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REVIEW ARTICLE

Review on Stem Cell Therapy of Neurological Disorders

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ABSTRACT

In recent years, there has been great interest in the use of stem cells for the treatment of neurological diseases. Thus, neurodegenerative disorders (e.g. Parkinson's disease, Alzheimer's disease, multiple sclerosis), vascular events (e.g. stroke) and traumatic diseases (e.g. spinal cord injury) have been admitted as incurable diseases. Different sources of cells for transplantation have been used, including neural progenitor cells, neural stem cells, or embryonic stem cells. In the last two decades the transplantation approach, by means of stem cells of different origin, has been suggested for the treatment of neurological diseases. A general strategy for stem cell transplantation to prevent or minimize neurological diseases is much more likely to be succeed. The present review deals with the introduction and historical aspects of stem cells, neurological disorders and stem cell therapy advancements.

Keywords: Stem cells, Neurological disorder, Transplantation, Neural stem cells, Embryonic stem cells

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1. Introduction

Due to the limited capacity of the central nervous tissue to regenerate, patients with brain damage have to suffer from lifelong disability. Till the early 1970s, all attempts at neural tissue transplantation proved to be a failure. The use of fetal neural tissue for cellular therapy provided the first unequivocal evidence that such grafts "take up," grow, and develop at least a limited two-way connection with the host International Journal of Current Trends in Pharmaceutical Research

brain, and to a variable extent, restore functional deficits in rodents. The clinical use of this procedure soon highlighted its limitations and led to the search for more reliable and acceptable stem cells capable of transformation into any specific cell-types, including neurons and glia¹. Depending upon the culture conditions, these cells could be made to secrete the desired neurotransmitters, in vivo. Around the

same time, stem cells capable of such transformations were isolated from adult bone marrow and many other tissues such as the umbilical cord blood, placenta, and amniotic fluid. Thus, the ethical concerns raised against the use of fetal or embryonic tissue were overcome. Stem cells may be the person's own cells (a procedure called autologous transplantation) or those of a donor (a procedure called allogenic transplantation). When the person's own stem cells are used, they are collected before chemotherapy or radiation therapy because these treatments can damage stem cells. They are injected back into the body after the treatment^{2,3}. Stem cells were originally defined in the hematological system, but more recently have been found in a multitude of other sites, including the brain. These cells all share the same properties of self-renewal and multipotentiality and various different types and therapeutic strategies have been defined with respect to the nervous system. We will briefly discuss the different types of stem cells and how they have been applied to neurological disease, especially Parkinson's disease, given the accepted view that this is the disease most amenable to cell replacement therapy⁴.

Embryonic stem cells (ESCs):

Embryonic stem cells are pluripotent cells with indefinite self-renewal capabilities as well as the ability to differentiate into all cell types derived from the embryonic germ layers. Embryonic stem cells are favorable in the research community because they are relatively easy to isolate, can grow indefinitely, and have the potential to develop into any type of adult cell. Human embryonic stem cells have now been isolated and grown in culture with enrichment for neuronal lineages, possible through exposure to a combination of growth factors and mitogens⁵.

Adult stem cells (ASCs):

Adult stem cells (ASCs) play a critical role in tissue maintenance and repair (Stem Cell Basics, 2010). Research on adult stem cells began in the 1950s with the discovery of multipotent hematopoietic and mesenchymal stem cells in bone marrow, which can generate a number of tissues. Bone Marrow-Derived Mesenchymal Stem Cells (BMSC) can be expanded and differentiated in vitro using various media formulations and culture surface conditions to direct them to different cell lineages. BMSCs have the ability to migrate to areas of injury, even crossing the blood-brain barrier. Although the reproducibility of BMSC therapies needs to be thoroughly examined, these early experiments suggest that BMSCs can be administered intravenously to CNS targets. One of the long held dogmas is that neurogenesis in the adult mammalian central nervous system (CNS) does not occur, although there is now ample evidence to suggest that this is not the case⁶. New neurons are derived in adulthood from a population of adult neural precursor cells (NPCs), which are primarily found in the subependymal layer of the ventricular zone and the dentate gyrus of the hippocampus, although they are also probably found in other sites.

Neural stem cells (NSCs):

The adult mammalian CNS contains NSCs which were first inferred from evidence of neuronal turnover in the olfactory bulb and hippocampus in the adult. Neural stem cells are

able to differentiate into neurons, astrocytes, oligodendrocytes and various forms of neural precursors moreover; in vivo delivery of these cells to animal models of neurodegenerative diseases was associated with varying degrees of functional recovery⁷. Most of the work on stem cells and the CNS refers to NSCs that are derived from the neuroepithelium of the developing embryo. These cells respond in vitro to mitogens such as epidermal growth factor (EGF) and fibroblast growth factor and it is possible to expand cells from any region of the brain. As development progresses to adulthood there is considerable debate over the origin of NSCs, with recent suggestions that these cells may also originate from glia. Radial glia have classically been considered to be "scaffolding" cells along which cortical neuroblasts migrate to reach their final destination, after which they differentiate into astrocytes⁸.

Bone marrow and non-neural Stem Cells (BMSC & NNSCs): An alternative source of autologous cells for grafting in patients with neurological disease are those derived from non neural sources including the bone marrow, which contains a range of stem cells. This includes the hematopoietic stem cell, which when transplanted into irradiated recipient can migrate into the brain and differentiate into microglia, astrocytes, and possibly neurons. In addition, there are mesenchymal stem cells or bone marrow stromal cells, which when engrafted into the adult brain are capable of migration and survival and in vitro can be made to express markers of astrocytes, oligodendroglia, and neurons⁹.

Hematopoietic stem cells:

Autologous Hematopoietic stem cells (HSCT) was largely preferred to allogeneic transplantation because of the lower risk of severe toxicity. Briefly, patients with autoimmune diseases can be considered for HSCT if: (i) their disease is severe enough to cause an increased risk of mortality or advanced and irreversible disability; (ii) the disease has been unresponsive to conventional treatments, so, Fassas and his colleague; 2003 recommended practice points to AHSCT for MS patients (a) AHSCT seems to be the best anti-inflammatory treatment as evidenced in MRI scans. Its clinical value remains to be validated in controlled trials. (b) MS types characterized by neurodegenerative pathogenic components are unlikely to benefit from ASCT. (c) Good candidates are young patients with rapidly evolving RR-MS or "malignant" MS¹⁰.

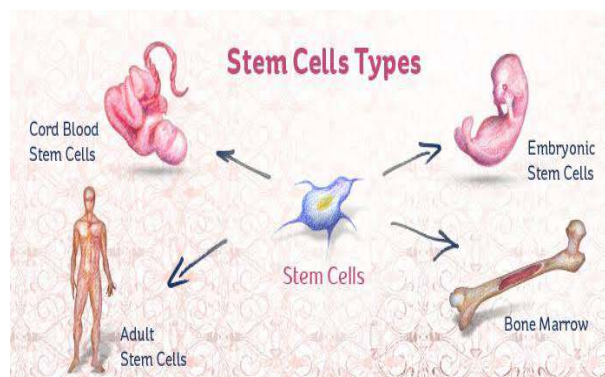


Fig 1: Types of Stem cells

2. Stem cells utility in neurological disorders

Neurological diseases are caused by a loss of neurons and glial cells in the central nervous system (CNS) or peripheral nervous system. Effective treatment of these neurological diseases is currently impossible. Stem cell therapy is a promising treatment option for these neurological diseases¹¹.

Alzheimer's Disease (AD):

Alzheimer's is a complex, fatal disease involving progressive cell degeneration, beginning with the loss of brain cells that control thought, memory and language. The disease, which currently has no cure, was first described by German physician Dr. Alzheimer, who discovered amyloid plaques and neurofibrillary tangles in the brain of a woman who died of an unusual mental illness. A compound similar to the components of DNA may improve the chances that stem cells transplanted from a patient's bone marrow to the brain will take over the functions of damaged cells and help treat Alzheimer's disease and other neurological illnesses¹².

A research team led by University of Central Florida professor Kiminobu Sugaya found that treating bone marrow cells in laboratory cultures with bromodeoxyuridine, a compound that becomes part of DNA, made adult human stem cells more likely to develop as brain cells after they were implanted in adult rat brains. It has long been recognized that Alzheimer's disease (AD) patients present an irreversible decline of cognitive functions as consequence of cell deterioration in a structure called nucleus basalis of Meynert. The reduction of the number of cholinergic cells causes interference in several aspects of behavioral performance including arousal, attention, learning and emotion. It is also common knowledge that AD is an untreatable degenerative disease with very few temporary and palliative drug therapies. Neural stem cell (NSC) grafts present a potential and innovative strategy for the treatment of many disorders of the central nervous system including AD, with the possibility of providing a more permanent remedy than present drug treatments. After grafting, these cells have the capacity to migrate to lesioned regions of the brain and differentiate into the necessary type of cells that are lacking in the diseased brain, supplying it with the cell population needed to promote recovery¹³.

Parkinson's disease:

Parkinson's disease is a progressive neurodegenerative disease characterized by rigidity, tremor and bradykinesia and associated with loss of function of dopaminergic neurons in the substantia nigra. Prevalence studies show that PD affects over 1% of the population over the age of 60. There are many different treatment methods of PD. L-DOPA is still fundamental drug in early periods of PD, dopaminergic agonists, rasagiline use in initial treatment for the disease, Catechol-O-methyltransferase inhibitors are effective with motor fluctuations. Apomorphine is another drug that can be used non-oral. Deep brain stimulation is also a widely used treatment method. None of this treatment provides a cure for PD. Moreover, although their effects decrease, side effects are emerging but stem cell therapy would induce long-term clinical improvement¹⁴.

Fetal mesencephalic tissue replacement studies were being performed since 1987 in order to increase dopaminergic neuron level in striatum. Until today, in human, dopaminergic cell transplantation was performed more than 300 cases in Parkinson's disease. The implants adapted with tissue and their continued viability has been proven with PET-scan and clinical improvement¹⁵. Embryonic stem cells (ESCs) also had been source for cell replacement therapy in PD. Kim et al. encouraged us about ESC replacement due to renewal ability and pluripotent nature of ESCs. In addition to pluripotent stem cells, adult stem cells have been used as a source for cell replacement therapy, for example MSCs. Although MSCs are obtained from bone, muscle tissue, maxillary tissue, dental pulp, liver, placenta, amniotic fluid, cord blood and synovial fluid, even mainly derived from the bone marrow. With the reprogramming methods, scientist can convert fibroblast or other types of somatic cells into neural precursors. Werning et al. have derived DA neurons from PSCs and observed improvement in rodent model of PD after engrafting iPSCs. Furthermore, continue testing with different cells except ESCs, MSC or iPSCs, Murrell et al. were generated dopaminergic neurons from olfactory mucosa in vitro and transplanted to hemiparkinsonian rat model. Olfactory neuroepithelial cells have some advantage as a source of stem cell for example, easy biopsy, regenerative capability, neurogenic differentiation potential; so, scientists may be mostly want to use olfactory neuroepithelial cells in future¹⁶.

Huntington's disease:

Transplantation repair in Huntington's disease provides different challenges for ENPs, in that the transplanted cells must homotypically reconstruct circuitry. To date, studies using NSCs in this disorder are limited but there is some evidence of appropriate neuronal differentiation with human NSCs, although the functional efficacy and connectivity of these cells in repairing the brain has not been demonstrated¹⁷.

Spinal muscular atrophy (SMA):

It is one of the most devastating childhood diseases since it affects babies from birth onwards (it can occasionally be detected during gestation), and in its more severe form type 1 or Werdnig-Hoffmann disease, in which patients cannot sit and some of them cannot control the position of their head. Life expectancy does not exceed 2 years. Type 2 SMA is an intermediate form whose onset is between 7 and 18 months of age; patients can sit but never stand and they can survive to adulthood. Type 3 SMA has its onset after the 30th month of life. The severity of the disease is classified by the degree of muscle weakness (before or after 3 years); the patient can walk but in some more severe forms they stop walking in adulthood. Finally type 4 SMA has its onset between the 10 and the 30th years of life; length of life is as with type 3 and patients can stand and walk and if well trained continue doing so all their life¹⁸. SMA is a genetic disease caused by a loss of function mutation of a telomeric gene called Survival Motor Neuron 1 (SMN1). The pathology is very variable and depends on the number of copies of another centromeric gene, the Survival Motor Neuron 2 (SMN2), which can transcribe for the same

protein although with a lower rate of expression. So far no pharmacological treatment has been shown to be effective, although the various clinical trials performed even recently need to be revisited, as there is a great variability of response to pharmacological treatment between different patients.

Spinal cord injury:

Traumatic spinal cord injuries are one of the challenging problems all around the world. Spinal cord is the main circuit, which transfers motor and sensorial signals between brain and body. After major spinal cord injury, ascending and descending neural systems lost their integrity with motor and sensorial structures in spinal cord and paralysis and anesthesia occur under lesion site. With this type central nervous system injury, serious cell losses in tissues occur, significant myelin loss is seen and it becomes almost impossible to repair neural connections. So it is not possible to gain appropriate results with only decompression and physiotherapy/rehabilitation. On the other hand, it has been shown that transplanted hematopoietic stem cells gained from bone marrow regenerate injured cells and repair myelin sheath. Spinal cord regeneration was tested in cell cultures and animal experiments firstly¹⁹. To induce regeneration of injured spinal cord, some methods like reducing scar size, Xirradiation, electrical stimulation, neurotropic factors, grafting, omentum transplantation, and neutralization of neurite growth inhibitors were tested. In recent years, transplanting cells like Schwann cells, olfactory glial cells, embryologic or adult stem cells have become popular and all these methods are named as cell therapy. As a result of these animal experiments, ideal cell type to transplant in spinal cord injuries is not known but strong evidences shows us that site-specific neural progenitor stem cells have to be. McDonalds et al. showed that, neural differentiated mice embryo genic stem cells transplanted to rat spinal cord could stay alive 9 days after traumatic spinal cord injury and these cells' differentiation to astrocyte, oligodendrocyte and neurons²⁰.

Traumatic brain injury (TBI):

Damage to the brain caused by external mechanical force such as rapid acceleration, blast wave, or penetration wound is defined as TBI, which often leads to impairment of cognition, physical, and psychological functions. TBI involves a complex disease process composed of the primary injury, including contusion and hemorrhage resulting from instant external mechanical disruption, and the triggered secondary injury caused by a cascade of metabolic, cellular, and molecular events such as the imbalance of glutamate and gamma-amino butyric acid, active oxygen and free radical formation, and impairment of the blood-brain barrier²¹. As primary injury occurs immediately after exposure to the external trauma, it can only be preventable. However, the prolonged characteristics of second injury provide a window of opportunity for treatment. Endogenous neurogenesis has been detected and reported during TBI. In TBI brain specimens, NSC/neural progenitor cell markers, including DCX, Sox2 and NeuroD, were increased in the perilesional cortex. In addition, NSCs along the SVZ reportedly undergo robust proliferation with increased regenerative capacity. However, this endogenous

regenerative neurogenesis is not enough to prevent and restore the damage. In addition, the heterogeneity of TBI pathophysiology makes it difficult to find a sufficiently effective therapy. In consideration of these facts, stem cell transplantations have been tested in both animal models and clinical trials of TBI, and have exhibited promising therapeutic benefits²².

Amyotrophic lateral sclerosis (ALS):

Amyotrophic lateral sclerosis; associated with the common upper and lower motor neuron degeneration, generally resulting in death due to respiratory failure an average of three years after the beginning of symptoms. Microglial activation, astrocytosis, lymphocyte infiltration and dendritic cells are accompanied with progressive degeneration of motor neurons. Cause of the disease is not known but glutamate excitotoxicity and oxidative stress, viral infections, autoimmune mechanisms, glial abnormal activity and reduction in trophic factor hypothesis are involved in etiopathogenesis. Definitive diagnosis of ALS is usually confirmed after a period of 1-2 years from the start of symptoms. Riluzole is a glutamate antagonist and the only known treatment of the disease. About 20% of life was found to be prolonged in patients using this drug. With other agents around 20 clinical studies have been conducted to date. Although some molecules results with promising studies in animal, however, riluzole is the only therapeutic drug approved for ALS with regard to prolonging survival time. Stem cell therapy is one of the treatment methods in order to stop the progression of the disease and if possible return loss of function. It is not a realistic expectation that stem cells integrate to neural network by replacing lost motor neurons. The hope is the halting of motor neuronal death. Stem cell transplantation studies have been shown to be effective in animal²². The studies continue about how stem cell effects in ALS. Stem Cell therapies for ALS utilize various types of stem cells to regenerating neurons and support surrounding cells through release of neurotropic factors, and study disease physiology. Different sources of stem cells include bone marrow, neural stem cells, mesenchymal stem cells, astrocyte precursor cells, and induced pluripotent stem cells. Autologous MSCs were isolated from bone marrow and most of cell-based clinical trials for ALS are based on the use of MSCs. Mazzini et al. has placed the autologous bone marrow derived hematopoietic cells into the spinal cord at TH7-TH9 level for 7 patients. They have showed that in patients with significant gains in the three-year follow-up results and reported that direct injection of autologous MSCs into the spinal cord in ALS patients is a safe method which does not show significant acute or chronic toxicity and is well tolerated.

Brain tumor:

Despite extensive surgical excision and radiotherapy and chemotherapy; malignant brain tumors such as glioblastoma multiforme remain virtually untreatable and lethal. The opposition to treatment is associated with their exceptional migratory nature and ability to insinuate themselves seamlessly and extensively into normal brain tissue, often migrating great distances from the primary tumor masses. Medulloblastoma is the most common among childhood

brain tumors and is incurable. Available treatments including radical surgical resection followed by radiation and chemotherapy have substantially improved the survival rate in this disease; however, it remains incurable in about one-third of patients. As well, in the case of recurrence, frequently associated with tumor dissemination and the main cause of death, therapeutic options are rarely available²³. The capability of human NSCs as an effective delivery system to target and disseminate therapeutic agents to medulloblastomas was demonstrated for the first time. One of the causes for the recurrence of medulloblastoma in children after standard treatment is the inherent tendency of tumor cells to metastatize through cerebrospinal fluid, leading to leptomeningeal dissemination. Throughout the entire spinal cord, human NSC F3.CD cells were found to distribute diffusely to metastatic medulloblastoma cells after injection in the cisterna magna, and the CD gene in NSCs functioned effectively and killed tumor cells.

Multiple sclerosis(MS):

MS is a chronic, demyelinating disease of the brain and spinal cord ,MS is 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. Unfortunately, the available treatments (Immunomodulatory and immunosuppressive) are not curative, they can reduce CNS inflammation and may delay progression, but control of disease is unsatisfactory in many patients ,a logical treatment approach to enhance neuroprotective mechanisms and to induce neuroregeneration through stem cell transplantation, stem cell therapy for MS can categorize to immune reconstruction or tissue reconstruction (remyelination), two distinct approaches can be considered to promote myelin repair, in one the endogenous myelin repair processes are stimulated through the delivery of growth factors, and in the second the repair process are augmented through the delivery of exogenous cells with myelination potential. Also, the effective treatment of MS requires modulation of the immune system, since demyelination is associated with specific immunological activation. Several types of stem cells having the capacity for promoting myelin repair, as well as modulating the immune response, are potential candidates for MS therapy²⁴.

Lysosomal storage diseases:

Most affected babies by lysosomal storage diseases show a diffuse CNS involvement. At present, no effective treatment is available for most of the lysosomal diseases, because the blood-brain barrier bars entry of enzyme preparations into the brain. However, therapeutic levels of enzymes could be achieved in the brain of animal models of lysosomal diseases by direct inoculation of genetically engineered mouse, fibroblasts or amniotic epithelial cells. In consideration of their widespread migratory ability, normal or genetically modified stem cells would allow widespread delivery of missing enzymes all over the brain. In a mouse model of mucopolysaccharidosis VII (MPS VII), a lysosomal disease caused by a genetic defect in the activity of b-glucuronidase (b-gluc), genetically engineered mouse overexpressing b-gluc were transplanted into the cerebral ventricle and resulted in reduction of lysosomal

storage in the mouse brain. Similarly, the transplantation of (b-gluc) overexpressing human NSCs into MPS VII mice and human NSCs migrated extensively all over the brain, produced high levels of b-glucosidase enzyme, and cleared lysosomal storage in the neuronal cytoplasm. In an earlier study, immortalized human NSCs were transplanted in a mouse model of Tay-Sachs disease in which abnormal lysosomal storage of GM2 ganglioside is found in the brain, resulting from total absence of hexosaminidase enzyme activity. After transplantation of human NSCs, there was a clearance of storage in neuronal cytoplasm in Tay-Sachs model mice. The results indicate that NSCs could serve as an excellent gene transfer vehicle for the treatment of diffuse CNS pathology in human lysosomal storage diseases, including Krabbe disease, Gaucher's disease, metachromatic leukodystrophy, and adrenoleucodystrophy^{24,25}.

Other neurological diseases:

Congenital metabolic diseases are a vast diagnosis group, which constitutes genetic diseases including metabolism disorders. It is a vast group including carbohydrate metabolism disorders, amino acid metabolism disorders, organic acid metabolism disorders, fatty acid oxidation and mitochondrial metabolism disorders, porphyrine metabolism disorders, purine or pyrimidine metabolism disorders,steroid metabolism disorders, mitochondrial malfunction, peroxisomal malfunction, lysosomal storage disorder. Most of them stem from the single gene mistakes encoding the enzymes, which facilitate a substance's conversion into another substance. In most disorders, the troubles are caused by the accumulation of toxic substances or the substance's reduced functions for the normal procedure due to inability of synthesizing. Congenital metabolic diseases are progressive and fatal, so they do not have a distinct and efficient treatment. The strategy of the treatment is to put back the enzymes that have to be in the central neural system. In 2004, Krivit stated that allogenic hematopoietic stem cells were used for the patients with lysosomal storage disease and leukodystrophy . The results are rather satisfactory. Similarly, successful stem cell applications on people with Krabbe's disease have been reported²⁵. The reason why stem cells are beneficial in these types of diseases is that the stem cells penetrated into the brain accompany the infiltration of microglial cells and their consequent help to replace the lost enzymes.

3. Conclusion

Stem cells are emerging as one of the most exciting new areas of neuroscience, not only in terms of revealing insights into normal development, but also as a therapeutic agent for a range of neurological diseases.Stem-cell-based technology offers amazing possibilities for the future. These include the ability to reproduce human tissues and potentially repair damaged organs (such as the brain, spinal cord, vertebral column the eye), where, at present, we mainly provide supportive care to prevent the situation from becoming worse.Todays, selection, generation and transplantation of stem cell, all of these major challenges but in the very near future we can say hopefully that stem cell therapies can be applied effectively. In light of these

findings, stem cell treatment is a cell substitution for the destroyed spinal cord or CNS, axon regeneration and/or application of a neurotropic factor to recover the neural tissue.

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