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Review

Regeneration of the damaged central nervous system through reprogramming technology: Basic concepts and potential application for cell replacement therapy

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ABSTRACT

Neural stem cell (NSC) transplantation provides a new approach for the repair of damage to the central nervous system (CNS), including that resulting from cerebral infarction and spinal cord injury (SCI). In the past, there were no reputable means of converting non-neural somatic cells into neural cells. This status was overturned by the establishment of induced pluripotent stem (iPS) cells, which have pluripotency akin to that of embryonic stem (ES) cells and can differentiate into most cells of the three germ layers. If differentiated somatic cells could be reprogrammed into iPS cells, and if these iPS cells could be induced to differentiate once again, it would be theoretically possible to obtain a large number of neural cells. However, this is not yet feasible due to the limitations of existing stem cell technology. Induction of neural cells from iPS cells is currently hindered by two distinct problems: 1) the preparation of specific types of targeted neural cells requires extensive cell culture, and 2) tumors are likely to form due to the presence of residual undifferentiated cells following transplantation of the induced cells. By contrast, direct induction methods permit the generation of target cells from somatic cells without the transitional iPS cell stage. This review outlines the present-day status of research surrounding the direct induction of NSCs from somatic cells, as well as the perspectives for the future clinical application of this technique for cell replacement therapy following CNS injury.
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Contents

Introduction

It is well-known that the mature human central nervous system (CNS) shows little potential for regeneration (CNS). In contrast to individuals with bone fractures, where the pre-fracture state is often restored by appropriate treatment, patients rarely achieve a full recovery after CNS injury resulting from trauma or neurodegeneration. In fact, patients with spinal cord injury (SCI), cerebral infarction or neurodegenerative diseases are likely to suffer from the pathological sequelae for the rest of their lives.

Abbreviations: cAMP, cyclic AMP; C/EBP, CCAAT-enhancer-binding protein; CNS, central nervous system; EB, embryoid body; EGF, epidermal growth factor; ES cell, embryonic stem cell; FGF-2, fibroblast growth factor-2; GSK, glycogen synthase kinase; iNSC, induced neural stem cell; iPS cell, induced pluripotent stem cell; LIF, leukemia inhibitory factor; NSC, neural stem cell; SCI, spinal cord injury; TGF, transforming growth factor.

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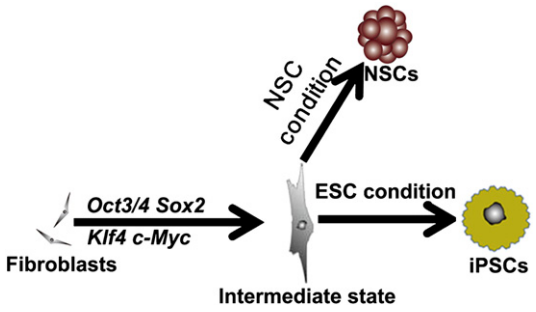

Fig. 1. Schematic diagram showing direct vs. indirect induction of NSCs. The direct conversion of fibroblasts into NSCs requires a three-fold shorter period of culture to obtain mature NSCs with gliogenic competency relative to the indirect induction of NSCs from iPS cells. These NSCs can be maintained by passage for more than 1 year.

Cell replacement therapy involves the transplantation of neural stem cells (NSCs) and is a promising regenerative strategy for the repair of CNS damage. A number of studies in mice, rats and other animal models report that NSC-transplantation can result in the recovery of function from neurological disorders that are conventionally difficult to treat, such as SCI (Ogawa et al., 2002), cerebral infarction (Oki et al., 2012), amyotrophic lateral sclerosis (Boulis et al., 2011) and Alzheimer's disease (Blurton-Jones et al., 2009). The clinical application of transplanted fetal brain-derived or embryonic stem (ES) cell-derived NSCs in humans engenders problems such as immunological rejection and ethical considerations; however, induced pluripotent stem (iPS) cell technology is expected to overcome these complications (Takahashi et al., 2007). This technology allows the preparation of NSCs from iPS cells derived from the patient's own somatic cells for subsequent autografting. In addition to iPS technology, there is an increasing interest in the direct induction of NSCs from somatic cells for potential autografting therapy following SCI (Fig. 1). Recent findings and perspectives for the use of cell replacement therapy to repair CNS damage, with a particular emphasis on the spinal cord, will be discussed in this review article.

iPS cell technology and cell replacement therapy for SCI

iPS cell technology is anticipated to allow the acquisition of cells from a mature somatic origin with pluripotency similar to ES cells. Multiple systems for inducing ES cell-derived populations associated with each germ layer have already been established, and the use of these systems is expected to similarly enable the induction of NSCs from iPS cells (Okada et al., 2008; Reynolds and Weiss, 1992). Thus, cell replacement therapy with autografting is likely to be feasible in the future. Many neurological diseases develop rapidly in elderly humans, and human iPS cells can even be obtained from the somatic cells of humans aged over 100 years (Yagi et al., 2012). Therefore, cell replacement therapy is also theoretically applicable to the treatment of patients of advanced age.

Despite this positive outlook, at least three problems need to be overcome before the autografting of NSCs established from human iPS cells can be realized. The first problem pertains to the time required to prepare the target cells (Okada et al., 2008; Takahashi and Yamanaka, 2006; Tsuji et al., 2010). Establishment of iPS cells from human cells is more time-consuming than their establishment from mouse cells (Takahashi et al., 2007), and the subsequent induction steps involve complex and rather prolonged incubation periods (Koch et al., 2009; Nori et al., 2011; Yagi et al., 2011). Studies using animal models of SCI show that NSC-transplantation during the subacute phase of injury (within 14 days of injury in rodents) is necessary for optimal functional recovery (Fig. 2) in view of the changes in the microenvironment of the injured spinal cord (Iwanami et al., 2005; Ogawa et al., 2002; Okada et al., 2006). With the currently established incubation techniques, however, it is difficult to establish iPS cells from somatic cells during this relatively short time frame for use in cell replacement therapy.

The second problem relates to the fact that NSCs must differentiate into neurons and glia to enable sufficient functional recovery following their transplantation into SCI patients (Kumagai et al., 2009; Nori et al., 2011; Tsuji et al., 2010). This is probably because the following processes all play a significant role in functional recovery: 1) incorporation of neurons derived from the transplanted cells into the host's neural circuit; 2) re-myelination by oligodendrocytes derived from the transplanted cells; and 3) trophic effects of astrocytes derived from the transplanted cells (Kumagai et al., 2009; Nori et al., 2011; Tsuji et al., 2010).

Regarding the differentiation potential of NSCs, NSCs induced from mouse pluripotent stem cells (ES and iPS cells) via embryoid body (EB) formation can differentiate specifically into neurons as long as they remain in the primary neurosphere state without undergoing passaging. If these cells undergo passaging and enter the secondary neurosphere

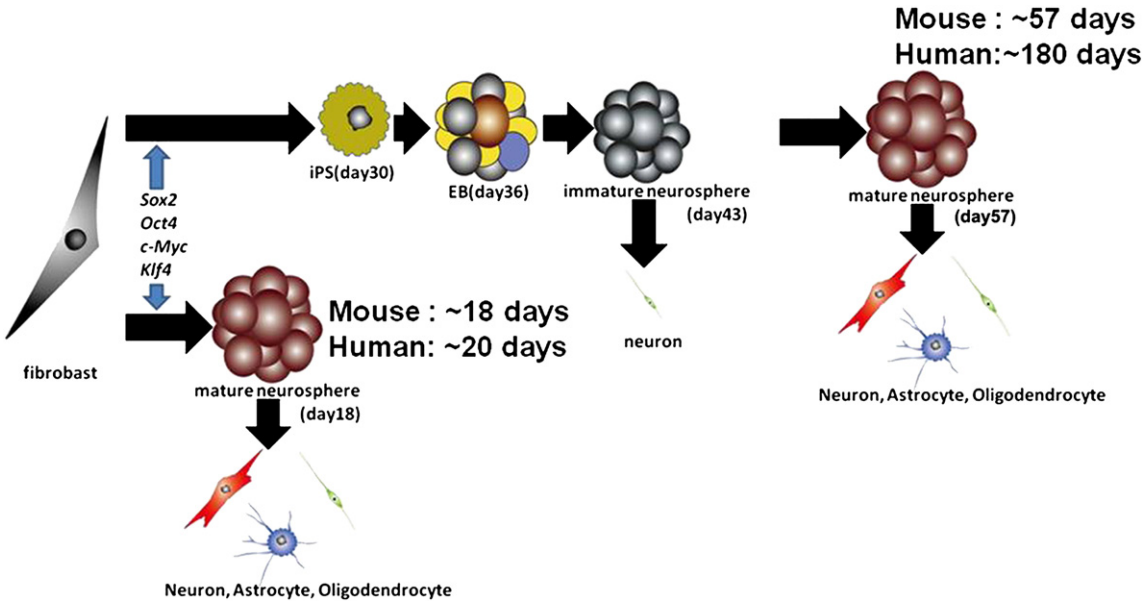

Fig. 2. Schematic diagram of autograft transplantation of induced NSCs. For the optimal treatment of SCI with cell replacement therapy, NSC transplantation must be performed in the subacute phase of injury. The rapid induction of mature NSCs by direct conversion may thus provide the best source of cells for this treatment.

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