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Holistic Approach to Axonal Regeneration in Cases of Spinal Cord Injury

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Abstract

Spinal Cord Injuries (SCIs) that result from trauma can cause the death of nerve cells and lead to distal neuronal death. The hostility of the lesion microenvironment imposes multiple conditions that must be met to achieve functional recovery. Considerable research indicated interactions and signaling, such as supporting cells, extracellular matrix, neurotrophic factors and biodegradable polymers for axonal regeneration. In recent years, researchers have been seeking novel biomaterials that are capable of stimulating cellular regeneration and promoting functional recovery. The ability of various biomaterials to create bridging structures and facilitate axonal growth has also been investigated. In this manuscript, we outline the progress researchers have made in developing holistic approaches to axonal regeneration in cases of spinal cord injury. We report on a number of therapeutic methods that could be used to promote neurological recovery and examine their clinical applicability. We also share a number of recent insights that have enhanced the feasibility of multiple channel bridges in the treatment of SCI.

Keywords: Biomaterial scaffolds; Stem cells; Schwann cells; Neurotrophic factors; Extracellular Matrix; Axonal regeneration

Introduction

The neurological deficits imposed by spinal cord injury (SCI) can have long-term effects, and longitudinally oriented damage and/or the impairment of neuronal cells can result in total paralysis [1-3]. Neuronal cell death is the primary pathogenetic mechanism in SCI; however, recent advances in stem cell therapy have increased the potential for such therapeutic techniques to benefit the replacement and regeneration of cells, the alleviation of degeneration symptoms, and the recovery of nerve function in the spinal cord [4-7]. Nonetheless, further development of stem cell therapy techniques has been hampered by logistical and ethical considerations [8-10], and the hostile microenvironment at the epicenter of the injury inhibits the survival, integration, and/or endogenous repair of transplanted cells [11,12]. These challenges have led researchers to adopt a holistic approach to the treatment of SCI - one that focus on altering the injury microenvironment in order to promote the survival and differentiation of transplanted cells [13-15]. This review provides a summary of multimodal interventions for the *in situ* alteration of the microenvironment in the treatment of SCI [7,16-20].

Biomaterial Scaffolds

Researchers have investigated the use of nerve guidance channels as biological scaffolds for axonal regeneration in SCI repair. These channels may be natural or synthetic and degradable or non-degradable [21-23]. They are meant to prevent the ingrowth of fibrous scar tissue, concentrate neurotrophic molecules released from damaged nerve stumps, and guide the growth of both proximal and distal nerve stumps [24]. Non-degradable channels comprise synthetic materials and provide a unified and controlled synthesis technology. Degradable channels preclude the need for permanent implantation of non-degradable material or the removal of non-degradable material *via* a second procedure. The natural materials used in degradable channels include collagen [25], alginate [26], hyaluronic acid [27], agarose [28], chitosan [29], fibrin [30], and methylcellulose [31], whereas the synthetic materials (polymers) used in non-degradable channels include poly(glycolic acid) (PGA) and copolymer poly(lactic-co-glycolic acid) (PLGA), polycarbonate polymers, poly 2-hydroxyethyl methacrylate (PHEMA-co-MMA), poly(lactic acid) (PLA), poly-ε-caprolactone (PCL), poly-N-(2-hydroxypropyl)-methacrylamide (PHPMA), poly(2-hydroxyethyl methacrylate) (PHEMA), degradable PLA-b-PHEMA copolymer, and self-assembling peptides (SAPs) [32-35]. The criteria used to select biomaterials vary among remediation strategies; however, biocompatibility, mechanical strength, plasticity, and biodegradability are usually deemed essential. Researchers have considered the potential for neural stem cells and mesenchymal stem cells to benefit spinal cord regeneration based on observations that these stem cells are already seeded within the biomaterial scaffold [25,35-39]. Using these biomaterials as scaffolds has been shown to enhance the functional recovery of damaged spinal cords by prolonging stem cell survival through nutritional support or by directly replacing neurons and their supporting cells.

Supporting Cells

Numerous studies have investigated the efficacy of support cells, such as stem cells and Schwann cells, in the regenerative treatment of SCI [40-42]. Stem cells are characterized by self-renewal and the ability to differentiate into neuronal cells. This allows neural cells which were lost after SCI to be replaced [6,43-45]. Stem cells have also been attributed with neuroprotective and axon regeneration-promoting effects. Extensive research has supported the feasibility of treating spinal cord injuries using embryonic stem cells [46], neural stem cell-derived progenitor cells [47], mesenchymal stem cells [7], nasal olfactory mucosal cells [48], and neonatal astroglial cells [49]. The potential use of Schwann cells modified to release neurotrophic factors has also been studied [50], as Schwann cells play a crucial role in the endogenous repair of peripheral nerves and are able to dedifferentiate, migrate, proliferate, express growth promoting factors, and myelinate regenerating axons [41,50-52]. Nonetheless, the use of support cells

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should be done in conjunction with other interventions in order to maximize axonal regeneration and functional recovery.

Extracellular Matrix

One approach that can be used to promote the repair of neurons and enhance neuronal plasticity in cases of SCI is the manipulation of the extracellular matrix (ECM) [53-56]. Changes in the composition and structure of ECM can contribute to the failure of regeneration [57]. Inflammation due to ECM disruption often leads to the release of hyaluronan fragments, tenascin, and sulfated proteoglycans. Thus, recovery from SCI is more likely to be achieved if the ECM environment is rendered more permissive through the manipulation of key components, such as inhibitory chondroitin sulphate proteoglycans, MMP, laminins, fibronectin, and collagen type IV [58,59]. Remodeling the ECM environment makes it possible to create a niche where the migration and proliferation of cells as well as the formation of nerve fascicle can be controlled. The *in situ* alteration of the ECM environment has also been shown to enhance the efficiency of cell transplantation methods [60,61]. Indeed, a clearly defined ECM environment helps to create a suitable niche for the regeneration of endogenous undifferentiated stem cells (including transplanted undifferentiated stem cells) [62], and stabilizing the ECM structure to reduce inflammation helps to create an environment conducive to tissue repair and the promotion of axonal plasticity following SCI [20,54,55]. In summary, microenvironment alteration can be used to control the fate of stem cells, prolong cell survival, facilitate neuroplasticity, and enhance differentiation into neuronal precursors. The current clinical applications of biomaterial scaffolds in SCI patients were summary in Table 1.

Neurotrophic Factors

Neurotrophic growth factors are central to the development and functional maintenance of the nervous system. They participate in neurogenesis, neuronal survival, axonal growth, synaptogenesis, and activity-dependent forms of synaptic plasticity [63-66]. Neuron survival and the regeneration of fiber tracts is aided by neurotrophic factors, including, neurotrophin-3 (NT-3) [67], neurotrophin-4/5 (NT-4/5) [68], brain-derived neurotrophic factor (BDNF) [69], glial cell line-derived neurotrophic factor (GDNF) [70], and ciliary neurotrophic factor (CNTF) [71]. BDNF promotes the survival of existing neurons as well as the growth and differentiation of new neurons and synapses. BDNF and NT-3 activate tropomyosin-related kinase (Trk) receptor signaling pathways, which tends to increase axonal sprouting while also providing neuroprotective effects. Endogenous levels of NT-3 and BDNF are typically low in healthy spinal cord tissue; however, the expression of Trk receptor proteins increases in both neuronal and non-neuronal cells following injury. NTs play important roles in many facets of nerve regeneration following traumatic CNS injury. NT treatments promote neuronal survival, enhance the regrowth and remyelination of axons, and increase synaptic plasticity. GDNF is a potent neurotrophic factor that provides neuroprotective effects and increases axonal regeneration, plasticity, and remyelination [72]. Preclinical models of SCI have demonstrated that neurotrophic factors are instrumental in the post-injury remodeling of spinal cord circuitry [19,63,64].

Guided Axonal Regeneration

Functional recovery depends on the successful regeneration of nerve fibers and their reconnection to target cells [73,74]. A neuron comprises a cell body (or soma), dendrites, and an axon. The dendrites receive signals, which are then passed through the cell body and out the end of the axon. During neuronal growth, when the proximal end of the axon reaches the distal end, the growth cone at the proximal end enters the neurodegenerative region, and demyelinated Schwann cells form endoneurial tubes with the surrounding basal lamina. The extracellular matrix subsequently interacts with some of the factors secreted by the neuron, thereby allowing the axon to reach its destination and complete nerve cell regeneration. However, defects in bridging due to glial scarring and post-traumatic cavitation associated with traumatic SCI can limit axonal regeneration and the functionality of synapses [75,76]. Thus, neurological recovery may require a graft to bridge a cavity, which acts to reduce neural tension and guide the regeneration of axons.

Implantable nanofabricated polymers are biodegradable and bioabsorbable and have demonstrated considerable promise in transplant surgery [25,77]. These non-toxic materials can be used to form robust bridges and scaffolds which facilitate nerve regeneration. Recent studies have also found that multiple poly (lactic-co-glycolic) channels can serve as bridges that physically direct the growth of axons across the injury while also optimizing the post-traumatic spinal cord microenvironment [78-80]. Numerous methods have been developed to synthesize bridges using natural or synthetic polymers [81], and certain biomaterials have been shown to provide neuroprotective benefits for SCI patients. For example, an investigation into the co-transplantation of QL6-SAP with neural stem/progenitor cells, Iwasaki et al. [82], the observed the preservation of motor neurons as well as the attenuation of perilesional inflammation. Other studies have reported remodeling the extracellular matrix using nanofibers, which serve as a scaffold and inhibit the formation of glial scars while facilitating the regeneration of axons [81,83]. Implanting nanofabricated polymers in multiple channels can help to overcome barriers to regeneration, provide physical axon guidance, prevent the formation of cavities, and protect regenerated neurons.

Authors	Biomaterial scaffolds	Stem cells	Functions and improvements
Xiao Z et al. [92].	collagen (NeuroRegen) scaffold	autologous bone marrow mononuclear cells	Partially autonomic nervous function improvement, and the recovery of somatosensory evoked potentials (SSEP) from the lower limbs was also detected.
Zhao Y et al. [93].	collagen (NeuroRegen) scaffold	human umbilical cord mesenchymal stem cells	Increased finger activity, enhanced trunk stability, defecation sensation, and autonomic neural function recovery, were observed in some patients.
Theodore N et al. [94].	Neuro-Spinal ScaffoldTM	-	By 6 months, 3 of 5 patients had converted from Abbreviated Injury Scale (AIS) A to AIS B(2) or C(1). One patient gained 10 points of hip and knee function by 6 months, with additional improvement and new ankle function at 12 months (increased motor score of 8). One patient converted from AIS A to B at 6 months, a late-occurring conversion that is extremely rare.
Theodore N et al. [94]	Neuro-Spinal ScaffoldTM	-	By 3 months, his neurological examination improved to an L1 AIS grade C incomplete injury. At 6-month postoperative follow-up, there were no procedural complications or apparent safety issues related to the scaffold implantation.

Table 1: The current clinical applications of biomaterial scaffolds in SCI patients.

Discussion

The application of biomaterial scaffolds in multiple channels has been shown to promote long-term axon growth, enhance the myelination of neurons, and inhibit scar formation. However, it should be considered the influence of enhancement factors that had been incorporated into implantable nanofabricated polymers, such as extracellular matrix, growth and neurotrophic factors, as well as other materials capable of modulating remyelination, axonal regeneration, and neurological recovery [84-92]. Bio-absorbable materials have an advantage in the covering of cofactors; these are released by degradation and have a controlled release effect [79]. For example, lentiviral vectors encoding Lingo-1 have been shown to negatively regulate myelination, and shRNA has been shown to promote functional recovery and nerve regeneration in cases of SCI [85]. Modified collagen hydrogels containing FGF-2 (bFGF) have also been shown to decrease the number of infiltrating astrocytes and promote neural regeneration in the treatment of SCI [86]. Thus, future research that investigates the use of biomaterial scaffolds in conjunction with cofactors should help improve the efficacy of SCI therapy.

The spinal cord contains myelin-sheathed neuronal tracts (including motor and sensory tracts), encased in white matter, which are responsible for afferent and efferent pathways [87,93]. These tracts guide nerve sprouting and stimulate the formation of nerve bundles, which may in-turn benefit axonal regeneration [88]. It was discovered that the use of multiple channel bridges in the treatment of SCI can direct the growth of neural fibers and facilitate spinal cord regeneration. In a similar study, plasmid-loaded multiple channel bridges were engineered to induce the growth of axons across the injury site [89,94]. Tuinstra et al. further established a multichannel bridge coating which was capable of delivering neurotrophin encoding lentiviruses to promote axonal regeneration following SCI [90]. Ideally, artificial tissue engineering techniques are meant to coat neural multichannel bridges with Schwann cells and macrophages, growth factors and neurotrophic factors, and an extracellular matrix in order to stimulate axonal growth and movement [54,64,91]. In summary, researchers should seek to improve the efficacy of SCI treatment, combined with the simultaneous transplantation of stem cells, by developing techniques which guide the regrowth of nerve cells.

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