Stem Cell Therapy: In Treatment of Neurodegenerative Diseases

Abstract
Over the past 25 years, stem cell therapies have become an attractive field to treat and investigate neurodegenerative diseases. Stem cells are undifferentiated cells with the ability of proliferation, regeneration, differentiation in other cells. Stem cells are divided into categories of embryonic and adult. In some other classification stem cells are divided into Totipotent, Multipotent and Unipotent cells. Stem cell therapy used in different diseases like neurodegenerative disease, inflammatory bowel disease, liver disease, diabetes, heart disease, bone disease, renal disease, chronic wounds, graft-versus-host disease, sepsis, lymphoblastic leukemia, myeloid leukemia, thalassemia, multiple myeloma, cycle cell anemia and respiratory diseases. In the current review, we detail the current state of stem cell research in neurodegenerative diseases, with a brief introduction about stem cell therapy. We also discuss the hurdles associated with stem cell therapies from bench to bedside. In this review, the final goal is the evaluation of cell therapy in the treatment of different neurodegenerative diseases like Parkinson’s disease, Huntington’s disease, Amyotrophic lateral sclerosis, Alzheimer, Spinal muscular atrophy, Stroke and the burden of these diseases on the society underline the need for the practice of stem cell therapies.

Keywords: Stem cell; Neurodegenerative disease; Neurons; Neurological disorders

Abbreviations: ND: Neurodegenerative Disease; PD: Parkinson’s Disease; AD: Alzheimer Disease; ALS: Amyotrophic Lateral Sclerosis; ES: Embryonic Stem; iPS: Induced Pluripotent Stem; MSCs: Mesenchymal Stem Cells; SOD1: Superoxide Dismutase 1; SMA: Spinal Muscular Atrophy

Introduction
Stem cells are undifferentiated cells that have the ability of proliferation, regeneration, conversion to differentiated cells and tissue production. Regeneration means that these cell have the ability of asymmetric division, which one of the resulting cells remains as stem cell while another cell, which is called daughter cell, becomes one cell of germ layer. Stem cells may remain inactive for a long time till they enter cell division again [1,2]. Stem cells are divided into two groups: embryonic and adult stem cells. Embryonic stem cells are derived from the zygote cell which is fertilized in vitro and usually is 4-5 day embryo that is in the form of a hollow ball called blastocyst. A Blastocyst is composed of three parts: the trophoblast layer that is surrounding blastocyst, a hollow cavity inside the blastocyst and inner cell mass that changes in the embryo. Since zygote cells can differentiate into placenta and fetal cells, sometimes they are considered as the only true totipotent stem cells. Because the inner cell mass of the blastocyst does not have the ability to differentiate into placenta cells, it is called the pluripotent cell. Non-differentiated cells other than embryonic stem cells can be found in differentiated cells of specific tissues after birth. These cells are called adult or non-embryonic stem cells, but a more accurate word for them is "somatic stem cells" because these cells also exist in children and umbilical cord. They are divided into two main categories: hematopoietic stem cells that can differentiate into blood cells and mesenchymal stem cells that are less differentiated. Nose, muscle, liver, skin, brain, retina and limbs of the eye are the other sources of adult stem cells. One of the most important advantages of adult stem cells over embryonic stem cells is because of the fact that they can be obtained without the need for destruction of embryo [3]. Different types of stem cells are shown in Figure 1. The pluripotent stem cell differentiates into the multipotent cell of 3 different germ layers (ectoderm, mesoderm and endoderm layer). The multipotent cell differentiates into unipotent cell of a specific cell lineage within its germ layer. If differentiation process is successful, the resulting cells will be called as progenitor cells or stem cell-like cells that have the capability of regeneration [4,6]. Stem cell therapy has been evaluated in various blood diseases (such as lymphoblastic leukemia, myeloid leukemia, thalassemia, multiple myeloma, cell cycle anemia). The aim of this review is to evaluate cell therapy in different diseases.

Stem Cell Therapy
Stem cells have the capacity to proliferate and differentiate into multiple cellular lineages. There are different classifications of stem cells that reflect the range of possible cell types they can produce, and the way in which they stem cells are derived. These include embryonic stem (ES) cells; progenitor cells, mesenchymal stem cells (MSCs), and induced pluripotent stem (iPS) cells [7]. To appreciate the potential applications of stem cell technology to neurodegenerative diseases, it is important to understand the characteristics of the various stem cell types available and the potential impact of cellular therapies on disease mechanisms.
Cellular Therapy for Neurodegenerative Diseases

Neurodegenerative diseases are characterized by the loss of neurons in the brain or spinal cord. Acute neurodegeneration may result from a temporally discrete insult, such as stroke or trauma, leading to a localized loss of neurons at the site of injury. Chronic neurodegeneration may develop over a long period of time and results in the loss of a particular neuronal subtype or generalized loss of neuronal populations. In the brain, Alzheimer’s disease (AD) and Huntington’s disease (HD) result in widespread loss of neurons, while Parkinson’s disease (PD) involves the specific and localized loss of dopaminergic (DA) neurons in the substantia nigra. In the brainstem and spinal cord, amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) involve the degeneration and loss of motor neurons (MNs) [8,9]. While this condition all exhibit unique neuronal pathologies, the exact mechanisms for neuronal loss are complex, making the identification of efficacious treatments elusive. Neurodegenerative diseases create a tremendous burden on society and despite decades of research, effective treatments do not exist. Cellular therapies are attractive options and the application of stem cell research to neurodegenerative diseases is rapidly expanding.

Alzheimer’s Disease

AD is the most frequent form of dementia; it is characterized by memory loss and cognitive decline. As the disease progresses, there is a widespread synaptic loss throughout the brain, involving the basal forebrain cholinergic system, amygdala, hippocampus and several cortical areas. There is an increased risk of developing AD with age, and the majority of AD cases are late-onset, developing over 65 years of age. Current treatment options for AD are centered on regulating neurotransmitter activity, such as treatment with acetylcholinesterase inhibitors to enhance cholinergic function, provide only partial and temporary alleviation of symptoms. Targeting the cholinergic system using stem cell therapies may provide environmental enrichment [10]. Neurogenesis in the hippocampus decreases as we age and is exacerbated in AD, therefore cellular therapies which enhance neurogenesis or replace lost neurons may also delay the progression of AD. Some studies showed that the mesenchymal stem cells derived from human umbilical cord injected into Alzheimer’s mice and observed that markers of glial activity, oxidative stress and apoptosis were decreased in mouse brain. Also cognitive abilities and learning and memory in mice were returned [11]. The corpus callosum is another structure that is affected early in Alzheimer’s disease. Some study demonstrates the feasibility of targeting the corpus callosum and identifies an effective immunosuppression regimen for transplanted neural stem cell survival, results supported further preclinical development of the corpus callosum as a therapeutic target in Alzheimer’s disease [12].

Parkinson’s Disease

PD is the second most common neurodegenerative disease, after AD, and characterized by progressive destruction of dopaminergic neurons in substantia nigra of midbrain, that is motor signs such as bradykinesia, rigidity; akinesia, stiffness and rest tremor are due to destruction of terminal dopaminergic neurons in basal ganglia including caudate nucleus and putamen which results in balance disorders. The Pathological hallmarks of PD are characterized by the presence of Lewy bodies composed of alpha-synuclei (α-syn) protein beyond the nigra and the cortex. Levodopa can improve the symptoms, but it cannot prevent neurons from destruction. Embryonic stem cells have the ability of differentiation of neural stem cells and subsequently dopaminergic neurons, but they have short survival time. Some research showed that combination of Noggin that is a bone morphogenic protein antagonist with stromal...
cells can increase production of progenitor neuroepithelial cells that have the potential of differentiating to dopaminergic neurons [13]. Mutations in genes such as SNCA cause PD in an autosomal dominant manner and patients have motor and non-motor symptoms that are typical for sporadic PD [14]. Mesenchymal cells injected into inferolateral ventricular area in Parkinson patients and observed significant improvement in symptoms such as facial gestures, gait and freezing episode [15].

**Huntington’s Disease**

HD is a fatal, intractable, autosomal dominant polyglutamine disease caused by the accumulation of CAG repeats in the huntingtin gene. Mutations in the huntingtin gene (HTT) lead to polyglutamine repetitions, causing psychiatric and physiologic alterations like dementia, personality changes, involuntary motor activity, and cognitive impairment associated with the progressive loss of medium spiny neurons (MSNs) in the striatum. There are many strategies for the treatment of HD, one strategy is to enhance neurogenesis and the other one is a cell therapy to protect neuronal cell populations or to replace dysfunctional or dying cells. Cells from HD patients were first reprogrammed into iPSC in 2010 [17], and alterations in electrophysiology, cell metabolism, adherence and toxicity were reported. Expansion of a CAG repeat alters the transport and release of BDFN and increases glutamate receptors, producing toxicity and oxidative stress in neuron and glial cells [18,19]. Stem-cell therapy aims to restore the brain function by replacing and protecting striatal neurons. At this time, using stem cells from the delivery of trophic factors and neuroprotection to prevent disease progression seems a more achievable clinical goal in HD than neuronal replacement.

**Amyotrophic Lateral Sclerosis**

ALS is an adult-onset fatal devastating neurodegenerative disorder that is characterized by progressive destruction of neurons of spinal cord and motor neurons of cortical brain [20] leading to fatal paralysis. Patients present with loss of coordination and muscle strength with transition to complete loss of muscle control. Death typically results from respiratory failure within 2-5 years of diagnosis. Multiple cell types and mechanisms are likely involved in ALS pathogenesis, which makes the development of conventional drug therapies difficult. The cause of ALS is not yet elucidated, however, mutations in genes SOD1, C9orf72, TDP-43, FUS/TLS, angiogenin, Matrin 3 [21,22] and others, have been associated with ALS. A stem-cell therapy could restore or preserve the function of both upper and lower motor neurons [23,24], and new neurons could become integrated into existing neural circuits [25,26]. Many studies have indicated that it is possible to generate motor neurons in culture from stem cells that include ESCs and NSCs. Mouse ESC-derived motor neurons transplanted into motor neuron injured rat spinal cord survived and extended axons into ventral root, and human ESCs transplanted into cerebrospinal fluid of rats with motor neuron injury migrated into the spinal cord and led to improved motor function [27,29].

**Stroke**

A stroke causes loss of a large number of neurons and glial cells. Therapies aimed at improving cerebral blood flow; there has been increasing emphasis on neuroprotective strategies. Cell therapy opens up new horizons in the treatment of this disease through facilitation of neuronal regeneration process. Animal studies and several preclinical trials confirm efficacy of cell therapy in functional improvement after stroke. Protection of neurons, regulation of immune system, increase of internal healing processes, vascular regeneration and stimulation of host brain plasticity and use of internal progenitors are its possible effects [30,33]. A variety of cell types have been tried for restoration of brain function after stroke, mostly in rodent models. The technical and ethical difficulties associated with these cells promoted a search for alternatives. Autologous somatic stem cells are a very attractive source; graft rejection is not an issue. Cerebral ischemia activates endogenous reparative processes, such as increased proliferation of neural stem cells (NSCs) in the subventricular zone (SVZ) and migration of neuronal progenitor cells (NPCs) toward the ischemic area. In this study data demonstrate the neuroprotective activity of MANF that facilitates differentiation and migration of NPCs, thereby increasing recruitment of neuroblasts in stroke cortex [34].

**Spinal Muscular Atrophy**

SMA is an autosomal recessive neurodegenerative disease caused by mutations in survival of motor neuron gene (SMN1), characterized by a selective and progressive loss of lower motor neurons resulting in degeneration of motor neurons in the spinal cord and muscular atrophy on limbs and trunk [35,36]. In humans, low levels of SMN protein may be produced by alternative splicing variants encoded by the SMN2 gene. Current pharmaceutical developments and gene therapy treatments focus on regulating SMN2 to treat SMA. Cellular therapies, however, have been examined in mouse models of SMA, where grafting of ES derived NPCs protected MNs from degeneration and improved survival [37]. The correction of SMN gene, using single-stranded oligonucleotide, was shown to restore the SMN gene profile in neurons derived from SMA-iPSC, converting SMN2 to SMN1 [38]. It is possible that for SMA, transient rescue of the developmental loss of SMN may be sufficient to confer efficacy, which may not be the case for other neurodegenerative diseases where long-term degeneration of the transplanted cells is a valid concern.

**Conclusion**

This review discusses the path for disease, treatment and prevention is through the unveiling of pathogenesis and physiological mechanisms that ultimately result in the phenotypic symptoms of diseases. Major issues associated with stem cell therapy by transplantation for neurodegenerative diseases. Importantly, these models might offer advantages in various aspects discussed along the text. Moreover, they complement in vivo studies that investigate the mechanisms involved in the pathogenesis of neurodegeneration. Stem cells from a variety of sources have shown effectiveness in improving motor function after neurodegenerative diseases in animal experiments and clinical trials.

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References


