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Review Article

New-Fangled Remedies in Grappling Neurodegenerative Ailments

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Abstract

Parkinson's Disease (PD), Huntington's Disease (HD), Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease (AD) like neurodegenerative ailments are provoked by loss of neurons and glia in the brain or spinal cord. stem cells such as Embryonic Stem Cells (ESCs), Mesenchymal Stem Cells (MSCs) and Neural Stem Cells (NSCs), spawn Neurons and glial cells successfully.

Also stem cell-based cell therapies are unraveled for neurodegenerative diseases. As a new field of personalized medicine, a novel advance unfolds a new class of pluripotent stem cells and induced Pluripotent Stem Cells (iPSCs), educed from patients' own skin fibroblasts. Transplantation of NSCs, neurons or glia drawn from stem cells in animal models of neurodegenerative maladies, manifested clinical rectification and also life elongation of these animals. stem cell-mediated gene transfer of therapeutic genes such as neurotrophic factors and enzymes can bring out more remedial welfare in these animals. Albeit the need of future investigation in this field, cell and gene therapy planted on stem cells, chiefly using neurons and glia derived from iPSCs, ESCs or NSCs, will become a gradation treatment for patients suffering from neurodegenerative sickness and also stroke and spinal cord injury.

Keywords: Alzheimer's disease; Amyotrophic Lateral Sclerosis (ALS); Cell Therapy; Huntington's Disease; induced Pluripotent Stem Cells (iPSCs); Neural Stem Cell; Parkinson's Disease

Introduction

The foundation for the budding of immanent powerful novel therapeutic tactics for human neurological distemper are the Cell replacement therapy and gene transfer to the diseased or bruised brain. The fact that has offended the elaboration of this propitious salutary approach is the dearth of suitable cell patterns for cell therapy in sufferers of neurological disorders. In latest days, Embryonic Stem Cells (ESCs), induced Pluripotent Stem Cells (iPSCs), Mesenchymal Stem Cells (MSCs) and Neural Stem Cells (NSCs) beget neurons and glial cells. This paved the way to develop stem cell-based brain transplantation remedies.

Many cell types are segregated from stem cells due to its pluripotent dexterity and its skill to renew themselves incessantly. Diverse organs and tissues are extracted from two types of

mammalian pluripotent stem cells, ESCs and EGCs. ESCs are drawn from the inner cell mass of blastocysts and Embryonic Germ Cells (EGCs) are acquired from post-implantation embryo by introduction of embryogenesis-related genes, iPSCs, a new class of pluripotent stem cells are inferred from adult somatic cells such as skin fibroblasts [1,2].

Recent Findings

New studies betokened that a merging expression of three neural lineage-specific transcription factors, *Ascl1*, *Brn2* and *Myt1l* can aid in transforming of patients' own fibroblasts directly in to neurons. Manifestation of multiple neuron specific proteins, propagation of action potentials, and development of functional synapses eventuate due to the induced Neuronal (iN) cells [3].

Human fibroblasts can be reprogrammed into Dopaminergic (DA) neurons with the help of coalition of some transcriptional factors *Mash1*, *Ngn2*, *Sox2*, *Nurr1* and *Ptx3* [4]. Tissues of more elevated developmental stages such as Hematopoietic Stem Cells (HSCs), amniotic fluid stem cells, bone marrow MSCs, adipose

tissue-derived stem cells, and NSCs can yield tissue-specific stem cells. multipotent NSCs are immanent to disseminate into three major cell types of CNS, neurons, astrocytes and oligodendrocytes as they have multipotent differentiation proficiency [5-10]. New doors of therapeutic application of these cells (neurons and glia) for neurological diseases are cooked up by some recent studies. In the learning human NSCs, with self-renewing abilities differentiated in to neurons and glia [11].

Advantageous Characteristics of NSC lines

For basic studies on neural development and cell replacement therapy or gene therapy studies, commencement of oncogenes and these immortalized NSC lines have backed in a plenty of ways.

- Genesis from a single cell makes the stable immortalized NSC cells homogeneous/single clone.
- Distended readily in vast amounts in an abrupt duration and unwavering expression of therapeutic genes can be achieved promptly [4,12-14].

Genetic manipulation and gene transfer into the CNS *ex vivo* is stilted by cogent contribution of Immortalized NSCs. genetically manipulated immortalized NSCs outlive, desegregate into host tissues and disseminate into both neurons and glial cells after transplantation to the unharmed or detriment brain *in vivo*. these cells were able to differentiate into neurons and glial cells and colonize the developing or degenerating CNS, both *in vivo* and *in vitro* [4,8]. Cell replacement and gene transfer to the ailed CNS using NSCs have provided the basis for the development of feasibly powerful novel sanative strategies for a generic gamut of human neurological diseases, including Parkinson's Disease (PD), Huntington's disease (HD), Alzheimer's Disease (AD), Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), Stroke, Spinal Cord Injury (SCI) and Brain Tumors [4,8,15].

Obstacles in Clinical Application of NSC-Based Cell Therapy

Before taking over NSC-based cell therapy in neurologically diseased patients,

- a) Ambiguity of origination of neurons or glia suitable for cellular grafts in great measure from NSCs.
- b) Ablation of safety concerns related to tumor development following NSC transplantation
- c) demand for understanding of mechanism by which transplantation of NSCs leads to a heightened functional recovery.

The faith for development of NSC-based therapies for neurodegenerative diseases can be grounded on persistent and vast progress in stem cell research in both basic and pre-clinical settings. This review aims on the utility of stem cells, particularly NSCs, as substrates for constitutional and functional repair of the

bruised brain.

Stem Cell Treatment in Parkinson's Disease

Ample Dropping of Dopamine (DA) neurons in the substantia nigra pars compacta and their terminals in the striatum account to Parkinson's disease [16] Divers predisposing factors for the dopamine depletion allied with the disease are programmed cell demise, viral contagion and environmental toxins. Dihydroxyphenyl Alanine (L-DOPA) is used as an effective treatment for PD, but it is of grave side effects [17,18]. More recently, surgical deep brain stimulation has been assumed as a booming therapy for PD patients [19].

Cell substitution, the discharge of specific neurotransmitters, and the evolution of neurotrophic factors that shield injured neurons and boost neuronal growth, happens following Transplantation of NSCs in the brain. Basically the Transplantation abate anatomic or functional insufficiency associated with injury or disease in the CNS. Recently in a study immortalized NSC lines, stimulated functional improvement in a rat model of PD succeeding transplantation into the striatum [8].

Even though many former studies have used gene transfer technology to develop remedy for PD by transferring the Tyrosine Hydroxylase (TH) gene, it created only one-sided refurbishment of behavioral and biochemical scarcity in PD animal models, since the cells employed did not carry sufficient amount of tetrahydrobiopterin (BH₄), a cofactor to support TH action.

When equating human iPSC lines derived by virus- and protein-based reprogramming and DA neurons educed from protein-based iPSCs, the latter were best fitted for transplantation since they presented gene expression, physiological and electrophysiological chattels similar to those of human midbrain DA neurons. Albeit further study is still required, cell therapy based on DA neurons derived from iPS cells or DA neurons right away converted from fibroblasts may become a reassuring treatment for PD patients in the forthcoming years.

Huntington's Disease, an Autosomal Dominant Neurodegenerative Disorder

This illness is portrayed by involuntary choreic movements, cognitive deterioration and emotional interruption [21,22].

A latest survey has chronicled advancements in motor and cognition performance in HD patients following fetal cell transplantation. This study may serve as a beneficial tactics in dwindling neuronal impairment in the HD brain. In HD patients, clinical triumph is pledged by Cell replacement therapy using human fetal striatal grafts. Transplantation of NSCs to reinstate degenerated neurons or genetically modified NSCs yielding neurotrophic factors have been used to shelter striatal neurons against excitotoxicity outrage [22].

These discoveries imply that proactively transplanted human NSCs were well amalgamated in the striatum and assisted the survival of host striatal neurons against neuronal injury. Human NSCs derived from ESCs could provide a feasible cellular source for cell therapy in HD, since they can be inflated indefinitely and individualize into any cell type desired [23-25].

Lou Gehric Disease, a Neurodegenerative Disorder

Lou Gehric disease ordinarily known as Amyotrophic Lateral Sclerosis (ALS), is a relentlessly advanced, adult onset neurodegenerative disarray characterized by degeneration and loss of motor neurons in the cerebral cortex, brain stem and spinal cord, inducing muscle withering and weakness, and ultimately to mortality within 5 years after the beginning of its clinical symptoms [26]. To date there is no efficacious remedy for patients afflicting from ALS.

Transplantation of NSCs isolated from fetal spinal cord was also cogent in detaining disease advancement in a mouse ALS model. A former study has disclosed that iPSCs isolated from an ALS patient were tell apart into motor neurons and these patient-derived neurons could be an exemplar cellular source for blocking out new drug candidates. Neurons and glia inspired from patient-derived iPSCs are autologous, readily affable, without immune rejection and with no ethical enigma. It is quixotic to anticipate the transplantation of stem cells or stem cell-educed motor neurons in ALS patients in a clinical frame will replace lost neurons, desegregate into existing neural circuitry and re-establish motor function. Rather than thwarting cell decease in host motor neurons through stipulation of neurotrophic agents by transplanted stem cells or stem cell-educed motor neurons is more pragmatic and an attainable approach [27].

Alzheimer's Disease and Novel Therapeutic Treatments

Alzheimer's disease is marked by degeneration and debiting of neurons and synapses throughout the brain the only conducive medicine presently available is acetylcholinesterase inhibitors which magnify cholinergic role but this is not sanative and only a short-lived measure [28,29].

In AD victims, failure of the presynaptic cholinergic system is a vital cause of cognitive afflictions where subsided activity of Choline Acetyl Transferase (ChAT), paramount to Acetylcholine (ACh) synthesis [30]. In some studies, Transplantation of F3. ChAT human NSCs in AF64A-treated mice completely refurbished the learning and memory capacity of AF64A animals [31]. A recent article on AD betokened that stem cell transplant therapy for AD is an elongation of the neural stem cells inure in neurological treatments, such as PD and stroke and could assist as an eminent healing path for AD [32].

Conclusion

To conclude many researches have revealed that ESC- or NSC derived neurons or glial cells minister as a bountiful cell source in cell-based therapy for patients tormenting from neurological ailments. Nevertheless, there exist grave alarms that circumscribe the use of stem cell-derived neurons or glial cells for this work. New studies are necessary to spot the waves for proliferation, differentiation and integration of NSCs and resolve favorable proviso of host brain environment for instilled NSCs to outlive, bloom and heal the harmed brain.

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