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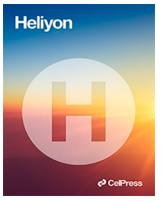

Review article

Application of"Spinal cord fusion" in spinal cord injury repair and its neurological mechanism

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ABSTRACT

Spinal cord injury (SCI) is a severely disabling and catastrophic condition that poses significant global clinical challenges. The difficulty of SCI repair results from the distinctive pathophysiological mechanisms, which are characterised by limited regenerative capacity and inadequate neuroplasticity of the spinal cord. Additionally, the formation of cystic cavities and astrocytic scars after SCI further obstructs both the ascending and descending neural conduction pathways. Consequently, the urgent challenge in post-SCI recovery lies in repairing the damaged spinal cord to reconstruct a functional and intact neural conduction circuit. In recent years, significant advancements in biological tissue engineering technology and novel therapies have resulted in a transformative shift in the field of SCI repair. Currently, SCI treatment primarily involves drug therapy, stem cell therapy, the use of biological materials, growth factors, and other approaches. This paper comprehensively reviews the progress in SCI research over the years, with a particular focus on the concept of "Spinal Cord Fusion" as a promising technique for SCI reconstruction. By discussing this important research progress and the neurological mechanisms involved, our aim is to help solve the problem of SCI repair as soon as possible and to bring new breakthroughs in the treatment of paraplegia after SCI.

Spinal cord injury (SCI) is a severely disabling and catastrophic disease that results from a variety of external factors including traffic accidents, high-altitude falls, violent trauma, sports injuries, and other traumatic events [1]. Injury to the spinal cord leads to limb dysfunction and paralysis, encompassing the loss of motor and sensory functions. Moreover, it can trigger autonomic nerve dysfunction such as urinary and faecal incontinence. SCI can also directly or indirectly cause severe complications including central neuralgia, lung infection, urinary tract infection, bedsores, deep vein thrombosis of the lower limbs, and limb deformities. Hence, individuals paralysed after SCI suffer a substantial burden on themselves, their families, and society owing to their incapacity for work, long-term rehabilitation requirements, consumption of significant medical resources, and expensive medical treatments. It has been estimated that the annual incidence of SCI in the world is 10.4–83/1,000,000 [2,3], in the United States the incidence of SCI is 54/1,

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000,000 with about 17,810 new cases per year [4–6], while in China, the situation is equally grim, with an annual incidence of SCI is approximately 23.7–60.6/1,000,000 [7,8]. Despite significant progress in understanding the pathophysiology and secondary injury mechanisms of SCI, effective treatments remain elusive in clinical practice because of the exceedingly limited regenerative capacity and irreversible damage to neuronal systems.

SCI repair remains a worldwide medical problem yet to be resolved. SCI causes severe damage to central nervous system, the reversal of which has proven to be very difficult. Achieving long-distance axon regeneration has proven to be a significant challenge in neuroscience, primarily because of the complex underlying pathophysiological hurdles involving the post-traumatic formation of cystic cavities and development of dense astrocyte scar [9–11]. These structural changes present formidable obstacles that block both ascending and descending neural conduction pathways. Furthermore, injured neurones are ensnared in an unfavourable microenvironment, featuring an inhibitory extracellular matrix (ECM) surrounding the injury site, inhibitory myelin-related proteins (e.g. NOGO-A, MAG, and OMgp), and a deficiency in regenerative factors that promote axon growth [11,12]. This inhospitable 'milieu' culminates in secondary cell injury and impedes neuronal regeneration. Thus, resolving these challenges is crucial for the success of future SCI therapies. In recent years, the field of SCI repair has witnessed notable advancements owing to the development of innovative bioengineering techniques and novel therapies. Currently, SCI therapy primarily involves drug therapy, stem cell therapy, biological materials, growth factors, and other forms of neural stimulation, all of which have demonstrated effectiveness in treating SCI. However, the therapeutic outcomes remain unsatisfactory. Based on this background, this review addresses SCI-related studies designed to introduce and propose the concept of "spinal cord fusion" (SCF), aiming to help solve the medical problems of SCI repair and bring new breakthroughs for SCI paraplegia treatment.

1. Previous study on spinal cord neural reconstruction

1.1. Human clinical reports

Two patients with SCI have recovered a substantial amount of neuromuscular function by bridging the transected spinal cord via axonal regrowth mechanisms. In 2005, Goldsmith et al. [13] reported a case of a 24-year-old female who underwent complete T6-T7 spinal cord transection after a high-speed ski accident. The injury led to the complete loss of motor, sensory, and bladder sphincteric functions below the T6-T7 level, classifying the injury as ASIA A SCI grade [14]. At 39 months post-injury, the patient underwent spinal reconstruction surgery, in which a 4 cm gap was left between the spinal stumps following precise removal of the scar tissue. The gap was filled with semi-liquid collagen, complemented by a pedicled omental graft to promote neural regrowth across the spinal cord gap, utilising collagen as a growth-promoting matrix. Six months postoperatively, the patient exhibited leg mobility with progressive strength gains in the trunk and abdominal wall observed within one year. Four years after reconstruction, the patient was able to ambulate over extended distances using a walker. Although a comprehensive neurophysiological assessment was not conducted, the observed improvements in limb function were impressive. In 2014, Tabakow et al. [15] documented a 38-year-old male who sustained a T9 traumatic SCI, resulting in clinical symptoms indicative of complete spinal cord transection (SCI grade: ASIA A). The patient underwent a spinal cord reconstruction procedure that involved resection of the glial scar, transplantation of previously cultured olfactory ensheathing cells and olfactory nerve fibroblasts from the patient's olfactory bulb into the injury site, and bridging of the 10 mm spinal gap using four autogenous sural nerves. After strict postoperative neurological rehabilitation over 19 months, the patient experienced partial recovery of autonomous lower limb movement and partial restoration of deep and shallow sensations. These two human clinical case reports collectively suggest that repair and reconstruction strategies for SCI hold promise as viable options, with potential success in enhancing functional recovery.

1.2. Inspiration from animal experiments

During the 1950s–1960s, Freeman [16], a neurosurgeon in America, conducted experiments on rats by completely transecting the spinal cord using a very sharp blade and then carefully rejoining the severed ends. Surprisingly, postoperative paraplegic rats exhibited the ability to walk several months after spinal cord transection, and a substantial number of newly formed axons were observed to bridge the transected area. These axons appeared to cross the transection site and innervate the distal end. Notably, electrical stimulation studies demonstrated the transmission of electrical signals across the transection site. Similar results were later observed in dogs. Freeman recognised that the experimental setting for acute surgical spinal cord transection differed significantly from the complex nature of clinical cord injuries. Spinal cord injuries involve broad and lengthy lesions that impede postoperative functional recovery. Freeman aimed to replicate this clinical scenario by designing surgical procedures that mimicked the clinical context. The researchers first removed the damaged area of the spinal cord, resected the vertebral body, shortened the spine, and joined the fresh parts of the spinal cord stump. This procedure facilitated animal walking post-spinal cord transection, as it allowed axon growth in the area of the spinal cord anastomosis. In 2012, Illis [17] highlighted the fruitless history of research focused solely on the lesion site and emphasised the significance of preserving an intact central nervous system for functional improvement. Freeman's approach exemplifies this concept by capitalising on the regenerative potential of otherwise healthy and intact spinal cord tissue while removing damaged and scarred segments.

2. Spinal cord fusion (SCF): a new technique for SCI repair and reconstruction

2.1. Concept of "spinal cord fusion"

Bittner, a Ph.D. physiologist in Texas, performed extensive research on peripheral nerve regeneration and demonstrated the membrane-fusing properties of polyethylene glycol (PEG) for acutely transected peripheral nerves [18–22]. Shi et al. [23–26] also demonstrated that the application of the hydrophilic polymer PEG to isolated adult guinea pig spinal cord injuries led to the recovery of anatomical tissue integrity, conduction of nerve impulses through the lesion, and behavioural recovery. Drawing upon the above research evidence of successful repair of SCI in both animals and humans, Ren and Canavero proposed a concept termed "spinal cord fusion (SCF)" [27–31]. This concept aimed to address the challenges of spinal cord reconstruction and functional repair following SCI caused by complete spinal cord transection.

The technique involves using a specialised surgical instrument, referred to as the "artificial gem knife", to precisely remove the injured segment of the completely transected spinal cord. Subsequently, a spinal cord fusogenic agent, primarily composed of the neuroprotective agent PEG (PEG Cocktails), was swiftly applied to reapproximate the spinal cord stumps, inducing the actual fusion of the freshly severed ends. This fusion process reconstructs the neural and electrical continuities of the previously injured spinal cord. Postoperatively, electrical stimulation was employed to expedite the regeneration of neuronal axons, ultimately facilitating the restoration of motor and sensory functions following SCI. SCF offers a promising approach to enhance the restitution of electrical continuity and the fusion rate of neuronal axons, thereby potentially accelerating the repair process and improving functional recovery after SCI.

2.2. Key steps to accelerating neuronal axon fusion

Acceleration of the spinal cord repair process is crucial. The primary objectives include minimising the extent of SCI and enhancing the rate of axonal growth across the transected spinal cord. To achieve these goals, SCF is implemented using fusogens to facilitate neural fusion and regrowth. Additionally, electrical stimulation can be employed to accelerate the overall processes of neural fusion, regrowth, and the restoration of neurophysiological functions. This comprehensive approach aims to optimise the repair and recovery processes following SCI in a systematic and scientifically sound manner.

2.2.1. Fusogens

Fusogens play a critical role in restoring the integrity of neural membrane following transection, thereby reinstating the electrophysiological conduction properties of the spinal cord. Controlled application of fusogens initiates axon growth approximately one week after treatment; such growth becomes more stable over time and is long-term [32]. Various molecular reagents, such as chitosan nanospheres [33], PEG-biopolymer matrix [29,34,35], IKVAV transmembrane-spanning peptide [36], and olfactory mucosa autografts [37] have been utilised as scaffolds in chronic SCI models to facilitate neuronal regrowth across gaps in the transected spinal cords. In contrast, PEG serves as a genuine fusogen by stabilising the membranes of transected neurones at the site of spinal cord transection, leading to the fusion of these transected axons with neighbouring axons across the transection site. This fusion expedites neural conduction and allows electrical stimulation to propagate within hours after spinal cord transection, as has been observed with neural fusion in peripheral nerves using a similar experimental approach. The timing of fusogen application is pivotal for successful neural fusion of the spinal cord. Transected spinal axons remain stable for only a brief window of about 10–20 min before undergoing fragmentation, a precursor to Wallerian degeneration. These severed neurones extend approximately 0.3 mm and remain viable for 3–7 days, with around 30 % of the proximal axons initiating regeneration within 6–24 h [29,32,34]. Therefore, the fusion agent must be applied rapidly (ideally within less than 10 min) at the junction of the severed spinal cord to optimise the efficacy of SCF. SCF relies on the swift application of PEG fusogen to achieve rapid fusion of two sharply transected spinal cord segments while minimising axon trauma at the transection site. This approach aims to accelerate the fusion process and minimise the detrimental effects on injured axons.

PEG, a relatively stable, non-toxic, and completely biocompatible, water-soluble linear polymer formed by ring-opening polymerisation of ethylene oxide's active anions, exhibits a molecular weight range from 0.4 to 100 kDa. Previous studies have demonstrated the neuroprotective properties of PEG, facilitating axonal membrane resealing and mitigating oxidative stress, thereby reversing persistent neuronal cell damage after injury [38]. Also, it can directly protect mitochondria, and effectively reduce acute necrosis and apoptosis while swiftly restoring the integrity of recently severed axons, making it a valuable asset in SCI therapy [18,30,38–40]. Despite its only recent adoption in SCI repair research, PEG has shown promising results. In a 2014 study [41], PEG 600 was used to bridge the gap between two spinal cord stumps in rats after transection, leading to axonal growth within one week. This growth continued steadily and proved to be long lasting, with substantial axon regeneration through the PEG bridge and the formation of new myelin sheaths. After eight months, the rats exhibited motor recovery [41]. While the fusion of transected spinal fibres by PEG may be limited (10–15 %), it is noteworthy that even these fused fibres, though not perfectly matched, may hold clinical significance. Studies indicate that only 10 % of the descending fibre bundles are sufficient to control certain limb movements in humans [42]. Therefore, the 10–15 % fibre bundle fusion achieved through PEG under these experimental conditions has considerable potential clinical significance. Moreover, experimental studies in rodent and dog SCI models have shown that PEG fusion outperforms other acute treatment strategies, including cell transplantation and gene therapy [30]. These findings underscore the potential of PEG as a valuable and superior option for promoting axon regeneration and functional recovery after SCI.

2.2.2. Electrical stimulation

Electrical stimulation can accelerate axon regeneration [43–45], promote the excitation of propriospinal neurones [46], and modulate injury currents [47]. SCF leverages postoperative electrical stimulation to accelerate SCF and facilitate sensorimotor recovery. A clinical study [44] in 2015 revealed that electrical stimulation enhanced peripheral nerve regeneration and effectively improved the sensory repair process of peripheral nerve injuries. Transcutaneous peripheral nerve stimulation for a short duration after SCI may offer a means to counteract axonal dysfunction and prevent chronic changes in axonal and muscle function, thus positively affecting the long-term outcomes of neurological rehabilitation [45]. Angeli et al. [46] demonstrated that the loss of autonomous motor control following the interruption of the descending fibres also triggers physiological changes in the excitability of the central nervous system. Repeated epidural electrical stimulation promotes the excitation of propriospinal neurones, which can support the propagation of spontaneous electrical commands to the "central pattern generators" in the cervical-lumbar spine. These neurones establish new synapses and neural circuits. Furthermore, Becker, three decades ago, highlighted the significance of prolonged electrical positivity during spinal shock as a primary hindrance to spinal cord repair in humans [47]. Accordingly, the delivery of a negative charge accelerates the recovery process by modulating the injury current. These collective findings underscore the potential of electrical stimulation as a valuable adjunct for promoting axon regeneration and functional recovery after spinal cord injuries, which has significant implications for neurological rehabilitation.

3. Current research progress of SCF domestically and internationally

3.1. Animal study

In recent years, SCF has been independently tested in Korea, China, and other countries, and remarkable results have been achieved in restoring motor function in rodents, dogs, and non-human primates. In South Korea, Kim et al. [48–52] conducted experiments involving acute transection of the cervical spinal cord (C5) in mice, rats, and dogs followed by reconstruction using the SCF technique. In mice, partial motor function is regained within 24 h and limb movement is observed after 2–4 weeks [48]. Subsequent immunohistochemical analysis confirmed restoration of spinal cord continuity across the transection site [50]. In rats, somatic-evoked potentials were recorded just 24 h postoperatively, with the rats able to stand and walk independently after two weeks [51,52]. Dogs exhibited a remarkable recovery of approximately 90 % sensorimotor function at three weeks postoperatively [49]. Similarly, in China, Ren's team employed the SCF technique to reconstruct complete SCI animal models at the thoracic spinal cord level (T10) in mice, rats, dogs and monkeys. The mice showed partial motor function restoration around 8–10 days post-surgery, with electrophysiological evidence of action potentials traversing the transection area [53]. Rats achieved independent walking capabilities four weeks after the operation, accompanied by somatic-evoked potentials detected through electrophysiology, and diffusion tensor imaging (DTI) demonstrated continuous morphological white matter fibres across the transection site [54]. Dogs regained motor function and ambulatory abilities after 60 days, with detected electrical signals traversing the transection site and DTI revealing comparable axonal continuity (Fig. 1(A-C)) [55]. Additionally, in cynomolgus monkeys, successful spinal cord repair was verified after spinal cord transection and reconstruction [56]. These collective findings provide robust evidence supporting the effectiveness of SCF in restoring

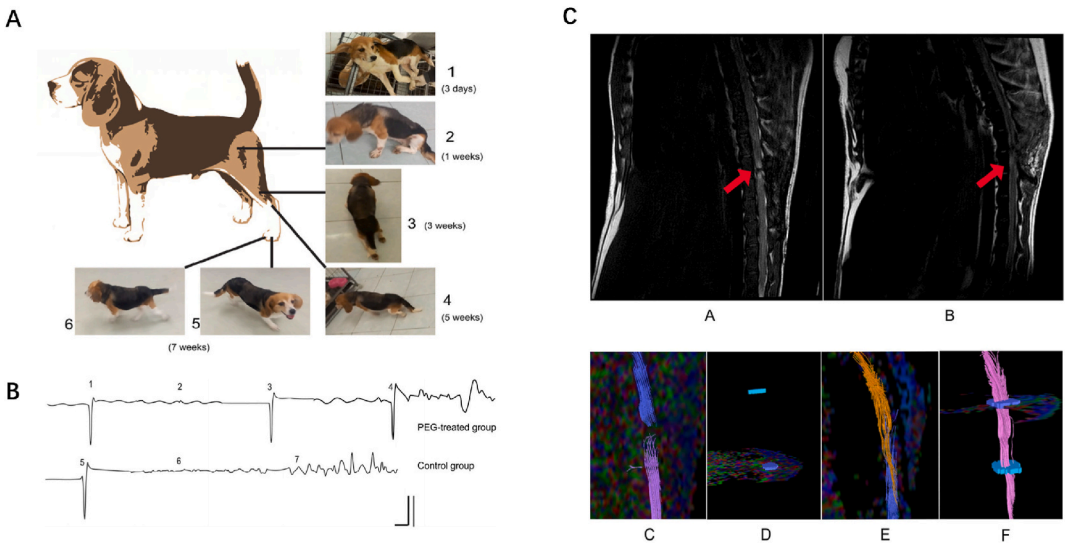

Fig. 1. Motor recovery of dogs using the SCF technique to reconstruct a complete SCI model A. After spinal cord at T10 was completely transected, motor recovery of dogs at day 3 and weeks 1, 3, 5, and 7 postoperatively. B. Electrophysiological detection: changes of spinal cord somatosensory-evoked potentials before spinal cord transection, immediately after transection and 2 months postoperatively. C. MRI examination: axon fusion in spinal cord transection detected by T2W and DTI images at 1 month postoperatively in both controls and PEG-treated animals [55].

motor function and promoting neural continuity in diverse animal models, thus holding great promise for clinical applications in SCI repair.

3.2. Clinical study

In 2019, our team established the Global Initiative to Cure Paralysis Alliance (GICUP) in Nanning, featuring the first SCF clinical transformation centre. The team initiated the first series of clinical trials of SCF (ChiCTR2000030788) at Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine. To date, 20 patients with paraplegic SCI have been recruited and treated with SCF surgery and no complications have been reported in the perioperative period. Preliminary results indicate that SCF can restore the morphological continuity of the spinal cord [57,58] (Fig. 2(A and B)). Neurophysiological assessments demonstrated that action potentials passed through the spinal cord transection area (Fig. 3(A-C)). Ongoing observations involve tracking the recovery of limb motor and sensory functions. Clinically, the operative methods for SCF are continuously being improved and optimised, and different operative procedures are being tailored to suit various patients with SCI. Currently, four major surgical plans are employed.

1) Spinal shortening surgery: primarily suitable for patients with acute complete SCI with injury areas generally not exceeding one spinal segment. This approach involves the removal of a single vertebral body, the injured spinal cord, and scar tissue from the SCI region. The upper and lower vertebral bodies are connected using a spinal internal fixation system, allowing close alignment of the two spinal cord ends. Subsequently, PEG is applied to the junction of the joined spinal cord stumps (Fig. 4).
2) Vascular pedicle hemisected spinal cord transplantation [57]: specifically designed for patients with chronic SCI with injury located in the thoracic segment, featuring only mild atrophy of the distal spinal cord. Based on a previous animal study [59], our team developed a novel procedure involving the resection of the spinal cord lesion and rotation of a short vascularized hemisection from one of the adjacent spinal cord stumps. First, the central area of the spinal injury, evaluated through radiological assessment and

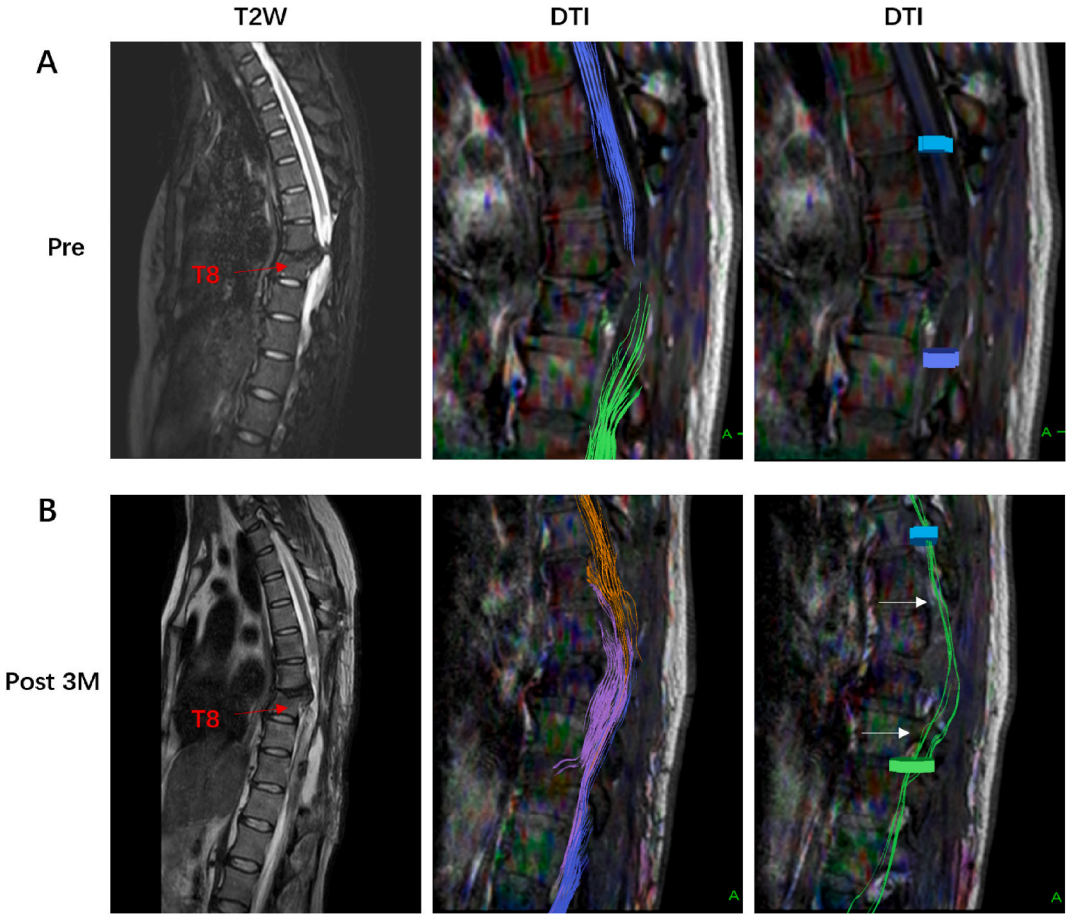

Fig. 2. Reconstruction of morphological continuity of the spinal cord in patients with SCI paraplegia using transplantation of a vascularized pedicle of hemisected spinal cord A. Preoperative T2W showed complete SCI and DTI showed complete breakdown of spinal cord. B. Three months postoperatively, T2W showed spinal cord reconnection and DTI showed morphological continuity of axons at the two transected spinal cord ends [57].

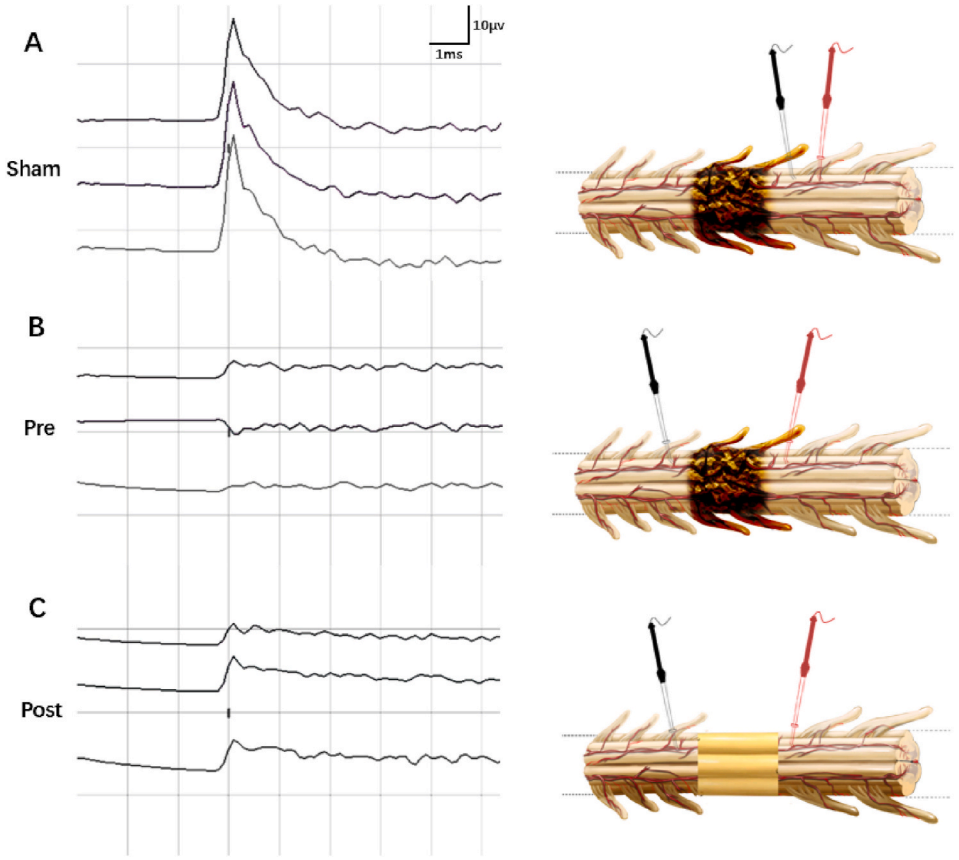

Fig. 3. Spinal cord evoked potentials (SCEP) in patients with SCI paraplegia showed signs of recovery postoperatively A. SCEP recorded at the distal normal spinal cord. B. Preoperative SCEP recorded at the SCI area. C. Postoperative SCEP recorded at the SCI area.

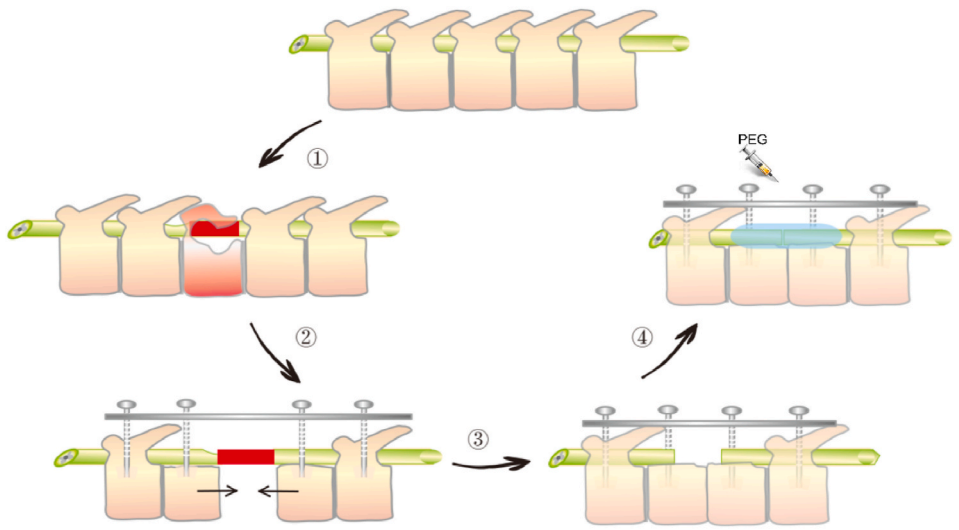

Fig. 4. Surgical procedures of spinal shortening surgery ①②. The single vertebral body, the injured spinal cord, and the scar tissue in SCI region are removed to produce two fresh ends of the spinal cord. ③. Using the spinal internal fixation system, the two vertebrae are connected so that the proximal and distal ends of the spinal cord are connected. In this way, the two spinal cord sections are closely joined, with no gaps in the sections. ④. PEG is locally applied at the end of the joined spinal cord stumps.

confirmed visually during surgery, is removed, leaving a gap surrounded by intact cord ends. Then, a vascularized hemicord attached by a pedicle of sufficient length is divided along the sagittal plane and turned over to fill the gap. One dorsal spinal artery is retained as the vascular pedicle at either the proximal or distal spinal cord stump to ensure adequate blood supply, and PEG is applied to both ends (Fig. 5(A-E)).

3) Sural nerve transplantation [58]: applied to patients with chronic SCI with injury areas close to the spinal cord and cauda equina or severe spinal atrophy at the distal end of the injured area. This technique involves the removal of contused spinal cord and scar tissue, followed by the arrangement of sural nerve segments into bundles, which are then sutured and transplanted into the spinal cord defect. Local application of the fusion agent is performed in both stumps of the spinal cord (Fig. 6(A-D)).
4) Vascularized allogeneic spinal cord transplantation: in accordance with the length of the SCI, the required spinal cord is obtained from a spinal cord donor and allotransplanted into the SCI recipient following the removal of the damaged spinal cord region. Notably, the donor spinal cord should carry the posterior intercostal artery pedicle to form a tunnel through the muscle space and anastomose with a perforator vessel of appropriate diameter in the paravertebral region of the recipient. The vascular pedicle should be appropriately placed during the operation to avoid tortuosity, disjunction, and torsion, and tension should be appropriate. After vascular reconstruction, the damaged area of the recipient's spinal cord is quickly resected and a spinal fusion agent is locally applied to the two ends. Neuroanatomically, this is a potentially effective bridging method to restore the continuity of the injured spinal cord because it can reconstruct the complete anatomical structure of the spinal cord segment, and the heterologous spinal cord has normal blood circulation; however, long-term immunosuppressive therapy is required to prevent rejection [60] (Fig. 7(A-D)).

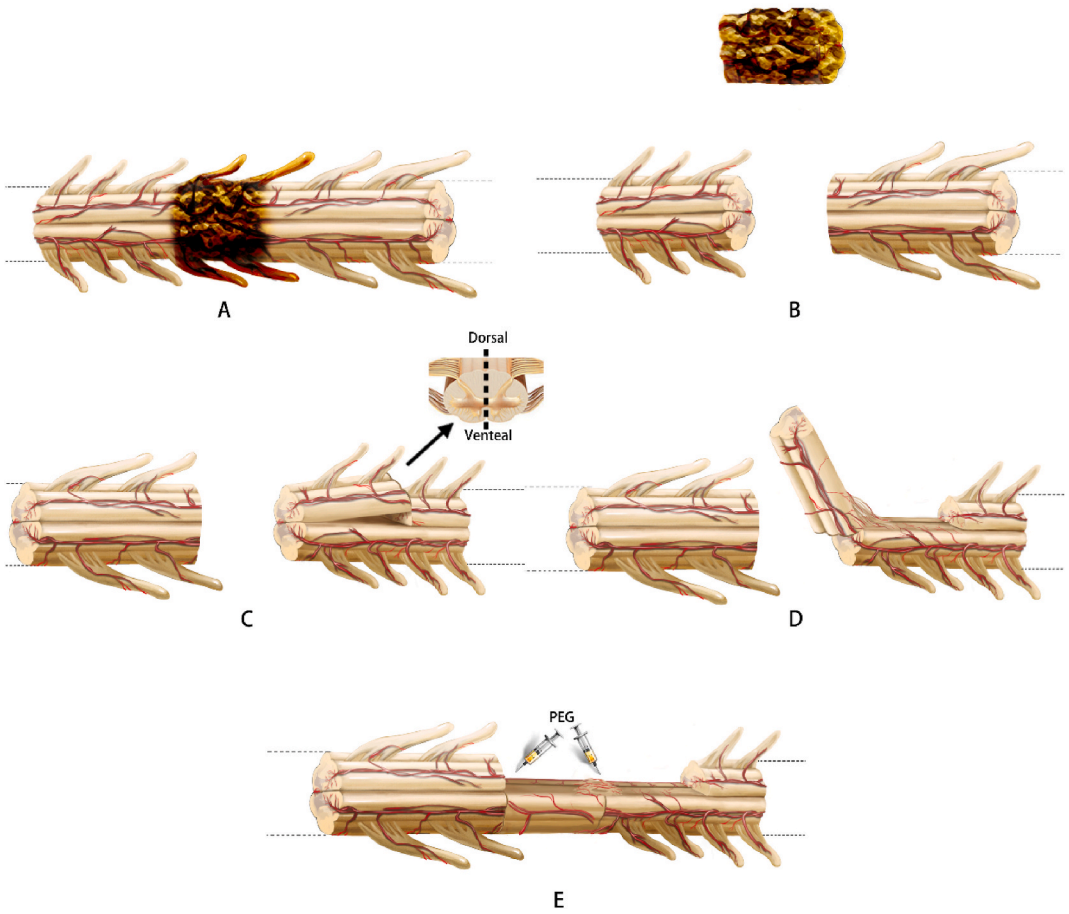

Fig. 5. Surgical procedures of transplantation of a vascularized pedicle of hemisected spinal cord A,B. The SCI area was removed to produce two fresh spinal cord stumps. C. Based on the effective length of the defect between two fresh spinal stumps, half of the spinal cord tissue with one side of the posterior spinal artery was cut from the distal or proximal spinal cord. The other side of the posterior spinal artery was maintained as the vascular pedicle to supply the blood flow. D. Then half of the spinal cord tissue was transplanted into the spinal cord defect area. E. PEG was topically applied to the two sites of spinal cord transection created after the transplantation to complete the SCF [57].

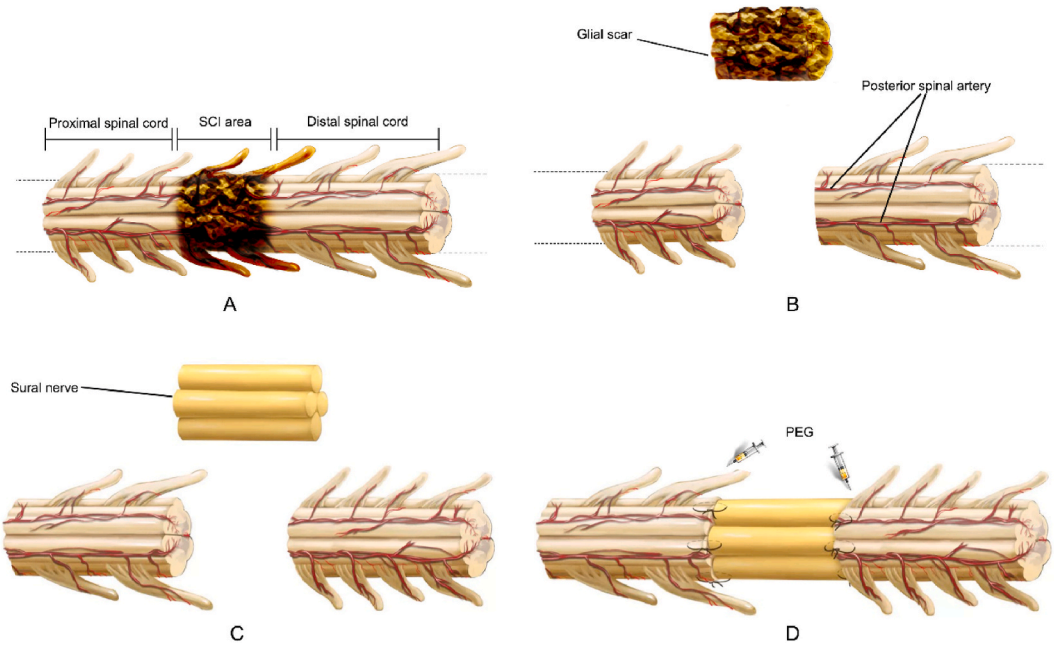

Fig. 6. Surgical procedures of sural nerve transplantation A,B. The area of SCI is removed to produce two acutely transected spinal cord stumps. C. Based on the effective length of the defect between two fresh spinal stumps, a section of sural nerve harvested from the patient's lower leg simultaneously, was divided into several bundles, maintaining the cranial and caudal orientation of all the bundles, and sutured side by side into one bundle. D. The sural nerve is autotransplanted to bridge the gap between the distal and proximal spinal cords. The sites of transection were topically applied with PEG to complete the SCF, and the two sites of transection are then anastomosed with suturing under the microscope [58].

4. Neurological mechanism of SCF

Scientists believe that long fibre tracts from the cerebral cortex to the spinal cord typically cannot regrow across a severed cord. However, the recovery of transected spinal cords in both humans and animals has been reported, which contradicts the mainstream viewpoints in academia and raises questions about the underlying neurological mechanisms. According to the literature, two neuronal systems from the brain to the spinal cord regulate the voluntary motor function of the extremities. The first system, known as the cortico-trunco-reticulo-propriospinal pathway (CTRPS), is a critical component of the spinal system, involving a segmental nervous system [61]. This multisynaptic pathway from the brain to the spinal cord connects nearby neurones sequentially over short segments from the cerebral cortex to the spinal cord to control extremity movements [61]. The other system, called the pyramidal tract (PyT), comprises long, fast signal-transmitting neurones that connect neurons in the cerebral cortex to those in the spinal cord, enabling the rapid transmission of motor commands. When the spinal cord is injured, the recovery of functional PyT through axon regrowth along the transected long neuronal tracts is very slow because axon regrowth can only be accomplished by regenerating long distances from the brain to the spinal cord. In contrast, the CTRPS, which is a shorter, multi-neuronal pathway, can quickly regrow and establish connections with spinal cord segments, thereby re-establishing the multi-neuronal pathways responsible for controlling movement and sensation [61].

4.1. Classical motor pathway - PyT

The PyT is a well-known motor pathway that has been extensively described in the literature. The tracts of the PyT primarily originate from the bilateral pyramidal cells in the cerebral cortex. The cell bodies of these upper motor neurones are located in the motor region of the anterior central gyrus of the frontal lobe (Betz cells). The axons of these motor neurones form the PyT, which includes both the corticospinal and corticonuclear tracts. After exiting the cerebral cortex, the axons of the corticospinal and corticonuclear tracts descend through the corona radiata and pass through the posterior limb and knee of the internal capsule, respectively. The corticospinal tract proceeds through the middle 3/5 of the midbrain and base of the pons. A significant portion of these fibres (approximately 75%–90 %) cross to the contralateral side at the medulla oblongata, forming the lateral corticospinal tract, which descends to terminate in the anterior horn cells of the spinal cord. Additionally, a smaller number of fibres do not cross, but instead form the ventral corticospinal tract, which crosses successively at each level of the spinal cord and terminates at the contralateral anterior horn of the spinal cord. The corticonuclear tract crosses to the contralateral side of each brain nucleus and terminates in each motor nucleus. PyT plays a crucial role in the motor system and governs the voluntary movements of skeletal muscles throughout the body. Notably, the lateral corticospinal tract predominantly controls the distal extremities, the ventral corticospinal tract regulates the

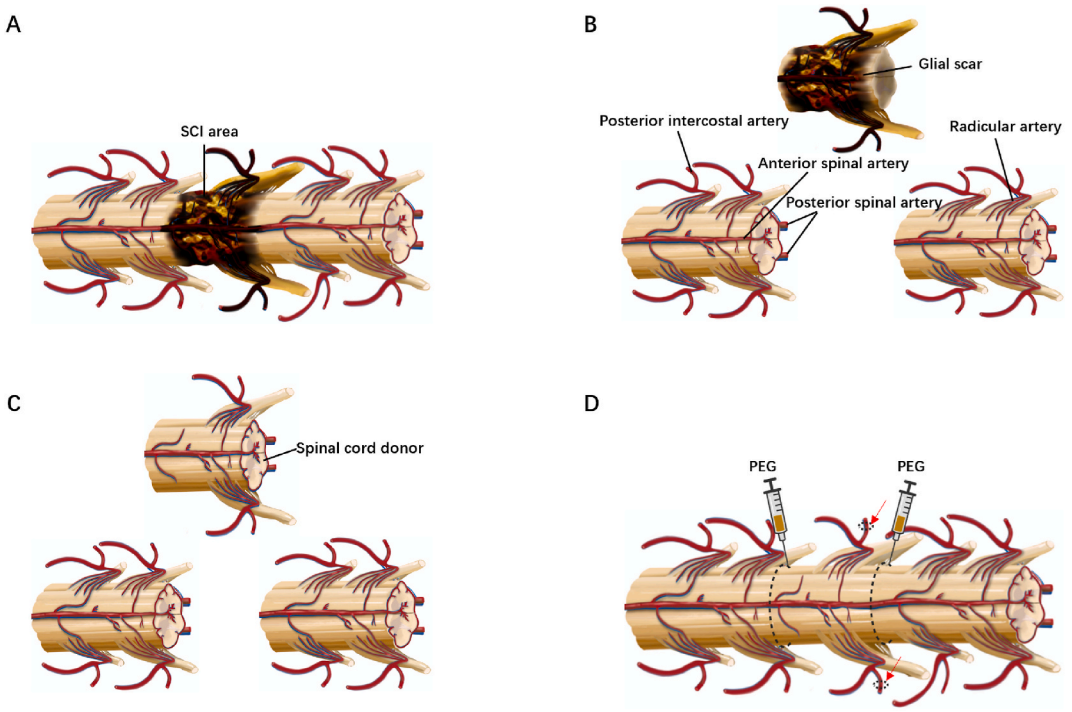

Fig. 7. Key surgical steps of vascularized allogeneic spinal cord transplantation A,B. The area of SCI is removed to produce two fresh severed ends of the spinal cord. C. Depending on the effective length of the defect, the required spinal cord is obtained from the allogeneic spinal cord donor. D. The donor spinal cord is transplanted to bridge the gap of the SCI recipient's injured area. PEG is applied to the two sites of transection, and the posterior intercostal artery and vein (red arrow) are anastomosed under the microscope. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

proximal or axial trunk muscles, and the corticonuclear tract primarily innervates the head and neck muscles. Here, we will focus on the neuronal mechanisms of the lateral corticospinal tract, which specifically controls the skeletal muscles of the distal extremities.

The PyT is widely recognised and accepted in the medical field as the main pathway controlling motor function. However, there may have been some initial misunderstandings regarding its dominant role in controlling movements. Approximately half a century ago, Lawrence and Kuypers [62,63] published two papers indicating that monkeys with bilateral corticospinal tract injuries exhibited persistent deficits in independent motor control of the fingers. Consequently, the belief has emerged that skilled human hand movements rely solely on a single-synaptic PyT pathway. This pathway involves direct projections from the primary motor cortex to the motor neurones of the spinal cord through millions of fibres exclusively situated in the corticospinal tracts. As a result, it was widely believed that damage to the PyT can lead to dyskinesia and, in severe cases, cause irreversible damage to neurons, potentially resulting in permanent paralysis. However, a more critical analysis of these studies revealed an intriguing phenomenon: motor function in affected animals recovered over time, even in the absence of continuous PyT connectivity. This finding suggests that the PyT is not the only motor pathway involved in recovery. The detailed mechanisms underlying this recovery remain unclear; however, it is plausible that pathways other than PyT may adapt and play a crucial role in motor recovery.

In 1964, Bucy et al. [64] showed that PyT in humans is not essential for the effective control of skeletal muscles. They found that in the absence of corticospinal fibres, other fibre systems, particularly multi-neuron mechanisms through the midbrain tegmental region, can generate useful, well-coordinated, powerful, and precise limb movements. Building on extensive studies on monkeys with bilateral corticospinal tract lesions, Lawrence and Kuypers [62,63] further confirmed in 1968 that the brainstem pathway serves as a fundamental system for motor control. This pathway is responsible for maintaining upright posture, orchestrating the integrated movement of the trunk and limbs, regulating gait, and controlling limb movement. Notably, transgenic rats lacking a PyT were still capable of walking because of the action of an interneuronal descending system originating from the reticular spinal tracts and extending to the spinal cord [65]. Moreover, Baker et al. [66] found that the control of hand movement predominantly arises from spinal cord neurones in the cortex, with some selective inputs from both the corticospinal and reticulospinal tracts, contributing to fine and flexible hand movements. Optimal functioning requires seamless hierarchical coordination between these two pathways. Therefore, although the PyT plays a crucial role in motor control, it is not the only pathway involved in motor control. Other neural pathways consisting of neurons covering the cortex, brainstem, and spinal cord participate indirectly and significantly in the regulation of motor activity.

4.2. Indirect motor pathway - CTRPS

4.2.1. Origin and structure of CTRPS

In 1937, after extensive research in primates and humans, Laruelle [67] reported that multiple connections between neurones were not limited to the well-known long pathway (PyT). Instead, an intrinsic interneural system exists within the grey matter of the spinal cord that facilitates electrical conductivity and involves several segments of the spinal cord. This short fibre system is known as the propriospinal interneural system. Within this system, electrical transmission between neurones is achieved through synapses formed by short fibres in close proximity to the grey matter, connecting adjacent segments of the spinal cord over short or very short distances [68,69]. Sherrington's pioneering research explored this cellular network more than a century ago. He demonstrated that axons derived from the grey matter of the spinal cord establish connections between both the proximal and distal spinal segments and that the intricate or lengthy projection of motor activity relies on the interconnection of multiple spinal segments. In the 1940s, Lloyd presented compelling electrophysiological evidence supporting the notion that the lumbosacral motor pools receive descending inputs transmitted by propriospinal neurones located in the cervical spinal cord [70,71]. This finding suggested that a continuous network of reticulospinal and propriospinal fibres extends from the brainstem to the spinal cord [72,73]. The majority of motor efferent neural inputs to human motor neurones are provided by indirect pathways from the motor cortex, such as the corticospinal pathway through the reticular spinal tract and the spinal interneuronal system. These pathways are critical components of motor reflexes, voluntary movement, and sensory processing.

Based on this point of view, we propose that there may be an indirect motor pathway called the cortico-trunco-reticulo-propriospinal pathway [27,29]. The CTRPS pathway comprises three distinct parts: the corticoreticular, reticulospinal, and propriospinal tracts. The reticular structure of the brainstem serves as a relay region within this pathway, and receives motor commands originating from the cerebral cortex. Subsequently, the motor signals are transmitted from the reticulospinal tract to the spinal cord. From there, they reach the propriospinal interneural system, which connects the brainstem to the cervical-lumbar "central pattern generator". Finally, the motor signals are directed to the corresponding motor neurones, thereby controlling and coordinating the limb movements (Fig. 8(A and B)).

4.2.2. CTRPS: the key to functional limb recovery after SCI

Substantial evidence has shown that this intraspinal network plays a crucial role in functional recovery after SCI due to its contribution to spinal circuit plasticity [72]. The potential for the substantial restoration of locomotor function could arise from the capacity to regenerate or redirect these intrinsic spinal pathways after SCI by establishing compact, functional synaptic connections [72]. Scientists believe that surviving propriospinal neurones extend their growth to the lesion site, increasing the number of potential contacts with motor neurones and thus facilitating synaptic remodelling. Bareyre et al. [73,74] demonstrated that transected axons from the corticospinal tract establish "new" contacts with surviving propriospinal neurones after SCI. These newly formed contacts help restore neuronal circuits, enabling the neurones to grow across the site of the spinal cord lesion, effectively creating an anatomical "bridge". This bridge allows descending signals to be transmitted to the distal regions beyond the lesion. In a mouse model, they also observed an increased growth of axons in the cortical-spinal tract following thoracic SCI. Notably, a significant number of these newly sprouted axons established connections with the propriospinal neurones located in the cervical enlargement of the spinal cord [73]. Similarly, using the pseudorabies virus, a *trans*-synaptic tracing technique, also confirmed the existence of newly formed synaptic linkages in lesioned animals via descending propriospinal neurones [72]. Furthermore, the suitability of propriospinal neurones as optimal neural substrates for motor recovery has gained additional validation because they exhibit responsive behaviour to various neuroregenerative approaches in experimental models of SCI [75,76]. Remarkably, primates have been observed to execute arm and hand movements, including dexterous finger movements and precise grip strength, even in the absence of a functioning PyT because of the neural circuits of the propriospinal system [77–80]. Courtine et al. [81] also provided evidence supporting the involvement of the propriospinal network in the recovery of distal motor function after SCI, rather than relying solely on the new long-distance regrowth of supraspinal axons [82]. The capacity of spinal neurones to facilitate recuperation after SCI is ascribed to two overarching yet simultaneous mechanisms: synaptic plasticity and plasticity in structural circuits. The former encompasses changes in the efficacy of established neural circuits, which could involve modifications, such as adjustments in neurotransmitter release or the density of post-synaptic receptors. The latter involves the sprouting of axon collaterals, enlargement of dendritic territories, and, for the context of this review, the regrowth of axons [83].

In summary, propriospinal neurones constitute a network spanning the length of the spinal cord, enabling the transmission of impulses from the brainstem network to motor neurones via interneurons. The inherent capability of propriospinal neurons to accept novel axon branches originating from different spinal pathways, along with their ability to extend their own axonal networks in reaction to SCI, underscores the essential contribution of these CTRPS in the post-SCI recovery mechanism [73,84].

4.2.3. Functional repair by SCF via CTRPS

CTRPS play a critical role in the recovery of sensorimotor function after SCF. In the SCF technique, a specially shaped, ultra-micro blade (made of carbon nanotubes) achieves complete transection at the nanoscale, minimising shape changes of the axons [85–88]. This sharp transection causes minimal nanoscale damage to the grey matter lamina and minimal damage to the axons in the white matter. In terms of objective surgery data, a sharp transection typically generates a force of less than 10 N, whereas the clinical forces causing SCI generate a force of approximately 26,000 N, a difference of 2600 times [89]. Transecting the spinal cord with minimal damage to a very thin layer of cells allows for immediate "re-sprouting" of new axons and dendrites around the grey matter neuropil at the site of transection. In contrast, clinical SCI usually causes a large area of local injury that is accompanied by axon interruption,

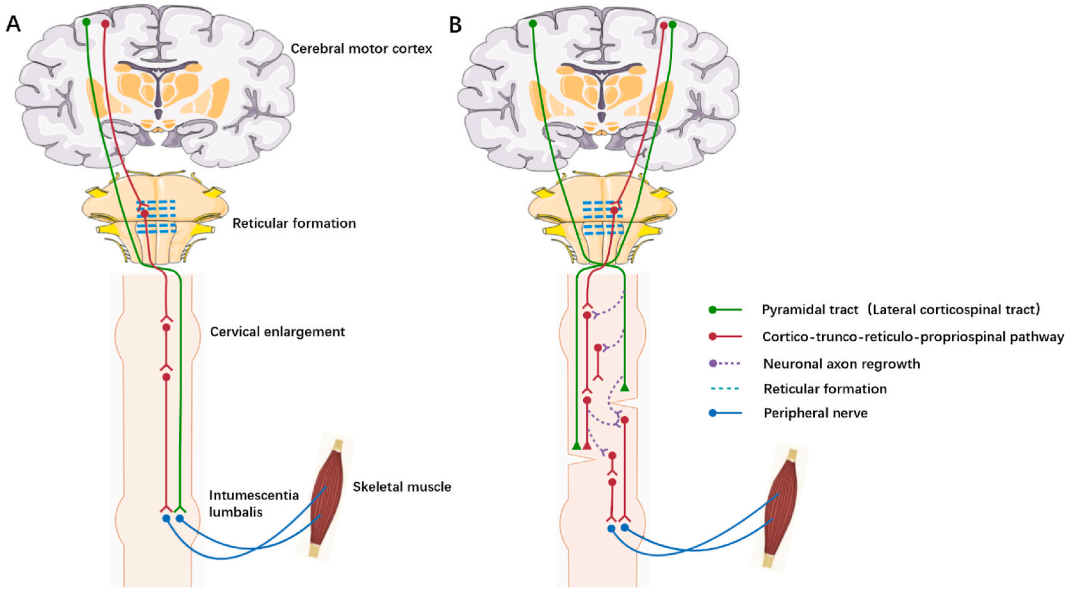

Fig. 8. Motion conduction pathway A. Normal motor conduction pathways; green represents the classical motor pathway (lateral corticospinal tract in the pyramidal tract), red represents indirect motor pathway (cortico-trunco-reticulo-propriospinal pathway). B. The rearrangement of new neural circuits within the spinal canal after SCI. Once the long pyramidal tract is damaged, axon recovery is very slow, mainly through the cortico-trunco-reticulo-propriospinal pathway to form new neural circuits, in which the axons of transected neurons regrow and connect to nearby interneurons, connecting the brain stem and cervical-lumbar "central pattern generator" of the propriospinal tract, which transmits motor instructions to the peripheral neurons and controls movement. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

haemorrhage, and inflammation, followed by scar and intraspinal cyst formation, which hinders the functional regeneration of neurones. More importantly, Fenrich and Rose [90] demonstrated that, unlike supraspinal neurones, propriospinal neurones can extend axons into and through the SCI region, which is rich in inhibitory neuroactive substances, i.e. they can penetrate the "hostile" pathophysiologic microenvironment of traumatic SCI. Even in patients with severe SCI, a substantial proportion (approximately 10 %) of propriospinal neurones survive [91], displaying resistance to retrograde cell death, and remain viable for at least 16 weeks after SCI. Because carefully controlled surgical transection in SCF is far less severe than that in clinical SCI, we can expect more propriospinal neurones to survive and more positive sensorimotor function recovery outcomes via CTRPS pathways by executing the SCF protocol.

After SCI, axons repair requires plasticity throughout the entire central nervous, including the brain, brainstem, and spinal cord, during which large-scale reorganization occurs [92]. After PEG-induced axonal fusion using the SCF protocol, the recovery process depends on neural axon regrowth/reorganization of the propriospinal tract of the CTRPS. These propriospinal neurones activate and coordinate the cervical-lumbar "central pattern generator", facilitating clinical restoration of sensorimotor function, despite the transection of all supraspinal axons previously innervating the central pattern generator region [82,93,94]. Notably, propriospinal neurones have better regenerative capacity than supraspinal neurones, especially in response to treatments such as electrical stimulation [72]. Electrical stimulation triggers neuroplasticity by increasing fundamental spinal excitability. This heightened state enables even minor inputs to lead to voluntary motor function [95]. This elicited synaptic neuroplasticity likely involves the descending motor axons, proprioceptive afferents, motor neurones, and interneurons. The CTRPS appears to play an important role in spinal cord repair and postoperative limb function recovery in SCF. SCF appears to cause minimal damage to the CTRPS, and the combined use of PEG and electrical stimulation appears to have additive effects on axon regrowth and spinal connectivity. By highlighting the capacity of the CTRPS pathway to mediate spontaneous functional recovery after severe SCI, this research not only challenges the conventional belief about limited recovery but also suggests a promising avenue for therapeutic interventions. The findings of pronounced functional recovery mediated by propriospinal relay connections offer a new perspective and underscore the need for further exploration of innovative approaches, such as SCF, in the quest for meaningful motor recovery following SCI.

5. Controversy in SCF

Prior to recent experimental work, the prevailing belief among neurologists was that a transected spinal cord could not be reconnected to restore neurological function. Previous attempts to connect the transected cords using various biological combinations had been unsuccessful. However, based on historical investigations and experimental research, scholars worldwide have challenged this long-held viewpoint, demonstrating that it is incorrect [61]. Despite considerable controversy, the feasibility and potential role of SCF in SCI remain controversial. Shaked, an American scholar, maintained that connecting transected cords using the SCF technique is still impossible [96]. However, Ausman's perspective was different. After reviewing the relevant literature on SCF therapy, he

highlighted the progress of SCF-related research. Ausman affirmed the importance and innovation of SCF research [61]. Dr. Sarr, a professor of surgery at the Mayo Clinic and editor-in-chief of the journal Surgery, also voiced his approval for the SCF technique. He believes "This is science that could result in a revolutionary change in spinal cord injured patients. We encourage everyone to keep an open mind about this topic of reconstruction of the traumatically severed spinal cord and the science of reinnervation" [97,98]. Our views on SCF may provide a promising new approach for future SCI repair therapy. The controversy surrounding the feasibility and potential of SCF for the treatment of SCI reflects the dynamic nature of scientific research. Differing perspectives are essential for driving the field forward and prompting researchers to continuously question, validate, and innovate.

6. Conclusion and prospect

SCI is a severely disabling injury of the central nervous system that presents significant challenges in clinical medicine owing to the limited regenerative capacity of the spinal cord and the inability to fully harness the well-known neuroplasticity of the nervous system. Although progress has been made in SCI therapy with advancements in bioengineering technology and new therapies such as stem cell therapy, functional biomaterials, and neural growth-promoting cytokines, numerous obstacles persist. The SCI repair strategy mainly involves restoring electrical continuity across the injured area and utilising alternative pathways to re-establish neural conduction above and below the level of the SCI. As a promising new approach, the SCF technique has achieved successful reconstruction of morphological continuity and electrical reconnection of the two ends of the transected spinal cord. Notably, SCF has successfully restored the sensorimotor function of the distal limbs in experimental models involving rodents, dogs, and nonhuman primates, thus offering a novel avenue for future SCI repair therapies. Although SCF has been a critical initial step in successfully reconstructing spinal cord morphological and histological continuity and achieving functional recovery in animal experiments, it requires further exploration for potential human clinical applications. Optimising the surgical programme for SCF and emphasising postoperative rehabilitation and functional training are crucial for advancing this approach. The current trend in SCI treatment involves the integration of intelligent medical technologies, bioengineering advancements, and other related fields by employing multi-type, multi-approach, and multi-means strategies to achieve breakthroughs in collaboration among medical professionals. The optimisation of existing methods and their integration with bioengineering and related disciplines can potentially lead to complementary advantages, enabling a comprehensive and effective approach for SCI repair. In conclusion, the pursuit of SCI repair and functional reconstruction is a complex and evolving field; however, with continuous research and innovation, new therapeutic breakthroughs have the potential to significantly improve the lives of individuals with SCI. Collaborative efforts among various disciplines and integration of cutting-edge technologies are essential for shaping the future of SCI treatment and rehabilitation.

Ethics statement

The animal study was reviewed and approved by the Institutional Animal Care and Use Committee of Harbin Medical University (HMUIRB-2008-06) and the Institute of Laboratory Animal Science of China (A5655-01). The clinical trial was approved by Medical Ethics Committee of Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine and registered on the open clinical registry site http://www.chictr.org.cn/showproj.aspx?proj=50526 (ChiCTR2000030788). All participants provided informed consent for the publication of their anonymized case details and images.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Tingting Shen: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Weihua Zhang:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Xiaogang Wang:** Software, Formal analysis, Data curation. **Xiaoping Ren:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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