

Cell-Based Therapy for Spinal Cord Injury

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Spinal cord injury (SCI) is a devastating event which results in significant and catastrophic dysfunction and disability. It physically and psychologically affects not only the individual, but also the family and society. Currently no effective therapies are available. SCI involves an initial mechanical insult such as compression, tissue tears and vertebral distortions followed by the secondary injury with a cascade of cellular and molecular events, which ultimately leads to a fluid-filled cyst [1,11,12]. Pathophysiological studies suggest that the disruption of spinal axons in the white matter and chronic progressive loss of myelin ensheathing the axons after SCI are the major causes for neurological deficits. Current treatments for SCI include surgery to stabilize the injury site and early administration of high doses of methylprednisolone to help limit the extent of secondary injury. Unfortunately, their clinical efficacy is modest with high risk of complications and patients still face significant neurological dysfunction and disability. Recently, stem cell-based strategies emerge as promising therapies for SCI since stem cells are supposed to be able to replace lost or dysfunctional neural cells and provide a permissive substrate for axonal regeneration. Using animal models of SCI, various cell sources have been examined on their efficacy in treating SCI including embryonic stem cells (ESCs), neural precursor cells (NPCs), oligodendrocyte precursor cells (OPCs), Schwann cells, olfactory ensheathing cells, and bone marrow stromal cells [2-7,9,10,13,14]. However, it remains unknown which cell type is optimal for the treatment of SCI. It is an important question we need to address before we move cell therapy to clinical trials.

Of all stem cell types, ESCs currently show the greatest potential for the widest range of cell therapies. The pluripotency and plasticity of ESCs isolated from inner cell masses have been demonstrated conclusively by many pioneering studies [8,16]. However, immune rejection and ethical controversy are major hurdles for clinical application of ESCs. Compared to other stem cells, NPCs are already committed to a neural fate and hence will be easier to differentiate into mature neural phenotypes. Therefore, they have been widely used in neurological disorder repair. Nevertheless, the difficulty in access to human tissues for cell isolation and limited expansion potential of NPCs hamper their application in the clinical setting. Other cell types such as Schwann cells, olfactory ensheathing cells, and bone marrow stromal cells are also subject to various limitations in differentiation potency and self-renewal capacity. Collectively, current cell therapies lack clinical feasibility due to limited cellular availability, ethical concerns, and the need for immunosuppression. A recent breakthrough in stem cell biology is the finding of induced pluripotent stem cells (iPSCs) technology [15,17]. Using iPSCs technology, researchers can achieve embryonic-like cells without the ethical dilemma. iPSCs, have the advantage of eliminating immune rejection concerns as they are obtained from host as well as have pluripotent behaviour. The generation of iPSCs from a patient's own somatic cells would potentially allow for a plentiful source of cell therapeutics for autotransplantation. Furthermore, the use of iPSCs largely circumvents political, ethical, and logistical roadblocks previously associated with other cell transplantation. Therefore, they

are considered to be an ideal cell source for transplantation therapy for the treatment of SCI.

However, it should be noted that iPSC-based therapies are still in their infancy, and many key issues need to be fully addressed before their clinical applications become a reality. We need to better understand the reprogramming mechanisms and generate safe, virus-free, and transgene-free autologous iPSCs at a relatively high efficiency; we need to establish defined pathogen-free and feeder-free culture conditions to cultivate iPSCs; we need to develop specific protocols for efficiently driving iPSCs to differentiate into targeted neural subtypes; and finally we need to fully evaluate the potential risks associated with transplantation of iPSCs. With the development of iPSC technology, we believe that iPSC-based therapies will be the future for the treatment of SCI.

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