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Editorial

Engineering approaches to enhance neural tissue regeneration

Nerve regeneration after degenerative conditions and traumatic injuries is critical in restoring function. Unfortunately, the inhibitory microenvironment that is often caused by inflammation and glial scarring after pathological disorders within the central nervous system (CNS) hinders regrowth. Comparatively, the peripheral nervous system (PNS) possesses better regenerative capacity. However, healing is still frequently sub-optimal in the presence of large lesions. In search for better therapeutic options, recent advances in biomedical engineering demonstrate that biomaterials and scaffold designs, along with controlled delivery of biochemicals, offer hope to repair damages in the nervous system. In this special issue, we compile recent progress in these aspects, covering topics ranging from biomaterial scaffold designs to engineering methods to impart micro−/nano-topographical signals, electrical stimulations and biochemical cues in a controlled fashion to direct the fate of neural cells for enhanced nerve regeneration.

We begin this special issue with Gu and his team highlighting the development of tissue engineered nerve implants as alternatives to autologous nerve grafts for the treatment of peripheral nerve injuries. In particular, they discussed the importance of material choices and scaffold designs and provided important perspectives on the preclinical and clinical outcomes of tissue-engineered nerve conduits. The intrinsic regenerative capacity of PNS tissues has helped advance the progress of scaffold designs for nerve regrowth and function restoration, leading to the clinical translation of biomedical engineered scaffolds. Hence, this review provides useful insights for future neural scaffold designs.

Besides the conventional approach of altering the material chemistry of scaffolds, new methods to enhance the functionality of bio-engineered nerve implants have also evolved to include additional exogenous factors that may guide and facilitate the restoration of nerve function. Chief among these factors is the introduction of physical contact guidance to cells and tissues. As pointed out by Wang *et al.*, topographical cues affect neurite outgrowth and extension. In addition, these physical signals also affect cell fate commitment. With the advances in scaffold fabrication techniques, the integration of such physical guiding signals into biomedical-engineered scaffolds is coming to fruition, showing encouraging results in many preclinical studies.

Besides scaffold implantation, the use of electrical stimulation is also seeing promising outcomes in many clinical trials. In these studies, electrical signals are utilized to stimulate and activate the remaining nerve connections found within patients. What remains less understood is the involvement of electrical stimulation in cellular differentiation and regenerative processes. Here, Liu *et al.*, describe the relevance and importance of electrical stimulation on stem cell differentiation, neurite outgrowth and regeneration, and discuss the possible mechanisms involved. It may be envisioned that with more thorough understanding of cellular mechanisms and responses, the use of electrical stimulation as a neural regenerative cue may be in the near future.

Although promoting axon regeneration and function is an ultimate goal of any nerve regeneration process, it is also increasingly recognized that glial cells play critical roles in supporting and maintaining the function of axons. In fact, since glial cells exist in large numbers and are almost uniformly distributed within the nervous system, these cells serve as a natural endogenous reservoir of cells for potential neuro-regenerative processes. Hence, the special issue is next followed by a review by Sypecka *et al.*, which highlights the roles and importance of glia, along with engineering methods to control the differentiation and transdifferentiation of glial cells for restorative purposes.

Finally, the modulation of biochemical signals after neural pathologies has been a long-standing approach to direct nerve regrowth. Here, 3 reviews are dedicated to focus on three broad classes of biochemical signals in the context of nerve injury treatment: proteins and low-molecular weight molecules (by Borschel, *et al.*), which are the most commonly utilized biochemicals; nucleic acid therapeutics (by Chew, *et al.*); and cell transplantation and signaling (by Sakiyama-Elbert, *et al.*). Importantly, the need for localized and sustained delivery for tissue regeneration, as opposed to systemic delivery that is currently used, is highlighted and emphasized in these reviews. Specifically, scaffold-mediated methods allow the combined application of scaffold design properties (material chemistry, topography and matrix compliance) with sustained biochemical signaling for a synergistic therapy for nerve regeneration.

Overall, biomedical engineering approaches offer promise for nerve regeneration and are likely to be the next phase of treatment for nerve function restoration both in the CNS and the PNS in the coming years. We hope that through this timely special issue, we present strong perspectives on the practical and translational considerations that are necessary for engineering practical scaffold designs for nerve tissue regeneration and provide more efficient treatments for patients.

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