Human Neural Stem Cell Transplants in Neurological Disorders: Current Trends and Future Options

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Introduction

Loss of neurons and glial cells is a common neuropathology in human neurological diseases. From acute stroke to chronic central nervous system (CNS) disorders like Parkinson's disease and Alzheimer's disease, neuronal and glial cell death and damage remain irreparable with existing therapies. During the past decade, cell replacement therapy, gene transfer, and selective repair of injured neural cells in diseased areas of human brain and experimental animal models have become active areas of research with potential for promising therapeutic developments in neurological diseases.

Several sources of stem cells, which have the pluripotency to differentiate into multiple cell types, have already been tested as possible candidates for therapy. These include embryonic stem cells (ESC) from the inner cell mass of blastocysts, embryonic germ cells (EGC) from postimplantation embryos, and induced pluripotent cells (iPC) derived from laboratory-treated adult somatic cell lines such as skin fibroblasts. Tissue-specific stem cells could also be obtained at later stages of embryonic development, although there are unresolved ethical issues surrounding procurement of such material for research purposes. Hematopoietic, bone marrow, and adipose tissue, as well as amniotic fluid and umbilical cord, are generally considered to be ethically acceptable sources of tissue-specific stem cells that could be isolated during late phases of human development.

For the purpose of treating neurological diseases, an ideal candidate would be the neural stem cells (NSC) with the potential for growth and differentiation into neuronal and glial cell lines. In humans, NSCs can be identified in embryonic, developing, and adult (developed) brain. Although there is evidence that new neurons are generated in adult human brain, in reality, the capacity of self-repair in adult CNS to a functional level is virtually nonexistent, which might suggest that the local environment around the area of injured or damaged brain prevents appropriate induction and transdifferentiation of local NSCs. Developing brain tissue has the highest amount of NSCs making human embryonic or fetal brain an ideal source of transplant for NSCs. Besides NSCs, neurons could also be derived from ESCs, EGCs, iPCs, bone-marrow-derived mesenchymal stem

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cells, and umbilical cord hematopoietic cells. Several research and therapeutic studies using non-NSCs are currently underway as possible therapy for neurological disorders. Mensenchymal stem cells are being evaluated as potential therapy in Parkinson's disease, multiple sclerosis, and motor neuron disease.

Parkinson's Disease

In Parkinson's disease, there is gradual loss of nigrostriatal dopaminergic neurons, and current therapies use levodopa or dopamine receptor agonists to raise striatal dopamine concentration. However, there is also degeneration of non-dopaminergic neurons in Parkinson's disease, and response to pharmacological therapies becomes increasingly unpredictable after some years due to changes in dopamine receptor kinetics and sensitivity with continued neuronal attrition. Transplantation of exogenous human fetal ventral mesencephalic tissue into neostriatum of patients with advanced Parkinson's disease confirmed that cell replacement can produce major, long-lasting improvement [1]. Subsequent trials of transplanting dopamine-producing cells derived from ESC, retina, adrenal gland, and bone marrow resulted in less sustained benefit, and none of these protocols was deemed suitable to be of therapeutic value. This observation reopened the debate whether dopaminergic stem cells transplanted into the striatum can effectively reintegrate and reinnervate the striatum to become functional, release dopamine in vivo, and repair or arrest the neurodegenerative process that lies at the heart of the pathology of Parkinson's disease. For dopaminergic neurons generated from the human ESC, survival after transplantation in animal models has been poor [2], and recent reports seemed to confirm that survival of transplanted fetal mesenchymal cells in the patient's brain was very low [3]. It remains unclear why the expansion rate of transplanted NSCs is slow and if this was influenced by the immunosuppressive therapy.

In a prospective study of heterotopic implantation of fetal tissue grafts in patients with Parkinson's disease, significant improvement was observed in the short term, leading to a reduction of pharmacological therapy with dopaminergic drugs in most patients [4]. The experience from this research seems to suggest that fetal tissue may survive in HLA-randomized host without immunosuppressive therapy. There was no change in histology between the fetal brain tissue explanted at the 3rd month and 11th year to suggest graft-versus-host reaction occurring over a period of time, and it has been proposed that fetal tissue transplant in human behaves as a surgical chimera.

Clearly, understanding the physiology of NSCs in the host environment is critical for the success of neural transplants. In an experimental study of stroke model, about a fifth (20 %) of focally brain-transplanted cells had survived at the end of the first month and had migrated to the contralateral hemisphere by the fourth month [5].

Huntington's Disease and Other Neurodegenerative Disorders

Graft of fetal striatal cells in Huntington's disease was associated with functional recovery, but it has been difficult to replicate the study [6]. Outcomes of NSC-based therapy have not been reported in Alzheimer's disease or motor neuron disease (amyotrophic lateral sclerosis). In theory, transplantation of cholinergic neurons can provide symptomatic benefit in Alzheimer's disease, but whether it would prevent progressive cognitive decline is unclear. Prospect for NSC transplant in motor neuron disease seems unlikely in the foreseeable future.

In Pelizaeus-Merzbacher disease, a rare inherited disorder of dysmyelination associated with mutation in human proteolipid protein gene, a phase 1 clinical trial is presently underway in the USA using a patented fetal-derived NSC (HuCNS-SC StemCells, Inc.) following a similar trial in another inborn error of metabolism (neuronal ceroid lipofuscinosis).

Multiple Sclerosis

Transplantation of remyelinating cells represents a possible treatment approach to repair myelin loss in multiple sclerosis. Experimental implantation

of peripheral-nerve-derived Schwann cells has not been reported to be successful. A major problem of NSC-based remyelination in multiple sclerosis is the multiple and disseminated nature of lesions, making heterotopic transplant or systemic administration of NSCs more plausible. In experimental models following systemic administration, NSCs migrated to the areas of demyelinating lesions, where some of the transplanted cells differentiated into oligodendrocyte progenitor cells and remyelinated axons [7].

Stroke

Transplantation of NSCs into brain areas injured by stroke offers a promising strategy for functional recovery in stroke patients. Experimental studies provide strong evidence that intravenously administered NSCs could selectively migrate into ischemic as well as hemorrhagic brain areas and differentiate into new neurons and/or glial cells, leading to functional recovery [8, 9]. Interestingly, there appears to be some capacity of stroke-damaged adult brain for neuronal replacement from its own NSCs [1]. Currently, there is an ongoing clinical trial of fetal-derived conditionally immortalized NSC in stroke in Glasgow, UK (ReN001 – ReNeuron Group plc).

Spinal Cord Lesions

The benefit of transplanted NSCs in injured spinal cord appears to be largely due to release of trophic factors and/or remyelination of axons, and experimental research confirms that implantation of human NSCs into damaged mouse spinal cord can generate new neurons and oligodendrocytes, leading to locomotor recovery [10]. There seems to be good correlation between the number of graft-derived oligodendrocytes, the amount of myelin, and the extent of functional recovery in one study [11], suggesting that transplantation of human NSCs is an attractive therapeutic option for focal spinal cord injury due to trauma and demyelination. Trial of patented human ESC-derived glial progenitor cell (GRNOPC1 – Geron Corporation) is awaiting regulatory approval in the USA.

Conclusion

There is adequate evidence that NSCs can circumvent blood–brain barrier and migrate to specific pathologic brain areas with tropism [12]. This opens the prospect of using heterotopic transplant of fetal or embryonic brain tissue as a therapeutic strategy in a number of neurological disorders. There may be additional benefit of heterotopic transplant from systemic neurotrophic factors and chemokines. Heterotrophic transplant also obviates the need for multiple transplants into different brain areas in diffuse or disseminated brain diseases. The emerging experience from at least one research study [4] indicates that heterotopic NSC transplants may have the potential to succeed without systemic immunosuppression and could still result in functional recovery and therapeutic benefit in patients with Parkinson's disease.

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