Spinal Cord Repair

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Spinal cord injury (SCI) is a debilitating condition, often leading to severe motor, sensory, or autonomic nervous dysfunction. Spinal Cord Repair is to promote spinal cord tissue regeneration and functional recovery through regenerative medicine.

Keywords: spinal cord injury ; extracellular vesicles ; exosomes ; tissue engineering ; scaffolds ; cells ; functional recovery

Spinal cord injury (SCI) refers to damage to the spinal cord that temporarily or permanently changes its function. As the holy grail of regenerative medicine, promoting spinal cord tissue regeneration and functional recovery are the fundamental goals. Yet, effective regeneration of injured spinal cord tissues and promotion of functional recovery remain unmet clinical challenges, largely due to the complex pathophysiology of the condition. The transplantation of various cells, either alone or in combination with three-dimensional matrices, has been intensively investigated in preclinical SCI models and clinical trials. In recent years, cell-based therapies have been immensely implemented to address multifaceted pathophysiological processes, aiming to promote neuroprotection, immunomodulation, axon regeneration, neuronal relay formation, and myelin regeneration. In this review, we summarize promising therapeutic potentials of neural stem/progenitor cells (NSPCs), mesenchymal stem/stromal cells (MSCs), dental pulp stem cells (DPSCs), oral mucosa stem cells (OMSCs), and olfactory ensheathing cells (OECs), as well as cell-based tissue engineering approaches to promote SCI repair and functional recovery. More recently, a new paradigm shift has emerged from cell therapy towards extracellular vesicles as an exciting “cell-free” therapeutic modality. The current review recapitulates recent advances, challenges, and future perspectives of cell-based spinal cord tissue engineering and regeneration strategies.

Despite substantial efforts and progress that have been made in the field of SCI treatment by cell or cell-embedded biomaterial transplantation, significant challenges remain. Efforts are needed to improve graft survival and host regeneration, establish and maintain functional synaptic connections, identify best neurons for improving connectivity, guide transplanted cells to appropriate targets and avoid maladaptive connectivity [1]. It is important to realize that enormous axon growth forcibly induced by cell grafts or neurotrophic cocktails is not always functionally beneficial. Regenerating axons can end abortively or form ectopic connections which could be detrimental to functional recovery [2]. To this end, neuromodulation strategies and rehabilitation could be employed to direct regenerating axons toward forming functional synapses with target neurons and facilitate clinically meaningful recovery after SCI [3]. Other important factors to consider include standardization, quality control, potency evaluation, scale-up, GMP manufacturing, and logistics of cell therapies. When 3D biomaterials are used to deliver cells, several issues need to be taken into consideration before clinical translation, such as biodegradation rate, biocompatibility, material safety, and hierarchical structures of the biomaterials. Lastly, while most preclinical cell transplantation studies are performed in the acute or subacute phase, chronic SCI remains understudied and is more of a challenge than acute or subacute SCI.

EV-based therapies also face many challenges toward clinical translation. One bottleneck lies in manufacturing scalable, clinical-grade EVs. Currently, EV isolation remains largely from parental cells cultured as monolayers on 2D plastic dishes. However, this culture condition is not physiologically relevant, and the production usually involves a large volume of medium, space, and intensive labor, while the yield of EVs is limited. To overcome this limitation, recently we engineered multiple 3D tissues, and applied two forms of mechanical stimulations (*i.e.*, *via* flow or stretching) inside bioreactors, for inducing EV secretions from those tissues. Under mechanical force stimulations, the EV secretions were greatly enhanced, in a process mediated by Yes-associated protein (YAP) mechanosensitivity. Additionally, EVs derived from mechanically stimulated tissues containing DPSCs were more potent in inducing axonal sprouting of cultured neurons than those without mechanical stimulations, suggesting the potential of those mechanically inspired EVs for the treatment of nerve injuries, including SCI and stroke [4]. Another challenge that hampers the clinical translation of EV is the lack of standardized isolation and purification method. So far, differential centrifugation remains the most commonly used EV separation and concentration method [5]. Other techniques include density gradients, precipitation, filtration, size exclusion chromatography, and immunoisolation. Separating non-vesicular entities from EVs has not been fully achieved,

and none of the current methods has both high recovery and specificity of the isolated EVs. Finally, other challenges include choosing and characterizing an appropriate cell source for EV production, and standardizing potency assays and quality control criteria.

To conclude, the use of cells and tissue-engineered constructs provide promising therapeutic strategies for SCI, while EV-based therapy has emerged as an exciting and attractive treatment modality to orchestrate the regenerative effects. Yet, despite tremendous encouraging findings of all these treatment options, key aspects such as safety, scale-up, GMP manufacturing, and quality control should be considered toward clinical translation. Until now, no randomized clinical trial has demonstrated the efficacy of a treatment approach for promoting functional recovery in SCI individuals. It is important to highlight that due to the complex pathophysiology of SCI, one single approach is unlikely to surmount the multifaceted hurdles. Apart from the biological interventions, other engineering strategies such as electrical neuromodulation and activity-based rehabilitation therapy shall be combined to win the fight against paralysis [6].

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