

REVIEW

Oligodendrocyte Fate after Spinal Cord Injury

Akshata Almad,^{1,2} F. Rezan Sahinkaya,^{1,2} and Dana M. McTigue^{2,3}

¹Neuroscience Graduate Studies Program, ²Center for Brain and Spinal Cord Repair, ³Department of Neuroscience, Ohio State University, 788 Biomedical Research Tower, 460 W. 12th Ave., Columbus, Ohio 43210

Summary: Oligodendrocytes (OLs) are particularly susceptible to the toxicity of the acute lesion environment after spinal cord injury (SCI). They undergo both necrosis and apoptosis acutely, with apoptosis continuing at chronic time points. Loss of OLs causes demyelination and impairs axon function and survival. In parallel, a rapid and protracted OL progenitor cell proliferative response occurs, especially at the lesion borders. Proliferating and migrating OL progenitor cells differentiate into myelinating OLs, which remyelinate demyelinated axons starting at 2 weeks post-injury. The progression of OL lineage cells into mature OLs in the adult after injury recapitulates development to some degree, owing to the plethora of factors within the injury milieu. Although robust, this endogenous oligogenic response is insufficient against OL loss and demyelination. First, in this review we analyze the major

spatial-temporal mechanisms of OL loss, replacement, and myelination, with the purpose of highlighting potential areas of intervention after SCI. We then discuss studies on OL protection and replacement. Growth factors have been used both to boost the endogenous progenitor response, and in conjunction with progenitor transplantation to facilitate survival and OL fate. Considerable progress has been made with embryonic stem cell-derived cells and adult neural progenitor cells. For therapies targeting oligogenesis to be successful, endogenous responses and the effects of the acute and chronic lesion environment on OL lineage cells must be understood in detail, and in relation, the optimal therapeutic window for such strategies must also be determined. **Key Words:** Myelin, polydendrocytes, excitotoxicity, inflammation, transplant, macrophage.

INTRODUCTION

Trauma to the spinal cord results in massive tissue destruction and cellular damage at and around the injury site. The initial physical assault to the spinal cord causes vascular rupture, hemorrhage and necrosis of neurons and glia at the injury site. This is followed by “secondary injury cascades,” including blood-brain barrier breakdown, reduced blood flow and ischemia, excitotoxicity, free radical production, and immune cell infiltration [1]. These events result in continued loss of neurons and glia. This review will focus on mechanisms involved in loss of oligodendrocytes (OLs) after spinal cord injury (SCI), spontaneous replacement of endogenous OLs, and therapies targeted at protecting or replacing OLs.

SPINAL CORD INJURY AND OLIGODENDROCYTE LOSS

Rodent models of SCI have been used extensively to gain insight into the cellular pathology occurring after injury. Research in the 1990s revealed that OLs are quite susceptible to damage after SCI, and are lost to acute necrosis and acute/subacute apoptosis [2–6]. In a rat spinal contusion model, acute OL loss was detected within 15 minutes postinjury with continual loss occurring for 4 h [2, 5]. Similarly, in a mouse SCI model, OL numbers decreased within 24 h and steadily declined by 3 to 7 days postinjury (dpi) [7]. Prolonged OL apoptosis has been detected for at least 3 weeks following rat spinal contusion; dying cells were especially prominent in degenerating axon tracts rostral and caudal to the injury site [3, 8]. Apoptotic OLs have also been noted in tissue from nonhuman primates and human patients revealing that this phenomenon is common across multiple injury models and after human SCI [3, 9, 10].

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Address correspondence and reprint requests to: Dana M. McTigue Ph.D., Department of Neuroscience, Ohio State University, 788 Biomedical Research Tower, 460 W. 12th Ave., Columbus, OH 43210. E-mail: dana.mctigue@osumc.edu.

Early mechanisms of OL loss

Many factors in the acute lesion environment can be toxic to OLs. For instance, proteolytic enzymes released from necrotic cells or damaged vessels can digest cells and vascular structures, which potentiates damage and structural

compromise. Blood components can induce apoptosis and necrosis of cultured oligodendrocyte progenitor cells (OPCs), and at low concentrations can inhibit OPC proliferation and migration [11]. Ischemia and reperfusion are also major contributors to free radical formation, including reactive oxygen and nitrogen species. The resulting oxidative stress damages cellular membranes, proteins, and DNA. OLs are particularly vulnerable to oxidative stress (and excitotoxicity, see as follows) due to their high metabolic activity, high levels of intracellular iron and low concentration of antioxidants, such as glutathione [12].

Another secondary injury cascade implicated in OL loss after SCI is excitotoxicity. Work by McAdoo et al. [13] showed that glutamate was elevated rapidly after SCI, and when comparable concentrations of glutamate were micro-injected into intact spinal cords, OL death ensued [14]. OLs express multiple glutamate receptor subtypes, including (2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid) (AMPA), kainate receptors, and n-methyl-d-aspartic acid (NMDA) receptors [15]. Thus, they are vulnerable to elevated glutamate levels. AMPA receptor activation can also stimulate OL progenitor migration [16]. Given that glutamate levels are likely highest in regions of greatest pathology, this pro-migratory OPC response may either serve to call in cell replacements for dying OLs and/or cause further cell death by drawing them into a toxic milieu of dying cells and lethal molecules.

Excitotoxicity is not restricted to glutamate, but also occurs following adenosine-5'-triphosphate (ATP) binding to P2X₇ receptors on OLs [17, 18]. ATP is elevated within 2 h after SCI and is likely released by multiple cell types, including OLs [17, 19]. Both glutamate and ATP lead to calcium overload, which can trigger multiple intracellular pathways leading to cell demise [19, 20]. In addition, cytokines such as tumor necrosis factor- α and interleukin (IL)-1 β , which are up-regulated within minutes after SCI [21, 22], can exacerbate excitotoxicity by impairing glutamate uptake [23].

Infiltrating neutrophils and activated microglia release products that can promote OL loss, including free radicals, pro-inflammatory cytokines, glutamate, and proteases (reviewed by Donnelly and Popovich [22]). Lymphocytes reach peak levels in the rodent spinal cord at ~1 week postinjury [24], and can lyse OLs directly [25] and/or induce apoptosis by releasing molecules that activate death receptors via tumor necrosis factor- α , IL-2, and interferon gamma (IFN γ). OL death may also occur through the death receptors Fas and p75 nerve growth factor receptor (p75^{NGFR}) via their respective ligands (FasL and NGF) [26–28]. In addition to apoptosis and necrosis, autophagy has recently been shown to occur for at least 21 days following spinal hemisection, with Beclin-1 expression (a promoter of autophagy) highest in OLs compared to neurons or astrocytes [29].

Chronic OL loss after SCI

OL apoptosis has been detected at 2 to 3 weeks after SCI and has been attributed to wallerian degeneration of axons. The hypothesis for wallerian loss of OLs is that axons provide trophic support for OLs; hence, the loss of axons results in subsequent loss of the associated OLs. In rodents, this diminution of OLs occurs several segments away from the epicenter, extending rostro-caudally along the degenerating axon tracts [6, 8]. However, a recent study determined that axon degeneration alone (in the absence of trauma) was not sufficient to kill OLs and in fact evoked OPC proliferation and new OL formation [30]. The authors contrasted this response to OL apoptosis rostral to spinal contusion in which they noted that markers of oxidative stress were present in OLs following contusion injury but not dorsal rhizotomy. Therefore, the lack of OL loss with pure axon degeneration could be due to lack of oxidative stress, or possibly from continued support of OLs from unsevered axons.

Microglia, macrophages, and OLs

Microglia and macrophages derived from infiltrating monocytes have both destructive and reparative properties after SCI (reviewed by Jones et al. [31]). Numerous studies have attempted to describe interactions of microglia/macrophages and OPCs/OLs. In a chemical demyelination model, infiltrating macrophages promote OPC recruitment [32], perhaps through release of growth factors or glutamate, as previously mentioned. Recent *in vitro* data revealed that microglia and macrophages isolated from contused rodent spinal cords produce factors that inhibit the growth of OPC-containing cell spheres isolated from the same spinal cords [33]. Work by our group showed that activation of intraspinal microglia using different receptor ligands results in either OPC death or OPC proliferation and marked OL genesis [34]. A follow-up study revealed that OPC proliferation and OL genesis occurring in response to intraspinal microglia activation was significantly reduced by iron chelation, revealing that available iron is necessary for a maximal pro-oligogenic response of microglial activation [35]. This is in accordance with *in vitro* evidence showing that the iron status of microglia affects their functional relationship with OPCs [36]. In addition, recent work by our group revealed that OPCs internalize macrophage-derived ferritin both *in vivo* and *in vitro*, suggesting ferritin may serve as a pro-oligogenic signal between macrophages and OPCs (Schonberg and McTigue, personal observation). It is clear that microglia/macrophages have considerable potential for shaping OPC responses to injury, and more research is needed to characterize the diverse interplay between these two cell types.

DEMYELINATION AND REMYELINATION AFTER SCI

Early work studying myelin damage after SCI noted prevalent vesicular degeneration of myelin and widening of peri-axonal spaces within hours after injury [37, 38]. Furthermore, a significant loss of major myelin proteins following SCI has been detected in rodents and monkeys [38–41]. Some of the earliest studies examining demyelination after SCI in cats and rodents determined that demyelination was fairly prevalent during the first 2 weeks postinjury [40–42]. This was confirmed in more recent work using tissue from dogs that had sustained a spontaneous SCI [43]. In human tissue, demyelinated axons have been detected to a variable degree along lesion borders from 1 to 22 years postinjury [9]. Thus, demyelination, especially acutely, appears to be a consistent finding after SCI and may contribute to functional deficits by abrogating action potential conduction through denuded segments.

The lack of large-scale, chronic demyelination after SCI is due, at least in part, to spontaneous remyelination by OLs and Schwann cells. Axon remyelination in the adult central nervous system (CNS) was first documented by Drs. Richard and Mary Bunge [44, 45]. Subsequent work has consistently detected axon remyelination after SCI, typically beginning around 2 weeks postinjury [40, 41]. Intriguingly, when axons are remyelinated by OLs, the myelin is thinner and the internodes are shorter compared to normal myelin [46]. Despite these characteristics, remyelination can restore axonal conduction velocity, as elegantly illustrated by Smith et al. [47]. As a proof of principal, studies by the Duncan laboratory [48] bolstered the notion that remyelination restores function. They showed that remyelination by transplanted OLs in myelin-deficient animals restored conduction velocity to near normal. Similarly, Jeffery and Blakemore [49] found that with the onset of remyelination, functional deficits disappeared in an ethidium bromide demyelination model. Thus, spontaneous remyelination after SCI likely preserves function of spared intact axons.

The phenomenon of remyelination likely also maintains axon integrity. Indeed, bare axons are thought to be vulnerable to pathological environments, and thereby more susceptible to transection [50]. There is a symbiotic relationship between axons and OLs that exceeds simple electrical insulation. Indeed, recent data shows that the absence of functional peroxisomes in OLs results in widespread axon damage and demyelination [51], indicating that the relationship between axons and OLs is complex and that OLs play much more than a passive insulating role. Persistent demyelination after SCI will likely exacerbate axonal loss [52], making OLs indispensable not only for the proper functioning of axons but also for their survival.

REPLACEMENT OF OLs BY ENDOGENOUS PROGENITORS AFTER SCI

Although remyelination after SCI has been acknowledged for many years, identifying the cells responsible for remyelinating axons was not clear-cut. However, work by Blakemore and Keirstead [53] revealed that mature OLs, which are post-mitotic, do not contribute to remyelination; instead, remyelination is mediated by endogenous proliferating progenitor cells. These OL progenitors cells (commonly called OPCs or polydendrocytes) are present throughout the adult gray and white matter, and respond to demyelination by proliferating and migrating into the demyelinated zone [53–56]. Adult OPCs, typically identified by Nerve/glial antigen 2 (NG2) or Platelet derived growth factor receptor (PDGFR α) expression, are thought to be a heterogeneous cell population, only some of which function as OPCs (for review, see Nishiyama et al. [57] and Trotter et al. [58]).

Work from our group revealed that NG2 cells proliferate for at least 4 weeks after SCI [59]. Several other groups have corroborated this robust proliferative response in rodents and primates [7, 60–65]. Interestingly, accumulation of mitotic NG2 cells is greatest along SCI lesion borders [66], which may be due to differential up-regulation of growth factors in this region [67]. Recent work by Sellers et al. [68] demonstrated differential cell fate of NG2 cells after SCI; NG2 cells generated 24 h after injury gave rise to astrocytes, whereas those generated 1 week postinjury produced OLs. However, more recent data using lineage tracing following SCI call the ability of OPCs to give rise to astrocytes after SCI into question [69]. Direct evidence that NG2 cells contribute to replacement of mature OLs after SCI was recently provided using the CNP-EGFP (2',3'-Cyclic-nucleotide 3'-phosphodiesterase gene-enhanced green fluorescent protein) mouse to definitively show that EGFP⁺NG2⁺ cells differentiate into OLs after SCI [70]. Thus, at least a portion of NG2 cells function as OL progenitors after SCI.

MAKING OF THE OLIGODENDROCYTES

After SCI, there is recapitulation of developmental factors integral to OL specification, migration, and differentiation. Two major factors regulating OL specification during development are the Sonic hedgehog and protein bone morphogenetic factor (BMP) (for review, see Nicolay et al. [71]). Sonic hedgehog, which is pro-oligogenic, is up-regulated acutely in neurons and OLs after injury, and remains high for several weeks [72]. A rise in BMP and its cognate receptor was observed for 2 weeks after injury [72–74]. BMP can drive stem/progenitor cells toward an astrocyte rather than OL fate [75].

Also, post-SCI treatment with a BMP antagonist favored differentiation of OPCs into OLs, suggesting that endogenous OL genesis may be hampered by up-regulated BMP [68, 76].

Survival and proliferation of OPCs

Developmentally, OPC survival and proliferation depend on many of the same growth factors and cytokines altered by CNS injury. For instance, platelet-derived growth factor-A (PDGF-A) is a potent mitogen that is essential for proper OL development [77, 78]. Animals lacking PDGF-A have severely reduced OL numbers, and mice over-expressing PDGF-A form a surplus of OLs [79–81]. Expression of PDGF-A after SCI has not been the specific focus of studies to date, but at least one microarray study determined that PDGF-A is decreased after SCI [82]. PDGF-A can also synergize with fibroblast growth factor-2 (FGF-2) and maintain OPCs in a continual mitotic renewal state [83–86]. Although PDGF levels after SCI are not definitively known, FGF-2 (an OPC mitogen on its own) is up-regulated for at least 28 days, corresponding to the time of active OPC proliferation [67, 87–90].

Another important factor in promoting OPC proliferation and OL survival is insulin-like growth factor (IGF) [91, 92]. IGF may play a role in oligogenesis after SCI as increased astrocytic production of IGF-1 was noted in a cryogenic SCI model [93]. Importantly, IGF can amplify the action of FGF-2 and PDGF on OPCs [94], suggesting it may increase the effectiveness of these factors if/when present after SCI. Ciliary neurotrophic factor (CNTF), a pleiotropic cytokine, is also important for OPC survival and proliferation [95, 96]. CNTF and its receptor are up-regulated early after SCI, and our laboratory detected a robust increase chronically in CNTF and its downstream signaling molecules along SCI lesion borders, which corresponds regionally and temporally to elevated OPC proliferation and maturation [67, 89, 97]. CNTF can also increase FGF-2 and receptors for FGF and IGF, thereby increasing the sensitivity of OL lineage cells to these factors [98, 99]. The pronounced oligogenesis after injury in the astrocytic glial scar region, and the ability of astrocytes to secrete PDGF, FGF-2, IGF, and CNTF reveal astrocytes likely sit center stage in terms of influencing post-SCI OL production.

Neurotrophins are another important class of molecules that have multiple effects on spinal cord parenchyma in general and OLs in particular. Neurotrophin (NT-3) promotes OPC survival and proliferation by activating the Mitogen-activated protein kinases (MAPK) signaling cascade [96, 100, 101]. After SCI, increased levels of NT-3 and brain-derived neurotrophic factor (BDNF) have been detected in rats and primates [102–104]. Interestingly, transplantation of fibroblasts over-expressing NT-3 or BDNF significantly increased the

number of new OLs and myelinated axons after SCI, suggesting that these signaling pathways can be enhanced [105].

Chemokines, best known as chemotactic molecules for inflammatory cells, also affect OL lineage cells. The chemokine CXCL1 influences OPC proliferation and migration developmentally [119] and is up-regulated acutely after SCI [106]. CXCL12 (also known as SDF-1 α) was very recently shown to promote OPC differentiation and remyelination; furthermore, the same study showed that NG2⁺ progenitors express CXCR4, the relevant receptor [107]. Previous work by Dziembowska et al. [108], published in 2005, showed that the chemokine receptor CXCR4 is important in OPC survival and migration [109]. Expression of CXCL12 and its receptor CXCR4 are increased after SCI, suggesting that CXCL12 may contribute to postinjury oligogenesis [110]. Although a number of other chemokines are present after SCI, their role in OL genesis has not been investigated.

To be or not to be: OPCs to OLs

The lineage progression from precursor cell to a myelinating OL requires the timely exit from the cell cycle and transcriptional initiation of differentiation and myelin genes. A number of growth factors, cytokines, cell cycle proteins, and transcriptional factors play a role in this process and their expression after SCI coincides with endogenous oligogenesis.

IL-1 β , a chemokine secreted by astrocytes and microglia (and to some extent by OLs), is up-regulated within 45 minutes after SCI, peaks at 12 h, and returns to basal levels by 48 h [21]. IL-1 β promotes OPC and OL survival, and also induces OPC differentiation by counteracting the proliferative actions of PDGF [111]. Leukemia inhibitory factor (LIF) belongs to the IL-6 family of cytokines and *in vitro* studies suggest that LIF enhances OPC differentiation [112]. Receptor-mediated LIF transport across spinal cord blood vessels has been detected during the first week postinjury [113]; therefore, endogenous systemic LIF may contribute to OPC differentiation after SCI. Another well-described cytokine is transforming growth factor (TGF) β 1, which is significantly increased, along with its receptors, after SCI in rodents and humans [114–116]. TGF β 1 may have divergent effects on OPCs. Studies have shown it can inhibit OPC proliferation and promote differentiation into mature OLs [117, 118]. However, a recent study revealed that TGF β 1 stimulates Jagged1 expression by astrocytes, which inhibits OPC differentiation [119]. Thus, the role of TGF β 1 on OL genesis after SCI is likely complex.

Many transcription factors also regulate OPC differentiation, some of which belong to the nuclear receptor super family. One such factor, thyroid hormone receptor is recognized as a potent regulator of OPC differ-

entiation, and decreased levels of thyroid hormone have been detected in SCI individuals [120]. Single or double knockouts of thyroid hormone receptor display normal OPC development but severe dysmyelination due to lack of OPC maturation [121]. Other nuclear receptors that regulate OPC differentiation are peroxisome proliferator activated receptor (PPAR)- δ and retinoic acid receptor [122–124]. Our laboratory has reported a temporal increase of PPAR- δ after SCI, first in NG2 cells, followed by expression in new OLs 1 to 4 weeks postinjury [125]. Thus, PPAR- δ displays the correct spatial-temporal distribution to contribute to postinjury OPC differentiation. Retinoic acid is thought to inhibit OL differentiation during development and thereby allow dispersal of OPCs throughout the tissue [124]. After SCI, a subpopulation of NG2 cells produce retinoic acid [126], which as previously stated may reduce differentiation of progenitors into mature OLs. Thus, many endogenous factors with the potential to regulate differentiation of progenitors are present after injury; manipulating these molecules may be an effective strategy to boost endogenous oligogenesis and improve myelination.

Turning on myelination

Axon-derived signals are known to regulate myelination. During development, OPCs express the notch receptor and axons express the notch ligand Jagged-1. As axons down-regulate Jagged-1, notch signaling is attenuated in OPCs, which allows them to differentiate into mature OLs that eventually myelinate the axon [127]. Reactivation of notch signaling has been reported after SCI, which could potentially hinder remyelination [128]. Another axon signal is polysialylated form of the neural cell adhesion molecule (PSA-NCAM), which can prevent OL myelination and is thought to contribute to demyelination in multiple sclerosis [129–131]. PSA-NCAM is increased after SCI and is expressed by reactive astrocytes [132], and thereby may prevent myelination of axons in or around the glial scar.

Leucine rich repeat and Ig domain containing 1 (LINGO-1) is an Nogo-66 Receptor (NgR) co-receptor expressed on the surface of OLs, and is an important negative regulator of myelination [133, 134]. Administration of a LINGO antagonist after SCI promoted both neuron and OL survival and improved functional recovery [135]. These results suggest that LINGO is present and functional after SCI, and may thereby reduce spontaneous remyelination.

Epigenetic and post-translational regulation

Histone deacetylases (HDACs) are proteins involved in chromatin remodeling by removal of acetyl groups from histones. HDAC activity, especially that of HDACs 1, 2, and 11, is necessary for OPC differentiation into mature OLs by promoting myelin gene expression and

repressing inhibitors of OPC differentiation [136, 137]. Pharmacological blockage of HDAC activity in demyelinating lesions resulted in inefficient remyelination, revealing that baseline HDAC activity is needed for myelin repair in the adult CNS [138]. To date, HDAC expression after SCI has not been investigated, except in a preliminary report [139]. Thus, we recently examined if HDAC messenger RNA (mRNA) levels are altered by spinal contusion in rats. We observed that HDAC1 levels were unaltered but HDAC2 mRNA dropped precipitously by day 3 after SCI (FIG. 1a, b). HDAC3 showed a progressive decline, which was significant at 7 to 14 dpi (FIG. 1c). HDAC-11 displayed a complex post-SCI pattern, in that it decreased at 3 dpi, but rose significantly at 14 dpi. The early loss of HDACs 2 and 11 postinjury may lead to increased transcription of OL differentiation inhibitors.

A relatively nascent field is post-transcriptional regulation of proteins in OLs by micro RNAs (miRNAs). miRNAs are small noncoding RNAs that typically block translation of target mRNAs. In the previous 2 years, studies have shown that the expression of many miRNAs is dynamically altered as OPCs differentiate into mature OLs [140, 141]. Three studies used OL-specific promoters to knockout Dicer, a protein necessary for miRNA production, which essentially eliminates miRNAs from OL and OPCs [141–143]. The results revealed either a developmental disruption in gliogenesis [143] or that progenitor cells were formed but were unable to differentiate [141, 142]. Furthermore, the studies revealed that miRNAs decrease expression of proteins needed to maintain cells in a proliferative state. For instance, miR-219 prevents translation of PDGFR α , Sox6, FoxJ3, Hes5, and ZFP238, all of which play a role in OPC proliferation or inhibition of differentiation [141, 142]. Importantly, what we believe to be the first article to examine miRNA expression after SCI demonstrated that expression of ~100 miRNAs are significantly altered by SCI [144]. Interestingly, several miRNA expressed by OLs during the differentiation process are significantly down-regulated during the first week post-injury [10, 141, 142, 144, 145], which could hamper differentiation acutely after SCI. Because this is precisely the time of maximal OPC proliferation [59], lack of these miRNAs may decrease the ability to leverage the large population of newly generated progenitors to fully differentiate into myelinating OLs and replace those lost to injury.

Thus, a great variety of factors (not all of which are described here) involved in OL formation, survival, and myelination are present after SCI and likely positively or negatively influence oligogenesis in the injured cord (FIG. 2). To understand the mechanisms integral to endogenous myelination and to maximize repair by endogenous or transplanted cells, much more work is

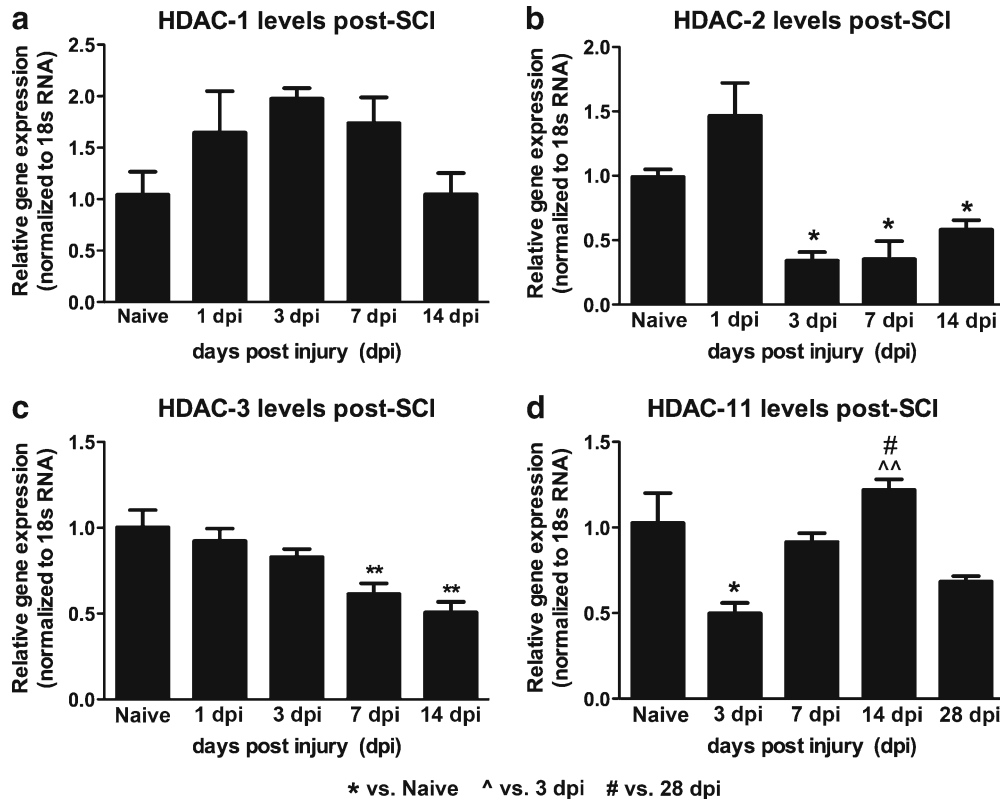


FIG. 1. Intraspinal histone deacetylase (HDAC) messenger RNA (mRNA) expression is altered after moderate spinal cord injury (SCI) in rats. A temporal gene expression profile using real-time polymerase chain reaction (PCR) was conducted for HDAC 1, 2, 3, and 11 after spinal contusion injury at T8 in rats. HDAC1 was not altered after SCI; HDAC-2 and 3 were significantly down-regulated by 1 week postinjury and remained low at 14 dpi (a–c). HDAC-11 mRNA levels decreased at 3 dpi then returned to naïve levels by 14 dpi (d). * $p < 0.05$ vs naïve; ** $p < 0.01$ vs naïve; ^ $p < 0.01$ vs 3 dpi, # $p < 0.05$ vs 28 dpi.

needed to clarify the environment in which these cells will be functioning.

SAFEGUARDING OLIGODENDROCYTES

Although spontaneous OL genesis and remyelination occur after SCI, it is clear that decreasing OL death would prevent early demyelination and may reduce axon degeneration and improve axon function. Thus, numerous therapeutic strategies have been tested to increase post-SCI OL survival. Several studies have shown that the anti-inflammatory agent minocycline promotes white matter sparing and OL protection after SCI, in part by inhibiting microglial production of pro-NGF [146–148]. Lee et al. [149] showed that methylprednisolone, a common treatment after SCI, protected OLs, but not neurons by blocking apoptosis. Methylprednisolone-mediated effects on OL protection in SCI patients have not yet been explored. Whitaker et al. [150] showed rolipram, an inhibitor of the cAMP-dependent phosphodiesterase 4 (PDE4), protects OLs from secondary injury cascades at 24 to 72 h after injury. In a follow-up study, rolipram was reported to increase axon conduction due to

remyelination, which was associated with improved behavioral outcomes [151].

Treatment with growth factors has also been attempted after SCI. For instance, administration of LIF, a cytokine implicated in OL survival, after SCI resulted in increased viability of OLs and decreased demyelination [152]. Exogenous BDNF treatment starting immediately or 3 days after injury decreased the number of apoptotic OLs [153]. Another group similarly demonstrated retrograde transport of BDNF via intramuscular injections in rats suppressed OL apoptosis after SCI [154]. Combining growth factor treatment and genetic manipulation of endogenous progenitors has also been attempted in rodent SCI [155]. The results showed that over-expression of MASH1/achaete-scute homolog 1 in conjunction with FGF-2 and EGF administration increased endogenous formation of OLs. Thus, several therapies targeting OL protection show promise in rodent SCI models.

NEW OLS WITH TRANSPLANTATION

Chronic persistence of demyelinated axons in the injured spinal cord of rodents [156] and humans [9]

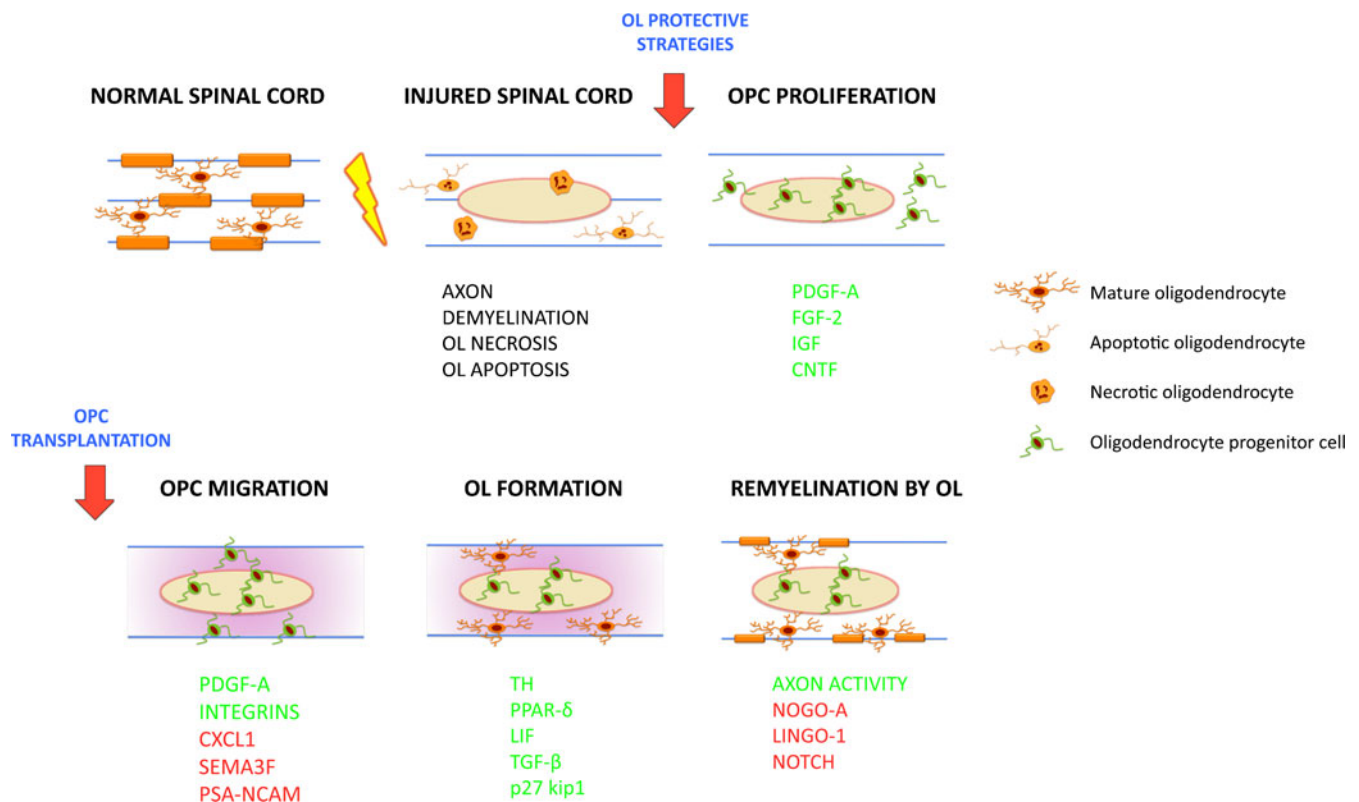


FIG. 2. Schematic of events involved in oligogenesis after injury to the spinal cord. This schematic represents that the normal spinal cord has axons myelinated by the oligodendrocytes (OL); however, after spinal cord injury (SCI), a series of events ensues that contribute to OL loss (see black) and formation. There is dramatic loss of OLs due to necrotic and apoptotic cell death resulting in axonal demyelination. Acute OL protective strategies (blue) after injury may help salvage OLs and prevent further loss. Oligodendrocyte progenitor cells (OPC) present in the spinal cord react to injury with extensive proliferation in the presence of numerous growth factors and cytokines. Once the OPCs proliferate, environmental and axonal cues regulate OPC migration to denuded axons. After reaching their destination, OPCs differentiate into mature OLs due to axonal signals and/or environmental factors, resulting in remyelination of the axons. Supplementing with stimulatory (green) and inhibitory (red) factors involved in each of the steps can further enhance endogenous OL formation. A common approach to increase OL numbers is subacute cell transplantation (blue), which is another therapeutic intervention that bolsters remyelination of axons after SCI. FGF-2 = fibroblast growth factor-2; IGF = insulin-like growth factor; PDGF-A = platelet-derived growth factor-A; CNTF = ciliary neurotrophic factor; LINGO = leucine rich repeat and Ig domain containing; PSA-NCAM = polysialylated form of the neural cell adhesion molecule; NGO = neurite outgrowth inhibitor; SEMA3F = Semaphorin-3F.

serves as a potential therapeutic target. In addition to preservation of OLs and boosting endogenous oligogenesis, recent strategies have used transplantation of pluripotent/glia restricted cells to improve remyelination after SCI. Although a variety of transplant studies have been conducted with distinct sources and cell types in SCI models, we will highlight a few relevant studies here that focus on CNS stem-cell based transplants (for excellent reviews, see Enzmann et al. [157], Coutts et al. [158], and Kulbatski et al. [159]). Early work by Utzschneider et al. [48] served as proof of principal that transplantation of OLs in myelin-deficient animals would lead to remyelination and axon potential conduction velocity to near normal values. One of the first experiments to test transplantation from a therapeutic standpoint was conducted in an ethidium bromide-demyelinating lesion in which postnatally derived OPCs remyelinated spinal cord lesions [160]. Subsequent studies showed that OPC transplant-derived remyelina-

tion resulted in reversal of functional deficits after demyelination [161]. Lee et al. [162] conducted a systematic analysis of transplantation of OPCs at 1 week postinjury in a rat spinal contusion model. They showed that OPCs migrated around the injury site and differentiated into mature OLs (not astrocytes or neurons). The transplants also improved functional recovery and increased the number of retrograde-labeled neurons in the brainstem.

An undifferentiated and pliable source of cell transplants is embryonic stem cells (ESC). McDonald et al. [163] tested the efficacy of transplanting neurally differentiated cells derived from mouse ESC into an injured rat spinal cord at 9 dpi. The cells survived, migrated, and differentiated into neurons, astrocytes, and OLs, resulting in significantly improved locomotor recovery [163]. In contrast, when undifferentiated rat neural stem cells were engrafted into injured cords, the majority of cells took on an astrocytic fate or remained as nestin positive cells

[164]. This discrepancy was attributed to species-specific differences in cell sources (rat vs mouse). The authors also suggested a prior need to differentiate the cells *in vitro* into restricted lineages before transplantation. The same group demonstrated that transplantation of embryonic glial restricted precursor cells over-expressing BDNF and NT-3 at 9 days after injury resulted in increased OL formation (15–30%), enhanced remyelination, and restored electrophysiological conduction resulting in improved locomotor function [165].

The importance of human ESC as a potential therapeutic strategy has been underscored and has been tested in multiple studies. When transplanted, these cells survived, differentiated into OLs, remyelinated axons, and mediated locomotor improvements in injured Severe Combined Immunodeficiency (SCID) mice [166]. Keirstead et al. [167] differentiated human ESCs into a pure population of OPCs *in vitro* and transplanted the cells at 1 week or 10 months after SCI in rats. The grafted OPCs survived, integrated, migrated, and differentiated into OLs at both time points after injury. However, OLs formed by acute transplants enhanced remyelination and improved behavioral scores, whereas the chronic transplants failed to do so. Thus, the window of opportunity for stem cell transplantation clearly closes at some point.

As the use of ESCs raises a number of ethical issues, newer studies are geared toward using adult cells, especially because patients could undergo autologous transplants. The combinatorial action of transplanting adult neural precursor cells 2 weeks after SCI in conjunction with minocycline treatment and a cocktail of growth factors showed robust differentiation of transplant cells into myelinating OLs that remyelinated axons and improved recovery on a battery of behavioral measures [168]. When transplants were performed at a more chronic time (8 weeks), again beneficial effects were not observed [167]. Other promising anatomical and behavioral results were seen when adult neural precursor cells were transplanted at 2 weeks, but not 8 weeks, postinjury in combination with immunosuppression and minocycline; ~50% of the cells differentiated into OL lineage cells and ensheathed spinal axons [168]. The reason for the limited window of opportunity for success in remyelinating cell transplants has been suggested to be the presence of astrocytic processes surrounding the demyelinated axons, which prevent the transplanted cells from reaching and remyelinating the axons [167]. Thus, performing transplants prior to the establishment of astrogliosis, or devising a way in which transplanted cells can intermingle between the astrocyte processes and axons, may be required for this strategy to work.

More recent data from the same group show exciting results when NPC transplants were combined with growth factor and chondroitinase treatment; the results revealed not

only enhanced OL formation by transplant cells, but also increased growth of descending axons [169]. Another recent study transplanted OPCs engineered to over-express CNTF, which increased transplant survival, integration, and differentiation into OLs [170]. The grafted cells remyelinated spinal axons, improved electrophysiological conduction and enhanced hind limb recovery in rats. A potential negative effect of stem cell transplantation was demonstrated by Hofstetter et al. [171], who noted that although adult neural stem cell transplants improved motor function after SCI, recovery was accompanied by allodynia due to graft-mediated axonal sprouting. Thus, caution should be used in transplant studies, as is true with any therapeutic manipulation.

The multiple studies showing efficacy of stem cell transplants culminated in the United States Food and Drug Administration approval of phase I clinical trials by Geron Corporation in which OPCs derived from human embryonic stem cells will be transplanted acutely (within 14 days) in 8 to 10 patients with complete American Spinal Injury Association (ASIA) A injuries. The first patient was enrolled in October 2010. This clinical trial represents an exciting advancement in SCI treatment in general and highlights the importance of the need for continued research centered on promoting endogenous repair responses, as well as providing therapeutic options to reduce cell death and increase cell replacement after SCI. Only with ongoing basic and clinical research can the devastating effects of spinal trauma become a thing of the past.

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