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A Review: Stem Cell Therapy for Neurological Disorders

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Abstract

The nervous system has limited self-regeneration ability, and many drugs used to treat neurological disorders often incur serious side-effects. Conventional treatment methods are often ineffective at targeting diversified pathologies of neurological diseases and breaching the blood-brain barrier. Consequently, stem cell therapy appears to be a viable option for treatment. Under right conditions, stem cells can be guided to differentiate into neurons and glial cells, providing vital regeneration of cells and tissues not possible with conventional treatment methods. Additionally, stem cell therapies are minimally invasive and less damaging to the patient's body. Stem cell transplants have been shown overall to be supportive measures of treatment and delay progression of neurodegenerative and neuromuscular diseases. Currently, mesenchymal stem cell treatments are the most widely explored as mesenchymal stem cells are relatively easy to harvest and transplant. With additional research done on optimal administration routes and microenvironmental factors that affect the efficacy of engraftment, other types of stem cells could also become viable options of treatment clinically. Yet, many difficulties must be overcome in research before stem cell therapies become safe and effective treatments. Risks associated with stem cell treatments include teratoma, tumorigenesis, and inflammation. Most significantly, transplanted stem cells incompatible with the host body could trigger immunorejection, causing grafts to fail. The review assessed levels of success achieved in research and evaluate clinical trials done on stem cell treatments of neurodegenerative disorders, neuromuscular diseases, hemorrhages, spinal cord injuries, as well as other supportive roles stem cells play in treatment.

Keywords: Cellular and molecular biology; Neurobiology; Stem cell therapy; Neurodegenerative diseases; Mesenchymal stem cells

1. Introduction

In recent years, stem cell therapy has become a new potential treatment for many previously uncurable diseases. Specifically, stem cell therapies have received significant successes in the treatment of leukemia and other types of cancers. Yet, one of the most promising potentials for stem cell therapies is in the field of neurological disorders, namely the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's disease, as well as other neurological pathologies such as spinal cord injury and multiple sclerosis. Despite many challenges in clinical studies due to poorly understood biological mechanisms of neurological disorders and stem cell differentiation post-transplant, a significant number of studies have shown that stem cell therapy is a non-invasive and moderately effective treatment of such diseases.

For patients suffering from neurological disorders, there is a wide range of stem-cell treatment options available, each harvested from a different source. Currently, the most common types of utilized stem cells are neural stem cells (NSCs), mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs). Each option has its respective advantages and disadvantages, with MSCs transplants

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being the most widely explored currently as they could be harvested and transplanted easily. However, other options could also be considered for their effectiveness and safety. Comparing current research that has been done on different types of stem cell therapies on neurological disorders could illuminate the optimal method of treatment for each type of illnesses, as well as demonstrating areas where more research is necessary. This research has pointed out the strong advantages of specific treatments, the risks associated with certain methods, as well as the ethical concerns generally connected with the field.

2. Discussion

2.1 MSCs Overview

Currently, a majority of stem cell research done on neurological disorders involves mesenchymal stem cells (MSCs). MSCs are able to differentiate into cartilages, bones, and other skeletal tissues. Compared to other stem cell treatments, MSCs possess a number of advantages: easily harvested from the bone marrow and the umbilical cord, no requirement for genetic matching, as well as low chance of immunorejection. Taken together, MSCs transplant became an optimal option for the treatment of multiple sclerosis, spinal cord injury, and stroke. Studies have shown that with patients who received MSCs transplant have shown improvement in motor rehabilitation. Compared to standard rehabilitation therapy, MSCs therapy has shown overall better improvement in neurological functions such as pinprick, light touch, and bladder function. MSCs' neuroprotective effects make them ideal candidates for multiple sclerosis treatment. Furthermore, MSCs treatments often come with non-severe side effects such as fever, headache, and numbness, with no serious side effects such as death or tumor observed.

A large number of MSC clinical trials and research have been conducted to treat neurodegenerative diseases due to MSCs' significant paracrine effects, stimulating the body's own cells into cell and tissue regeneration. Furthermore, MSCs' immunomodulation effects have been shown to regulate neuroinflammations triggered by dysfunctional neuroresponses. In clinical trials, MSCs have been shown to secrete growth factors such as endothelial growth factors which promote angiogenesis, restoring nutrients and oxygen to the damaged brain tissues (Rahbaran, 2022). MSCs have also been shown to secrete neuroprotective factors which promote hippocampal neurogenesis. MSCs secreted exosomes have been used in exosome treatments which can reduce the effect of aß deposition and increase neuronal memory cells in Alzheimer's Disease (AD) patients (Chen, 2021). These exosomes could breach the blood-brain barrier, increasing dopamine levels and decreasing apoptosis of dopaminergic neurons in Parkinson's Disease (PD) patients (Chen, 2020). MSC exosome treatments were also shown to be able to repress glial cell functions and restore neural dysfunction in ALS mouse models.

Co-administration of MSCs with other bioactive substances were also investigated to treat neurodegenerative diseases. Administration of MSCs with resveratrol, a Sirt1 activator, allowed MSCs to engraft in the hippocampus of the AD murine model, increasing learning memory and neurogenesis (Wang, 2018).

In patients suffering from neurodegenerative diseases, routes of MSCs administration seemed to significantly affect treatment results. Intraventricularly administered MSCs have been shown to secrete microRNA which reduces nuclear kappa B expression, decreasing production of inflammatory cytokines and down-regulating cell proliferation. MicroRNA have also been shown to induce astrocyte activation and promote synaptogenesis in AD rat models (Nakano, 2020). However, in a phase I clinical trial, intracranially administered MSCs did not slow pathological development or trigger adverse side-effects in patients within a period of three months.

In animal models, MSCs injections have been shown to secrete neuroprotective factors which promote hippocampal neurogenesis, protecting neuronal tissues from oxidative stress. However, this treatment was not observed to slow disease progression within a 24-month period, and the neuroprotective effects observed in animal models were not present (Kim, 2013).

Much research has also been done on the use of MSCs to treat neuromuscular diseases such as amyotrophic lateral sclerosis (ALS) and muscular dystrophy. MSCs' paracrine effects, ability to stimulate the bodies' own cells for regeneration, make them optimal candidates for stimulating regeneration of depleted muscle tissues and neurons in patients with neuromuscular diseases. In particular, co-injection of MSCs with other substances has been investigated

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to improve engraftment, or the migration of stem cells to the desired location and start regeneration, in animal and human models. Co-administration of MSCs with cytokine reception antagonists have been shown to be able to bypass certain undesirable microenvironmental factors (Greco SJ & Rameshwar, 2008). MSC treatments' efficacy are largely varied by microenvironmental factors, as inflammatory state of recipient muscle cells vary outcome. Studies have shown that intramuscular co- injection of MSCs with macrophages can increase engraftment. One study showed that MSCs transplantation successfully restored 5% to 50% of skeletal myofibers in dogs with Golden Retriever muscular dystrophy. However, this technique failed in human trials as intra-arterial infusion led to atrial fibrillation and thalamic stroke (Sampaolesi, 2006).

Overall, human clinical trials using MSCs have yielded limited results. In nine Duchenne Muscular Dystrophy patients who received umbilical cord-MSCs transplantation, pulmonary function improved in all nine patients, yet there was no significant limb muscle strength improvement. Implantation of Cardiosphere-Derived cells and Bone Marrow-Derived cells showed no significant improvement of motor activity in patients (Aminzadeh, 2018). Optimum dosage of MSCs implantation must be determined, as there were signs that repeated transplantation of autologous MSCs could slow ALS progression (Siwek, 2020).

MSC treatments have also been used as a tool to treat hemorrhages. Hemorrhages are particularly hard to treat as they involve primary damage and secondary damage. Primary damage is the mechanical damage caused by the bursting of the blood vessel, while secondary damage is caused by the release of toxic materials such as thrombin, erythrocyte lysate, and free radicals. In research, MSC secretome showed anti-inflammatory effect in subarachnoid hemorrhage rat models by polarization of the microglia to an anti-inflammatory phenotype, reducing pro-inflammatory cytokines in the parietal complex and the hippocampus (Park, 2012). Furthermore, Adipose Tissue MSCs can stably proliferate to lower risks of apoptosis in hemorrhage rat models and increase levels of vascular endothelial growth factors and neural function score.

Some research has been done using MSCs in the treatment of spinal cord injuries. Spinal cord injuries are dangerous conditions that could cause permanent paralysis in parts of the body. These injuries are particularly difficult to treat as injuries to the central nervous system cause chemical and immune system changes, hindering attempts at regeneration.

In one research, autologous MSCs harvested from the patient's bone marrow were directly transplanted to the patients' spinal cords and re-injected using lumbar tapping. In a six-month period, six out of ten patients showed improvement in motor power of their upper limbs. Three patients showed improvements in completion of daily activities and electrophysiology and decrease in injury cavities in MRI scans. These results illustrate that MSCs could promote neuro-regeneration, stabilizing pathological developments (Han, 2021).

2.2 NSCs Overview

NSCs are multipotent stem cells that have the ability to differentiate into neurons and glial cells. When treated with different growth factors such as Fibroblast GF Growth Factors, Epidermal Growth factors, or Glial-Derived Neutrophic Growth Factors, NSCs can differentiate into neuronal cells, astrocytes, or oligodendrocytes. In current studies, NSCs are most commonly used to treat multiple sclerosis and Parkinson's Disease. In theory, they are ideal sources to replenish depleted brain cells and tissues due to neurodegenerative diseases. Yet, NSCs are often hard to harvest as they are limited to the hippocampus and usually in contact with cerebrospinal fluid. As a result, most NSCs are harvested from the fetal brain, raising ethical concerns. Currently, research is being done using induced pluripotent stem cells (iPSCs) to generate neuronal progenitor cells, which might prove to be a viable way to harvest NSCs in the future.

Most research using NSCs involve Alzheimer's Disease. AD is characterized by the degeneration of dopaminergic and cholinergic neurons or motor neurons. As AD patients often exhibit different pathological developments, cell therapy must be specifically targeted to a specific group of patients. Early phases of AD development often involve the hippocampal circuitry, making it a target for NSCs transplantation. In AD mice transplanted with NSCs, a significant increase in trophic factors (NSC secretome) was shown to decrease the level of tau phosphorylation, a key pathological characteristic of AD.

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It is key to investigate the effects of microenvironmental conditions of the central nervous system on the efficacy of NSC treatments. Environmental conditions such as the blood-brain barrier may prevent maximum engraftment of NSCs transplantations. In some cases, transplanted NSCs form cell clusters which decreases their ability to travel to the desired sites. One possible improvement to bypass undesirable factors is the application of NSCs-extracellular vehicles, nanosized particles secreted by cells that can carry soluble molecules. Research has shown that sensorimotor control was improved after EVs carried NSCs to injury sites, reducing neuronal apoptosis.

Another route of treatment targets the neuro-signaling pathways of the central nervous system. Treatment of donor cells with compounds that allow axonal extension promoted axonal outgrowth which allows extensive integration into the CNS. In AD mice, NSCs overexpressing enzyme choline acetyltransferase improved physical performance of mice population as one of the causes of AD is the reduction in acetylcholine neurotransmitter levels (Park, 2013).

NSCs' paracrine effects have also been explored to ameliorate conditions and slow pathological development of neurodegenerative disease. NSCs transplantations have been shown to decrease neuroinflammation and promote neurogenesis, synaptogenesis, and the release of neuroprotective substances (Lilja, 2015).

In the human body, endogenous NSCs are usually silenced. However, they could be activated under pathological conditions, such as the release of thrombin, erythrocyte lysate, excitatory amino acid, free radicals, or other bioactive substances caused by intracerebral hemorrhage. Subsequently, the efficacy of NSCs treatments is largely affected by factors of the central nervous system.

In patients paralyzed by spinal cord injuries, attempts have been made to manipulate NSCs to regenerate depleted neurons and cell tissues, restoring senses to the body. NSCs treated with Glial Neutrophic Growth Factors (GDNF) have been shown to differentiate to a larger extent compared to unmodified NSCs in treating patients suffering from cervical spinal cord injury.[15] Furthermore, researchers found that NSCs transplantation can decrease inflammation caused by spinal cord injuries and reduce M1 macrophage activation, achieve immunomodulation, and increase neurological performance (Cizkova, 2007).

Many studies have been done on using NSCs to promote recovery from post-spinal cord injury. In particular, one clinical trial studied differentiation of NSI-566 neural stem cells post engraftment in the treatment of spinal cord injury.

In NSI-566 studies on rat and primate models, spinal grafting has been shown to significantly improve neurological function and promote extensive axonal routing (Curtis, 2018).In a similar human study, four patients with injuries in different parts of the spine were injected with NSI-566 cells intraspinally with an observation period of 553 days, evaluating their neurophysiology, imaging, and presence of antibodies post-injection. The data has seen no significant change in quality-of-life scores in all four patients. In all four patients, diffusion tensor imaging reflected stable appearance of the injury site and the surrounding sites with no signs of decay or improvement (Cheng, 2016).

In conclusion, it is critical to understand and improve the translation between animal and human studies, increasing efficacy of certain treatments and reducing possible risks associated with other treatments (Balez, 2016).

2.3 IPSCs Overview

Induced pluripotent stem cells are relatively new in discovery. They are derived from adult somatic cells and reprogrammed back to an embryonic pluripotent state. Currently, much debate exists over the "stemness" and iPSCs, evaluating their degree of differentiation when entering the human body. Yet, one significant advantage of using iPSCs is that they do not involve the moral issues of using embryonic stem cells as they do not physically harm any human embryos.

IPSCs are ideal sources for disease modeling as they can be used to stimulate brain tissues which are hard to acquire. Neurons, oligodendrocytes, and astrocytes can all be differentiated from iPSCs. Typically, neurodegenerative diseases develop at old age, requiring elderly animal models. Yet, it is impractical and expensive to wait years for these models. One study has been able to derive iPSCs from individuals with Hutchinson-Gilford Progeria Syndrome, which possess a truncated product of the LMNA gene, triggering faster aging. These iPSCs are optimal for usage in AD or HD pathological studies.

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Studies have shown that iPSCs are able to reset the epigenome, resetting some factors to a juvenile state, reversing the aging effect of neurodegenerative pathologies. Yet, one challenge of using iPSCs to regenerate neurons in AD patients is that these newly generated neurons often exhibit the same phenotypic neuropathology such as abnormal aß levels and elevated tau phosphorylation (Krencik, 2011).

2.4 IPSCs derived Astrocytes

As the most abundant glial cell type in the central nervous system, astrocytes provide important neural support such as synaptogenesis, synaptic plasticity, metabolic support to neurons, as well as myelination of white matter. Astrocytes often exhibit different reactive phenotypes in response to various stimulus. A1 astrocytes are induced by injuries, secreting toxic molecules and leading to neurodegenerative diseases. A2 astrocytes are induced by ischemia, releasing neuroprotective cytokines, modulating neuroinflammation, and inhibiting cell apoptosis. In AD patients, astrocytes exhibited increased aß production, altered cytokine release, and dysfunctional CA2+ homeostasis.

In current studies, iPSCs have been used to differentiate into neuroepithelial cells, eventually induced into NSCs. In turn, long-time expansion of NSCs via growth factors and terminal differentiation of maturation are key steps of conversion into astrocytes (Liu, 2013). These efforts may allow extensive astrocyte studies and efficient astrocyte transplantations in neuro-deficient patients.

2.5 ESCs Overview

Embryonic stem cells are stem cells harvested from the human blastocysts with high pluripotency. Currently, a limited number of clinical trials utilized embryonic stem cells due to their risks of uncontrolled differentiation, possibly leading to tumorigenesis. Furthermore, using ESCs for treatment involves ethical concerns of destroying human embryos. What limited studies on ESCs there were yielded some result. One study showed that under certain conditions, ESCs can differentiate into ganglionic eminence-like progenitor cells, which can develop into GABAergic and cholinergic cells which can be adapted into endogenous neuronal circuits, restoring abilities of spatial memory and learning (Duncan, 2017).

3 General Comparison

MSCs, as the most widely experimented and easiest to harvest type of treatment, is significantly more reliable and efficient compared to other treatments in the treatment of neurodegenerative diseases, spinal cord injuries, and hemorrhages. NSCs have the advantage of being native to the nervous system, and under the right conditions, they could be accurately guided to achieve the desired effects of regeneration. In cases of paralysis, NSC transplantations have been shown to be effective at decreasing inflammation and promoting regrowth. With additional studies on animal models and patients, the range of application of NSCs could be widened. Yet, NSCs difficulty to acquire is a significant disadvantage. As a relatively new technology, iPSCs development is still in nascent stages, especially in the field of neurological disorders. However, it has already been shown to be an effective supportive measure that triggers multiple beneficial neurological pathways. Its accessibility and manageability excel beyond other treatments. There are relatively few treatments that involves ESC due to its ethical concerns and difficulty to harvest.

4 Ethical Considerations

Evidently, although stem cell therapies prove to be potential treatments of a variety of diseases in the future, currently, ethical concerns remain to be a significant obstacle to overcome. Firstly, many believe that using stem-cell therapy is playing-God, as the basic cell-line construction of the human body is altered. More significant ethical considerations perhaps include the creation and destruction of Embryos in the process of ESCs research. Much research involves the usage of stem cells derived from human embryos, and this process has been prohibited in many countries. In countries such as the United States, restrictions have been placed on such research as many argue,

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"deriving stem cells destroys the blastocyst, an unimplanted embryo at the sixth to eighth day of development" (Harvard Stem Cell Institute, 2021). Other concerns include payment to oocyte donors and the privacy concerns of the donors. As a result, many researchers instead create embryos for ESCs research purposes (Lo, 3009). Such research is again criticized for playing God and disrupting the natural harmony. The manipulation of all types of stem cells involve the question of informed consent in clinical trials, as the patients have to be informed of the potential risks and ethical concerns of their treatments. Ethical and legal guidelines need to be established regarding the trial of stem cells treatments and the methods of harvest.

5 Conclusion

Overall, stem cell therapies appear to be a viable option of treatment for many neurological diseases and illnesses. In particular, MSCs and NSCs transplants were shown to be promising methods of treatment for neurodegenerative diseases, neuromuscular diseases, hemorrhages, and spinal cord injuries. MSCs and NSCs have proven to be the most effective methods of treatment, and future research should focus on improving the efficacy of such treatments. Clinical studies of iPSCs and ESCs remain limited as these types of stem cells typically play supporting roles in treatment, promoting neurogenesis and revitalization of the neural network. The exact association between stem cell transplants and regeneration of neurological pathways should be studied in more details. Aside from the prospects, certain risks of stem cell therapies must be assessed before clinical trials. NSCs' cell identities must be assessed to avoid cell line switching and uncontrolled differentiation. Furthermore, karyotype analysis of pre-transplant stem cells can be performed to avoid chromosomal rearrangements and tumorigenesis. Ethical concerns should also be taken into consideration, as research should be carried out in accordance with government guidelines and with moral and ethics in mind. In conclusion, stem cell therapies are treatments with significant potential if risks and ethical concerns could be overcome.

5.1 Future Prospects

In future research, risks of stem cell therapies should be assessed, evaluating the invasiveness of transplant surgical procedures. Translation between animal studies and human trials should be studied, as many treatment methods that have been shown to be effective in animals fail to show therapeutic effects when trialed in humans. Furthermore, research on microenvironmental factors should be done to increase efficiency of treatments by increasing engraftment and allowing transplanted stem cells to travel to the desired area. In addition, to maximize engraftment and dosage of cells delivered to target areas, optimal administration routes should be determined, a route that bypasses undesirable microenvironmental conditions.

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