

Review Article

Recent Advances in Cell and Functional Biomaterial Treatment for Spinal Cord Injury

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Spinal cord injury (SCI) is a devastating central nervous system disease caused by accidental events, resulting in loss of sensory and motor function. Considering the multiple effects of primary and secondary injuries after spinal cord injury, including oxidative stress, tissue apoptosis, inflammatory response, and neuronal autophagy, it is crucial to understand the underlying pathophysiological mechanisms, local microenvironment changes, and neural tissue functional recovery for preparing novel treatment strategies. Treatment based on cell transplantation has become the forefront of spinal cord injury therapy. The transplanted cells provide physical and nutritional support for the damaged tissue. At the same time, the implantation of biomaterials with specific biological functions at the site of the SCI has also been proved to improve the local inhibitory microenvironment and promote axonal regeneration, etc. The combined transplantation of cells and functional biomaterials for SCI treatment can result in greater neuroprotective and regenerative effects by regulating cell differentiation, enhancing cell survival, and providing physical and directional support for axon regeneration and neural circuit remodeling. This article reviews the pathophysiology of the spinal cord, changes in the microenvironment after injury, and the mechanisms and strategies for spinal cord regeneration and repair. The article will focus on summarizing and discussing the latest intervention models based on cell and functional biomaterial transplantation and the latest progress in combinational therapies in SCI repair. Finally, we propose the future prospects and challenges of current treatment regimens for SCI repair, to provide references for scientists and clinicians to seek better SCI repair strategies in the future.

1. Introduction

Spinal cord injury (SCI) is a complex and challenging destructive disease of the central nervous system, resulting in permanent motor and sensory dysfunction due to disruption of neural circuits composed of descending motor neurons and ascending sensory neurons. In addition, because SCI is a serious injury caused by multiple primary and secondary mechanisms simultaneously or sequentially, it often results in chronic consequences such as respiratory dysfunction, cardiovascular complications, neuropathic pain, spasticity, bladder and bowel dysfunction, and mental illness [1, 2]. The most common causes of SCI include traffic accidents, falls, and violence but can also be caused by inappropriate sports and recreational activities [3]. According to

2020 data from the National Center for SCI, about 294,000 people in the United States suffer from spinal cord injuries, with about 17,810 new cases each year. According to statistics, the incidence rate of SCI in China is about 25 to 60 cases per million people, and the age of onset is mostly 40 to 60 years old. The incidence rate is significantly higher in males than in females. Globally, there are 3.6 to 195.4 cases of SCI per million people, of which male patients can reach 78% [4, 5]. SCI has an enormous impact on the patient's personal life, social life, and professional development, followed by a tremendous psychological and financial burden, which brings great pressure to both family and society [6, 7]. Although the current clinical treatment regimens can improve the prognosis of patients with SCI to a certain extent, due to its complex pathophysiological mechanism,

there is currently no effective treatment. To improve the recovery effect of SCI patients, scholars have conducted extensive and in-depth basic research on the pathophysiological mechanism and treatment strategies of SCI. Some spinal nerve regeneration methods have shown good results in animal models, and some of the findings have entered the clinical trial stage. This study started from the physiological anatomy of the spinal cord and the pathophysiological change mechanism of SCI and discussed the regeneration and repair mechanism and strategies of spinal cord nerves. We focused on the latest methods and progress in the treatment of SCI based on cell and functional biomaterials and their combination therapy. We also collated and analyzed preclinical and clinical studies of SCI.

2. Anatomy and Physiology Function of the Spinal Cord

2.1. Anatomy of the Spinal Cord. The spinal cord originates from the end of the neural tube during the embryonic period, and the lumen of the primitive neural tube forms the central canal of the spinal cord. The spinal cord in the lower part of the central nervous system retains segmental structure and connects with 31 pairs of spinal nerves distributed in the trunk and extremities. The spinal cord is located in the spinal canal and is surrounded by 3 layers of membranes (dura mater, arachnoid, and pia mater), which are consistent with the curvature of the spine. The spine itself consists of cervical, thoracic, lumbar, and caudal segments [8]. The upper end is connected to the medulla oblongata at the foramen magnum, and the lower end is tapered, called the conus medullaris, with a total length of about 42-45 cm, a transverse diameter of 1-1.2 cm at the widest point, and a weight of about 20-25 g. The conus medullaris continues downward as a filament of connective tissue called filum terminal, which ends at the back of the coccyx and serves to fix the spinal cord. The spinal cord consists of gray matter surrounding the central canal and white matter located peripherally. In the transverse section of the spinal cord, a small central canal can be seen in the center, surrounded by an "H"-shaped gray matter, and the gray matter is surrounded by white matter. Spinal cord gray matter is a complex composed of the cell bodies of motor neurons and interneurons, glial cells, and blood vessels. Spinal white matter is composed of glial cells and nerve fibers in ascending and descending tracts. Among them, oligodendrocytes, astrocytes, and microglia are present in the spinal cord [9, 10]. Astrocytes are related to the migration of neurons in the embryonic development stage, and when the nervous system matures, they constitute the structural basis of other cells. Astrocyte foot processes are involved in the formation of the blood-brain barrier and play an important role in protection to the central nervous system. Oligodendrocytes are involved in myelin formation, and microglia are associated with immune function in the nervous system [8]. Between cells in the spinal cord, there is an extracellular matrix, which is mainly composed of growth factors, hyaluronic, laminin, thrombospondin, fibronectin, proteoglycans (such-like chondroitin sulfate proteoglycan and heparan sulfate

proteoglycan), Tenascin-C/-R, and other proteins. Interactions of neurons, glial cells, and the extracellular matrix form the structural framework of the spinal cord. In fact, cell differentiation, migration, proliferation, survival, synapse formation, and axonal growth also mainly depend on the interaction between glial cells and the extracellular matrix. The spinal cord has three main arteries supplying blood, and the blood distribution between different segments is not identical, and the blood-spinal cord barrier (BSCB) plays a protective role in the spinal cord [11].

2.2. Physiology Function of the Spinal Cord. The function of the spinal cord is as follows. First, it receives somatic and visceral sensory information in most areas of the body, and this information is relayed in the spinal cord for preliminary integration and analysis. Part of the relayed information is transmitted upward to the higher center, and part is transmitted to motor neurons and other spinal cord neurons. Second, an ascending conduction pathway is sent to upload the relayed sensory information and the information of the spinal cord itself to the higher center. Third, it sends out motor fibers, manages body movement and visceral activity, and is the lower center of body and visceral movement. Fourth is the center of various basic reflexes. Last, through the descending conduction pathway, it relays the information transmitted by the superior center, accepts the control and regulation of the superior center, and completes the functions of the superior center.

3. Pathophysiological Changes of SCI

3.1. Primary and Secondary Injuries. The pathological process of SCI includes primary and secondary injuries [3] (Figure 1). The former refers to mechanical damage to the spinal cord caused by trauma, including instantaneous or sustained mechanical compression, contusion, stretch, laceration, or even transection, with or without spinal fracture or dislocation [12, 13]. Primary injury can cause mechanical and physical damage to neural tissues such as neurons and oligodendrocytes and at the same time cause damage to the vascular structure of the spinal cord, resulting in intramedullary hemorrhage and damage to the blood-spinal cord barrier [14]. This leads to various pathological reactions such as spinal cord edema, hemorrhage, or ischemia and ultimately leads to tissue destruction and cell death through mechanisms such as inflammatory response, lipid peroxidation, oxygen free radical formation, oxidative stress, nerve excitotoxicity, and ion imbalance [3, 15-17]. Secondary injury refers to a pathological process that starts within a few minutes after the primary injury and can last for a long time. It induces a variety of molecular biochemical cascade reactions in tissues, cells, etc., eventually leading to aggravation of SCI and hindrance of regeneration and repair of nerve tissue. In recent years, studies have also shown that autophagy is a cytoprotective mechanism for neurological diseases and injuries. After spinal cord injury, regulating autophagy can promote neuroprotection and functional recovery while reducing neuronal apoptosis and inhibiting inflammatory responses. However, excessive autophagy

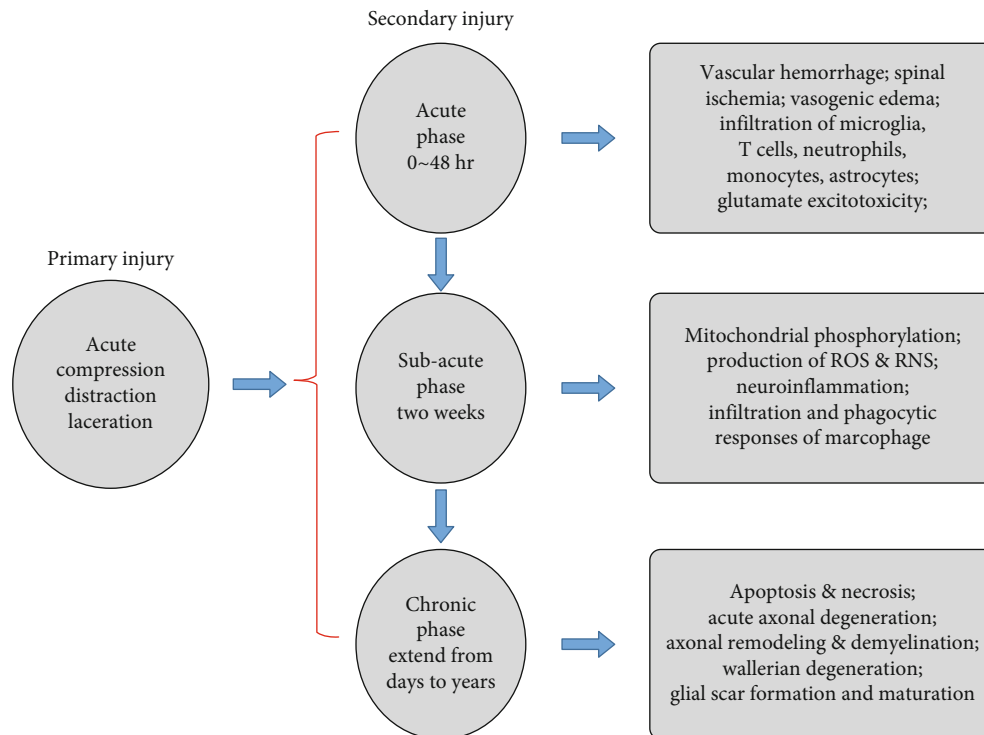


FIGURE 1: The mechanism of pathophysiological changes after SCI.

may activate apoptosis or other cell death mechanisms and lead to the secretion of proinflammatory factors, thereby affecting the recovery of nerve regeneration [18–20].

Secondary injuries are usually divided into the following stages: acute phase (<48 h), subacute phase (48 h–14 days), intermediate phase (14 days–3 months), and chronic phase (>3 months) [13, 21]. The acute phase is the first stage of secondary injury, which may include inflammation, lipid peroxidation, death of necrotic cells, spinal cord edema, free radical formation, calcium influx, ion disturbance, and excitotoxicity caused by neurotransmitter accumulation [3, 13, 22]. If combined with vascular injury, which leads to the enhanced permeability of the blood-spinal cord barrier, the damage of vascular endothelial cells, and the local exudation of immune cells and proteins, the situation will be further aggravated [23, 24]. In the subacute phase, astrocytes at the injury site will proliferate and transform into reactive astrocytes. The infiltration and phagocytic responses of macrophage can also be observed. Over time, the glial scars gradually develop [13, 24, 25]. The formation of glial scars is beneficial in rebuilding the damaged blood-spinal cord barrier, thereby reducing cell exudation, producing antioxidants, reducing edema, restoring ion balance, and reducing excitotoxic effects. However, it also has a certain inhibitory effect on the regeneration and repair of nerve tissue in the late stage [25]. In the intermediate phase, the scar formed by astrocytes matures, followed by axonal sprouting heralding the onset of nerve regeneration [26]. The chronic phase is typically characterized by cyst formation and Waller's degeneration, as well as inflammation, apoptosis, and nerve demyelination [27, 28] (Figure 2).

According to the location and degree of spinal cord injury and clinical manifestations, we often divide it into different syndromes. These include central cord syndrome, anterior cord syndrome, conus medullaris syndrome, cauda equina syndrome, and Brown-Sequard syndrome. The central spinal cord syndrome mostly occurs in the injured area of the cervical spine, and the conus medullaris syndrome and the cauda equina syndrome are mostly related to the injury of the conus medullaris and lumbosacral nerve roots. Anterior cord syndrome and Brown-Sequard syndrome are often accompanied by varying degrees of motor function loss and changes in pain and temperature sensation.

3.2. Effects of SCI on Resident Cells. After SCI, changes in the local microenvironment can cause dynamic changes in resident cells such as neurons, astrocytes, oligodendrocytes, and microglia, including cell phenotype, number, and distribution. Understanding the dynamic changes of cell behavior could help develop better strategies for neural regeneration.

3.2.1. Neurons and Neural Progenitor Cells (NPCs). The neurons of the spinal cord are divided into different categories, including motor neurons, sensory neurons, excitatory neurons, inhibitory neurons, and relay neurons of the spinal cord itself. After SCI, the damage and apoptosis time and degree of damage of various types of neurons are different. In the transection injury model, neurons undergo apoptosis 1 hour after injury and are localized to the injury site [29]. In the compression injury model, neuronal apoptosis can persist from 1 hour to 2 weeks after injury [30]. In addition, injury disrupts the continuity of ascending or descending

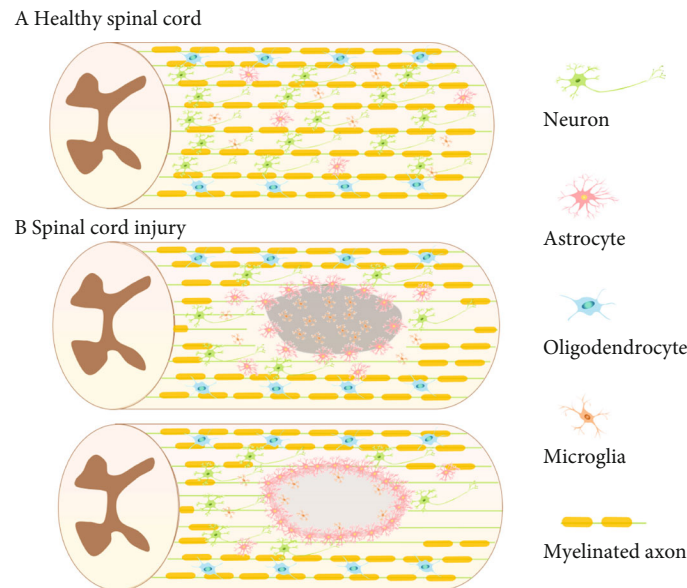


FIGURE 2: Structural changes in healthy and injured spinal cords: (a) healthy spinal cord and (b) SCI. The acute phase is the first stage of secondary injury, which may include inflammation, lipid peroxidation, spinal cord edema, free radical formation, and excitotoxicity caused by neurotransmitter accumulation. In the subacute phase, astrocytes at the injury site will proliferate and transform into reactive astrocytes. The infiltration and phagocytic responses of macrophage can also be observed. The glial scars gradually develop which is beneficial to rebuild the damaged blood-spinal cord barrier. The chronic phase is typically characterized by cyst formation and Waller's degeneration, as well as inflammation, apoptosis, and nerve demyelination.

nerve fibers, leading to the Wallerian degeneration [31]. Following SCI, many endogenous NPCs migrate to the injured area and proliferate and differentiate into neural cells to rebuild damaged neural network circuits [32]. NPCs can differentiate in different directions under different stimulation conditions [33]. Strengthening the research on the plasticity of NPCs will help us formulate neural regeneration strategies by regulating the proliferation, differentiation, and migration of endogenous NPCs and improve the ability of neural regeneration [34].

3.2.2. Astrocytes. Astrocytes are the most abundant cells in the nervous system. They can provide a variety of neurotrophic factors and energy substances, regulate the metabolism of glutamate and potassium ions and the water content in the spinal cord, and participate in various physiological behaviors of neurons. They also play a role in the resistance to oxidative stress and excitotoxicity [35, 36]. Naive astrocytes are typically activated within hours of SCI and undergo a transition to reactive astrocytes, which play an important role in wound healing in the acute phase but ultimately form dense glial scars, which hinder the regeneration and repair of neural network circuits [37]. Recently, it has been found that Nrf2 is a major transcriptional regulator of cellular antioxidant stress response in astrocytes; its regulation of antioxidant system plays a key role in the early stage after spinal cord injury. Increased Nrf2 activity in astrocytes can improve the inflammatory response after spinal cord injury and promote the recovery of motor function [38].

3.2.3. Oligodendrocytes and Oligodendrocyte Precursor Cells. Oligodendrocytes are involved in the formation of myelin, and primary injury of the spinal cord and secondary excitotoxicity and reactive oxygen species can have a serious impact on them. Damage to oligodendrocytes and myelin inhibits the propagation of action potentials, decreases effective conduction of nerve signals, and will lead to functional impairment [39]. Studies have reported that oligodendrocytes were significantly reduced within 15 minutes after SCI in rats and peaked within hours [40]. Oligodendrocytes are produced from their precursor cells. Oligodendrocyte precursor cells are the most proliferative cells in the nervous system. They can proliferate and differentiate into oligodendrocytes and Schwann cells after SCI and thereby promote axonal remyelination [41]. Some scholars regulate the proliferation and differentiation of oligodendrocyte precursor cells through various pathways, such as regulating BMP signaling and Nrg1 signaling, indicating that it is also an important factor and therapeutic target for SCI repair [42].

3.2.4. Microglia. Microglia are immune cells with self-renewal ability and are an important part of the immune function of the central nervous system [43, 44]. After SCI, microglia are rapidly activated and persist for longer periods of time. Activated microglia can polarize and secrete inflammation-related factors with multiple effects on neuronal survival and the local microenvironment [45]. Different microglia phenotypes were found in injured spinal cord by a single nuclear RNA sequencing technique, suggesting that in the future, people can use multiple potential immunotherapy

targets to regulate microglia-induced inflammation-related pathological changes [46].

3.3. Factors Affecting Nerve Regeneration

3.3.1. Syringomyelia. Following SCI, early massive cell death and degeneration of spinal cord structure lead to a loss of parenchymal tissue in the central area of the injury, forming cystic cavities with extracellular fluid, connective tissue bands, and infiltrating macrophages [47, 48]. The presence of CSF pressure within the cystic lumen may cause the smaller lumen to fuse with each other and expand, further impeding axonal regeneration and cell migration [49, 50]. Researchers need to adopt more effective regeneration strategies to overcome the hindrance of syringomyelia on nerve regeneration to reshape the connection circuits of neural networks.

3.3.2. Inflammatory Response. The immune cells of the central nervous system mainly include microglia and macrophages around blood vessels, meninges, choroid plexus, and periventricular. Microglia, as resident cells of the central nervous system, are rapidly activated after SCI, transform into phagocytic microglia, and migrate and aggregate to the site of injury at the same time [51, 52]. A strong local inflammatory response also promotes infiltration of macrophages into lesions [53]. Microglia can secrete anti- or pro-inflammatory cytokines, neurotrophic factors, chemokines, growth factors, etc. while removing toxic substances and cellular debris through phagocytosis [51]. After injury, microglia activate, proliferate, and migrate to the injury site, which can help maintain local cellular homeostasis, but a large number of proinflammatory factors released by them can also induce neuronal death, and the pathological mechanism may involve oxidative stress, ionic imbalance, etc. [54–56]. Studies have reported that M2-activated subset of microglia has a lower proinflammatory response than M1-activated subset of microglia and are more conducive to axonal growth [57, 58]. Therefore, researchers are also trying to promote the regeneration and recovery of neural tissue after SCI by regulating the phenotype of microglia and macrophages.

3.3.3. Glial Scar. After SCI, astrocytes, the most abundant resident cells in the central nervous system, begin to proliferate and transform into reactive astrocytes, which interweave to isolate the injured area from the normal area [59]. Over time, reactive astrocytes around the lesion begin to surround fibroblast-like pericytes, eventually forming an astrocyte scar [60, 61]. Glial scar is often considered to be the main obstacle to nerve regeneration because it hinders the growth of neurons, but some studies have also pointed out that it helps to repair the damaged blood-brain barrier, effectively preventing damage from spreading while improving inflammation response [59, 62–65]. Research into regulating the formation and development of scars has potential therapeutic implications for promoting SCI recovery.

3.3.4. Chondroitin Sulfate Proteoglycan. Chondroitin sulfate glycoproteins are widely expressed in the central nervous

system and are closely associated with cell migration and axonal growth [66, 67]. CSPGs include neurocan, versican, brevican, phosphacan, and NG2 [68]. After SCI, the inflammatory response greatly increases the secretion of CSPGs from cells, and the deposited CSPGs promote the formation of glial scars and hinder axonal regeneration [69]. Furthermore, CSPGs have inhibitory effects on the migration and differentiation of oligodendrocyte precursor cells, thereby inhibiting remyelination [70]. Studies have shown that chondroitinase ABC (ChABC) is a potential therapeutic strategy against the inhibition of CSPGs, which promotes axonal growth and functional improvement after SCI by degrading CSPGs [71].

3.3.5. Other Relevant Factors. SCI leads to oligodendrocyte death and myelin damage, which affects nerve signaling. At the same time, myelin-related components such as myelin-associated protein (MAG) and oligodendrocyte myelin glycoprotein (OMgp) are also the inhibited factors of axonal growth [72]. In addition, neurite outgrowth inhibitor (NOMO), Repulsive Guidance Molecule A, etc. also inhibit axon regeneration and repair through their respective signaling pathways [73, 74].

4. Neural Repair Mechanisms in SCI

After SCI, the final repair effect is often unsatisfactory due to its limited ability of nerve regeneration. The injury-induced syringomyelia, glial scarring, inflammatory responses, and the local inhibitory microenvironment caused by release and accumulation of axonal growth-inhibiting substances also play an important role. At present, the recognized nerve repair mechanism of SCI includes two aspects. On the one hand, the intrinsic motor nerves of the spinal cord regenerate through their axons, cross the area of injury, establish connections with distant neurons, and remodel neural circuits [75]. Some scholars have constructed functional biomaterials by combining natural or synthetic biomaterials with growth factors, anti-inflammatory cytokines, drugs, antibodies, nanoparticles, etc., through their specific therapeutic targets, which can effectively promote the disconnected nerve axon regeneration [76–78]. On the other hand, the transplanted exogenous NPCs or the endogenous NPCs migrated to the injured area formed relay neurons through differentiation, which played a bridging role and promoted new synaptic connections and neural circuit formation [79–82]. It is worth mentioning that when using functional biomaterials, the activated endogenous neural stem cells showed stronger neuronal differentiation ability and neural stem cell recruitment ability; in addition, exogenous neural stem cells cotransplanted with functional biomaterials are able to survive longer at injury site and enhance differentiation into neurons [33, 83, 84].

5. Treatment Strategies for SCI

5.1. Current Clinical Treatment of SCI. The current treatments after SCI include maintaining the stability of the spinal cord after injury, early surgical decompression, and

corresponding treatment measures from the aspects of neuroprotection and nerve regeneration. The goal of postinjury spinal cord fixation is to avoid additional trauma, while early surgical decompression relieves persistent compression and avoids further expansion of ischemia and nerve tissue damage [13, 85, 86].

Neuroprotective strategies include drug therapy such as glucocorticoid methylprednisolone, sodium channel blocker riluzole, and nondrug therapy such as cerebrospinal fluid drainage, blood pressure augmentation, and therapeutic hypothermia. Methylprednisolone can enhance neuron survival after injury by regulating the release of anti-inflammatory cytokines and attenuating oxidative stress, and riluzole reduces excitotoxicity influence to cells by preventing sodium influx and regulating glutamine release. Combined treatment of cerebrospinal fluid drainage and blood pressure augmentation can increase the blood supply and perfusion pressure in the injured area and prevent ischemic injury. Therapeutic hypothermia can reduce the basal metabolic rate of the central nervous system and improve the inflammatory response at the site of injury, while also reducing oxidative stress and excitotoxicity [15, 87–90].

In recent years, research in the field of nerve regeneration has gradually become a hot spot in the field of SCI repair, especially treatment strategies based on cell transplantation and functional biomaterials, which have given people better expectations for the prognosis of SCI patients. In addition, treatment regimens for Rho-ROCK inhibitors and anti-NOGO antibodies have also shown certain therapeutic effects in animal models and clinical trials [91, 92].

5.2. Cell Therapy for SCI. Cell-based regenerative therapy is a very promising direction for the treatment of SCI, including both exogenous cell transplantation and enhancement of endogenous stem cell function [93–95]. We can achieve better regenerative treatment effects by selecting different types and states of cells, as well as different treatment methods and intervention timings [96, 97]. Transplanted cells can replace damaged and lost neural tissue, secrete essential neurotrophic factors, modulate the local microenvironment and immune responses, and provide the substrate and support needed for regeneration of axonal, remyelination, and neural tissue repair [98–101]. Of course, cell transplantation therapy also faces some problems, such as local tumor formation, poor cell differentiation, enhanced immune response of transplanted cells, and low cell survival rate, which need to be further solved.

5.2.1. Selection of Transplanted Cells

(1) Neural Stem Cells. Neural stem cells are self-renewing cells with multiple differentiation potentials that can differentiate into neurons, astrocytes, and oligodendrocytes under different conditions [102, 103]. The theoretical basis for the transplantation of neural stem cells for the treatment of SCI is that, on the one hand, neurons differentiated from neural stem cells can act as relay neurons to integrate into the broken neural circuit; on the other hand, oligodendrocytes differentiated from neural stem cells can participate

in the formation of myelin sheaths and promote the regeneration and repair of axons and signal transduction [81, 104, 105]. According to literature reports, transplanted neural stem cells can survive and differentiate in multiple directions at the site of injury and at the same time play a role in regulating local immune function by promoting the infiltration of anti-inflammatory M2 macrophages [106, 107]. Scholars are trying to use neural stem cell transplantation for clinical research; considering the variety of the type and function of neurons in the spinal cord tissue, whether the neural stem cells transplanted can successfully differentiate into subtypes of neurons that we need, especially the spinal interneurons and spinal motor neurons whose functions are seriously affected because of the damage, is still worth our further discussion.

(2) Mesenchymal Stem Cells. Mesenchymal stem cells are self-renewing cells with multiple differentiation potentials [108]. It can perform tissue regeneration repair by differentiation into osteoblasts, chondrocytes, myocytes, and adipocytes [109–112]. Studies have shown that mesenchymal stem cells can enhance tissue protection and promote neural tissue repair and neovascularization by secreting neurotrophic factors and regulating immune function [113, 114]. Significant tissue repair and reduction of peripheral inflammatory cell infiltration can be observed in animal models of SCI treated with MSCs [115]. Reviewing recent studies on MSCs in the treatment of SCI, the possible mechanisms of MSC transplantation to promote tissue regeneration include regulating immune responses (regulation of macrophage phenotype M1 to M2 and reducing inflammatory cell infiltration), inhibiting apoptosis (inhibiting inflammatory corpuscles), promoting angiogenesis, and promoting regeneration of axons and myelin [116–121]. In addition, MSCs are important candidates for regenerative medicine because of their ease of acquisition, ease of storage, low immunogenicity, and strong proliferative capacity [108, 122–124]. In preclinical studies, the use of MSCs for the treatment of SCI has yielded promising results. However, in the clinical studies that have been performed, the therapeutic effect of MSC transplantation for SCI varies. In a clinical study of 277 patients, 43.3% showed improvement in clinical function [124]. In another study of 44 patients, there was no significant recovery of neurological function after MSC treatment and the treatment effect was poor [125].

(3) Induced Pluripotent Stem Cells. Induced pluripotent stem cells are cells with self-renewal and multidifferentiation potential, which are generated by genetic modification and reprogramming of differentiated somatic cells, avoiding ethical and immune rejection, and bringing more possibilities to regenerative medicine [126–129]. Studies have shown that iPSC-derived neural stem cells can be used for the repairing treatment of SCI, acting as relay neurons at the injury site to form a neural circuit, and promoting neovascularization and remyelination, ultimately improving functional recovery [130, 131]. Another study also pointed out that iPSC-derived NSCs have the tumorigenicity. In this study, neural cells derived from iPSCs were transplanted for treatment.

Although these treatments were initially effective and motor function was improved, but during follow-up, tumor formation at the site of cell transplantation also resulted in a poor prognosis [132].

(4) *Astrocytes*. Naive astrocytes are activated after SCI to form reactive astrocytes that prevent the expansion of injury and inflammatory responses, and the formation of astrocyte scars is often thought to inhibit axon regeneration [59, 63, 65, 133]. However, it has been reported that inhibiting the growth of reactive astrocytes by genetic modification does not promote tissue regeneration but rather reduces the regenerative capacity of axons [65]. Studies have shown that, as the most abundant glial cells in the central nervous system, astrocytes form the basis of the structural framework between cells, provide a variety of neurotrophic factors, and provide support for the stability of the internal environment [134, 135]. After SCI, activated astrocytes interweave into networks that can provide physical support for axonal regeneration. Considering the above roles, astrocytes have been used to explore the treatment of SCI, and studies have shown that they can survive, integrate, and migrate at the injury site and show some potential for neuroprotection and functional improvement [136]. How to better exert the beneficial effects of astrocytes still needs more in-depth research.

(5) *Oligodendrocyte Precursor Cells*. Oligodendrocyte precursor cells can be rapidly activated after SCI, proliferate massively, and differentiate into oligodendrocytes and Schwann cells to promote remyelination [137]. Animal experiments have shown that the transplantation of oligodendrocyte precursor cells in the treatment of SCI has a certain recovery effect. It can be used as a substrate for remyelination, regulate local immune function, and secrete a variety of nutritional factors, cytokines, chemokines, etc. [129, 138, 139]. Further evidence is needed to support how oligodendrocyte precursor cells exert their role in the treatment of SCI.

(6) *Olfactory Ensheathing Cells*. Olfactory ensheathing cells are specialized types of glial cells present in the peripheral and central nervous systems and are found in the olfactory mucosa and olfactory bulb [140, 141]. It secretes neurotrophic factors, promotes angiogenesis, has phagocytic functions, and regulates local immune responses [142–144]. Some scholars have transplanted olfactory ensheathing cells to treat SCI. The results of animal models show that olfactory ensheathing cells produce extracellular matrix, which supports and guides the growth of axons and improves motor function [2, 145]. It has also been reported that olfactory ensheathing cells at different culture stages have different nerve repair effects and that cells cultured for less than three weeks have better therapeutic effects than cells cultured for seven weeks [146]. At present, olfactory ensheathing cells have been used in clinical trials for the treatment of SCI, and the safety and efficacy need to be confirmed by a larger number of clinical samples.

(7) *Schwann Cells*. Schwann cells are the most numerous glial cells in the peripheral nervous system and are an

important part of nerve regeneration in the peripheral nervous system [147]. In animal models of SCI, Schwann cells can promote remyelination, provide growth factors and extracellular matrix components, reduce cyst formation, enhance axon regeneration in the central nervous system, and ultimately improve motor and sensory function [148–152]. In clinical studies that have been performed, autologous Schwann cell transplantation and continuous follow-up have shown that patients' motor and sensory functions have improved, and autonomic function has also recovered to some extent [153].

(8) *Genetically Modified Cells*. With the development of gene technology and cell culture technology, scholars are also trying to use gene-modified cells to treat SCI. It can more efficiently express the required protective nerve growth factor, enhance the differentiation of neural stem cells or progenitor cells into neurons, and improve the survival rate of transplanted cells, thereby improving the effect of cell therapy and promoting the regeneration and repair of SCI [154–156]. According to literature reports, human umbilical cord blood mononuclear cells genetically modified with VEGF, GDNF, and FGF2 significantly improve the therapeutic effect compared with the nontransduced cells when transplanted into the site of SCI [157, 158]. Some scholars have used Wnt4-modified neural stem cells to stimulate nerve regeneration while enhancing the differentiation of cells into neurons, which ultimately significantly improves neural repair and functional recovery [159]. There are also studies reported that the chondroitinase ABC (ChABC) gene and tumor suppressor gene (PTEN) of adipose-derived mesenchymal stem cells were modified by gene modification technology. By promoting the expression of chondroitinase ABC (ChABC) and downregulating the expression of tumor suppressor gene (PTEN), it can enhance cell survival and function and reduce the inhibitory effect of glial scar [160]. In the future, gene-modified cell therapy also has great application potential.

5.2.2. *Enhancing the Survival and Function of Transplanted Cells*. With the increasing number of attempts to treat SCI with cell transplantation, some problems have also been identified, for example, the survival rate of transplanted cells is low, the extravasation of transplanted cells at the injury site, and how to make the transplanted cells function better at the injury site. Researchers have also made many attempts in this regard. Intrathecal injection of neurotrophic factors (e.g., BDNF), growth factors (e.g., IGF-1), etc. has been reported to enhance the survival of transplanted cells [161]. Using genetic modification techniques to modify cells to express more factors required for cell survival has also been used in multiple preclinical studies [157, 162, 163]. The combined transplantation of cells and functional biomaterials with specific therapeutic targets not only facilitates cell adhesion and prevents cell extravasation but also enhances the survival rate of transplanted cells and promotes stem cells to differentiate in beneficial directions. Functional biomaterials themselves can also act as a support for axonal growth and promote regeneration and repair of

neural tissue [164, 165]. In addition, application of an external electric field promotes cell migration and differentiation; alleviates the barrier inhibition of glial scars to increase the integration of transplanted cells into the host; and genetically modifies the major histocompatibility complex and CD47 of transplanted cells to reduce central nervous system immune rejection has all been shown to be effective [61, 166–169].

5.2.3. Utilization of Endogenous Stem Cells. Another direction of cell therapy is to fully exploit the regenerative potential of endogenous stem cells [170]. Following SCI, endogenous stem cells in the spinal cord proliferate, migrate to the injury site, and further differentiate into neurons, astrocytes, and oligodendrocytes to promote tissue regeneration [171]. Improving the understanding and regulation of these cells will help us promote our ability to use endogenous stem cells for tissue regeneration and increase therapeutic targets for SCI. It has been reported that intrathecal injection of the growth factors EGF and FGF2 increases the proliferative capacity of endogenous stem cells and facilitates tissue repair [161, 172]. Some scholars have also found that the small molecule drug metformin can activate endogenous stem cells and promote their differentiation into neurons and oligodendrocytes [173]. The transplantation of exogenous stem cells also has a certain stimulating effect on endogenous stem cells and makes them develop and differentiate in the direction that is beneficial to nerve regeneration [174]. The related signaling pathways and therapeutic targets that regulate the proliferation, migration, and differentiation of endogenous stem cells still require further study.

5.3. Functional Biomaterials for the Treatment of SCI. After SCI, the huge gap formed by the loss of neural tissue is the main obstacle to axon regeneration and neural circuit repair. At the same time, the therapeutic effect of simple cell therapy is limited by local severe inflammatory response, extravasation of transplanted cells, and poor cell survival rate. In order to achieve a more ideal therapeutic effect, people try to transplant and integrate biomaterials into the injured spinal cord tissue. Initially, people only tried to find suitable biomaterials, which, through certain processing, were structurally suitable for implantation into the injured area and acted as a “bridge” to support and guide axon regeneration [175]. With the development of medicine, biology, tissue engineering, chemistry, and other technologies and the deepening of people’s understanding of the pathophysiological changes of SCI, scholars began to modify biomaterials to have specific biological functions [176–179]. The emergence of functional biomaterials has brought new hope for the repair of spinal cord injuries. Through specific therapeutic targets, it can better improve the local inhibitory microenvironment, promote axonal and angiogenesis, reduce scarring, regulate immune response, and ultimately contribute to neural tissue repair [178–183].

5.3.1. Characteristics of Functional Biomaterials. Essential elements of functional biomaterials include good biocompatibility, suitable biodegradability, and low immunogeni-

city [179, 184]. Most of them have directional channels or fibers or three-dimensional porous structure, which not only conducive to cell migration and adhesion and directional growth of axons but also have certain regulatory effects on cell differentiation [185, 186]. In addition, functional biomaterials can carry a variety of biomolecules such as growth factors, drugs, antibodies, genes, enzymes, and exosomes through physical, chemical, and biological modifications and help tissue repair through different therapeutic targets, and at the same time, by adjusting the electrical conductivity, mechanical properties, structural morphology, etc. of the material, the optimal therapeutic effect can be achieved [176–179, 185, 187, 188].

5.3.2. Types of Functional Biomaterials. We divide functional biomaterials into the following four categories according to their main components and preparation methods: natural materials, synthetic materials, composite materials, and micro-/nanomaterials [189–191]. Natural materials have similar biological properties to tissues, are less toxic, and can be degraded, but some materials may also cause severe local inflammatory reactions. People try to find a balance between the mechanical strength and degradation rate of materials suitable for tissue repair, so that they can degrade at a suitable rate while meeting the requirements of certain tissue mechanical strength, so as to achieve matching with tissue repair [184, 192–194]. Commonly used natural materials include agarose, collagen, gelatin, chitosan, alginate, fibrin, hyaluronic acid, and extracellular matrix. Synthetic materials have many advantages which combine the required mechanical properties and degradability for tissue engineering design while also satisfying their economics, reliability, toxicity, and biocompatibility [193, 195–197]. Synthetic materials mainly include degradable polymers (PGA, PCL, PLA, PLGA, and PEG), nondegradable polymers (PHEMA and PHPMA), synthetic polypeptide molecules, and conductive polymers. In order to realize the complementary advantages of two or more biomaterials, composite materials emerge as the times require, which may have better tissue engineering properties and bioremediation effects [190, 198–200]. Nanomaterials also have promising applications in tissue damage repair, including nanofibrous scaffolds as well as nanoparticles [188, 201]. Micro-/nanofibrous scaffolds prepared by electrospinning techniques have been used in preclinical studies [186, 202–204]. In addition, 3D printing technology for the treatment of SCI is also one of the research hotspots in the field of organ and tissue regeneration in recent years. Tissue construction is based on self-assembly and bionics. Using a variety of biomaterials and biomolecules provides targeted and individualized treatment of tissue damage [203, 205, 206].

5.3.3. Therapeutic Targets of Functional Biomaterials. After SCI, due to the complex and dynamic changes in the pathophysiological mechanisms affecting nerve repair, people have developed and prepared a variety of functional biomaterials based on injury factors and nerve repair mechanisms, which have shown gratifying effects in animal models. Clinical trials have been carried out. From the perspective of

promoting axonal growth and reformation of neural circuits, some scholars have combined PLGA microspheres loaded with FGF2 with a biopolymer mixture hydrogel containing hyaluronic acid and methylcellulose, which can repair SCI through local delivery and sustained release effects [207]. Some scholars also combine collagen with neurotrophic factor 3 (NT-3)/brain-derived nerve growth factor (BDNF) through the collagen binding domain and use the slow-release characteristics of recombinant collagen and the biological properties of growth factors to construct bioactive scaffolds [208, 209]. Zhang et al. used hydrogel scaffolds encapsulated with a variety of microRNAs and neurotrophic factors for animal model research, by regulating the expression of proinflammatory genes and extracellular matrix deposition-related genes and promoting local protein synthesis in growth cones that play an important role in axonal growth and development to improve nerve damage [210]. Histological, behavioral, and electrophysiological analysis showed that the above bioactive scaffolds could effectively promote the growth of axons and ultimately promote tissue repair. Some scholars have also studied immunomodulation as a therapeutic target. Fan et al. combined collagen with Fab fragments of EGFR antibodies to construct bioactive scaffolds and improved the microenvironment of axon regeneration through the regulation of myelin-related inhibitors by EGFR antibodies [84]. Some scholars have combined carriers with drugs, growth factors, anti-inflammatory cytokines, etc. to construct anti-inflammatory functional biomaterials, which can regulate the immune response and microenvironment after injury by regulating the phenotype and number of macrophages and microglia at the injury site and ultimately promote functional recovery [211–214]. From the perspective of promoting angiogenesis, Wang et al. designed a collagen scaffold loaded with vascular endothelial growth factor (VEGF), which not only promotes neovascularization but also contributes to functional recovery [215]. On this basis, a functional collagen scaffold containing both stromal cell-derived factors and paclitaxel liposomes was further developed. Histological analysis showed that the scaffold had a synergistic effect on promoting axonal and angiogenesis in the lesion area [216]. Some scholars have regarded scar tissue as a therapeutic target. In order to reduce the hindrance of scar tissue with high expression of chondroitin sulfate caused by injury, methylcellulose hydrogel containing stromal cell-derived factor-1 α was combined with chondroitinase. The functional bioactive scaffolds can maintain ChABC activity with long-term slow release and enhance the recruitment of endogenous neural precursor cells, ultimately promoting tissue regeneration [217–219]. Some scholars have also used exosomes for the treatment of spinal cord injury. The exosomes derived from human mesenchymal stem cells were immobilized on the peptide-modified hydrogel with adhesion and transplanted into the spinal cord injury. Unlike the systemic delivery of exosomes, this treatment modality provides an extracellular matrix containing exosomes to nerve tissue at the site of injury, reducing neuronal inflammation and oxidative stress. At the same time, the exosomes maintain better activity and sustained release effect [220]. Considering the mechanism of

nerve repair, how to promote the formation of relay neurons at the injury site through functional biomaterials is also the focus of research. According to reports, collagen is used as the main component of the bioactive scaffold, through the preparation process and method to make it have a certain appearance characteristics and then modify it with the stromal cell-derived factors, neurotrophic factors (NT-3 and BFGF), genes, antibodies (cetuximab), and drugs (paclitaxel) which can effectively promote the migration and survival of endogenous neural stem cells and induce them to differentiate into neurons, eventually forming complete neural circuits [76, 221, 222]. Nanomaterials also have their own unique functional properties, and studies have shown that the structure and morphology of nanofibers have an impact on the therapeutic effect [185, 186, 188]. Fibers with a diameter of 400 nanometers were more effective in promoting cell migration and growth of protrusions than nanofibers with diameters of 800 nanometers and 1200 nanometers [223]. Furthermore, oriented nanofibers promote the growth of nascent axons, which may be involved in glutamate transport [224]. It has also been reported that oriented nanofibers can promote the recruitment and migration of endogenous neural stem cells and guide them and exogenous neural stem cells to differentiate into neurons, expressing higher levels of neuron-related proteins [225–227]. Nanoparticles are widely used in drug delivery systems due to their unique advantages, which can successfully reach and stay at the injury site for a long time, and achieve the purpose of promoting injury repair by continuously releasing growth factors, drugs, etc. [228]. Li et al. designed a nanoparticle containing the polypeptide CAQK (CAQK-MET-NPs) for targeted delivery of metformin. While exerting anti-inflammatory, antioxidant, and neuroprotective effects, it overcomes the disadvantages of poor water solubility and low bioavailability of drugs and ultimately promotes spinal cord repair and motor function improvement [229].

5.4. Combination Therapy of Cells and Functional Biomaterials. SCI leads to disruption of neural circuits, tissue loss, and cyst formation. Both cell transplantation and functional biomaterial transplantation have been proven to effectively promote the repair of nerve tissue after SCI. In order to improve the therapeutic effect and repair efficiency, people have tried to combine cells with functional biomaterials to treat SCI.

5.4.1. Methods of Combining Cells with Functional Biomaterials. The methods of combining cells and functional biomaterials to treat SCI mainly include the following: the first mixes cells with functional biomaterials in vitro to form a tissue-like matrix, which is then implanted at the injury site. The second is the simultaneous injection of self-assembled biomaterials and cells into the injury site to form tissue scaffolds containing cells in vivo. The first two are mostly used for gel materials. The third type is to plant cells on the prepared bioactive scaffolds in vitro and then implant the scaffolds with cells into the damaged area. Most of the scaffolds have a fixed shape. The fourth type is to implant prefabricated scaffolds into the injury and then inject cells around the material to promote the integration

of the biomaterial with the injured tissue. The latter two categories are mostly used for solid-state biomaterials [230].

5.4.2. The Role of Cells Combined with Functional Biomaterials. Functional biomaterials can not only fill the lesion cavity and provide physical support for axonal regeneration, but their unique biological functions can also effectively promote axonal growth and angiogenesis, regulate immune responses, alleviate scar inhibition, and help transplant cell survival and differentiation. Transplanted cells can secrete trophic factors necessary for nerve repair and promote axon regeneration and endogenous stem cell migration, and neural stem/progenitor cells can also differentiate into relay neurons to integrate damaged neural circuits. In addition, biomolecules released from functional biomaterials and transplanted cells can also downregulate the concentration of growth inhibitory components (cells, myelin debris, inflammatory cytokines, etc.) caused by nerve injury and improve the local microenvironment (Figure 3). It has been reported in the literature that mouse neural stem cells were planted on a PLGA scaffold with a special morphology and transplanted into the SCI. Animal models had the highest behavioral scores and the best treatment outcomes and significantly improved transplant cell survival compared to scaffold or cell therapy alone [231–233]. In other studies, NPCs from the neonatal rat telencephalon were combined with a collagen scaffold modified with cetuximab for SCI repair, regulating cell differentiation behavior and promoting axon regeneration by inhibiting downstream signaling pathways activated by myelin-related inhibitors. The results showed that in the experimental group, the differentiation of neural precursor cells into neurons was increased, the regeneration of axons was enhanced, and the functional recovery effect was better [234–237]. Other scholars have planted human umbilical cord blood mesenchymal stem cells on silk fibroin/alginate scaffolds carrying glial cell-derived nerve growth factors, increasing neuronal survival at the injury site, and promoting tissue repair by slow-release effect of functional scaffolds and biological effects of growth factors and transplanted cells. The combination of cells and functional bioscaffolds showed higher therapeutic efficiency and better repair results compared to the cell-free transplantation group and the group using only the scaffold without biological modification alone [238]. In another study, some scholars modified a hydrogel scaffold composed of hyaluronic acid and methylcellulose with platelet-derived growth factors and then cotransplanted neural precursor cells with bioactive scaffolds for the treatment of SCI. The bioactive scaffold significantly improved the survival rate of transplanted cells and induced the differentiation of neural precursor cells into oligodendrocytes. The experimental group showed better tissue repair and functional recovery compared to the simple transplanted cell group [164]. Lu et al. reported the synergistic effect of neural stem cells and functional bioscaffolds containing multiple growth factors. In an animal model of severe SCI, GFP-expressing neural stem cells were transplanted at the injury site in combination with a fibrin matrix containing a cocktail of growth factors (brain-derived neurotrophic factor, neurotrophic factor-3,

glial cell-derived neurotrophic factor, epidermal growth factor, basic fibroblast growth factor, acidic fibroblast growth factor, hepatocyte growth factor, insulin-like growth factor, platelet-derived growth factor, vascular endothelial growth factor, and calpain inhibitors). The results indicate that transplanted stem cells can differentiate into neurons, and a large number of axons can be seen growing through the damaged area, forming abundant synapses with host cells, and ultimately improving functional recovery [82]. With the maturity of cell culture technology and the innovation and development of functional biomaterials, the combination of the two in the treatment of SCI may bring better prognosis for SCI patients in the future.

6. Prospects and Challenges

The regeneration and repair process of SCI is complex and affected by many factors, and its pathophysiological mechanism still needs further research by scholars. In recent years, many preclinical studies have been carried out based on cell transplantation, functional biomaterials, and their combination therapy, and some studies have been carried out to the clinical trial stage. Although evidence shows that most of the research is beneficial to the repair of SCI and the improvement of motor function, there are still many problems before it can be used in clinical practice and for the benefit of patients. Different types of SCI, patient conditions including age and underlying diseases, severity of injury, and different lesion volumes are suitable for different treatment modalities. When using cell transplantation to treat SCI, the selection of cell types, the number of cells to be transplanted, and the exact location and method of transplantation will affect the therapeutic effect. Inappropriate treatment may result in poor cellular viability, poor cell differentiation, and tumor formation, all of which need to be further addressed and standardized. In addition, due to the complexity of organisms, the biological functions of some cells have two sides, and it is necessary to explore the balance point of treatment. For example, naive astrocytes are activated after SCI to form reactive astrocytes, which prevent the expansion of the injury and inflammatory response, and their eventual formation of astrocyte scars is often considered to inhibit the regeneration of axon. However, some scholars inhibited the growth of reactive astrocytes by gene editing but did not help tissue regeneration. On the contrary, studies showed that the regeneration ability of axons was reduced. Oligodendrocyte precursor cells can differentiate into oligodendrocytes and Schwann cells, which act as substrates for remyelination, regulate local immune function, and secrete a variety of trophic factors, cytokines, chemokines, etc. They aid in myelination and tissue repair. However, they can also hinder axonal regeneration by promoting CSPG deposition to form inhibitory glial scars. Researchers need to use a variety of research methods such as omics sequencing to reveal the dynamic changes and interactions of cells in the process of growth and differentiation, so as to achieve better therapeutic effects. When using functional biomaterials to treat SCI, the key point is whether the tissue structure and biological function can be simulated

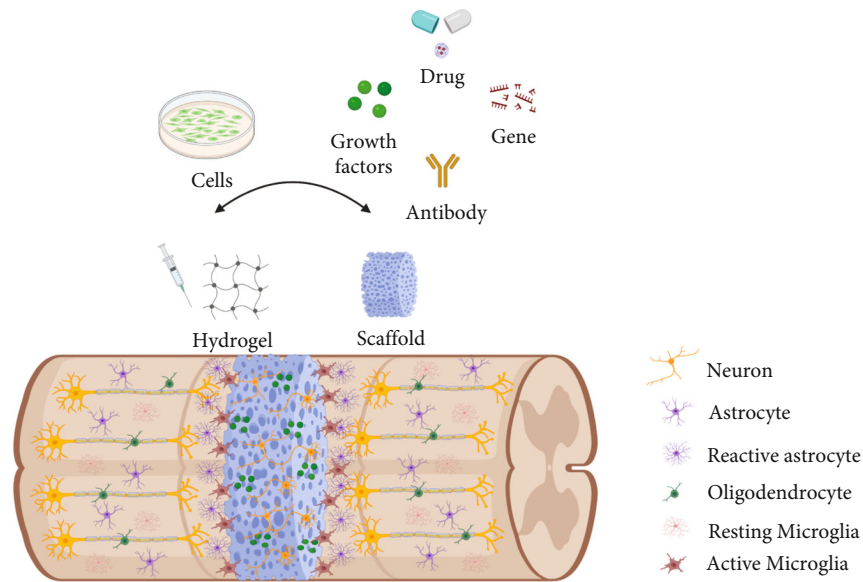


FIGURE 3: Combination therapy of cells and functional biomaterials. Functional biomaterials can not only fill the lesion cavity and provide physical support for axonal regeneration, but their unique biological functions can also effectively promote axonal growth and angiogenesis, regulate immune responses, alleviate scar inhibition, and help transplant cell survival and differentiation. Transplanted cells can secrete trophic factors necessary for nerve repair and promote axon regeneration and endogenous stem cell migration, and neural stem/progenitor cells can also differentiate into relay neurons to integrate damaged neural circuits. In addition, biomolecules released from functional biomaterials and transplanted cells can also downregulate the concentration of growth inhibitory components (cells, myelin debris, inflammatory cytokines, etc.) caused by nerve injury and improve the local microenvironment.

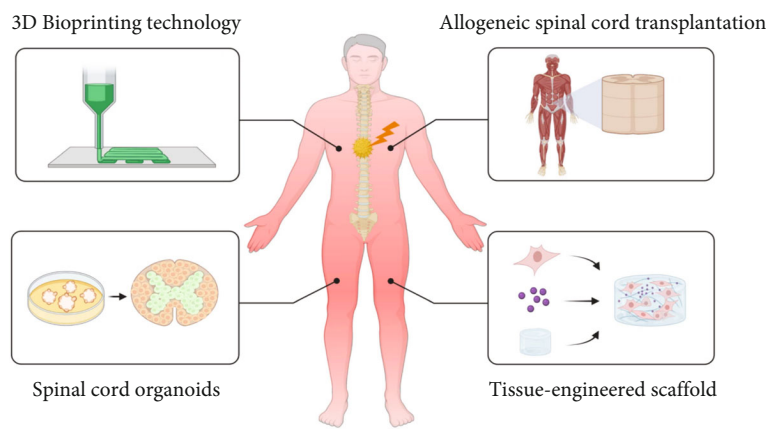


FIGURE 4: Advanced approaches to treating SCI.

to the greatest extent, whether the functional biomaterials can release biomolecules continuously and provide nerve cells, axonal structures, and extracellular matrix similar to natural tissues at the same time, and whether it can repair injury through specific therapeutic targets while having the degradation properties and degradation products that match the tissue recovery. Combining functional biomaterials with cell transplantation for the treatment of SCI is a promising treatment modality. This combined strategy provides the transplanted cells with a physical matrix for adhesion, proliferation, and differentiation and improves the survival rate of cell transplantation. Functional biomaterials play a regulatory role through specific therapeutic targets and are more conducive to the formation and continuous growth of new

axons, forming tissue bridges, integrating the materials into the host, and finally forming a complete neural circuit. In addition to the treatment modalities highlighted in this article, other single or combined strategies (cells and growth factors, cells and pharmacological agents, etc.) have also been used to treat SCI. Considering the complexity and diversity of the pathophysiological mechanisms of SCI, combined strategies often show better therapeutic effect. In addition, technologies such as allogeneic spinal cord tissue transplantation, spinal cord organoid research, and bioengineered spinal cord-like tissue construction have also been tried to be applied to the treatment of SCI (Figure 4). How to assess the effect of treatment after spinal cord injury is also critical. In addition to behavioral improvements,

scholars have also used neural tracers to evaluate the repair effect of neural networks, including biotinylated dextran amine (BDA) and horseradish peroxidase (HRP). Tracers can be injected into specific areas of neural tissue, transported anterograde or retrograde, and analyzed in tissue sections after arriving at a distance. In addition, neurotropic viruses, electromyography, magnetic resonance imaging (MRI), and diffusion tensor imaging (DTI) have also been used to evaluate neural networks [239–242].

In this paper, we started from the anatomical structure of the spinal cord, the pathophysiological changes after injury, and the regeneration and repair mechanism of spinal cord nerves, and then, we discussed treatment methods based on functional biomaterials and cell transplantation. All in all, considering the complex pathophysiological mechanisms and dynamic changes of SCI, the combined therapy of the two has great potential for clinical translation in the future and is expected to provide new hope for patients suffering from SCI. Of course, the combination therapy strategy also requires the cooperation of scholars from different disciplines such as medicine, chemistry, biology, and tissue engineering to provide more effective and safer treatment options for SCI.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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