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# Regulation of Oligodendrocyte Differentiation: Relevance for Remyelination

Olaf Maier

*Institute of Cell Biology and Immunology, University of Stuttgart  
Germany*

## 1. Introduction

A major distinguishing feature of the vertebrate nervous system is the formation of myelin sheaths. The myelin sheath has two main functions. First, it electrically insulates the axon thereby enabling saltatory conduction and highly increasing conduction velocity. This also strongly reduces energy consumption since restoration of ion gradients occurs only at the nodes of Ranvier (i.e. at less than 1 % of the axonal surface). Second, the myelin sheath is important for trophic support and protection of the axon (Nave, 2010).

Oligodendrocytes (OLG) are the myelinating cells of the central nervous system (CNS). In contrast to Schwann cells, the myelinating cells of the peripheral nervous system (PNS), OLG form multiple extensions. Each of these extensions forms a myelin sheath after contacting an axon. Due to the synthesis and maintenance of multiple myelin sheaths OLG are highly metabolic active and thus produce large amounts of reactive oxygen species. Moreover, they contain a large amount of iron, which can cause free radical formation. Accordingly, OLG are highly vulnerable to lipid peroxidation and DNA damage due to oxidative stress. It is therefore not surprising that OLG cell death as well as myelin degradation (demyelination) are features of many acute and chronic diseases of the CNS, e.g. trauma, ischemia, spinal cord injury, Alzheimer's Disease and even schizophrenia (McTigue & Tripathi, 2008; Bradl & Lassmann, 2010). Ultimately demyelination results in axonal degeneration and decline of neuronal functions.

Demyelination or dysmyelination (impaired myelin synthesis) are the defining feature of CNS white matter diseases (leukodystrophies). Primary and secondary leukodystrophies can be distinguished. Whereas in primary leukodystrophies, myelin and OLG are directly affected, in secondary leukodystrophies the function of other cells, e.g. astrocytes, is perturbed resulting indirectly in OLG cell death and demyelination. Examples for primary leukodystrophies are Pelizaeus-Merzbacher disease (PMD) and spastic paraplegia type 2 (SPG2), which are characterized by dysmyelination in the CNS (Inoue, 2005), as well as globoid cell leukodystrophy (Krabbe's disease) and metachromatic leukodystrophy. These diseases are caused by impaired degradation of the major myelin lipids galactosylceramide (GalCer) and sulfatide, respectively, and are characterized by progressive demyelination and mental retardation (Wenger et al., 2000; Gieselmann, 2003). The best example for an inherited secondary leukodystrophy is Alexander disease, which is caused by mutation of the astrocytic intermediate filament protein GFAP (Johnson, 2004).

The most common demyelinating diseases are multiple sclerosis (MS) and neuromyelitis optica (NMO), which are both characterized by an autoimmune attack of the immune system on the CNS. Whereas it is generally accepted that, in MS, OLG are the primary target of the immune attack, it has been recently discovered that aquaporin 4, localized in astrocytes, is the primary target in NMO (Roemer et al., 2007; Parratt & Prineas, 2010). The resulting dysfunction and death of astrocytes then causes demyelination and OLG death.

After demyelination the function of the affected area is restored by remyelination, the intrinsic repair mechanism after demyelination. Remyelination of demyelinated axons in the CNS occurs when OLG progenitor cells (OPC) proliferate, migrate to the site of damage, locally differentiate into mature OLG and finally produce new myelin sheaths that are wrapped around the naked axon (C. Zhao et al., 2005). Therefore remyelination largely resembles the developmental myelination process and accordingly knowledge of all steps relevant for developmental OLG differentiation and myelination is essential for potential therapies based on tissue regeneration (Franklin & ffrench-Constant, 2008).

Here I will review main aspects of myelin formation in the CNS starting with the synthesis and transport of myelin components and the morphological differentiation of OLG, which culminates in the formation of multiple myelin sheaths. I will then discuss intrinsic and extrinsic factors that regulate OLG differentiation. Finally, I will address specific aspects of remyelination and will draw attention to differences between developmental myelination and remyelination, e.g. due to changes in the CNS microenvironment.

## 2. Differentiation of oligodendrocytes

Most aspects of OLG biology have been studied in rodents and in rodent-derived cells. These studies have revealed that the differentiation of OLG is a highly regulated process, in which several stages can be distinguished. During embryonal development neural stem cells in the ventral ventricular zone of the CNS (and later also in more dorsal areas) develop into OPC. These cells are characterized by the expression of the ganglioside A2B5, the chondroitin sulfate proteoglycan NG2 and the platelet-derived growth factor receptor  $\alpha$  (PDGFR $\alpha$ ; Nishiyama et al., 1999). OPC proliferate and migrate throughout the CNS to their final destination. Around birth the OPC start to differentiate and extend multiple processes. Those branches that do not find an axon retract and OPC that cannot make axonal contact undergo apoptotic cell death. When a process makes contact with an axon, the cell synthesizes myelin components and vast amounts of membrane, which is wrapped several times around the axon. After extrusion of the cytoplasm the formation of the compact myelin sheath is completed (Baumann & Pham-Dinh, 2001; Bradl & Lassmann, 2009). These stages are characterized by the sequential expression of cellular marker molecules. Concomitantly, OPC-specific marker molecules are lost (see Fig. 1).

### 2.1 Myelin structure and composition

The myelin sheath is not homogeneous. The compact myelin, which is important for the electrical insulation of the axon, can be distinguished from several regions of non-compact myelin (Sherman & Brophy, 2005). These include the adaxonal and abaxonal plasma membranes, which face the axon and the extracellular matrix (ECM), respectively, the radial component, important for energy and metabolite transport within the myelin sheath, and

the paranodal loops. These are the main contact sites between myelin and axon and are especially relevant for the functionality as well as structural integrity of the nodes of Ranvier (Tait et al. 2000).

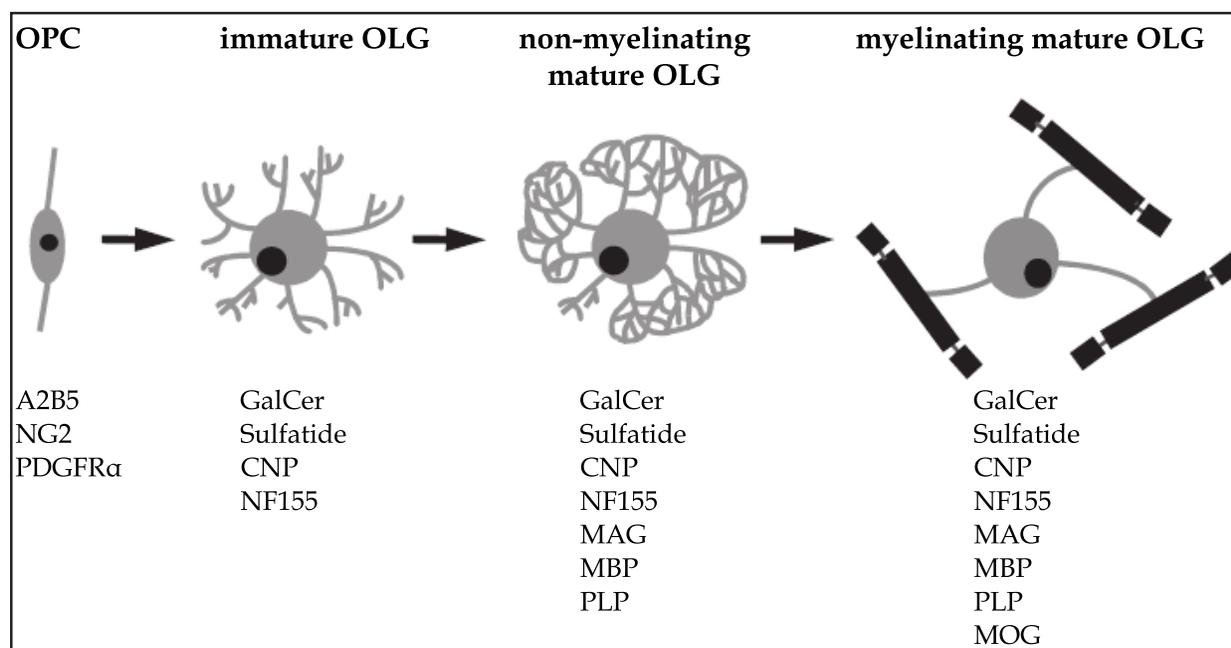


Fig. 1. Schematic representation of OLG developmental stages. Indicated are stages of OLG differentiation ultimately resulting in myelin sheath formation (black) as well as proteins and lipids specific for these developmental stages (adapted from Maier et al., 2005).

To fulfil its function of electrical insulation, the myelin sheath is highly enriched in lipids, which comprise approx. 70 % of its dry weight. The most abundant myelin lipids are cholesterol and the glycosphingolipids GalCer and its sulfated form sulfatide. Cholesterol is essential for myelin formation (Saher et al. 2005) while GalCer and sulfatide are important for the correct formation of the paranodal loops (Dupree et al., 1998; Marcus et al. 2006). The major myelin proteins are proteolipid protein (PLP), its derivative DM20 and myelin basic protein (MBP), which comprise together approx. 80 % of the total myelin proteins (Brunner et al. 1989; Griffiths et al., 1998). PLP/DM20 and MBP are localized in the compact internodal myelin and are required for the compaction of the myelin sheath. Important non-compact myelin proteins are, e.g., 2'3'-cyclic nucleotide 3'-phosphodiesterase (CNP), localized throughout the non-compact myelin, myelin-associated glycoprotein (MAG) in the adaxonal membrane, myelin/oligodendrocyte glycoprotein (MOG) in the abaxonal membrane and the 155 kDa isoform of neurofascin (NF155) in the paranodal loops (Brunner et al., 1989; Schachner & Bartsch, 2000; Tait et al., 2000). For a comprehensive description of myelin composition see, e.g., Baumann & Pham-Dinh, 2001; Aggarwal et al., 2011.

## 2.2 Synthesis and transport of myelin components

Each OLG myelinates all contacted axons simultaneously and completes the initial wrapping of axons within 12 to 18 hours (Watkins et al., 2008). To achieve this task OLG have to synthesize tremendous amounts of myelin in a very short time (Pfeiffer et al., 1993).

Accordingly, synthesis and transport of myelin components must be highly coordinated in time and space. Moreover, since the composition of the myelin membrane and the membrane of the OLG soma differ significantly, myelin components must be sorted prior to their transport to the myelin sheath. Three main steps required for this polarized transport can be distinguished: i) the sorting of proteins and lipids destined for the different plasma membrane domains, ii) the directed transport towards the different plasma membrane domains along the cytoskeleton and finally iii) the specific targeting to and incorporation into the correct membrane domain. Since these aspects are relevant for the understanding of OLG differentiation, here I will discuss briefly some features of the synthesis and transport of myelin proteins and consequences of incorrect protein synthesis and/or transport, focussing on the major proteins PLP and MBP. Due to space limitations I will not address the directed transport and targeting to the myelin sheath (see, e.g., Krämer et al., 2001, Anitei & Pfeiffer, 2006; Maier et al., 2008)

The exact routes by which transmembrane proteins are transported to the myelin sheath are not well understood and distinct transport pathways towards the myelin sheath have been discussed (Krämer et al., 2001; Anitei & Pfeiffer, 2006; Maier et al., 2008). In general, transmembrane proteins, such as PLP, are synthesized at the endoplasmic reticulum and transported via the Golgi apparatus to the plasma membrane. For PLP there is good evidence that the newly synthesized protein is first transported to the plasma membrane of the cell soma. From there it is internalized and stored in late endosomes before it is finally transported by a transcytotic pathway to the myelin sheath (Trajkovic et al., 2006; Feldmann et al., 2011). Surprisingly, although PLP deletion results in neuronal degeneration, it has only minor effects on myelin formation (Garbern et al. 2002). In contrast, overexpression of PLP causes its accumulation in late endosomes and/or lysosomes together with cholesterol and results in missorting of several membrane markers indicating that major trafficking pathways are affected thereby ultimately interfering with myelination and OLG viability (Simons et al., 2002). Indeed, most cases of PMD are caused by PLP gene duplication resulting in a massive overexpression of PLP demonstrating the relevance of these findings for human disease. In addition, missense mutations in PLP can result in PMD or SPG2 due to the accumulation of PLP in the ER resulting in an unfolded protein response and finally in OLG cell death (Krämer-Albers et al., 2006).

MBP is a multi-functional protein and several isoforms of MBP have been described (Boggs, 2006). In contrast to PLP, MBP is a cytoplasmic protein and is therefore synthesized at free ribosomes in the cytoplasm. Myelin-specific MBP isoforms mediate myelin compaction by interconnecting the cytoplasmic leaflets of the myelin membrane. Accordingly, MBP must have strong adhesive properties. To preclude these adhesive properties taking effect in the cell soma, the MBP messenger RNA (mRNA) is transported into the OLG processes where the protein is synthesized and directly associates with the myelin membrane. To prevent premature MBP protein synthesis the MBP mRNA is incorporated into granules which are transported along microtubules into the OLG branches (Barbarese et al., 1995). This incorporation is mediated by the mRNA binding factor hnRNP A2, which is highly expressed during OLG differentiation (Maggipinto et al., 2004). The importance of correct MBP expression for myelination is demonstrated by the finding that MBP absence causes dysmyelination. This is exemplified by the severe reduction of compact myelin in the so called shiverer mouse due to partial MBP deletion (Roach et al., 1985).

### 2.3 Morphological differentiation: role of the cytoskeleton

An intact cytoskeleton is essential for all aspects of OLG biology. Both actin filaments and microtubules are essential for the coordinated transport of myelin components to the myelin sheath and the actin cytoskeleton is important for OPC migration. Of particular interest is the role of the cytoskeleton during the morphological differentiation of the OLG.

Each of the multiple branches of the OLG forms a myelin sheath upon axonal contact. One OLG can thus myelinate up to 40 different axons (Pfeiffer et al., 1993). Outgrowth of cellular processes is therefore a fundamental property of OLG and both microtubules and actin filaments are essential to coordinate the morphological changes accompanied with OLG differentiation (Richter-Landsberg, 2008; Bauer et al., 2009). In general, microtubules are especially important for process outgrowth and stabilization whereas actin filaments are more important for the formation of the lamellipodium that initiates the formation of the myelin sheath.

Both depolymerization and stabilization of microtubules perturb the formation of myelin-like membrane sheets *in vitro* indicating that microtubule turnover is required for correct myelination (Benjamins & Nedelkoska, 1994). Nevertheless, a stable microtubular cytoskeleton is required to promote outgrowth and maintenance of cellular processes during OLG differentiation. Indeed, acetylated tubulin, indicative for stable microtubules is present in OLG branches. Moreover, microtubules can be stabilized by associated proteins such as MAP2c and tau (Richter-Landsberg & Gorath, 1999). Tau, in particular, has been implicated in stabilization of microtubules in OLG branches. Whereas OPC express tau isoforms with three microtubule binding domains, differentiating OLG predominantly express tau isoforms containing four microtubule binding domains, which may promote microtubule stability. Moreover, phosphorylation of tau is decreased during OLG differentiation, thereby promoting interaction of tau with microtubules and microtubule stabilization (Richter-Landsberg, 2008). In addition to stabilizing proteins, microtubules are modulated by proteins that promote their disassembly. One prominent protein that mediates microtubule disassembly is stathmin. Accordingly, stathmin expression is downregulated during OLG differentiation (Liu et al., 2003).

Similar to microtubules actin filaments are important for outgrowth and stabilization of OLG extensions. The actin cytoskeleton has been especially implicated in the formation of the lamellipodium, which initiates the enwrapment of the axon. Important regulators of actin cytoskeleton dynamics are proteins of the Rho family of GTPases (Ridley, 2006). Indeed, several members of this family, namely RhoA, Rac and Cdc42 have been implicated in OLG process outgrowth and myelination (Liang et al., 2004, Thurnherr et al., 2007, Rajasekharan et al., 2009). Activation of both Rac and Cdc42 promotes myelination, whereas activation of RhoA inhibits OLG differentiation. An important downstream effector of Rho GTPases that has been implicated in OLG process outgrowth and myelination is the neuronal Wiskott Aldrich Syndrome Protein (nWASP) (Bacon et al. 2007). Activation of nWASP, e.g. by Cdc42, can activate the Arp2/3 complex, which acts as a nucleating factor for actin filament polymerization thereby promoting the formation of the actin network required for lamellipodium formation (Ridley, 2006).

Not surprisingly, several myelin components are interacting with the cytoskeleton thereby facilitating the coordination of the myelination process. Of particular relevance are the

cytoplasmic myelin proteins CNP and MBP (Dyer & Benjamins, 1989). CNP can interact with both actin filaments and microtubules and acts as a microtubule assembly protein (De Angelis et al., 1996; Lee et al., 2005). Consequently, CNP is essential for OLG arborization and membrane expansion during myelination. Although cytoplasmic, CNP is anchored to the plasma membrane by isoprenylation and inhibition of CNP isoprenylation perturbs arborization and OLG differentiation (Lee et al., 2005; Smolders et al., 2010). Similar to CNP, MBP can interact with both actin filaments and microtubules and is important for cytoskeleton integrity in OLG. Dephosphorylated MBP, which is predominantly localized in myelin, stabilizes microtubules and enhances microtubule polymerization (Galiano et al., 2006). Moreover, dephosphorylated MBP can act as membrane anchoring protein for actin filaments (Boggs, 2006).

### 3. Regulation of oligodendrocyte differentiation

OLG differentiation is a highly regulated multistep process. Here I will discuss intrinsic and extrinsic factors that regulate OLG differentiation and myelination. Although the understanding of the interplay between the intrinsic and extrinsic factors that orchestrate OLG myelination is far from complete, I will also address how these factors can initiate and modulate signaling pathways implicated in OLG differentiation.

#### 3.1 Intrinsic factors

In culture, OPC synthesize myelin components and form myelin-like membrane sheets in absence of CNS-derived factors suggesting that differentiation into mature OLG is an intrinsic property of these cells. Differentiation is predominantly regulated on the level of gene transcription and protein translation and much progress has been made in the characterization of these intrinsic factors for OLG differentiation. However, it is still far from understood how the function of these intrinsic factors is coordinated to mediate OLG differentiation.

On the level of gene transcription promoting and repressing transcription factors of OLG differentiation have been identified. Transcription factors that promote differentiation of OPC into mature OLG are, e.g., Olig1, Olig2 and Nkx2.2 and Sox10 (Liu & Casaccia, 2010; Miron et al., 2011). Especially relevant for the initiation of OLG differentiation is the concomitant expression of Olig2 and Nkx2.2 (Zhou et al., 2001). Most transcription factors that promote differentiation are, however, expressed in all stages of OLG development indicating that their presence is not sufficient to induce OLG differentiation. Indeed, several transcription factors that are expressed in OPC, such as Hes5, Id2, Id4, Sox5 and Sox6, strongly inhibit OLG differentiation (Liu & Casaccia, 2010; Miron et al., 2011). Blocking the expression of these inhibitory factors is essential to promote OLG differentiation and there is increasing evidence that this is achieved by epigenetic mechanisms.

In principle, epigenetic inhibition of gene expression can be achieved by two major mechanisms: i) repression of transcription by DNA or histone modification and ii) inhibition of protein translation by microRNAs (miRNAs). Both mechanisms are operational during OLG differentiation. The predominant modification of histones relevant for OLG differentiation is deacetylation, which inhibits gene transcription. Indeed, activity of histone deacetylases is essential for OPC generation and their

development into mature OLG. Histone deacetylases can, e.g., bind to the promoter region of OLG differentiation repressors such as Hes5 and Id4 thereby preventing their expression and thus promoting OLG differentiation (Liu & Cassacia, 2010; Copray et al., 2011). In addition, expression of other proteins can be regulated by histone deacetylation. Thus, the expression of stathmin is repressed by this mechanism during OLG differentiation (Liu et al., 2003) thereby promoting microtubule polymerization and stabilization of the outgrowing OLG branches.

MiRNAs are small non-coding RNAs of approximately 23 nucleotides that are processed from larger precursor RNAs by the RNaseIII enzymes Dicer and Drosha. By binding to the 3' untranslated region of mRNAs one miRNA can inhibit the translation of multiple mRNAs (Bartel, 2004). Expression of Dicer increases during OLG differentiation and conditional knockout of Dicer in OLG results in dys- or demyelination depending on the stage of Dicer repression (Dugas et al., 2010; X. Zhao et al., 2010). In these studies miR219 and miR338 have been identified as important regulators of OLG differentiation. Both miR219 and miR338 can directly suppress the inhibiting transcription factors Sox6 and Hes5 thereby promoting OLG differentiation (Dugas et al., 2010; X. Zhao et al., 2010). An additional target of miR219 is the PDGFR $\alpha$ , (Dugas et al., 2010), which, although important for OPC proliferation and migration, inhibits OLG differentiation (see next section).

### 3.2 Extrinsic factors

Although *in vitro* OLG can form myelin-like membranes in the absence of axons, there is ample evidence that *in vivo* myelination is coordinated by the presence of axons. However, in contrast to the PNS, where axonal expression of neuregulin-1 type III determines the myelination by Schwann cells (Taveggia et al., 2005), no master regulator for myelination in the CNS has been identified. It is more likely that several factors act together to initiate and promote myelination in the CNS. In general, signals modulating OLG differentiation can be divided into two classes: long-range signals such as growth factors and short-range signals such as ECM and cell adhesion molecules (see Table 1 for important factors regulating OLG behavior). Since the differentiation into a myelinating phenotype is an intrinsic property of OLG while myelination of the axon has to be tightly controlled, it is perhaps not surprising that many axonal factors inhibit OLG differentiation. Here I will address some of the exogenous factors that modulate myelination and subsequently discuss how these signals may be integrated to result in the induction and modulation of myelin formation.

#### 3.2.1 Modulation of oligodendrocyte differentiation by neurons

During embryonic development neurons prevent premature differentiation of OPC. For this purpose they express inhibitory proteins at the axonal surface, e.g. the polysialylated form of the neural cell adhesion molecule (PSA-NCAM), which is a general inhibitor of cell adhesion (Charles et al., 2000). In addition, neurons express molecules that can directly inhibit OLG differentiation. Examples are Jagged and the Leucine-rich repeats and Ig domain-containing, neurite outgrowth inhibitor (Nogo) receptor-interacting protein-1 (LINGO-1). Jagged is the axonal ligand of the Notch receptor in the OLG membrane and activation of the Notch signaling pathway interferes with OLG development (S. Wang et al., 1998). LINGO-1 is part of the Nogo-66 receptor complex in the axonal membrane and

interaction of this receptor complex with OLG proteins such as Nogo-A and MAG can inhibit axonal growth. Conversely, inactivation of LINGO-1 promotes myelination suggesting that LINGO-1 is a key inhibitor of OLG differentiation (Mi et al., 2005). Since LINGO-1 is also expressed by OLG, homophilic LINGO-1 interactions may also interfere with OLG development.

An important factor for the induction of OLG differentiation is the electrical activity of neurons (Demerens et al., 1996) most likely by the release of adenosine which may activate purinergic receptors at the OLG surface (Stevens et al., 2002). Very recently it has been shown that also the neurotransmitter glutamate, released at the synapse upon action potentials, can promote OLG differentiation (Wake et al., 2011).

It is likely that *in vivo* the direct contact of an OLG extension with the axon is important to initiate OLG myelination. The best candidate for an axonal molecule required to induce myelination is the ECM molecule laminin-2, since laminin-2 deficiency causes myelination defects in mice and humans (Chun et al., 2003; Colognato et al., 2005). In addition, neuregulin-1 promotes OLG differentiation (Z. Wang et al., 2007). Other molecules that may be involved in the interaction between OLG and axon and thus promote OLG maturation are gangliosides, which can bind to MAG at the OLG cell surface (Yang et al., 1996).

### 3.2.2 Modulation of oligodendrocyte differentiation by astrocytes

The intimate relationship of OLG with astrocytes is demonstrated by the formation of gap junctions between these cell types (Orthmann-Murphy et al., 2008). In addition to the direct exchange of molecules via these cell-cell interaction sites, astrocytes modulate OLG function by the release of growth factors and by the deposition of ECM molecules.

Astrocytes are the primary source of growth factors in the CNS (Moore et al., 2011). Among these are, e.g., PDGF-AA and fibroblast growth factor-2 (FGF-2), which mediate proliferation and migration of OPC (Milner et al., 1997; Baron et al., 2000). PDGF-AA is also important for OLG survival in presence of laminin-2 (Baron et al., 2003). However, both PDGF-AA and FGF-2 inhibit OLG differentiation at least *in vitro* (Noble et al., 1988; Bansal & Pfeiffer, 1994). Moreover, astrocytes inhibit OLG maturation during CNS development by secretion of bone morphogenetic proteins (BMP), which are strong suppressors of OLG differentiation (See et al., 2004). Besides these inhibitory factors, however, several factors secreted by astrocytes promote OLG differentiation and myelination. Prominent examples are insulin-like growth factor-1 (IGF-1), leukemia inhibitory factor (LIF) and ciliary neurotrophic factor (CNTF) (McMorris et al., 1986; Stankoff et al., 2002). Interestingly, electrical activity of axons causes the release of LIF from astrocytes (Ishibashi et al., 2005), providing a link between neuronal and astrocytic modulation of myelination. Moreover, astrocytes affect OLG function by synthesizing ECM-molecules, such as fibronectin and tenascin C (Price & Hines, 1985; Götz et al., 1997). Fibronectin promotes proliferation and migration of OPC (Milner et al., 1996; Baron et al., 2002), which is important during embryonal development. However, fibronectin impairs morphological differentiation of OLG *in vitro* (Buttery & French-Constant, 1999; Maier et al., 2005). Similarly, tenascin C inhibits process outgrowth and myelin membrane formation of OLG (Czopka et al., 2009).

Factor	Predominant source	Effect on OLG
<i>Soluble Factors</i>		
Adenosine	neurons	promotes differentiation
Glutamate	neurons	promotes differentiation
PDGF-AA	astrocytes	promotes migration and proliferation; inhibits differentiation
FGF-2	astrocytes	promotes migration and proliferation; inhibits differentiation
IGF-1	astrocytes	promotes differentiation
CNTF	astrocytes	promotes differentiation
LIF	astrocytes	promotes differentiation
BMP	astrocytes	inhibits differentiation
<i>Membrane proteins</i>		
LINGO-1	neurons	inhibits differentiation
Jagged	neurons	inhibits differentiation
PSA-NCAM	neurons	inhibits interaction with axon
Neuregulin-1	neurons	promotes myelination
<i>ECM molecules</i>		
Laminin-2	neurons	promotes differentiation
Fibronectin	astrocytes	promotes migration and proliferation; inhibits differentiation
Tenascin C	astrocytes	inhibits migration and differentiation
<i>Other factors</i>		
Electrical activity	neurons	promotes differentiation

Table 1. Neuronal and astrocytic factors that regulate OLG behaviour and differentiation

### 3.2.3 Modulation of oligodendrocyte signaling pathways by extrinsic factors

It is obviously essential that the signals supplied by these extrinsic factors are integrated at the OLG cell surface, followed by signal transduction into the cell and modulation of signaling pathways resulting in OLG differentiation. Here I will focus on two main aspects that are important to coordinate signaling pathways in the developing OLG. First, the interaction of ECM molecules, in particular laminin-2 and fibronectin, with receptors on the OLG cell surface and the modulation of these interactions by growth factors. Second, the multiple roles of the Src-family non-receptor tyrosine kinase Fyn in OLG maturation.

ECM molecules such as laminin-2 and fibronectin interact predominantly with integrin receptors in the plasma membrane. Integrins are heterodimeric proteins consisting of one  $\alpha$ - and one  $\beta$ -subunit. OLG express a limited number of integrins, namely  $\alpha\beta1$ -,  $\alpha\beta3$ - and  $\alpha\beta5$ -integrins, which bind to ECM-molecules containing an RGD-motif such as fibronectin

and vitronectin, and  $\alpha 6\beta 1$ -integrin, which can bind to laminin-2. Proliferation and migration of OPC, stimulated by PDGF, are mediated by activation of  $\alpha v\beta 1$  and  $\alpha v\beta 3$ -integrins, implicating RGD-containing ECM-molecules in these processes (Milner et al., 1996; Baron et al., 2002). The importance of  $\alpha 6\beta 1$  integrin for myelination was indicated by applying antagonists of the  $\beta 1$ -subunit, which inhibit myelination *in vitro* and *in vivo* (Buttery and French-Constant, 1999; Relvas et al., 2001). However, the OLG-specific knockout of the  $\beta 1$ -subunit does not cause demyelination (Benninger et al., 2006) indicating that another laminin-2 receptor is present in the OLG membrane. Indeed, dystroglycan has been identified as a receptor for laminin-2, which is required for myelination (Colognato et al., 2007). The  $\beta 1$ -subunit in OLG is, however, important for cell survival *in vivo* (Benninger et al., 2006). Interestingly, in presence of laminin-2 the PDGFR $\alpha$  dissociates from  $\alpha v$ -containing integrins and instead interacts with  $\alpha 6\beta 1$ -integrin causing a change in signaling from cell proliferation to cell survival (Baron et al., 2003). Similarly, laminin-2 causes the interaction of the neuregulin receptor erbB2 with  $\alpha 6\beta 1$ -integrin. This causes a switch in neuregulin signaling from cell proliferation towards cell survival and differentiation (Colognato et al., 2004). These examples show how integrins coordinate short range (ECM-mediated) and long range (growth factors, cytokines) signals, which are both required to regulate cell behaviour.

Although it is still far from understood how the signals received at the plasma membrane are further processed to promote OLG differentiation, several signaling pathways have been identified. For example, binding of laminin-2 to  $\alpha 6\beta 1$ -integrin promotes OLG differentiation and myelination by the activation of integrin-linked kinase (Chun et al., 2003). Moreover, activated  $\alpha 6\beta 1$  integrin binds to the Src family kinase Fyn and this interaction is important for the modulation of the PDGF and neuregulin signaling pathways described above and thus for OLG survival and differentiation (Colognato et al., 2004). Indeed, Fyn has been identified as a key regulator of OLG differentiation. The relevance of Fyn for myelination is exemplified by the finding that the OLG-specific knockout of Fyn results in hypomyelination *in vivo* (Biffiger et al., 2000). Fyn has been implicated in various aspects of OLG biology ranging from migration to myelination. Importantly, Fyn kinase activity is activated by interaction with cell adhesion molecules such as NCAM120 and contactin in the OLG membrane which may interact with axonal proteins thereby initiating myelination (Krämer et al., 1999). Moreover, Fyn can act as a bridge between integrins or other membrane receptors and the cytoskeleton and, depending on the developmental stage of the OLG and the corresponding expression of potential interaction partners, Fyn may bind to different proteins thereby explaining its diverse roles in OLG differentiation. In OPC, binding of PDGF to its receptor PDGFR $\alpha$  results in recruitment of Fyn and modulation of the actin cytoskeleton thereby increasing OPC migration (Miyamoto et al., 2008). Later in OLG development, integrin signaling via Fyn promotes morphological differentiation by activating Rac and Cdc42 and inactivating RhoA, again implicating modulation of the actin cytoskeleton in this process (Liang et al., 2004). Interestingly, LINGO-1 suppresses OLG differentiation and myelination by inactivation of Fyn kinase thereby activating RhoA signaling pathways (Mi et al., 2005). Besides modulating the actin cytoskeleton, Fyn can also affect the microtubular network via binding to tau thereby stabilizing microtubules and thus promoting process outgrowth and OLG differentiation (Klein et al., 2002).

## 4. Remyelination

Remyelination as the natural regenerative mechanism after a demyelinating insult is the basis of the functional recovery of the affected neurons (Bruce et al., 2010). Since mature OLG are incapable to myelinate nude axons (Crang et al., 1998; Watkins et al., 2008), remyelination requires the de novo differentiation of OPC. Importantly, OPC, characterized by the expression of NG2 and PDGFR $\alpha$ , are present throughout the adult CNS (Polito and Reynolds, 2006) and remyelination is usually very effective after transient demyelination. However, the new myelin sheaths are frequently shorter and thinner than the original sheaths thus giving rise to so-called shadow plaques (Franklin and ffrench-Constant, 2008). Moreover, in chronic diseases, such as MS, remyelination is often incomplete and ultimately fails in most patients resulting in increased neurodegeneration and progressive disease. A main goal for the treatment of chronic demyelinating diseases is therefore to increase the remyelination of the affected axons and thus at least partially restore axonal function.

Two main strategies are followed to improve remyelination: promotion of the endogenous remyelinating capacity and transplantation of exogenous stem cells or progenitor cells. Cell transplantation studies are predominantly performed in animals suffering from dysmyelination, such as the shiverer mouse, or by chemically induced demyelination to ensure that the observed myelination is due to the transplanted cells. In such studies it has been shown that several cell types are able to (re)myelinate CNS axons, such as neural stem cells, Schwann cell precursor cells, olfactory ensheathing cells and OPC (J. Yang et al., 2009). Of these, fetal OPC, possibly derived from induced stem cells, are probably suited best for CNS remyelination (Franklin, 2002; Tepavcevic & Blakemore, 2005). One problem in studying the potential of exogenous OPC to differentiate and (re)myelinate axons after transplantation is that endogenous OPC inhibit the migration and survival of transplanted OPC (O'Leary and Blakemore, 1997). Accordingly, endogenous OPCs have to be eliminated, e.g. by X-ray treatment (Hinks et al., 2001), which may cause conditions that differ from those in most demyelinating diseases. Several other obstacles in cell transplantation are: i) finding a cell source that is abundant enough to repopulate the CNS without causing ethical problems, ii) the delivery of the cells to the CNS and iii) their migration through the CNS to the demyelinated areas.

Irrespective of these considerations, the most useful strategy depends predominantly on the disease one wants to treat. Thus in primary inherited leukodystrophies, such as PMD, the most useful therapy would be the transplantation of allogeneic OPC. In contrast, in MS endogenous OPC are present in and around chronic demyelinated lesions indicating that the environment that these OPC encounter is not permissive for differentiation (Wolswijk, 1998). It is therefore unlikely that transplanted cells will be able to sufficiently migrate and differentiate under these conditions. Irrespective of the cellular source it is therefore essential to modulate the environment resulting in conditions that are permissive for remyelination.

### 4.1 Inhibitors of remyelination in the diseased CNS

Although remyelination does occur in MS and can be very efficient in a subset of MS patients even after a long disease course (Patrikios et al., 2006; Patani et al., 2007), remyelination eventually fails in most patients. Two obvious potential reasons for

remyelination failure are axonal loss or depletion of the endogenous OPC pool. Although such a scenario cannot be excluded in some cases, it is unlikely to be the predominant reason for remyelination failure since in most lesions axons are still preserved and OPC are present in or around the lesion site, often in close proximity of a demyelinated axon. This strongly suggests that inhibitory factors are present in the lesion area that impair OLG differentiation and remyelination. Indeed, in MS a block of OLG differentiation in chronic lesions has been observed (Kuhlmann et al., 2008). This impaired remyelination is characterized by the accumulation of OPC that remain in an undifferentiated stage resulting in a failure to generate myelinating OLG (Goldschmidt et al., 2009). In general, disease-dependent and disease-independent factors can be distinguished that may affect remyelination and in this section I will summarize several of these factors.

The demyelinated axons themselves may repress the interaction with OLG branches and thus their remyelination by the expression of inhibitory cell adhesion molecules. Nude axons in chronic MS-lesions re-express PSA-NCAM, which inhibits OLG differentiation during development (Charles et al., 2000, 2002). Similarly, there is good evidence that expression of LINGO-1 in the lesion area inhibits efficient remyelination (Mi et al., 2007). Moreover, OPC functions may be changed in demyelinating diseases. It has, e.g., been shown that stathmin levels are increased in MS patients, which may contribute to reduced OLG differentiation and remyelination failure in MS lesions (Liu et al., 2005).

Several changes in the environment surrounding the recruited OPC may contribute to the inhibition of cell differentiation. Most relevant in the context of demyelinating diseases is that myelin components strongly inhibit OLG differentiation and (re-)myelination, which is at least partially due to inactivation of Fyn kinase activity (Kotter et al., 2006; Baer et al., 2009). Accordingly, it is essential that the myelin debris that is present in the lesion due to the demyelination process is efficiently removed to allow OPC differentiation and thus remyelination to proceed. Clearance of myelin debris is mediated predominantly by activated microglia, the resident immune cells of the CNS, and macrophages that have entered the CNS parenchyma from the periphery (Neumann et al., 2009). However, it should be kept in mind that microglia can act as antigen presenting cells after ingestion of myelin debris and thus may activate myelin-specific T-cells that have entered the CNS. Moreover, reactive microglia can produce proinflammatory cytokines and reactive oxygen species. Therefore activated microglia may actually enhance the demyelination process (Lassmann & van Horssen, 2011).

In addition to activation of microglia, demyelination results in the activation of astrocytes. Depending on the signals that these astrocytes receive, their activation can be beneficial or detrimental for the remyelination process (Williams et al., 2007). Activated astrocytes secrete growth factors and ECM molecules, e.g. PDGF-AA, FGF-2 and fibronectin, which promote proliferation of OPC and their recruitment to the lesion area. Other factors secreted by astrocytes can promote differentiation of these OPC to mature OLG (see section 3.2.2). However, some of these astrocyte-derived factors can have opposing effects. The chemokine CXCL1, e.g., can stimulate OPC proliferation but also acts as a stop signal for OPC migration (Tsai et al., 2002; Filipovic & Zecevic, 2008). Since in MS, astrocytes surrounding chronic lesions can secrete CXCL1 they may therefore repress the recruitment of OPC to the lesion site (Omari et al., 2006). Moreover, the persistent presence of fibronectin and other ECM molecules, e.g. chondroitin sulfates and hyaluronic acid, can impair OLG

differentiation and may, together with astrocyte proliferation, result in the formation of a glial scar thus impairing the remyelination process (Kotter et al., 2011; Miron et al., 2011). This is particularly the case in chronic demyelination when repair mechanisms have failed. In this respect, it has been speculated that the formation of a glial scar is the consequence rather than the cause of remyelination failure (Franklin & Kotter, 2008).

The major disease-independent factor that impedes remyelination is age. In general, regenerative mechanisms are less efficient in old animals compared to young animals and this has also been observed for remyelination. This age-related effect is predominantly due to impaired recruitment of the OPC to the lesion area and a delay in their subsequent differentiation to myelinating OLG (Sim et al., 2002). There may be several reasons for this effect. First, OPC themselves may be less efficient in migration and differentiation. Indeed, the response to growth factors differs in adult OPC compared neonatal OPC possibly delaying the recruitment of OPC into lesion areas (Lin et al., 2009; Cui et al., 2010). Furthermore, histone deacetylases are less active in OPC of adult animals. This can impair the repression of inhibitory transcription factors, which is required for OLG differentiation (Shen et al., 2008) and thus result in a delay of OLG differentiation. It should, however, be mentioned that adult OPC are highly efficient in myelination of nude axons when transplanted into the CNS of shiverer mice indicating that the intrinsic myelinating capacity of adult OPC is not reduced compared to neonatal OPC provided they are in an environment that is permissive for myelination (Windrem et al., 2004). It is therefore more likely that age-related changes in the CNS environment result in a delay of OLG differentiation. One likely cause for impaired OLG differentiation in demyelinating diseases is that adult microglia and macrophages are less efficiently recruited to the lesion area resulting in a delayed clearing of myelin debris (Neumann et al., 2009). Accordingly, the prolonged presence of myelin in the lesion prevents OLG differentiation and may even close the therapeutic window in which remyelination can proceed (Kotter et al., 2011).

#### 4.2 Initiation and promotion of remyelination

Although present throughout the CNS, adult OPC do not differentiate spontaneously into myelinating OLG implying that they are in a quiescent stage. Accordingly, OPC have to be activated by extrinsic factors, which are most likely derived from activated microglia and astrocytes, as these cells are highly sensitive to injury-induced environmental changes. Similar to developmental myelination, several stages of OPC activation can be distinguished during remyelination, starting with OPC proliferation and migration to the lesion site followed by cell differentiation (Franklin & French-Constant, 2008).

Major progress in the elucidation of the requirements for remyelination has been done in MS and animal models of MS. In MS, the immune system attacks the OLG resulting in demyelination and neurodegeneration and virtually all components of the innate and adaptive immune system have been implicated in the demyelination and/or neurodegeneration in MS lesions (Gandhi et al., 2009; Kasper & Shoemaker, 2010). Interestingly and perhaps paradoxically, there is increasing evidence that inflammation is also important for remyelination. First, remyelination is abundant in immunologically active MS lesions whereas it is rarely observed in chronic, immunologically less active lesions (Goldschmidt et al., 2009). Second, genome studies of remyelination have revealed that pro-inflammatory cytokines are important for OLG regeneration. Indeed, the pro-inflammatory

cytokine tumor necrosis factor (TNF) is important for remyelination after cuprizone-induced demyelination (Arnett et al., 2001, 2003). Third, as mentioned above, activated microglia and macrophages are required to clear the myelin debris from the lesion area, which is a prerequisite for remyelination. Interestingly, clearing of myelin debris by microglia can be enhanced by infiltrating myelin-specific T cells (Nielsen et al., 2009). Fourth, T cells and microglia can promote OLG proliferation and differentiation by producing neurotrophic factors such as brain derived neurotrophic factor (BDNF; Hohlfeld et al. 2006; Neumann et al., 2009). Indeed, T cells are required for efficient remyelination (Bieber et al., 2003).

Although inflammation can promote remyelination and the immune response might therefore be beneficial for neuroregeneration in MS, MS is predominantly an inflammatory disease (Lassmann & van Horssen, 2011). Maintaining an acute inflammatory milieu in order to improve remyelination may therefore be harmful to the patient. Nevertheless, immunomodulation may be a promising immediate approach to promote remyelination. Indeed, glatiramer acetate and FTY720 (fingolimod), two compounds that are approved for MS therapy, may promote remyelination. Glatiramer acetate, a polypeptide resembling MBP, alters the T cell response in MS from a pro-inflammatory Th1 to an anti-inflammatory Th2 phenotype. Interestingly, these glatiramer acetate-specific Th2 cells produce IGF-1 and BDNF and promote oligodendrogenesis and myelin repair in chemically induced demyelination (Skihar et al., 2009). The sphingosine-1-phosphate analogue FTY720 is used predominantly to inhibit the egress of T cells from secondary lymphoid organs. In addition, FTY720 can promote OLG differentiation (Miron et al., 2010) and as FTY720 can enter the CNS parenchyma it may thus directly promote remyelination.

Another direct approach to promote remyelination might be the injection of adult stem cells. Indeed, intracerebral or intraventricular injection of stem cells results in effective myelination in various models of demyelination. However, due to the multiple focal lesions in MS a systemic application is probably required. It is therefore promising that intravenous administration of adult neural and bone-marrow derived stem cells can enhance remyelination and ameliorate symptoms in experimental autoimmune encephalomyelitis (EAE), the animal model of MS (Pluchino et al., 2003; J. Yang et al., 2009). However, there is some evidence that this effect is predominantly due to the immunomodulatory function of stem cells (Pluchino et al., 2005) and it is still a matter of debate whether stem cells can indeed translocate into the CNS parenchyma and directly myelinate demyelinated axons (Franklin and French-Constant, 2008; Franklin & Kotter, 2008).

Since OPC are present in chronic MS lesions but fail to differentiate the most relevant approach to improve remyelination will be to change the environment within the lesion from inhibitory to permissive for myelination. This would largely increase the therapeutic window in which remyelination can occur and thus would be expected to protect axons from further degeneration. Also in this field some promising results have been obtained. Of particular interest is the observation that the inhibitory effect of myelin components on OLG differentiation due to inactivation of Fyn can be antagonized by pharmacological inhibition of the RhoA signaling pathway (Baer et al., 2009). Moreover, suppression of the OLG differentiation inhibitor LINGO-1 by a specific antagonist stimulates OLG differentiation and promotes remyelination and axonal integrity in EAE (Mi et al., 2007, 2009).

## 5. Conclusion

OLG differentiation and myelination are extremely complex and highly regulated processes and disturbance of myelination is associated with various CNS diseases. Understanding of OLG differentiation is essential to establish neuroprotective therapies that are based on remyelination. Of particular relevance to develop such therapies is a profound knowledge of the intrinsic and extrinsic factors that coordinate myelination. The role of astrocytes and microglia are of special interest in view of their ambiguous role in neurodegenerative diseases. Here the challenge will be to minimize their role in neurodegeneration and maximize their role in neuroprotection and regeneration. A promising approach may therefore be to modulate astrocytes in such a way that the release of pro-myelinating factors is increased whereas the release of molecules detrimental for myelination is reduced. Concerning microglia it will be important to promote their capacity to efficiently clear the myelin debris in the lesions while at the same time minimizing their harmful effects since the presence of myelin debris is arguable the most important inhibitory factor for remyelination.

Much progress has been made to improve remyelination in model systems. Nevertheless currently no therapy directly aimed at improving remyelination exists and it is therefore now the question how this knowledge can be translated into therapeutic approaches. The most effective approach to achieve remyelination therapy will certainly depend on the diseases to treat. The first diseases, in which it is realistic to directly improve remyelination with cell-based therapies, will most likely be leukodystrophies, such as PMD. For chronic MS it is less likely that cell transplantation is a realistic treatment option. Here the promotion of the endogenous remyelination capacity is more promising, which will largely depend on the generation of a permissive environment for OLG differentiation. The progress that has been made in the last decade makes one cautiously optimistic that therapies based on remyelination are becoming a feasible scenario for the treatment of MS-patients.

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Immunology is the branch of biomedical sciences to study of the immune system physiology both in healthy and diseased states. Some aspects of autoimmunity draws our attention to the fact that it is not always associated with pathology. For instance, autoimmune reactions are highly useful in clearing off the excess, unwanted or aged tissues from the body. Also, generation of autoimmunity occurs after the exposure to the non-self antigen that is structurally similar to the self, aided by the stimulatory molecules like the cytokines. Thus, a narrow margin differentiates immunity from auto-immunity as already discussed. Hence, finding answers for how the physiologic immunity turns to pathologic autoimmunity always remains a question of intense interest. However, this margin could be cut down only if the physiology of the immune system is better understood. The individual chapters included in this book will cover all the possible aspects of immunology and pathologies associated with it. The authors have taken strenuous effort in elaborating the concepts that are lucid and will be of reader's interest.

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Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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