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Novel challenges of stem cell therapy in neurodegenerative disorders

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ABSTRACT

Neurodegenerative diseases are characterized by progressive dysfunction, loss & death of neurons. In recent years, neurons and glial cells have been successfully generated from stem cells, by this from stem cell brain transplantation therapies have been carried out by the investigators. If we are able to replace the lost neurons and glial cells through the stem cell therapy then we are able find a way to cure many neurodegenerative diseases. In this study three main types of neurodegenerative diseases like Parkinson's disease, Multiple Sclerosis, Alzheimer's diseases & it's pathology will be known with underlying causes, followed by current treatments and finally from this review we can understand the current evidence for the role of stem cells in treating these neurodegenerative disorders.

1. INTRODUCTION

Neurodegenerative diseases, like Alzheimer's diseases, Parkinson's disease (PD), stroke, Multiple Sclerosis, Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), are characterized by progressive neurodegenerative changes or due to apoptosis of neurons, leading to permanent loss of sensation & paralysis at the site of the injury[1]. So far no successful treatment for neurodegenerative diseases has been developed, Stem cells are capable of repairing injured nervous tissue by replacing damaged cells, neuroprotection or creating an environment which is used in the regeneration by endogenous cells[2].

This study reveals about the most advancing stem cell therapy that plays a major role in treating various disorders like neurological, cardiac, joint, etc. As the Stem cells have the ability to produce specialized cells the affected cells can be replaced by the new cells. The transplantation of stem cells may provide effective treatments due to the self-renewing and multipotent nature of these cells, by this replacement of lost or dysfunctional cells. Meanwhile, these Adult stem cells and Human embryonic stem cells (ESCs) have been coaxed to repair and replace nerve cells in neurodegenerative diseases. There is a solid progression in stem cell research in both basic and preclinical settings. It shows there is a hope for development of stem cell-based cell therapies for neurodegenerative diseases.

Stem cells uses & their limitations: Stem cells were discovered in the early 1960s. Stem cells are defined as the cells that are capable of self-renewal and has an ability to differentiate into multiple types of cells. Based on their differentiation abilities stem cells can be categorized as totipotent, pluripotent, or multipotent is shown in fig 1.

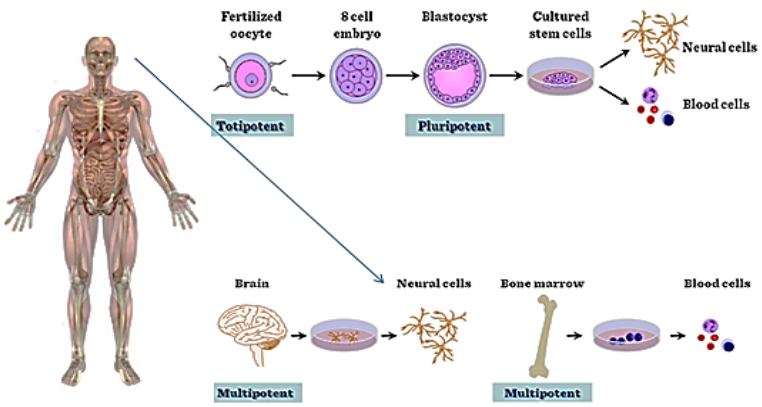

Figure.1.Types of stem cells

Naturally occurring stem cells include fetal stem cells (FSCs), Embryonic stem cells (ESCs), and Adult stem cells. Obtained from the blastocyst, ESCs are pluripotent and proliferate well in culture. Given these two qualities, these have an ability to germinate into a variety of different cell types. ESCs have the most ability to be used in a clinical aspects, since they are able to give rise to multiple types of cells; however, they shows multiple uses and the risk of adverse reactions, such as an immune reaction or tumor formation or both. As a source of multipotent stem cells, fetal organs contain FSCs. Several advantageous of FSCs are migration capabilities, lack of teratoma formation, Adaptability to their environment, and rejections *in-vivo*[3].

Naturally occurring stem cells have their own limitations, scientists have developed a method to increase pluripotency within non-pluripotent cells. Later the cells are termed as induced pluripotent stem (iPS) cells. iPS cells have possibility of using a patient's own somatic cells, through reprogramming, for treatment. iPS are used for the treatment of neurodegenerative disease as they have the ability to replace those lost & destroyed cells during the progression of disease[4]. However, these iPS cells have some limitations as well. The process of creating these types of cells is low in efficiency.

Stem cells & neurodegenerative diseases: The discovery of neural stem cells (NSCs) have nullified the previous idea that the adult CNS was not capable of neurogenesis. But, neurogenesis occurs throughout life is shown in figure 2. These NSCs give rise to glial-restricted precursors (GRPs) and neuronrestricted precursors, both will differentiate into oligodendrocytes, astrocytes, or neurons. These NSCs are believed to reside within the sub granular zone of the hippocampal dentate gyrus and sub ventricular zone of the lateral ventricle wall, where neurogenesis occurs. Another study reveals that the transplanted NSCs will get isolated from a 9-week-old human fetus and have an ability to get differentiate into neural cells and improve the development of neurons in aged rats[5]. Hence, the idea of using NSCs for neurodegeneration treatment has been started.

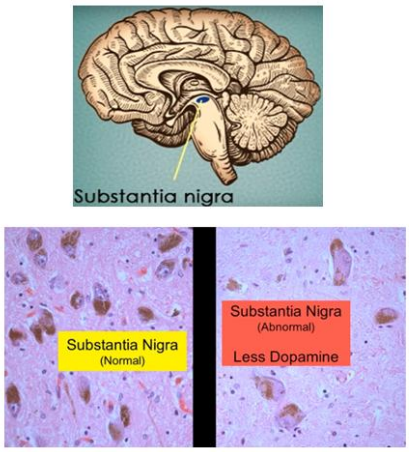

Figure.2. Loss of dopaminergic neurons in the substantia nigra

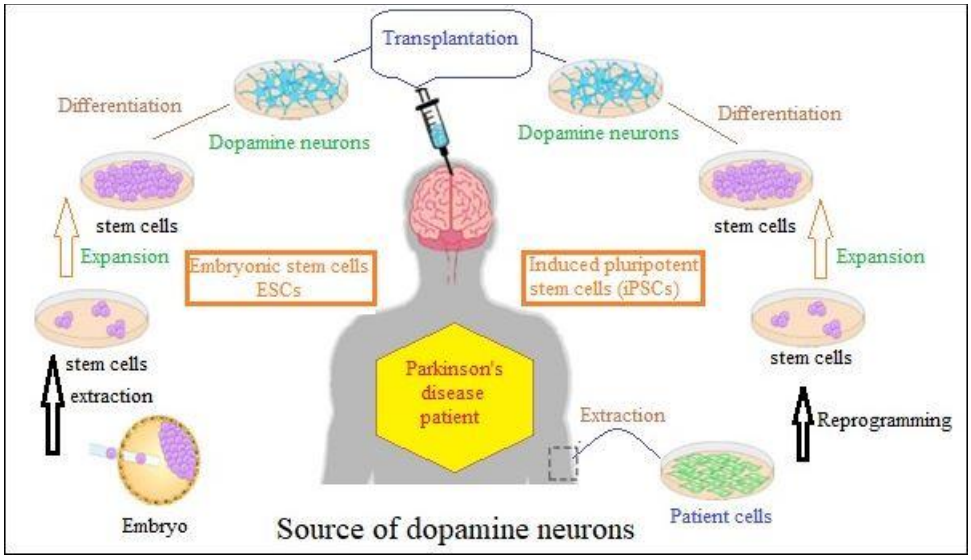

Figure.3. ES cells and IPS cells are the source of dopamine neurons

Parkinson's disease: It is a neurodegenerative disease which results in the loss of dopaminergic neurons in the substantia nigra is shown in fig 3, which leads to loss of motor function. Lewy body formation and neuritis are the pathological signs of this disease, and the specific etiology is still unknown[6].

Current treatment for PD include both drug therapy and surgery. However, these treatments are purely palliative. The drug treatment for PD is surviving dopamine neurons with L-Dopa, which they convert to dopamine. Eventually, all the remaining dopamine neurons die and treatment with L-Dopa is ineffective. MSCs [Mesenchymal stem cells] have been proposed as a potential treatment for PD. Investigations shows that the use of MSCs in a PD mouse model to observe a potential neuroprotective effect on neuronal loss[7]. Fig 4 describes Both ES cells and IPS cells which provide a robust source of dopamine neurons.

Alzheimer disease: It is one of the most common causes of dementia. AD, known for its quintessential hallmarks of amyloid-β peptide (Aβ) plaques and neurofibrillary tangles, results in the death of several types of neuronal lineage cells within multiple regions of the brain, specifically cholinergic neurons is shown in figure 5.

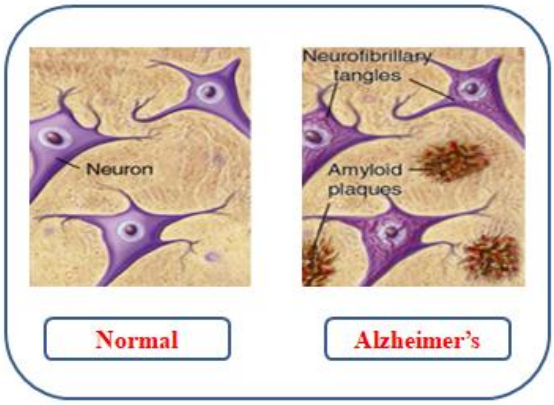

Figure.4. Amyloid plaques and neurofibrillary tangles of Alzheimer's

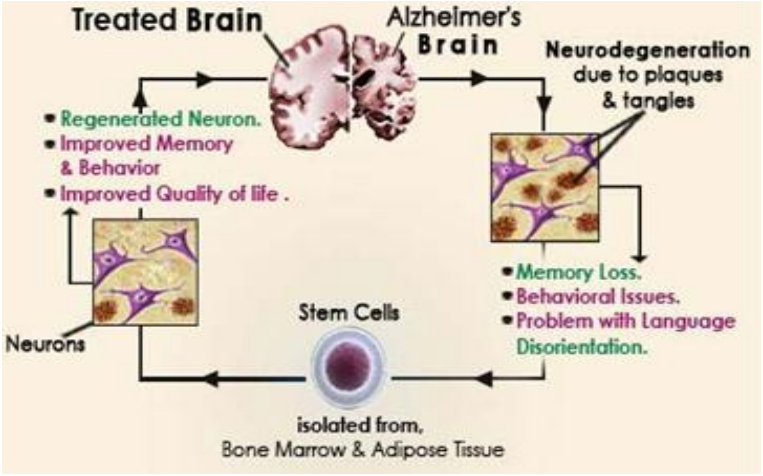

Figure.5. Stem cell treatment for Alzheimer's

Currently available drugs for the treatment of AD are purely for symptoms[8] and among these drugs are the cholinesterase inhibitors. Cholinesterase inhibitors delay in its degradation and it leads to improvement of cognition. However, these types of drugs have a modest effect, it may vary from individual to individual[9]. Another type of drug available for AD patients is an *N*-methyl-aspartate (NMDA) receptor antagonist named Memantine. Memantine prevents the NMDA receptors from overstimulation that can lead to toxicity[10].

Since the current treatments have only marginal effects, Investigations has shown that injecting NSCs [Neonatal stem cells] into the hippocampal regions of the brain of an AD mouse. Interestingly, the mice have improved in cognitive function and there was no change in the existing Aβ plaques or neurofibrillary tangles. The discovery of brain-derived neurotrophic factor, which is important for neuronal outgrowth, and synapse formation increased, which leads to improved cognitive function through increased synaptic density is shown in fig 6. This demonstration shows that cognition could be

improved without a need for modifying the existing pathological conditions[11].

Multiple sclerosis: CNS autoimmune disease, the myelin sheath, the primary target, is degraded and this degradation affects neurons. Unlike AD, PD, and ALS, MS predominately affects young adults and has a higher rate of occurrence in females[12]. Current approaches for MS treatment include monoclonal antibodies, chimeric molecules, and hematopoietic stem cells (HSCs). The general aim of HSCs for MS treatment is to completely correct the immune system within the patient[13].Investigations has proved that 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[14].

The use of myelin-forming cell transplantation is to restore the myelin at the sites of myelin loss. But the transplanted myelin-forming cells are very limited in their growth and ability to regenerate myelin. Therefore, stem cells are used for cell transplantation treatments in MS. HSCs were autologous transplanted to relapse-the remitting MS patients. Neurological improvement was observed after transplantation[15] as shown in fig 7.

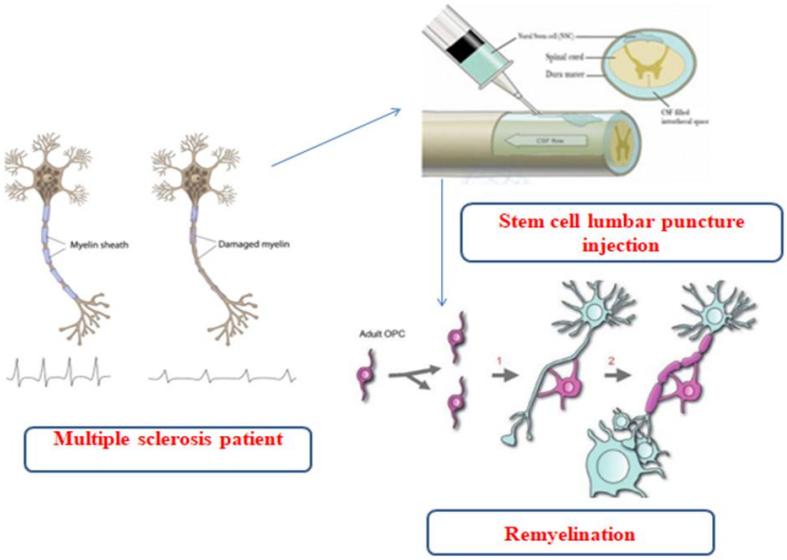

Figure.6. Use of stem cells to repair multiple sclerosis

2. CONCLUSION

This review has discussed the major issues associated with the stem cell therapy for neurodegenerative diseases. The ability to use stem cells to study neurodegenerative diseases has received much attention of late, but it is still not clear whether these cells can truly recapitulate the pathogenic processes in these disorders. It may be that they are ultimately better for doing this in Neuro developmental disorders of the CNS. More realistically it is in the realm of disease modeling and drug screening that they offer most hope, especially given the distributed neuronal pathology seen in all neurodegenerative disorders of the CNS.

Abbreviations: Aβ, amyloid-β peptide; AD, Alzheimer disease; ESC, embryonic stem cell; FSC, fetal stem cell; hiPS, human induced pluripotent stem; iPS, induced pluripotent stem; MS, multiple sclerosis; MSC, mesenchymal stem cell; NMDA, *N*-methyl-D-aspartate; NSC, neural stem cell; PD, Parkinson disease.

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