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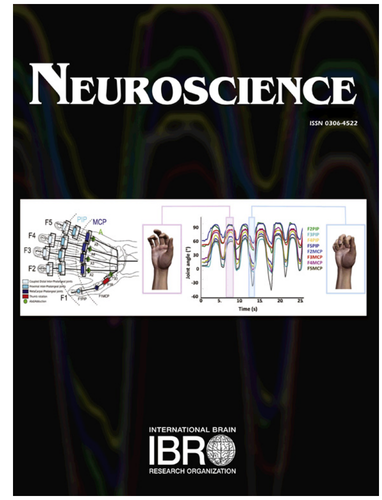

Review

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Oligodendrogliogenesis and axon remyelination after traumatic spinal cord injuries in animal studies: A systematic review

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ABSTRACT

Extensive oligodendrocyte death after acute traumatic spinal cord injuries (TSCI) leads to axon demyelination and subsequently may leave axons vulnerable to degeneration. Despite the present evidence showing spontaneous remyelination after TSCI the cellular origin of new myelin and the time course of the axon ensheatment/remyelination remained controversial issue. In this systematic review the trend of oligodendrocyte death after injury as well as the extent and the cellular origin of oligodendrogliogenesis were comprehensively evaluated. The study design was based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-guided systematic review. PubMed and EMBASE were searched with no temporal or linguistic restrictions. Also, hand-search was performed in the bibliographies of relevant articles. Non-interventional animal studies discussing different types of myelinating cells including oligodendrocytes, Schwann cells and oligodendrocyte progenitor cells (OPCs) were evaluated. The extent of oligodendrocyte death, oligodendrocyte differentiation and remyelination were the pathophysiological outcome measures. We found 12,359 studies, 34 of which met the inclusion criteria. The cumulative evidence shows extensive oligodendrocytes cell death during the first week post-injury (pi). OPCs and peripheral invading Schwann cells are the dominant cells contributing in myelin formation. The maximum OPCs proliferation was observed at around 2 weeks pi and oligodendrogliogenesis continues at later stages until the number of oligodendrocytes return to normal tissue by one month pi. Taken together, the evidence in animals reveals the potential role for endogenous myelinating cells in the axon ensheathment/remyelination after TSCI and this can be the target of pharmacotherapy to induce oligodendrocyte differentiation and myelin formation post-injury.

Keywords: Spinal cord injury; Myelin; Oligodendrocytes; Schwann cells; Progenitors; Oligodendrogliogenesis

INTRODUCTION

Traumatic spinal cord injury (TSCI) is a devastating event involving approximately between 3.6 and 195.4 cases per million annually in different countries (Jazayeri et al., 2015). The acute trauma initiate a cascade of progressive events which last by one year after injury and cause secondary injury (Rowland et al., 2008). Based on different degenerative events during the secondary injury various regenerative and repair strategies have been proposed and are under development to induce axon regeneration and remyelination which can be categorize in 3 different classes: cell-based strategies (Keirstead et al., 2005, Priest et al., 2015), drug therapies (Nagoshi et al., 2015) and tissue engineering approaches (Piantino et al., 2006, Fuhrmann et al., 2016). In some cases the outcomes of animal studies have provided the rationale for clinical trials (clinicaltrials.gov). Although many studies propose the advantageous of acute intervention in order to restrict the progress of secondary events (Fehlings et al., 2016), the endogenous regenerative responses at later times post-injury may also provide some extra therapeutic opportunities.

Oligodendrocytes are myelinating cells residing in central nervous system (CNS). During development oligodendrocytes are mostly derived from neuroepithelial zones, where neuroepithelial stem cells (i.e. stem cells of the nervous system) differentiate into oligodendrocyte precursor cells (OPCs). Subsequently, OPCs differentiate into pre-myelinating oligodendrocytes and finally into mature myelinating oligodendrocytes (van Tilborg et al., 2018). Myelination is a dynamic and plastic process with an excess of OPCs being generated and remained throughout adulthood which are recruited to drive remyelination in case of injury or neurodegenerative diseases (Gautier et al., 2015).

After SCI oligodendrocyte death leads to axon demyelination and leave axons vulnerable to degeneration (Hill et al., 2001, Houle and Jin, 2001, Hassannejad et al., 2018). Spontaneous remyelination after injury has been revealed in some studies (Bartholdi and Schwab, 1998, Horky et al., 2006, McDonough et al., 2013, Hesp et al., 2015, Assinck et al., 2017). Mature oligodendrocyte, OPCs as well as Schwann cells (i.e. peripheral resident myelinating cells) have been introduced as the cells contributing in remyelination after SCI. It has been shown that after injury OPCs and Schwann cells that are quiescent in normal conditions become activated, develop a larger cytoplasm and thinner cell processes. They proliferate and recruited to the injury site to restore the damage caused by dying oligodendrocytes through expression of neurotrophic factors to establish a growth promoting environment and enwrapping neuronal axons to remyelinate nude axons (for excellent review, see de Castro et al. (2013)).

The extent of oligodendrocyte death, endogenous remyelination and contribution of each of the aforementioned cells in myelin formation have been evaluated separately in different time points from immediate to chronic phases. However, the spatial and temporal pattern of myelin formation as well as prominent cell type contributing in axon ensheathment/remyelination in each time point or various regions of cord have not yet fully addressed. In this study the fate of mature oligodendrocytes and their proliferative potential after injury, cell sources to compensate the extensive loss of oligodendrocyte and also the extent of remyelination after injury have been systematically evaluated in order to reveal the appropriate time points to augment spontaneous remyelination. Based on the present evidence myelinating cells respond to TSCI in a way that after initial loss the number of oligodendrocytes approaches to the normal levels after about one month post-injury. The majority of oligodendrocytes are lost at the epicentre and adjacent regions, however, OPCs proliferation and subsequent differentiation to myelinating cells (both oligodendrocytes and Schwan cells) are the main route to compensate the extensive demyelination after injury. Invading peripheral Schwann cells also contribute in remyelination. Taken together, the evidence in animals suggests an important potential role for endogenous myelinating cells in the axon ensheathment/remyelination after TSCI.

METHODS

Search and Selection of Studies

We searched Embased and MEDLINE via Ovid SP on 9 November 2013 and we updated this search on 24 October 2015 and 7 September 2018. Keywords were determined based on research team discussion, experts' opinion, literature reviews, controlled vocabulary (Medical Subject Headings = MeSH and ExcerptaMedica Tree = EMTREE) and review of the records retrieved in the initial search. The search strategy was then developed with assistance of a medical information specialist. The following keywords and MeSH terms were used: "Spinal cord injury", "trauma", "cell", and "pathophysiology" Search results were exported into EndNote X5. Also, a detailed review of the reference lists of the most relevant publications was performed.

Eligibility Criteria

All the articles investigating the pathophysiology of TSCI in animal after acute traumatic mechanical spinal cord injury including compression, contusion, hemisection and transection were included. Publications that did not specify cell type, and exact time points for the pathophysiological events were not included. In addition, in order to increase the homogeneity of included studies, we excluded studies reporting on humans (i.e. all clinical studies and case reports), non-mechanical injuries, including thermal and ischemic injuries and other interventions. Finally, non-original articles, including review articles and letters were excluded. No restrictions in regard to period of publication and language were applied.

Selection Process

Two authors independently assessed each article based on the title, abstract and finally the full-text (ASM & MM, SA & ZH). In a case of disagreement, a third independent person (VRM) assessed the article and the final decision was made accordingly.

Outcome Measures

Different types of myelinating cells including oligodendrocytes, Schwann cells and OPCs, which are believed to be committed to oligodendrocyte lineage, were evaluated. Cell death, differentiation and proliferation rates for the aforementioned cell types were the pathophysiological outcome measures.

Data Extraction and Quality Assessment

Data were extracted to a data extraction form developed in our group by two independent members. On this form, general information about each article including the title, authors' name, publication date, information about method including study design (type/severity/level of injury), time of assessments, animal number and animal characteristics (strain, sex, age or weight), method(s) of evaluation and finally the research question and relevant results were recorded.

In order to control the quality of the included articles, two independent reviewers evaluated each article according to the criteria for TSCI (Hassannejad et al., 2016). Briefly, the quality of each article was assessed based on 15 items including: 1. species; 2. using appropriate tests; 3. severity of injury; 4. level of injury; 5. age/weight; 6. number of animals per group; 7. designation of strain; 8. definition of control; 9. description of statistical analysis; 10. bladder expression; 11. genetic background; 12. method of allocation to treatments; 13. description of the reasons to exclude animals from the experiment during the study (attrition); 14. blindness of assessors of the original investigators; 15. regulations and ethics

RESULTS

Description of the Included Studies

The search yielded to 12,359 records. After screening the articles, 520 articles were included for the full-text review. A final 34 articles were included for outcome evaluation. The search flowchart and selection methods are presented in Fig. 1. Furthermore, characteristics of the included studies are presented in Table 1. The quality assessment of 34 included studies was then assessed and the results are presented in the Table 2.

Figure 1

Table 1

Table 2

Oligodendrocytes and oligodendrocyte progenitor cells

There were 29 studies discussing the fate of oligodendrocytes as well as OPCs after TSCI (Griffiths and McCulloch, 1983, Blight, 1985, Shuman et al., 1997, Bartholdi and Schwab, 1998, Salgado-Ceballos et al., 1998, Yong et al., 1998, Abe et al., 1999, Li et al., 1999, Frei et al., 2000, Casha et al., 2001, Grossman et al., 2001, McTigue et al., 2001, Warden et al., 2001, Dong et al., 2003, Wu et al., 2005, Zai and Wrathall, 2005, Horky et al., 2006, Yang et al., 2006, Lytle and Wrathall, 2007, Rabchevsky et al., 2007, Tripathi and McTigue, 2007, Ceruti et al., 2009, Sellers et al., 2009, Wang et al., 2009, Barnabe-Heider et al., 2010, McDonough et al., 2013, Huang et al., 2014, Hesp et al., 2015, Assinck et al., 2017).

A total of 287 CreER transgenic mice (2 studies), 135 Swiss Webster mice (one study), 56 mice (species not available, 2 studies), 299 Sprague-Dawley rats (6 studies), 365 Fischer rats (2 studies), 28 Long-Evans rats (one study), 62 Lewis rats (2 studies), 32 rats (species not available, one studies), 26 mongrel cats (one study) and 5 Rhesus monkeys (one study) underwent TSCI. Also, the number of animals was not mentioned in 11 studies: C57BL6 mice (one study), CD1 mice (one study), Wistar rats (2 studies), Sprague-Dawley rats (3 studies), Fisher rat (one study), cat (species not specified, one study), rat (species not specified, one study) and mice (species not specified, one study).

The collected data included the results of immunohistochemistry, light and electron microscopy and flow cytometry. The markers and methods used to identify the cell types (i.e., oligodendrocytes and OPCs) and to detect apoptosis are summarized in Table 3.

Table 3

The extent of oligodendrocytes death at the lesion center and adjacent regions after TSCI

The earliest evaluated time point was 15 minutes pi, when the number of oligodendrocytes ($CC1^+$) significantly decreased at the epicenter as well as 2 mm caudal and rostral to the injury site (Grossman et al., 2001). Reduction in the number of oligodendrocytes persisted ±3 mm away from the lesion site, however, it was not statistically significant comparing to the uninjured tissue at this time point (Grossman et al., 2001). By one hour pi, no noticeable changes were observed 3 to 10 mm rostral and caudal to the lesion epicentre (Wang et al., 2009).

Four hours pi, a further 50% of oligodendrocytes were lost at the epicenter (Grossman et al., 2001) and according to Li et al. (1999) a small, statistically non-significant portion of this reduction was due to apoptosis. At 6 hours pi, $TUNEL^+$ cells were detected at the epicenter and 1-2 mm distal to the injury, most of them displaying oligodendrocyte characteristics (double-labelled with CNPase) (Casha et al., 2001, Grossman et al., 2001). Eight and 24 hours pi, a persistent significant reduction in the number of oligodendrocytes was seen at distances up to 2 mm rostral and caudal to lesion epicenter (Bartholdi and Schwab, 1998, Grossman et al., 2001).

At 24 hours pi, the number of apoptotic oligodendrocytes ($TUNEL/CNPase^+$) at the white matter (WM) of epicenter approximately doubled compared to controls (Huang et al., 2014). Also, in spared WM at the epicenter, the density of mature oligodendrocytes decreased significantly by 24 hours pi (Lytle and Wrathall, 2007). At this time point, 1.5 mm rostral and caudal to the injury site, as well as epicenter, $CC1^+$ oligodendrocytes were significantly reduced (Lytle and Wrathall, 2007). Accordingly, 24 hours pi PLP (proteolipid protein) mRNA expression was mostly absent in the central necrotic area which indicated a significant loss of oligodendrocytes in this area (Frei et al., 2000). Li et al. (1999) reported, using TUNEL assay, a statistically non-significant presence of apoptotic cells rostral (T1-T7) and caudal (T10-L2) (where the epicenter was T8-9) 24 hour pi after moderate and severe injuries (Li et al., 1999).

At 2 days pi, the total number of mature oligodendrocytes ($CC1^+$) decreased to less than half of the naïve animals at the epicenter and ventral-lateral funiculi up to 14 mm distal to the injury site (Rabchevsky et al., 2007).

At day 3, the number of apoptotic oligodendrocytes ($TUNEL/CNPase^+$) was higher than day 1 as well as control animals, at the epicenter (Huang et al., 2014) and within 4 mm distal to the epicenter (Yong et al., 1998). From the third day, $TUNEL\text{-}MBP^+$ (Myelin basic protein) cells were found sparsely scattered in the WM remote from the epicenter (Abe et al., 1999). It is likely that from the third day onwards, the zone of apoptotic oligodendrocytes spread to sites remote from the epicenter. At 4 days pi, the number of apoptotic cells significantly decreased in caudal (T12, and L2 where the injury is applied at T8-9) and rostral segments (T1, T5, and T7) in moderate and severe compression (Li et al., 1999). The labelled cells were randomly distributed in the ventral, lateral and dorsal columns of the WM; most of them were located in the subpial region. However, very few labelled cells were found in grey matter (GM) (Li et al., 1999). The mentioned trend of oligodendrocytes apoptotic death is represented in Fig. 2.

Figure 2

At 7 days pi, the number of CC1$^+$ cells reduced significantly in all zones up to 14 mm distal to the injury compared to control animals (Rabchevsky et al., 2007). Also, in ventrolateral WM, the density of mature oligodendrocytes was less than 50% of that in normal uninjured mice (Lytle and Wrathall, 2007). In epicenter cross-sections, the proportion of oligodendrocytes to all survived cell types was reduced from 93% to %86 cells per section. Indeed, most oligodendrocytes in the impact site died within the first week after injury (McTigue et al., 2001). In another study, cell counts in the dorsal fasciculus above the lesion, as well as lateral tracts above and below the lesion, showed that TUNEL$^+$ cells (presumably oligodendrocytes, because they were negative for GFAP, neurofilament, OX-6 and BS-1 markers) first appeared by 3 days pi, becoming maximal in number between days 5 and 7 (Abe et al., 1999). Also, two other studies confirmed that 7 days pi was the time point when the number of apoptotic oligodendrocytes reached the maximum (Casha et al., 2001, Huang et al., 2014).

At 8 days pi, apoptotic oligodendrocytes were most numerous in 7 and 13 mm rostral to the epicenter (Shuman et al., 1997). Also, eight days after T9 level hemisection in C57BL/6J mice, a selective loss of oligodendrocytes were observed 3-7 mm rostral and caudal to epicenter. Staining for CC1 and caspase-3 (a protein that is associated with apoptosis) confirmed activated caspase-3 was expressed in oligodendrocytes on injured side of this area but neither in the intact side of the cord nor in control sections. From double-labelling of CC1 and caspase-3, it was also concluded that approximately 10–15% of oligodendrocytes in this region expressed both epitopes. At this time point in the areas up to 5 mm from the epicenter, a significant loss of oligodendrocytes was observed on the injured side. Moreover, ultrastructural examination at 5-7 mm away from the epicenter showed prominent apoptotic features (Dong et al., 2003). In transection models from day 2 to 8, in situ hybridization revealed that a large area surrounding the epicenter was completely free from MBP mRNA, indicating complete loss of oligodendrocytes within this zone (Bartholdi and Schwab 1998).

By 9 dpi, a significant increase in the number of apoptotic oligodendrocyte was seen in rostral (T1 to T7) and caudal segments (T10, T12, and L2) (Li et al., 1999).

The number of apoptotic oligodendrocytes varied between moderate and severe injuries. After moderate injury the highest number of apoptotic cell death occurred in T7 and T10 segments while in severe injury the lesion size extended and the highest number of apoptosis observed in the T7 and T12 segments. In all examined segments there were more apoptotic oligodendrocytes in severely than in moderately injured rats. However, the difference was not statistically significant (Li et al., 1999).

By 10 days pi, oligodendrocytes were still present in areas with degenerating axons, Wallerian degeneration (WD) zone (i.e., 3 to 10 mm caudal and rostral to injury epicenter). However, the number of oligodendrocytes was significantly reduced to less than half of oligodendrocytes in sham operated animals (number of Olig2$^+$ cells: ~ 60, 50, and 100 in dorsal ascending tracs, corticospinal tract and sham, respectively) (Wang et al., 2009).

In the second week after injury, the number of apoptotic oligodendrocytes declined significantly in lateral tracts above and below the injury site and the dorsal column (Abe et al., 1999), but they were still present 1-2 mm distal to the epicenter (Casha et al., 2001). The epicenter itself was already devoid of oligodendrocytes; only an amorphous mass of cell debris and MBP-positive macrophages were observed at the lesion epicenter, where MBP mRNA was almost absent. The very few MBP mRNA expressing cells detected in the dorsal funiculi that were probably due to invading Schwann cells (Bartholdi and Schwab 1998).

The oligodendrocyte processes formed a defined border separating the lesion area from the spared tissue (Bartholdi and Schwab 1998). In WM areas remote from the lesion, signs of WD became very prominent; at the center of the degeneration zone MBP mRNA$^+$ oligodendrocytes were lost; however, levels of MBP mRNAs strongly increased at the borders of the lesion (Bartholdi and Schwab, 1998).

Yong et al. also detected a second peak of oligodendrocyte apoptosis at 14 days pi (Yong et al., 1998). Since, at this time point the authors did not specify the areas where the TUNEL/RIP$^+$ cells were present, this second peak could be due to death in the WD zones rather than the epicenter where the first peak of apoptotic oligodendrocytes was observed at 5-7 days pi.

Apoptotic cell death of oligodendrocytes continued by the third weeks pi (Crowe et al., 1997, Shuman et al., 1997). At this time point, oligodendrocytes apoptosis had decreased slightly in rostral blocks, in contrast to 7 mm caudal to the lesion epicenter where apoptosis increased

(Shuman et al., 1997). Between 8 and 30 days pi, a delayed apoptosis of oligodendrocytes continued specifically in distal zones both rostral and caudal (Dong et al., 2003).

By the fourth week after injury, in WM at the epicenter, the density of apoptotic oligodendrocytes reduced to the normal level (Lytle and Wrathall, 2007); also at 1.5 mm rostral and caudal to the injury epicenter in two injured mice the density of oligodendrocytes returned to the levels of uninjured controls (Lytle and Wrathall, 2007). Thus by the fourth week, the number of oligodendrocytes seemed to stabilize and remain constant thereafter (McTigue et al., 2001). The summary of OL's death is schematically presented in Fig. 2.

The response of oligodendrocyte progenitor cells to TSCI

At 24 hours pi, the proportion of BrdU/Olig2$^+$ cells dropped dramatically from ~ 90% in control to almost 40% at the epicenter (McDonough et al., 2013), which shows that OPCs that were proliferating before injury either die or do not activate a proliferation program to a significant extent after TSCI (Horky et al., 2006). Meanwhile, a peak of NG2$^+$ cell proliferation was observed at the 1.5 mm away from the epicenter (Lytle and Wrathall, 2007), and a small increase in number of NG2$^+$ cells at the WM 5 and 10 mm caudal to the epicenter was detected (Wu et al., 2005). The NG2$^+$ cells as well as newly formed oligodendrocytes were surrounding lesion borders (Hesp et al., 2015).

At day 2 pi, the number of NG2$^+$ cells were increased by 50% compared to controls at the distal ventrolateral funiculi but did not change at the epicenter (Rabchevsky et al., 2007). One to three days pi, the number of proliferating OPCs (BrdU/NG2$^+$ cells) in spared WM increased slightly but insignificantly compared to control animals (25 and ~10 cells/mm^2, respectively), whereas in GM (borders and spared GM), the number was significantly higher (>40 cells/mm^2). Most of the NG2$^+$ cells proliferated at lesion borders (1-2 mm distal from epicenter) (Lytle and Wrathall, 2007, Tripathi and McTigue, 2007), significantly more than control animals (Ceruti et al., 2009) while decreasing at the epicenter compared to control (Lytle and Wrathall, 2007). In areas 2-4 mm distal to the epicentre, as well as lesion borders, half of the dividing cells were NG2$^+$ at day 3 and some of the NG2$^+$ cells were co-labelled with GFAP (marker of astrocytes) (Zai and Wrathall, 2005, Ceruti et al., 2009). There were only a few proliferating CC1$^+$ cells in the lesion area and WM distal to the epicentre (Ceruti et al., 2009).

Later, during 4-7 days pi, OPCs continued to proliferate at the WM and GM lesion borders and some evidence of oligodendrogliogenesis was revealed along the lesion borders (Tripathi and McTigue, 2007). At day 7, the total number of NG2$^+$ cells were higher at the spared WM at the epicentre compared to control animals (Lytle and Wrathall, 2007). There was small reduction in $NG2^+$ cells compared to day 2 (Rabchevsky et al., 2007), yet remained 8 times higher than control animal, comprising over 80% of the proliferating cells at the lesion borders (Ceruti et al., 2009). At the ventrolateral funiculi, an increase in total number of mature oligodendrocytes was observed (Rabchevsky et al., 2007). In another study, the number of proliferating $NG2^+$ cells (BrdU/NG2) were reported to increase up to three times within the epicentre (both at the spared and lesion areas) and up to 6 times rostral and caudal to the epicentre (< 2 mm) (McTigue et al., 2001).

At the first week pi, in 5 mm caudal from the epicentre, an increased number of $NG2^+$ cells was observed in WM. Also, $NG2^+$ cells in the WM from subpial region 5 mm distal to the epicentre were predominantly co-labelled with GFAP (Wu et al., 2005).

The OPCs that had proliferated during the first week, kept proliferating during the second week (7-14 dpi) at the GM lesion borders, whereas at the WM lesion borders the number remained similar to 7 days pi. The proliferation of OPCs at the borders led to higher numbers of newly formed oligodendrocytes in this areas during the first three days (~17 cells/mm^2) compared to control animals (<5 cells/mm^2) (Tripathi and McTigue, 2007). *In-situ* hybridization of MBP mRNA at the lesion borders showed an increase in MBP expression in WM and GM at 8 days pi. These MBP-expressing cells, displayed the initial signs of remyelination by forming loose network of cells at the lesion borders (Bartholdi and Schwab, 1998). At 9 days pi Mcdonough et al. reported a decrease in proportion of $BrdU^+$ cells that expressed Olig2 at epicentre and regions next to the epicenter, both in WM and GM (McDonough et al., 2013). This could be due to the onset of differentiation of OPCs to a committed cell lineage when an upward trend is seen in the proportion of oligodendrocytes compared to previous time points (McDonough et al., 2013).

By the second week pi a continual trend in the reduction of the extent of $NG2^+$ and $Olig2^+$ cells was seen reaching that of normal controls and remaining at this level afterwards (McTigue et al., 2001, McDonough et al., 2013). Also, in the regions that OPCs were highly proliferative during 1-3 days (i.e. spared WM), the number of oligodendrocytes was doubled compared to day 3, indication of the oligodendrogliogenesis process. An excess of oligodendrocytes was also observed in spared GM (>40 cells/mm^2) where the OPCs proliferated within the first three days after injury. As expected, the greatest increase in number of oligodendrocytes was detected in the area where OPCs had proliferated i.e. WM and GM lesion borders (>50 cells/mm^2). The highest proliferation rate occurred 1-2 mm distal from the epicentre (Tripathi and McTigue, 2007). The new oligodendrocytes formed a border between the lesion epicentre and the intact regions (Tripathi and McTigue, 2007). Similarly, it has been reported that the number of oligodendrocytes was significantly increased in areas distant from the injury epicentre (> 6 mm), mainly in WM close to the border of the pia-matter (Rabchevsky et al., 2007, Hesp et al., 2015). By this time, the density of proliferating $NG2^+$ cells was still higher at the epicentre and up to 2 mm away from the lesion epicentre (~3.8 and ~4.5-fold, respectively) compared to the control animals (McTigue et al., 2001). However, at 4 weeks pi, the density of the proliferating $NG2^+$ cells at the epicenter was in the normal level (Horky et al., 2006).

At 4 weeks pi, the total number of $NG2^+$ cells was higher in rostral and caudal spared WM, and at the epicentre (~ 76, ~ 63, and ~ 64 cells/mm^2) compared to control animals (~ 40 cells/mm^2) (Lytle and Wrathall, 2007). This observations validated that $NG2^+$ cells were continuously proliferating during the first month while preserving their progeny (Hesp et al., 2015).

McTigue et al. reported a decrease in the total number of $NG2^+$ cells at the epicentre and rostral to the levels even less than uninjured animals, and a slight decrease compared to week 2 but still higher than caudal sections of normal tissue (McTigue et al., 2001). However, these cells were still proliferating at higher rates than in controls (~20-25 NG2/$BrdU^+$ cells/section as opposed to ~5 cells/section in naïve) (McTigue et al., 2001). Similarly, the proliferation rate has been reported to decline after 4 weeks pi, but remaining 3-9 fold higher than control animals (Hesp et al., 2015). The highest number of $NG2^+$ cells was observed 5-10 mm rostral and caudal to the epicentre (Wu et al., 2005), whereas, at the WM of the epicentre, the number of oligodendrocytes returned to normal amount (Lytle and Wrathall, 2007).

At 6 weeks pi, although the number of $NG2^+$ cells was still higher than controls (Rabchevsky et al., 2007), a very few proliferating cells were seen distal (2-4 mm) to the epicentre. However, one-fourth of the total oligodendrocytes were proliferative in this region, which is presumably the result of the $NG2^+$ cells proliferation at the early stages (Zai and Wrathall 2005). The number of oligodendrocytes had returned to normal, validating the recovery of oligodendrocyte population by this time (Rabchevsky et al., 2007). These newly formed oligodendrocytes ran processes along the axons, and initiated remyelination from 6 weeks pi to as late as 9 weeks pi (Hesp et al., 2015). The fluctuation in proliferation rate of OPCs in epicenter and distal regions has been schematically demonstrated in Fig. 3.

Figure 3

Extensive oligodendrogliogenesis occurred during the first 7 weeks after injury leading to the recovery of oligodendrocytes (Bartholdi and Schwab, 1998, Horky et al., 2006, Rabchevsky et al., 2007, Tripathi and McTigue, 2007, Hesp et al., 2015). As opposed to NG2 expression that declined at 8 and 12 weeks pi (Wu et al., 2005) and was rarely detected at weeks 7 and 9 (Yang et al., 2006), the number of proliferating oligodendrocytes ($BrdU^{+}/APC^{+}$ or $CC1^{+}$) continuously increased at 3 (Horky et al., 2006) 7, 9, 15, and 29 weeks pi (Yang et al., 2006). The vast majority of new oligodendrocytes at 3-4 months pi, was derived from OPCs (Barnabe-Heider et al., 2010, Assinck et al., 2017). McTigue et al. reported that the proliferative response of OPCs remains elevated compared to normal animals up to 4 weeks pi, and returns back to normal levels at 10 weeks pi (McTigue et al., 2001). In mice, on the other hand, the total number of $NG2^{+}$ cells escalated 4, 5, 6, 7, and 9 weeks pi in both WM and GM compared to uninjured control animals (Hesp et al., 2015). This shows a long-term maintenance of the OPCs population in both rats and mice and it overall reveals that proliferation of OPCs during the first two weeks is the source of newly formed oligodendrocytes and remyelination at later times. The oligodendrogliogenesis and total number of oligodendrocytes over time after injury outlined in Fig. 4.

Figure 4

OPCs are the main source of new mature oligodendrocytes after TSCI and the reduction in the extent of OPCs at chronic phase after injury is a result of oligodendrocyte differentiation. This assumption has been confirmed using mapping the fate of OPCs after injury (Assinck et al., 2017). There was significantly more oligodendrocytes at 12 weeks pi compared with 3 weeks pi. Reciprocally, there was lower percentage of recombined OPCs (17%) at 12 weeks pi compared with 3 weeks pi (35%) (Assinck et al., 2017).

Schwann Cells

A total of 11 studies reporting data concerning Schwann cells and the comprehensive information as specified above were retrieved (Gilson and Stensaas, 1974, Matthews et al., 1979, Griffiths and McCulloch, 1983, Blight, 1985, Bartholdi and Schwab, 1998, Brook et al., 1998, Salgado-Ceballos et al., 1998, Yang et al., 2006, Hui et al., 2010, James et al., 2011, Assinck et al., 2017). The experimental data of these studies were based on observations in 70 Sprague-Dawley rats (one study), 87 Lewis rats (two studies), 108 Long-Evan rats (2 studies), 24 Wistar rat (one study), 233 CreER transgenic mice (one study), 35 cats (2 studies), 30 zebrafish (one study) and 5 Rhesus monkeys (one study).

Reported data were based on immunohistochemistry, light and electron microscopy techniques. Also in one study the fate and origin of Schwann cells at the desired time was elucidated using the technology of CreER transgenic mice. In the earlier studies the presence of Schwann cells in the CNS parenchyma was identified using ultrastructural evaluations, Schwann cells produce thicker and more compact sheaths comparing to oligodendrocytes. While in the recent articles the expression of the P_0 was chosen as the marker of the myelinating Schwann cells. A schematic comparison between the morphology and composition of myelin generated by Schwann cells in the CNS versus that derived from OPC differentiation is depicted in Fig. 5.

Figure 5

Myelin production by Schwann cells is a protracted process, which occurs in moderate to severe spinal cord injuries (data were not available for mild injuries). The migration of Schwann cells to the spinal cord parenchyma was reported to be limited due to the presence of astrocytes (Franklin and Blakemore, 1993). Eventually, in moderate to severe injuries, where the supportive cells, particularly astrocytes, suffer considerable damage, Schwann cells can migrate to the CNS tissue (Salgado-Ceballos et al., 1998). The extensive presence of dividing Schwann cells suggests that these cells are at least partly responsible for axon ensheathment/remyelination after injury (Hui et al., 2010).

The number of proliferative Schwann cells increases over time after injury. In one study evaluating the proliferative potential of $P75^+$ Schwann cells in Rhesus monkeys, a 14-fold increase in the number of BrdU positive Schwann cells was detected at 25 weeks compared to 7 weeks pi, while there was no proliferative Schwann cells in non-injured control (Yang et al., 2006).

At one week pi, Schwann cells or their precursors appeared caudal to the lesion (0.5-2 mm from the epicenter). The precursors were small, undifferentiated cells lacking a basement membrane and were in association with sprouts of invading axons near the roots (Gilson and Stensaas, 1974, Blight, 1985). Also, bipolar spindle-shaped cells with ovoid nucleus were randomly dispersed, which is a typical morphology of migrating Schwann cells (Brook et al., 1998). In zebrafish, division of Schwann cells was observed at day 10 after injury which probably is the onset for ensheathment/remyelination (Hui et al., 2010).

At the second week pi, the presence of Schwann cells were also detected in the dorsal funiculi (Bartholdi and Schwab, 1998), they possessed basement membrane, elongated nucleus and were closely associated with individual axons (Gilson and Stensaas, 1974, Matthews et al., 1979).

By the third week, groups of axons myelinated by Schwann cells were frequent around the cystic cavity and base of the dorsal columns (Griffiths and McCulloch, 1983). Up to one month pi, many unmyelinated fibers were enveloped by Schwann cells, either isolated or in small clusters (Salgado-Ceballos et al., 1998). In addition, many axons appeared to be remyelinated by Schwann cells (Hui et al., 2010, James et al., 2011).

Six weeks pi, at the dorsal column, there were fascicles with thin perineural sheath containing up to 50 axons and restricted to immediate regions of the lesion site (Matthews et al., 1979). By two months pi, many of myelinated axons had grown toward the scar matrix. Those in dorsal region were apparently myelinated by Schwann cells (Matthews et al., 1979, Salgado-Ceballos et al., 1998). At this time, approximately one third of the fibers were myelinated and the ratio of myelinated axons by Schwann cells to oligodendrocytes was about 8:1 (Salgado-Ceballos et al., 1998). It is worth noting that in this report the authors assume that thick myelin sheaths are associated with Schwann cells.

As the injury progressed into chronic stages (3 and 4 months), many axons had dense, healthy myelin sheaths and it was often associated with the presence of Schwann cells (Salgado-Ceballos et al., 1998, James et al., 2011). The Schwann cells contribution in remyelination of the axons in dorsal column was also confirmed by co-staining of axons (NF 200) and Schwann cell-associated myelin (P_0) (James et al., 2011). In this study P_0 reactivity was detected at 4 and 12 weeks but not one week pi. Remyelination by Schwann cells continued by 12 months pi (Salgado-Ceballos et al., 1998).

Although the Schwann cells contribution in remyelination after SCI is a well-shown evidence, the origin of the present Schwann cells in the CNS parenchyma is still a contentious issue. In a recent study at 12 weeks pi fate mapping experiments revealed that the most majority of Schwann cells (about 70-80%) which contribute in myelin production after TSCI were derived from Olig2$^+$ and PDGFRα$^+$ CNS OPCs rather than P_0 expressing peripheral myelinating Schwann cells (Assinck et al., 2017). OPC-derived myelinating Schwann cells were mainly found in the dorsal column (Assinck et al., 2017).

DISCUSSION

Extensive oligodendrocytes cell death during the first two weeks after injury leave a broad number of denuded axons in the epicenter as well as distal regions. Oligodendrocyte cell death occurs through both mechanisms of apoptosis and necrosis while apoptosis was initially detected in epicenter and was extended rostro-caudally.

Along with the mature oligodendrocytes, many OPCs are lost at early stages, however, as early as one day pi they start proliferation at the lesion borders and spared tissues. Later, differentiation of these newly formed OPCs compensate the lack of oligodendrocytes. Oligodendrogliogenesis continues at later stages until the number of oligodendrocytes return to normal (by one month pi). Despite differences between animals after TSCI, the glial response to injury and in particular myelinating cells shares similarities.

Recently numerous studies in the field of spinal cord regeneration has been focused on oligodendrocyte protection and enhancing remyelination after TSCI. Demyelination is a part of secondary injury cascade which initiate immediately after injury. The present preclinical evidence reveals the potential of remyelination in adult tissue. Remyelination of spared and growing axons occurs through a two-step process: 1. providing a sufficient population of myelinating cells and 2. induction of remyelination.

Therefore, a key determinant of the success of remyelination after injury is the proliferative ability of myelinating cells. In this study according to the included articles it can be concluded that oligodendrocytes within a demyelinated region of spinal cord are not induced to divide in the presence of demyelinated axons and the survived oligodendrocytes are post-mitotic and do not contribute to the remyelination in adult CNS. However, it should be noted that the oligodendrocyte proliferation after TSCI was not fully refute and there are some studies discussing the proliferative ability of oligodendrocytes within a demyelinated region of spinal cord (Vick et al., 1992). According to the fact that the Schwann cells and OPCs proliferation after injury is a prerequisite to remyelination, the finite proliferative potential of oligodendrocytes after injury may be the cause of low contribution of mature oligodendrocytes in remyelination.

OPCs constitute the dominating proliferating cell population in the intact adult spinal cord (Horky et al., 2006, Sellers et al., 2009, Barnabe-Heider et al., 2010). Indeed, according to accumulating evidence in this study spinal cord injury results in changing the proliferation rate of OPCs over time and within the first two weeks the proliferation rate of OPCs reaches to a maximum at both regions of epicenter and lesion border (Fig. 3). Reduction in the proliferation is followed by the oligodendrocyte differentiation, as demonstrated by detection of an elevated number of oligodendrocytes one week after injury which reaches to the normal level by about one month pi. Endogenous remyelination after TSCI was also confirmed by detection of an increase in the expression of MBP at first week pi compared to earlier days (Bartholdi and

Schwab, 1998, Horky et al., 2006, McDonough et al., 2013, Hesp et al., 2015, Assinck et al., 2017). However, Assinck et al. through fate mapping of the OPCs showed that although there was a significant increase in the extent of new myelin from 3 to 12 weeks pi, the total myelin did not demonstrate a significant change and they attribute this to the myelin turn over and replacement between 3 and 12 weeks pi (Assinck et al., 2017).

Schwann cells that normally reside in peripheral nervous system, participate in remyelination of the denuded axons within the cord through a protracted process. Abundant preclinical (Martin et al., 1996, Oudega and Xu, 2006, Guest et al., 2013, Deng et al., 2015, Kanno et al., 2015) and clinical studies (Saberi et al., 2008, Anderson et al., 2017) have been conducted to evaluate the safety and efficacy of Schwann cell transplantation for repair of injured spinal cord. After peripheral nerve injury Schwann cells dedifferentiate into non-myelinating Schwann cells and proliferate extensively. These newly formed non-myelinating Schwann cells migrate within the lesion and involved in nerve regeneration through expression of neurotrophic factors and neural cell adhesion molecules, recruitment of macrophages for removal of myelin debris as well as myelination or ensheathment of growing axons after differentiation into myelin-forming Schwann cells. A moderate improvement of motor function after Schwann cell transplantation was also concluded in a systematic review discussing the efficacy of Schwann cell transplantation for motor function recovery after spinal cord injuries in animal models (Hosseini et al., 2016). There is some evidence showing that spinal cord injuries and disruption of the glia limitations induce Schwan cells invasion within the CNS parenchyma and remyelination (Gilson and Stensaas, 1974, Matthews et al., 1979, Griffiths and McCulloch, 1983, Blight, 1985, Franklin and Blakemore, 1993, Bartholdi and Schwab, 1998, Salgado-Ceballos et al., 1998, Hui et al., 2010, James et al., 2011). Besides of cell migration evidence, considerable proliferation of Schwann cells in the lesion confirm the participation of these cells in axon ensheathment/remyelination after TSCI.

Schwann cells mostly contributed in ensheathment/remyelination of axons in the dorsal column. Although in the most studies this observation has been attributed to the route of peripheral Schwann cells invasion, one recent study through a comprehensive evaluation of the fate of OPCs showed that CNS OPCs are the main origin of remyelinating Schwann cells in the dorsal column (Assinck et al., 2017). Axon ensheathment/remyelination by Schwann cells continued to one year pi.

In conclusion, the cumulative evidence shows that in animal models, the number of oligodendrocytes approaches to the normal levels after about one month pi. The majority of oligodendrocytes are lost at the epicentre and adjacent regions, however, OPCs proliferation and subsequent differentiation to myelinating cells (both oligodendrocytes and Schwann cells) are the main route to compensate the extensive demyelination after injury. Invading peripheral Schwann cells also contribute in remyelination. Therefore, pharmacotherapy for enhancing OPCs proliferation and differentiation to mature myelinating cells (oligodendrocytes or Schwann cells) can be the therapeutic target (Imamura et al., 2015) and the evidence-based trends obtained for oligodendrocyte apoptosis, proliferation and differentiation can be used as a guide to design preclinical and in the next step clinical studies.

Limitations of the work:

Although the evidence shows that oligodendrogliogenesis and axon ensheathment/remyelination after TSCI is a continual process by the chronic phase, we do not yet know whether the newly myelinated axons are functional, since mature oligodendrocyte can remyelinate even dead axons or artificial fibers (Lee et al., 2012, Lee et al., 2013). Therefore, the functional benefit of the new formed myelin remains to be clear.

CONFLICT OF INTREST STATEMENT

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

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FIGURE LEGENDS AND TABLES

Fig. 1. PRISMA Flow diagram

Fig. 2. Evidence-based representation of temporal and spatial progress of oligodendrocytes apoptotic death after traumatic spinal cord injuries (TSCI): The extent of cell death is showed at the epicenter and the areas adjacent to the epicenter (i.e. 1-14 mm). The first sign of apoptotic death was observed at the epicentre at 6-24 hours post-injury. At day 3-7 the maximum number

of apoptotic oligodendrocytes was detected at the epicentre. After this time point, the majority of oligodendrocytes are dead (no results were reported at the epicentre after day 7: dash line as the hypothetic cell death trend). On the other hand, in the areas adjacent to the epicenter (distal), oligodendrocytes apoptosis was maximized at around 7 days post-injury. All the related data regardless of the method and reporting format are compiled in this schematic figure.

Fig. 3. Temporal proliferative response of oligodendrocyte progenitor cells (OPCs) in response to TSCI: Proliferation rate at the epicentre decreases within a few days after injury compared to normal animals in which a constant low proliferation rate of progenitor cells is observed (horizontal dash line). However, the proliferation rate reached to a maximum in the epicenter at one week post-injury. At the lesion border and distal area, the proliferation of OPCs increases and peaks within 1-2 weeks post-injury, followed by a decrease to approach normal levels by the 10th week.

Fig. 4. Evidence-based temporal representation of the total number of mature oligodendrocytes: The total number of oligodendrocytes decreases dramatically due to extensive cell loss during the first week pi. At day 7, the earliest evidence of MBP mRNA was reported at the lesion borders which indicates a trigger for remyeliantion. During the second week, more progenitor cells are formed contributing to the subsequent increase in the number of mature oligodendrocytes. Oligodendrogliogenesis, i.e. increase in the number of newly formed mature oligodendrocytes, is followed by proliferation of progenitor cells from the second week onward until the total number of oligodendrocytes reaches to the number of cells in normal controls (dash line).

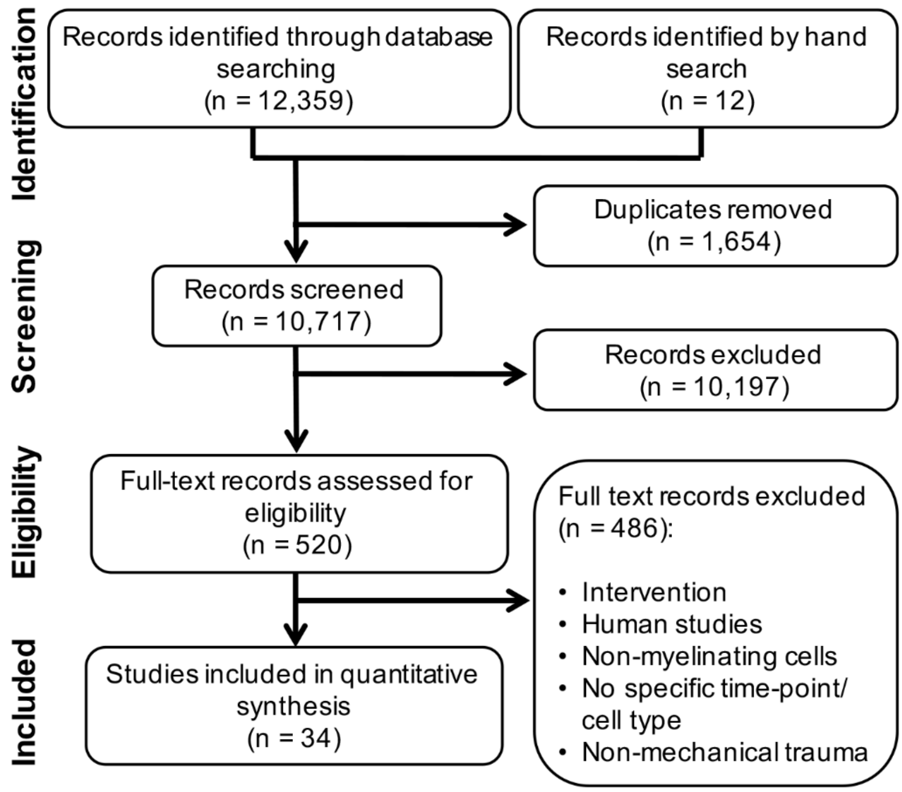
Fig. 5. Axon demyelination and remyelination after traumatic spinal cord injury (TSCI): (A) in the normal adult CNS tissue myelin sheath is produced by oligodendrocyte and each cell forms one segment of myelin for several adjacent axons. (B) TSCI results in extensive oligodendrocyte death and subsequently axon demyelination. Survived oligodendrocytes are post-mitotic and their contribution in remyelination is negligible. (C) However, increased proliferation and recruitment of oligodendrocyte progenitor cells (OPCs) and their differentiation to the mature myelinating oligodendrocytes at the injury site compensate the lack of myelin forming cells. (D) Schwann cells originated from peripheral nervous system or differentiated from OPCs are another contributing cells for myelin formation after TSCI. Myelin sheath formed by Schwann cells have thicker thickness and mainly contains P0,

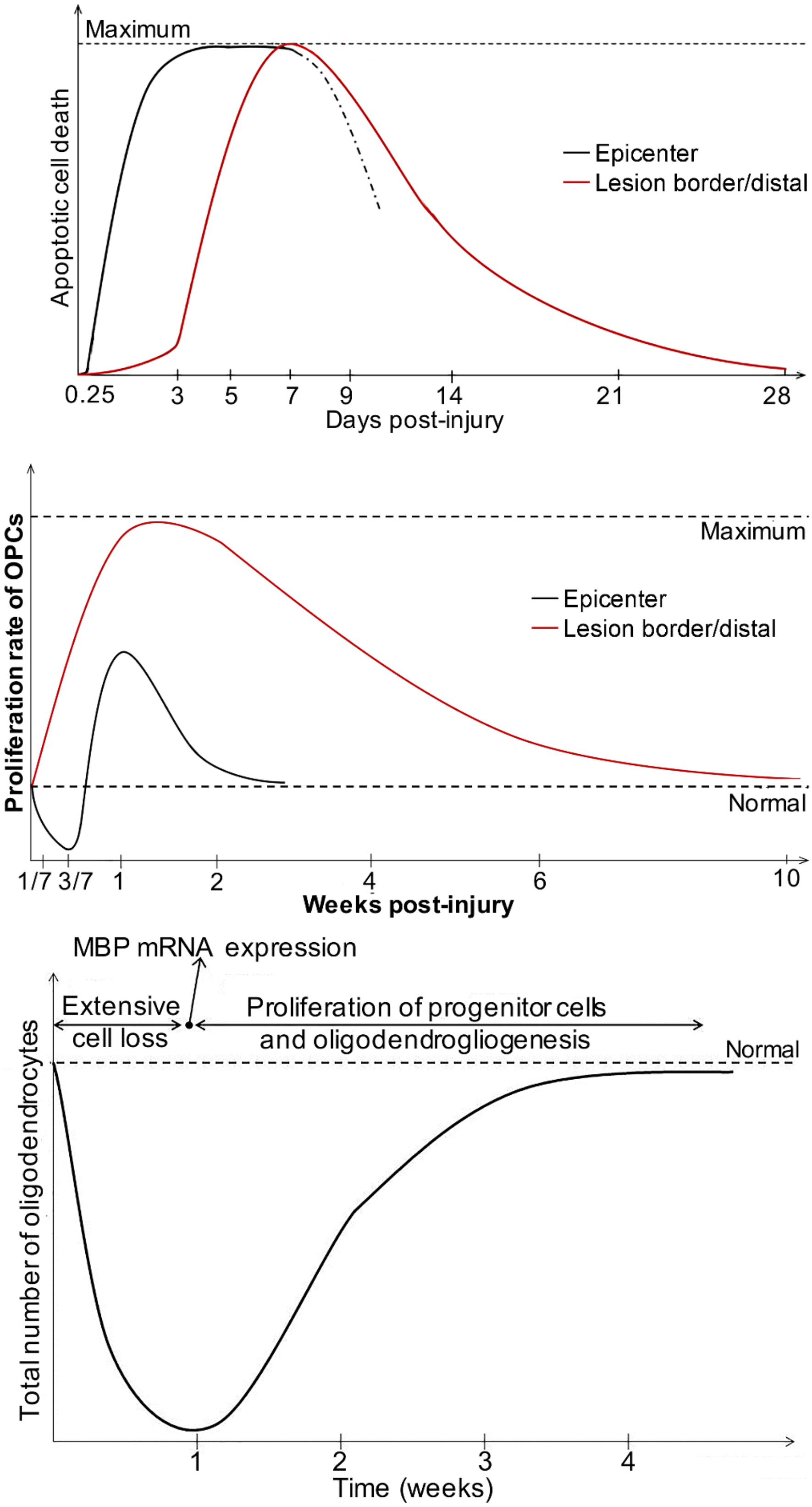
peripheral myelin protein 22 kD (PMP22) and myelin basic protein (MBP). Also, each Schwann cell can wrap only on axon. However, myelin produced by oligodendrocytes has thinner thickness and contains myelin proteolipid protein (PLP), 2',3'-Cyclic nucleotide 3'-phosphohydrolase (CNPase), receptor interacting protein (RIP) and myelin basic protein (MBP).

Table 1 Characteristics of included studies

Table 2 Quality assessment of included studies

Table 3 Summary of the markers and methods used to identify the cell types (i.e., oligodendrocytes and oligodendrocyte progenitor cells) and to detect apoptosis





Maximum
Apoptotic cell death
Epicenter
Lesion border/distal
0.25
3
5
7
9
14
21
28
Days post-injury
Proliferation rate of OPCs
Maximum
Epicenter
Lesion border/distal
Normal
1/7
3/7
1
2
4
6
10
Weeks post-injury
MBP mRNA expression
Extensive cell loss
Proliferation of progenitor cells and oligodendrogliogenesis
Normal
Total number of oligodendrocytes
1
2
3
4
Time (weeks)

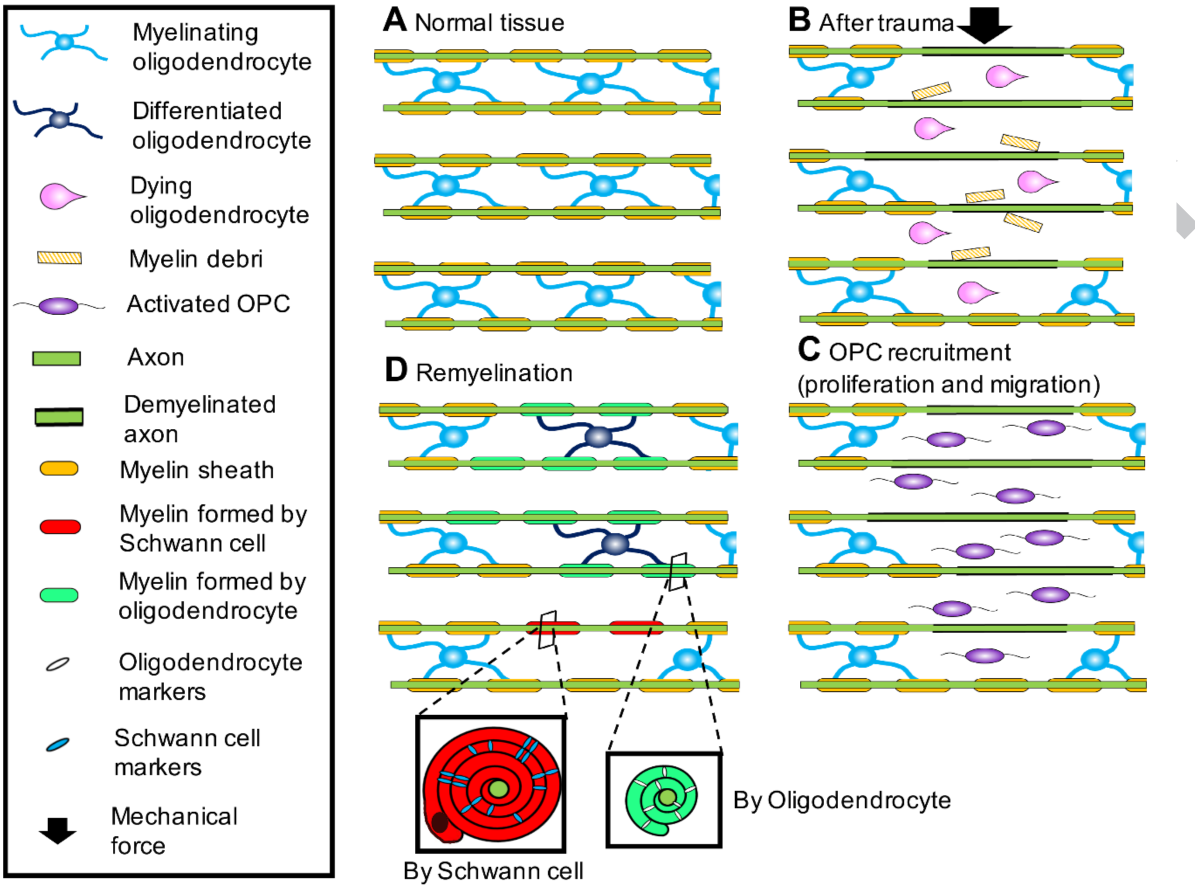


Table 1 Characteristics of the included studies

	First author, Year	Sample Size (T/Inj./Cont.)[1]	Gender/ Species/ Weight (g) or Age	Method/ Level of Injury	Severity of Injury	Method of Evaluation	Time (post-injury)[3]
1	Abe 1999	N[2]/N/N	M/ Wistar rat/4 W	Complete transection T11	razor blade	Immunohistochemistry, TUNEL	3, 5, 7, 14D
2	Assinck 2017	233/at least 3/2	M&F/ CreER transgenic mice	Contusion T9-10	Infinite Horizons Impactor, 70 kdyne	FACS, BrdU, Immunohistochemistry	3, 12 W
3	Barnabe-Heider 2010	54/9/N	M&F /FoxJ1-CreER, Cx30-CreER and Olig2-CreER mice/2-8.5 M	Transection T4,T10	Dorsal funiculus was cut transversely without reaching the gray matter	Immunohistochemistry, TUNEL, BrdU	14 D, 4 M
4	Bartholdi 1998	36/at least 2/1	N/Lewis rat/8 W	Hemisection T10	2/3 of spinal cord depth	Immunohistochemistry	6, 24 H, 2, 4, 8, 14 D
5	Blight 1985	26/5/10	F/Mongrel cats/Adult	Compression T9	A 13 g cylindrical brass weight was dropped by a pin in the	Light and electron microscopy	2, 7 D, 3, 8 M

					tube 20 cm above T9		
6	Brook 1998	24/at least 3/N	M/Wistar rat/ 200–250	Compression T11-T12	Balloon inflated with 40 µl distilled water and left in place for 5 minutes	Immunohistochemistry	2, 7, 14, 28 D
7	Casha 2001	N/N/N	F/Wistar rats/220-260	Compression C7-T1	Moderately severe, Kerr Lougheed aneurysm clip, 35 g closing force, clip compression	Immunohistochemistry, TUNEL, Electron microscopy	1, 3, 7, 14 D
8	Ceruti 2009	N/5/N	M/CD1 mice/ Adult	Compression T5-T8	Clip compression, closing force of 24 g, 1 min	Immunohistochemistry, BrdU, Light microscopy, Haematoxylin eosin staining, luxol fast blue staining, Methyl green pyronin staining	24, 72 H, 1 W
9	Dong 2003	27/at least 6/N	N/ Mice/ 25–30	Hemi-transection T9	Transection on the right side only	Immunohistochemistry, Electron microscopy	8, 30 D
10	Frei 2000	26/5/5	F/Lewis rat/2 W	Contusion T8	Moderate to severe injury contusion, NYU	Immunohistochemistry	7 D
11	Gilson 1974	51/N/N	N/Lewis rat/ 150	Hemi-transection T1-T2	Severe, razor, interrupted the dorsal columns, leaving the lateral funiculi intact	Light microscopy	1, 4, 7,14 D
12	Griffiths 1983	9/1/N	N/Cat/N	Contusion L2	100, 150, 200 g/cm	light and electron microscopy	1:30 H, 1, 3, 21, 42 D
13	Grossman 2001	56/5/N	F/SD[4] rat/ 200–250	Contusion T8	Incomplete contusion, 10g, 2.5cm	Electron microscopy, Immunohistochemistry	15 min, 4 H, 8, 1, 2 D
14	Hesp 2015	(Mice) 29/N/N (Rats) 35/N/N	M&F/Mice/12 weeks F/SD rat/250	Compression T9 mouse T8 rat	Moderate-severe (75 kDyne force; mouse),moderate (150 kDyne force; rat) contusion injury Infinite Horizons device	Immunocytochemistry	0, 7, 14, 28, 42, 70 D

					(Precision Instruments)		
15	Horky 2006	344/5/5	F/Fisher rat/160-185	Hemisection T8	Hemi	BrdU, Immunohistochemistry	1D, 1 M
16	Huang 2014	108/N/N	N/SD rat/250-320	Compression L1	Custom-made screw	Immunohistochemistry, TUNEL	1, 3, 7 D
17	Hui 2010	30/6/6	N/Zebrafish/ 3–4 cm	Compression 15–16th vertebrae	1 S with a number-5 Dumont forceps	BrdU, Transmission electron microscopy, Immunohistochemistry	3, 7, 10, 15 D, 1 M
18	James 2011	70/at least 4/N	F/SD rat/ Adult	Compression T10	Infinite Horizon impactor, moderate severe (159 kDyn)	Immunohistochemistry	1 D, 1, 2, 4, 12 W, 6 M
19	Li 1999	32/4/N	M/Rat /370	Compression T1, T5, T7, T8–9, T10, T12, L2	Compression, 35-50 g, 5 min	Hematoxylin and eosin, Immunohistochemistry, Luxol fast blue, TUNEL	4, 9 D
20	Lytle 2007	N/at least 2/N	F/C57BL6 mice/5-7 W	Contusion T8-9	2g, 2.5cm Mild	Immunohistochemistry, BrdU	1, 3, 7, 28D
21	Matthews 1979	80/20/20	M/LE[5] rat/Adult	Transection T5	Strict aseptic technique	Light and electron microscopy	15, 30 90 D
22	McDonough 2013	135/10/5	F/Swiss Webster mice/6-8 W	Compression T10	Laterally compressed the spinal cord to a thickness of 0.35 mm and held for 15 s using one pair of modified forceps	Immunocytochemistry, BrdU, Nissl staining	1, 2, 3, 4, 6, 8, 10, 12 W
23	McTigue 2001	N/at least 4/N	F/Fischer/rat/170	Contusion T8	Oohio state electromagnetic spinal cord injury device (rapidly displace spinal tissue 1.1 mm f), moderate to severe	Immunohistochemistry, BrdU	7, 14, 28D
24	Rabchevsky 2007	N/6/6	F/SD rat/200–225	Contusion T10	Moderate, NYU injury device	Immunohistochemistry	2, 7, 14, 42 D
25	Salgado-Ceballos 1998	28/at least 3/N	F/LE rat/14-16 W	Contusion T9	weight-drop, severe	Electron microscopy	1, 2, 4, 6, 12 M
26	Sellers 2009	N/N/N	N/Mice/8 W	Hemisection T9-10	cutting the dorsla spinal cord tissue until the central	Immunohistochemistry, Flow cytometry,	1, 2 W

					canal could be visualized		
27	Shuman 1997	N/at least 3/N	N/ Rat/ N	Contusion T10	NYU weight drop device, 25g-cm	Immunohistoc hemistry	8, 21 D
28	Tripathi 2007	24/at least 5/N	F/SD rat/225–264	Contusion T8	Moderate spinal contusions using the OSU injury	Electron microscopy, BrdU	1, 3, 4, 7, 14 D
29	Wang 2009	36/at least 3/N	F/SD rat/230-250	Transection T8	microscissors transected both the dorsal ascending tract and corticospinal tract bilaterally	Electron microscopy, Immunocytoc hemistry	10, 30 D
30	Warden 2001	21/3/3	F/Fisher rat/ 155-165	Transection T7-8	Junction between T7-T8 cord segments, microscissors lesion the dorsal funiculi and dorsal horns bilaterally	Immunohistoc hemistry, TUNEL	4, 24 H, 3, 7, 14, 28 D
31	Wu 2005	N/5/5	M/SD rat/ 280-330	Contusion T11-12	2mm weighting 30g was gentely placed on dura for 10 min	Immunohistoc hemistry, NG2, GFAP, DAPI, 3CB2, GFAP	1 D, 1, 4, 8, 12 W
32	Yang 2006	5/1/1	M/Rhesus monkey/6–14 Y	Hemi-section C6-C7	Right-sided, 30, 50, 65% hemi-section	Immunohistoc hemistry, BrdU, Electron microscopy	7 W and 7 M
33	Yong 1998	N/N/N	F/SD rat/300-350	Contusion T9-T10	Severe, weight-drop method with the NYU impactor, using 50.0 g/cm force	Immunohistoc hemistry, TUNEL	1, 3, 7, 14, 28 D
34	Zai 2005	40/at least 4/N	F/SD rat/ 225–275	Contusion T8	10g-2.5cm-2.4mm	Immunohistoc hemistry, BrdU	3, 7, 42 D

[1] T: the number of total animals used in the study; Inj.: the number of injured animals in each experimental group; Cont.: the number of animals (i.e. normal, sham operated or laminectomy) in each control group
[2] N: not specified
[3] S: second; Min: minute; H: hour; D: day; W: week; M: month; Y: year
[4]SD: Sprague-Dawley
[5]LE: Long-Evans

Table 2 Quality assessment of included studies

	First author and Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	Abe 1999	+	+	+	+	+	?	+	?	+	+	?	?	?	?	+
2	Assinck 2017	+	+	+	+	+	+	+	+	+	+	+	+	+	+	?
3	Barnabe-Heider 2010	+	+	+	+	+	+	+	+	+	+	?	?	+	?	?
4	Bartholdi 1998	+	+	+	+	+	+	+	+	+	+	+	?	?	?	?
5	Blight 1985	+	+	+	+	+	+	+	+	?	?	?	?	?	?	?
6	Brook 1998	+	+	+	+	+	+	+	?	+	?	+	?	?	?	?
7	Casha 2001	+	+	+	+	+	?	+	?	?	+	+	?	+	?	?
8	Ceruti 2009	+	+	+	+	+	+	+	+	+	?	+	?	?	?	?
9	Dong 2003	+	+	+	+	+	+	+	+	+	?	?	?	?	?	?
10	Frei 2000	+	+	+	+	+	+	+	+	+	+	?	?	?	?	?
11	Gilson 1974	+	+	+	+	+	?	?	?	?	?	?	?	?	?	?
12	Griffiths 1983	+	+	+	+	+	+	+	+	+	+	+	?	?	?	?
13	Grossman 2001	+	+	+	+	+	+	+	+	+	?	?	?	?	?	?
14	Hesp 2015	+	+	+	+	+	?	+	?	+	+	+	?	+	?	?
15	Horky 2006	+	+	+	+	+	+	+	+	+	+	+	?	+	?	?
16	Huang 2014	+	+	?	+	+	?	+	+	+	+	?	?	?	+	?
17	Hui 2010	+	+	+	+	+	+	+	+	+	?	-	?	?	?	?
18	James 2011	+	+	+	+	+	+	+	+	+	+	+	?	?	?	?
19	Li 1999	+	+	+	+	+	+	+	?	+	?	?	?	?	?	?
20	Lytle 2007	+	+	+	+	+	+	+	+	+	+	+	?	+	?	?
21	Matthews 1979	+	+	+	+	+	+	+	+	?	?	+	?	?	?	?
22	McDonough 2013	+	+	+	+	+	+	+	+	+	+	+	?	+	?	?
23	McTigue 2001	+	+	+	+	+	+	+	+	+	+	?	?	?	?	+
24	Rabchevsky 2007	+	+	+	+	+	+	+	+	+	+	+	?	+	?	?
25	Salgado-Ceballos 1998	+	+	+	+	+	+	?	+	+	+	+	?	?	?	?
26	Sellers 2009	+	+	+	+	+	?	+	?	?	?	?	?	?	?	?
27	Shuman 1997	+	+	+	+	+	+	+	+	+	+	?	?	?	?	?
28	Tripathi 2007	+	+	+	+	+	+	+	+	+	+	+	+	?	?	+
29	Wang 2009	+	+	+	+	?	+	+	+	+	?	?	?	?	?	?
30	Warden 2001	+	+	+	+	+	+	+	+	+	?	+	?	?	?	?
31	Wu 2005	+	+	+	+	+	+	+	?	?	+	+	?	?	?	?
32	Yang 2006	+	+	+	+	+	+	+	+	+	+	?	?	?	?	?
33	Yong 1998	+	+	+	+	+	?	+	?	+	+	+	?	+	?	+
34	Zai 2005	+	+	+	+	+	+	+	+	+	?	?	?	?	?	?

1. Species; 2. Using appropriate tests; 3. Severity of injury; 4. Level of injury; 5. Age/weight; 6. Number of injured animals per group; 7. Designation of strain; 8. Definition of control (normal, sham operated or laminectomy); 9. Description of statistical analysis; 10. Regulation and ethics; 11. Bladder expression; 12. Blindness of assessor; 13. Genetic background; 14. Method of allocation to treatments; 15. Description of the reasons to exclude animals from the experiment during the study (attrition), where + means clearly specified, ? has not specified clearly, and – specified as it has not been considered in the study.

Table 3 List of the markers and methods used to identify the cell types (i.e., oligodendrocytes and OPCs[1]) and to detect apoptosis

Cell types/Assessment type	Markers/ Method of Assessment
Mature oligodendrocytes	CC1(anti-APC [2]) CNPase [3] PLP [4] MBP [5] RIP [6]

OPCs	Olig2 NG2 [7] PDGFRα [8]
Proliferation assay	BrdU (Bromodeoxyyuridine)
Apoptosis assay	TUNEL (Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling) Caspase-3 expression

[1] Oligodendrocyte Progenitor Cells
[2] Anti-Adenomatous Polyposis Coli
[3] 2',3'-Cyclic nucleotide 3'-phosphohydrolase
[4] Myelin Proteolipid Protein
[5] Myelin Basic Protein
[6] Receptor Interacting Protein
[7] Neuron-Glial Antigen 2
[8] platelet-Derived Growth Factor Receptor-alpha

Highlights

- Extensive oligodendrocyte death during the first two weeks after TSCI leave a broad number of denuded axons
- OPCs start proliferation at the lesion borders and spared tissues as early as one day after injury
- Within the first two weeks after injury the proliferation rate of OPCs reaches to a maximum
- Differentiation of newly formed OPCs compensate the lack of oligodendrocytes
- OPC-derived Schwann cells as well as invading peripheral Schwann cells also contribute in remyelination after TSCI