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Nerve Guidance Conduits for Spinal Cord Injury

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Abstract

Every year, between 250,000 and 500,000 people become spinal cord injured worldwide. Since no effective therapeutic plan, injuries result in life-long disability and a broad range of secondary complications. The spinal cord as a part of the central nervous system (CNS) has a limited regeneration capacity compared with that of the peripheral nervous system. CNS axons do not regenerate appreciably in their native environment because of an impermeable glial scar formation and blocked synaptic target. The current therapeutic approach to SCI patients mainly aims at eliminating further damage to the spinal cord. Much of the research effort in this area has focused on nerve guidance conduits to enhance regeneration across nerve gaps. Nerve guidance conduits are predominantly fabricated as hollow tubes or as porous foam rods because of the ease in the manufacturing of these devices. Recently, multi-channeled conduit is very promising because of its guidance capacity and mimicking natural tissue. A combination of multi-channel structure with nanofibrous matrix was also shown that the physical structure of the basement membrane of the neural matrix and nanofibrous structure of the nerve conduit has facilitated the differentiation of NSCs into neurons. However, very attractive innovative technologies were adapted in the nerve guidance conduits production, significant improvements are still required for the advancement of therapeutic strategy to clinical practice.

Keywords: nerve tissue engineering, multi-channel conduit, nanofibrous matrix.

1. INTRODUCTION

A spinal cord injury can be described as damage to the spinal cord that causes loss of sensation and motor control which affect the social, personal, professional, and psychological life of patients (Anon n.d.). The reasons for spinal cord injury can be listed as auto and motorcycle accidents (50%), falls (31%), acts of violence (13%), and sports injury (10%), and some diseases like tumors (Chen et al. 2013). Injuries result in life-long disability and a broad range of secondary complications. In the spinal cord injury, timing, location, and severity of the injury are important parameters. After damage, SCI has stages like the acute phase (seconds to minutes), subacute phase (minutes to weeks), and chronic phase (months to years). In subacute and chronic phases, the central part of the spinal cord contains cyst filled with fluid, astrocytes. Astrocytes are the capability of releasing some extracellular matrix and inhibitory molecules and leads to glial scar formation. A glial scar is a complicated form of cells and inhibitory molecules which is known as a barrier for neuroregeneration and synaptic transmission to the target cells (Tsintou, Dalamagkas, and Seifalian 2015).

2. TREATMENT STRATEGIES FOR SCI

The current therapeutic approach for SCI is conditioning the injury site with the strategies that aim to reduce cell death and minimize the extent of the injury and to eliminate further damage to the spinal cord (Tsintou, Dalamagkas, and Seifalian 2015). Recently, there are some promising approaches to SCI. One of them is cell-based therapy compromise the stem cells transplantation or injection to the injured site (Mothe and Tator 2012). In this concept, stem cells seem very promising because of their differentiation potential to the desired cell types. As a part of the central nervous system, neural stem/progenitor cells have been used as treatment investigation frequently. The other cell types investigated in SCI are mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells. All types of cells have their own advantages and disadvantages for the treatment. The limiting factor for stem cell transplantation for SCI is based on inhospital environment around the injury and the absence of an integration surface for the stem cell attachment. It was also determined that free injection to the cells inside to the lesion causes unexpected results like tumor formation, rosettes, teratomas, and cellular masses because of the host response (Li and Lepski 2013). Another strategy for SCI treatment is biomolecular delivery with bioactive molecules. One of the examples of the bioactive molecules is the growth factor which has a trophic effect on the cells (Tsintou, Dalamagkas, and Seifalian 2015). Besides, cell-based and bioactive molecule-based strategies, scaffold-based or/and combinational based therapies seem very promising in nerve tissue regeneration. In the case of SCI, scaffold-based treatment concentrated on hydrogels and nerve guidance conduits. The investigation on hydrogel for SCI is based on their injectable and resorbable nature with the advantages of application and fill the cavity of the injured site (Courtine and Sofroniew 2019). The hydrogels also support the axonal growth inside of them but their poor mechanical properties after a certain time and in the case of

collapse forms of the degraded material can be destructive for the newly regenerated axons and axonal outgrowth (Tang-Schomer et al. 2014). Guidance is an important parameter for nerve tissue engineering because of the support the nerve tissue regeneration to the end of the regeneration process.

3. NERVE GUIDANCE CONDUITS

Nerve guidance conduits are another scaffold-based strategy used in SCI. The nerve guidance channels are very attractive forms of biomaterials in peripheral nerve tissue regeneration. Some commercial form of them was also used in the clinic. In the case of SCI treatment, there was no clinically approved form of nerve guidance channels. Various bioengineered nerve conduits have been developed different biomaterials approved for clinical use, such as type I collagen, polyglycolic acid (PGA), poly-DL-lactide-cocaprolactone (PLCL), and polyvinyl alcohol (PVA) (Nectow, Marra, and Kaplan 2012). Much of the research effort has focused on nerve guidance conduits to enhance regeneration across nerve gaps. The ideal properties of a nerve guidance channel can be summarized as nerve guidance channel should promote axonal growth, neurotrophic factor release, target tissue innervation and also prevent scar tissue formation (Manoukian et al. 2020). Up to now, different forms of the nerve guidance conduit were prepared with their specific properties like biodegradability and porosity, controlled release of some bioactive components, electrical activity, intraluminal channel structure, cell incorporated conduits, and oriented matrix structure (Straley, Foo, and Heilshorn 2010).

The methods for the production nerve guidance conduits are generally traditional methods like electrospinning, injection molding, phase separation, freeze-dry, and lyophilizing and wire heating processes which are adapted to the form of conduit (Huang and Huang 2006). Investigation showed that multi-channeled conduit was very promising because of their guidance capacity of mimicking natural tissue and advantages of axonal growth and functional restoration after spinal cord injury (SCI) (Sun et al. 2019). In the next section, some successful approaches to the multi-channel conduit investigation were summarized.

4. MULTI-CHANNEL NERVE GUIDANCE CONDUITS DESIGNED FOR SPINAL CORD INJURY

The most important properties of the multi-channel conduit are its mimicking tubular microstructure of the spinal cord. Based on this advantage, in spinal cord injury treatment, researches were concentrated on optimizing the best conduit structure. For this aim, (Thomas et al. 2013) were investigated the effect of the channel density and porosity of micro-channeled conduit on axonal growth after spinal cord injury. They were determined that the axon density within the bridge increased with the increase in the channel number. Increasing the bridge porosity increased the number of axons, which correlated with the extent of cell infiltration throughout the bridge. Channels and bridge porosity influence the re-growth of axons through the injury.

Another investigation was performed with the combination of the methods of phase separation and molding techniques to mimic micro/nano architecture of the spinal cord with the using synthetic polymer poly-(L-Lactic acid) (Sun et al. 2019). In this approach, molding was used to mimic the tubular microstructure of the spinal cord, and phase separation was used to obtain a nanofiber matrix which was the properties of the natural extracellular matrix. The combination of a multichannel structure with a nanofibrous matrix was shown that the physical structure of the basement membrane of the neural matrix and nanofibrous structure of the nerve conduit was facilitated the differentiation of NSCs into neurons. Compared to the ladder-like nerve conduits, the extracellular matrix (ECM)– mimicry nanostructures in the NNCs promoted directional nerve fiber growth within the channels. The *in vivo* performance of nanofibrous and multichannel conduits showed that nanofibrous nerve conduit implants possess great potential in the future application for SCI treatment and nerve regeneration (Zeng et al. 2014).

The usage of the natural polymer collagen to mimic the nanofibrous architecture of the extracellular matrix was performed with electrospinning technique (Liu et al. 2012). They obtained an electrospinning membrane and rolled around it and insert membrane inside a tubular membrane and obtained multi-channel collagen conduit with aligned fibers. The *in vitro* experiments showed that aligned fibers resulted in elongated astrocytes and directed the orientation of neurite outgrowth from DRGs along fiber axes. *In vivo* performance of this conduit with a rat hemisection model was shown that cellular penetration was regardless of fiber orientation but aligned fibers appeared more structurally intact to surrounding tissue on day 30. In the treatment strategy with this collagen electrospun conduit, astrocytes were found only at the boundary of the lesion site, and no astrocyte accumulation was observed in the implantation area at any time point. They concluded that this finding indicates the feasibility of fabricating 3D spiral constructs using electrospun collagen fibers and demonstrated the potential of these scaffolds for SCI repair.

Another combinational approach is the addition of some bioactive factors to functionalize conduit since it was known that bioactive factors have a specific effect on cell behavior. One of them was the addition of the laminin to an electrospun silk nano-fibers matrix (You et al. 2020). *In vitro* performance of the bioactive factor, laminin and nanofiber silk combination were observed as directional neurite extension of PC12 cells which was provided by bioactive stimulus and physical guidance, respectively. In a spinal cord injury model *in vivo*, showed that bio-functionalized conduits displayed superior integration with the host tissue due to enhanced cell infiltration and tissue ingrowth. Compared to a single-channel conduit, the multichannel conduit improved spinal cord regeneration by tissue ingrowth and axonal regeneration which indicated that the conduit architectures play critical roles in spinal cord regeneration.

As a new technique, a 3D printed multi-channel conduit model was also adopted to spinal cord regeneration studies (Koffler et al. 2019). With the using microscale continuous projection printing method, a complex CNS structure for the spinal cord injury was created from polyethylene glycol–gelatin methacrylate (PEG–GelMA). In this study, also the combination of the neural progenitor cells (NPCs) inside the conduit was performed to support axon regeneration and form new ‘neural relays’ across sites of complete spinal cord injury *in vivo* in rodents. Results were showed that injured host axons regenerate into

3D biomimetic scaffolds and synapse onto NPCs implanted into the device. With the implantation of the NPCs, the extensions of axons out of the scaffold and into the host spinal cord were observed which were important for synaptic transmission and functional outcomes.

5. CONCLUSION

Spinal cord injury is a complex and life-quality-disrupting condition. Today, there is no effective treatment strategy; the best choice is to aim to reduce cell death and minimize the extent of the injury and to eliminate further damage to the spinal cord. Biomaterial approaches to SCI repair are slowly but steadily advancing. Although the combinational approach seems very promising, significant improvements are still required to apply in clinical practice.

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