

# Oligodendrocyte Myelination in the Mammalian CNS

Q. Richard Lu\* • Veerakumar Balasubramanian • Raniero L. Peru

Department of Developmental Biology and Kent Waldrep Foundation Center for Basic Neuroscience Research on Nerve Growth and Regeneration, University of Texas  
Southwestern Medical Center, Dallas, TX 75390, USA

Corresponding author: \* qrichard.lu@utsouthwestern.edu

## ABSTRACT

Oligodendrocyte myelination is essential for the proper function of the mammalian central nervous system. The generation of myelinating oligodendrocytes is regulated by complex but coordinated signals during CNS development. Recent discoveries of critical transcriptional regulators for oligodendrocyte differentiation and axonal signals for myelin sheath production have significantly advanced our understanding of the molecular mechanisms governing oligodendrocyte myelinogenesis. This review highlights current perspectives on the origin of oligodendrocytes and the intrinsic and extrinsic regulation of oligodendrocyte differentiation and myelinogenesis. Potential implications of myelin in health and disease are also explored.

**Keywords:** epigenetic, glial, neuregulin, Olig1, Olig2, origin, Sox, transcriptional regulation

**Abbreviations:** AEP, anterior entopeduncular area; BDNF, brain-derived neurotrophic factor; BMP, bone morphogenetic protein; CNS, central nervous system; FGF, fibroblast growth factor; GRP, glial restricted precursors; LGE, lateral ganglion eminence; LIF, leukemia inhibitory factor; MBP, myelin basic protein; MGE, medial ganglion eminence; NGF, nerve growth factor; NRG, neuregulin; NT3, neurotrophin-3; PDGF, platelet-derived growth factor; PDGFR $\alpha$ , platelet-derived growth factor receptor alpha; PLP, proteolipid protein; PSA-NCAM, polysialic acid-neural cell adhesion molecule; Shh, sonic hedgehog; SVZ, subventricular zone; TSA, Trichostatin A

## CONTENTS

INTRODUCTION.....	118
ORIGINS OF OLIGODENDROCYTES DURING CNS DEVELOPMENT.....	119
Oligodendrocyte specification in the developing spinal cord.....	119
Oligodendrocyte specification in the developing brain.....	119
Oligodendrocytes in the adult brain.....	120
Oligodendrocyte lineage development.....	120
INTRINSIC CONTROL OF OLIGODENDROCYTE MATURATION.....	120
bHLH factor family.....	121
HMG domain containing Sox gene family.....	122
Homeodomain protein family.....	122
Zinc finger protein family.....	122
Epigenetic control of oligodendrocyte differentiation.....	123
EXTRINSIC CONTROL OF OLIGODENDROCYTE MATURATION.....	123
Axonal signals in myelination.....	123
Neuregulin.....	123
Neurotrophic factors.....	124
Electrical activity.....	124
Extra cellular matrix proteins.....	125
MYELINATION IN HEALTH AND DISEASE.....	125
CONCLUDING REMARKS.....	126
ACKNOWLEDGEMENTS.....	126
REFERENCES.....	126

## INTRODUCTION

Myelination is the evolutionary conserved process by which myelin sheath spirally wraps around axons to insulate them (Raine 1984). Axonal insulation by oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS) enhances saltatory conduction, which is essential for the normal function of the vertebrate nervous system, particularly for motor and cognitive functions. Myelination between exposed nodes of Ranvier allows action potentials to propagate efficiently and maximizes axonal conduction velocity in a

spatially-compact manner. Although a few invertebrates possess a myelin-like structure, axonal ensheathment by compact myelin is a unique feature of the vertebrate nervous system (Zalc and Colman 2000). Various pathological insults and nerve injuries may damage CNS myelin and therefore disrupt normal transmission of nerve impulses, eventually leading to myelin-related disorders such as multiple sclerosis and the leukodystrophies (Berger *et al.* 2001; Trapp *et al.* 1998). At present, the mechanisms underlying myelinating disease formation and myelin repair are poorly understood.

Oligodendrocytes in rodents are generated during em-

bryonic stages and become mature perinatally after immature oligodendrocytes extend their processes for axonal ensheathment (Raine 1984). In most vertebrates including humans, the process of myelination continues postnatally and into adulthood. It includes process extension, axonal recognition, myelin synthesis, and ensheathment. Recent discoveries of a series of critical transcriptional regulators and extracellular signaling molecules for oligodendrocyte development underscore the complexity of the myelination process, which is controlled by the coordinated action of multiple factors in a spatially and temporally specific manner (Miller 2002; Wegner 2001). In this review we will discuss various aspects of oligodendrocyte specification and maturation, as well as their function in CNS development and disease pathogenesis.

## ORIGINS OF OLIGODENDROCYTES DURING CNS DEVELOPMENT

### Oligodendrocyte specification in the developing spinal cord

Oligodendrocyte precursor cells (OPCs) originate from a specialized ventral domain, called the pMN, in the developing spinal cord at an early embryonic stage around embryonic day 12.5 (e12.5) (Miller and Reynolds 2004; Richardson *et al.* 2000). OPCs generated in the ventral germinal zone migrate laterally and dorsally to populate the entire spinal cord before terminally differentiating into mature myelin-forming oligodendrocytes (Fig. 1A). The expression of PDGFR $\alpha$  is recognized as an indicator of the initial population of OPCs (Pringle and Richardson 1993). In addition to PDGFR $\alpha$ , several transcriptional regulators that specify OPC formation have been used to mark the initial appearance of OPCs (Miller and Reynolds 2004; Richardson *et al.* 2000). bHLH transcriptional factors Olig1 and Olig2 define the earliest domains of the oligodendrocyte lineage prior to PDGFR $\alpha$  in the developing neural tube (Lu *et al.* 2000; Takebayashi *et al.* 2000; Zhou *et al.* 2000).

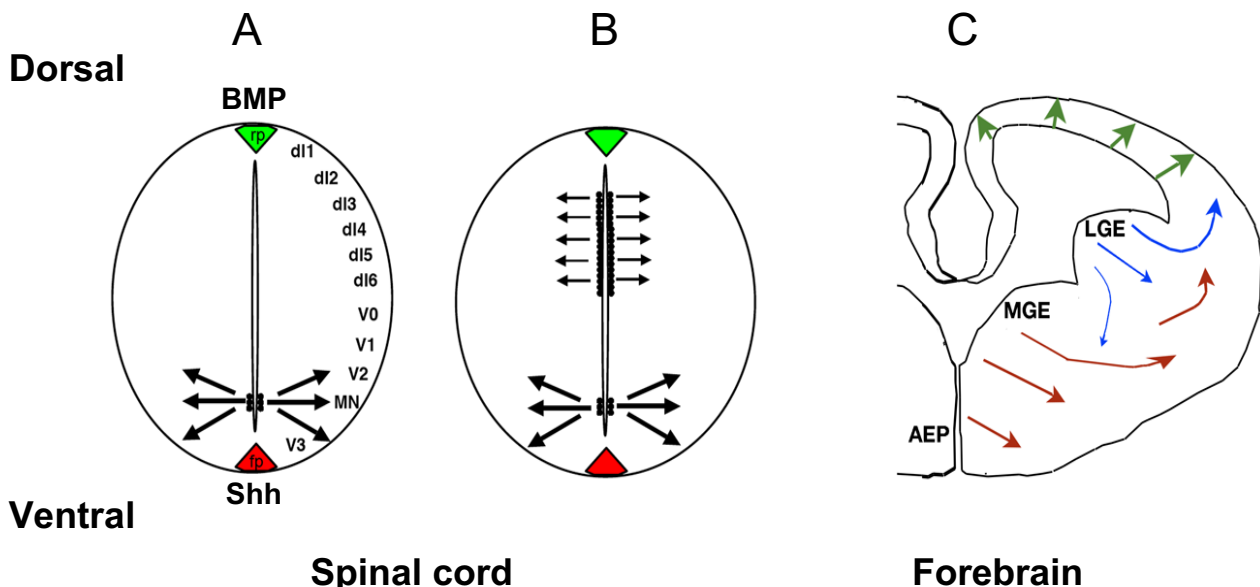
Progenitor cells deriving from the dorsal half of the spinal cord also produce oligodendrocytes during late embryonic stages. OPCs can be detected in *Nkx6.1* and *Nkx6.2* double mutants lacking the ventral source of oligodendrocytes (Cai *et al.* 2005; Vallstedt *et al.* 2005). Fate-mapping of the progeny of dorsally expressing Cre lines (e.g. *Dbx2-Cre* and *Mash1-Cre*) suggests that a subset of oligodendro-

cytes are derived from radial glia in the dorsal spinal cord during late embryogenesis (Battiste *et al.* 2007; Fogarty *et al.* 2005). Therefore, dorsal progenitor cells of the spinal cord can generate OPCs in addition to ventral progenitors (Fig. 1B).

### Oligodendrocyte specification in the developing brain

In a similar fashion to the spinal cord, OPCs in the anterior part of the CNS forebrain initiate from the ventral region of the telencephalon including the medial ganglionic eminence (MGE) and lateral ganglionic eminence (LGE) begin around e14.5 (Woodruff *et al.* 2001). OPC populations in the thalamus, hypothalamus and developing cerebellum appear to be generated from the ventricular zone of the ventral diencephalon such as anterior entopeduncular area, AEP (Pringle and Richardson 1993; He *et al.* 2001; Richardson *et al.* 2006) (Fig. 1C).

Recent studies suggest that forebrain OPCs develop in multiple sequential waves (Kessaris *et al.* 2006). The first wave of OPCs appears to derive from the ventral domain of the MGE that populates the ventral forebrain. The second wave of OPCs emanates from the dorsal regions of GE (LGE), while the third wave occurs after e18 and is of cortical progenitor origin (Kessaris *et al.* 2006). In general, oligodendrocytes are progressively generated from ventral to dorsal and from caudal to rostral regions. OPCs arise from dorsal cortical progenitor cells during late embryonic stages and appear to play a major role in myelination of the cortex. Hence, postnatal ablation of an essential oligodendrocyte specification gene *Olig2* leads to profound deficits in cortical myelination (Yue *et al.* 2006; Cai *et al.* 2007). A population of OPCs generated during earlier waves appears to undergo cell death (Kessaris *et al.* 2006). This might reflect some local advantages of cortically-derived OPCs in terms of cortical myelination over the ventral OPCs generated during earlier embryonic stages (Kessaris *et al.* 2007). However, the ventrally-derived oligodendrocytes were found to progressively populate the subcortical white matter in the *Olig2* mutant with myelination deficits (Yue *et al.* 2006), suggesting that ventrally derived oligodendrocytes can contribute to cortical myelination when myelination is limited.



**Fig. 1 Multiple developmental sources of oligodendrocytes.** (A-B) Cross-sections of the spinal cord show ventral and dorsal OPC sources at early (A, e.g. e12.5) and late (B, e.g. e16.5) embryonic stages along with their migration pathways. The oligodendroglial fate of dorsal and ventral progenitors are regulated by a gradient of morphogenetic factors BMP and Shh, respectively. (C) The diagram depicts the regions of OPC production in a coronal section of the developing telencephalon. Arrows show potential OPC migration routes.

## Oligodendrocytes in the adult brain

Oligodendrocyte myelination appears to be a continuous event during development and in adulthood (Kaplan and Hinds 1980; McCarthy and Leblond 1988; Yates and Juraska 2007). In the adult forebrain, stem cells from the subventricular zone (SVZ) are a source for new oligodendrocyte generation (Levison and Goldman 1993; Luskin and McDermott 1994; Menn *et al.* 2006). These cells may potentially participate in myelin repair (Gensert and Goldman 1997; Blakemore and Keirstead 1999; Franklin 2002). It is worth mentioning that OPCs are present in the corpus callosum and other white matter regions and undergo cell division during normal and injured conditions. At present, the extent to which mobilization of adult SVZ stem cells or local endogenous OPCs contributes to myelin repair after injury remains unresolved.

## Oligodendrocyte lineage development

The lineage relationship between oligodendrocytes and other neural subtypes has been the subject of intensive study and debate. Although oligodendrocytes and astrocytes have been believed to derive from a common glial progenitor, a fate-mapping study with an *Olig1-Cre* line indicates that *Olig1+* cells are expressed in specific progenitor cell pools that give rise to oligodendrocytes and motor neurons in the developing spinal cord (Lu *et al.* 2002). Whether motoneurons and oligodendrocytes derive from shared lineage progenitor cells or from separate progenitor cell pools remains a matter of debate (Richardson *et al.* 2000). However, the current consensus is that *Olig+* cells give rise to motoneuron precursors and OPCs sequentially at different developmental stages (Kessaris *et al.* 2001; Richardson *et al.* 1997) (Fig. 2A). This is consistent with a recent lineage tracing study of *Ascl1+* (also previously known as *Mash1*) cells at different developmental time points, revealing that *Mash1+* cells generate dorsal horn interneurons at early embryonic stages and subsequently late-born oligodendrocytes (Battiste *et al.* 2007).

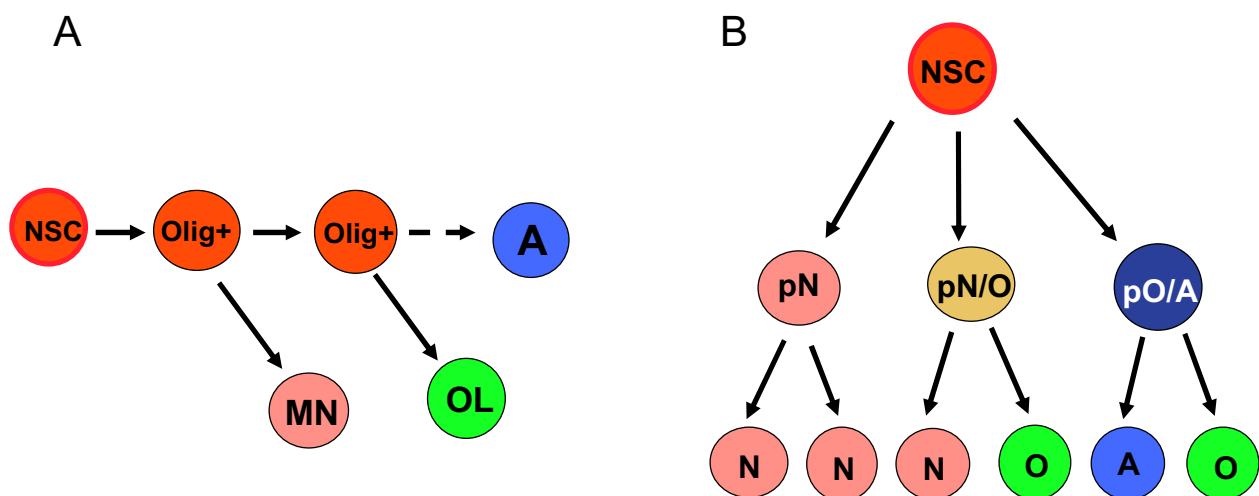
Similarly, Petryniak and colleagues show that *Dlx1/2* homeodomain transcription factors act on a common progenitor to determine neuronal versus oligodendroglial cell fate acquisition in the ventral embryonic forebrain (Petryniak *et al.* 2007). In addition, studies on the origin of oligodendrocytes in the brain indicate that SVZ type B cells can either generate oligodendrocytes alone or oligodendrocytes

and neurons (Menn *et al.* 2006). These observations have led to a paradigm shift in our understanding of oligodendrogenesis. During development, oligodendrocytes may not be derived exclusively from glial restricted progenitors (GRP) as previously thought, they can be also generated from a lineage-restricted progenitor cell pool that gives rise to a subset of early-born neurons in the CNS (Richardson *et al.* 1997; Kessaris *et al.* 2001; Noble *et al.* 2004) (Fig. 2B).

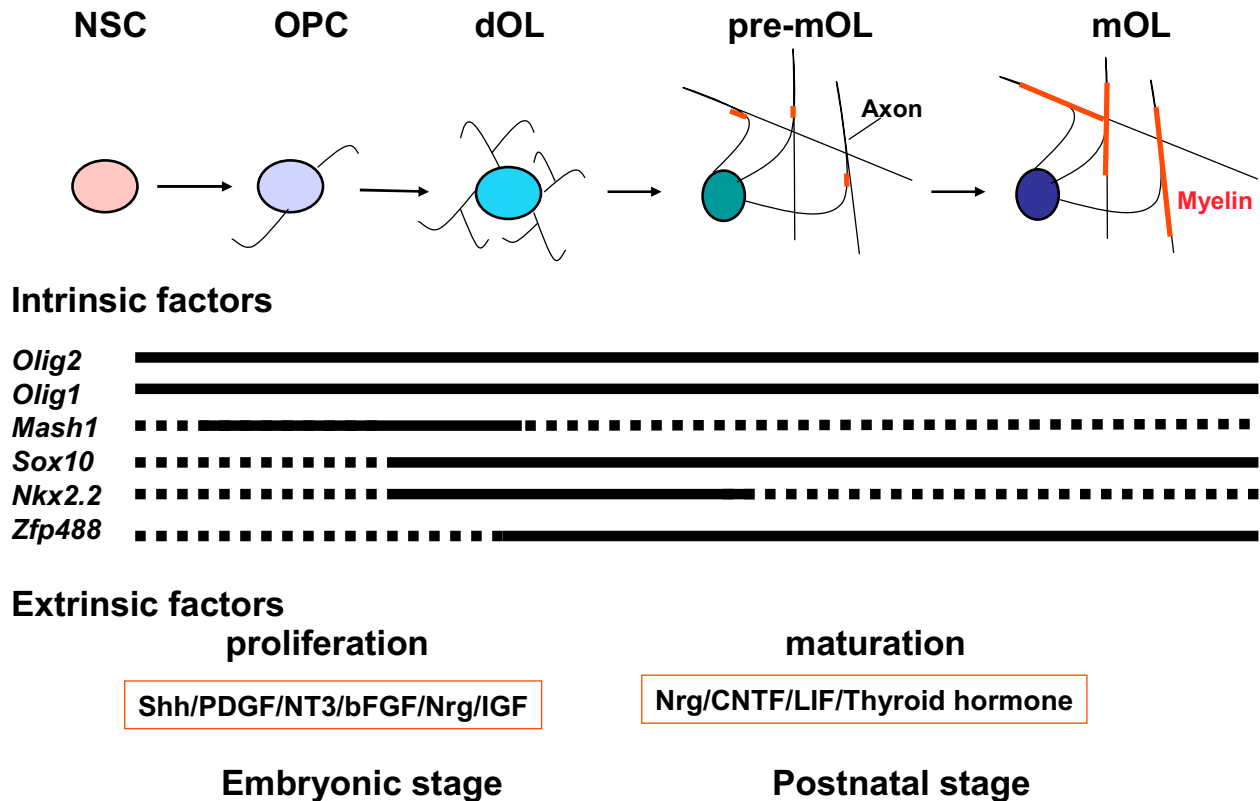
Recently, Wu *et al.* found that ablation of *Olig1*-expressing cells results in the elimination of essentially all motoneurons and oligodendrocytes including PDGFR $\alpha$ + OPCs and differentiated oligodendrocytes (Wu *et al.* 2006). In the *Olig1+* cells-ablated spinal cord, they observed a population of late-appearing *Olig2+* cells formed outside of the pMN domain such as in the ventricular zone adjacent to the floor plate and the dorsal region. Based on the assumption that *Olig2* expression represents oligodendrocyte progenitors, they concluded that oligodendrocyte precursors can be generated even after all motoneuron precursors have been eliminated and that motoneuron and oligodendrocytes do not share a common lineage-restricted progenitor. However, several lines of evidence indicate that *Olig2+* cells may also identify other cell lineages including astrocytes (Masahira *et al.* 2006; Cai *et al.* 2007). It remains unclear whether *Olig2+* cells formed after motoneuron elimination strictly represent oligodendrocyte precursors, particularly since there is a complete absence of PDGFR $\alpha$ + OPCs. An alternative possibility is that these late-born *Olig2+* cells may represent a population of astrocytes given that astrocytes were largely spared in their ablation study (Wu *et al.* 2006). Nonetheless, the loss of both motoneurons and oligodendrocytes in the *Olig*-ablated spinal cord is consistent with the derivation of both cell lineages from *Olig+* progenitor cell pools.

## INTRINSIC CONTROL OF OLIGODENDROCYTE MATURATION

Myelination in the CNS is a complex process, which is regulated not only by various extracellular signals but also by a network of intrinsic factors. The ability of OPCs to differentiate and synthesize myelin proteins is controlled by intracellular molecules via transcriptional and post-transcriptional mechanisms. Recent studies indicate that a network of DNA-binding transcription factors including the basic helix-loop-helix (bHLH) proteins, homeodomain proteins, HMG-domain proteins and zinc finger proteins play a



**Fig. 2 Oligodendrocyte lineage development.** Schematic diagram depicts two models for oligodendrocyte lineage development in the CNS. (A) Sequential model. In the developing ventral spinal cord, it is generally believed that *Olig+* cells give rise to motoneuron (MN) precursors and OPCs sequentially at different developmental stages. (B) Lineage restricted progenitor model. Oligodendrocytes can be derived directly from NSCs or from lineage restricted progenitors such as intermediate progenitors for neurons and oligodendrocytes or glial restricted progenitor cells (GRP or pO/A). Although lineage restricted neuronal progenitors (pN) have been identified, at present, those lineage restricted progenitors such as pN/O or pO/A (GRP) progenitors are not yet defined *in vivo*. NSC, neural stem cells; N, neurons; O, oligodendrocytes, A, astrocytes.



**Fig. 3 Intrinsic and extrinsic regulation of the oligodendrocyte maturation process.** Schematic diagram depicts the major stages of oligodendrocyte development. Oligodendrocyte maturation involves the progression of cell lineage development as, in a sequential order, OPCs, immature differentiated OLs (dOL), premyelinating OLs (pre-mOL), and mature myelinating OLs (mOL). Several intrinsic transcription factors and extrinsic factors known to regulate oligodendrocyte development in a stage-specific manner (solid lines) are indicated. Oligodendrocyte precursors proliferate at embryonic stages whereas their maturation occurs mainly at postnatal stages and is accompanied by increased myelin component expression followed by myelin sheath assembly.

crucial role in the establishment of myelination in the CNS (Wegner 2001). In this section we will summarize the intrinsic control of oligodendrocyte myelination with an emphasis on transcriptional regulation (Fig. 3).

**bHLH factor family**

bHLH factors *Olig1* and *Olig2* are initially expressed in the ventral spinal cord and are regulated by Sonic hedgehog (Shh). They mark the earliest oligodendrocyte lineage cells in the pMN domain (Lu *et al.* 2000; Takebayashi *et al.* 2000; Zhou *et al.* 2000). During early embryonic stages, *Olig2* cooperates with pro-neural factors such as *Ngn2* to promote MN differentiation (Mizuguchi *et al.* 2001; Novitsch *et al.* 2001). When proneural genes become down-regulated, *Olig2* appears to cooperate with a homeodomain protein *Nkx2.2* to promote oligodendrocyte fate specification (Zhou *et al.* 2001). High level of *Olig2* appears to act as an inhibitor of MN differentiation genes such as *Hb9* and instruct ventral progenitor cells in the pMN domain to adopt an oligodendroglial fate (Lee *et al.* 2005).

Gene targeting studies in mice have demonstrated that *Olig2* is essential to the formation of the entire population of oligodendrocytes and somatic MNs in the spinal cord (Lu *et al.* 2002; Takebayashi *et al.* 2002; Zhou and Anderson 2002). Whereas a small population of oligodendrocyte precursors is able to form specifically within the ventral region of the forebrain and hindbrain of *Olig2* mutants, *Olig1/2* double mutants result in a complete absence of oligodendrocytes in the CNS. These studies suggest that the functions of *Olig1/2* are partially redundant for oligodendrocyte formation (Lu *et al.* 2002; Zhou and Anderson 2002).

*Olig1/2* are expressed in both OPCs and myelinating oligodendrocytes (Lu *et al.* 2000; Zhou *et al.* 2000). While their role in oligodendrocyte specification has been eluci-

dated, the function of *Olig1/2* in postmitotic OPC maturation remains elusive. Although *Olig2* null mutation leads to a complete loss of oligodendrocytes in the developing spinal cord, *Olig1* mutation causes a delay in oligodendrocyte maturation. In a recent study, *Olig1* mutants produced by the removal of the neomycin selection cassette from the *Olig1* targeting locus exhibit severe myelination deficits during postnatal CNS development (Xin *et al.* 2005). OPCs in *Olig1* mutants can develop and migrate throughout the brain and extend their processes to contact axons, but they fail to assemble myelin sheaths around the axon. Thus, the process of myelination in the mutants is arrested prior to the onset of myelin specific gene expression. Furthermore, these data also indicate that axonal recognition and myelination by oligodendrocytes are distinct processes (Xin *et al.* 2005) (Fig. 3).

Another recent study has indicated that remyelination does not occur in *Olig1* mutant adult mice with experimentally induced focal demyelination (Arnett *et al.* 2004) and highlights the importance of *Olig1* during episodes of remyelination. Discrepancies in different loss-of-function studies may be due to different genetic backgrounds and aberrant transcription of neighboring genes of the *Olig1* locus (Balabanov and Popko 2005; Xin *et al.* 2005). The presence of a strong transcriptional enhancer for PGK (phosphoglycerate kinase) in the neomycin selection cassette in the *Olig1* targeting locus may influence expression of nearby genes such as the *Olig1* homolog, *Olig2*. In spite of this, all data support the importance of *Olig1* in oligodendrocyte myelination (Balabanov and Popko 2005). Moreover, coding variants of *OLIG1* in demyelinating diseases such as multiple sclerosis were recently identified although their link to the disease susceptibility remains to be established (Goris *et al.* 2006).

Another bHLH protein *Mash1* has been recently implicated in oligodendrogenesis (Parras *et al.* 2004, 2007). Although *Mash1* is known to play a major role in neurogenesis



(Guillemot *et al.* 1993; Casarosa *et al.* 1999; Helms *et al.* 2005), it is expressed in a subset of OPCs in the ventral ventricular zone of the developing CNS and accompanied by oligodendrocyte progenitor markers *Olig2*, *Olig1*, and *PDGFR $\alpha$* . In *Mash1* null embryos, the formation of a subset of OPC populations is significantly reduced between E11.5 and E13.5, however, OPCs derived from *Mash*-negative progenitors are produced to compensate for early deficits in the developing brain and spinal cord (Parras *et al.* 2004, 2007).

Although OPCs are derived from both *Mash1*-dependent and -independent progenitors in the developing CNS, it is not clear whether *Mash1* expression distinguishes distinct oligodendrocyte subtypes. In addition, *Mash1* expression is maintained in brain and optic nerve OPCs at postnatal stages and adulthood (Wang *et al.* 1998; Kondo and Raff 2000; Parras *et al.* 2004), however, at present, the precise function of *Mash1* in oligodendrocyte maturation and myelination is still unknown. Addressing this issue may require the analysis of mice with a conditional ablation of *Mash1* at postnatal stages.

A series of inhibitory HLH factors (i.e. Id2 and Id4) with DNA-binding basic domain are found to negatively regulate oligodendrocyte differentiation. Over-expression of Id2 and Id4 in oligodendrocyte progenitors prevents differentiation and consequently decreases myelin gene expression (Kondo and Raff 2000; Gokhan *et al.* 2005). Id2/4 downregulation and their extra-nuclear translocation coincide with the onset of oligodendrocyte differentiation (Kondo and Raff 2000; Wang *et al.* 2001). In addition, activation of the Notch pathway by Jagged1 blocks differentiation and maturation of oligodendrocyte progenitors. This inhibition is likely mediated through the induction of inhibitory bHLH Hes5 by Notch signaling (Wang *et al.* 1998). Collectively, these data suggest that negative HLH factors are part of a network of the intracellular regulators that control the timing of oligodendrocyte precursor differentiation.

### HMG domain containing Sox gene family

The Sox family of proteins are transcription factors with a high-mobility-group (HMG) domain, which play an important role during oligodendrocyte development. They can be grouped into ten major groups (A-J) based on their sequence similarity of the HMG domain (Bowles *et al.* 2000; Wegner 2001). In particular, all members of group E proteins such as Sox 8, Sox9 and Sox10 are known to be expressed in the oligodendrocyte lineage (Stolt *et al.* 2005).

In *Sox10* mutant mice, OPCs can be produced but fail to mature into myelinating oligodendrocytes in the developing neural tube (Stolt *et al.* 2002). Moreover, overexpression of *Sox10* promotes expression of myelin genes, such as *Mbp* (Stolt *et al.* 2002). Although *Sox8* is co-expressed with *Sox10* in developing oligodendrocytes, targeted replacement of *Sox10* by *Sox8* cannot effectively reverse the deficits of terminal oligodendrocyte differentiation in *Sox10*-null spinal cords, suggesting a functional disparity between *Sox10* and *Sox8* in oligodendrocyte maturation (Kellerer *et al.* 2006).

Another class E member, *Sox9* is initially expressed in the ventral neural progenitors of the neural tube and is subsequently restricted to glial cells of the CNS (Stolt *et al.* 2003). *Sox 9*, precedes *Sox10* and *Sox8*, is expressed in the early phase of oligodendrocyte-lineage formation, however, it is downregulated in differentiated oligodendrocytes. Targeted mutagenesis indicates that *Sox9* is crucial for the proper development of both oligodendrocytes and astrocytes (Stolt *et al.* 2003). *Sox9* may functionally compensate for the absence of *Sox10* in order to maintain OPC generation. In the developing spinal cord of *Sox9* null mice, the reduction of gliogenesis is accompanied by the increased MN and V2 interneuron production in the ventral ventricular zone (Stolt *et al.* 2003). This suggests that *Sox9* is another major molecular component that controls the fate switch from neurogenesis to gliogenesis in the developing spinal

cord.

Group D Sox proteins (Sox D; Sox 5 and Sox 6) were found to compete against group E Sox proteins, Sox9 and Sox10, for DNA binding sites. Even though they are expressed in oligodendrocyte lineage cells, Sox5 and Sox6 negatively regulate oligodendrocyte specification, differentiation, and migration. Sox D proteins may modulate the activity of Sox E proteins for appropriate timing and progression of OPC differentiation at different stages of oligodendrocyte development (Stolt *et al.* 2006). The fact that these Sox protein groups interact with each other suggests that a complex regulatory network controls and defines oligodendrocyte fate specification and differentiation.

### Homeodomain protein family

The homeodomain transcription factor family plays critical roles in neural fate specification including oligodendrocyte differentiation. Nkx2.2, Nkx6.1, and Nkx6.2 (also known as Gtx2) are homeodomain transcription factors that are expressed in the oligodendrocyte lineage. Although initial expression of Nkx2.2 is restricted to the P3 domain of the ventral ventricular zone adjacent to the floor plate in the developing chick neural tube, it appears subsequently to expand dorsally into the *Olig2* expression domain (pMN) (Kessaris *et al.* 2001). In cooperation with *Olig2*, Nkx2.2 promotes oligodendrocyte differentiation (Zhou *et al.* 2001). Although Nkx2.2 is dispensable for OPC formation, it is critical for oligodendrocyte differentiation and maturation (Qi *et al.* 2001).

Nkx6.1 and Nkx6.2 appear to act upstream of *Olig2* and regulate its expression in a dose-dependent manner (Vallstedt *et al.* 2005). *Olig2* expression is delayed and diminished greatly in the developing spinal cord of *Nkx6.1* mutant mice. In *Nkx6.1/Nkx6.2* double null mutants, the specification of oligodendrocyte precursors and MNs cannot be initiated due to the lack of *Olig2* (Cai *et al.* 2005; Vallstedt *et al.* 2005). However, in the dorsal region of the spinal cord, oligodendrocyte formation is largely unaffected in the double mutants. This suggests that oligodendrocyte specification from dorsal and ventral precursors is mediated by independent mechanisms. At present, it is not clear whether oligodendrogenesis defects observed in *Nkx6* mutants are due to a patterning defect in the ventral spinal cord or to the specific role of *Nkx6* in oligodendrocyte lineage development. In contrast to *Nkx6.1*, *Nkx6.2* expression is more restricted to myelinating oligodendrocytes. Loss of function studies indicate that Nkx6.2 regulates axon-glia interactions needed for proper myelin paranode formation (Southwood *et al.* 2004).

### Zinc finger protein family

Members of zinc finger superfamily have been shown to play an important role in oligodendrocyte differentiation. Among them, Myt1 is cloned by virtue of its binding to cis-regulatory elements of the myelin proteolipid protein (*Plp*) gene, the most abundantly transcribed CNS myelin gene (Kim and Hudson 1992). Myt1 is a zinc-dependent and DNA-binding protein of the unusual Cys-Cys-His-Cys (C2HC) class. Although it is named Myt1 (myelin transcription factor 1), this protein is widely expressed in the developing nervous system (Kim *et al.* 1997). Myt1 is preferentially expressed in the progenitors of oligodendrocytes. However, the role of Myt1 in oligodendrocyte differentiation remains unclear. Retroviral-mediated expression of a dominant negative form of Myt1 containing four zinc-finger domains inhibits oligodendrocyte differentiation *in vitro*, although over-expression of intact Myt1 partially suppresses OPC differentiation. These data indicate that Myt1 maintains oligodendrocytes as immature progenitor pools and modulates their transition from progenitors to terminally-differentiated oligodendrocytes (Nielsen *et al.* 2004).

In addition, a ubiquitously expressed Zn-finger transcription factor Yin Yang 1 (YY1) appears to bind and en-

hance transcription of the *Plp* promoter (Berndt *et al.* 2001). By searching for the promoters of genes regulated by HDACs during oligodendrocyte differentiation, He and colleagues identified the consensus DNA binding sequence of YY1 as a common binding motif (He *et al.* 2007). By specifically ablating YY1 in oligodendrocyte lineage cells, the authors indicated that YY1 is essential for oligodendrocyte progenitor cell differentiation. In addition, YY1 appears to repress transcriptional inhibitors of myelin gene expression (*Tcf4* and *Id4*) by recruiting histone deacetylase-1 (HDAC1) to their promoters during oligodendrocyte differentiation (He *et al.* 2007).

In a screen for genes down-regulated in the optic nerves of 14-day old *Olig1* null mice, *Zfp488*, a previously uncharacterized nuclear zinc-finger transcriptional regulator, was recently identified (Wang *et al.* 2006). In the developing CNS, *Zfp488* is restricted to differentiated oligodendrocytes. Its expression increases in parallel with that of major myelin genes such as *Mbp* and *Plp*. Furthermore, *Zfp488* is absent in the spinal cord or the brain of *Olig1* null animals, indicating that *Zfp488* is a direct or indirect downstream target gene for *Olig1*. Interestingly, *Zfp488* is a nuclear protein possessing transcriptional repression activity (Wang *et al.* 2006). In the developing chick neural tube, *Zfp488* promotes oligodendrocyte precursor formation upon Notch activation. In addition, the zinc finger protein *Zfp488* cooperates with the bHLH transcription factor *Olig2* to promote OPC maturation (Wang *et al.* 2006). Several lines of evidence indicate that the interaction between zinc-finger proteins and proneural bHLH proteins such as X-Myt1/proneural bHLH factors is a common theme for terminal neuronal differentiation (Bellefroid *et al.* 1996; Nakakura *et al.* 2001; Acar *et al.* 2006). For example, the Zn-finger protein X-Myt1 is able to promote ectopic neuronal differentiation only in cooperation with bHLH transcription factors such as X-NGNR-1 (Bellefroid *et al.* 1996). Consistent with these observations, the same physical and functional interactions of the zinc finger protein (*Zfp488*) with the bHLH factor (*Olig2*) that promote oligodendroglial maturation may also reflect a similar mechanism for zinc finger/bHLH cooperation in regulating oligodendroglial differentiation during development (Wang *et al.* 2006).

### Epigenetic control of oligodendrocyte differentiation

Epigenetic modifications at the histone, DNA methylation, chromatin, and miRNA level control the expression of cell-type specific transcription factors and thereby regulate the establishment and maintenance of oligodendrocyte specification and differentiation (Hsieh and Gage 2004; Cheng *et al.* 2005). Similarly, myelin specific gene expression is tightly controlled by multiple levels of epigenetic modulation of chromatin components.

Modifications of nucleosomal histones may have a direct influence on chromatin conformations and regulate oligodendrocyte differentiation. Histone deacetylases (HDAC), a family of chromatin modifiers, appear to be necessary for oligodendrocyte maturation and myelin gene expression in culture (Marin-Husstege *et al.* 2002) and in developing animals (Shen *et al.* 2005). Blocking the activity of classes I and II HDACs by HDAC inhibitors (e.g. valproic acid or TSA) inhibits oligodendrocyte myelination (Shen *et al.* 2005). These pharmacological inhibition studies suggest that the activity of HDACs controls the timing of oligodendrocyte differentiation. While inhibition of histone deacetylase activity at early postnatal stages resulted in significant hypomyelination, no effect was observed on myelin gene expression after initiation of myelinogenesis. However, it is not clear whether a single or different members of HDACs act in concert to regulate oligodendrocyte differentiation and myelination during CNS development.

Activation of histone acetylation in isolated oligodendrocyte progenitors seems to not only prevent their differentiation, but also revert these OPCs back into a neural

stem cell-like state, which is more receptive to neuronal or astroglial differentiation-inducing signals (Liu *et al.* 2007). Liu *et al.* further proposed that plasticity of OPCs is regulated, at least partially, by the activity of histone deacetylases and acetylases, given that “memory” of a cellular phenotype requires epigenetic code establishment. However, it is worth noting that the isolated A2B5<sup>+</sup> cells may not be confined to a homogeneous population of OPCs. Neural progenitors present within heterogeneous A2B5<sup>+</sup> populations may potentially respond to the HDAC inhibitors and differentiate into neurons and astrocytes.

HDAC activity induces the closed conformation of chromatin, which can be further stabilized by methylation on specific lysine residues in the histone tails (Lachner *et al.* 2001; Nakayama *et al.* 2001). These modifications may in turn render the DNA inaccessible to specific transcription factors. Apart from histone modification, DNA methylation can be another level of epigenetic regulation that controls oligodendrocyte differentiation. The DNA methylation status of key oligodendrocyte-specific transcription factors such as *Sox10* is correlated with reduced expression of myelin genes and oligodendrocyte dysfunction (Iwamoto *et al.* 2005). However, the precise mechanisms by which specific epigenetic regulators control the development of oligodendrocyte progenitors into functionally myelinating cells remain to be established.

### EXTRINSIC CONTROL OF OLIGODENDROCYTE MATURATION

A variety of growth factors and axonal factors have been implicated in proliferation and maturation of OPCs (Miller 2002). For example, growth factors such as Sonic hedgehog (*Shh*), BMP, fibroblast growth factors and hormones including thyroid hormones such as triiodothyronine (T3), have primary effects on OPC expansion and differentiation (Barres *et al.* 1994a; Alberta *et al.* 2001; Younes-Rapoza *et al.* 2006). There is a growing consensus that oligodendrocyte myelination is regulated by axonal signals, consistent with the fact that oligodendrocytes ensheath axons not dendrites even in culture (Lubetzki *et al.* 1993). Several lines of evidence indicate that signals from axons regulate OPC development and myelination (Bozzali and Wrabetz 2004; Coman *et al.* 2005). Myelin gene expression and oligodendrocyte myelination are increased after co-culture with neurons (Macklin *et al.* 1986; Demerens *et al.* 1996). Induction of optic nerve OPC formation is dependent on retinal axonal cues (Gao and Miller 2006). Recently, several direct or indirect axonal signals that promote myelination have been identified (Bozzali and Wrabetz 2004). They include neuregulin (*Nrg*), electrical activity, neurotrophins, extracellular matrix proteins, etc. As discussed below, we focus on the role of axon-glia signaling in CNS myelination (Fig. 3).

#### Axonal signals in myelination

##### Neuregulin

An axon-derived molecule, neuregulin plays an important role in myelination of the nervous system. Neuregulin-1 (*Nrg1*) belongs to a family of membrane associated and secreted factors that have an EGF-like domain at their N-termini. It has three type of isoforms (type I, II and III) derived from alternative splicing. *Nrg1* types I and II participate in paracrine signaling, while *Nrg1* type III participates in juxtacrine signaling (Adlkofer and Lai 2000; Falls 2003; Nave and Salzer 2006). Neuregulins activate members of EGF receptor subfamily of protein tyrosine kinases (PTKs) known as ErbBs, including ErbB2, ErbB3 and ErbB4 (Nave and Salzer 2006).

*Nrg1* signaling plays an essential role in Schwann cell myelination. In *Nrg1* or *ErbB2* or *ErbB4* knockout mice, Schwann cell precursor formation cannot be detected at E10.5 (Meyer and Birchmeier 1995). Mice lacking *ErbB3* are completely devoid of precursors and myelinating

Schwann cells (Riethmacher *et al.* 1997). Overexpression of Nrg1 type III in neurons of transgenic mice induces Schwann cell hypermyelination leading to the formation of thicker myelin sheath around the axons (Michailov *et al.* 2004). In addition, by reducing *Nrg1* together with *ErbB2/ErbB3* gene dosages in compound heterozygous mice, Michailov and colleagues suggest that a threshold level of NRG1 type III is essential for the thickness of myelin sheath produced by Schwann cells (Michailov *et al.* 2004).

Although Nrg1 signaling determines the onset and extent of myelination by Schwann cells in the PNS, it is currently unclear whether or not and to what extent Nrg1 regulates oligodendrocyte myelination in the CNS. Studies on cultured OPCs have shown that Nrg1 has a trophic and mitogenic effect on OPCs but inhibits oligodendrocyte differentiation (Canoll *et al.* 1996). However, its role in oligodendrocyte differentiation varies considerably between *in vitro* and *in vivo* studies. Cells from a spinal cord explant of *Nrg1* null animals fail to generate OPCs when cultured at E9.5 (Vartanian *et al.* 1999). In addition, in a study using spinal cord explants from *ErbB2* knockout mice, Park *et al.* demonstrated that ErbB2-mediated signaling is necessary for the terminal differentiation of OPCs (Park *et al.* 2001). However, it is not clear the extent to which oligodendrocyte myelination is dependant on Nrg1/erbB signaling in the CNS.

*Nrg1* expression is observed in the ventral ventricular zone of the spinal cord and the forebrain (Park *et al.* 2001). This observation is consistent with the initial sources of oligodendrocyte lineage development. However, it is currently unclear whether or how Nrg1 regulates oligodendrocyte myelination. Recent studies indicate that Bace1 ( $\beta$ -site amyloid precursor protein-cleaving enzyme1 or  $\beta$ -secretase) regulates myelinogenesis and myelin sheath thickness in the CNS. In *Bace1*-null mice, there is an accumulation of the unprocessed form of full-length Nrg1 in the absence of  $\beta$ -secretase activity, resulting in a reduction of both myelin gene expression and oligodendrocyte myelination (Hu *et al.* 2006; Willem *et al.* 2006). These observations indicate that the processed form of Nrg1 may function as a ligand to promote axonal ensheathment by oligodendrocytes and Schwann cells (Hu *et al.* 2006; Willem *et al.* 2006). Even though neuregulin signaling between Schwann cells and oligodendrocytes is analogous, the extent to which neuregulin signaling regulates myelination in the CNS and PNS may vary. Further studies with *in vivo* spatiotemporally specific mutagenesis of Nrg signaling components are required to determine the role of Nrg/ErbB signaling in CNS myelination.

### Neurotrophic factors

The neurotrophin growth factor family includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4/5. They have been shown to play an important role in the growth and survival of specific neuronal populations through their selective binding to cognate receptors (Trk) (i.e. NGF to TrkA, BDNF and NT-4/5 to TrkB, and NT-3 to TrkC) and pan-neurotrophin receptor p75 (Gentry *et al.* 2004; Rosenberg *et al.* 2006). It has been proposed that neurotrophins possess dual roles in neural development. They are thought to promote survival and differentiation of neuronal subsets during early neurogenesis while serving as key regulators in glial differentiation at late developmental stages (Rosenberg *et al.* 2006).

Recent studies have shown that neurotrophins modulate neuron-glia interactions and control myelination by either acting selectively on neurons, or directly on oligodendrocytes. The effects on oligodendrocyte proliferation and differentiation are diverse among members of the neurotrophin family as they either promote or inhibit oligodendrocyte differentiation. For example, NT-3 appears to act directly to promote the proliferation and survival of oligodendrocytes. In conjunction with PDGF, NT-3 stimulates clonal

expansion of oligodendrocyte precursor cells (Barres *et al.* 1994b; Kumar *et al.* 1998). Loss of NT-3 and its receptor TrkC results in profound deficits in OPC production (Kahn *et al.* 1999). Neurotrophins may influence oligodendrocyte development in a regionally specific manner. BDNF appears to promote *Mbp* expression in oligodendrocytes isolated from basal forebrain, but does not affect cortical oligodendrocytes (Du *et al.* 2003). The selective expression of neurotrophin receptors among regionally distinct oligodendrocytes may account for the responsiveness to specific neurotrophin-related signals. This functional heterogeneity suggests that oligodendrocytes may be comprised of heterogeneous populations.

Transplantation of genetically modified fibroblasts that secrete NT-3 and/or BDNF, into spinal cord-injured rats, was shown to increase the production of new oligodendrocytes and myelination (McTigue *et al.* 1998). NT-3- and BDNF-induced myelinogenesis results, at least in part, from expansion of endogenous oligodendrocyte progenitors. These findings may have significant implications for the development of treatment strategies for chronic demyelinating diseases or other CNS injuries.

Recent studies indicate that the balance of different neurotrophic factors has a critical role in modulating myelination since neurotrophic factors may exhibit opposite effects on the myelination in different nervous tissues. While promoting oligodendrocyte differentiation, BDNF and NT3 have inverse effects on Schwann cell myelination (Chan *et al.* 2001; Cosgaya *et al.* 2002). In addition, the effects of neurotrophins on oligodendrocyte development appear to be dosage-dependent. While NGF enhances oligodendrocyte survival at low concentrations, (Cohen *et al.* 1996), it induces apoptosis of mature oligodendrocytes at high concentrations (Casaccia-Bonnel *et al.* 1996). Intriguingly, neurotrophic effects on myelination can be divergent between the PNS and the CNS. While promoting Schwann cell PNS myelination, NGF/TrkA signaling inhibits oligodendrocyte myelination in the CNS (Chan *et al.* 2004). Although the molecular mechanisms underlying the divergent effects of neurotrophins in CNS and PNS myelination are not clear, it is suspected that expression of distinct receptors in neurons and oligodendrocytes may contribute to the differences in neurotrophic effects. These observations further indicate that growth factors modulate receptivity to myelination depending on intrinsic axonal properties (Chan *et al.* 2004).

Other neurotrophic factors, of the CNTF family, including LIF, cardiotrophin-1, and oncostatin M, elicit a promyelinating effect (Vos *et al.* 1996). CNTF family members act via gp130 kDa receptor on oligodendrocytes to promote their final maturation, although they have a role in astrocyte differentiation (Stankoff *et al.* 2002). Thus, integration of signaling pathways mediated by different neurotrophic factors may fine-tune the complex process of myelination in the nervous system.

### Electrical activity

Electrical activity has been shown to modulate OPCs development at various stages of development. Inhibition of electrical activity by the sodium channel blocker tetrodotoxin (TTX) prevents the initiation of myelination *in vitro* and *in vivo* (Demerens *et al.* 1996). In addition, induction of repetitive electrical activity by  $\alpha$ -scorpion toxin enhances myelination (Demerens *et al.* 1996), suggesting that neuronal signaling is necessary for oligodendrocyte myelination. Recent work indicates that the electrical activity indirectly upregulates the expression of purinergic receptors on the surface of oligodendrocytes and triggers synaptic release of adenosine (Stevens *et al.* 2002). Adenosine has been shown to act through the purinergic receptor A2 to promote oligodendrocyte myelin formation by inhibiting OPC migration and proliferation (Stevens *et al.* 2002).

To complicate matters, a recent study has revealed that astrocytes are capable of mediating electrically induced myelination. Ishibashi *et al.* suggest that ATP released by

axons during electrical stimulation acts on astrocytes and in turn stimulates the release of LIF, which promotes oligodendrocyte myelination (Stankoff *et al.* 2002; Ishibashi *et al.* 2006). This finding suggests that astrocytes may have a novel role in axon-oligodendrocyte interactions and demonstrates that the myelination of postmitotic OPCs is activity-dependent, consistent with the notion that cellular microenvironments play a crucial role in normal oligodendrocyte myelination. At present, the precise roles of astrocytes in modulating oligodendrocyte myelination remain to be clarified.

### Extra cellular matrix proteins

Extra cellular matrix (ECM) proteins like laminin are known to be expressed in neurons and regulate oligodendrocyte migration and maturation (Buttery and French-Constant 1999; French-Constant and Colognato 2004). Integrins are functionally versatile ECM protein receptors. As transmembrane glycoproteins, they consist of  $\alpha$  and  $\beta$  heterodimeric chains and are primarily involved in signal transduction processes between extra-cellular and intra-cellular compartments (French-Constant and Colognato 2004). Oligodendrocytes are known to express a limited repertoire of integrins (Baron *et al.* 2005). Several studies indicate that the expression pattern of various integrins is developmentally regulated. Individual integrins are required for distinct phases of oligodendrocyte development and proper myelination such as  $\alpha\beta1$  for migration,  $\alpha\beta3$  for proliferation, and  $\alpha\beta5$  for differentiation of OPCs (Buttery and French-Constant 1999; Blaschuk *et al.* 2000; Colognato *et al.* 2004; Liang *et al.* 2004). In addition, myelin proteins such as Plp can form a complex with integrins to modulate receptor signaling and regulate oligodendrocyte myelination (Gudz *et al.* 2002).

Recent study indicates that laminin-2 potentiates the survival and myelination of newly formed OPCs in response to physiological levels of PDGF or Nrg1, while  $\alpha6$ -integrin null animals exhibit increased OPC apoptosis and a reduction in the number of mature oligodendrocytes compared to wild type animals (Colognato *et al.* 2002). These data suggest that signals conveyed by integrin-growth factors are important for oligodendrocyte survival and differentiation. In addition, upon axonal contact, integrins appear to mediate a switch from PI(3)K-dependent to MAPK-dependent survival signaling, therefore promote oligodendrocyte differentiation. Thus, Colognato *et al.* proposed a model that integrins switch growth factor signaling pathways to promote survival of oligodendrocytes upon axonal contact (Colognato *et al.* 2002).

Although many axonal signals promote myelination, several axonal cell-adhesion molecules (CAMs) such as PSA-NCAM are inhibitory for myelination (Charles *et al.* 2000). Removal of PSA-NCAM on axonal surface via antibodies or enzymatic cleavage, increases myelination both *in vivo* and *in vitro* (Charles *et al.* 2000). Similarly, adhesion molecule L1, which is predominantly expressed on the axonal surface (Persohn and Schachner 1987), is drastically reduced during myelination (Coman *et al.* 2005). Thus, the onset of myelinogenesis depends on a balance between positive and negative axonal signals during development.

### MYELINATION IN HEALTH AND DISEASE

Multiple sclerosis (MS) is the most common neurodegenerative disorder resulting from demyelination in the CNS (Franklin 2002). In addition, recent studies indicate that myelination deficits are also indicated in many neuropsychiatric disorders such as Alzheimer's disease (AD), mood disorders and Schizophrenia.

Although in Alzheimer's disease major emphasis has been placed on neuronal death and synaptic impairment induced by  $\beta$ -amyloid peptide (Selkoe and Schenk 2003; Selkoe 2004), substantial white matter damage and its consequences for brain function point to an important role of oli-

godendrocytes in AD pathogenesis and progression. The observations of oligodendrocytes and myelin impairment in AD are supported by neurochemical, electrophysiological and imaging studies (Malone and Szoke 1985; Roher *et al.* 2002; Bartzokis 2004; de Leeuw *et al.* 2004).

The presence of A $\beta$  proteins ( $\beta$ -amyloid protein) is observed in the white matter of AD patients (Roher *et al.* 2002). While A $\beta$  aggregates have been generally considered to be responsible for neuronal and vascular degeneration in AD, they are also detrimental to cholesterol rich membranes, such as myelin sheaths (Bartzokis 2004). It has been reported that exposure of mature oligodendrocytes to A $\beta$  causes oligodendrocyte death and this cytotoxic effect can be minimized by co-culture with astrocytes or in the presence of pro-inflammatory cytokines (Ramirez *et al.* 2005; Roth *et al.* 2005). A $\beta$  senile plaques stimulate production of cytotoxic reactive oxygen species in neurons and this process is further enhanced in the presence of iron released from dying oligodendrocytes (Varadarajan *et al.* 2000). In general, these studies suggest that oligodendrocyte damage occurs in the AD brain and contributes to AD formation, but it is not clear whether this effect is secondary to disease progression or a primary event occurring at the onset of disease progression.

Since A $\beta$  is primarily responsible for plaque formation in AD, A $\beta$  precursor protein cleaving enzymes have been highlighted as potential drug targets in the treatment of AD. One of the cleavage enzymes called Bace1 has been considered to be a drug target based on transgenic animal studies (Cai *et al.* 2001; Luo *et al.* 2001). However, recent studies indicate that Bace-1 not only targets A $\beta$  proteins, but also is crucial for myelination in both PNS and CNS (Hu *et al.* 2006; Willem *et al.* 2006). These studies raise some concerns over the use of Bace-1 as a pharmacological target to treat AD.

Multiple lines of evidence now indicate that oligodendrocytes and myelination are critical for neuronal connectivity, dysfunction of which is the central abnormality of schizophrenia (Davis *et al.* 2003; Segal *et al.* 2007; Uranova *et al.* 2007). Disconnection between prefrontal and posterior areas, alerted connectivity and synaptic protein expression have been demonstrated in schizophrenia (McGlashan and Hoffman 2000; Winterer *et al.* 2003; Stephan *et al.* 2006). There has been a considerable overlap between the cognitive deficits of schizophrenia and demyelinating diseases such as metachromatic leukodystrophy (MLD) and multiple sclerosis (Stevens 1988; Baumann *et al.* 2002; Haroutunian and Davis 2007; Kumperscak *et al.* 2007). Post-mortem studies of schizophrenic patients have shown myelin and oligodendroglial abnormalities in the prefrontal cortex and caudate nucleus (Flynn *et al.* 2003; Uranova *et al.* 2007). Aside from these immunohistological studies, microarray analysis of prefrontal cortex of schizophrenic patients has identified significant down-regulation of major oligodendrocyte related gene products (Hakak *et al.* 2001). Interestingly, some of the ultrastructural changes observed in MAG-deficient mice resemble the structural features of schizophrenic brains (Segal *et al.* 2007; Uranova *et al.* 2007). Furthermore, recent genetic interaction studies have linked Olig2 and its interacting genes such as the neuregulin receptor ErbB4 to schizophrenia susceptibility (Georgieva *et al.* 2006). In addition, hypermethylation of the Sox10 promoter, a key regulator for oligodendrocyte differentiation, results in Sox10 downregulation which is correlated with schizophrenia (Iwamoto *et al.* 2005). Together, these data point to the possibility that abnormal oligodendrocyte function could be a primary etiological event in schizophrenia.

In addition to the involvement in myelinating diseases and neuropsychiatric disorders, a recent study suggests that oligodendrocytes are also involved in the development of neural plasticity, specifically in the establishment of ocular dominance columns of the visual cortex (McGee *et al.* 2005). Nogo-66/NgR receptor is required for the myelin derived Nogo, MAG and Omgp signaling, which is responsible for limiting axonal regeneration after pathological insult (McGee *et al.* 2005). By using Nogo-66 receptor mutant



mice, Macgee *et al.* studied the experience-driven visual cortex plasticity during and after the critical period. Whereas ocular dominance plasticity in wild type mice is limited after the critical period, Nogo-66 receptor mutant mice exhibit the ability to undergo experience-driven ocular dominance plasticity even after the critical period. This study highlights the importance of the Nogo receptor and its myelin derived ligands in delimiting neural plasticity in the developing visual cortex.

## CONCLUDING REMARKS

Recent molecular, genetic, and biochemical studies have significantly advanced our knowledge regarding the mechanisms of oligodendrocyte formation and function. Identification of multiple sources for oligodendrocyte generation can potentially enhance our capacity to promote myelin repair after injury. Great progress has been made in the identification of intracellular molecules, such as transcriptional and epigenetic factors, as well as extracellular molecules such as axonal signals. These intrinsic and extrinsic factors control and modulate different phases of oligodendrocytes development and myelination. Although curative treatments for demyelinating diseases elude our grasp at present, such knowledge has increased our understanding of oligodendrocyte biology and etiology of myelin related-diseases. Advances in human and mouse genetics highlight the importance of oligodendrocytes in the regulation of neuronal plasticity and connectivity as well as neurological pathogenesis. Thus, an understanding of oligodendroglial myelination in its entirety will eventually aid us in the identification of potential drug targets for various neurological disorders of the CNS.

## ACKNOWLEDGEMENTS

We thank Dr. Jane Johnson, Mr. Edward Hurlock and Ms. Jenny Hoang for critical reading of the manuscript. This work is supported by grants from the National Multiple Sclerosis Society, Wadsworth Foundation, and National Institutes of Health (R01NS050389 to QRL). QRL is a Harry Weaver Neuroscience Scholar and a Basil O'Connor Scholar.

## REFERENCES

- Acar M, Jafar-Nejad H, Giagtzoglou N, Yallampalli S, David G, He Y, Delidakis C, Bellen HJ (2006) Senseless physically interacts with proneural proteins and functions as a transcriptional co-activator. *Development* **133**, 1979-1989
- Adlkofer K, Lai C (2000) Role of neuregulins in glial cell development. *Glia* **29**, 104-111
- Alberta JA, Park SK, Mora J, Yuk D, Pawlitzky I, Iannarelli P, Vartanian T, Stiles CD, Rowitch DH (2001) Sonic hedgehog is required during an early phase of oligodendrocyte development in mammalian brain. *Molecular and Cellular Neuroscience* **18**, 434-441
- Arnett HA, Fancy SP, Alberta JA, Zhao C, Plant SR, Kaing S, Raine CS, Rowitch DH, Franklin RJ, Stiles CD (2004) bHLH transcription factor Olig1 is required to repair demyelinated lesions in the CNS. *Science* **306**, 2111-2115
- Balabanov R, Popko B (2005) Myelin repair: developmental myelination redux? *Nature Neuroscience* **8**, 262-264
- Baron W, Colognato H, ffrench-Constant C (2005) Integrin-growth factor interactions as regulators of oligodendroglial development and function. *Glia* **49**, 467-479
- Barres BA, Lazar MA, Raff MC (1994a) A novel role for thyroid hormone, glucocorticoids and retinoic acid in timing oligodendrocyte development. *Development* **120**, 1097-1108
- Barres BA, Raff MC, Gaese F, Bartke I, Dechant G, Barde YA (1994b) A crucial role for neurotrophin-3 in oligodendrocyte development. *Nature* **367**, 371-375
- Bartzokis G (2004) Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiology of Aging* **25**, 5-18
- Battiste J, Helms AW, Kim EJ, Savage TK, Lagace DC, Mandyam CD, Eisch AJ, Miyoshi G, Johnson JE (2007) Ascl1 defines sequentially generated lineage-restricted neuronal and oligodendrocyte precursor cells in the spinal cord. *Development* **134**, 285-293
- Baumann N, Turpin JC, Lefevre M, Colsch B (2002) Motor and psycho-cognitive clinical types in adult metachromatic leukodystrophy: genotype/phenotype relationships? *The Journal of Physiology-Paris* **96**, 301-306

- Bellefroid EJ, Bourguignon C, Hollemann T, Ma Q, Anderson DJ, Kintner C, Pieler T (1996) X-MyT1, a Xenopus C2HC-type zinc finger protein with a regulatory function in neuronal differentiation. *Cell* **87**, 1191-1202
- Berger J, Moser HW, Forss-Petter S (2001) Leukodystrophies: recent developments in genetics, molecular biology, pathogenesis and treatment. *Current Opinion in Neurology* **14**, 305-312
- Berndt JA, Kim JG, Tosic M, Kim C, Hudson LD (2001) The transcriptional regulator Yin Yang 1 activates the myelin PLP gene. *The Journal of Neurochemistry* **77**, 935-942
- Blakemore WF, Keirstead HS (1999) The origin of remyelinating cells in the central nervous system. *The Journal of Neuroimmunology* **98**, 69-76
- Blaschuk KL, Frost EE, ffrench-Constant C (2000) The regulation of proliferation and differentiation in oligodendrocyte progenitor cells by alphaV integrins. *Development* **127**, 1961-1969
- Bowles J, Schepers G, Koopman P (2000) Phylogeny of the SOX family of developmental transcription factors based on sequence and structural indicators. *Developmental Biology* **227**, 239-255
- Bozzali M, Wrabetz L (2004) Axonal signals and oligodendrocyte differentiation. *Neurochemical Research* **29**, 979-988
- Buttery PC, ffrench-Constant C (1999) Laminin-2/integrin interactions enhance myelin membrane formation by oligodendrocytes. *Molecular and Cellular Neuroscience* **14**, 199-212
- Cai H, Wang Y, McCarthy D, Wen H, Borchelt DR, Price DL, Wong PC (2001) BACE1 is the major beta-secretase for generation of Abeta peptides by neurons. *Nature Neuroscience* **4**, 233-234
- Cai J, Chen Y, Cai W, Hurlock E, Wu H, Kerner SG, Parada LF, Lu QR (2007) A crucial role for Olig2 in white matter astrocyte development. *Development* **134**, 1887-1899
- Cai J, Qi Y, Hu X, Tan M, Liu Z, Zhang J, Li Q, Sander M, Qiu M (2005) Generation of oligodendrocyte precursor cells from mouse dorsal spinal cord independent of nrx6 regulation and shh signaling. *Neuron* **45**, 41-53
- Canoll PD, Musacchio JM, Hardy R, Reynolds R, Marchionni MA, Salzer JL (1996) GGF/neuregulin is a neuronal signal that promotes the proliferation and survival and inhibits the differentiation of oligodendrocyte progenitors. *Neuron* **17**, 229-243
- Casaccia-Bonnel P, Carter BD, Dobrowsky RT, Chao MV (1996) Death of oligodendrocytes mediated by the interaction of nerve growth factor with its receptor p75. *Nature* **383**, 716-719
- Casarosa S, Fode C, Guillemot F (1999) Mash1 regulates neurogenesis in the ventral telencephalon. *Development* **126**, 525-534
- Chan JR, Cosgaya JM, Wu YJ, Shooter EM (2001) Neurotrophins are key mediators of the myelination program in the peripheral nervous system. *Proceedings of the National Academy of Sciences USA* **98**, 14661-14668
- Chan JR, Watkins TA, Cosgaya JM, Zhang C, Chen L, Reichardt LF, Shooter EM, Barres BA (2004) NGF controls axonal receptivity to myelination by Schwann cells or oligodendrocytes. *Neuron* **43**, 183-191
- Charles P, Hernandez MP, Stankoff B, Aigrot MS, Colin C, Rougon G, Zalc B, Lubetzki C (2000) Negative regulation of central nervous system myelination by polysialylated-neural cell adhesion molecule. *Proceedings of the National Academy of Sciences USA* **97**, 7585-7590
- Cheng LC, Tavazoie M, Doetsch F (2005) Stem cells: from epigenetics to microRNAs. *Neuron* **46**, 363-367
- Cohen RI, Marmor R, Norton WT, Mehler MF, Kessler JA (1996) Nerve growth factor and neurotrophin-3 differentially regulate the proliferation and survival of developing rat brain oligodendrocytes. *The Journal of Neuroscience* **16**, 6433-6442
- Colognato H, Baron W, Avellana-Adalid V, Relvas JB, Baron-Van Evercooren A, Georges-Labouesse E, ffrench-Constant C (2002) CNS integrins switch growth factor signalling to promote target-dependent survival. *Nature Cell Biology* **4**, 833-841
- Colognato H, Ramachandrapa S, Olsen IM, ffrench-Constant C (2004) Integrins direct Src family kinases to regulate distinct phases of oligodendrocyte development. *The Journal of Cell Biology* **167**, 365-375
- Coman I, Barbin G, Charles P, Zalc B, Lubetzki C (2005) Axonal signals in central nervous system myelination, demyelination and remyelination. *The Journal of Neurological Science* **233**, 67-71
- Cosgaya JM, Chan JR, Shooter EM (2002) The neurotrophin receptor p75NTR as a positive modulator of myelination. *Science* **298**, 1245-1248
- Davis KL, Stewart DG, Friedman JI, Buchsbaum M, Harvey PD, Hof PR, Buxbaum J, Haroutunian V (2003) White matter changes in schizophrenia: evidence for myelin-related dysfunction. *Archives of General Psychiatry* **60**, 443-456
- de Leeuw FE, Barkhof F, Scheltens P (2004) White matter lesions and hippocampal atrophy in Alzheimer's disease. *Neurology* **62**, 310-312
- Demerens C, Stankoff B, Logak M, Anglade P, Allinquant B, Couraud F, Zalc B, Lubetzki C (1996) Induction of myelination in the central nervous system by electrical activity. *Proceedings of the National Academy of Sciences USA* **93**, 9887-9892
- Du Y, Fischer TZ, Lee LN, Lercher LD, Dreyfus CF (2003) Regionally specific effects of BDNF on oligodendrocytes. *Developmental Neuroscience* **25**, 116-126
- Falls DL (2003) Neuregulins: functions, forms, and signaling strategies. *Expe-*

- rimental Cell Research* **284**, 14-30
- French-Constant C, Colognato H** (2004) Integrins: versatile integrators of extracellular signals. *Trends in Cell Biology* **14**, 678-686
- Flynn SW, Lang DJ, Mackay AL, Goghari V, Vavasour IM, Whittall KP, Smith GN, Arango V, Mann JJ, Dwork AJ, Falkai P, Honer WG** (2003) Abnormalities of myelination in schizophrenia detected *in vivo* with MRI, and post-mortem with analysis of oligodendrocyte proteins. *Molecular Psychiatry* **8**, 811-820
- Fogarty M, Richardson WD, Kessaris N** (2005) A subset of oligodendrocytes generated from radial glia in the dorsal spinal cord. *Development* **132**, 1951-1959
- Franklin RJ** (2002) Why does remyelination fail in multiple sclerosis? *Nature Reviews Neuroscience* **3**, 705-714
- Gao L, Miller RH** (2006) Specification of optic nerve oligodendrocyte precursors by retinal ganglion cell axons. *The Journal of Neuroscience* **26**, 7619-7628
- Gensert JM, Goldman JE** (1997) Endogenous progenitors remyelinate demyelinated axons in the adult CNS. *Neuron* **19**, 197-203
- Gentry JJ, Barker PA, Carter BD** (2004) The p75 neurotrophin receptor: multiple interactors and numerous functions. *Progress in Brain Research* **146**, 25-39
- Georgieva L, Moskvina V, Peirce T, Norton N, Bray NJ, Jones L, Holmans P, Macgregor S, Zammit S, Wilkinson J, Williams H, Nikolov I, Williams N, Ivanov D, Davis KL, Haroutunian V, Buxbaum JD, Craddock N, Kirov G, Owen MJ, O'Donovan MC** (2006) Convergent evidence that oligodendrocyte lineage transcription factor 2 (OLIG2) and interacting genes influence susceptibility to schizophrenia. *Proceedings of the National Academy of Sciences USA* **103**, 12469-12474
- Gokhan S, Marin-Husstege M, Yung SY, Fontanez D, Casaccia-Bonnel P, Mehler MF** (2005) Combinatorial profiles of oligodendrocyte-selective classes of transcriptional regulators differentially modulate myelin basic protein gene expression. *The Journal of Neuroscience* **25**, 8311-8321
- Goris A, Yeo TW, Maranian M, Walton A, Ban M, Gray J, Compston A, Sawcer S** (2006) Novel Olig 1-coding variants and susceptibility to multiple sclerosis. *The Journal of Neurology Neurosurgery and Psychiatry* **77**, 1296-1297
- Gudz TI, Schneider TE, Haas TA, Macklin WB** (2002) Myelin proteolipid protein forms a complex with integrins and may participate in integrin receptor signaling in oligodendrocytes. *The Journal of Neuroscience* **22**, 7398-7407
- Guillemot F, Lo LC, Johnson JE, Auerbach A, Anderson DJ, Joyner AL** (1993) Mammalian achaete-scute homolog 1 is required for the early development of olfactory and autonomic neurons. *Cell* **75**, 463-476
- Hakak Y, Walker JR, Li C, Wong WH, Davis KL, Buxbaum JD, Haroutunian V, Fienberg AA** (2001) Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proceedings of the National Academy of Sciences USA* **98**, 4746-4751
- Haroutunian V, Davis KL** (2007) Introduction to the Special Section: Myelin and oligodendrocyte abnormalities in schizophrenia. *International Journal Neuropsychopharmacology* **10**, 499-502
- He W, Ingraham C, Rising L, Goderie S, Temple S** (2001) Multipotent stem cells from the mouse basal forebrain contribute GABAergic neurons and oligodendrocytes to the cerebral cortex during embryogenesis. *The Journal of Neuroscience* **21**, 8854-8862
- He Y, Dupree J, Wang J, Sandoval J, Li J, Liu H, Shi Y, Nave KA, Casaccia-Bonnel P** (2007) The transcription factor Yin Yang 1 is essential for oligodendrocyte progenitor differentiation. *Neuron* **55**, 217-230
- Helms AW, Battiste J, Henke RM, Nakada Y, Simplicio N, Guillemot F, Johnson JE** (2005) Sequential roles for Mash1 and Ngn2 in the generation of dorsal spinal cord interneurons. *Development* **132**, 2709-2719
- Hsieh J, Gage FH** (2004) Epigenetic control of neural stem cell fate. *Current Opinion in Genetics and Development* **14**, 461-469
- Hu X, Hicks CW, He W, Wong P, Macklin WB, Trapp BD, Yan R** (2006) Bace1 modulates myelination in the central and peripheral nervous system. *Nature Neuroscience* **9**, 1520-1525
- Ishibashi T, Dakin KA, Stevens B, Lee PR, Kozlov SV, Stewart CL, Fields RD** (2006) Astrocytes promote myelination in response to electrical impulses. *Neuron* **49**, 823-832
- Iwamoto K, Bundo M, Yamada K, Takao H, Iwayama-Shigeno Y, Yoshikawa T, Kato T** (2005) DNA methylation status of SOX10 correlates with its downregulation and oligodendrocyte dysfunction in schizophrenia. *The Journal of Neuroscience* **25**, 5376-5381
- Kahn MA, Kumar S, Liebl D, Chang R, Parada LF, de Vellis J** (1999) Mice lacking NT-3, and its receptor TrkC, exhibit profound deficiencies in CNS glial cells. *Glia* **26**, 153-165
- Kaplan MS, Hinds JW** (1980) Gliogenesis of astrocytes and oligodendrocytes in the neocortical grey and white matter of the adult rat: electron microscopic analysis of light radioautographs. *The Journal of Comparative Neurology* **193**, 711-727
- Kellerer S, Schreiner S, Stolt CC, Scholz S, Bosl MR, Wegner M** (2006) Replacement of the Sox10 transcription factor by Sox8 reveals incomplete functional equivalence. *Development* **133**, 2875-2886
- Kessaris N, Fogarty M, Iannarelli P, Grist M, Wegner M, Richardson WD** (2006) Competing waves of oligodendrocytes in the forebrain and postnatal elimination of an embryonic lineage. *Nature Neuroscience* **9**, 173-179
- Kessaris N, Pringle N, Richardson WD** (2001) Ventral neurogenesis and the neuron-glia switch. *Neuron* **31**, 677-680
- Kessaris N, Pringle N, Richardson WD** (2007) Specification of CNS glia from neural stem cells in the embryonic neuroepithelium. *Philosophical Transactions of the Royal Society B-Biological Sciences* in press
- Kim JG, Armstrong RC, v Agoston D, Robinsky A, Wiese C, Nagle J, Hudson LD** (1997) Myelin transcription factor 1 (Myt1) of the oligodendrocyte lineage, along with a closely related CCHC zinc finger, is expressed in developing neurons in the mammalian central nervous system. *The Journal of Neuroscience Research* **50**, 272-290
- Kim JG, Hudson LD** (1992) Novel member of the zinc finger superfamily: A C2-HC finger that recognizes a glia-specific gene. *Molecular and Cellular Biology* **12**, 5632-5639
- Kondo T, Raff M** (2000) The Id4 HLH protein and the timing of oligodendrocyte differentiation. *The EMBO Journal* **19**, 1998-2007
- Kumar S, Kahn MA, Dinh L, de Vellis J** (1998) NT-3-mediated TrkC receptor activation promotes proliferation and cell survival of rodent progenitor oligodendrocyte cells *in vitro* and *in vivo*. *The Journal of Neuroscience Research* **54**, 754-765
- Kumperscak HG, Plesnicar BK, Zalar B, Gradisnik P, Seruga T, Paschke E** (2007) Adult metachromatic leukodystrophy: a new mutation in the schizophrenia-like phenotype with early neurological signs. *Psychiatric Genetics* **17**, 85-91
- Lachner M, O'Carroll D, Rea S, Mechtler K, Jenuwein T** (2001) Methylation of histone H3 lysine 9 creates a binding site for HP1 proteins. *Nature* **410**, 116-120
- Lee SK, Lee B, Ruiz EC, Pfaff SL** (2005) Olig2 and Ngn2 function in opposition to modulate gene expression in motor neuron progenitor cells. *Genes and Development* **19**, 282-294
- Levison SW, Goldman JE** (1993) Both oligodendrocytes and astrocytes develop from progenitors in the subventricular zone of postnatal rat forebrain. *Neuron* **10**, 201-212
- Liang YL, Fu Y, Chen SG, Cai XM, Su JM, Jin JW, Ma DZ, Li ZX, Zhang W, Zha X** (2004) Integrin beta1 subunit overexpressed in the SMMC-7721 cells regulates the promoter activity of p21(CIP1) and enhances its transcription. *FEBS Letters* **558**, 107-113
- Liu A, Han YR, Li J, Sun D, Ouyang M, Plummer MR, Casaccia-Bonnel P** (2007) The glial or neuronal fate choice of oligodendrocyte progenitors is modulated by their ability to acquire an epigenetic memory. *The Journal of Neuroscience* **27**, 7339-7343
- Lu QR, Sun T, Zhu Z, Ma N, Garcia M, Stiles CD, Rowitch DH** (2002) Common developmental requirement for Olig function indicates a motor neuron/oligodendrocyte connection. *Cell* **109**, 75-86
- Lu QR, Yuk D, Alberta JA, Zhu Z, Pawlitzky I, Chan J, McMahon AP, Stiles CD, Rowitch DH** (2000) Sonic hedgehog-regulated oligodendrocyte lineage genes encoding bHLH proteins in the mammalian central nervous system. *Neuron* **25**, 317-329
- Lubetzki C, Demerens C, Anglade P, Villarroya H, Frankfurter A, Lee VM, Zalc B** (1993) Even in culture, oligodendrocytes myelinate solely axons. *Proceedings of the National Academy of Sciences USA* **90**, 6820-6824
- Luo Y, Bolon B, Kahn S, Bennett BD, Babu-Khan S, Denis P, Fan W, Kha H, Zhang J, Gong Y, Martin L, Louis JC, Yan Q, Richards WG, Citron M, Vassar R** (2001) Mice deficient in BACE1, the Alzheimer's beta-secretase, have normal phenotype and abolished beta-amyloid generation. *Nature Neuroscience* **4**, 231-232
- Luskin MB, McDermott K** (1994) Divergent lineages for oligodendrocytes and astrocytes originating in the neonatal forebrain subventricular zone. *Glia* **11**, 211-226
- Macklin WB, Weill CL, Deininger PL** (1986) Expression of myelin proteolipid and basic protein mRNAs in cultured cells. *The Journal of Neuroscience Research* **16**, 203-217
- Malone MJ, Szoke MC** (1985) Neurochemical changes in white matter. Aged human brain and Alzheimer's disease. *Archives of Neurology* **42**, 1063-1066
- Marin-Husstege M, Muggironi M, Liu A, Casaccia-Bonnel P** (2002) Histone deacetylase activity is necessary for oligodendrocyte lineage progression. *The Journal of Neuroscience* **22**, 10333-10345
- Masahira N, Takebayashi H, Ono K, Watanabe K, Ding L, Furusho M, Ogawa Y, Nabeshima Y, Alvarez-Buylla A, Shimizu K, Ikenaka K** (2006) Olig2-positive progenitors in the embryonic spinal cord give rise not only to motoneurons and oligodendrocytes, but also to a subset of astrocytes and ependymal cells. *Developmental Biology* **293**, 358-369
- McCarthy GF, Leblond CP** (1988) Radioautographic evidence for slow astrocyte turnover and modest oligodendrocyte production in the corpus callosum of adult mice infused with 3H-thymidine. *The Journal of Comparative Neurology* **271**, 589-603
- McGee AW, Yang Y, Fischer QS, Daw NW, Strittmatter SM** (2005) Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor. *Science* **309**, 2222-2226
- McGlashan TH, Hoffman RE** (2000) Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Archives of General Psychiatry* **57**, 637-648

- McTigue DM, Horner PJ, Stokes BT, Gage FH (1998) Neurotrophin-3 and brain-derived neurotrophic factor induce oligodendrocyte proliferation and myelination of regenerating axons in the contused adult rat spinal cord. *The Journal of Neuroscience* **18**, 5354-5365
- Menn B, Garcia-Verdugo JM, Yaschine C, Gonzalez-Perez O, Rowitch D, Alvarez-Buylla A (2006) Origin of oligodendrocytes in the subventricular zone of the adult brain. *The Journal of Neuroscience* **26**, 7907-7918
- Meyer D, Birchmeier C (1995) Multiple essential functions of neuregulin in development. *Nature* **378**, 386-390
- Michailov GV, Sereda MW, Brinkmann BG, Fischer TM, Haug B, Birchmeier C, Role L, Lai C, Schwab MH, Nave KA (2004) Axonal neuregulin-1 regulates myelin sheath thickness. *Science* **304**, 700-703
- Miller R, Reynolds R (2004) Oligodendroglial lineage. In: Lazzarini RA (Ed) *Myelin Biology and Disorders* (Vol 1), Elsevier Academic Press, New York, pp 289-310
- Miller RH (2002) Regulation of oligodendrocyte development in the vertebrate CNS. *Progress in Neurobiology* **67**, 451-467
- Mizuguchi R, Sugimori M, Takebayashi H, Kosako H, Nagao M, Yoshida S, Nabeshima Y, Shimamura K, Nakafuku M (2001) Combinatorial roles of olig2 and neurogenin2 in the coordinated induction of pan-neuronal and subtype-specific properties of motoneurons. *Neuron* **31**, 757-771
- Nakakura EK, Watkins DN, Schuebel KE, Sriuranpong V, Borges MW, Nelkin BD, Ball DW (2001) Mammalian Scratch: a neural-specific Snail family transcriptional repressor. *Proceedings of the National Academy of Sciences USA* **98**, 4010-4015
- Nakayama J, Rice JC, Strahl BD, Allis CD, Grewal SI (2001) Role of histone H3 lysine 9 methylation in epigenetic control of heterochromatin assembly. *Science* **292**, 110-113
- Nave KA, Salzer JL (2006) Axonal regulation of myelination by neuregulin 1. *Current Opinion in Neurobiology* **16**, 492-500
- Nielsen JA, Berndt JA, Hudson LD, Armstrong RC (2004) Myelin transcription factor 1 (Myt1) modulates the proliferation and differentiation of oligodendrocyte lineage cells. *Molecular and Cellular Neuroscience* **25**, 111-123
- Noble M, Proschel C, Mayer-Proschel M (2004) Getting a GR(i)P on oligodendrocyte development. *Developmental Biology* **265**, 33-52
- Novitsch BG, Chen AI, Jessell TM (2001) Coordinate regulation of motor neuron subtype identity and pan-neuronal properties by the bHLH repressor Olig2. *Neuron* **31**, 773-789
- Park SK, Miller R, Krane I, Vartanian T (2001) The erbB2 gene is required for the development of terminally differentiated spinal cord oligodendrocytes. *The Journal of Cell Biology* **154**, 1245-1258
- Parras CM, Galli R, Britz O, Soares S, Galichet C, Battiste J, Johnson JE, Nakafuku M, Vescovi A, Guillemot F (2004) Mash1 specifies neurons and oligodendrocytes in the postnatal brain. *The EMBO Journal* **23**, 4495-4505
- Parras CM, Hunt C, Sugimori M, Nakafuku M, Rowitch D, Guillemot F (2007) The proneural gene Mash1 specifies an early population of telencephalic oligodendrocytes. *The Journal of Neuroscience* **27**, 4233-4242
- Persohn E, Schachner M (1987) Immunoelectron microscopic localization of the neural cell adhesion molecules L1 and N-CAM during postnatal development of the mouse cerebellum. *The Journal of Cell Biology* **105**, 569-576
- Petryniak MA, Potter GB, Rowitch DH, Rubenstein JL (2007) Dlx1 and Dlx2 Control Neuronal versus Oligodendroglial Cell Fate Acquisition in the Developing Forebrain. *Neuron* **55**, 417-433
- Pringle NP, Richardson WD (1993) A singularity of PDGF alpha-receptor expression in the dorsoventral axis of the neural tube may define the origin of the oligodendrocyte lineage. *Development* **117**, 525-533
- Qi Y, Cai J, Wu Y, Wu R, Lee J, Fu H, Rao M, Sussel L, Rubenstein J, Qiu M (2001) Control of oligodendrocyte differentiation by the Nkx2.2 homeodomain transcription factor. *Development* **128**, 2723-2733
- Raine CS (1984) Morphology of myelin and myelination. In: Morell P (Ed) *Myelin* (2<sup>nd</sup> Edn), Plenum, New York, pp 1-50
- Ramirez G, Toro R, Doheli H, von Bernhardt R (2005) Protection of rat primary hippocampal cultures from A beta cytotoxicity by pro-inflammatory molecules is mediated by astrocytes. *Neurobiology of Disease* **19**, 243-254
- Richardson WD, Kessaris N, Pringle N (2006) Oligodendrocyte wars. *Nature Reviews Neuroscience* **7**, 11-18
- Richardson WD, Pringle NP, Yu WP, Hall AC (1997) Origins of spinal cord oligodendrocytes: possible developmental and evolutionary relationships with motor neurons. *Developmental Neuroscience* **19**, 58-68
- Richardson WD, Smith HK, Sun T, Pringle NP, Hall A, Woodruff R (2000) Oligodendrocyte lineage and the motor neuron connection. *Glia* **29**, 136-142
- Riethmacher D, Sonnenberg-Riethmacher E, Brinkmann V, Yamaai T, Lewin GR, Birchmeier C (1997) Severe neuropathies in mice with targeted mutations in the ErbB3 receptor. *Nature* **389**, 725-730
- Rohrer AE, Weiss N, Kokjohn TA, Kuo YM, Kalback W, Anthony J, Watson D, Luehrs DC, Sue L, Walker D, Emmerling M, Goux W, Beach T (2002) Increased A beta peptides and reduced cholesterol and myelin proteins characterize white matter degeneration in Alzheimer's disease. *Biochemistry* **41**, 11080-11090
- Rosenberg SS, Ng BK, Chan JR (2006) The quest for remyelination: a new role for neurotrophins and their receptors. *Brain Pathology* **16**, 288-294
- Roth AD, Ramirez G, Alarcon R, von Bernhardt R (2005) Oligodendrocytes damage in Alzheimer's disease: beta amyloid toxicity and inflammation. *Biological Research* **38**, 381-387
- Segal D, Koschnick JR, Slegers LH, Hof PR (2007) Oligodendrocyte pathophysiology: a new view of schizophrenia. *The International Journal of Neuropsychopharmacology* **10**, 503-511
- Selkoe DJ (2004) Alzheimer disease: mechanistic understanding predicts novel therapies. *Annals of Internal Medicine* **140**, 627-638
- Selkoe DJ, Schenk D (2003) Alzheimer's disease: molecular understanding predicts amyloid-based therapeutics. *Annual Review of Pharmacology and Toxicology* **43**, 545-584
- Shen S, Li J, Casaccia-Bonnel P (2005) Histone modifications affect timing of oligodendrocyte progenitor differentiation in the developing rat brain. *The Journal of Cell Biology* **169**, 577-589
- Southwood C, He C, Garbern J, Kamholz J, Arroyo E, Gow A (2004) CNS myelin paranodes require Nkx6-2 homeoprotein transcriptional activity for normal structure. *The Journal of Neuroscience* **24**, 11215-11225
- Stankoff B, Aigrot MS, Noel F, Wattilliaux A, Zalc B, Lubetzkii C (2002) Ciliary neurotrophic factor (CNTF) enhances myelin formation: a novel role for CNTF and CNTF-related molecules. *The Journal of Neuroscience* **22**, 9221-9227
- Stephan KE, Baldeweg T, Friston KJ (2006) Synaptic plasticity and dysfunction in schizophrenia. *Biological Psychiatry* **59**, 929-939
- Stevens B, Porta S, Haak LL, Gallo V, Fields RD (2002) Adenosine: a neuronal transmitter promoting myelination in the CNS in response to action potentials. *Neuron* **36**, 855-868
- Stevens JR (1988) Schizophrenia and multiple sclerosis. *Schizophrenia Bulletin* **14**, 231-241
- Stolt CC, Lommes P, Sock E, Chaboissier MC, Schedl A, Wegner M (2003) The Sox9 transcription factor determines glial fate choice in the developing spinal cord. *Genes and Development* **17**, 1677-1689
- Stolt CC, Rehberg S, Ader M, Lommes P, Riethmacher D, Schachner M, Bartsch U, Wegner M (2002) Terminal differentiation of myelin-forming oligodendrocytes depends on the transcription factor Sox10. *Genes and Development* **16**, 165-170
- Stolt CC, Schlierf A, Lommes P, Hillgartner S, Werner T, Kosian T, Sock E, Kessaris N, Richardson WD, Lefebvre V, Wegner M (2006) Sox10 proteins influence multiple stages of oligodendrocyte development and modulate Sox10 protein function. *Developmental Cell* **11**, 697-709
- Stolt CC, Schmitt S, Lommes P, Sock E, Wegner M (2005) Impact of transcription factor Sox8 on oligodendrocyte specification in the mouse embryonic spinal cord. *Developmental Biology* **281**, 309-317
- Takebayashi H, Nabeshima Y, Yoshida S, Chisaka O, Ikenaka K (2002) The basic helix-loop-helix factor olig2 is essential for the development of motoneuron and oligodendrocyte lineages. *Current Biology* **12**, 1157-1163
- Takebayashi H, Yoshida S, Sugimori M, Kosako H, Kominami R, Nakafuku M, Nabeshima Y (2000) Dynamic expression of basic helix-loop-helix Olig family members: implication of Olig2 in neuron and oligodendrocyte differentiation and identification of a new member, Olig3. *Mechanisms of Development* **99**, 143-148
- Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L (1998) Axonal transection in the lesions of multiple sclerosis. *The New England Journal of Medicine* **338**, 278-285
- Uranova NA, Vostrikov VM, Vikhrevva OV, Zimina IS, Kolomeets NS, Orlovskaya DD (2007) The role of oligodendrocyte pathology in schizophrenia. *International Journal of Neuropsychopharmacology* **10**, 537-545
- Vallstedt A, Klos JM, Ericson J (2005) Multiple dorsoventral origins of oligodendrocyte generation in the spinal cord and hindbrain. *Neuron* **45**, 55-67
- Varadarajan S, Yatin S, Aksenova M, Butterfield DA (2000) Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. *The Journal of Structural Biology* **130**, 184-208
- Vartanian T, Fischbach G, Miller R (1999) Failure of spinal cord oligodendrocyte development in mice lacking neuregulin. *Proceedings of the National Academy of Sciences USA* **96**, 731-735
- Vos JP, Gard AL, Pfeiffer SE (1996) Regulation of oligodendrocyte cell survival and differentiation by ciliary neurotrophic factor, leukemia inhibitory factor, oncostatin M, and interleukin-6. *Perspectives in Developmental Neurobiology* **4**, 39-52
- Wang S, Sdrulla A, Johnson JE, Yokota Y, Barres BA (2001) A role for the helix-loop-helix protein Id2 in the control of oligodendrocyte development. *Neuron* **29**, 603-614
- Wang S, Sdrulla AD, diSibio G, Bush G, Nofziger D, Hicks C, Weinmaster G, Barres BA (1998) Notch receptor activation inhibits oligodendrocyte differentiation. *Neuron* **21**, 63-75
- Wang SZ, Dulin J, Wu H, Hurlock E, Lee SE, Jansson K, Lu QR (2006) An oligodendrocyte-specific zinc-finger transcription regulator cooperates with Olig2 to promote oligodendrocyte differentiation. *Development* **133**, 3389-3398
- Wegner M (2001) Expression of transcription factors during oligodendroglial development. *Microscopy Research and Technique* **52**, 746-752
- Willem M, Garratt AN, Novak B, Citron M, Kaufmann S, Rittger A, de Strooper B, Saffitz P, Birchmeier C, Haass C (2006) Control of peripheral nerve myelination by the beta-secretase BACE1. *Science* **314**, 664-666
- Winterer G, Coppola R, Egan MF, Goldberg TE, Weinberger DR (2003) Functional and effective frontotemporal connectivity and genetic risk for

- schizophrenia. *Biological Psychiatry* **54**, 1181-1192
- Woodruff RH, Tekki-Kessarlis N, Stiles CD, Rowitch DH, Richardson WD** (2001) Oligodendrocyte development in the spinal cord and telencephalon: common themes and new perspectives. *International The Journal of Developmental Neuroscience* **19**, 379-385
- Wu S, Wu Y, Capecchi MR** (2006) Motoneurons and oligodendrocytes are sequentially generated from neural stem cells but do not appear to share common lineage-restricted progenitors *in vivo*. *Development* **133**, 581-590
- Xin M, Yue T, Ma Z, Wu FF, Gow A, Lu QR** (2005) Myelinogenesis and axonal recognition by oligodendrocytes in brain are uncoupled in Olig1-null mice. *The Journal of Neuroscience* **25**, 1354-1365
- Yates MA, Juraska JM** (2007) Increases in size and myelination of the rat corpus callosum during adulthood are maintained into old age. *Brain Research* **1142**, 13-18
- Younes-Rapoza V, Berendonk J, Savignon T, Manhaes AC, Barradas PC** (2006) Thyroid hormone deficiency changes the distribution of oligodendrocyte/myelin markers during oligodendroglial differentiation *in vitro*. *The International Journal of Developmental Neuroscience* **24**, 445-453
- Yue T, Xian K, Hurlock E, Xin M, Kernie SG, Parada LF, Lu QR** (2006) A critical role for dorsal progenitors in cortical myelination. *The Journal of Neuroscience* **26**, 1275-1280
- Zalc B, Colman DR** (2000) Origins of vertebrate success. *Science* **288**, 271-272
- Zhou Q, Anderson DJ** (2002) The bHLH transcription factors OLIG2 and OLIG1 couple neuronal and glial subtype specification. *Cell* **109**, 61-73
- Zhou Q, Choi G, Anderson DJ** (2001) The bHLH transcription factor Olig2 promotes oligodendrocyte differentiation in collaboration with Nkx2.2. *Neuron* **31**, 791-807
- Zhou Q, Wang S, Anderson DJ** (2000) Identification of a novel family of oligodendrocyte lineage-specific basic helix-loop-helix transcription factors. *Neuron* **25**, 331-343