Stem Cells: An Answer to Treat Neurodegeneration?

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Abstract

The demographic studies carried out in India reveal that approximately 10% of the population is over the age of 60. Statistics also reveal that by the year 2021, every seventh person will be a senior citizen. This pattern of ageing poses some serious health issues because with age comes age related disorders. The most pronounced amongst these are the neurodegenerative disorders, which are primarily characterized by neuronal loss/death in the brain or the spinal cord. In the brain, Alzheimer’s disease (AD) and Huntington’s disease (HD) result in loss of neurons, while specific and localized loss of dopaminergic neurons can be seen in Parkinson’s disease (PD). Loss and degeneration of motor neurons in the brainstem and spinal cord is a characteristic feature of Amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA). In India, approximately 6 million people are living with these disorders. Though it is known that these disorders have neural pathologies, the exact mechanism behind neuronal loss is not yet clearly understood. As a result deciphering efficacious treatment methods for such disorders remains elusive. This lack of treatment methods poses a global burden on the society. Research is extensively carried out to target these diseases at a cellular level. Increasing attention over the past few years has been given to the treatment of neurodegenerative disorders by the use of stem cells. This review will focus mainly on current stem cell research carried out for neurodegenerative diseases, particularly in context to AD, PD, HD and ALS.

Keywords: Alzheimer disease; Amyotrophic lateral sclerosis; Neurodegeneration; Parkinson disease; Huntington’s disease; Multiple sclerosis; Stem cells

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: Gliarial-Restricted Precursor; hiPSC: Human Induced Pluripotent Stem; iPS: Induced Pluripotent Stem; mDA: Midbrain Dopaminergic; MS: Multiple Sclerosis; MSC: Mesenchymal Stem Cell; NMADANMethyl-D-Aspartate; NSC: Neural Stem Cell; PD: Parkinson Disease

Introduction to Stem Cells

Regeneration or repair of neurons is not a new concept. The human nervous system has the capacity to repair itself after injury. Electrical signals amongst neurons are sufficiently delivered through the creation of new pathways and thus recovery of function is attained [1]. A variety of cell types are required for such a pathway which aid in new growth, provision of nutritive trophic molecules for neuronal survival and also for the delivery of tropic cues for directing neuronal processes to appropriate targets. Such a complex array of pathway needs to be clearly understood as well as directed. This can be seen as the epicenter of regenerative neuroscience, and stem cells are some of the earliest tools which neuroscientists have used in this quest.

Stem cells are immature, undifferentiated cells that have the capacity to proliferate and differentiate into multiple cellular lineages. This ability of stem cells makes them suitable for regenerative strategies. Besides, stem cells are also able to migrate and distribute within the CNS once implanted, be obtained from patients and can also be easily manipulated using various viral and non viral gene transfer methods. On the basis of their differentiation abilities, stem cells can be classified into totipotent, pluripotent or multipotent. Totipotent stem cells, which can be isolated only from the four-cell stage of the embryo, are capable of differentiating into any type of cell within the body, including the extra embryonic tissue. The blastocyst of the embryo, serves as the site for pluripotent stem cells, capable of giving rise to ectoderm, mesoderm and endoderm, which are the three major tissue lineages. Multipotent cells, found in many tissues and organs within the human body, are more limited in their renewal and differentiation and can mainly differentiate into cells of the tissue in which they are found [2]. Naturally occurring stem cells includes embryonic stem cells (ESCs), fetal stem cells (FSCs) and adults stem cells (ASCs). These naturally occurring stem cells, however, have several limitations ranging from teratoma formations to ethical and moral issues. Recently it was shown that adult stem cells can be converted into pluripotent stem cells by the introduction of four specific genes. The latter cells are termed as induced pluripotent stem (iPS) cells. Specific transcription factors such as Oct4, Sox4, KLF4 and c-Myc are used to induce pluripotency [2]. This discovery revolutionized the field of regenerative medicine. However, these induced cells were found to have limitations as well. Although we may still have to prove the efficacy and safety of these cells and stem cell based therapy may still have hurdles to overcome but the future is still very promising. Extensive research is being done on stem cells and there uses in various ailments. Generation of cells and tissues from human stem cells for cell-based therapies is one of the most potential applications. Stem cells, allowed to differentiate in specific cell types, offer the possibility of replacing damaged cells in treating diseases such as rheumatoid arthritis, spinal cord injury, macular degeneration, stroke, diabetes, burns, heart disease and osteoarthritis. For example, it may become possible to generate healthy heart muscles and then transplant them into patients with chronic heart ailments. Preliminary studies on mice have shown that transplantation of bone marrow stromal cells in damaged hearts has proved to be beneficial [3]. Further, Stem cells are also widely used to test the efficacy of new drugs. Human

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Received October 23, 2015; Accepted November 21, 2015; Published November 29, 2015

Citation: Bandhavkar S (2015) Stem Cells: An Answer to Treat Neurodegeneration?. Brain Disord Ther 4:194. doi:10.4172/2168-975X.1000194

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pluripotent stem cells are used to test the safety of new medicines. For example, potential anti-tumor drugs can be tested using cancer cell lines. Some of the major ongoing researches are summarized in the (Figure 1 and 2).

Advantages and Disadvantages Associated with the Use of Stem Cells

Stem cells are incredible cells which act like body’s repair kits, having the ability to morph into other cells of the body and soon we will be able to replace damaged/diseased cells with the use of these stem cells. Extraordinary research on stem cells is underway which is completely changing the way we look and model disease, our ability to understand why we get sick and even develop drugs. Over decades, stem cells may allow people to look at Alzheimer’s, diabetes and other major diseases the way we look at polio today, as a preventable disease. Some of the major advantages associated with the use of stem cells are it will allow benefits in the fields of therapeutic cloning and regenerative medicine. It may lead to development of cures and treatments to various degenerative disorders, cancers, diabetes etc. With this research, it may be possible for scientists and doctors to test the efficacy of drugs and medicines without animal or human testers. They may further play a key role in reversal of aging and can also be used to cure developmental defects before they happen, possibly by correcting the defects before the child is born thus improving the quality of life. Stem cells can also be widely used in organ transplantations, use of which may drastically reduce the chances of rejection.

However, with all its advantages, stem cell research is still associated with some disadvantages. Being an emerging technology, the long term effects are yet to be understood. Use of embryonic stem cells requires killing of the embryo which poses an ethical dilemma. Further these embryonic cells cannot be used for all ailments. The moral argument is another big one when it comes to this topic. Many people believe that altering the basic structure of a human’s genes is putting hands somewhere they should not be. The moral issue is the most frequently argued. Research using stem cells for heart ailments showed that these stem cells narrowed the arteries [4]. Further, used of stem cells involves high uncertainty and technological advances need to be made before being completely sure of their benefits. It is being said that stem cells in the far future can be used in developing human clones, although this may be in good intentions, but this may also have devastating consequences, as we saw with nuclear research.

Emerging Stem Cell Sources

Stem cells are commonly obtained from the embryo, fetus, umbilical cord and various adult organs such as brain, liver, bone marrow, heart and gut. The therapeutic use of these stem cells for treating various ailments has reached the stage of human clinical trials. Recent findings, however, suggest a few more sources to obtain these adult stem cells which include tooth, hair and testis. It is also proposed that stem cells derived from these sources have various advantages over the traditional sources. The major sources of obtaining stem cells from dental tissue are from human dental pulp (DPSCs) or human dental pulp (DPSCs). Extensive research is now underway to differentiate DPSCs into neural stem cells and supply these neural stem cells directly to the brain. Another major breakthrough was the isolation of stem cells from hair follicles and their differentiation into neuronal stem cells. One of the major issues associated with adult stem cells is the limited number of cells that are obtained. Therefore, adult stem cells in human skin/hair follicles are readily accessible and expandable are a valuable source for regenerative medicine [5]. Stem cells isolated from testicular cells have helped in overcoming the major barriers associated with stem cell therapies. Firstly the controversies relating to use of embryos and egg cells are avoided and secondly rejection reactions after transplants are also avoided. These testicular cells have shown to efficiently differentiate into neural cells, which is the reason why it has garnered increasing attention [6]. These studies however are in their preliminary stages and extensive research yet needs to be carried out with these stem cells.

Stem Cells and Neurodegenerative Diseases

Over the past 20 years, stem cell technologies have become an increasingly popular for investigating and treating neurodegenerative diseases. The discovery of and research over neural stem cells has helped in establishing the idea that neurogenesis indeed takes place in the CNS. The major areas where Neuronal stem cells (NSCs) reside are believed to be the subventricular zone of the lateral ventricle wall and the subgranular zone of the hippocampal dent gyrus. A study has revealed improvements in cognition of aged rats when NSCs were transplanted [1], Thus the idea of using NSCs for neurodegeneration is intriguing. A major parameter that needs to be kept in mind while developing stem cell treatments for neurological diseases is the understanding of the pathologies of the specific diseases. Each disease needs to be carefully assessed and treatment needs to be tailored.
accordingly. The occurrences of the major neurodegenerative disorders is shown in the (Figure 3).

Alzheimer’s Disease

Worldwide, Alzheimer’s disease affects 44 million people and the estimated global cost over Alzheimer’s is about $605 billion. Thus making Alzheimer’s the most common neurodegenerative disease. It is estimated that there will be 615,000 new cases by 2029 and 959,000 by 2050 [7]. Mutations are linked to as the major causes of AD, which leads to increased production of beta-amyloid peptide. As this peptide aggregates it becomes toxic to the brain resulting ultimately into neuritic plaques. Though the exact physiological function of Amyloid precursor protein (APP) is unknown, it is believed to play a role in adult neurogenesis. Neurofibrillary tangles, synaptic deterioration and neuronal death are also a characteristic of Alzheimer patients. Reduction in neurotransmission as a result of loss of acetylcholine neurons and synapses can also be seen in patients. As a result acetylcholinesterase inhibitors are given to patients to slow down the breakdown of acetylcholine. Another type of drug available is an N-methyl-D-aspartate (NMDA) receptor antagonist named memantine which prevents overstimulation of NMDA receptors that leads to toxicity. These drugs, however, are not a cure and hence it is necessary to find definitive treatment. This is where stem cells step in. One study showed that the use of NSCs derived from ESCs for Alzheimer’s improved the memory of patients. The NSCs did not reduce the beta-amyloid levels but the levels of brain derived neurotrophic factor (BDNF) rather increased, which in turn increased the number of synapses, further improving cognition [8]. Promising results in the treatment of AD can be seen with the use of iPSCs. Neuronal stem cells were successfully derived from adult fibroblasts which produce nerve growth factor (NGF). These genetically engineered fibroblasts are currently being examined in a phase I trial for AD [9]. This therefore shows great hope for the use of iPSCs in the treatment of AD. Furthermore, given the widespread loss of neurons in AD, targeting multiple systems simultaneously may be advantageous.

Parkinson’s Disease

Parkinson’s disease is the second most common neurodegenerative disease, affects 1% of the population by the time they reach 60 years of age [10,11] and is characterized by degeneration of nigrostriatal dopaminergic neurons. Accumulation of Lewy bodies, which cause destruction of neurons, is a characteristic hallmark in Parkinson’s. Tremors, muscle rigidity, unstable gait and posture are some severe motor deficits manifesting in patients. Current treatments include drug regimens and surgery. These treatments, however, are simply aimed at managing the symptoms. As patients show decreased level of dopamine, precursor of dopamine: L-dihydroxyphenyl alanine (L-DOPA) is provided. This is because dopamine itself cannot cross the blood brain barrier. This treatment, however, becomes ineffective with time, as all of the remaining dopamine neurons die. Of all the neurodegenerative disorders, the use of stem cells has been extensively studied in Parkinson’s. A potential treatment for PD is proposed through the use of mesenchymal stem cells (MSCs). Park et al., [12] investigated the neuro-protective effect of MSCs in a PD mouse model and observed that a significant number of dopaminergic neurons and tyrosine hydroxylase-positive cells were preserved. Stem cells from human dental pulp (DPSCs) have been reported to possess superior neuronal plasticity towards dopaminergic neurons as compared to stem cells from human exfoliated deciduous teeth (SHED). Human SHED and DPSCs were exposed to midbrain cues (SHH, fibroblast growth factors and basic fibroblast growth factor) and their molecular, immunophenotypical and functional characterization was performed at different time points of induction. The data obtained revealed that DPSCs showed higher SHH receptor levels and lower basal TH expression [8]. This report gave insights for the use of DPSCs for treatment of Parkinson’s disease. The use of adult olfactory stem cells for recovery of dopaminergic neurons was studied by Murell et al., [13]. Further, NSCs derived from ESCs have also proved to be beneficial. It has been shown by Kim et al., [14] that these stem cells show electrophysiological and behavioral properties expected of neurons from the midbrain. Transplantation of growth factor producing MSCs and NPCs also protects DA neurons and protects functional recovery in rodent models of PD. Altogether, to improve the efficacy of cellular therapies for PD cellular replacement and environmental enrichment as a combination needs to be employed.

Huntington’s Disease

Huntington’s disease is an autosomal dominant polyglutamine neurodegenerative disease caused by accumulation of CAG repeats in the huntingtin gene and characterized by chorea and progressive dementia. HD further manifests with involuntary motor activity, personality changes and cognitive impairment. This is associated with loss of medium spiny neurons (MSNs). MSNs are basically GABAergic neurons and their loss is accompanied by cortex, brainstem and hippocampus degeneration. Despite knowing the genetic basis for HD, the exact mechanism is not clearly understood and no definitive treatment is available. Rather only anti-depressants and drugs that suppress movement are available to alleviate the symptoms. Cell therapy in HD is aimed at restoring the brain function by replacing the MSNs. Projection neurons contained in fetal striatal tissue when intrastriatally grafted, in animal models, re-established connections with the globus pallidus [15]. This corticostriatopallidal circuitry reconstruction was sufficient to reverse motor and cognitive deficits in rats and monkeys [15]. This tissue did not go on to develop any mutation and thus this method seemed to offer good hope in replacing damaged neurons [16]. Another potential source for treating HD has been through NSCs derived from ESCs and ASCs. When neural precursor cells were transplanted into HD rat models, these precursor cells were found to differentiate and express antigens characteristic of neurons. This means a striatal phenotype was achieved [10]. A 22% increase in their striatal volume was seen in rats receiving the transplantation when compared to a placebo group [17]. The positive effects of NSCs are thought to be due to release of BDNF released by the transplanted NSCs. In addition, IPSCs derived from fibroblasts of HD patients were also found to treat HD. Replacing the CAG repeat by normal repeat, through homologous recombination, and then allowing the neurons to differentiate into neurons, showed that the correction was sustained. Furthermore it was found that phenotypes associated with HD and the pathogenic signaling pathways were reversed [18].
Amyotrophic Lateral Sclerosis

ALS, or Lou Gehrig’s disease, is an adult onset neurodegenerative disorder affecting the cerebral cortex, the spinal cord and brainstem and characterized by progressive dysfunction and degeneration of motor neurons. A marked loss of coordination and muscle strength can be seen in patients, eventually resulting in complete loss of muscle control. Within 2-5 years of diagnosis, death may occur as a result of respiratory failure [11]. Stem cell therapy must therefore aim at restoring function of both upper and lower motor neurons. A study performed on ALS disease mouse model revealed the role of neural progenitor cells in progression of this disease. Neurogenesis was found to be stimulated accompanied by proliferation of neural progenitor cells as there was degeneration of neurons [19].

Transplanted NSCs were found to be effective in treating ALS. Disease progression was delayed and the survival time was found to be increased. Thus protecting the neurons from ALS environment can be attained through neurotropic factors produced by transplanted cells. The ability of stem cells to provide environmental enrichment via GDNF, VEGF and IGF-1 expression has also been extensively studied because it is crucial to protect the remaining MNs in ALS. Preclinical studies are currently being carried out that demonstrate that motor neuron loss can be slowed by astrocyte replacement. Cell transplantation into cervical spinal cord is also a promising therapeutic strategy. iPS cells derived from 82 year old patient successfully produced motor neurons. The use of MSCs also has the capacity to treat ALS [20]. It is likely that treatment efficacy in future will be best examined into earlier stage patients.

Multiple Sclerosis

Multiple sclerosis, a CNS autoimmune disease, is recognized pathologically by presence of plaques of inflammatory demyelination. Based on the progression of inflammatory destruction, these plaques are classified into acute, chronic active and chronic silent. A characteristic loss of oligodendrocytes and myelin surrounding the axon can be seen at the cellular level. There is no treatment as such for MS, although numerous therapies have been approved by the FDA so as to alleviate the symptoms. Current approaches for the treatment of MS include monoclonal antibodies, chimeric molecules and hematopoietic cells. CG4 oligodendrocyte progenitor cells are showing hope for the treatment of MS [21]. Much research has been carried out to understand the role of ESCs in the treatment of MS. In addition, NSCs have also been found to be useful in treatment of MS. The areas of demyelination are characterized by the presence of NSCs which are differentiated into mature cells. (Table 1).

Conclusion

Clinical applications of stem cells, whether as ESCs, FSCs, adult stem cells or iPS cells is increasingly becoming a reality. However, great care needs to be taken while moving forward. Transplanted stem cells need to be observed and possibly controlled for their migratory patterns. In 2008, the International Stem Cell Research released a set of recommended guidelines for development of stem cell based treatments [22]. These include use of experts, new oversight criteria, emphasizing risks and the equality of benefits of stem cell treatments. The advancement of this technology is building, the number of clinical trials on stem cells will also increase tremendously. Conceivably some will become standard treatments. However before clinical application of stem cells can be realized, the issues presented above do need to be resolved. To make this hope a reality, scientists and clinicians, must work together with the guidance and assistance of regulatory agencies [1].

References


<table>
<thead>
<tr>
<th>Stem cell type</th>
<th>Source</th>
<th>Pros</th>
<th>Cons</th>
</tr>
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<tbody>
<tr>
<td>ES cell-derived NSCs</td>
<td>ICM of blastocyst</td>
<td>Pluripotent, unlimited proliferation and stable karyotype</td>
<td>Tumorigenicity, ethical considerations, purification (markers), and require neural specification</td>
</tr>
<tr>
<td>Embryonic NSCs</td>
<td>Embryonic CNS</td>
<td>Neural lineage-committed, non-tumorigenic and regionally specific</td>
<td>Long-term maintenance and ethical considerations</td>
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<tr>
<td>Adult NSCs</td>
<td>SVZ and SGL of hippocampus</td>
<td>Neural lineage-committed</td>
<td>Long-term maintenance, restricted potential?, and limited availability</td>
</tr>
<tr>
<td>Non-NSCs</td>
<td>Bone marrow, skin, umbilical cord, blood etc.</td>
<td>No ethical considerations, plentiful/accessibility, and generate autologous cells</td>
<td>Require neural specification, and restricted potential?</td>
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Table 1: Comparison of possible sources of NSCs. The table illustrates some of the important pros and cons of each of the four stem cell types able to give rise to neural cells. ICM (Inner Cell Mass).


