Adult-Derived Pluripotent Stem Cells

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Key words
- Adult-derived neural stem cells
- Cell transplantation
- Clinical trial
- Induced pluripotent stem cells
- Spinal cord injury

Abbreviations and Acronyms
CNS: Central nervous system
ES cells: Embryonic stem cells
iPS: induced pluripotent stem
NPCs: Neural precursor cells
SCI: Spinal cord injury

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The global incidence of spinal cord injury (SCI) is 15–40 cases per million people, with the socioeconomic and healthcare costs amounting to nearly $10 billion per annum in the USA alone. Despite substantial advances in medical care and surgical technology, many patients with SCI still experience significant long-term neurologic disability. Cellular transplantation offers a promising therapy to address the multifactorial nature of SCI in both the subacute and chronic phase of the injury to promote central nervous system repair and regeneration and to augment existing therapies. Adult-derived stem cells are the least ethically challenging stem cells but, until recently, a major hurdle has been inducing pluripotency to generate the required neural lineages. Improved generation and transfection techniques, combined with positive experimental outcomes in SCI models, suggest that adult-derived induced pluripotent stem cells could be a genuine alternative to embryonic stem cells for clinical treatments. For translation from bench to bedside, the efficacy of induced pluripotent stem cell–derived neural stem and progenitor cells in suitable SCI models needs to be validated further and backed up with rigorous early-stage clinical trials.

INTRODUCTION

Spinal cord injury (SCI), which results from trauma (contusion and compression of the spinal cord) (96) or progressive neurodegeneration, is a devastating condition. Individuals experience significant functional and sensory deficits, an increased risk of comorbidities, as well as emotional, social, and financial burdens.

EPIDEMIOLOGY: INCIDENCE AND IMPACT ON INDIVIDUALS AND HEALTHCARE

The estimated annual global incidence of SCI is 15–40 cases per million (75). Of these, approximately 55% are at the cervical level (C1 to C7–T1), and thoracic (T1 to T11), thoracolumbar (T11–T12 to L1–L2), and lumbosacral (L2 to S5) injuries each account for approximately 15% of SCIs.

PATHOPHYSIOLOGY

Spinal cord injury involves both a primary (physical) and secondary (the subsequent physiological cascade) injury (108). The primary injury damages both upper and lower motor neurons and disrupts motor, sensory, and autonomic functions (including cardiac output, vascular tone, and respiration). Pathophysiological processes occurring in the secondary injury phase (inflammation, ischemia, lipid peroxidation, production of free radicals, disruption of ion channels, axonal demyelination, glial scar formation [astrogliosis], necrosis, and programmed cell death) are paradoxically also responsible for exacerbating the initial damage and creating an inhibitory milieu that prevents successful endogenous efforts of repair, regeneration, and remyelination. The spatial and temporal dynamics of these secondary mediators (reviewed in [4]) are fundamental to SCI pathophysiology and offer exploitable targets for therapeutic intervention.

WHY CELL THERAPY?

Despite considerable advances in surgical technology, current treatments for SCI have limited efficacy (34, 90). Cellular transplantation therapy is particularly well suited to addressing the multifactorial nature of SCI and can be used in the subacute and chronic phase of the injury. Some of the main goals are to attenuate inflammatory, oxidative, and excitotoxic damage as well as to regenerate and restore lost or compromised axonal conduction by replacing myelin-making oligodendrocytes.

CELL TYPES AND SOURCES

Different sources and types of cells, including stem/progenitor cells (embryonic stem cells, neural progenitor cells, bone marrow mesenchymal stem cells) and nonstem cells (olfactory ensheathing cells and Schwann cells), have been extensively studied experimentally and/or are being tested in clinical trials for SCI. The advantages and disadvantages of each have been extensively described and compared elsewhere (22, 66, 92, 93, 105, 114, 130); therefore, here we comment only on the sources of stem cells in the context of SCI.

EMBRYONIC STEM CELLS

Human embryonic stem (ES) cells are self-renewing, pluripotent in nature, and can produce cells from all three germ layers (110). They are derived from donated

embryos either from in vitro fertilization procedures or created by somatic cell nuclear transfer specifically. Many groups have demonstrated successful transplantation, survival, and differentiation of ES cells into all 3 neural cell types in rodent models of SCI using predifferentiated cells (35, 53, 59, 70) and genetically modified cell lines to improve differentiation and survival potential (7, 9, 29, 39). Recent therapeutic strategies for SCI have focused on the differentiation of ES cells into either motor neurons (31, 89, 94) or oligodendrocyte precursors (17, 49, 67, 76) with both approaches demonstrating functional recovery. Providing a biological scaffold (fibrin, poly(e)-caprolactone) to support ES cell transplantation and cellular regrowth—a particular hurdle in SCI repair—further enhanced functional recovery from SCI (33, 45, 46, 119-121). Despite these promising results, there is a continual risk of tumorigenesis, the allogenic nature of ES cells requires patient immunosuppression, and the ethically challenging source of the cells makes their clinical translation difficult.

FETAL STEM CELLS

Fetal sources of neural precursor cells (NPCs) are already in use clinically; nonimmortalized (primary) fetal NPCs are currently in clinical trials in Switzerland for SCI (22).

The vast majority of experimental studies examining the potential of NPCs in the various SCI models have used those derived from the brain, rather than the spinal cord. The phenotypic fate of NPCs is highly regionally and temporally specified in the brain and spinal cord (28, 86, 88, 124). It is possible, therefore, that the choice of the timing and anatomic region of NPC isolation will be determined by the specific predominant differentiated phenotype required of the implanted cells.

Nonneural types of fetal cells that are not yet in trials for SCI but are, or have been, for other conditions include stromal or mesenchymal cells from the umbilical cord blood, amniotic fluid, and bone marrow (22).

ENDOGENOUS PROGENITOR CELLS

Stem/progenitor cells have been identified in the central canal adult of the mammalian spinal cord (21, 91). They proliferate extensively following SCI (2) or in response to the infusion of exogenous growth factors (42). Although the potential of stimulating the proliferation and subsequent differentiation of endogenous NPCs to affect repair is clear, it needs to be seen alongside the possible risks, including epileptogenesis and oncogenesis (56, 61).

ADULT-DERIVED CELLS

The least ethically controversial type of stem cell is of adult derivation and has been in medical use for more than 40 years (36, 102). Hematopoietic and mesenchymal cells—both found in bone marrow—can differentiate to form blood cells and bone, fat, and cartilage, respectively. Mesenchymal cells can also be derived from other sources, including adipose tissue (131). Experimentally, adult neural/progenitor cells are normally harvested from the subventricular zone of the brain or spinal cord of rodents, and then amplified as neurospheres prior to transplantation. Adult-derived NPCs contain precursors for neurons, oligodendrocytes, and astroglia and demonstrate multipotent ability to differentiate along an oligodendrocyte lineage (48, 85). In the dysmyelinated spinal cords of shiverer mice and in SCI models, NPCs ensheathed injured axons, generated new myelin, and improved locomotor function (16, 48).

Despite the obvious benefits of adult derivation, there is limited evidence of the ability of nonneural cells to differentiate along neuronal lineages (58, 122), with their greatest benefit being through neurotrophic and proangiogenic actions (87). The major hurdle, until recently, has been inducing pluripotency in adult progenitor or fully mature cells. In addition, autologous derivation of neural tissue is rarely, if at all, feasible. The autologous derivation of nonneural tissue for subsequent neutralization through the generation of induced pluripotent stem (iPS) cells or direct conversion is incompatible with clinical needs given the time required to complete current derivation, purification, and retrospective characterization techniques (57).

Fetal NPCs have been immortalized by ReNeuron for clinical trials in stroke (22). A similar approach could be used for adult NPCs in order to overcome the supply limitations of their clinical potential and to minimize or reduce the ethical impact of clinical application by using a very small number of standardized and well-characterized lines.

Adult-derived iPS cells may be able to bridge this gap with an ethically sound and easy source of cells with reduced risk of complications for patients.

iPS CELLS

iPS cells are derived from somatic cells through the expression of specific exogenous genes or proteins and in many ways resemble embryonic stem cells morphologically, antigenically, and phenotypically. They have been generated from embryonic or fetal mouse (32) and human somatic cells, such as skin or liver cells as well as from stem cells, including mesenchymal and neural stem cells.

In 2006, Takahashi and Yamanaka successfully induced pluripotency in adult somatic cells using four retrovirally transfected transcription factors: Octamer 3/4 (Oct3/4), SRY-box containing gene 2 (Sox2), Krüppel-like factor 4 (Klf4), and the protooncogene cytoplasmic Myc protein (c-Myc) in fibroblasts (126). Since then, several methods have been developed to overcome the implications and possibly deleterious consequences of protooncogene activation and genomic integration of exogenous genes (104). It has been found, however, that the absence of tumorigenesis (by generating iPS cells without c-Myc) does not guarantee a lack of oncogenicity of secondary neurospheres (78).

The advantages of adult sources of iPS cells over embryonic-derived cells (107) are several-fold: 1) they lack the ethical challenges of fetal/embryonic tissue sources, 2) NPCs from the adult central nervous system (CNS) are in very limited supply from postmortem tissue and can be either impractical or unethical to biopsy for transplantation, and 3) neural transdifferentiation of nontransfected nonneural cells (i.e., using an epigenetic approach) has so far not been proven feasible, despite recurring claims to the contrary largely based on ill-conceived and ill-designed studies (26, 64).

METHODS OF GENERATING iPS CELLS

Generation of iPS cell lines from adult mouse skin fibroblasts by Takahashi et al., selecting for *Fbx15* and *Nanog* expression (80, 104, 117) and human iPS cells from

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