PSA-NCAM: The neural cell adhesion molecule NCAM has been well-characterized to play crucial roles in neuronal motility and axon guidance (Maness and Schachner, 2007). NCAM comes in different alternatively spliced isoforms and with a number of post-translational modifications. With regard to myelination, it is polysialic acid (PSA)-modified NCAM that has been characterized as a negative regulator of axon-OLG interaction. More specifically, it has been shown that disappearance of PSA-NCAM from both axonal and oligodendroglia surfaces coincides during development with OLG differentiation and the initiation of myelination (Bartsch et al., 1990; Charles et al., 2000; Jakovcevski et al., 2007; Trotter et al., 1989). Notably, downregulation of PSA-NCAM from OLG surfaces was found to be critical for efficient myelination and myelin maintenance (Charles et al., 2000; Fewou et al., 2007). Mechanistically, the presence of PSA on either the axon, the OLG or both has been proposed to interfere with signaling pathways required for efficient process extension and wrapping of the myelin sheath and to not simply block NCAM function (Fewou et al., 2007). Given these negative regulatory roles of PSA-NCAM, the observation that PSA-NCAM is re-expressed on the surface of about 11–19% of demyelinated axons within MS lesions has led to the interpretation that this re-expression could contribute to the limitations in remyelination seen in MS (Charles et al., 2002).

In addition to the above inhibitory role, however, PSA-NCAM has been found to be required on OPCs for their ability to respond to chemotactic cues, such as PDGF (Decker et al., 2000; Zhang et al., 2004). Thus, PSA-NCAM expression on OPCs may be critical for efficient recruitment to the site of injury, while its persistence appears to limit the efficiency of remyelination.

3. Neurotransmitters: Glutamate and ATP

Electrical activity has long been proposed to regulate developmental myelination (Colello et al., 1995; Demerens et al., 1996; Shrager and Novakovic, 1995), and it has more recently also been implicated in experience-dependent “adaptive” myelination (Bergles and Richardson, 2015; Fields, 2015; Purger et al., 2015). The picture that is currently emerging predicts that initiation of myelination can occur independent of axonal signals but that myelination is fine-tuned and modulated by axonal signals, including the ECM protein laminin and synaptic vesicle release regulated by electrical activity (Bechler et al., 2015; Hines et al., 2015; Mensch et al., 2015). Main molecular mediators of the latter are thought to be well-known neurotransmitters, in particular glutamate and ATP, even though GABA has also been suggested to contribute to the regulation of OPC differentiation and possibly myelination (Arellano et al., 2015; Lin and Bergles, 2004; Zonouzi et al., 2015). The communication between OPCs and unmyelinated axons during developmental myelination as well as remyelination is thought to occur primarily through synaptic contacts (Almeida and Lyons, 2014; Bergles et al., 2010; Etxeberria et al., 2010; Gallo et al., 2008; Kukley et al., 2007; Lin and Bergles, 2004; Ziskin et al., 2007). Functionally, this axo-glia interaction

has been implicated in the regulation of OPC proliferation and differentiation, even though the direction of this regulation still appears inconclusive (Fannon et al., 2015; Gibson et al., 2014; Mangin et al., 2012). At later stages of the OLG lineage, non-synaptic axonal neurotransmitter release has been shown to stimulate myelination without affecting OLG differentiation (Wake et al., 2011). This effect was suggested to be mediated by signaling through *N*-methyl-d-aspartate receptors (NMDARs) and metabotropic glutamate receptors. However, knockout of the obligate NR1 subunit of the NMDAR in cells of the OLG lineage (conditional *Grin1* knockout) did not reveal an effect on *in vivo* myelination or the pathophysiology of the demyelinating animal model EAE (De Biase et al., 2011; Guo et al., 2012). These data indicate the existence of additional and/or alternate receptors responding to axonal release of glutamate and regulating myelination. Interestingly, it was recently demonstrated that glutamate, via activation of sodium-dependent glutamate transporters and transient inactivation of the actin-binding domain of calcium calmodulin-dependent kinase IIβ (CaMKIIβ), stimulates OLG process outgrowth at least *in vitro* (Martinez-Lozada et al., 2014). Intriguingly, the thickness of myelin sheaths in CaMKIIβ (*Camk2b*) knockout mice is reduced (Waggener et al., 2013), thus implicating the above pathway in the fine-tuning of CNS myelination. In addition, and despite the above mentioned absence of a myelination phenotype in conditional *Grin1* knockout mice, NMDAR signaling was found to enhance the efficiency of myelination in the presence of the growth factors neuregulin and brain-derived neurotrophic factor (BDNF) (Lundgaard et al., 2013), suggesting that glutamate may regulate (re)myelination at several steps and via several pathways. In this context it is also of note that next to the aforementioned direct effects, glutamate signaling can promote OLG differentiation and (re)myelination indirectly via the activation of metabotropic glutamate receptors on astrocytes (Fulmer et al., 2014). Such activation was in a model of toxin-induced demyelination found to increase the synthesis and release of BDNF, which in turn has been characterized to stimulate OLG differentiation and (re)myelination through TrkB receptor-mediated signaling (Fulmer et al., 2014; VonDran et al., 2011; Vondran et al., 2010; Wong et al., 2013; Xiao et al., 2010). Such pro-myelinating effects of BDNF have also been described for models of spinal cord injury and stroke (McTigue et al., 1998; Ramos-Cejudo et al., 2015).

A second neurotransmitter signal implicated in CNS myelination is ATP. Similar to glutamate, ATP is released from axons in an activity-dependent fashion, and has been shown to subsequently promote myelination via an indirect mechanism that involves the conversion of ATP to adenosine, which then triggers the release of leukemia inhibitory factor (LIF) from neighboring astrocytes via the activation of purinergic P2 receptors (Fields, 2006; Ishibashi et al., 2006; Spiegel and Peles, 2006; Stevens et al., 2002).

Despite the above described positive regulatory aspects of glutamate and ATP, it is worth mentioning that an excess of both excitatory neurotransmitters, as often seen upon CNS injury, can have detrimental consequences by causing neuronal and oligodendroglia cell death as well as white matter damage (Fern et al., 2014; Matute, 2011; Matute and Ransom, 2012). On the other hand, increases in extracellular glutamate may also increase the motility of OPCs via the formation of a signaling complex including AMPARs, integrins, calcium-binding proteins, and the myelin proteolipid protein (PLP), and to, thereby, promote repopulation of demyelinated areas with cells of the OLG lineage (Gudz et al., 2006; Harlow

et al., 2015). Thus, when considering the regulation of mechanisms involving neurotransmitters in the context of remyelination, it will be important to establish a permissive glutamate and ATP homeostasis that ensures efficient OPC migration and allows myelination to be modulated by the axonal release of the same transmitters that at pathologically high levels can cause cell death.

Closing Remarks

Throughout the past several years, significant advances have been made toward a better understanding of the molecular mechanisms regulating developmental myelination and their potential relevance for the regeneration of the myelin sheath under pathological conditions. Remarkably, more detailed analyses of the environmental changes associated with demyelination have uncovered the importance of extracellular cues, inhibitory as well as permissive/promotional, and their roles in defining the well-balanced conditions needed for successful regeneration of the myelin sheath. Importantly, the realization that pathological inhibition of remyelination by changes in the extracellular milieu as well as age-associated decline in remyelination may be reversible, has provided hope that pharmacological approaches targeting pathways that are mediated by extracellular cues and aimed at mobilizing endogenous (or if necessary transplanted) progenitors are a realistic and viable proposition for enhancing regenerative processes leading to myelin sheath formation (Franklin, 2002; Franklin and Goldman, 2015; Laursen and Ffrench-Constant, 2007). Notably, while the current clinical focus seems to have emerged on blocking inhibitory cues such as LINGO-1, targeting the dysregulation of permissive/promotional pathways should not be dismissed. Moreover, the multifaceted nature of the majority of the pathways initiated by most extracellular cues may favor approaches that target downstream signals located at critical convergent points (Grinspan, 2015) and/or mechanisms of particular significance for remyelination. Much progress has been made and the promise that is built on existing research and clinical data is high. In keeping with the momentum, future work will likely further advance our understanding and reveal the true clinical impact of targeting extracellular signals and their downstream pathways in promoting remyelination.

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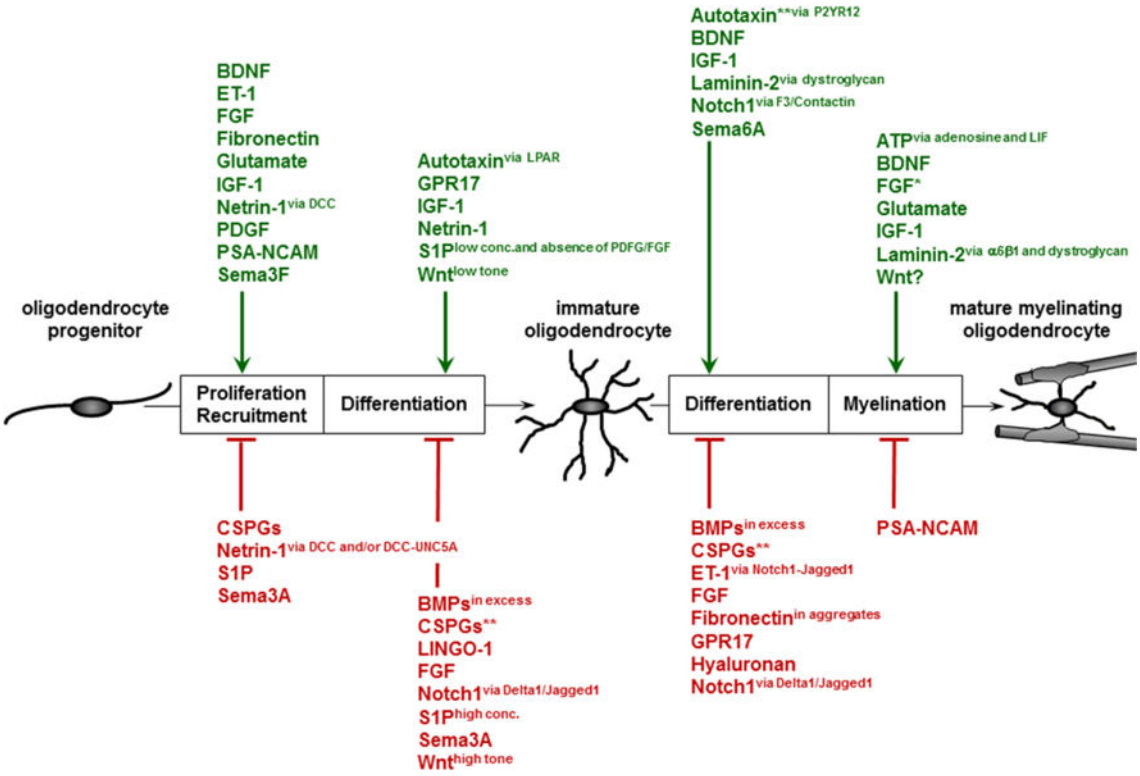

Figure 1. Schematic representation of extracellular cues acting as permissive/promotional (top; green) and/or inhibitory (bottom; red) cues at the different stages along the OLG lineage

Note that most cues play multiple roles by affecting OLGs at more than one stage along the lineage. In some cases, cues may exert inhibitory effects at one stage while playing a promotional/permissive role at another stage (see for example: GPR17 ligands and FGF). *myelin thickness only; ** process outgrowth only.