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NARRATIVE REVIEW

Stem cell therapy as a promising approach in the treatment of neurodegenerative disorders

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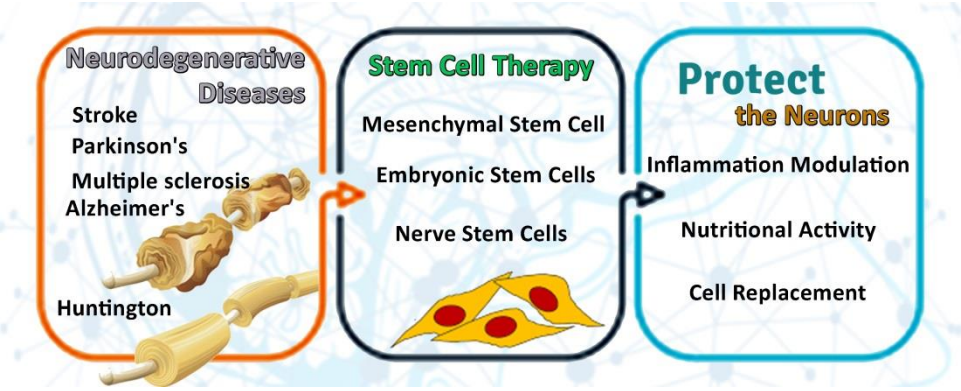
Highlights

- Neurodegenerative diseases are correlated with the loss of glial cells or neurons.
- The stem cell therapy is a promising and emerging approach for neurodegenerative diseases.
- Stem cells use different mechanisms to protect neurons.

Graphical Abstract



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Abstract

Neurodegenerative diseases in humans such as Parkinson's disease, Alzheimer's disease, stroke, multiple sclerosis, and Huntington's disease are associated with the loss of neurons or glial cells in the central nervous system. There are limited therapeutic approaches for these diseases, making stem cell therapy a promising and novel method for these diseases. A variety of cells have been used to treat these diseases. These cells include mesenchymal stem cells, embryonic stem cells, nerve stem cells, etc. These cells use various mechanisms to protect neurons. These mechanisms include nutritional activity, inflammation modulation, cell replacement and so on. Of course, there are some challenges with this therapeutic approach, for example, different treatment approaches need to be chosen for different diseases. Also, the cell type used in a particular disease should be specifically selected. In addition, points such as the administrated dose, the method of transfer, etc. must be controlled. Also, the cells should be used in such a way that they do not cause further problems such as malignancy and the immune system activation. In this study, we review the effective evaluations taken in the cell therapy field against neurological disorders including Parkinson's, Alzheimer's, stroke, Huntington's, and multiple sclerosis, and then we describe the challenges and hopes in this field.

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Introduction

Stem cells can be considered as building units for various organs of the body. These cells have an interesting capability to differentiate into different kinds of cells in the body, while they can be maintained by asymmetric division, with simultaneous proliferation for the original stem cell generation. These cells are found in almost all human tissues (1). Embryonic stem cells (ESCs) have the capability to transform into all tissues of the body. But adult stem cells have a more limited differentiation capacity. So, stem cells are defined differently by "potency" (2, 3). This term indicates to the capability of stem cells to differentiate into various kinds of cells. Stem cells called "totipotent" and "pluripotent" have the most power to differentiate. The cells in the morula have the most differentiating power and can be differentiated into all parts of the body and even the placenta. Blastocytes, are composed of cells that form a hollow hole and contain an inner mass cell that is the same as ESCs. The mentioned stem cells are pluripotent and cannot differentiate into the placenta. However, they can be differentiated into all different body tissues and organs (4, 5).

In contrast to other types of cells (6), stem cells with pluripotent capability could differentiate into multipotent types of stem cell, such as hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and nerve stem cells (NSCs). These cells have a lower ability to differentiate and are committed to differentiating into a specific system or organ. For instance, nerve stem cells could differentiate into brain cells and cells of the nervous system. "Multipotent" stem cells could produce precursor stem cells that are "oligopotent" or "unipotent" (4, 7). Thus, the differentiating potent of recent cells is greatly reduced and they can only differentiate into some types or even just one cell type. Until a few years ago, the process of differentiation of stem cells was considered unidirectional. Though, by injecting certain agents into differentiated cells, such as fibroblasts, *in vitro* conditions can produce cells that are capable of proliferation. These cells are identified as induced pluripotent stem cells (iPSCs) (4, 8). The process of stem cell differentiation and their use in neurodegenerative diseases is illustrated in Figure 1.

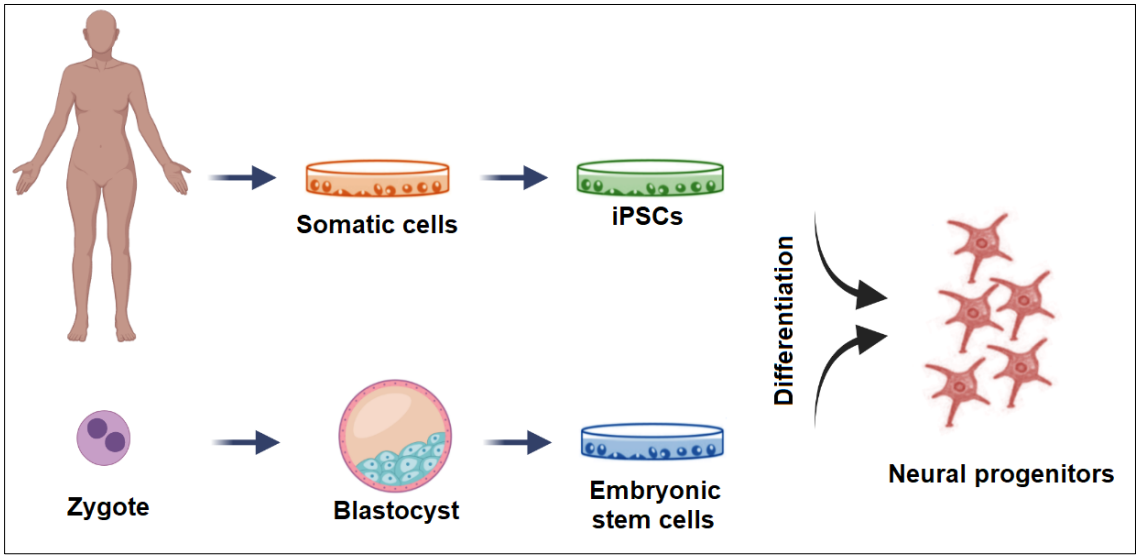

Figure 1. The process of cell differentiation of stem cells for the neurological diseases' treatment. Induced pluripotent stem cells (iPSCs) could differentiate from the somatic cells while embryonic stem cells were got from the inner cell mass of blastocysts.

The use of stem cells in neurodegenerative diseases is to repair tissue, replace neurons, or at least prevent further progression of the disease. These cells in the damaged nerve areas can act as paracrine or produce new neurons. All of the cells described above could potentially be used to treat neurodegenerative disorders. However, NSCs seem to be more appropriate and rational options for the neurological disorders' treatment. Because the use of these cells requires access to the depths of patients' brains, they cannot be used for autologous therapies. One way to access these cells is to obtain them from aborted embryos and use them

allogeneically. This process is accompanied by some limitations such as ethical limitations and may also cause cancer or stimulate the immune system. Because of such limitations, the use of embryonic stem cells and iPSCs has been considered in this field, which can be differentiated into nerve cells. Because pluripotent stem cell has infinite proliferative ability and can become cancer cells, their direct use is not considered. Rather, they first differentiate into target cells. In addition, hematopoietic and MSCs could be employed to treat neurological diseases (9-11). In this narrative review study, we introduce stem cell therapy strategies to overcome neurological disorders including Huntington's, Alzheimer's, Parkinson's, stroke, multiple sclerosis, and as well as the challenges and opportunities of this therapeutic approach.

Alzheimer's Disease

Alzheimer's disease (AD) is defined as the loss of neuronal cells and synapses in brain tissue. These impairments are more common in the amygdala, the basal forebrain, the cortical area, and the hippocampus. In this disease, cognitive function and memory of individuals gradually decrease, which eventually leads to dementia and death (12). There are now no effective treatments for this disease, and only acetylcholinesterase inhibitors are available that enhance cholinergic function, and are only a temporary approach. In the pathology of Alzheimer's disease, amyloid-beta (Aβ) levels increase as insoluble and soluble peptides. This is due to the digestion of amyloid precursor protein (APP) (13). In one study, mouse models of PDAPP, as transgenic models of Alzheimer's, were treated with anti-Aβ antibodies, which led to the recovery of processes such as choline uptake and acetylcholine release in the hippocampus, which resulted in improved learning procedure (14).

Chronic lowering of beta-amyloid levels in the brain is a treatment for Alzheimer's. For example, enzymes such as insulin-degrading enzyme, neprilysin, cathepsin, and B plasmin can lower beta-amyloid levels and be considered as a treatment for Alzheimer's disease (15). Recent reports have shown that transmission of a human neprilysin-expressing lentivirus in Alzheimer's mouse models reduces beta-amyloid deposition in the brain and reduces nerve damage in the hippocampus and frontal cortex (16). Also, brain transfer of fibroblasts that overexpress neprilysin significantly reduces the accumulation of amyloid plaques aggregation in the brains of Alzheimer's mice (17). Such studies may suggest that the use of beta-amyloid digestive proteases could be an appropriate approach to treating Alzheimer's. Delivery of these proteases via human NSCs could be an appropriate adjunctive therapy approach.

Nerve growth factor (NGF) can maintain cell survival and improve excitatory toxicity, aging, and amyloid toxicity in experimental models (15). Therefore, they could possibly be employed in the treatment of nervous diseases, including Alzheimer's. It is not possible to transfer this factor peripherally because it cannot cross the blood-brain barrier because of its polarity and size. Therefore, gene therapy can be effective to solve this problem. Using this method can directly deliver NGF to the brain and release them at a distance of 2 to 5 millimeters (18). In a clinical trial, the NGF gene was transferred to the brain via modified fibroblasts for expression of this gene. The results of this study showed almost no side effects in the long run. This approach also showed an improvement in the components of dementia. Subsequent studies also showed that cortical fluorodeoxyglucose levels increased (19). Despite their potential as stem cells that could be genetically engineered and transfer genes, they can be used instead of fibroblasts to reduce the risk of transplant rejection (15).

Parkinson's disease

Parkinson's disease (PD) is a neurological disease defined by the loss of dopamine neuronal cells in parts of the brain. The cause of Parkinson's disorder is not fine understood; however, some risk factors for dopamine neurons have been identified. These mechanisms include viral infection, environmental toxins, and apoptosis. L-dihydroxyphenylalanine (L-DOPA) has been identified as an efficient therapeutic approach for Parkinson's disease, a dopamine precursor. The use of this substance for a long time has many side effects (20). Some approaches may be helpful in treating the disease in Parkinson's disease in early stages (21), however, it may

not be a viable solution for advanced symptoms (22). Aging can also cause morphological changes in the brain with Parkinson's. With age, the function of the nigrostriatal dopamine system in the brain decreases (23). Stem cell utilization can be a good option for treating the early stages of Parkinson's and preventing it from developing to more violent phases (21). Transfer of stem cells to the brain causes them to be absorbed in dopaminergic defective areas. This leads to the capacity of nerve cells through the process of differentiation as well as the release of neurotrophic factors (22). Also, the development of dopaminergic neurons is promoted by the acquisition of astroglial phenotypes by transferred stem cells into the brain (24, 25). Therefore, stem cell transfer to the human brain can be used as a primary treatment approach for Parkinson's. These cells can also be used in combination with common dopaminergic therapies to treat Parkinson's.

In experimental studies and among *in vivo* models of Parkinson's disease, rodents and monkeys are mostly used. And more than 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or 6-hydroxypopamine is used in these animals. Intravenous administration of cells is less invasive and this is an important advantage for this type of transfer. But the disadvantage of this method is that the homing process is not done well and therefore cannot be well differentiated into the target cells, such as dopaminergic neuronal cells in Parkinson's (26). In Parkinson's disease, the blood-brain barrier usually loses its integrity, however it may prevent injected cells from reaching the brain. Although the use of some stem cell resources has ethical limitations, methods have been developed that extract stem cells from resources that are not ethically disputable (27). IPSC cells arising from the reprogramming of differentiated cells have the potential to produce dopaminergic neurons. IPSCs help the survival of neurons and improve the behavioral motions of Parkinson's rat models by activating the sonic hedgehog pathway in combination with the WNT signal (28). Intrastriatal injection of neuronal precursors increased the differentiation and survival of nerve cells. This test was not associated with any tumor necrosis. No graft rejection was also observed (29). Fetal brain stem cell transplantation (fNSCs) in a case with Parkinson's disorder improved the condition and later discontinued L-dopa treatment, and it was later discovered that the person was still releasing dopamine from transplanted dopaminergic cells (30). Another study on this cell type in the treatment of people with Parkinson's older than 60 years and younger than 60 years showed that these cells are more efficient in younger people, which may be due to the different effects of niches on the efficiency of transplanted cells (31).

Many studies have revealed that the transfer of hESCs, iPSCs, and fNSCs can be effective in experimental models of Parkinson's. The main advantage of iPSCs over other cells is that they are autologous and we will not have cells with graft rejection. When blood cells or skin cells are reprogrammed, they can produce iPSCs. These reprogrammed cells can differentiate into dopaminergic precursors or dopamine mature nerve cells (32, 33). But there are some challenges to using iPSCs in the clinic that need to be overcome. The first challenge in using iPSC in the production of dopaminergic neurons is to ensure their effectiveness. IPSC-differentiated neurons should have the same effect as dopaminergic neurons in the human fetus. Due to the impossibility of extending laboratory results to clinical conditions, more clinical trials are needed to determine the method of cell injection, the appropriate cell dose, and the site of cell injection (34). The second challenge in using of these cells is the graft rejection or cause complications such as tumorigenesis. To prevent malignancy, it is necessary that the remains of nondifferentiated iPSCs/hESCs be less than one percent. Patient-derived iPSCs may have mutations in some of their genes, such as SNCA, LRRK2, GBA, etc. (35, 36). These issues may be related to the resource of the donors of iPSC or their reprogramming methods. The next challenge is the effectiveness of iPSC production and the purity of iPSC-derived cells, and this problem can be solved by adding some chemicals (37). The fourth issue is screening the most appropriate cases with Parkinson's. To achieve better efficacy and safety, patients should be treated in early stages of disease progression (38).

Stroke

Stroke is a disease of the nervous system defined by an absence of blood source to the brain and the death of brain tissue cells in a core area. There are two kinds of stroke, including hemorrhagic and ischemic stroke. The

ischemic type occurs by a blocked blood vessel, while a hemorrhagic type happens by a ruptured blood vessel in the brain. Ischemic stroke is more usual than hemorrhagic stroke and accounts for about 85% of strokes, while 15% of strokes are hemorrhagic (39). Systemic hyperfusion, embolism, and thrombosis are some of the conditions that lead to limited blood flow to the brain, resulting in insufficient oxygen and glucose reaching the brain and causing ischemic stroke. Apoptosis, inflammation, oxidative stress, neurotoxicity, and excitotoxicity are some of the mechanisms that occur due to a lack of oxygen to the brain. Damaged cells around the core area of the infarct are rapidly destroyed by the process of necrosis. In the area around the core region, the penumbra, neurons, and supporting cells can survive or die over a period of time. The antithrombotic drug is only acceptable treatment for stroke disease, but its administration is restricted to a short period of time (40). Therefore, the use of clinical alternative therapies seems very necessary.

Cells with various resources including umbilical cord and bone marrow, neuroepithelial or teratocarcinoma cell lines, and fetal brain can be used in stroke disorder. Some cell lines in animals and one clinical trial line have improved stroke (41). In most cases, transplanted cells provide nutritional factors that improve cell function and survival. However, to achieve clinically valuable therapies, cells must be capable to replace dead nerve cells, regenerate axons, and reparation of disrupted neural circuits (42). Providing nutrients, modulating the immune system, and replacing cells can be major functions of transplanted stem cells (Figure 2).

In a study of animal models, human embryonic stem cells were employed for transplantation into the brains of stroke rats. This study displayed that new neuronal cells can migrate to the stroke area in the brain. Other studies have also shown that monkey embryonic stem cell lineages were transplanted into mice with stroke lesions and that these cells could differentiate to a variety of neuronal and glial cells, interact with the affected areas, and improve the symptoms of stroke. Such treatments would be much more effective if stem cells were genetically engineered and the expression of certain genes, such as an anti-apoptotic gene, was increased (43).

Neuronal stem cells can replace stroke-damaged neurons in rodent brains. These cells can make new striatal neurons and migrate to the affected area (41, 44). It must be determined whether endogenous neurogenesis can improve defects in stroke. And it is important to regenerate cortical neurons because their function is damaged in most ischemic brain lesions. It is also essential to understand the differentiation of the brain's own neuronal stem cells into cortical neurons. The efficiency of cell-based therapies is dependent to increase the survival of differentiated neurons and their proper placement in neural circuits (42).

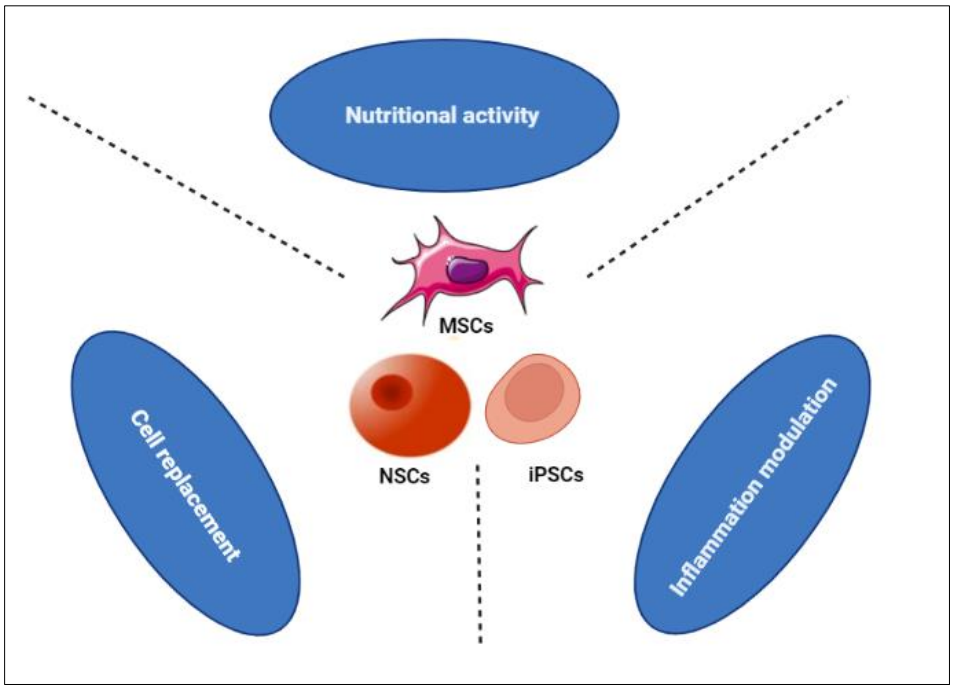

Figure 2. Role of transplanted stem cells. The stem cells provide nutrients, modulating the immune system, and replacing cells after transplantation.

Huntington's disease

Huntington's disease (HD) is known to be an incurable and fatal disease. Symptoms of this disease include chorea or excessive spontaneous movements as well as progressive dementia. The death of striatum neurons causes this disease. This disease is predominant as an autosomal recessive disorder (45). Although the genes and proteins involved in Huntington's disease are known, Huntington's pathophysiological mechanisms are not well understood, which interferes with therapeutic interventions. An appropriate approach to reducing Huntington's nerve damage is to transfer human brain tissue. One study found that embryonic cell transplantation could improve patients' cognitive and motor function (46). However, prior to this clinical trial, studies on Huntington's animal models showed that translocation of fetal striatal cells improved neuronal function in these animal models (47).

In cell therapy for Huntington's disorder, the main goal is to maintain brain function, which is done by protecting and replacing striatal neurons. This strategy may not be sufficient in progressive neocortical destruction. In Huntington's animal models, cell replacement by embryonic striatal nerve cell transplantation improves performance, and some evidence from clinical trials suggests that this could also happen in Huntington's patients (41). In contrast, the methods of stem cell therapy are still in their early stages, and regeneration of striated neural circuits in animals has not been shown. Study on laboratory models shows that replacement of fetal striatal neurons can be effective. However, the use of human neuronal stem cells in the brains of Huntington's rats showed that motor impairments were reduced through trophic mechanisms (48, 49). It seems that the transfer of neurotrophic and neuroprotective factors prevents the progression of the disease and is a suitable clinical goal for neuronal replacement (42).

Multiple sclerosis

In multiple sclerosis (MS), the myelin sheath surrounding the axon is destroyed by inflammation. This can lead to impaired nerve conduction and in many patients can lead to major disabilities. The process of chronic demyelination, which is caused by the loss of axons due to chronic inflammation, is a major cause of poor neurological function. Therapeutic approaches that suppress or modulate the immune system can only be partially effective against MS. Cells called oligodendrocyte precursors (OPCs) are abundant in the brain to produce myelin (50). Myelin regeneration occurs at different stages of MS to varying degrees, and OPCs also exist in lesions with chronic demyelination in MS. Research has focused on the re-myelination process by the above cells and the factors that result in the impairment of this process. In MS and demyelinated lesions, astrocyte-derived hyaluronan has been shown to accumulate, thus preventing the endogenous maturation of OPCs (51). Another way to treating MS is to use the transplantation of remylating cells. Studies have revealed that the transplantation of adult human OPCs and OPCs derived from ESCs can myelinate demyelinated neurons in the spinal cord and brain of mice (50, 52). However, inflammation in transplanted areas raises the concern that it may destroy transplanted OPCs or prevent them from maturing. Due to this, the use of immunosuppressants and anti-inflammatory drugs is essential. Another point is that demyelinated lesions of MS are not focused and distributed in different regions of the central nervous system. So, an effective treatment is the migration of OPC to these different places. In one study, it was found that after systemic administration of neuronal stem cells to mice, these cells migrated to inflammatory demyelinating regions, and some of them differentiated into OPCs and re-myelinated axons (53, 54). Most cells also did not differentiate and suppressed inflammatory mechanisms. Of course, the influences of aging on stem cells and precursors are very complex and affect many cell-based therapeutic processes (55-58).

Conclusion

Cell therapy approaches, especially stem cells, are a new and promising field of research. Cell therapy can be a good way to overcome neurological disorders including Parkinson's, Alzheimer's, multiple sclerosis, stroke, and so on. There is promising evidence in animal model studies that could be helpful for the administration of

stem cells in clinical phases. Different mechanisms make stem cells effective in treatment. These effects are achieved through nutritional activities, neuroprotection, immune modulation, etc. Of course, there are some challenges in this regard, for example, in the treatment of different diseases, different approaches must be adopted. In Parkinson's, one type of nervous system is targeted, while in stroke and MS, the nervous system is distributed and a variety of nervous systems are targeted, so cell replacement mechanisms are challenging. Another issue is the type of cell used, and before using it, we need to know which kind of stem cell is appropriate for which type of neurological disorder. Ancillary items such as the used dose, method of delivery, etc. should also be controlled. In addition, the administrated cells should be used in such a way that they do not cause further problems such as malignancy and activation of the immune system. However, further laboratory and clinical studies are needed to apply safe cell therapies in neurological disorders.

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