Myelin Restoration: Progress and Prospects for Human Cell Replacement Therapies

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REVIEW

Myelin Restoration: Progress and Prospects for Human Cell Replacement Therapies

Gregory B. Potter · David H. Rowitch · Magdalena A. Petryniak

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Abstract Oligodendrocytes are the primary source of myelin in the adult central nervous system (CNS), and their dysfunction or loss underlies several diseases of both children and adults. Dysmyelinating and demyelinating diseases are thus attractive targets for cell-based strategies since replacement of a single presumably homogeneous cell type has the potential to restore functional levels of myelin. To understand the obstacles that cell-replacement therapy might face, we review oligodendrocyte biology and emphasize aspects of oligodendrocyte development that will need to be recapitulated by exogenously transplanted cells, including migration from the site of transplantation, axon recognition, terminal differentiation, axon wrapping, and myelin production and maintenance. We summarize studies in which different types of myelin-forming cells have been transplanted into the CNS and highlight the continuing challenges regarding the use of cell-based therapies for human white matter disorders.

Keywords Myelin · Transplantation · Oligodendrocyte · Development · Pelizaeus–Merzbacher disease · Cell-replacement · Leukodystrophy

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Abbreviations

ATP	Adenosine triphosphate
CNP	2′,3′-Cyclic nucleotide-3′phosphodiesterase
CNS	Central nervous system
CNTF	Ciliary neurotrophic factor
EAE	Experimental autoimmune encephalomyelitis
GalC	Galactocerebrosidase
IGF-1	Insulin-like growth factor 1
iPSCs	Induced pluripotent stem cells
miRs	MicroRNAs
MAG	Myelin-associated glycoprotein
MBP	Myelin basic protein
MOG	Myelin/oligodendrocyte glycoprotein
MS	Multiple sclerosis
MSC	Mesenchymal stem cells
mTOR	Mammalian target of rapamycin
NSCs	Neural stem cells
O2A	Oligodendrocyte-type 2 astrocyte precursor
OPCs	Oligodendrocyte precursors
PDGFR	Platelet derived growth factor receptor
Plp	Proteolipid protein
PMD	Pelizaeus–Merzbacher disease
PNS	Peripheral nervous system
PTEN	Phosphatase and tensin homolog
T3	3,5,3-Triiodothyronine (thyroid hormone)
Tcf4	Transcription factor 4
YY1	Ying Yang 1

Introduction

Over the past several decades, the concept of cell-based therapies to treat human neurological disorders has attracted considerable interest, focused, most notably, on

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transplantation of fetal midbrain cells for Parkinson's disease. White matter disorders in pediatric and adult populations collectively account for significant morbidity and mortality. Recent pre-clinical research in mouse models has focused on exogenous cell-based oligodendrocyte therapeutic approaches in an effort to restore myelin and improve functional outcome. Although significant progress has been made, much remains to be learned regarding the basic biology of engraftment, optimal methods of immune suppression, the capability for efficient and robust myelination, and restoration of function, before such therapies will be optimized for use in the treatment of human disorders. In this review, we highlight key aspects of endogenous oligodendrocyte development that will need to be recapitulated by exogenously transplanted cells, including migration from the site of transplantation, axon recognition, terminal differentiation, axon wrapping and myelin production and maintenance. We review results of transplanting various precursors of myelin-forming cells into the central nervous system (CNS) in preclinical models of multiple sclerosis (MS), spinal cord injury and leukodystrophy, and highlight difficult questions regarding human research of such cell-based therapies for white matter disorders.

Introduction to Oligodendroglia

Although glia cells far out number neurons in the vertebrate brain, many fundamental questions of glial development and biology remain unanswered. First described as "nerve glue" by Virchow (1846), we now understand that glia are active participants in the development, maintenance and function of the brain (Allen and Barres 2009). The two major neuroepithelial glial derivatives of the CNS are astrocytes and oligodendrocytes. We focus in this review upon the myelinating cells of the CNS, the oligodendrocytes (Fig. 1).

In the CNS, oligodendrocytes are responsible for the synthesis and maintenance of the myelin sheaths that surround the axons. The myelin sheath allows for formation of nodes of Ranvier (Sherman and Brophy 2005), required for saltatory propagation of nerve impulses along the length of the axon. This results in a faster and more efficient neural impulse than in uninsulated nerve fibers. In addition, myelination allows the close approximation of numerous ensheathed axons without signal cross-talk and the ability for nerve signals to be sent over long distances with high fidelity, enabling rapid and reliable communication between distant areas of the nervous system, and increased packing of axons in a smaller area and hence more complexity in brain function (Zalc 2006).

Structure and Composition of Myelin

Comprising ~70% lipid and ~30% protein, myelin is arranged as multiple lamellar wraps around an axon (Baumann and Pham-Dinh 2001). New work suggests a surprising complexity of myelin proteins, many of which are of as yet unknown function (Linker et al. 2009). In general, the length of the wrap varies with the diameter of the axon with longer sheaths covering larger axons. In the rodent cortex, a typical wrap covers ~600 μm of the axon and are separated by a ~30 μm nodes of naked axon (Murtie et al. 2007). These "nodes of Ranvier" play a major role in nerve conduction, as their specialized collection of voltage gated sodium channels allows for the action potential impulse to jump from node to node along the axon (Fig. 1c; Schafer and Rasband 2006). At the nodes, the wrapping of the myelin sheath is less compacted and forms loops that retain small amounts of cytoplasm. Each of these loops contact the axon to form the paranodal region or paranode (Fig. 1c). The paranodes contain cytoskeletal filaments that appear to tighten the axonal–paranodal connection (Poliak and Peles 2003).

While quite abundant in the CNS, the structural composition of myelin remains incompletely understood. In vertebrates, myelin lipids contain cholesterol, phospholipids, and glycolipids. They are rich in glycosphingolipids, in particular galactocerebrosides and their sulfated derivates such as the galactosylceramide (GalC), which accounts for ~20% of all lipids by dry weight in mature myelin (Baumann and Pham-Dinh 2001). The myelin proteins are, for the most part, specific components of myelin and are used as markers of oligodendrocytes. The major CNS myelin proteins, myelin basic protein (MBP) and proteolipid protein (Plp) are thought to constitute ~25% of the total proteins (Baumann and Pham-Dinh 2001; Jahn et al. 2009). MBP, which makes up ~8% of myelin proteins, is a cytoplasmic and hydrophilic protein that interacts with the lipids in the myelin membrane by electrostatic and hydrophobic interactions; it pulls the inner phospholipid layers within the cytoplasm together to form the major dense lines seen by electron microscopy (Fig. 1d). Various isoforms of MBP are produced by alternative splicing, but the major human isoforms of 18.5 and 17.2 kilo-Dalton (kDa) constitute ~95% of the MBPs (Harauz et al. 2009). MBP plays a major role in myelin compaction in the CNS, as mice that lack MBP exhibit tremors, seizures, and ataxia and have very thin or absent myelin sheaths. Plp, which makes up ~17% of myelin proteins, is ~25 kDa and comprises four hydrophobic α-helixes spanning the whole thickness of the lipid bilayer (Fig. 1d). Plp likely acts to stabilize myelin, as oligodendrocytes without Plp are still competent to myelinate axons and ensemble myelin sheaths, yet the myelin shows abnormities in lamellar

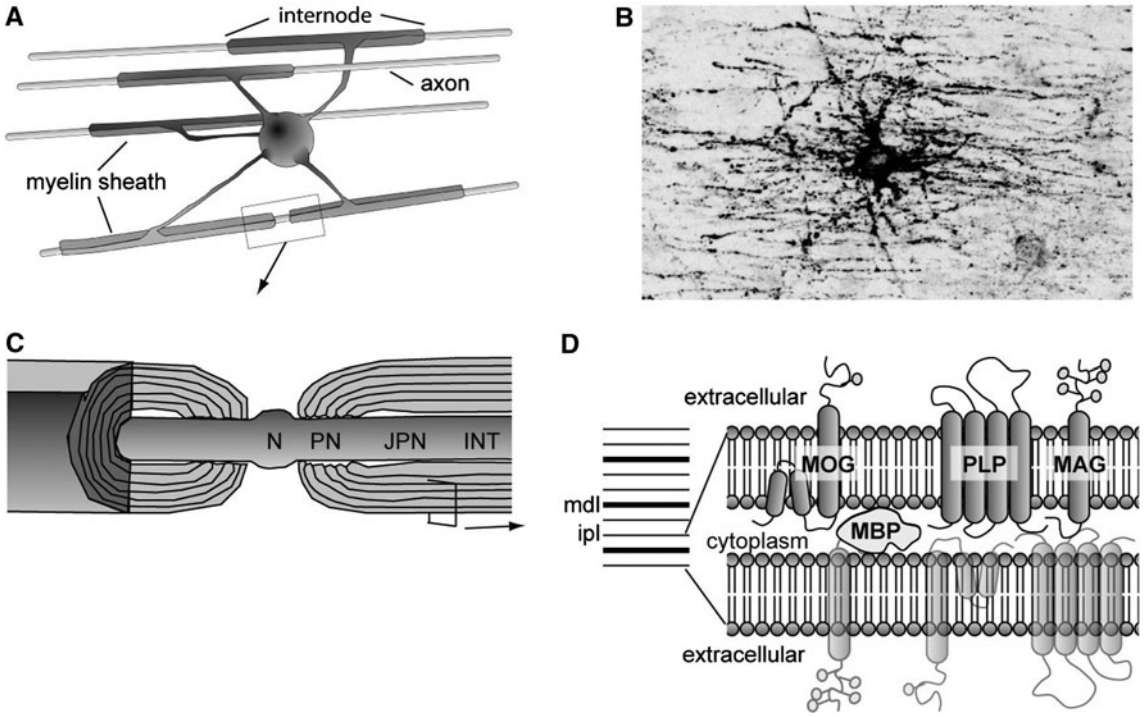

Fig. 1 Myelinating oligodendrocyte of the CNS. **a** A representation of a myelinating oligodendrocyte extending several processes to wrap nearby axons with myelin sheaths. Although not depicted here, a typical oligodendrocyte can have up to 50 extensions that myelinate different axons of varying diameters. The Node of Ranvier is *boxed* and shown at higher magnification in **c**. **b** Numerous myelinating extensions are visible in this myelinating oligodendrocyte labeled in human corpus callosum by immunohistochemistry for an oligodendrocyte-specific protein. **c** Multiple wraps of myelin membrane encompass the axon along its length except at the Node of Ranvier (*N*), a the site of salutatory conduction. The oligodendrocyte lamellae contact the axon at the paranode (*PN*), which lies adjacent to the juxtaparanode (*JPN*). *INT* internodal region of axon. **d** *Left* a schematic of the major dense lines (*mdl*) and intraperiod lines (*ipl*) of the myelin sheath, typically visualized by electron microscopy. *Right* at the molecular level, these structures are composed of lipids and proteins that form compact myelin. The mdl arises from the close apposition of the cytoplasmic side of the oligodendrocyte plasmid membrane brought together by the intracellular protein MBP, as an example. Hundreds of proteins are associated with myelin, including the well-characterized transmembrane proteins myelin-associated glycoprotein (MAG), myelin/oligodendrocyte glycoprotein (MOG), and proteolipid protein (Plp)

structure. Mice with mutations in Plp show early perinatal lethality, indicating that Plp expression is necessary for normal myelin function (Campagnoni and Skoff 2001).

Additional proteins, such as 2′,3′-cyclic nucleotide-3′phosphodiesterase (CNP), myelin-associated glycoprotein (MAG), and myelin/oligodendrocyte glycoprotein (MOG) comprise 4, 1, and 1% of myelin proteins, respectively (Fig. 1d; Jahn et al. 2009). The enzymatic activity of CNP has yet to be shown in vivo as 2′,3′-nucleotides have not been detected in the brain. CNP's function is unknown, however over-expression of CNP in transgenic mice perturbs myelin formation and generates aberrant membrane expansion (Gravel et al. 1996). It is not found in compacted myelin, but is most highly expressed in the cytoplasm of the non-compacted sheath and in the paranodal loops (Rasband et al. 2005; Trapp et al. 1988). MAG is a glycosylated transmembrane protein with an extracellular domain that bears homology to the immunoglobulin superfamily. MOG is located on the outermost lamellae of compact myelin sheaths, and its presence correlates with late stages of oligodendrocyte maturation. It is a highly immunogenic protein, and is capable of eliciting an autoantibody response to generate a mouse model of MS (Storch et al. 1998).

One caveat to bear in mind is that classical methods used to purify myelin proteins could select for certain classes of proteins based on their structure or other physical properties (Royland et al. 1992). Recent work coupling liquid chromatography with mass spectrometry highlights this point by identifying hundreds of previously unknown myelin proteins, many of which are uncharacterized (Ishii et al. 2009; Jahn et al. 2009).

Disorders of Myelination in Humans

Myelination is crucial for human CNS function, as emphasized by diseases or disorders that impair oligodendrocyte generation, differentiation, or myelin production and maintenance. Inherited myelin diseases, called leukodystrophies, can cause dysmyelination (improper formation

of myelin), hypomyelination (inadequate levels of myelin), or demyelination (loss or breakdown of myelin). Some dysmelinating or hypomyelinating diseases present during fetal life or early infancy, as observed in the connatal form of Pelizaeus–Merzbacher disease (PMD) in which a major component of the myelin sheath, Plp, is abnormal. A large variety of PLP1 point mutations and gene duplications have been described (Sarret et al. 2010) and any PLP1 mutation is considered pathological in patients with hypomyelination and neurological dysfunction characteristic of PMD. Demyelinating leukodystrophies are also characteristic of metabolic diseases such as Krabbe's disease, in which the lysosomal enzyme GalC is defective, resulting in accumulation of psychosine, a metabolite toxic to oligodendrocytes (Pastores 2009).

Inflammatory demyelinating diseases, in which oligodendrocytes are targeted by the immune system, are exemplified by MS, the most common cause of neurological dysfunction in young adults (Compston and Coles 2002). MS is generally thought to result from an autoimmune inflammatory response towards components of the myelin sheath (Steinman et al. 2002). As the disease progresses, a spectrum of pathologies are observed in which some white matter areas contain evidence of remyelinating axons, while other areas are almost completely demyelinated. It is thought that sustained loss of myelin results in axonal dysfunction and neuronal death and underlies the irreversible neurological impairments of MS (Hauser and Oksenberg 2006). The variability in remyelination of MS lesions has lead to the notion that dysregulation of myelin repair is a factor that could account for disease progression (Franklin and Ffrench-Constant 2008)

Oligodendrocyte Precursors

Much of what we know about oligodendrocyte development is derived from work done in rodents. In the developing mouse forebrain, oligodendrocytes precursors (OPCs) are generated in a temporal ventral-to-dorsal progression, with the earliest precursors produced from ventricular zone progenitors within the medial ganglionic eminence (Kessaris et al. 2006; Petryniak et al. 2007). After generation, OPCs migrate and populate all parts of the forebrain. Around E16, progenitors within the lateral ganglionic eminences generate OPCs, followed by production from cortical progenitors after birth. The later waves of OPCs appear to be functionally interchangeable with early produced OPCs (Kessaris et al. 2006). Postnatally, NG2-proteoglycan expressing cells, known as $NG2^+$ cells, polydendrocytes or synantocytes, are widely distributed throughout the white and grey matter and express markers of oligodendrocyte precursor cells (Butt et al. 2002; Nishiyama et al. 2009; Trotter et al. 2010). Whether $NG2^+$ cells are OPCs or represent a "fourth type" of neuroepithelial cell in CNS is controversial (Nishiyama et al. 2009).

In the embryonic mouse spinal cord, the majority of OPCs are generated from the ventral pMN progenitor domain starting ~E10 (Timsit et al. 1995), with a small proportion of OPCs produced by dorsal progenitor domains after ~E13 (Cai et al. 2005). The specification of spinal cord oligodendrocytes requires interplay between cell-intrinsic and regionally restricted extrinsic factors, including Shh- and BMP-signaling (Agius et al. 2004) and expression of the oligodendrocyte lineage transcription factor 2 and other transcription factors (Rowitch 2004).

OPCs migrate extensively throughout the CNS before their differentiation into myelin-forming oligodendrocytes (de Castro and Bribian 2005). As they migrate, they extend processes that sample the extracellular environment for motility and guidance factors. Platelet derived growth factor (PDGF), a mitogenic and migratory factor, acts through OPC-expressed PDGF-receptor (PDGFR) to initiate and promote migration through extracellular regulated kinase signaling and an undetermined pathway that couples Fyn kinase to Cdk5 phosphorylation of WAVE2 (Frost et al. 2009; Miyamoto et al. 2008). Migration can be maintained through voltage operated calcium channels and intracellular calcium signals, while chemoattractive or chemorepulsive factors such as Semaphorin 3F or netrin, respectively, direct OPCs towards their targets (Paez et al. 2009; Simpson and Armstrong 1999; Spassky et al. 2002). The signals that tell an OPC to stop migrating in the forebrain are unknown; in the developing spinal cord, CXCR2 controls positioning of OPCs by arresting their migration (Padovani-Claudio et al. 2006; Tsai et al. 2002). Without a doubt, additional factors will be identified that signal between OPCs and their environment to properly and uniformly distribute these cells throughout the brain.

Once an OPC has reached its final destination, it undergoes a remarkable cellular transformation to become a myelinating oligodendrocyte. This process can be divided into several steps: OPC to oligodendrocyte differentiation, axon recognition, wrapping and compaction, and myelin maintenance.

OPC to Oligodendrocyte Differentiation

Differentiation of the mitotically active OPC into an oligodendrocyte capable of myelinating (a pro-oligodendrocyte or pro-OL) requires cell cycle withdrawal, downregulation of OPC genes (such as PDGFR) and the upregulation of oligodendrocyte genes necessary for the upcoming events of process extension and elongation, myelin synthesis, and compaction. Established pathways associated with OPC maturation include thyroid hormone

signaling. The active form of thyroid hormone, 3,5,3-triiodothyronine (T3), binds to nuclear T3 receptors to regulate transcription. OPCs exposed to T3 in culture will rapidly differentiate into MBP-expressing oligodendrocytes (Barres et al. 1994). OPC differentiation can proceed in the absence of T3, yet T3 regulates the onset of oligodendrocyte maturation and is required to achieve the appropriate number of myelinating oligodendrocytes (Baas et al. 1997; Rodríguez-Peña 1999). T3 controls the expression of several myelin-associated genes, such as MBP, CNP, and Plp (Ibarrola and Rodriguez-Pena 1997). Lack of sufficient T3 during gestation results in abnormal development of virtually all organ systems in humans, a syndrome called cretinism (Cao et al. 1994). In particular, the brain is severely affected, and functional defects include mental retardation and ataxia (Delange 2000). Thyroid hormone levels peak during the onset of myelination and hypothyroidism leads to a striking reduction in myelination (Sarlième et al. 2004).

Activation of the PI-3 kinase pathway has been shown to regulate OPC differentiation both in culture (Ebner et al. 2000; Romanelli et al. 2009) and in vivo (Flores et al. 2000). Constitutively active Akt transgenic mice show striking hypermyelination (Narayanan et al. 2009), that is prevented by downstream inhibition of mammalian target of rapamycin (mTOR) by rapamycin. The tumor suppressor *Pten* lies upstream of PI-3 kinase pathway to inhibit its activation. However, no effect on remyelination was observed after lysolecithin gliotoxic injury in spinal cords of mice with *Pten* conditionally ablated in the oligodendrocyte lineage, suggesting that regulation of PI-3 kinase pathway in OPCs is dispensable during myelin repair (Harrington et al. 2010).

Other pathways may serve to delay OPC maturation in development and remyelination. For example, activation of the canonical Wnt signaling pathway, via β-catenin stabilization and transcription factor 4 (Tcf4)-mediated gene activation, may serve as an important inhibitory mechanism for repressing oligodendrocyte differentiation and thus suppressing Wnt-signaling might be necessary for OPCs to mature into pro-OLs (Ye et al. 2009). Recently, Notch pathway activation has been shown to regulate OPC maturation in development and remyelination (Zhang et al. 2009), consistent with Notch activity in human MS (John et al. 2002).

Activation of the mTOR enables differentiation of OPCs, most likely by decreasing the expression of helix-loop-helix transcription factors such as inhibitors of differentiation family members Id2 and Id4, and Wnt-family members such as Tcf4. Inhibiting mTOR activity arrests oligodendrocyte differentiation at the OPC stage (Tyler et al. 2009). The transcription factor Ying Yang 1 (YY1), acting as a repressor of transcriptional inhibitors Tcf4 and Id4, is also involved in this process; lack of YY1 arrests differentiation of OPCs after they exit the cell cycle (He et al. 2007). These findings raise several additional points of interest. First, it is interesting to note that exogenous rapamycin may serve as a canonical Wnt inhibitor by down-regulating Tcf4, an obligate component of the Wnt transcriptional activation apparatus. Further studies to integrate roles of mTOR, Wnt and YY1 are warranted.

Secondly, it is relevant to note that the mTOR inhibitor, rapamycin (Tacrolimus), is commonly used as an immunosuppressive and could be used in human OPC transplant approaches. If so, the role of rapamycin could be conjectured to have either negative effects, e.g. causing decreased differentiation of OPCs and less myelin production; or conversely, positive effects by delaying maturation to allow for maximal expansion of immature OPCs that retain proliferative competence and their ability to migrate into a wider region from their implantation site. These considerations illustrate the critical role of dialogue between basic glial biologists and their clinical–translational counterparts, as well as questions that may ultimately only be answered in the context of human studies.

Extrinsically, electrical activity of the axon might be important in OPC maturation. Action potential firing causes release of adenosine triphosphate (ATP) and adenosine, both of which can influence oligodendrocyte differentiation. ATP released from axons triggers release of leukemia inhibitory factor from astrocytes, which promotes myelination (Ishibashi et al. 2006). Adenosine inhibits OPC proliferation and stimulates differentiation and expression of myelin-related genes (Stevens et al. 2002).

Recently, microRNAs (miRs) were shown to be necessary and sufficient to promote oligodendrocyte differentiation. One miR in particular, miR-219, arrests proliferation, suppresses expression of OPC-related genes, and activates expression of pro-OL genes. Thus, miRs might effectively coordinate the rapid transition from mitotically-active OPCs to pro-OLs (Dugas et al. 2010; Zhao et al. 2010).

Axon Recognition and Attachment

The pro-OLs send out multiple sail-like extensions from their cytoplasmic membrane, each of which forms a segment of sheathing around an axon. Oligodendrocytes can myelinate up to 60 axons, typically within $\sim$20–30 μm of its cell body (Fig. 1b; Baumann and Pham-Dinh 2001). The mechanism underlying how a pro-OL process identifies an axon and chooses which axon to myelinate is unknown. The pro-OL process must distinguish between dendrites and axons, and will only wrap axons of a particular diameter, typically around 1–2 μm. A few candidate molecules that might mediate axon–oligodendrocyte interactions have been identified. The nectin-like (Necl) cell adhesion

molecules have been implicated as axonal membrane factors that might mediate initial axon–oligodendrocyte interaction and adhesion. Necl-1 and Necl-3 transmembrane proteins expressed by neurons could mediate homo- and heterophilic interaction with Necl molecules expressed by oligodendrocytes, although this has yet to be demonstrated within the CNS in vivo (Park et al. 2008; Pellissier et al. 2007). In the CNS, recognition of oligodendrocytes and axons and formation of the spiraling loops might be mediated, in part, by MAG (Martini and Schachner 1997). In MAG-null mice, myelin-formation is delayed and some axons are surrounded by two or more myelin sheaths, suggesting that MAG could be involved in the signaling between oligodendrocyte process and axons (Montag et al. 1994).

Contact between axons and oligodendrocytes is also important for oligodendrocyte survival. Neurons release growth factors, such as PDGF-A, fibroblast growth factor 2, insulin-like growth factor (IGF)-1, neurotrophin-3 and ciliary neurotrophic factor (CNTF), which are important for oligodendrocyte survival (Barres et al. 1993b). Only oligodendrocytes that manage to ensheath an axon survive, whereas those that fail, degenerate (Barres et al. 1992). Likewise, decreasing the number of axons reduces the number of oligodendrocytes significantly (Barres et al. 1993a).

Finally, it is interesting to note that purely physical factors could be sufficient for myelin wrapping. Increasing the concentration of OPCs plated upon cultured axons accelerates their maturation. Remarkably, high density OPCs seeded onto axons previously fixed with paraformaldehyde are able to differentiate and form compact myelin with the same timing and robustness as OPCs plated onto live axons (Rosenberg et al. 2008). Although this does not preclude molecules fixed to the axonal surface from directing oligodendrocyte maturation, these results suggest that active signaling between oligodendrocytes and axons are not required for myelination in co-cultures. Furthermore, the addition of polystyrene beads manipulated to adhere to axons accelerates differentiation of low-density OPCs by restricting the availability of axonal space (Rosenberg et al. 2008). Thus physical characteristics of the microenvironment can influence OPC differentiation.

Wrapping and Compaction

After oligodendrocytes have established proper contact with the axonal membrane, they start to extend their membrane by spirally wrapping it around the axon. Oligodendrocytes become highly polarized and establish distinct membrane trafficking pathways that allow directed transport of proteins and lipids to the extending processes (Maier et al. 2008). Since each oligodendrocyte is able to produce up to 50 myelinated segments on multiple axons, they have to synthesize a tremendous amount of membrane in a short time (Pfeiffer et al. 1993). The synthesis of most of the myelin lipids starts in the endoplasmic reticulum and different components of the myelin sheath are likely pre-assembled in membrane microdomains of lipid rafts (Debruin and Harauz 2007). Membranes are trafficked to the wrapping process as vesicles that utilize soluble NSF attachment protein receptors and motor proteins for directed transport along the polarized cytoskeleton, although the mechanisms remain to be determined (Feldmann et al. 2009; Larocca and Rodriguez-Gabin 2002). Myelin cannot be synthesized without cholesterol, and proper synthesis and trafficking of cholesterol is essential for myelination (Saher et al. 2005). Key components underlying intracellular cholesterol trafficking have recently been elucidated after careful analysis of mutations in Niemann-Pick C (NPC) proteins, NPC1 and NPC2 (Peake and Vance 2010). NPC1, a multi-spanning membrane protein, and NPC2, a soluble protein, are present in lysosomes and late endosomes and coordinate the movement of cholesterol out of these intracellular compartments. Transport of cholesterol by NPC proteins is essential for proper myelination, as mice with null mutations in NPC1 show extensive hypomyelination of the corpus callosum (German et al. 2002). The cytoplasm of the differentiating and mature oligodendrocytes has well-developed Golgi apparatus and abundant ribosomes to handle the tremendous myelin protein synthesis and transport that are required for myelination. Importantly, protein synthesis can occur in the growing myelin process, probably allowing for rapid inclusion of important myelin proteins (Gould et al. 2000). For example, MBP mRNA is localized to the oligodendrocyte process (Trapp et al. 1987).

The leading edge of the oligodendrocyte process forms an initial wrap, and then moves underneath the growing membrane sheet. The extensive cytoskeletal organization of microtubules and microfilaments that occur during wrapping were recently reviewed elsewhere, and are mediated, in part, by extracellular and intracellular signals and internal protein interactions (Bauer et al. 2009). After approximately three wraps, the myelin sheath begins a process of compaction, in which the cytoplasm is extruded from both the intracellular and extracellular sheet. Compaction is a crucial part of myelin formation, as it is responsible for the highly specific insulating function of the sheath. The process of compaction is still being resolved. MBP is likely involved since *shiverer* mice, which lack MBP, display loosely wrapped axons (Readhead and Hood 1990). The highly charged and modular surface of MBP is thought to bring together and reorganize the intracellular lipid membranes to form the major dense line characteristic of compacted myelin seen using electron microscopy (Harauz et al. 2009).

The number of wraps, and hence the thickness of the myelin sheath, is proportional to the diameter of the axon. The ratio of the inner axonal diameter to the total outer diameter, known as the g-ratio, is consistently ~ 0.75 within the rodent CNS (Chomiak and Hu 2009). The axon likely participates in the regulation of myelin thickness. Single oligodendrocytes can myelinate several axons with different diameters. Instead of forming myelin of a fixed diameter, these oligodendrocytes generate thicker myelin around larger axons (Waxman and Sims 1984). This suggests that the axon specifies, in a localized way, the number of myelin lamellae formed by a single oligodendrocyte process. The signaling factors between axons and oligodendrocytes that coordinate the extent of myelination with the caliber of the axon have not yet been identified. Some clues, however, come from the study of the myelinating cells of the peripheral nervous system (PNS), the Schwann cells. Neuregulin type III, expressed by neurons, signals through ErbB receptors on Schwann cells to modulate the extent of myelination (Nave and Salzer 2006). Receptor activation stimulates the PI3K-AKT pathway to promote myelination. To curb excessive myelination in the PNS, neuregulin stimulation also stabilizes Dlg1 in Schwann cells, which in turn stabilizes PTEN. More PTEN is then available to inhibit AKT activation, which blocks myelination (Cotter et al. 2010). Thus, neuregulin signaling both promotes myelination and also regulates the extent of myelination in the PNS. Importantly, the correlation between axon diameter and myelin thickness and length seen during developmental myelination is less apparent in remyelination in disorders such as MS, resulting in thinner and shorter sheath segments (Bradl and Lassmann 2010). The underlying mechanisms for this difference remain uncertain, but emphasize that damaged axons could differ dramatically in their ability to be sufficiently myelinated in vivo or by exogenously transplanted cells.

Myelin Maintenance

Mature oligodendrocytes support membranes up to 100-times the weight of their cell body. Therefore, it is not surprising that oligodendrocytes purportedly have the greatest rate of oxidative metabolic activity of any cell in the brain on a per volume basis, with cell respiration rates at least twofold that of neurons (Connor and Menzies 1996). This high metabolic rate requires oligodendrocytes to consume large amounts of ATP and oxygen, with hydrogen peroxide or reactive oxygen species as potentially toxic byproduct (McTigue and Tripathi 2008). Within the multiple wraps that make up the myelin sheath, cytoplasmic pockets that form channels at the paranodal loops (the edges of the myelin sheath), the inner tongue (the segment of the oligodendrocyte extension that wraps and remains approximated to the axon), and radial components likely serve as conduits for the transport of vesicles, proteins and mRNAs in the maintenance of the myelin (Bauer et al. 2009). While some components of myelin are very stable, there are myelin proteins and lipids that are continuously replenished throughout the lifetime of the cell. The turnover of myelin proteins varies and can range from 2 weeks to >100 days (Sabri et al. 1974). The precise regulation of protein and lipid production and membrane targeting is necessary for myelin integrity; for example, increased overexpression of Plp in transgenic mice leads to myelin instability and oligodendrocyte death (Karim et al. 2007).

Myelination of axons is essential for their proper function and survival. Long-term axonal integrity depends on oligodendrocyte factors such as CNPase, myelin peroxisomes, MAG, and CNTF (Nave and Trapp 2008). Similarly, myelin health depends on axonal signals as demonstrated by anterograde myelin sheath degradation that occurs after transection of optic nerves; the molecular mechanisms of this effect are largely unknown, but can be rescued by exogenous application of trophic factors such as IGF-1 and CNTF (Barres et al. 1993a). Recent evidence has indicated that expression of prion protein in PNS axons is required for the maintenance of Schwann cell myelin, yet a similar requirement in the CNS was not found (Bremer et al. 2010). Undoubtedly, molecules and signaling factors necessary for axon–oligodendrocyte maintenance are still awaiting discovery.

Cell Transplantation

Having described the processes associated with normal functions of CNS oligodendrocytes, we will now consider the cell types that could provide therapeutic myelinating functions upon transplantation. Oligodendrocytes are the primary source of myelin in the adult CNS, and their dysfunction or loss underlies several diseases of both children and adults (Keirstead 2005). Dysmyelinating and demyelinating diseases are thus attractive targets for cell-based strategies, since they are in effect primarily caused by the loss of a single, relatively homogeneous cell type, the myelinating oligodendrocyte (Goldman et al. 2006). As mentioned above, OPCs are highly migratory, they can continue to expand and then terminally differentiate in response to local axon-derived cues. Indeed, transplantation studies have demonstrated the potential of transplanted OPCs and their capacity for remyelination in disease models (unpublished observations, Fig. 2, and Windrem et al. 2008).

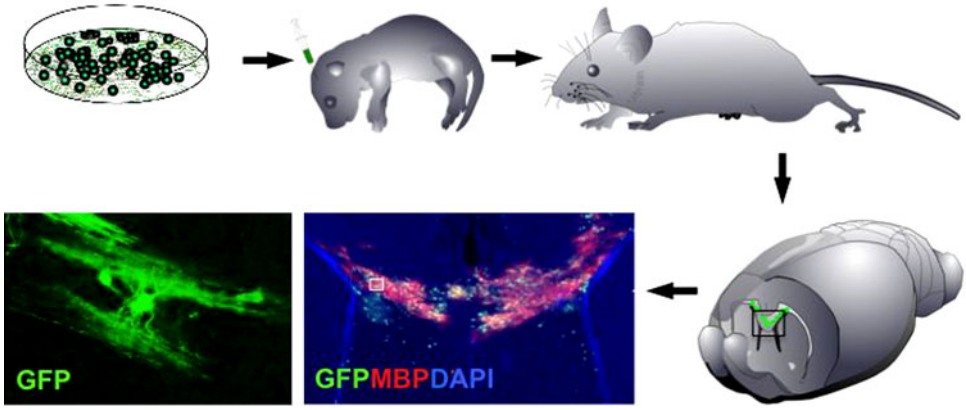

Fig. 2 Cell transplantation. Clockwise from *top left* cultured green fluorescent protein (*GFP*)-tagged oligodendrocyte precursors are transplanted into the lateral ventricles of newborn *shiverer* mice, which serve as a model of congenital leukodystrophy. The neurological benefits within recipients can be evaluated before their brains are analyzed by immunohistochemistry for GFP and myelin proteins such as MBP. GFP/MBP-expressing cells engraft and incorporate throughout the corpus callosum, with GFP^+ cells exhibiting the branched morphology of mature, myelinating oligodendrocytes

Myelinating Cell Types

The first reports of myelinating-cell transplantation used cells of the PNS, Schwann cells, to demonstrate that exogenously supplied cells are capable of forming myelin upon grafting (Aguayo et al. 1977; Aguayo et al. 1976; Blakemore 1977). Subsequent studies showed that grafts containing oligodendrocyte progenitors were also capable of myelinating focal areas of chemically induced demyelination and congenital CNS dysmyelination (Blakemore and Crang 1988; Crang and Blakemore 1989; Crang et al. 1991; Duncan et al. 1988; Gansmuller et al. 1986; Lachapelle et al. 1983). Since that time, investigators have shown a wide range of cell types capable of differentiating into myelin-producing cells upon transplantation: $O2A^+$ cells from optic nerve cultures, olfactory ensheathing cells, neural stem cells (NSCs) cultured as neurospheres from the olfactory bulb, forebrain subventricular zone, and spinal cord of developing and adult CNS, oligospheres, $A2B5^+$ cells, and MOG^+ and $PDGFR^+$ oligodendrocyte lineage restricted precursors (Crang et al. 2004; Franklin and Blakemore 1997; Gibney and Mcdermott 2009; Groves et al. 1993; Milward et al. 1997; Pluchino et al. 2003; Rao 1999; Sasaki et al. 2006; Windrem et al. 2004).

The capabilities of these various cell types to engraft and successfully restore myelin are quite different. For example, multipotent NSCs cultured as neurospheres isolated from fetal or adult CNS mainly differentiate into astrocytes and only a few oligodendrocytes when transplanted into spinal cord injury models (Chow et al. 2000; Vroemen et al. 2003). $A2B5^+$ progenitors isolated from embryonic or adult white matter generate almost equal numbers of astrocytes and oligodendrocytes upon transplantation into *shiverer* mice (Windrem et al. 2004).

The capacity of transplanted cells to migrate and myelinate depends upon the developmental stage of the source tissue. Transplantation of oligodendrocyte progenitors collected at different developmental stages has demonstrated that embryonic oligodendrocyte progenitors may be more adept at widespread remyelination than postnatal progenitors. When embryonic, neonatal, and adult canine mixed glial populations were transplanted into neonatal hypomyelinated *shaking pups*, all cells myelinated and survived long-term. However, cells that did not yet express markers of OPC differentiation obtained from fetal pups at the onset of canine myelination led to the most extensive myelination. Presumably, the fetal progenitors cells were more capable of widespread migration along axonal tracts than their postnatal counterparts (Archer et al. 1997). These results have been confirmed using human fetal and adult $A2B5^+$ glial progenitors. Fetal progenitors myelinate more extensively than adult cells, although with a relatively delayed onset of myelin production, that may be due to ongoing proliferation and migration of these cells (Windrem et al. 2004). Furthermore, the data suggest that oligodendrocyte progenitors from humans and canines are able to migrate more extensively and exhibit more robust myelination compared to their rodent counterparts, most likely reflecting the longer periods of oligodendrocyte proliferation, migration and maturation of higher order mammals (Windrem et al. 2008).

Migration, proliferation, and differentiation of various precursor types have not been quantified extensively, and additional studies are required to clarify the intrinsic characteristics of human and rodent oligodendrocytes progenitors. However, the enhanced proliferative ability of fetal cells versus onset of differentiation and myelin formation are important factors when considering therapeutic

applications. Ongoing proliferation allows production of more OPCs in the CNS of recipients and therefore could allow for more extensive engraftment and myelin production. On the other hand, significant delay before the onset of myelination by transplanted fetal cells limits early recovery of the white matter disorder. Notably, OPCs from adult human subcortical white matter transplanted into *shiverer* mice generate oligodendrocytes more efficiently and ensheathed more recipient axons per donor cell than did fetal OPCs (Windrem et al. 2004). Similarly, adult rodent OPCs leads to faster recovery of locomotion than embryonic counterpart after spinal cord injury (Cao et al. 2005). Thus, adult OPCs might be more appropriate for remyelination of small, localized white matter lesions while fetal OPCs are more applicable for widespread demyelinating injuries common in leukodystrophies.

Transplant Animal Models

In general, recipients of transplanted cells fall into two broad categories: (1) normal neonatal or adult animals and (2) animals with inherited or experimentally-induced white matter disorders.

The introduction of OPCs into normal animals can elucidate aspects of oligodendrocyte biology that would not otherwise be ascertainable. For example, the first wave of oligodendrocytes generated in the embryonic forebrain are thought to be at a competitive disadvantage since almost all oligodendrocytes in adult animals are progeny of later-born OPCs (Kessaris et al. 2006). However, transplantation of the earliest born embryonic progenitors into newborn wild-type mice showed that they are able to survive and persist into adulthood (Petryniak et al. 2007). This suggests that embryonic OPCs are not destined for death or intrinsically disadvantaged compared to postnatal OPCs, as previously suggested. Importantly, these results also confirm that embryonic OPCs are able to differentiate and incorporate long-term in transplant recipients and compete with endogenous OPCs for limited mitogenic factors or target axons.

OPCs can be tagged before transplantation, and then visualized in recipient animals (Fig. 2). The ability to track and examine a small number of oligodendrocytes in a normal environment allows straightforward assessment of migration from the transplant site, and morphological characterization of the oligodendrocytes, including the myelinating processes, nodes of Ranvier, and intracellular components (Fig. 2). This approach was used to study the ability of green fluorescent protein-labeled spinal cord NSCs to survive, migrate, proliferate, and differentiate in the intact adult spinal cord, and also allowed direct comparison of neurosphere versus dissociated cell grafts. In this setting, $\sim$75% of spinal cord NSCs differentiated into oligodendrocytes, typically within 1 week of transplant. Cells transplanted as neurospheres show improved proliferation and survival compared to dissociated cells (Mothe et al. 2008).

Several animal models of white matter disorders have been used as recipients for transplanted cells. Focal white matter lesions can be induced by injection of toxins such as lysolecithin and ethidium bromide into white matter tracts (Merrill 2009). Diffuse CNS demyelination can be stimulated by a 4 to 6-week diet of cuprizone. There are several models of spinal cord injury and focal ischemia that lead to demyelination with partial sparing of axons. Spinal cord lesions can be created using weight drop contusion and ischemic insult can be produced by a 90 min middle cerebral occlusion (Merrill 2009). Experimental autoimmune encephalomyelitis (EAE) is an autoimmune mouse model of progressive relapsing-remitting demyelination similar to MS. It is produced by active immunization of rats, mice, or marmosets using whole brain or spinal cord homogenates or purified myelin proteins (i.e. PLP, MOG, or MBP). Susceptibility and severity of demyelination is dependant upon specific major histocompatibility haplotypes, and therefore varies between different rodent strains (Skundric 2005).

Several mouse models of leukodystrophies are commonly used as recipients: *shiverer* mice, which lack MBP, are the most common. *Jimpy* mice, which lack Plp and represent a mouse model of PMD, exhibit a more severe CNS phenotype, and usually die by 30 days. Thus, while more appropriate as a specific model of a human disorder, the short life span of *jimpy* could preclude its practical use in pre-clinical studies that require a longer time for grafts to function in myelination (Windrem et al. 2008). *Twitcher* mice, a model of Krabbe's disease or globoid cell leukodystrophy, carry a mutation in the *GalC* gene, and exhibit oligodendrocyte loss in the CNS by 3 weeks of age.

Functional recovery and/or prolonged survival has been demonstrated with transplantation in different rodent models of human disorders, including spinal cord injury, EAE, PMD, and Krabbes disease (Einstein et al. 2006; Learish et al. 1999; Lee et al. 2005; Pluchino et al. 2003; Vroemen et al. 2003). In all these models, exogenous cells were shown to form compact myelin sheaths, although a direct comparison of different cell types and their efficiency to re-myelinate axonal tracts or restore function was not studied. Likely, the underlying pathophysiology of the white matter disorder needs to be taken into account and instruct the most appropriate cells type to use. The mechanism of injury may play an important role, as an inflammatory process leading to demyelination such as MS is quite different from a genetic hypomyelinating lesion of a leukodystrophy, and this is still different from an acute hypoxic or traumatic injury (such as spinal cord contusion)

where there is disruption or injury to multiple cellular components. Factors important for engraftment, the time course of myelination, OPC survival and functional recovery are likely to differ between a genetic absence of myelin formation and ongoing, inflammatory lesions. The progressive nature of many disorders, such as PMD or MS, involves dysregulation of homeostatic responses to initial demyelinating lesions over time. Therefore, the ability of cells to restore myelin and result in function recovery in different environments may vary. For example, bipotent OPCs from neonatal spinal cord differentiate into OPCs, but not astrocytes, when transplanted into contused and demyelinated spinal cords (Groves et al. 1993). In addition, cells may need to be engineered to not only myelinate, but also deliver an enzyme to endogenous oligodendrocytes to prevent ongoing demyelination, as would be required for treatment of Krabbe's disease (Pellegatta et al. 2006; Strazza et al. 2009).

Optimizing Cell-Transplantation Approaches

In order to be successful, transplanted OPCs must be able to recapitulate many aspects of oligodendrocyte development, including migration, axon recognition, differentiation, myelination, and long-term myelin maintenance. However, transplanted cells must perform these tasks in an environment very different than encountered during development. For example, growth factors such as sonic hedgehog (Lu et al. 2000) and guidance molecules such as semaphorin and plexins (Cohen et al. 2003) expressed during development are greatly diminished in the adult brain, the migratory distance travelled by engrafted cells is typically greater than during development, and downregulation of extracellular matrix components in the mature brain such as tenascin-C could impair differentiation and myelination (Garwood et al. 2004). Therefore, cells may need to be stimulated or altered depending on the intended therapeutic indication to improve expansion or allow for more rapid myelination. As outlined previously, multiple intrinsic and extrinsic factors are important for OPC survival and differentiation during development, and it will be critical for future studies to define the components necessary for exogenous OPC survival and differentiation. CNTF is a previously identified neurotrophic factor that promotes OPC survival and differentiation in vitro. Recently, it was reported that OPCs modified to express CNTF showed improved survival and remyelination when transplanted into injured spinal cord. Importantly, significantly more animals that received the modified OPCs showed functional improvement in hindlimb locomotor activity (Cao et al. 2010). Similarly, stimulation of the CNTF receptor system using treatment of NSCs in vitro with interleukin-6 increased the myelination capability of NSCs when transplanted into *shiverer* brain slices (Zhang et al. 2006). In addition, pre-treatment of NSCs with noggin, an antagonist of bone morphogenic protein signaling shown to enhance OPC differentiation, stimulates their capacity to myelinate when transplanted into the CNS of *shiverer* mice (Izrael et al. 2007).

During development, astrocytes and neurons release factors and activate intercellular signals that improve the survival of OPCs and enhance myelination. Thus, does a heterogeneous population of cells, inclusive of oligodendrocyte, astrocytic or neuronal precursors, improve engraftment? No direct comparison between purified OPC and NSC transplants has been reported to address this question. However, work in which multipotent neurospheres were transplanted in an EAE model showed robust remyelination, reduced axonal loss and glial scarring, and functional recovery (Pluchino et al. 2003). Notably, the majority of new OPCs in demyelinated regions were of endogenous origin, indicating that in addition to direct remyelination, transplanted neural precursors also act as regulators of endogenous oligodendroglia and of reactive astrogliosis. Mesenchymal stem cells (MSCs) have been reported to promote oligodendrogenesis in slice culture and co-culture experiments (Li et al. 2009; Rivera et al. 2008), suggesting that directed differentiation of endogenous progenitors along the oligodendrocyte-lineage by transplanted cells may be another general mechanism by which myelination could be improved. Caution is warranted, however, since production of astrocytes or neurons by multipotent transplanted cells or non-CNS cell types by MSCs may not be beneficial, as in spinal cord transplants where excessive astrocyte differentiation results in allodynia (Hofstetter et al. 2005). In these cases, the application or pre-treatment of OPC cultures with factors normally supplied by astrocytes or neurons, when identified, might be preferable.

An important aspect of cell-replacement paradigms that needs to be addressed in future studies is that cells not only must retain the ability to form compact myelin, but to produce myelin sufficiently similar to "normal" myelin in sheath length, nodes of Ranvier, myelin thickness, myelin composition and ability to maintain axonal health. Further comparisons to cells engrafted during normal development may be necessary to determine how appropriately cells are able to myelinate. Thus far, comparison of transplanted cells to endogenous remyelination found that g-ratio and nodal frequency were similar, although less than typical of normal oligodendrocytes (O'Leary and Blakemore 1997). Myelin sheath thickness gradually increased with time but did not return to normal within a 12-month period. One month after transplantation, the number of lamellae surrounding remyelinated axons was about the same for large and small diameter axons and thus there was no significant correlation between axon diameter and myelin sheath

thickness. Myelin sheath thickness increased marginally by 6 and 12 months and this was accompanied by the development of a significant and minor correlation between axon diameter and myelin sheath thickness. The extent of remyelination by transplanted OPCs was similar to spontaneous remyelination observed in cuprizone or lysolecithin treated animals (O'Leary and Blakemore 1997).

Therapeutic Applications

Several hurdles must be overcome before cell-transplantation might be used as a successful therapeutic intervention for white matter disorders. The best cell type for transplantation, how cells integrate and differentiate in vivo, and the most effective transplantation paradigm are all unanswered questions.

Furthermore, a significant limitation for therapeutics will be the ability to obtain sufficient numbers of cells at the appropriate stage of differentiation to result in robust repair. Expansion of cells in culture may modulate their ability to engraft, depending on the media utilized. Whether cells expanded in culture retain the same capabilities to myelinate as freshly harvested progenitors is also unclear. Encouragingly, an immortalized OPC-like cell line, rat CG4 cells, can be passaged up to 48 times in culture without a significant decrease in engraftment or myelin production when transplanted into the myelin deficient rat (Tontsch et al. 1994). Still, one must be cautious in interpretation of these results until a functional assessment of the transplanted cells is performed. Nevertheless, several other studies demonstrate that the ability of OPCs to engraft and myelinate decreases over time in culture (Feltri et al. 1992; Groves et al. 1993; Trotter et al. 1993). Culturing oligodendrocyte-lineage cells may make them less likely to myelinate when transplanted, as they lose their proliferative ability and differentiate in vitro (Richter and Roskams 2008).

Geron corporation and their collaborators have generated almost pure populations of OPCS from human embryonic stem cells (Nistor et al. 2004). The OPCs can form myelinating oligodendrocytes when transplanted into shiverer mice. In January of 2009, Geron began the first human clinical trial using these embryonic stem cell derived OPCs in a Phase I study as a potential therapy for acute spinal cord injury.

With the advent of induced pluripotent stem cells (iPSCs), limitations of quantity and differentiation capacity might be overcome as cells can be maintained in a pluripotent proliferative state for long periods of time. The proper culture conditions to differentiate iPSCs into oligodendrocytes capable of robust engraftment and myelination are under active investigation (Faulkner and Keirstead 2005; Hu et al. 2009; Keirstead et al. 2005; Nistor et al. 2004; Sharp et al. 2009). Cell-replacement using OPCs derived from iPSCs generated from patients have the exciting possibility of long-term engraftment without immunological rejection. In addition, if necessary, iPSC cells could be genetically modified to deliver or express factors that are lacking in the patients or would improve myelin replacement.

Human OPCs derived from unexpected sources, including haemopoietic stem cells and human fetal MSCs, could also serve as candidates for cell-transplantation therapies (reviewed by Kemp et al. 2010). MSCs can be derived from various sources, including blood, liver, and bone marrow. Intriguingly, human fetal MSCs derived from first trimester blood can be differentiated into a small population of oligodendrocyte-like cells in vitro when exposed to an oligodendrocyte differentiation medium previously used to induce highly enriched OPC cultures from NSCs (Chen et al. 2007; Kennea et al. 2009). Additional research will be required to determine the functionality of MSC-derived oligodendrocytes before they can be utilized as a therapeutic source of OPCs.

Towards Implementation of Cell-Based Therapies: Future Prospects and Concerns Regarding Human Clinical Trials

Although this review has focused on various lines of evidence that suggest promise for the use of cell-based therapies in demyelinating disease conditions in humans, there are significant concerns regarding use of therapeutic cell-based approaches in human studies, particularly in non-fatal disorders (Burt et al. 2008; Hyun et al. 2008), or when convincing pre-clinical data is lacking (Patoine 2009). Rigorously controlled pre-clinical and human clinical Phase I studies are essential to evaluate the safety of cell therapies. The recent report of tumors developing several years after injection of poorly characterized human fetal brain-derived cells into a patient with ataxia telangiectasia has heightened anxiety about potential for neoplasia (Amariglio et al. 2009), in addition to concerns regarding requirements for long-term immunosuppression. Because NSC treatment options are limited in western countries, we have seen an increase in numbers of so called "stem cell tourists", seeking stem-cell based therapies for neurological disorders with questionable oversight in locations such as China, Russia and India (Kiatpongsan and Sipp 2009). Unfortunately, these poorly defined treatments are not adequately documented and do not allow reliable evaluation of their safety or efficacy, and have been characterized as offering more "hype" than "hope" (Ryan et al. 2010). In the United States, clinical trials are underway to examine the safety of human fetal neural progenitor transplantation into patients with the fatal "connatal" form

of PMD as well as Batten's disease, another fatal disorder (Clinical Trials Identifier NCT01005004). Weighing the potential for cell-based therapies with life-long management or potential decreased quality of patient's lives, there is a significant responsibility for institutions to carefully consider the risks and benefits to patients with non-fatal, yet progressive, conditions such as MS, spinal cord injury and cerebral palsy (Duncan et al. 2008).

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References

Agius E, Soukkarieh C, Danesin C et al (2004) Converse control of oligodendrocyte and astrocyte lineage development by Sonic hedgehog in the chick spinal cord. Dev Biol 270:308–321

Aguayo AJ, Charron L, Bray GM (1976) Potential of Schwann cells from unmyelinated nerves to produce myelin: a quantitative ultrastructural and radiographic study. J Neurocytol 5:565–573

Aguayo AJ, Attiwell M, Trecarten J et al (1977) Abnormal myelination in transplanted Trembler mouse Schwann cells. Nature 265:73–75

Allen NJ, Barres BA (2009) Neuroscience: Glia—more than just brain glue. Nature 457:675–677

Amariglio N, Hirshberg A, Scheithauer BW et al (2009) Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. PLoS Med 6:e1000029

Archer DR, Cuddon PA, Lipsitz D et al (1997) Myelination of the canine central nervous system by glial cell transplantation: a model for repair of human myelin disease. Nat Med 3:54–59

Baas D, Bourbeau D, Sarlieve LL et al (1997) Oligodendrocyte maturation and progenitor cell proliferation are independently regulated by thyroid hormone. Glia 19:324–332

Barres BA, Hart IK, Coles HS et al (1992) Cell death and control of cell survival in the oligodendrocyte lineage. Cell 70:31–46

Barres BA, Jacobson MD, Schmid R et al (1993a) Does oligodendrocyte survival depend on axons? Curr Biol 3:489–497

Barres BA, Schmid R, Sendnter M et al (1993b) Multiple extracellular signals are required for long-term oligodendrocyte survival. Development 118:283–295

Barres BA, Lazar MA, Raff MC (1994) A novel role for thyroid hormone, glucocorticoids and retinoic acid in timing oligodendrocyte development. Development 120:1097–1108

Bauer NG, Richter-Landsberg C, Ffrench-Constant C (2009) Role of the oligodendroglial cytoskeleton in differentiation and myelination. Glia 57:1691–1705

Baumann N, Pham-Dinh D (2001) Biology of oligodendrocyte and myelin in the mammalian central nervous system. Physiol Rev 81:871–927

Blakemore WF (1977) Remyelination of CNS axons by Schwann cells transplanted from the sciatic nerve. Nature 266:68–69

Blakemore WF, Crang AJ (1988) Extensive oligodendrocyte remyelination following injection of cultured central nervous system cells into demyelinating lesions in adult central nervous system. Dev Neurosci 10:1–11

Bradl M, Lassmann H (2010) Oligodendrocytes: biology and pathology. Acta Neuropathol 119:37–53

Bremer J, Baumann F, Tiberi C et al (2010) Axonal prion protein is required for peripheral myelin maintenance. Nat Neurosci 13:310–318

Burt RK, Loh Y, Pearce W et al (2008) Clinical applications of blood-derived and marrow-derived stem cells for nonmalignant diseases. JAMA 299:925–936

Butt AM, Kiff J, Hubbard P et al (2002) Synantocytes: new functions for novel NG2 expressing glia. J Neurocytol 31:551–565

Cai J, Qi Y, Hu X et al (2005) Generation of oligodendrocyte precursor cells from mouse dorsal spinal cord independent of Nkx6 regulation and Shh signaling. Neuron 45:41–53

Campagnoni AT, Skoff RP (2001) The pathobiology of myelin mutants reveal novel biological functions of the MBP and PLP genes. Brain Pathol 11:74–91

Cao XY, Jiang XM, Dou ZH et al (1994) Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. N Engl J Med 331:1739–1744

Cao Q, Xu XM, Devries WH et al (2005) Functional recovery in traumatic spinal cord injury after transplantation of multi-neurotrophin-expressing glial-restricted precursor cells. J Neurosci 25:6947–6957

Cao Q, He Q, Wang Y et al (2010) Transplantation of ciliary neurotrophic factor-expressing adult oligodendrocyte precursor cells promotes remyelination and functional recovery after spinal cord injury. J Neurosci 30:2989–3001

Chen Y, Balasubramaniyan V, Peng J et al (2007) Isolation and culture of rat and mouse oligodendrocyte precursor cells. Nat Protoc 2:1044–1051

Chomiak T, Hu B (2009) What is the optimal value of the g-ratio for myelinated fibers in the rat CNS? A theoretical approach. PLoS ONE 4:e7754

Chow SY, Moul J, Tobias CA et al (2000) Characterization and intraspinal grafting of EGF/bFGF-dependent neurospheres derived from embryonic rat spinal cord. Brain Res 874:87–106

Cohen RI, Rottkamp DM, Maric D et al (2003) A role for semaphorins and neuropilins in oligodendrocyte guidance. J Neurochem 85:1262–1278

Compston A, Coles A (2002) Multiple sclerosis. Lancet 359:1221–1231

Connor JR, Menzies SL (1996) Relationship of iron to oligodendrocytes and myelination. Glia 17:83–93

Cotter L, Ozcelik M, Jacob C et al (2010) Dlg1-PTEN interaction regulates myelin thickness to prevent damaging peripheral nerve overmyelination. Science 328:1415–1418

Crang AJ, Blakemore WF (1989) The effect of the number of oligodendrocytes transplanted into X-irradiated, glial-free lesions on the extent of oligodendrocyte remyelination. Neurosci Lett 103:269–274

Crang AJ, Franklin RJ, Blakemore WF et al (1991) Transplantation of normal and genetically engineered glia into areas of demyelination. Ann N Y Acad Sci 633:563–565

Crang AJ, Gilson JM, Li WW et al (2004) The remyelinating potential and in vitro differentiation of MOG-expressing oligodendrocyte precursors isolated from the adult rat CNS. Eur J Neurosci 20:1445–1460

de Castro F, Bribian A (2005) The molecular orchestra of the migration of oligodendrocyte precursors during development. Brain Res Brain Res Rev 49:227–241

Debruin LS, Harauz G (2007) White matter rafting—membrane microdomains in myelin. Neurochem Res 32:213–228

Delange F (2000) The role of iodine in brain development. Proc Nutr Soc 59:75–79

Dugas JC, Cuellar TL, Scholze A et al (2010) Dicer1 and miR-219 are required for normal oligodendrocyte differentiation and myelination. Neuron 65:597–611

Duncan ID, Hammang JP, Jackson KF et al (1988) Transplantation of oligodendrocytes and Schwann cells into the spinal cord of the myelin-deficient rat. J Neurocytol 17:351–360

Duncan ID, Goldman S, Macklin WB et al (2008) Stem cell therapy in multiple sclerosis: promise and controversy. Mult Scler 14:541–546

Ebner S, Dunbar M, McKinnon RD (2000) Distinct roles for PI3K in proliferation and survival of oligodendrocyte progenitor cells. J Neurosci Res 62:336–345

Einstein O, Grigoriadis N, Mizrachi-Kol R et al (2006) Transplanted neural precursor cells reduce brain inflammation to attenuate chronic experimental autoimmune encephalomyelitis. Exp Neurol 198:275–284

Faulkner J, Keirstead H (2005) Human embryonic stem cell-derived oligodendrocyte progenitors for the treatment of spinal cord injury. Transpl Immunol 15:131–142

Feldmann A, Winterstein C, White R et al (2009) Comprehensive analysis of expression, subcellular localization, and cognate pairing of SNARE proteins in oligodendrocytes. J Neurosci Res 87:1760–1772

Feltri ML, Scherer SS, Wrabetz L et al (1992) Mitogen-expanded Schwann cells retain the capacity to myelinate regenerating axons after transplantation into rat sciatic nerve. Proc Natl Acad Sci USA 89:8827–8831

Flores AI, Mallon BS, Matsui T et al (2000) Akt-mediated survival of oligodendrocytes induced by neuregulins. J Neurosci 20:7622–7630

Franklin RJ, Blakemore WF (1997) Transplanting oligodendrocyte progenitors into the adult CNS. J Anat 190(Pt 1):23–33

Franklin RJM, Ffrench-Constant C (2008) Remyelination in the CNS: from biology to therapy. Nat Rev Neurosci 9:839–855

Frost EE, Zhou Z, Krasnesky K et al (2009) Initiation of oligodendrocyte progenitor cell migration by a PDGF-A activated extracellular regulated kinase (ERK) signaling pathway. Neurochem Res 34:169–181

Gansmuller A, Lachapelle F, Baron-Van Evercooren A et al (1986) Transplantations of newborn CNS fragments into the brain of shiverer mutant mice: extensive myelination by transplanted oligodendrocytes. II. Electron microscopic study. Dev Neurosci 8:197–207

Garwood J, Garcion E, Dobbertin A et al (2004) The extracellular matrix glycoprotein Tenascin-C is expressed by oligodendrocyte precursor cells and required for the regulation of maturation rate, survival and responsiveness to platelet-derived growth factor. Eur J Neurosci 20:2524–2540

German DC, Liang CL, Song T et al (2002) Neurodegeneration in the Niemann-Pick C mouse: glial involvement. Neuroscience 109:437–450

Gibney SM, Mcdermott KW (2009) Sonic hedgehog promotes the generation of myelin proteins by transplanted oligosphere-derived cells. J Neurosci Res 87:3067–3075

Goldman SA, Lang J, Roy N et al (2006) Progenitor cell-based myelination as a model for cell-based therapy of the central nervous system. Ernst Schering Res Found Workshop 60:195–213

Gould RM, Freund CM, Palmer F et al (2000) Messenger RNAs located in myelin sheath assembly sites. J Neurochem 75:1834–1844

Gravel M, Peterson J, Yong VW et al (1996) Overexpression of 2′,3′-cyclic nucleotide 3′-phosphodiesterase in transgenic mice alters oligodendrocyte development and produces aberrant myelination. Mol Cell Neurosci 7:453–466

Groves AK, Barnett SC, Franklin RJ et al (1993) Repair of demyelinated lesions by transplantation of purified O-2A progenitor cells. Nature 362:453–455

Harauz G, Ladizhansky V, Boggs J (2009) Structural polymorphism and multifunctionality of myelin basic protein. Biochemistry 48:8094–8104

Harrington EP, Zhao C, Fancy SP et al (2010) Oligodendrocyte PTEN is required for myelin and axonal integrity, not remyelination. Ann Neurol 68:703–716

Hauser S, Oksenberg J (2006) The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron 52:61–76

He Y, Dupree J, Wang J et al (2007) The transcription factor Yin Yang 1 is essential for oligodendrocyte progenitor differentiation. Neuron 55:217–230

Hofstetter CP, Holmström NA, Lilja JA et al (2005) Allodynia limits the usefulness of intraspinal neural stem cell grafts; directed differentiation improves outcome. Nat Neurosci 8:346–353

Hu BY, Du ZW, Zhang SC (2009) Differentiation of human oligodendrocytes from pluripotent stem cells. Nat Protoc 4:1614–1622

Hyun I, Lindvall O, Ahrlund-Richter L et al (2008) New ISSCR guidelines underscore major principles for responsible translational stem cell research. Cell Stem Cell 3:607–609

Ibarrola N, Rodriguez-Pena A (1997) Hypothyroidism coordinately and transiently affects myelin protein gene expression in most rat brain regions during postnatal development. Brain Res 752:285–293

Ishibashi T, Dakin KA, Stevens B et al (2006) Astrocytes promote myelination in response to electrical impulses. Neuron 49:823–832

Ishii A, Dutta R, Wark GM et al (2009) Human myelin proteome and comparative analysis with mouse myelin. Proc Natl Acad Sci USA 106:14605–14610

Izrael M, Zhang P, Kaufman R et al (2007) Human oligodendrocytes derived from embryonic stem cells: effect of noggin on phenotypic differentiation in vitro and on myelination in vivo. Mol Cell Neurosci 34:310–323

Jahn O, Tenzer S, Werner HB (2009) Myelin proteomics: molecular anatomy of an insulating sheath. Mol Neurobiol 40:55–72

John GR, Shankar SL, Shafit-Zagardo B et al (2002) Multiple sclerosis: re-expression of a developmental pathway that restricts oligodendrocyte maturation. Nat Med 8:1115–1121

Karim SA, Barrie JA, McCulloch MC et al (2007) PLP overexpression perturbs myelin protein composition and myelination in a mouse model of Pelizaeus-Merzbacher disease. Glia 55:341–351

Keirstead HS (2005) Stem cells for the treatment of myelin loss. Trends Neurosci 28:677–683

Keirstead HS, Nistor G, Bernal G et al (2005) Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. J Neurosci 25:4694–4705

Kemp K, Mallam E, Scolding N et al (2010) Stem cells in genetic myelin disorders. Regen Med 5:425–439

Kennea N, Waddington S, Chan J et al (2009) Differentiation of human fetal mesenchymal stem cells into cells with an oligodendrocyte phenotype. Cell Cycle 8:1069–1079

Kessaris N, Fogarty M, Iannarelli P et al (2006) Competing waves of oligodendrocytes in the forebrain and postnatal elimination of an embryonic lineage. Nat Neurosci 9:173–179

Kiatpongsan S, Sipp D (2009) Medicine. Monitoring and regulating offshore stem cell clinics. Science 323:1564–1565

Lachapelle F, Gumpel M, Baulac M et al (1983) Transplantation of CNS fragments into the brain of shiverer mutant mice: extensive myelination by implanted oligodendrocytes. I. Immunohistochemical studies. Dev Neurosci 6:325–334

Larocca JN, Rodriguez-Gabin AG (2002) Myelin biogenesis: vesicle transport in oligodendrocytes. Neurochem Res 27:1313–1329

Learish RD, Brüstle O, Zhang SC et al (1999) Intraventricular transplantation of oligodendrocyte progenitors into a fetal

myelin mutant results in widespread formation of myelin. Ann Neurol 46:716–722
Lee WC, Courtenay A, Troendle FJ et al (2005) Enzyme replacement therapy results in substantial improvements in early clinical phenotype in a mouse model of globoid cell leukodystrophy. FASEB J 19:1549–1551
Li QM, Fu YM, Shan ZY et al (2009) MSCs guide neurite directional extension and promote oligodendrogenesis in NSCs. Biochem Biophys Res Commun 384:372–377
Linker RA, Brechlin P, Jesse S et al (2009) Proteome profiling in murine models of multiple sclerosis: identification of stage specific markers and culprits for tissue damage. PLoS One 4:e7624
Lu QR, Yuk D, Alberta JA et al (2000) Sonic hedgehog-regulated oligodendrocyte lineage genes encoding bHLH proteins in the mammalian central nervous system. Neuron 25:317–329
Maier O, Hoekstra D, Baron W (2008) Polarity development in oligodendrocytes: sorting and trafficking of myelin components. J Mol Neurosci 35:35–53
Martini R, Schachner M (1997) Molecular bases of myelin formation as revealed by investigations on mice deficient in glial cell surface molecules. Glia 19:298–310
McTigue DM, Tripathi RB (2008) The life, death, and replacement of oligodendrocytes in the adult CNS. J Neurochem 107:1–19
Merrill JE (2009) In vitro and in vivo pharmacological models to assess demyelination and remyelination. Neuropsychopharmacology 34:55–73
Milward EA, Lundberg CG, Ge B et al (1997) Isolation and transplantation of multipotential populations of epidermal growth factor-responsive, neural progenitor cells from the canine brain. J Neurosci Res 50:862–871
Miyamoto Y, Yamauchi J, Tanoue A (2008) Cdk5 phosphorylation of WAVE2 regulates oligodendrocyte precursor cell migration through nonreceptor tyrosine kinase Fyn. J Neurosci 28:8326–8337
Montag D, Giese KP, Bartsch U et al (1994) Mice deficient for the myelin-associated glycoprotein show subtle abnormalities in myelin. Neuron 13:229–246
Mothe AJ, Kulbatski I, Parr A et al (2008) Adult spinal cord stem/progenitor cells transplanted as neurospheres preferentially differentiate into oligodendrocytes in the adult rat spinal cord. Cell Transplant 17:735–751
Murtie JC, Macklin WB, Corfas G (2007) Morphometric analysis of oligodendrocytes in the adult mouse frontal cortex. J Neurosci Res 85:2080–2086
Narayanan SP, Flores AI, Wang F et al (2009) Akt signals through the mammalian target of rapamycin pathway to regulate CNS myelination. J Neurosci 29:6860–6870
Nave K-A, Salzer JL (2006) Axonal regulation of myelination by neuregulin 1. Curr Opin Neurobiol 16:492–500
Nave KA, Trapp BD (2008) Axon-glial signaling and the glial support of axon function. Annu Rev Neurosci 31:535–561
Nishiyama A, Komitova M, Suzuki R et al (2009) Polydendrocytes (NG2 cells): multifunctional cells with lineage plasticity. Nat Rev Neurosci 10:9–22
Nistor GI, Totoiu MO, Haque N et al (2004) Human embryonic stem cells differentiate into oligodendrocytes in high purity and myelinate after spinal cord transplantation. Glia 49:385–396
O'Leary MT, Blakemore WF (1997) Use of a rat Y chromosome probe to determine the long-term survival of glial cells transplanted into areas of CNS demyelination. J Neurocytol 26:191–206
Padovani-Claudio DA, Liu L, Ransohoff RM et al (2006) Alterations in the oligodendrocyte lineage, myelin, and white matter in adult mice lacking the chemokine receptor CXCR2. Glia 54:471–483
Paez PM, Fulton DJ, Spreuer V et al (2009) Golli myelin basic proteins regulate oligodendroglial progenitor cell migration through voltage-gated Ca^{2+} influx. J Neurosci 29:6663–6676
Park J, Liu B, Chen T et al (2008) Disruption of Nectin-like 1 cell adhesion molecule leads to delayed axonal myelination in the CNS. J Neurosci 28:12815–12819
Pastores GM (2009) Krabbe disease: an overview. Int J Clin Pharmacol Ther 47(Suppl 1):S75–S81
Patoine B (2009) NerveCenter: media focus on 'miracle cure' for cerebral palsy pits science vs. hype. Ann Neurol 66:A9–A11
Peake KB, Vance JE (2010) Defective cholesterol trafficking in Niemann-Pick C-deficient cells. FEBS Lett 584:2731–2739
Pellegatta S, Tunici P, Poliani PL et al (2006) The therapeutic potential of neural stem/progenitor cells in murine globoid cell leukodystrophy is conditioned by macrophage/microglia activation. Neurobiol Dis 21:314–323
Pellissier F, Gerber A, Bauer C et al (2007) The adhesion molecule Necl-3/SynCAM-2 localizes to myelinated axons, binds to oligodendrocytes and promotes cell adhesion. BMC Neurosci 8:90
Petryniak MA, Potter GB, Rowitch DH et al (2007) Dlx1 and Dlx2 control neuronal versus oligodendroglial cell fate acquisition in the developing forebrain. Neuron 55:417–433
Pfeiffer SE, Warrington AE, Bansal R (1993) The oligodendrocyte and its many cellular processes. Trends Cell Biol 3:191–197
Pluchino S, Quattrini A, Brambilla E et al (2003) Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. Nature 422:688–694
Poliak S, Peles E (2003) The local differentiation of myelinated axons at nodes of Ranvier. Nat Rev Neurosci 4:968–980
Rao MS (1999) Multipotent and restricted precursors in the central nervous system. Anat Rec 257:137–148
Rasband MN, Tayler J, Kaga Y et al (2005) CNP is required for maintenance of axon-glia interactions at nodes of Ranvier in the CNS. Glia 50:86–90
Readhead C, Hood L (1990) The dysmyelinating mouse mutations shiverer (shi) and myelin deficient (shimld). Behav Genet 20:213–234
Richter MW, Roskams AJ (2008) Olfactory ensheathing cell transplantation following spinal cord injury: hype or hope? Exp Neurol 209:353–367
Rivera FJ, Kandasamy M, Couillard-Despres S et al (2008) Oligodendrogenesis of adult neural progenitors: differential effects of ciliary neurotrophic factor and mesenchymal stem cell derived factors. J Neurochem 107:832–843
Rodríguez-Peña A (1999) Oligodendrocyte development and thyroid hormone. J Neurobiol 40:497–512
Romanelli RJ, Mahajan KR, Fulmer CG et al (2009) Insulin-like growth factor-I-stimulated Akt phosphorylation and oligodendrocyte progenitor cell survival require cholesterol-enriched membranes. J Neurosci Res 87:3369–3377
Rosenberg SS, Kelland EE, Tokar E et al (2008) The geometric and spatial constraints of the microenvironment induce oligodendrocyte differentiation. Proc Natl Acad Sci USA 105:14662–14667
Rowitch DH (2004) Glial specification in the vertebrate neural tube. Nat Rev Neurosci 5:409–419
Royland JE, Wiggins RC, Konat GW (1992) Myelin isolation: comparison of sedimentation and flotation techniques. Neurochem Int 21:171–175
Ryan KA, Sanders AN, Wang DD et al (2010) Tracking the rise of stem cell tourism. Regen Med 5:27–33
Sabri MI, Bone AH, Davison AN (1974) Turnover of myelin and other structural proteins in the developing rat brain. Biochem J 142:499–507
Saher G, Brugger B, Lappe-Siefke C et al (2005) High cholesterol level is essential for myelin membrane growth. Nat Neurosci 8:468–475
Sarlième LL, Rodríguez-Peña A, Langley K (2004) Expression of thyroid hormone receptor isoforms in the oligodendrocyte lineage. Neurochem Res 29:903–922

Sarret C, Combes P, Micheau P et al (2010) Novel neuronal proteolipid protein isoforms encoded by the human myelin proteolipid protein 1 gene. Neuroscience 166:522–538

Sasaki M, Black JA, Lankford KL et al (2006) Molecular reconstruction of nodes of Ranvier after remyelination by transplanted olfactory ensheathing cells in the demyelinated spinal cord. J Neurosci 26:1803–1812

Schafer DP, Rasband MN (2006) Glial regulation of the axonal membrane at nodes of Ranvier. Curr Opin Neurobiol 16:508–514

Sharp J, Frame J, Siegenthaler M et al (2009) Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants improve recovery after cervical spinal cord injury. Stem Cells 28:152–163

Sherman DL, Brophy PJ (2005) Mechanisms of axon ensheathment and myelin growth. Nat Rev Neurosci 6:683–690

Simpson PB, Armstrong RC (1999) Intracellular signals and cytoskeletal elements involved in oligodendrocyte progenitor migration. Glia 26:22–35

Skundric DS (2005) Experimental models of relapsing-remitting multiple sclerosis: current concepts and perspective. Curr Neurovasc Res 2:349–362

Spassky N, de Castro F, Le Bras B et al (2002) Directional guidance of oligodendroglial migration by class 3 semaphorins and netrin-1. J Neurosci 22:5992–6004

Steinman L, Martin R, Bernard C et al (2002) Multiple sclerosis: deeper understanding of its pathogenesis reveals new targets for therapy. Annu Rev Neurosci 25:491–505

Stevens B, Porta S, Haak LL et al (2002) Adenosine: a neuron-glial transmitter promoting myelination in the CNS in response to action potentials. Neuron 36:855–868

Storch MK, Stefferl A, Brehm U et al (1998) Autoimmunity to myelin oligodendrocyte glycoprotein in rats mimics the spectrum of multiple sclerosis pathology. Brain Pathol 8:681–694

Strazza M, Luddi A, Carbone M et al (2009) Significant correction of pathology in brains of twitcher mice following injection of genetically modified mouse neural progenitor cells. Mol Genet Metab 97:27–34

Timsit S, Martinez S, Allinquant B et al (1995) Oligodendrocytes originate in a restricted zone of the embryonic ventral neural tube defined by DM-20 mRNA expression. J Neurosci 15:1012–1024

Tontsch U, Archer DR, Dubois-Dalcq M et al (1994) Transplantation of an oligodendrocyte cell line leading to extensive myelination. Proc Natl Acad Sci USA 91:11616–11620

Trapp BD, Moench T, Pulley M et al (1987) Spatial segregation of mRNA encoding myelin-specific proteins. Proc Natl Acad Sci USA 84:7773–7777

Trapp BD, Bernier L, Andrews SB et al (1988) Cellular and subcellular distribution of 2′,3′-cyclic nucleotide 3′-phosphodiesterase and its mRNA in the rat central nervous system. J Neurochem 51:859–868

Trotter J, Crang AJ, Schachner M et al (1993) Lines of glial precursor cells immortalised with a temperature-sensitive oncogene give rise to astrocytes and oligodendrocytes following transplantation into demyelinated lesions in the central nervous system. Glia 9:25–40

Trotter J, Karram K, Nishiyama A (2010) NG2 cells: properties, progeny and origin. Brain Res Rev 63:72–82

Tsai H-H, Frost E, To V et al (2002) The chemokine receptor CXCR2 controls positioning of oligodendrocyte precursors in developing spinal cord by arresting their migration. Cell 110:373–383

Tyler WA, Gangoli N, Gokina P et al (2009) Activation of the mammalian target of rapamycin (mTOR) is essential for oligodendrocyte differentiation. J Neurosci 29:6367–6378

Virchow R (1846) Ueber das granulirte Aussehen der Wandungen der Gehirnventrikel. Allg Z Psychiat 3:242–250

Vroemen M, Aigner L, Winkler J et al (2003) Adult neural progenitor cell grafts survive after acute spinal cord injury and integrate along axonal pathways. Eur J Neurosci 18:743–751

Waxman SG, Sims TJ (1984) Specificity in central myelination: evidence for local regulation of myelin thickness. Brain Res 292:179–185

Windrem M, Nunes M, Rashbaum W et al (2004) Fetal and adult human oligodendrocyte progenitor cell isolates myelinate the congenitally dysmyelinated brain. Nat Med 10:93–97

Windrem MS, Schanz SJ, Guo M et al (2008) Neonatal chimerization with human glial progenitor cells can both remyelinate and rescue the otherwise lethally hypomyelinated shiverer mouse. Cell Stem Cell 2:553–565

Ye F, Chen Y, Hoang T et al (2009) HDAC1 and HDAC2 regulate oligodendrocyte differentiation by disrupting the beta-catenin-TCF interaction. Nat Neurosci 12:829–838

Zalc B (2006) The acquisition of myelin: a success story. Novartis Found Symp 276:15–21 (discussion 21–25, 54–57, 275–281)

Zhang PL, Izrael M, Ainbinder E et al (2006) Increased myelinating capacity of embryonic stem cell derived oligodendrocyte precursors after treatment by interleukin-6/soluble interleukin-6 receptor fusion protein. Mol Cell Neurosci 31:387–398

Zhang Y, Argaw AT, Gurfein BT et al (2009) Notch1 signaling plays a role in regulating precursor differentiation during CNS remyelination. Proc Natl Acad Sci USA 106:19162–19167

Zhao X, He X, Han X et al (2010) MicroRNA-mediated control of oligodendrocyte differentiation. Neuron 65:612–626