Tissue Engineering For Nervous Regeneration: A Review

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Introduction: *This article presents advances in regenerative medicine aimed at the regeneration of nervous and neuronal tissue, focusing on the regeneration of neurons, axons, and nerve regeneration. We will review the techniques currently existing, the most used or promising ones, in search of advances to regenerate this type of tissues.* ***Objective:*** *With this review, we want to describe the current knowledge about regenerative medicine and tissue engineering oriented to nerve tissue repair.* ***Methodology:*** *A search of articles was carried out between 2007 and 2018, which was restricted to the articles that included the keywords; Tissue Engineering, Neurodegenerative Diseases, Regenerative Medicine, Axonal Regeneration, Neuronal Regeneration, Tissue Regeneration. We will mention techniques such as implantation.* ***Conclusions:*** *with this review, we could observe that most of the techniques mentioned work better when combined, taking advantage of each one to promote a higher regeneration of the different tissues.*

Key words: *Tissue Engineering, Neurodegenerative Diseases, Regenerative Medicine.*

Introduction

Globally, the burden of neurological disorders has increased in the past twenty-five years due to an aging population, despite declining death rates from strokes and communicable neurological disorders.[1]

In the central nervous system (CNS) of adult mammals, most of the injured axons do not regenerate, whereas at the peripheral nervous system (SNP) level, long-distance axon regeneration and substantial functional recovery can occur. Both extracellular molecules and the neuron's intrinsic growth capacity influence regenerative success.[2]Some injuries to the spinal cord and peripheral nerves alter the quality of life of patients who suffer from them.[3,4]

The development of nervous system tissue regeneration techniques aims to provide methods for functional repair and restoration of motor and sensory function.[6,7] The transplantation of Schwann cells, which synthesizes and secretes neurotrophic factors, L1 adhesion molecules, and extracellular matrix to guide and promote axonal growth and myelination, has been tried as an alternative to regenerate peripheral nerves.[5,8,9] It has also been shown that the use of molecular therapies

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combined with cell therapies and scaffolds of biomaterials in the central nervous system has increased understanding about the appropriate requirements and conditions for spinal cord repair.[10]

In addition, stem cell transplantation (including multiple stem cells) has been used, based on its ability to self-renew and proliferate, as well as its plasticity.[11,12] Although the use of stem cells can contribute to maintaining cellular homeostasis and accelerate healing, they have also been associated with the genesis of tumors, metastasis and other diseases.[12]

The use of regenerative medical therapies that promote nerve regeneration has become promising strategies. These procedures are based on the use of stem cells, different types of scaffolding, and materials and bioactive molecules, all of which will be addressed in this review.

Supports used in nerve regeneration

Peripheral nerve injuries are a global clinical problem, due to their significant effect on the quality of life of patients. Therefore, strategies aimed at repairing such injuries have emerged; among these are grafts, which have presented an evolution both of the materials used and their structure. In principle, grafts composed of natural materials from autologous, allogeneic, and xenogenic tissues were used. Later, materials such as polymers derived from extracellular matrix components, polysaccharides, and proteins were used as an alternative. Regarding the structure, structures were initially constructed two-dimensional, and currently, tri-dimensional (3D) structure compounds have been developed. Some studies have used nerve autografts to repair large peripheral nerve defects. However, due to the limited sources of these and the inevitable sensory loss of the donor area after obtaining a nerve graft, it is challenging to meet the increasing requirement for repair peripheral nerve damage.[14,15]

Many researchers have attempted to develop more effective biomaterials to create alternatives to grafts and promote nerve regeneration. The structures that recreate the 3D microenvironment to aid tissue growth and regeneration are called supports or scaffolds and must comply with characteristics such as flexibility, biocompatibility, and resistance to structural collapse during implantation.[9,16,17]

Guan S et al. used embryonic neural tissue and dissected samples from the hippocampus of Sprague-Dawley rats, fabricated porous chitosan (Cs)/gelatin (Gel) scaffolds containing hyaluronic acid (HA) and heparan sulfate (HS) through lyophilization. Subsequently, cell viability assays, scanning electron microscopy and fluorescence microscopy revealed that the presence of HA and HS on scaffolds significantly promoted adhesion of stem cells and neural stem (NS/PC), and supported long-term growth in the three-dimensional environment and multilineage differentiation with neuronal differentiation. Concluding that Cs / Gel / HA / HS composite scaffolds were suitable for neural cell adhesion, survival, and growth, they could offer new options for neural tissue engineering applications.[18]

S. H. I Qin et al. studied scaffolds composed of collagen and fibroblastic growth factor (FGF), for regeneration in a spinal cord hemisection model. The results showed that this strategy improves the survival rates and motor abilities of the rats that underwent the implant with this scaffold, suggesting that it could be a tool used to promote the recovery of lost functionality.19

Other scaffolds available for neural regeneration on a submicron scale with electrical conductivity and neurotrophic activity were made with electrospun nanofibers of polylactic acid-co-glycolic acid (PLGA) combined with nerve growth factor (NGF) that was chemically immobilized on the fiber surface. These fibers supported the formation of neurons and their growth, a promising strategy in nerve conduction.[20]

Regeneration of neurons

In addition to the lack of cell regeneration, neurodegenerative diseases are characterized by the early loss of function and subsequent death of neurons affecting specific neuronal subpopulations that show a unique susceptibility to the development of this type of disease.[21] Amyotrophic lateral sclerosis represents an example of these disorders, where degeneration of motor neurons occurs that leads to muscle

weakness, paralysis, and early death of the patient.[22] Recent studies have provided information on neuronal regeneration, a highly regulated and complex process. However, the molecular mechanisms that determine the regenerative capacity of stem cells and the ability of newly generated neurons to direct their axons towards specific targets remain elusive.[23]

In this sense, some researchers have used neurotransmitters such as dopamine and serotonin to control the neurogenesis of the lesions. In 2015, Scott et al. used neurotransmitters to support the neuronal regeneration process, demonstrating that serotonin promotes the regeneration of adult motor neurons, in addition to increasing the proliferation of progenitor cells of embryonic motor neurons and adult cells such as radial ependymal glial cells.[24]

The coordinated development of the brain stem and spinal target neurons is essential for the generation of a precisely functioning locomotor system. Signals that coincide with the development of these remote regions of the central nervous system can be redistributed during regeneration of the spinal cord. Reimer et al. explain that the descending axons have a significant influence on the plasticity of the progenitor cells of the spinal column during development and after an injury to vertebrates; these researchers demonstrated that descending brain dopaminergic projections promote the generation of motor neurons at the expense of V2 interneurons in the developing zebrafish spinal cord by activating the D4a receptor, which acts on the urchin pathway. Inhibition of this essential signal during early neurogenesis leads to a lasting reduction in the number of motor neurons and impaired motor responses. Importantly, during successful spinal cord regeneration in adult zebrafish, endogenous dopamine promotes the generation of spinal motor neurons, and dopamine agonists augment this process, describing a supraspinal control mechanism for the development and regeneration of specific types of spinal cells that use dopamine as a signal.[25]

It must be considered that neurotrophins play critical roles in the development of the nervous system and in synaptic plasticity in adults, protecting neurons from degeneration, and improving the differentiation of neural stem cells by activating tyrosine kinase (trk) receptors and other signaling routes. Song et al. proposed that peripherally applied brain-derived neurotrophic factor (BDNF) can act in the regeneration of the central axons of ascending sensory neurons. For this, they performed a sciatic nerve conditioning lesion as a model to increase the expression of endogenous BDNF in sensory neurons and injected exogenous BDNF into the peripheral nerve or tissues. Delivery of exogenous BDNF to the sciatic nerve or paw pad of rats significantly increased the number of dorsal root ganglia neurons and regenerated sensory axons in the injured spinal cord. The authors concluded that endogenous BDNF in DRG and the spinal cord are required for improved regeneration of ascending sensory neurons after sciatic nerve injury, and peripherally applied BDNF may have therapeutic effects on spinal cord injury.[26]

Likewise, studies have been conducted for other types of injuries to the central nervous system caused by projectiles, such as penetrating brain injury. These types of injuries cause extensive cell death and permanent loss of the brain parenchyma. In a study published in 2015, researchers developed a scaffold to repair this type of lesion, considering that penetrating brain injuries and other traumatic brain injuries can show factors that inhibit growth occur, as well as inhibit the regeneration of the injured tissue. The authors decided to use the soluble Nogo receptor (sNgR) to prevent the action of myelin proteins on the lesion surface and allow regeneration. The supports used were composed of type I collagen and released the therapeutic agent sNgR after being implanted in a penetrating brain injury in seven rats. To check the performance of these scaffolds, another group of seven rats was implanted with scaffolds that did not contain the agent. The results obtained showed that the group of animals implanted with the sNgR scaffold better covered the injured surface, favored its vascularization, without infiltration of other cells such as macrophages.[27]

Regeneration of axons

Through complex mechanisms that guide axons to the proper pathways, axonal growth leads to optimal functioning and neural system formation. Damage to these networks can be repaired by neuro regenerative processes, which in turn can restore synapses between injured axons and postsynaptic terminals. Axonal orientation and neuro regenerative response depend on proper axonal growth and correct responses of the axonal growth cone to signaling molecules (mainly membrane fusion proteins of the SNARE complex, NSF soluble binding protein receptors), as well as the correct synapses with appropriate objectives.[28]

Gene therapy has been used in axon regeneration to improve the structural and functional parameters of cells and nervous tissue after spinal cord injury, as demonstrated in a study conducted at Kazan State Medical University, in which the potential of mononuclear cells of the umbilical cord blood (UCB-MCs), genetically modified with vascular endothelial growth factor (VEGF) and glial cell-derived neurotrophic factor (GNDF), was observed using an adenoviral vector to release these factors of growth. The study examined the efficacy of missing tissue, severe glial scarring, extension of axonal regeneration, and recovery of motor function. The results showed that the adenoviral vehicle was effective and stable for neuronal cells in vivo.[29]This study, like other studies, demonstrated that transplantation of genetically modified cells has a stimulating effect on the regeneration of the central nervous system after trauma or injury.[30,31]

After a peripheral nerve injury, torn axons can regenerate and reinnervate major organs. However, reinnervation of distal organs and functional recovery are generally deficient because regeneration of axons is randomly resulting in aberrant reinnervation.[32] Faced with this type of injury, neurotrophic factors (NTFs) have been shown to be involved in axon growth pathways.[33] A study carried out by the Institute of Neurosciences and the Department of Cell Biology of the Autonomous University of Barcelona in Spain, took into account the levels of the NTFs and their concentrations to analyze the effect of these growth factors on the regeneration of motor axons and sensory using models in vitro and in vivo, because high levels of NTFs or their release over a long period could induce regress in terms of regeneration, optimal doses were applied in the study to stimulate sensory and motor axonal regeneration for different NTFs such as GDNF (glial cell line-derived NTF), FGF-2, nerve growth factor (NGF), NT-3 (neurotrophin 3), and BDNF (brain-derived neurotrophic factor). They observed that the application of GDNF and FGF-2 provided the highest motor and neuro-sensory regeneration, the application of NGF and NT-3 selectively improved sensory neuritic growth in vitro which is lost in the model in vivo, and that the application of BDNF in selected doses promotes axonal motor growth in vivo and in vitro.[34]

Although there are limiting factors in the use of these strategies, many of the results are promising in tissue, physiological, and functional improvement in injuries involving axon damage.

Regeneration of nerves

The repair or regeneration of nerves is of vital importance since this type of injury, mainly related to trauma, tumors and iatrogenic injuries, leads to neurological deficits and functional disability. In the search to repair this tissue, different techniques have been implemented, ranging from the implantation of grafts, passing through cellular and molecular therapy, up to the implantation of 3D scaffolds. With respect to stem cells, those that have been used most frequently in regeneration of peripheral nerves are embryonic stem cells (ESCs), neuronal stem cells (NSCs), mesenchymal stem cells (MSCs), bone marrow-derived stem cells (BMSCs) and adipose tissue-derived (ADSCs), amniotic fluid-derived stem cells (ATDSCs) and umbilical cord-derived (UC-MSCs), skin-derived precursor stem cells (SKP-SCs) and derived cells of hair follicles (HFSCs). Specific stem cells contribute to the enhancement of neurotrophic action by providing a beneficial microenvironment for neural cells, an example being MSCs that synthesize and release a variety of neurotrophic growth, the SKP-SCs, and ADSCs respectively increase and regulate

the expression of these factors.[35]

In a study by Al-zer et al., they used Schwann cells (SC) for regeneration of the peripheral nerve. The dental pulp of adult humans contains different populations of stem cells, showing wide diversity and potentials, Schwann cells derived from dental pulp stem cells (DPSC) showed adequate growth in culture, and induction of differentiation in SC. The DPSC population may be considered in the future for regeneration of peripheral nerves after induction in SC in vitro, as a superior alternative source of SC compared to the source of autologous cells or nerve donors. DPSCs are cost-effective with acceptable proliferation rates and do not require complicated surgical procedures.[36]

Another study by Sowa et al. In 2017 generated functional Schwann cells using somatic cell reprogramming procedures, demonstrating their ability to promote regeneration of peripheral nerves. Normal human fibroblasts were phenotypically converted to SC by transduction of the SOX10 and Krox20 genes, followed by culture for 10 days, resulting in approximately 43% of directly converted Schwann cells (dSC). Finally, the genetically modified cells were seeded onto a hydrogel scaffold that was subsequently implanted into a sciatic nerve lesion in rats. The dSCs expressed SC-specific proteins and neurotrophic factor secretion. The dSCs also showed myelin formation capacity both in vitroas well as in vivo. Furthermore, transplantation of dSCs into the sciatic nerve in mice resulted in significantly accelerated nerve regeneration and improved motor function at a level comparable to the transplant of SC obtained from a peripheral nerve. The authors concluded that dSC induced with this protocol could be a new therapeutic alternative in regeneration not only of peripheral nerves, but also of central nerves, as well as for neurodegenerative disorders related to SC dysfunction. Therefore with clinical applications not only for nerve injuries peripheral but also for brain and spinal cord injuries and for demyelinated CNS disorders, including multiple sclerosis.[37]

Yurie H et al. studied the efficacy of 3D bio-scaffolds in the regeneration of the sciatic nerve model in mice, as a search for new tools for the treatment of peripheral nerve injuries. In this work, six scaffolds were developed from human dermal fibroblasts using a 3D bioprinter. Twelve adult male rats having a right sciatic nerve transection were used. In six rats 3D bio scaffolds were used to bridge a 5mm nerve gap with 8mm scaffolds; in the other six rats, silicone tubes were used to compare the effects between one and the other scaffolding. The results of the kinematic analysis revealed that the angle of the toe to the metatarsal bone was significantly higher when the 3D bio-scaffolds were used than the silicone scaffolds. The electrophysiological studies revealed a potential muscle action that was significantly higher with the 3D bio-scaffold than with the silicone scaffold. Finally, the histological and morphometric studies showed the presence of neural cells in all the regions of the regenerated nerves and the presence of many well-myelinated axons when the 3D bio-scaffolds were used.[38]

For the repair of peripheral nerves, the Sondell method, which uses scaffolds of decellularized nerves using sciatic nerve tissue, has been described. This method has demonstrated to be efficient, as it removes nerve cells and myelin at the site of nerve injury and reduces the response immune after nerve xenografts. [39] Hudson proposed a method that is an improvement on the method outlined above, where the scaffold designed by his research group maintains the membrane and structural components, improving nerve regeneration after transplantation.[40]

In a study conducted at the department of neurosurgery and Sun Yat-sen University in Guangzhou, China, the Hudson's method was improved by completely removing the myelin components and preparing demyelinated acellular scaffolds for nerve tissue. The supports were manufactured from the sciatic nerve of rats and showed that these scaffolds, unlike those used in the Hudson method, allow regeneration of myelin-free peripheral nerves, while in the Hudson method, although regeneration of the peripheral nerve occurred, components of myelin remain. Additionally, the nerves regenerated from the demyelinated scaffold were thicker and denser than those regenerated from the scaffold proposed by Hudson.[40]

Conclusions

Concluding that Cs/Gel/HA/HS composite scaffolds were suitable for neural cell adhesion, survival, and growth, they could offer new options for neural tissue engineering applications. These scaffolds can also prevent infections, multiple surgeries, and additional costs to the patient. The biggest challenge with scaffolding lies in choosing biomaterials with the right combination of properties.

Each type of lesion will require an optimized and specific delivery system, with different combinations of cells and biomolecules. Tissue regeneration will largely depend on the type of cells used and the diffusion of bioactive substances.

Therapies based on stem cells, scaffolds, neurotrophic factors and bioactive, non-invasive molecules in combination with rehabilitation, will pave the way for the future of neural regenerative medicine.

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