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Role of endogenous Schwann cells in tissue repair after spinal cord injury☆

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Abstract

Schwann cells are glial cells of peripheral nervous system, responsible for axonal myelination and ensheathing, as well as tissue repair following a peripheral nervous system injury. They are one of several cell types that are widely studied and most commonly used for cell transplantation to treat spinal cord injury, due to their intrinsic characteristics including the ability to secrete a variety of neurotrophic factors. This mini review summarizes the recent findings of endogenous Schwann cells after spinal cord injury and discusses their role in tissue repair and axonal regeneration. After spinal cord injury, numerous endogenous Schwann cells migrate into the lesion site from the nerve roots, involving in the construction of newly formed repaired tissue and axonal myelination. These invading Schwann cells also can move a long distance away from the injury site both rostrally and caudally. In addition, Schwann cells can be induced to migrate by minimal insults (such as scar ablation) within the spinal cord and integrate with astrocytes under certain circumstances. More importantly, the host Schwann cells can be induced to migrate into spinal cord by transplantation of different cell types, such as exogenous Schwann cells, olfactory ensheathing cells, and bone marrow-derived stromal stem cells. Migration of endogenous Schwann cells following spinal cord injury is a common natural phenomenon found both in animal and human, and the myelination by Schwann cells has been examined effective in signal conduction electrophysiologically. Therefore, if the inherent properties of endogenous Schwann cells could be developed and utilized, it would offer a new avenue for the restoration of injured spinal cord.

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Key Words

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Research Highlights

(1) Following spinal cord injury, endogenous Schwann cells invaded the lesion site, involving in tissue repair and axonal regeneration and myelination.
(2) Invaded Schwann cells can move a long distance away from the injury site both rostrally and caudally.
(3) Endogenous Schwann cells can be induced to migrate by minimal insults within the spinal cord and integrate with astrocytes under certain circumstances.
(4) Endogenous Schwann cells can be promoted to migrate into the spinal cord by exogenous cell transplantation.

Abbreviations

SCI, spinal cord injury; PNS, peripheral nervous system; CAM, cell adhesion molecules; CNS, central nervous system; OECs, olfactory ensheathing cells; BMSCs, bone marrow stromal cells; GFAP, glial fibrillary acidic protein

INTRODUCTION

To date cell transplantation therapies have been considered a major method in a promising strategy for the treatment of spinal cord injury (SCI) both in pre-clinical research and clinical trials. Schwann cells are one of the cell types which are most widely studied and most commonly used for cell transplantation to restore the injured spinal cord[1-2]. Schwann cells are a major cellular component of the peripheral nerve, and as a glial cell type in the peripheral nervous system (PNS), they are responsible for the axonal myelination and ensheathing. In addition, Schwann cells play a crucial role in endogenous repair of peripheral nerves, including axonal regeneration following a PNS injury[3].

Many studies have shown that Schwann cells express a variety of factors which contain members of the neurotrophin family including neurotrophin-3, brain-derived neurotrophic factor, and nerve growth factor, as well as cilliary neurotrophic factor, glial cell line-derived neurotrophic factor, and fibroblast growth factor. Schwann cells also produce surface molecules such as L1/Ng-cell adhesion molecules (CAM) and N-CAM. In addition, Schwann cells secrete substrates such as laminin, fibronectin, and collagen. All these factors, molecules, and substrates have been demonstrated to support or promote the axonal growth both in PNS and central nervous system (CNS)[3-4].

These unique features make Schwann cells a potential candidate for a cellular approach to repair the injured spinal cord. In the experimentally contused spinal cord, implantation of Schwann cells fills the cavity, limits further tissue loss, and promotes regeneration of severed axons, resulting in functional recovery[5]. Transplanted Schwann cells are capable of myelinating regenerating axons or remyelinating demyelinated axons[6-7]. More importantly, axons remyelinated by transplanted Schwann cells exhibited restoration of conduction through the lesion with reestablishment of normal conduction velocity[8].

Normally, Schwann cells are not present in the spinal cord, however, they have been found invading the lesion area following SCI in rodent[9], nonhuman primate[10], and human[11-15], indicating that they most likely are involved in endogenous repair. Interestingly, several studies have reported that transplantation of olfactory ensheathing cells (OECs), bone marrow stromal cells (BMSCs), and cultured Schwann cells may induce the migration of host Schwann cells from PNS into the injury site of spinal cord[16-17]. This invasion of endogenous cells in a transplant suggests that host Schwann cells may contribute to the recovery observed in such transplants[1]. The purpose of this mini review is to discuss the role of the endogenous Schwann cells in tissue recovery with or without cell transplantation following SCI.

ENDOGENOUS SCHWANN CELLS IN REPAIRED TISSUE

Our observation and others have revealed that the spinal cord has inherent ability to repair itself following injury[9, 15, 18], although it is limited and slow. Following spinal cord contusion (such as 25 mm height setting), the entire gray matter and dorsal white matter were destroyed at the injury epicenter. Consequently, numerous fibroblasts from activated pia mater and Schwann cells from dorsal roots invade the lesion epicenter due to the destruction of glial limitans. Two weeks later, the lesion cavity appears and the glial scar forms, which lines the spared tissue surrounding the cavity. At the same time, newly formed tissue, which is called initial endogenous repaired tissue, can be seen at the dorsal portion of the lesion cavity. The newly formed repaired tissue faces the lesion cavity, which is filled with macrophages, and is connected to the spared tissue with trabeculae containing fibroblasts, blood vessels and nerve fibers[9, 19]. The formation of the glial scar and repaired tissue can be considered as endogenous repair in response to the traumatic injury to the spinal cord. This endogenous repaired tissue, different structurally from either regular connective tissue scar or normal cord tissue, contains blood vessels, fibroblasts, collagen fibers, Schwann cells, and some regenerating axons. According to our own observation, the endogenous repaired tissue can be divided morphologically into three irregular zones: fibrotic zone, cellular zone, and axonal zone[18] (Figures 1, 2).

Fibrotic zone: Residing under the dorsal pia matter, the fibrotic zone consists mainly of invading fibroblasts, collagen fibers, and newly formed blood vessels; it also contains some invading Schwann cells, regenerating axons (myelinated or ensheathed by Schwann cells), macrophages and sometimes bubble-like structures, which may be related to the degenerating axons. Regenerating axons, myelinated or unmyelinated, are usually assembled into small bundles, surrounded by a thin layer of fibroblasts. This morphology is similar to what is seen in the peripheral nerves. The whole fibrotic zone appears as a quasi-loose connective tissue, distinguishable from the close cellular zone.

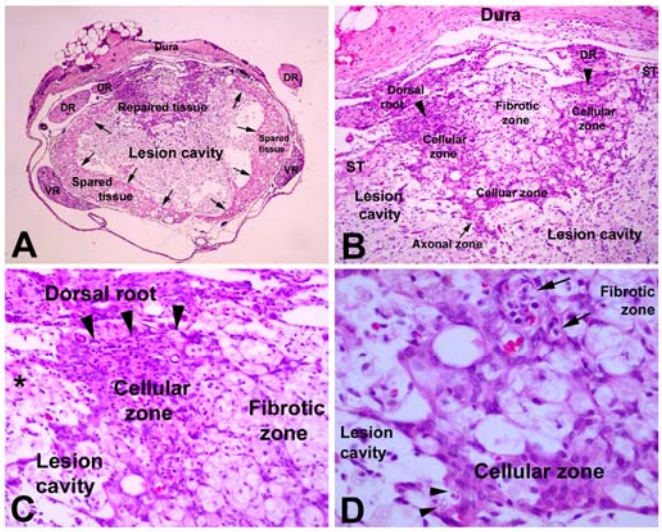

Figure 1 Endogenous repaired tissue in cross section from injury epicenter of a rat (6 weeks after 25 mm contusion; hematoxylin-eosin staining).

(A) The repaired tissue located at the dorsal part of damaged cord, connects bilaterally to the spared tissue, and neighbors the lesion cavity, which is surrounded by the glial scar (arrows) and spared tissue.

(B) Under higher magnification, the repaired tissue can be divided into three different zones: fibrotic, cellular and axonal. The fibrotic zone is surrounded by a U-shape cellular zone. The axonal zone does not appear clearly due to its small amount of axons at this moment.

(C) The cellular zone, connecting to both spared tissue (*) and fibrotic zone, consists mainly of Schwann cells migrating from dorsal root (arrowheads).

(D) Regenerating axons (myelinated fibers) with hematoxylin-eosin staining are difficult to identify at the axonal zone (arrowheads), cellular zone and fribrotic zone (arrows).

DR: Dorsal root; VR: ventral root. Magnifications: 4 × (A), 10 × (B), 20 × (C), 40 ×(D). Replicated from reference [18] with permission.

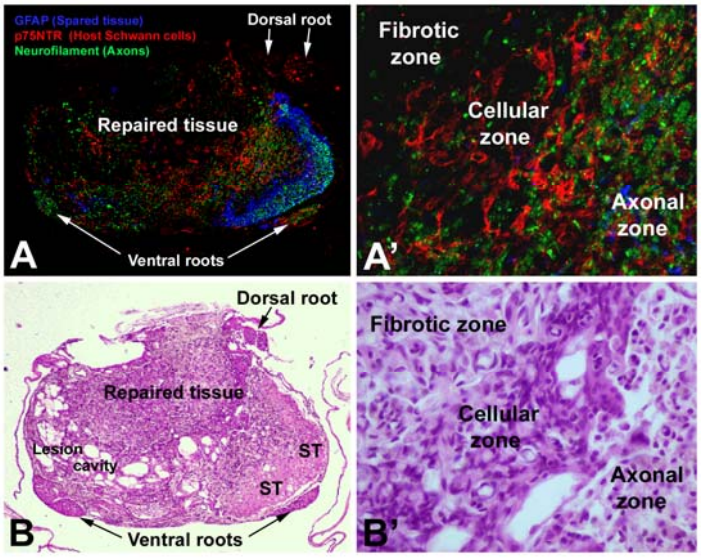

Figure 2 Fluorescent images of Schwann cells and axons.

Neighboring cross paraffin sections of injury epicenter from a rat 14 weeks after contusion were immunostained with antibodies against $p75^{NTR}$ (Schwann cells), neurofilament and glial fibrillary acidic protein (A) and routinely stained with hematoxylin-eosin (B) as comparison. A' and B' are the local magnifications of A and B, respectively. Schwann cells derived from the dorsal root are distributed in three zones of the repaired tissue (with higher density in the cellular zone) and spared tissue. Axons are also present in three zones of the repaired tissue and spared tissue, but the axonal zone (regenerating axons) and spared tissue (spared or regenerating axons) have a higher density of axons. ST: Spared tissue. Magnifications: 4 × (A, B), 40 × (A', B'). Replicated from reference [18] with permission.

Cellular zone: The cellular zone is composed of densely compacted, reactive young cells, and forms a clear U-shaped shell surrounding the fibrotic zone together with the pia matter at the dorsal border of the damaged cord. These young cells appear as immature Schwann cells and are often observed connecting to the cells from the dorsal roots, indicating that these young cells may migrate from the dorsal roots. The cellular zone also contains blood vessels and some myelinated axons detected by P0 antibody (against myelin protein zero of peripheral nerve), but less than that in the axonal zone in count. At the earlier stage of tissue repair, the cellular zone is thin and small, but it can become thick and expand in size with time or following intervention treatments.

Axonal zone: Usually, the axonal zone neighbors on the cellular zone ventrally and faces the lesion cavity. It has the smallest size in untreated spinal cord when compared with the other two zones. It has a characteristic feature that it consists mainly of unmyelinated axons and myelinated axons positively stained by P0 antibody. The axons may form into small bundles usually without fibroblasts surrounding them. These bundles can be arranged either loosely or densely, depending on the amount of axons. At the later stage of the spinal cord injury, axons in this zone may increase in number. However, this increase is limited and slow if the injured spinal cord receives no treatment.

Under the fluorescence microscope, Schwann cells labeled with antibodies $p75^{NTR}$ were found distributed in the dorsal and ventral roots, endogenous repaired tissue including fibrotic zone, cellular zone and axonal zone, and spared tissue, indicating that these Schwann cells migrate from the spinal roots. In the cellular zone, Schwann cells appear denser than the other zones; in the axonal zone, Schwann cells are present together with numerous regenerating axons detected with antibody SMI-31, consistent with images observed in P0-immunostaining samples.

Blood vessels are also distributed in all three zones and some of the blood vessels including capillaries are located close to the regenerating axons. However, these blood vessels lack an integrated blood-brain barrier, demonstrated by the glial fibrillary acidic protein (GFAP) immunostaining showing that these blood vessels are not surrounded by the perivascular feet of astrocytes as seen in the uninjured spinal cord tissue or in the spared cord tissue of injury site. In addition, repaired tissue may contain ependyma-derived cells from central canal[18, 20].

MYELINATION BY ENDOGENOUS SCHWANN CELLS

Many studies have shown that regenerating axons or spared demyelinated axons were myelinated and ensheathed by the endogenous Schwann cells, which have been observed by electron microscopy; transplanted Schwann cells were also able to myelinate axons[4, 6, 9, 19]. The myelin sheaths formed by Schwann cells at the injury site also can be detected by monoclonal antibody P0[21-22].

P0-positive myelination showed characteristics in different areas. For example, P0-positive myelin sheaths in the fibrotic zone form small fascicles encircled by a layer of fibroblasts, showing the PNS style. P0-positive myelin sheaths in the cellular zone do not form fascicles but scatter among densely compacted Schwann cells. In the axonal zone, numerous P0-positive myelin sheaths are aggregated and are dense in appearance. In the spared tissue, the P0-possitive myelin sheaths (regenerating or demyelinated axons) are distributed unevenly[18] (Figures 3A–D).

Demyelination occurs in the white matter of spinal cord following traumatic injury, due to the delayed death of apoptotic oligodendrocytes[23], and poor remyelination of demyelinated axons that can persist long after SCI both in experimental animals[24] and human patients[12]. Under this situation, the endogenous Schwann cells and myelination formed by Schwann cells are always seen at the injury area and area adjacent to it of the injured spinal cord[18]. The endogenous Schwann cells have also been reported to appear in the injured spinal cord in various animal models[25-30]. In a human case, it was found that a regenerating axon was myelinated by both endogenous Schwann cells and oligodendrocytes[13], indicating that events that Schwann cells invade the lesion area and myelinate regenerating or demyelinated axons are a common phenomenon, which reveals a natural requirement for the self repair of spinal cord following injury.

Studies have revealed that remyelination of demyelinated axons by endogenous Schwann cells[31] occurred, which resulted in the reestablishment of relatively normal impulse conduction velocity in some animal models of CNS demyelination[30, 32-34]. Axons remyelinated by transplantation of cultured Schwann cells from rats or human also exhibited restoration of conduction through the lesion[7-8].

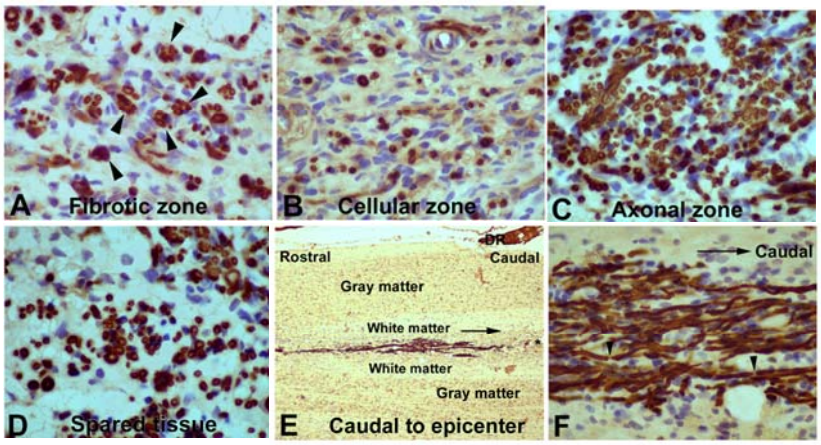

Figure 3 P0-positive myelin sheaths in different areas of rats with chronically contused spinal cord (P0 immunostaining; A–D, cross section; E, F: horizontal section).

(A) In the fibrotic zone, P0-positive myelin sheaths (myelinated fibers, dark brown in color) form small fascicles encircled by a layer of fibroblasts (arrowheads), showing the PNS style.

(B) P0-positive myelin sheaths in the cellular zone do not form fascicles but scatter among densely compacted Schwann cells.

(C) In the axonal zone, numerous P0-positive myelin sheaths are aggregated and are dense in appearance.

(D) In the spared tissue, the P0-positive myelin sheaths (regenerating or demyelinated axons) are distributed unevenly.

(E) P0-positive myelin sheaths found 15 mm caudal to the injury site. They are distributed along with a small longitudinal cyst (*) in the dorsal funiculus. The arrows indicate the direction of Schwann cell movement. DR: Dorsal root.

(F) The local magnification of E, clearly showing the P0-positive myelin sheaths. The node of Ranvier is pointed by arrowheads. Nuclei of both Schwann cells and other cells of spinal cord were stained in purple with hematoxylin.

Magnifications: 4 × (E), 40 × (A–D, F). Replicated from reference [18] with permission.

ARE ENDOGENOUS SCHWANN CELLS ABLE TO MIGRATE OUTSIDE OF THE INJURY SITE?

In general, transplanted Schwann cells were restricted to the site of implantation due to limited migratory ability and lower survival rate[35-36], which included transplantation into the contused spinal cord of rats. However, immunological demyelination with[37] or without[38] a contusion injury, and ethidium bromide-induced demyelination[31, 39] were found to facilitate the migration of transplanted Schwann cells from the site of implantation. The mechanisms of migration are not clear.

Our observation with endogenous tissue repair following spinal cord contusion injury of rats illustrates endogenous Schwann cells not only migrate into the lesion epicenter, but also move away from the epicenter both rostrally and caudally. Intriguingly, these migrating Schwann cells usually move along the surrounding area of tapering lesion cavity (Figures 3E, F). Another characteristic is that they myelinate a population of demyelinated axons[18]. Taken together, under a suitable environment, either implanted or host Schwann cells are able to migrate a long distance from the implantation site or SCI epicenter, benefiting the tissue repair and myelination after SCI, especially a chronic injury. However, the mechanisms remain to known.

DO SCHWANN CELLS INTEGRATE WITH ASTROCYTES?

Unlike OECs, Schwann cells do not migrate into astrocyte-containing areas. Coculture of Schwann cells with astrocytes showed that these two cell types separate into distinct, nonoverlapping areas, suggesting that Schwann cells and astrocytes are mutually excluded[40-41]. When transplanted into normal white matter, Schwann cells do not migrate extensively and show poor long-term survival[42-44]. It has been predicted that transplanted Schwann cells would be unable to migrate and proliferate within astrocyte-rich environments (such as those that occur in trauma or chronic demyelination), and would therefore be unable to integrate extensively within damaged CNS[35, 40].

However, the mutual exclusivity between Schwann cells and astrocytes is not absolute. For example, axonal myelination of CNS by Schwann cell can eventually occur in the astrocytic environment of the myelin deficient 'shaking pup'[45]. Raisman and his coworkers have shown that Schwann cells grafted into the CNS induced a transient but marked host astrocytic hypertrophy, but this minimal astrocytic response did not appear to impede the migration of the donor Schwann cells[46-47].

In our previous studies, we found that after removal of glial scar with a method of rose Bengal-based phototoxis, numerous Schwann cells migrate into the spared tissue and myelinate the demyelinated or regenerating axons, where asctrocytes were still present[48]. This observation revealed that, at least under certain conditions, it is possible for Schwann cells to integrate with astrocytes in chronic SCI.

DOES MINOR INJURY CAUSE SCHWANN CELL MIGRATION?

It has been well established that spinal cord injury induces peripheral Schwann cells to migrate into the lesion site from the dorsal roots[9]. This is probably attributive to some kind(s) of factors or signals related to the injury. It has been reported that at the chronic stage of spinal cord injury a secondary injury can cause damage to neuronal cells[49]. In our previous observations, however, there were no neurons at the lesion epicenter; therefore no neuronal death occurs when the glial scar ablation was performed. Our results have demonstrated that after scar ablation, a large number of endogenous Schwann cells invaded the spared tissue tested by intense P0-positive myelination[48]. Rose Bengal-based scar ablation is a kind of minor injury to the spared tissue of the spinal cord, and does not additionally impair the cord tissue and descending and ascending conduction. In fact, the invasion of endogenous Schwann cells induced by photochemical scar ablation may be beneficial to the tissue repair and the functional recovery on conduction and locomotion.

CAN CELL TRANSPLANTATION PROMOTE INFILTRATION OF HOST SCHWANN CELLS?

In addition to the induction of Schwann cells migrating to the injury site by traumatic lesion and minor injury such as rose Bengal-based photochemical scar ablation, they may also be induced to migrate by cell transplantation. Hill *et al*[16] have observed the invasion of endogenous p75-positive Schwann cells into Matrigel and fibrin cables containing transplanted lysed Schwann cells (with and without surrounding polymer channels, respectively) placed into completely transected spinal cord. This suggested that grafted Schwann cells may induce host Schwann cells migrating into the injury epicenter and these endogenous Schwann cells may play an important role in the repair observed after transplantation of Schwann cells.

It has been reported that the host Schwann cells invade the core of transplanted olfactory ensheathing cells at the injury site and, while grafted olfactory ensheathing cells were reduced in number due to cell death, there was an increase in number of endogenous Schwann cells[50]. Our own results also demonstrated that the injury epicenter of spinal cord was filled with p75-positive Schwann cells and P0-positive myelination in rat with transplantation of olfactory lamina propria and olfactory ensheathing cells[51]. Based on the observations mentioned above, it was concluded that olfactory ensheathing cells have created a CNS environment that facilitates migration and integration of infiltrating endogenous Schwann cells[50, 52].

BMSCs transplanted into the injury site of rat spinal cord also can induce numerous endogenous Schwann cells to invade the transplant, making the graft larger and more densely packed with cells (especially endogenous Schwann cells) than BMSC grafts[53-54]. BMSCs have been demonstrated to have some bridging capacity in sharp transection models which get populated by endogenous Schwann cells[1].

Taken together, traumatic SCI including severe and minor, as well as cell transplantation with Schwann cells, OECs, and BMSCs may promote migration of endogenous Schwann cells into the injury epicenter. These invaded endogenous Schwan cells may play a critical role in tissue repair, axonal regeneration, and probably functional recovery. The positive effect of endogenous Schwann cells should be considered as a means or treatment of chronic SCI. However, the mechanisms are unknown, and it needs to be further studied.

SIGNIFICANCE OF ENDOGENOUS TISSUE REPAIR WITH SCHWANN CELLS

It has been well established that endogenous Schwann cells invade and migrate into the lesion site after SCI

caused either by contusion[4, 10], transection/hemisection[6], or photochemical insult[55]. Several other studies using various animal models have also reported the presence of endogenous Schwann cells in the injured spinal cord[25-26, 29, 56-57]. In addition, these invaded Schwann cells could myelinate or ensheath large numbers of generated or demyelinated axons within the injury site[9]. Moreover, remyelination by endogenous Schwann cells was found to be effective in conducting action potentials[8]. All these observations indicate that the invasion of endogenous Schwann cells is definitely beneficial to the anatomical repair and axonal regeneration, or even functional recovery.

More importantly, the phenomenon of Schwann cell invasion into the injured spinal cord and their association with axons is not only restricted to animal models, but is also found in chronic human SCI[11-12, 15, 58-59], suggesting that Schwann cell invasion into the lesion site following SCI is a common natural phenomenon. Therefore, the ability of endogenous Schwann cells to migrate into the injured spinal cord may offer an exciting new avenue for further research in the field of spinal cord repair. Should mechanisms or treatments be invented that evoke enough Schwann cells to migrate from the nerve roots into the lesion site, then possibly a new, minimally invasive, repair strategy may be conceived. This kind of strategy would circumvent the need for time-consuming *in vitro* culture systems and invasive transplantation methods if endogenous Schwann cells were indicated for tissue repair in the future[3].

However, as we have known, the role of endogenous Schwann cells has not been well documented, including that if endogenous Schwann cells are beneficial to the survival of neurons, and the establishment of new synaptic connection in injured spinal cord. The disadvantage of endogenous Schwann cells in recovery of injured spinal cord may be related to the formation of Schwannoma[59] and neuropathic pain[60]. Therefore, further study on the role and regulation of the endogenous Schwann cells in injured spinal cord is needed.

CONCLUSION

Following spinal cord injury, numerous endogenous Schwann cells migrate into the lesion site from the nerve roots, involving in the formation of repaired tissue and myelination of regenerating and demyelinated axons. They are able to travel a long distance for myelinating axons rostrally and caudally from the injury site. The endogenous Schwann cells could be induced to move by minimal invasive insult, such as photochemical glial scar ablation, or transplanted cells including exogenous Schwann cells, OECs, and BMSCs. Should these inherent abilities of endogenous Schwann cells be developed and utilized for tissue repair and axonal regeneration, it would shed light into the strategies for the restoration of injured spinal cord in animal experiments and clinical trials.

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