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Article Review

Regenerative Potential of Stem Cell Therapy in Mitigating Brain Cell Atrophy and Enhancing Neuroprotection in Neurodegenerative Diseases

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ABSTRACT

Stem cell therapy has shown great potential in regenerating neurons in the brain, offering hope for the treatment of neurodegenerative diseases characterized by progressive neuronal atrophy. These therapies target key mechanisms of neuronal loss, including protein aggregation, oxidative stress, and inflammation, while promoting neuroprotection through neurogenesis and angiogenesis. The development of induced pluripotent stem cells (iPSCs) has addressed challenges related to immune rejection and ethical concerns associated with the use of embryonic stem cells. Despite advancements, challenges such as immune responses, tumorigenesis risks, and efficient delivery methods remain. Future research should focus on optimizing cell sources, improving targeted delivery systems, and exploring combination therapies to enhance treatment efficacy and safety. With successful integration, stem cell therapy has the potential to revolutionize the management of neurodegenerative diseases, ultimately improving patient outcomes and quality of life.

INTRODUCTION

Neural Stem Cell (NCS) therapy requires the implantation of neural stem cells into the diseased brains as a treatment for neurodegenerative diseases. NSCs can proliferate, differentiate, and renew themselves, thus qualifying them as versatile elements to be used in repairing and regenerating damaged neural tissues. The therapy thus works by replacing the damaged neurons to form complete circuits and secreting neurotrophic factors to support neuron survival and synaptic plasticity.(4) NSC therapy, in general, can have great prospects for conditions such as an ischemic stroke, Alzheimer's disease, and Parkinson's disease. It limits the loss of brain tissues, improves cognitive functions, and develops motor abilities. There are several sources of NSCs, which have been implicated in the process of transplantation, including primary tissue isolation, induced pluripotent stem cells, embryonic stem cells, and somatic cell based trans differentiation.(4)

Recent interest has been concerned with the treatment of neurodegenerative diseases by stem cell therapy. These are progressive disorders in which the functions of neuron and glial cells are lost(5). Presently, there are no effective treatments for these conditions: AD, PD, ALS, HD, and MS. The ability of stem cells to develop into neuron and various other kinds of glial cells allows them to offer new avenues for treatment.(6) Stem cells, whether embryonic or adult, have received

considerable attention since researchers continue to unlock their potential in the repair or replacement of damaged brain tissues that seems nearly impossible at one time: neuron regeneration.(7) Neuroregenerative medicine, based on the organism's repair resources, is a forerunner among these innovative approaches to treatment. Additionally, combining the latest achievements of stem cell therapy with nanomedicine and gene therapy helps to expand the possibilities in the context of complex neurological disorders management; however, some questions do arise as to the best possible sources of stem cells and their effectiveness in therapy, as well as some ethics issues, particularly in cases when embryonic or foetal tissues are used.(8,9) Future research may have much in store in the way of hope, given that stem cell therapies may prevent neurodegeneration and may help improve prospects for millions of affected people around the world.(10)

Alzheimer's disease (AD) is a relentless neurodegenerative condition, characterized by the death of neurons and synapses that give rise to cognitive decline and loss of memory(11,12). The characteristic pathological features of AD include Aβ plaques and neurofibrillary tangles mainly composed of hyperphosphorylated tau protein. Aβ plaques disrupt synaptic signalling, cause oxidative stress, and trigger neuroinflammation, leading to further neuronal damage. Tau tangles destabilize microtubules, affecting the transport of nutrients and signals in neurons. (12)Activated microglia that accumulate contribute to chronic inflammation, exacerbating damage to neurons. The primary mechanisms through which Aβ oligomers induce synaptic dysfunction are disruption of synaptic plasticity resulting in progressive loss of memory due to breakdowns in neural circuits.

Emerging neurotherapeutic approaches might be offered with hope as the volume of literature for stem cell therapies and regenerative medicine intended for neurodegenerative diseases is increasing.(11) Such is the case with the great potential offered by MSCs to slow disease progression in ALS and HD. The recalibration of therapeutic responses in MS has also been brought about by the HSCs. Current advances on the horizon in regenerative medicine combine stem cell technology, tissue engineering, and gene therapy to provide a multifaceted approach in the treatment of such complex diseases.(11)

RESEARCH METHODS

This review was conducted by collecting and analyzing the latest literature on the use of neuronal stem cell therapy in the treatment of neurodegenerative diseases, such as Alzheimer's, Parkinson's, and ALS. Sources of information include clinical and preclinical research, studies on the mechanisms of brain damage in neurodegenerative diseases, and the development of delivery techniques and combination therapies. The research also explores the main challenges faced in the implementation of this therapy, including biological and ethical risks, as well as efforts to improve the effectiveness and safety of treatment.

RESULTS AND DISCUSSION

Overview of Stem Cell Therapy

Even when considering the application of this stem cell therapy, as reviewed from many studies, it points to the ability not only to treat but even reverse the course of neurodegenerative disorders. Most promising is the preclinical and clinical work on stem cell based interventions in diseases like Alzheimer's disease (AD), Parkinson's disease (PD), and ALS(8,13). Also, combined strategies that encompass stem cell therapy with emerging nanotherapeutic strategies have been increasingly gained attention because treatment efficacy becomes improved through better cellular delivery systems and specific pathway intervention in neurodegeneration(9,14).

Nanomedicine in combination with cell therapies opens new avenues for treating neurodegenerative diseases with improved targeted delivery and with minimal side effects. The review discussed the critical advances in combined strategies applied to AD, PD, and ALS thus pointing out that crossing point between nanotechnology and stem cell therapy will remain one of the pivotal factors in the development of innovative and effective treatments(9).

There are also specific advantages of using NSCs in the treatment of brain diseases since they are capable of differentiating into both neurons and glial cells, meaning this enables them to have a regenerative capacity that is very valuable in neurodegenerative conditions. However, major limitations are still in place with NSC transplantation those concerning survival, integration, and long term functionality. The research is still continued over those limitations in order to maximize future treatments' effectiveness(15,16).

Mechanisms of Brain Cell Atrophy in Neurodegenerative Diseases

Degenerative disease of the neurons leads to cerebral atrophy due to molecular and cellular dysfunctions that progressively damage neurons and their structures. Failure of proteins to maintain native structure: In most of these diseases, there is failure of proteins to keep their native structure. For example, they form amyloid beta aggregates in Alzheimer disease or alpha synuclein aggregates in Parkinson disease(10). Such proteins start accumulating in the neuron and, in due course, go on to form toxic aggregates. Protein accumulation deranges the normal homeostasis of cells, leading to synaptic failure and cell death. Accumulation is central to pathologies in many neurodegenerative diseases: their direct contributions to neuronal loss and brain shrinkage(17).

Critical also is neuroinflammation. In diseases such as Alzheimer's, the aggregated protein plaques elicit a chronic inflammatory response from microglia, part of the immune cells in the brain. Activated microglia induce the release of proinflammatory cytokines that propagate neuronal damage. Though inflammation is the body's first defence (12)mechanism at these sites of damage, chronic neuroinflammation creates a harmful environment that progresses more rapidly with neuronal death and brain atrophy(12).

This damage is further contributed by oxidative stress due to the susceptibility of neurons exposed to high levels of ROS, causing oxidative damage to critical cellular constituents, DNA, proteins, and lipids. It impairs function and survival, adding to the neuronal loss(11,12). In concert with this damage, impairment of mitochondrial functions leads to a deficit in energy supply within the neurons. Inadequate supply is highly vulnerable to highly energy dependent neurons, with dysfunctional mitochondria causing an acceleration of cell death. As such, it becomes a major determinant of brain atrophy(18).

Synaptic Dysfunction is considered an early indicator of neurodegeneration. A failure in synaptic integrity leads to the failure of communication between neurons and weakening the neural circuitry of the brain. As long as synapses stop functioning between neurons, cognitive and motor functions start losing their strength, eventually leading to the overall loss of neurons(11).

Furthermore, impaired neurogenesis partial inability of the brain to regenerate its neurons worsens it. In a normal brain, there is constant replacement of neurons by the neural stem cells at structures such as the hippocampus; however, this process is reduced in neurodegenerative diseases due to events like inflammation and reduction of growth factors. Without it, the brain deprives its ability of self regeneration by replacing dead neurons with new ones and, therefore, loses the possibility of gradually maintaining its structure and function, thereby increasing the process of brain atrophy together with functional degeneration(5).

Mechanisms of Brain Cell Atrophy in Neurodegenerative Diseases:

Brain cell atrophy in neurodegenerative diseases is mediated by a multitude of intricate mechanisms, which are basically neuroinflammation, oxidative stress, and synaptic dysfunction. These mechanisms lead to progressive neuronal loss, eventually causing cognitive and motor dysfunctions, which are prominent in diseases such as AD, PD, and ALS.

1. Neuroinflammation

Mechanism: Neuroinflammation is one of the hallmarks of neurodegenerative diseases, in which activated microglia and astrocytes release proinflammatory cytokines, causing chronic inflammation and neuronal damage. For example, in AD, the presence of amyloid beta plaques triggers persistent activation of microglia that further release inflammatory molecules damaging surrounding neurons.

Target via stem cell therapy: Inflammation reducing drugs, specifically through the use of stem cells, is derived; first and foremost, mesenchymal stem cells produce their respective cytokines and growth factors, which restores balance for inflammation(19,20).

MSCs mitigate oxidative inflammatory effects in regulating cytokines and growth factors; the other cells of the brain induce switching from proinflammatory to turn more anti-inflammatory; significantly plays a part in inhibiting long-term neuroinflammation

2. Oxidative Stress

Mechanism: Oxidative stress has been considered to lack balance between the enhanced formation of reactive oxygen species with the brain's capacity to eliminate oxidative damage. The form of damage caused by oxidation is denaturation proteins, lipids, and DNA. It has also been noted that oxidative stress plays a role in the pathogenesis of PD because of dopaminergic neuronal degeneration the main neuronal type involved in motor activities.

Stem Cell Target: Stem cells, particularly NSCs and iPSCs, are capable of providing protection against oxidative stress by releasing neuroprotective factors that include BDNF and GDNF. The latter is known to ensure neuronal survival and protect the neurons from ROS dependent damage. The transplanted cells can also provide antioxidant enzymes that can balance the redox status of the targeted brain regions(2).

3. Synaptic Dysfunction

Mechanism: Disrupted synaptic function is one of the earliest features in neurodegenerative diseases leading to neuronal communication and the resultant cognitive decline. Synaptic plasticity in Alzheimer's disease is affected when tau and amyloidbeta build up, which results in memory and learning deficits in patients. In ALS, synaptic degeneration of the motor neurons contributes to a decrease in muscle strength leading to paralysis.

Stem Cell Target: Stem cells will replace dead neurons and also help to maintain the health of the remaining synapses, restoring synaptic function. For instance, NSCs can integrate into brain circuits that are impaired. This will improve synaptic plasticity and rebuild lost synaptic connections. In PD, the transplantation of dopaminergic neurons that are derived from iPSCs holds promise in reestablishing motor function through the restoration of synaptic connection between basal ganglia neurons that is lost(2,20).

Challenges and Limitations of Stem Cell Therapy

Stem cell therapy encounters various significant challenges and limitations: the first being immune rejection, an issue more related to stem cells other than those of the patient, especially those obtained from other sources like embryonic stem cells. Researchers have taken to using induced pluripotent stem cells generated from the patient's own cells, which means that an immune response risk may well be bypassed. This does not only lessen the risk of rejection but also negate any ethical dilemma associated with the use of embryonic stem cells, since iPSCs avoid destroying embryos(11,12). However, ethical concerns over the use of genetic manipulation as well as longterm use of iPSCs cannot be ignored and must be considered seriously.

A second and perhaps more important concern has to do with delivery and engraftment. Effective therapy will require stem cells to be targeted to specific regions of the brain. Currently utilized methods of delivering stem cells can be invasive and may also inadvertently destroy host tissues surrounding the delivery site. Once implanted, these cells present significant challenges in terms of longterm survival and integration into the existing neural network. Cells that are not integrated would therefore have minimal effects as a therapeutic treatment. Greater progress in noninvasive delivery modes and greater understanding of the microenvironment of the brain will enhance the efficacy of stem cell therapy.(12)

Finally, there is the potential for tumorigenesis with therapies using stem cells. Stems, especially pluripotent, can multiply infinitely. This can be a very useful feature for regeneration but, of course, becomes a concern for uncontrolled proliferation or growth that could lead to tumour formation. Due to this risk of tumorigenesis, the growth and differentiation of stem cells should be closely monitored, and their behaviour strictly controlled in such a way that they cannot revert into the undifferentiated state. Scientists are already studying some methods to surmount these potential complications, such as several ways to steer differentiation and constrain proliferation of the transplanted cells. All these may come to a head in being the ultimate breakthrough for the potential application of stem cell therapy in the clinical setting, particularly for neurodegenerative diseases.(12)

Future Directions and Research Opportunities:

The future of stem cell therapy in dealing with neurodegenerative disease is rife with the promise of such directions and promising research towards attaining higher efficacy and accessibility. Optimizing cell sources and delivery modes stands out as an central area here; sortof research has been carrying on to identify what sourcesWhether it is from adult or fetal tissue, IPSCs, or any other sourceare the best for a most feasible therapeutic outcome at less risk(5,11). Delivery methods are of comparable importance. Improved techniques, including targeted delivery systems and minimally invasive delivery routes, are under investigation to enhance the specificity and safety of stem cell treatments. These improvements might create a way for much more effective therapies that target areas of damage in the brain but minimize some of the potential complications of traditional delivery routes(12).

Another really promising strategy is the evaluation of combinations of treatments, joining stem cells with pharmacological or other regenerative therapies. This strategy suggests integrating the benefits from each single treatment, possibly leading to synergistic effects that favor better overall treatment outcomes. For instance, combining stem cell therapy with neuroprotective drugs or antiinflammatory agents could create a more favorable survival and integration environment for the implanted cells. More exciting will be delivering therapeutic agents using stem cells directly into the damaged areas of the brain, so that the efficacy can be targeted at site(18).

Last but not least, the path to clinical application entails rigorous clinical trials and regulatory approvals. Many studies are currently being performed to evaluate the safety and efficacy of various stem cell therapies in humans, which is an essential step for having a strong evidence base before their eventual use in clinical practice. In the course of these trials, such insights will therefore not only hone treatment algorithms but also inform regulatory frameworks governing stem cell applications. Regulatory agencies are increasingly keenly aware that such regulatory frameworks should allow for clear guidelines that will facilitate innovative developments in and approvals for new stem cell therapies while ensuring patient safety(13). Through this interplay between research advance and regulatory processes, stem cell therapy will be made available and standard for the treatment of neurodegenerative diseases. Thus patients with such diseases and their families will have new hope(14).

Table 1. Outcomes of Stem Cell Therapy in Preclinical and Clinical Studies

Stem Cell Type	Disease Model	Outcome	Key Findings	References
iPSCs	Alzheimer's Disease (preclinical)	Improved cognitive function, reduced amyloid plaques	Enhanced neurogenesis, reduced neuroinflammation	(CecerskaHeryć et al., 2023a)
NSCs	Parkinson's Disease (preclinical)	Increased dopamine production, improved motor functions	Supported neuron survival, neurotrophic secretion	(19)
MSCs	ALS (clinical trial)	Slowed disease progression, improved motor function	Immune modulation, reduced oxidative stress	(CecerskaHeryć et al., 2023a)
ESCs	Huntington's Disease (preclinical)	Delayed onset of symptoms, improved neuronal health	Replaced damaged neurons, reduced inflammation	(20)

CONCLUSION

Stem cell therapy is being hailed as one of the promising transformative approaches to curing neurodegenerative diseases because it could replace the lost mechanisms behind atrophy and promote regeneration. While considerable advances have been made towards understanding the therapeutic benefit of stem cells, immune rejection, delivery issues, and risks of tumorigenesis form significant hurdles that have to be systematically addressed to maximize their efficacy and safety(14). Future research directions include optimization of cell sources and delivery methods, use of combination therapies that augment the overall treatment effect, and advancing clinical trials to provide robust evidence for regulatory approval. The continued development of this field will allow successful integration into clinical practice, revolutionizing management of neurodegenerative diseases and bringing new hope to patients for better outcomes and quality of life. At the end of the day, it is going to take a concerted team effort from research scientists, clinicians, and regulatory authorities to tackle all of these complex issues and achieve all that this means for regenerative medicine.

REFERENCES

1. Yang L, Liu SC, Liu YY, Zhu FQ, Xiong MJ, Hu DX, et al. Therapeutic role of neural stem cells in neurological diseases. Vol. 12, Frontiers in Bioengineering and Biotechnology. Frontiers Media SA; 2024.
2. Limone F, Klim JR, Mordes DA. Pluripotent stem cell strategies for rebuilding the human brain. Vol. 14, Frontiers in Aging Neuroscience. Frontiers Media S.A.; 2022.
3. Cecerska-Heryć E, Pękała M, Serwin N, Gliźniewicz M, Grygorcewicz B, Michalczyk A, et al. The Use of Stem Cells as a Potential Treatment Method for Selected Neurodegenerative Diseases: Review. Vol. 43, Cellular and Molecular Neurobiology. Springer; 2023. p. 2643–73.
4. Chen W. Neural Stem Cells Therapy to Treat Neurodegenerative Diseases. In: E3S Web of Conferences. EDP Sciences; 2021.
5. Schoonheim MM, Strijbis EMM. Repair what is lost: Neuroprotection through neural stem cells in progressive MS. Vol. 4, Cell Reports Medicine. Cell Press; 2023.
6. Nguyen H, Zarriello S, Coats A, Nelson C, Kingsbury C, Gorsky A, et al. Stem cell therapy for neurological disorders: A focus on aging. Vol. 126, Neurobiology of Disease. Academic Press Inc.; 2019. p. 85–104.
7. Vassal M, Martins F, Monteiro B, Tambaro S, Martinez-Murillo R, Rebelo S. Emerging Pro-neurogenic Therapeutic Strategies for Neurodegenerative Diseases: A Review of Pre-clinical and Clinical Research. Molecular Neurobiology. Springer; 2024.
8. Cecerska-Heryć E, Pękała M, Serwin N, Gliźniewicz M, Grygorcewicz B, Michalczyk A, et al. The Use of Stem Cells as a Potential Treatment Method for Selected Neurodegenerative Diseases: Review. Vol. 43, Cellular and Molecular Neurobiology. Springer; 2023. p. 2643–73.
9. Tai YT, Svendsen CN. Stem cells as a potential treatment of neurological disorders. Vol. 4, Current Opinion in Pharmacology. Elsevier BV; 2004. p. 98–104.
10. Yang L, Liu SC, Liu YY, Zhu FQ, Xiong MJ, Hu DX, et al. Therapeutic role of neural stem cells in neurological diseases. Vol. 12, Frontiers in Bioengineering and Biotechnology. Frontiers Media SA; 2024.
11. Su R. Mesenchymal Stem Cell Exosomes as Nanotherapeutic Agents for Neurodegenerative Diseases. Vol. 2022, Highlights in Science, Engineering and Technology FBB. 2022.
12. Wu YP, Chen WS, Teng C, Zhang N. Stem cells for the treatment of neurodegenerative diseases. Molecules. 2010 Oct;15(10):6743–58.
13. Park HJ, Lee PH, Bang OY, Lee G, Ahn YH. Mesenchymal stem cells therapy exerts neuroprotection in a progressive animal model of Parkinson's disease. J Neurochem. 2008 Oct;107(1):141–51.
14. Qin C, Wang K, Zhang L, Bai L. Stem cell therapy for Alzheimer's disease: An overview of experimental models and reality. Vol. 5, Animal Models and Experimental Medicine. John Wiley and Sons Inc; 2022. p. 15–26.
15. Li M, Chen H, Zhu M. Mesenchymal stem cells for regenerative medicine in central nervous system. Vol. 16, Frontiers in Neuroscience. Frontiers Media S.A.; 2022.
16. Hachimi-Idrissi S. Stem cell therapy in neurological disorders: promises and concerns. Exploration of Neuroprotective Therapy. 2023 Oct 31;346–62.
17. Hussain Y, Agarwal P. Efficacy and Potential of Stem Cell Therapy for Alzheimer's Disease [Internet]. Available from: www.JSR.org

18. Isaković J, Šerer K, Barišić B, Mitrečić D. Mesenchymal stem cell therapy for neurological disorders: The light or the dark side of the force? Vol. 11, Frontiers in Bioengineering and Biotechnology. Frontiers Media S.A.; 2023.
19. Su R. Mesenchymal Stem Cell Exosomes as Nanotherapeutic Agents for Neurodegenerative Diseases. Vol. 2022, Highlights in Science, Engineering and Technology FBB. 2022.
20. Chen W. Neural Stem Cells Therapy to Treat Neurodegenerative Diseases. In: E3S Web of Conferences. EDP Sciences; 2021