

Research advances in stem cell transplantation combined with fibrin scaffold for spinal cord injury in an aging society

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Abstract

Older patients with spinal cord injury (SCI) had higher injury severity scores, longer hospital stays, and were significantly more likely to be discharged to an institution rather than younger patients. Treating SCI and promoting neural tissue regeneration is a major challenge for current medical technologies in an aging society. Tissue engineering scaffolds can provide a microenvironment suitable for cell survival and promote nerve tissue regeneration, and thus have become a promising therapeutic intervention. Among them, fibrin scaffold has become one of the most promising scaffolds for spinal cord regeneration due to its excellent biocompatibility, biodegradability, and high degree of integration with tissues. This article reviews the characteristics of an ideal fibrin scaffold and the role of fibrin scaffolds in the treatment of SCI in aging patients. Meanwhile, we explore the potential of stem cell transplantation combined with fibrin scaffold for the treatment of SCI. Through extensive and in-depth studies, this review will serve as a practical guide for the development of applications of fibrin scaffold combined with stem cell transplantation and provide direction for possible future work.

Keywords: Fibrin scaffolds, stem cells, spinal cord injury, tissue engineering scaffolds, aging

Introduction

Spinal cord injuries (SCI) are often caused by motor vehicle collisions. The occurrence of SCI not only causes severe physical and psychological damage to the patients themselves but also imposes an enormous economic burden on families and society [1]. When the spinal cord is damaged, the connection between the brain and the body

is forcibly interrupted, resulting in severe sensory and motor dysfunction of the limbs below the damaged segment. The characteristics of SCI patients have changed as the population has aged. In a previous report from the United States, older patients in the acute phase had higher injury severity scores, longer hospital stays, lower Glasgow Coma Scale scores, and were significantly more likely to be discharged to an institution rather than younger patients [2]. According to the new standard of 7% of the total population aged 65 years, 91 countries in the world have now entered into an aging society, including Japan, Italy, and Germany. Therefore, how to treat late-life SCI in an aging society becomes a very delicate issue.

The pathophysiological mechanisms after SCI include primary and secondary injury. The initial mechanical trauma causes a primary injury, such as tissue hemorrhagic edema and neuronal cell necrosis in the injured spinal cord, which subsequently triggers severe secondary injury, such as tissue ischemia and necrosis, nerve conduction fiber fragmentation, demyelination, and glial scar proliferation. This cascade of pathological changes leads to endogenous spontaneous repair processes that contribute little to the recovery of spinal cord function [3, 4]. In addition, a large

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amount of tissue loss occurs after severe SCI, resulting in a glial/fibrotic scar at the center of the SCI site that continues to expand over time, leading to further tissue injury [5].

Currently, there are medical symptomatic, physiotherapeutic rehabilitation, stem cell transplantation, and surgical intervention modalities used to treat SCI in aging people, but there is no single treatment modality that can completely restore the injured spinal cord structure and function. The reasons for the failure of spinal cord regeneration are mainly attributed to the following two points: poor axonal regeneration ability and the inhibitory hostile microenvironment at the injured site after trauma [6]. When the central nervous system is injured, a large number of glial cells, macrophages, and stromal cells are accumulated at the injury site. Subsequently, molecules that inhibit the axon growth, such as chondroitin sulfate proteoglycan, are accumulated, eventually leading to the formation of glial scar, the lack of neurotrophic factors, the destruction of myelin, and the demyelination of axons and other secondary injuries. This series of secondary injuries impeded the growth of axons toward synapses, forming a physical and chemical barrier to spinal cord regeneration, ultimately leading to the failure of spinal cord regeneration [7-9] (Figure 1A). Currently, the research hotspot for SCI in the elderly focuses on the mechanistic aspects of spinal cord regeneration, including biological stem cell transplantation, tissue engineering, gene therapy, and drug screening, among which stem cell transplantation is one of the high-potential approaches [10].

Stem cells, which are used for transplantation, have the function of self-renewal. They can differentiate into glial cells or neural progenitor cells (NPCs) along specific neural lineage under the appropriate environment, so as to replace and renew the necrotic or apoptotic cells in the injured area, ultimately repairing the damaged spinal cord [11]. Research has discovered that aging-related secretory phenotype manifests in the spinal cord of aged mice following injury, enhancing the suitability of the injury microenvironment for cell transplantation in aged mice [12-14]. This suggests that the aged spinal cord may provide a favorable environment for stem cell transplantation in older individuals. However, the analysis of SCI in elderly rats has led to the conclusion that age is a factor influencing functional recovery, as it is associated with increased axonal injury and demyelination [15]. This is consistent with the observed higher activation of microglial cells, oxidative stress, and expression of inflammation-related genes in elderly rats following SCI compared to young rats [16-18]. This increases the likelihood of axonal growth impairment occurring after stem cell transplantation into the injured area. Studies have found that tissue engineering scaffold technology can provide support and guidance for newly generated axons while preventing newly generated axons from being damaged by scar tissue, thereby improving the survival rate of transplanted cells [19].

Tissue engineering scaffolds can provide a suitable microenvironment for cell survival, limit local inflammatory responses, inhibit apoptosis, promote nerve regeneration,

and promote axon myelination [20]. Among them, the fibrin scaffold has emerged one of the most promising scaffolds for spinal cord regeneration in the elderly, owing to its excellent biocompatibility, biodegradability, and tissue integration capabilities [21].

Fibrin is a blood clotting protein synthesized by the liver. It is one of the most important proteins for promoting blood coagulation, accelerating wound healing, and promoting tissue regeneration [22]. Fibrin is formed by thrombin cleavage of fibrinogen *in vivo* and can spontaneously condense into three-dimensional multimers with sponge-like structures. Based on this property, fibrin can be injected into the human injury site in liquid form and transformed into a solid-state scaffold after entering the body [23], which may be useful for improving the microenvironment of the injury site, aiding in cell transplantation as well as neuroprotection [24, 25]. The results of a previous study showed that neural stem cells (NSCs) expressing green fluorescent protein, when embedded in a growth factor-rich fibrin matrix, were transplanted into the injured spinal cord. The results showed that the transplanted stem cells differentiated into neurons and helped the elongation of axons connect with the host cells to form rich synapses, which ultimately promoted the recovery of spinal cord function [26].

In this review, we focused on the advantages and roles of fibrin scaffolds in promoting neurological functional recovery in the elderly. Meanwhile, we summarized the potential that different types of stem cells combined with fibrin scaffolds in the treatment of SCI, especially in the elderly. Finally, the challenges and prospects of stem cell transplantation combined with fibrin scaffold application in SCI were pointed out.

Connections of fibrin scaffolds to SCI

As a fibrous biopolymer, fibrin can stop bleeding and promote wound healing by forming a temporary matrix around the lesion [27]. Fibrin is a component of the extracellular matrix, which aids in the repair of damaged areas by facilitating cell adhesion, binding to extracellular matrix proteins, and interacting with various growth factors [28]. The variation in the ratio of fibrinogen to thrombin can regulate the mechanical properties of fibrin hydrogels, thereby effectively treating spinal cord injuries in the elderly [29]. Clinical studies have found that local injection of a single dose of VX-210 or a placebo containing a fibrin sealant onto the injured dura mater during decompression/stabilization surgery may improve the quality of life in elderly patients with spinal cord injury [30]. Because of its high biocompatibility, fibrin can serve as a carrier for stem cell transplantation or as an injectable biomaterial to promote nerve regeneration. After SCI, while axons in the central nervous system cannot regenerate, they can promote axon healing by expanding new axon buds in the peripheral nerves [31]. According to this property, Tsai *et al.* [32] used fibrin matrix as a hollow nerve conduit to bridge the nerve defect area and encourage axon regeneration

and growth. King *et al.* [25] injected fibrin/fibronectin into the injured part of the spinal cord in young adult male rats and observed new axon growth in the scaffold one week later. In addition, Lu *et al.* [26] found that the fibrin scaffold containing growth factors can effectively support the long-distance axon growth and interconnection of NSCs implanted with severe SCI in rats. It can be seen that fibrin, as a new natural scaffold material, holds promising research prospects for the repair of SCI.

Biological characteristics of suitable fibrin scaffolds

Scaffold materials are the foundation of tissue engineering scaffolds, and an ideal fibrin scaffold should possess the following properties.

Biocompatibility

Fibrin scaffolds play a role in directly contact with peripheral nerves and tissues. Therefore, it is necessary to have scaffolds with excellent biocompatibility to meet the requirements of nerve regeneration. Good biocompatibility facilitates cell adhesion, does not cause inflammation, provides a good microenvironment for cell growth, and can be used safely within the human body. In addition, appropriate biocompatibility can facilitate axonal growth by incorporating biomolecules such as full-length proteins or shorter peptide chains that mimic the native extracellular matrix [33].

Biodegradability

The ideal biological scaffold should have a good affinity with tissues during the process of organism degradation. To provide space for nerve regeneration after injury, avoiding additional harm caused by the secondary procedure of scaffold removal [20]. In addition, the biodegradation rate should align with the nerve regeneration rate,

which can be artificially regulated or self-regulated to avoid scaffold degradation too fast or too slow to provide adequate supporting effects for SCI.

Physical property

The biological scaffold material should have mechanical properties that are compatible with spinal cord lesions: adequate strength, hardness, and elasticity [34]. A good fibrin scaffold not only promotes axonal regeneration but also withstands the forces generated during spinal movement and the surrounding muscle tissues, so as to provide adequate protection for spinal cord regeneration. Ideally, SCI biomaterials can support axon growth with appropriate stiffness and provide space for axons to pass through or enter the scaffold.

Three-dimensional solid structure

A good fibrin scaffold can promote wound healing by establishing a three-dimensional spatial architecture and providing enough space for stem cells to adsorb on the scaffold surface. In addition, the three-dimensional porous structure can help cells interact by simulating the extracellular matrix, which is important for cell survival and growth [35].

The role of fibrin scaffolds in SCI

Creating a microenvironment for cell regeneration

Fibrin provides a loose microenvironment for cell adhesion and axonal regeneration by adhering to other embedded proteins. Fibrin-based scaffold materials have significant potential as matrices for the delivery of growth factors or cell therapy after SCI. In particular, studies have shown that fibrin scaffolds can be used as carriers of neurotrophic factors to support the regeneration of injured

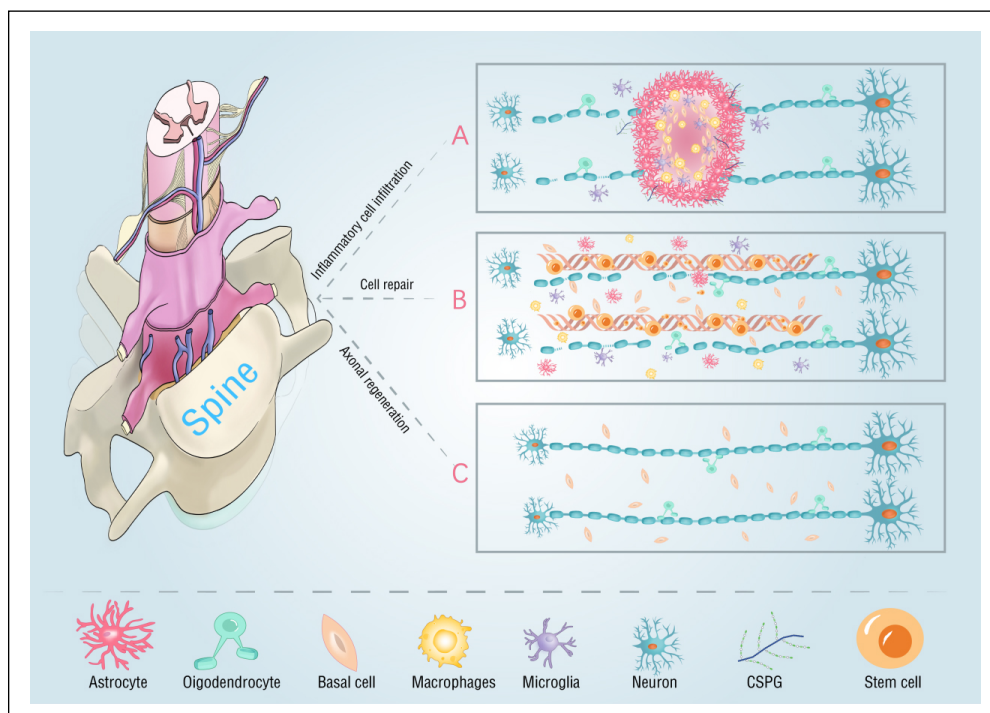


Figure 1. (A) After SCI, inflammatory cells infiltrated and wrapped around the damaged axons, forming a glial scar that impedes axon regeneration. (B) Some repair mechanisms after transplantation of fibrin scaffold containing stem cells into the injured spinal cord. The number of neurons and oligodendrocytes differentiated from the transplanted cells increased, and the number of other inflammatory cells decreased. (C) The axon regeneration and neural circuit recovery after transplantation of fibrin scaffold and stem cells.

nerves [36]. In addition, the axial holes, channels, and arranged fibers are conducive to controlling the growth direction of the nerve structures [37]. The porosity of a well-designed fibrin scaffold is beneficial for enhanced cell adhesion, which is critical for providing a larger bridge distance.

Providing a platform for cell attachment

Fibrin is a natural nano scaffold that provides a platform for stem cell transplantation, promoting cellular activity and extracellular matrix deposition [38]. Due to its high biocompatibility, fibrin is used to support stem cell transplantation for attachment and growth to promote nerve regeneration. Previous studies have shown that fibrin scaffolds are widely used to support the differentiation of embryonic stem cell-derived NPCs into neurons and oligodendrocytes, as well as the development of an effective cell delivery platform for neurons derived from pluripotent stem cells [39]. Willerth *et al.* [40] confirmed through research that fibrin scaffold can be used as a platform for neural tissue engineering to treat SCI. Other studies have shown that mesenchymal stem cells (MSCs) cultured in

fibrin glue exhibit robust viability and enhanced differentiation potential, promoting MSCs to differentiate into neurons [41, 42].

Fibrin scaffold combined with stem cell transplantation for spinal cord repair

Although various medical technologies have changed with each passing day, there is no effective way to solve the problem of nerve regeneration. Stem cell transplantation have shown the potential of neuroprotection and nerve regeneration in SCI, with various targets and responses to stimuli, such as regulating inflammatory response, providing nutritional support, and improving plasticity [43]. The therapeutic principles of stem cells for SCI include replacement of damaged neurons and glial cells, secretion of trophic factors, inhibition of glial scar formation, and promotion of axon regeneration. Among these, it is more important that stem cell transplantation can prevent or replace damaged glial cells, especially oligodendrocytes, which can promote the remyelination of surviving axons

Table 1. Fibrin scaffold combined with different types of stem cells for treatment of SCI.

| Stem cell types | Experimental methods | Outcome | Ref. |
|------------------|--|--|------|
| ESC-derived NPCs | NPCs + fibrin scaffold containing HBDS, NT-3, and PDGF. | NPCs↑ and neuron↑ | [45] |
| ESCs | Retinoic acid was added to EBs to induce mouse ESCs to become NPCs and implanted into fibrin scaffolds of different concentrations. | Optimal concentrations for scaffold polymerization were 10 mg/mL of fibrinogen and 2 NIH units/mL of thrombin. The optimal aprotinin concentration was determined to be 50 µg/mL for dissociated EBs (2D) and 5 µg/mL for intact EBs in 3D fibrin scaffolds. | [40] |
| iPSCs | An 8-day (4-/4+) protocol using soluble retinoic acid in the last 4 days and a 6-day (2-/4+) protocol using soluble retinoic acid and the small molecule sonic hedgehog agonist purmorphamine. | In iPSCs and ESCs, the proportion of neurons generated by EBs generated by 2-/4+ protocol is higher. | [46] |
| BM-MSCs | BM-MSCs were affixed with fibrin glue and injected inside or around the graft. | Repaired rat sciatic nerve. | [42] |
| BM-MSCs | Female adult rats were subjected to SCI. 60 days after lesion, rats were randomly distributed in four groups: (1) Rats immunized with complete Freund's adjuvant + PBS (vehicle; PBS-I); (2) Rats with SR + FGM-MSCs; (3) Rats with SR + INDP + FGM-MSCs; (4) Rats only with INDP. | Treatment with INDP alone significantly increased motor recovery, anti-inflammatory cytokines, regeneration-associated molecules, axonal regeneration, and neurogenesis. | [47] |
| AD-MSCs | The derived progenitors, tagged with fluorescent tracker dye were delivered in rat T10 contusion SCI using fibrin hydrogel. | Fibrin niche aided stable differentiation of rat ADMSCs into neural progenitors. | [48] |
| NSCs | NSCs were implanted into fibrin matrix containing growth factor cocktails. | The injured spinal cord extended a large number of axons and formed neuronal relay, and the electrophysiological function of the rats recovered at the same time. | [26] |
| NSCs | Fresh NSCs were isolated from transgenic Fischer 344 rat embryos expressing GFP and embedded in fibrin matrix containing growth factors. | The graft completely filled the lesion cavity and differentiated into two types of neurons (axons extended very far from the host spinal cord) and glial cells. | [49] |

[44] (Figure 1B-C). The fibrin scaffold technology can provide support and guide the growth of stem cell-derived axons, provide protection for new axons, avoid scar tissue invasion, reduce the apoptosis of transplanted stem cells, and improve the survival rate of transplanted cells. The following are some of the hot research topics in recent years on the combination of stem cells and SCI (Table 1).

Embryonic stem cells

Embryonic stem cells (ESCs) can differentiate into a variety of neuronal cell types, which has great potential as a cell replacement therapy after SCI. It has been shown that an appropriate fibrin scaffold can enhance the activity of ESC-derived NPCs [50, 51]. Johnson *et al.* [45] embedded ESC-derived NPCs containing growth factor and heparin-binding delivery system (HBDS) and found that the combination of neurotrophin-3 (NT-3), platelet-derived growth factor (PDGF) and fibrin scaffold could increase the number of NPCs at the site of SCI. The results prove that the application of fibrin scaffold can help to increase the survival and differentiation of ESC-derived NPCs at the injured site, and this discovery will help to increase the feasibility of fibrin scaffold combined with stem cell transplantation in the treatment of SCI. In addition, Willerth *et al.* [40] experimentally determined the culture conditions suitable for proliferation and differentiation of ESCs in fibrin scaffold. The optimal concentration for fibrin scaffold polymerization is 10 mg/mL of fibrinogen and 2 NIH units/mL of thrombin. After 14 days of continuous culture in the scaffold, ESCs were found to differentiate into neurons and astrocytes by immunohistochemistry. Therefore, there is a certain possibility for the treatment of spinal cord injuries in the elderly population through the combination of ESCs and fibrin scaffolds.

Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) reprogram terminally differentiated somatic cells into pluripotent stem cells by introducing specific transcription factors into adult somatic cells [52, 53]. After reprogramming under specific conditions, the differentiated somatic cells returned to the totipotent state. Montgomery *et al.* [46] designed two systems to investigate whether iPSCs, when combination with fibrin scaffold, could increase the number of iPSCs differentiated into neural cells. The results confirmed that the differentiation ability of iPSCs on the fibrin scaffold platform was improved, and the promotion of neurons generated from murine iPSC-derived EBs seeded in fiber could be maximized using the 2-/4+ differentiation protocol. Bahareh *et al.* [54] discovered that fibronectin hydrogels can enhance cell viability and promote the differentiation of iPSCs into pre-oligodendrocytes. These experiments verified that 3D fibrin can improve the survival rate of transplanted stem cells and the degree of transformation into neural cells. At the same time, it provides ideas and references for combining stem cell transplantation with fibrin scaffold for the treatment of SCI in aging society.

Mesenchymal stem cells

The combination of MSCs and a fibrin scaffold can promote the migration of mesenchymal cells across the blood-brain barrier in rats, facilitate the reconstruction of the neural glial cell pool, and induce differentiation into neuron-like cells and oligodendrocyte-like cells [38, 55]. The most commonly used MSCs in combination with fibrin for treating SCI are bone marrow mesenchymal stem cells (BM-MSCs) and adipose-derived mesenchymal stem cells (AD-MSCs). MSCs promote angiogenesis by expressing angiogenic factors, such as vascular endothelial growth factor (VEGF) [56]. In addition, MSCs can be used to promote axonal regeneration and myelination of the myelin sheath in nervous system injury, which is beneficial for nerve regeneration [42, 57, 58]. García Elisa *et al.* [59] observed mechanical retraction, increase of axonal fibers and recovery of motor and sensory function in rats after implantation of fibrin scaffold and BM-MSCs into injured spinal cord. Zhang *et al.* [60] demonstrated that the combined use of a fibrous scaffold and BM-MSCs significantly improved motor function in elderly rats compared to the use of the fibrous scaffold or BM-MSCs alone. Mukhamedshina *et al.* [61] investigated the effect of the combination of AD-MSCs and fibrin matrix on the post-traumatic response of the spinal cord in rats. The experiment showed that the application of AD-MSCs reduced the expression of astrocytes in the SCI area, and the combination of AD-MSCs and fibrin matrix significantly increased the expression of platelet-derived growth factor receptor (PDGFR) and HSPA1b mRNA, while decreasing the expression of ionized calcium-binding adapter molecule 1 in the central canal. Liu *et al.* [62] randomly divided the rat model of SCI into four groups: control group (laminectomy group), SCI group (laminectomy + spinal cord transection group), fibrin group (fibrin transplantation immediately after SCI), fibrin cell group [fibrin scaffold containing ectodermal mesenchymal stem cells (EM-SCs) implanted after SCI]. In comparison, it has been proven that the combination of ectodermal mesenchymal stem cells and fibrin scaffold in the treatment of SCI in rats is superior to the use of fibrin scaffold alone in terms of cell apoptosis rate, number of nerve fibers, myelin sheath thickness, and motor score. In the treatment of spinal cord injury in middle-aged and elderly patients, the combined use of acidic fibroblast growth factor (aFGF) secreted by MSCs and fibrin glue gel may help promote moderate neural regeneration [63, 64]. In addition, a large number of experiments support the conclusion that the fibrin niche contributes to the stable differentiation of rat MSCs into neural progenitor cells and promotes nerve tissue regeneration [47, 48, 65].

Neural stem cells

Neural stem cells (NSCs) are a group of cells that possess the ability to self-renew and differentiate into neurons and various types of glial cells. The transplanted neural stem cells replace the injured neurons and glial cells through renewal, thus reconnecting the injured spinal cord. Lu *et*

al. [26] implanted NSCs into the fibrin matrix containing the growth factor cocktail, and found that a large number of axons extended in the injured spinal cord and formed neuronal relay, which improved the electrophysiological function of rats. Then, Lu *et al.* [49] separated fresh NSCs from transgenic Fischer 344 rat embryos expressing green fluorescent protein (GFP) and embedded them in fibrin matrix containing growth factors. The results showed that the graft completely filled the lesion cavity and differentiated into two types of neurons (the axons extended very far from the host spinal cord) and glial cells. Subsequently, Robinson *et al.* [66] experimentally verified the conclusions by Lu *et al.* [49]. Self-assembling peptide nanofiber scaffolds (SAPNS), which possess a fine three-dimensional structure and cell compatibility, can induce the differentiation of NSCs into neurons *in vitro* and promote axonal regeneration and improve hind limb motor function when transplanted *in vivo* [67]. Similarly, Arulmoli *et al.* [68] reported a novel composite scaffold composed of fibrin, hyaluronic acid, and laminin that can support the function of human neural stem/progenitor cells (HNSPCs). This composite biomaterial scaffold has physical properties suitable for HNSPCs and the central nervous system, supports the proliferation and differentiation of human neural stem/progenitor cells, and attenuates the rapid cell-mediated scaffold degradation. This has set a benchmark for the treatment of central nervous system injuries with biomaterials.

Summary and outlook

In this review, we have briefly discussed different types of stem cell transplantation combined with fibrin scaffold for the treatment of SCI. SCI is a devastating neurological injury, and there is no single treatment that can completely restore the injured spinal cord structure and function. Currently, the focus of SCI research is on stem cell transplantation and tissue engineering scaffolds, but each has its own limitations. It is difficult to control the direction and amount of differentiation of stem cells when they are transplanted into the injured spinal cord alone, and it is difficult to ensure the healthy survival of transplanted stem cells in a poor microenvironment. Therefore, the use of tissue engineering scaffold technology can provide support and guidance for the newborn axons, and at the same time can avoid the characteristics of the newborn axons being invaded by scar tissue. It is a very potential research direction to combine the two technologies in the treatment of SCI.

However, at present, our research on the combination of fibrin scaffold and stem cell transplantation is still in the early stages of exploration, and there are numerous directions that warrant further worthy of exploration and development. Therefore, the following is our outlook for the future of this topic. First, we need to search for more types of stem cells and compare their ability to differentiate into neurons to find the most suitable type for transplantation. Second, in the future research, we can focus on the mor-

phology and physical properties of the fibrin scaffold. Update the existing fibrin scaffold technology, improve the mechanical properties of fibrin scaffold, and provide the best transplantation site for stem cells to protect them for better proliferation and differentiation. Third, in the future, we can broaden our perspective and combine fibrin scaffold with stem cell transplantation and growth factors for research. The advantages of different substances should be fully exploited to better reduce neuronal damage after SCI, promote axon growth and rebuild the damaged spinal cord tissue.

Conclusions

In a word, for SCI, especially for elderly SCI, the current clinical treatment effect is not satisfactory. Based on the understanding of the pathological changes of SCI, with the deepening of research on stem cell transplantation combined with fibrin scaffold, this treatment strategy may be a promising choice for the regenerative treatment of SCI patients.

Declarations

Author contributions: TJ and ZC jointly wrote the manuscript and produced and revised pictures and tables. YH participated in critical revision of the manuscript for intellectual content. XT and YL sorted out and screened the relevant literatures. HY designed the outline and revised the paper. All authors have read and approved the final version of this manuscript.

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