stem cell research&therapy

REVIEW

Stem cells for the treatment of neurodegenerative diseases

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Abstract

Stem cells offer an enormous pool of resources for the understanding of the human body. One proposed use of stem cells has been as an autologous therapy. The use of stem cells for neurodegenerative diseases has become of interest. Clinical applications of stem cells for Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, and multiple sclerosis will increase in the coming years, and although great care will need to be taken when moving forward with prospective treatments, the application of stem cells is highly promising.

Introduction

Since their discovery, stem cells have altered the perception of the human body and revolutionized medical research. The understanding of how the human body develops and repairs itself has improved [1]. Because of this, we are able to expand upon the possibilities of stem cell use within the human body. As a result, interest in stem cells as therapies has increased [1].

Research into the use of stem cells for the treatment of neurodegenerative diseases, such as Alzheimer disease (AD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS), has become a growing interest in the medical community. Each of these diseases affects different areas and structures of the central nervous system (CNS). An extensive initiative to investigate stem cells as possible treatments for these four diseases has occurred. Stem cells hold a great opportunity for each of these diseases as a form of replacement or protective therapy. Although this is not meant to be an all-inclusive review of current stem cell research within neurodegenerative disease, we review the major opportunities and obstacles stem cells hold for the future of treatments for AD, PD, ALS, and MS.

Stem cells and their opportunities and limitations

Stem cells were discovered in the early 1960s [2,3], and knowledge about their characteristics and composition has come a long way. Stem cells are generally defined as cells that are capable of self-renewal and that possess the ability to differentiate into multiple types of cells. On the basis of their differentiation abilities, stem cells can be classified as totipotnet, pluripotent, or multipotent. Totipotent stem cells are capable of differentiating into any type of cell within the body, including extra-embryonic tissue, and can be isolated from only the four-cell stage of the embryo. Isolated from the blastocyst of the embryon, pluripotent stem cells are capable of differentiation into any cell within the body, and so they are able to give rise to cells from any of the three major tissue lineages: ectoderm, mesoderm, and endoderm. Multipotent stem cells are capable of differentiation into only the select types of cells from which they are derived and can be isolated from various sources within the adult human body. As the human body develops, the margin of differentiation capability begins to be reduced from a totipotent state to a pluripotent state and lastly to a multipotent capability.

Naturally occurring stem cells generally include embryonic stem cells (ESCs), fetal stem cells (FSCs), and adult stem cells. Obtained from the blastocyst, ESCs are pluripotent and proliferate quite well in culture. Given these two qualities, ESCs appear to offer both a significant number of cells and the ability to germinate into a variety of different cell types [4]. ESCs have the most ability to be used in a clinical setting since they are able to give rise to multiple types of cells; however, there are multiple ethical concerns with their use [5,6] and the risk of adverse reactions, such as an immune reaction or tumor formation or both [7].

As a source of multipotent stem cells, fetal organs contain FSCs. The several advantageous qualities of FSCs include their adaptability to their environment, migration capabilities, lack of teratoma formation, and rejections *in vivo* [8].

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Adult stem cells are classically defined as multipotent cells, which are defined by their tissue of origin. Multiple areas within the adult body, including bone marrow, muscle, brain, and liver, contain an endogenous adult stem cell population [1]. The key benefit of adult stem cells is their potential use in autologous therapies, in which cells can be harvested and used within the same patient. This benefit eliminates the ethical concerns and risks that ESCs bear. As advantageous as adult stem cells appear to be, the limited differentiation ability restricts universal use within the body.

Because naturally occurring stem cells have limitations, scientists have developed a method for increasing pluripotency within non-pluripotent cells. The latter cells are termed induced pluripotent stem (iPS) cells, and multiple studies cite the reprogramming process that uses specific transcription factors, such as *Oct4*, *Sox2*, *Klf4*, and *c-Myc*, to induce pluripotency [9-12]. Some argue that the use of only two of these factors is sufficient for iPS cell formation [13,14]. iPS cells open up the possibility of using a patient's own somatic cells, through reprogramming, for treatment. However, iPS cells have limitations as well. First, the process of creating these types of cells is low in efficiency [15]. The fact that a large number of starting cells are needed for the reprogramming process makes this a challenging beginning. Second, the use of viruses for transduction of the pluripotency factors within iPS cells poses a problem of possible integration into the host genome if these factors become reactivated [16]. Lastly, iPS cells have the ability the produce teratomas, although the risk is less significant compared with ESCs [16]. Researchers have attempted to address these disadvantages. The low efficiency of reprogramming iPS cells may be related to the p53-mediated DNA damage [17], and so inhibiting p53 may increase the conversion of the cells but may increase the risk of tumorigenesis from iPS cells as well. The second issue has been attacked in two ways. One is to use non-viral transfection [18], although the efficacy still needs to be worked out and long-term control of the gene expression may be difficult. Another approach would be the use of Cre-recombinase excisable viruses [19] or delivery of recombinant protein [20]. However, we still must prove the functionality and safety of the resulting cells, and stem cell-based therapy may still have hurdles to overcome but its future is very promising.

Stem cells and neurodegenerative diseases

Neurodegenerative diseases hold an opportunity for the clinical use of stem cells. In neuroscience, the discovery of neural stem cells (NSCs) and subsequent research [21] have nullified the previous idea that the adult CNS was not capable of neurogenesis [22,23]. Indeed, neurogenesis occurs throughout life. NSCs are believed to reside within the subventricular zone of the lateral ventricle wall and the subgranular zone of the hippocampal dentate gyrus, where neurogenesis occurs [22,24]. NSCs give rise to glial-restricted precursors (GRPs) and neuron-restricted precursors, both of which differentiate into astrocytes, oligodendrocytes, or neurons [23]. Another study demonstrated that transplanted NSCs isolated from a 9-week-old human fetus have the ability to differentiate into neural cells and improve cognition in aged rats [25]. Hence, the idea of using NSCs for neurodegeneration treatment is intriguing.

However, NSCs are not so easy to access as a source of stem cells for possible use to treat neurodegenerative diseases. Previously, many studies have suggested the use of bone marrow-derived mesenchymal stem cells (MSCs) for regeneration of neural cells since MSCs are present in bone marrow and are relatively easily accessible within the human body. However, the consensus now is that naive MSCs do not become neural cells. Our previous study suggests that MSCs can be dedifferentiated into cells similar to iPS cells by increasing the expression of a single ESC gene, *nanog*. We were able to transdifferentiate MSCs into neural cell lineage after dedifferentiation. This result indicates that we may be able to use adult stem cells as an autologous source to create iPS cells. This technology and iPS cells together may offer the potential for autologous neuroregenerative therapies to be developed along with the ease of access to a patient's own cells. Another key factor for the development of stem cell treatments for neurological diseases will be the understanding of the pathology of the specific disease. Each disease will need to be assessed individually and each treatment will need to be tailored accordingly.

Alzheimer disease

As one of the most common causes of dementia, AD affects 5.3 million Americans [26]. AD, known for its quintessential hallmarks of amyloid-β peptide (Aβ) plaques and neurofibrilary tangles [21,27-29], results in the death of several types of neuronal lineage cells within multiple regions of the brain [29-31], specifically cholinergic neurons [23]. Discovered in 1987, the human amyloid precursor protein (APP) gene is located on chromosome 21 and codes for a type I transmembrane protein [32]. Aβ plaques are generated by γ- and β-secretases that cleave APP at specific amino acids [33], and neurofibrilary tangles are composed of tau proteins that are hyper-phosphorylated, resulting in neuron impairment [34]. Both of these hallmarks lead to cognitive impairment and loss of memory [29]. However, the direct pathogenesis of AD still eludes researchers [35].

Currently available drugs for the treatment of AD are purely for symptoms [36] and among these drugs are the cholinesterase inhibitors [33,37]. After acetylcholine is

released from the synapse, cholinesterase inhibitors delay its degradation, leading to improved cognition [33]. However, these types of drugs have only a modest effect, which can be variable among patients [38]. Another type of drug available for AD patients is an *N*-methyl-D-aspartate (NMDA) receptor antagonist named memantine [33]. Memantine prevents the NMDA receptors from overstimulation that can lead to toxicity [33]. Since the current treatments have only marginal effects and greatly vary in their effectiveness in patients, the need for new treatments is great. It is estimated that there will be 615,000 new cases by 2029 and 959,000 by 2050 [26]. Owing to this increase in the number of new cases, a great burden will be placed on health-care systems [26]. The need for a proper treatment or cure for AD is imperative.

Recently, Blurton-Jones and colleagues [29] published a study in which they injected NSCs into the hippocampal regions of the brain of both a transgenic AD mouse model and an age-matched non-transgenic mouse model. Interestingly, the mice improved in cognitive function and there was no change to the existing Aβ plaques or neurofibrilary tangles [29]. Instead, the authors discovered brain-derived neurotrophic factor, which is important for neuron outgrowth, and synapse formation increased [39], leading to improved cognition through increased synaptic density [29]. This demonstrated cognition could be improved without the need for modifying the existing pathological conditions [29].

Although the physiological function of APP is not clear, recent reports indicate that it may play an important role in regulating stem cell biology or adult neurogenesis [40]. We found that APP increased chemokine levels to alter cell migration [41]. We also showed that increased APP caused glial differentiation of human NSCs *in vitro* and *in vivo*. This may create the problem of how to regenerate neurons by augmentation of NSCs when APP levels are high. Also, increased levels of APP, found in Down syndrome patients, who develop AD in later life, may exhaust endogenous NSC populations because of increased premature glial differentiation of the cells [42]. This APP function may need to be considered for neuroregenerative therapies under a pathogenic APP environment within the AD brain. Increased levels of APP in the brain not only reduce NSCs, which may increase the risk of AD, but also increase the level of glial differentiation of stem cells upon transplantation, reducing the efficacy of therapy to improve cognitive function [42,43]. Thus, the levels of APP may need to be reduced before transplantation of stem cells, and our previous study showed significant neurogenesis from NSC transplantation in APP transgenic mice but only after APP level was reduced by phenserine treatment [34]. NSCs may also be useful to augment growth factors. A transgenic model of AD showed improvement in cognition by release of BDNF (brain-derived neurotrophic factor) after NSCs [29]. NSCs are also reported to express neurotrophic factors and promote axonal growth in spinal cord injury [44].

Many experimental studies show a beneficial neuroprotective effect of hemopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF), erythropoietin (EPO), granulocyte-macrophage colony-stimulating factor (GM-CSF), stem cell factor, vascular endothelial growth factor (VEGF), and stromal cell-derived factor-1-alpha (SDF-1-alpha) in ischemic stroke [45,46]. Bone marrow-derived MSCs are reported to protect or reduce ischemic damage by releasing insulin-like growth factor-1 (IGF-1) in transient ischemic model animals. Furthermore, NSCs modified by transfection of vascular endothelial growth factor provided neuroprotection after transient focal cerebral ischemia [47]. Despite promising results from animal models, the lack of data in humans hampers efficacy assessments of growth factors on neurodegenerative disease therapy. In clinical study with stroke patients, MSC-treated patients showed significant and consistent improvement in the Barthel index and modified Rankin score over the control patients during the follow-up period up to 12 months [48]. More recently, a long-term follow-up study of intravenous autologous MSC transplantation in patients with ischemic stroke showed very promising results [49]. These results may support the use of stem cells to augment growth factor in AD in the future.

Parkinson disease

First described in 1817, PD, the second most common neurodegenerative disease [50], is a neurological degenerative disease that results in the loss of dopaminergic neurons within the substantia nigra [51,52], leading to a loss of motor function. Lewy body formation and neuritis are the pathological hallmarks of this disease, and the specific etiology is still unknown [52]. PD itself is not fatal but complications from the disease can lead to death.

Current treatments for PD include drug regimens and surgery. However, these treatments are purely palliative. The current drug treatment for PD supplies the surviving dopamine neurons with L-Dopa, which they convert to dopamine [53]. Eventually, however, all of the remaining dopamine neurons die and treatment with L-Dopa is ineffective [53].

MSCs have been proposed as a potential treatment for PD. Park and colleagues [54] investigated the use of MSCs in a PD mouse model to observe a potential neuroprotective effect on neuronal loss. MSCs significantly preserved the number of dopaminergic neurons and tyrosine hydroxlase-positive cells *in vitro* and *in vivo* [54].

In a different study, Murrell and colleagues [55] proposed the use of adult olfactory stem cells for recovery of dopaminergic neurons in PD. The adult olfactory stem cells were differentiated into NPCs and were capable of becoming dopaminergic-like neurons both *in vitro* and *in vivo* [55]. NSCs have also been investigated for their use as possible treatments for PD. Yasuhara and colleagues [56] tested the use of NSCs on the behavioral benefits and protective effects in PD *in vivo*. When NSCs were immediately transplanted after 6-hydroxydopamine lesion formation in mice, tyrosine hydroxlase neurons were protected and PD symptoms were reduced [56].

The study of Kim and colleagues [57] supports the use of ESCs for cell replacement therapy as the authors have shown that highly enriched populations of midbrain NSCs can be derived from mouse ESCs. The dopamine neurons generated by these stem cells show electrophysiological and behavioral properties expected of neurons from the midbrain [57]. To move forward with these studies, further experiments must be developed to show methods of enriching the cell of interest and demonstrate that these cells show functions that will assist in treating the disease.

Other studies have investigated the use of iPS cells, derived from mouse fibroblasts, to produce neural progenitor cells, which are multipotent adult stem cells, for injection into 6-hydroxydopamine-lesioned rats [58]. The injected derived iPS cells were capable of migration to various areas of the brain, differentiated into glia and neurons, and integrated into the host brain [58]. Additionally, the efficiency of their experiment was high, and almost all of the animals showed high numbers of tyrosine hydroxlase-positive cells [58]. The study of Iacovitti and colleagues [59] supports this by deriving midbrain dopaminergic (mDA) neurons from a commercially available human induced pluripotent stem (hiPS) cell line, IMR90 clone 4. The authors were able to produce cells that followed the same lineage pathway as H9 human ESCs and that showed the same expression levels of dopamine and DOPAC (dihydroxyphenylacetic acid) [59]. The mDA hiPS cells that were transplanted into 6-OHDA-leisioned PD rats not only survived in the long term but also integrated into the host brain, but it was also noted that many $Nestin^{+}$ tumor-like cells remained at the site of graft [59]. The future success of cell replacement therapies for PD will depend on the ability to select the appropriate mDA cell lineage.

Amyotrophic lateral sclerosis

ALS, also known as Lou Gehrig's disease, is a neurodegenerative disease affecting the spinal cord and brain stem and typically is adult-onset. Specifically, the upper and lower motor neurons die, leading to progressive paralysis [60]. Over 150 years ago, the classic hallmarks of this disease, including the death of motor neurons and progressive atrophy, were described [50]. Generally, the mean onset age is 55 years, and prognosis after diagnosis is only 2 to 5 years [50]. The cause of ALS is still unknown.

In 2006, Chi and colleagues [61] performed a study that observed the role of neural progenitor cells in an ALS disease mouse model. Interestingly, the degeneration of the motor neurons stimulated neurogenesis and neural progenitor cell proliferation [61]. In another study, Corti and colleagues [62] transplanted NSCs positive for both Lewis X and a chemokine receptor into the spinal cord. Disease progression was delayed and survival time increased for transplanted mice because of an integration of the transplanted cells into the spinal cord [62]. These studies may indicate that neurotropic factors produced by transplanted stem cells protect neurons from the environment of ALS and increase neurogenesis. Since abnormality of astrocytes is one of the hallmarks of ALS, replacement of glia cells by adult glial progenitors [63] and GRPs [64] has been proposed. Studies by Maragakis and colleagues [63] and Rothstein and colleagues [64] show that astrocyte dysfunction occurs in human ALS and $SOD1^{G93A}$ animal models. The authors showed success in transplantation of lineage-restricted astrocyte precursors, GRPs. GRPs not only survived in the diseased environment but also differentiated into astrocytes and reduced microgliosis in $SOD1^{G93A}$ rat cervical spinal cord [64]. These findings demonstrate the potential ability for transplantation-based astrocyte replacement and show that cell transplantation to the cervical spinal cord is a promising therapeutic strategy for slowing focal motor neuron loss associated with ALS [64]. These preclinical animal studies are promising and may develop into clinical applications in the near future. On the other hand, replacement of degenerating motor neurons may create some controversy because of the lack of knowledge of whether the patients' cells produce healthy motor neurons and the ability of these cells to survive under the pathological condition. A recent study gives us an optimistic view of the development of neuroregeneration therapy of ALS. Dimos and colleagues [65] successfully produced motor neurons from iPS cells derived from an 82-year-old patient with familial ALS.

In 2008, Mazzini and colleagues [66] published a clinical-based experiment in which MSCs were autologously transplanted to ALS patients through a spinal cord injection. The authors state that the results of this study show that MSCs are safe for clinical use for treatment of ALS and showed a slowing in the decline in the forced vital capacity and functional rating scores of some patients [66]. However, as the study notes, this experiment was performed on a small number of patients and will need to be replicated with a large number of patients

in order to verify the results [66]. Mazzini's group [67] did replicate this experiment with a larger number of patients, publishing the results in 2010. Although similar results were obtained, the study lacked significant changes in the progression of the disease, which were obtained in the previous study [67].

Multiple sclerosis

One of the major qualities of MS, a CNS autoimmune disease, is the initial relapse-remitting cycle of the disease, eventually leading to progression of the disease without relapses [68]. The myelin sheath, the primary target, is degraded and this degradation affects neurons [50]. Unlike AD, PD, and ALS, MS predominately affects young adults and has a higher rate of occurrence in females [50]. MS is also a heterogeneous disease, and so the degree of the disease can range from fairly benign to extremely debilitating and the stages of disease can range from only relapses to progressive [68]. Again, currently available treatments are purely symptomatic.

Current approaches for MS treatment include monoclonal antibodies, chimeric molecules, and hematopoietic stem cells (HSCs) [69]. The general aim of HSCs for MS treatment is to completely correct the immune system anomaly within the patient [69]. A study by Aharonowiz and colleagues [70] investigated the use of human ESC-derived neural precursor cells into the cerebral ventricles of an MS mouse model. The transplanted human ESC-derived neural precursor cells reduced the clinical signs of MS and had a neuroprotective effect by immunosuppression within the mice [70].

The use of myelin-forming cell transplantation to restore myelin at sites of myelin loss has been experimented with since the 1970s [71]. However, the myelin-forming cells, especially those cells that are linage-restricted, are very limited in their growth and ability to regenerate myelin [71]. Therefore, stem cells might hold the answer for cell transplant treatments in MS [71]. In 2009, Burt and colleagues [72] published a study in which non-myeloablative HSCs were autologously transplanted to relapse-remitting MS patients. Neurological improvement and a slowing in progression were observed after transplantation [72].

Conclusions

Clinical application of stem cells, whether ESCs, FSCs, adult stem cells, or iPS cells, is increasingly becoming a reality. However, great care will need to be taken when moving forward. The pathological environments of neurodegenerative diseases will need to be assessed to observe their effect on transplanted stem cells. Additionally, the migratory patterns of transplanted stem cells will need to be observed and possibly controlled. With movement toward clinical use of stem cells, protocols will have to undergo extensive scrutiny of their preclinical safety and benefit analyses, projected experiments, and informed consent protocols [73].

In 2008, the International Society for Stem Cell Research released a set of recommended guidelines for the development of stem cell-based treatments [74]. These recommendations include the use of experts in stem cell biology for peer review of research ranging from preclinical to clinical, emphasizing risks involved with stem cell-based therapies within the voluntary informed consent, new oversight criteria for medical innovative care that falls outside of the realm of a clinical trial, and the equality of benefits of stem cell treatments [74].

In regard to the number of clinical trials, the number of AD and PD versus ALS and MS clinical trials is highly skewed. The reason for this perhaps is that, once their condition is diagnosed, ALS and MS patients have a limited prognosis. AD and PD patients have a longer prognosis. Potentially, the US Food and Drug Administration is more inclined to initiate clinical trials for ALS and MS because of the risk-to-benefit relationship. However, an increase in clinical trails for AD and PD is inevitable because of the high cost of 'human life' these two diseases present, along with the financial burden of cost of care.

Although the issues presented above do need to be resolved before the clinical application of stem cells can be realized, the advancement of these technologies is building. The number of stem cell clinical trials will increase tremendously and conceivably some will become standard treatments.

Abbreviations

Aβ, amyloid-β peptide; AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; CNS, central nervous system; ESC, embryonic stem cell; FSC, fetal stem cell; GRP, glial-restricted precursor; hiPS, human induced pluripotent stem; iPS, induced pluripotent stem; mDA, midbrain dopaminergic; MS, multiple sclerosis; MSC, mesenchymal stem cell; NMDA, *N*-methyl-D-aspartate; NSC, neural stem cell; PD, Parkinson disease.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ED contributed to the composition of the manuscript. SM contributed to the composition and editing of the manuscript. KS contributed to the conception, composition, and editing of the manuscript. All authors read and approved the final manuscript.

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