REVIEW ARTICLE

Evaluating the Therapeutic Effects of Mesenchymal Stem Cell Therapy in Huntington's Rodent Models

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Abstract

Huntington's disease is a fatal neurodegenerative disorder caused by CAG repeat expansion in the HTT gene, leading to progressive motor impairment, cognitive decline, and neuronal loss in the striatum and cortex. Current treatments are limited to symptom management, requiring the need for disease-modifying regenerative therapies. This review examines whether mesenchymal stem cell (MSC) therapy represents a promising therapeutic strategy for Huntington's disease. Evidence from preclinical rodent studies consistently demonstrates that MSC transplantation improves motor coordination, preserves striatal volume, and enhances neuronal survival. These effects are largely attributed to the secretion of neurotrophic factors, reduction of neuroinflammation, and support of tissue repair. MSCs are particularly attractive for regenerative medicine because they possess immunomodulatory properties and can release a wide range of protective signaling molecules that promote neuronal survival and reduce inflammatory damage. In several experimental models of Huntington's disease, transplanted MSCs have been shown to migrate toward injured brain regions and release trophic factors that help stabilize neuronal networks and slow neurodegeneration. However, therapeutic outcomes vary depending on factors such as the disease model used, the stage of disease at the time of treatment, and the route of cell administration. These variables influence the survival, integration, and functional impact of transplanted cells. Overall, these findings highlight MSC therapy as a promising approach to slowing neurodegeneration in Huntington's disease and support further optimization and translation of MSC-based therapies for Huntington's disease and other neurodegenerative disorders.

Keywords

Biomedical and Health Sciences, Neuroscience, Huntington's Disease, Mesenchymal Stem Cells, Huntington's Rodent Models

Introduction

Huntington's disease is a fatal hereditary neurodegenerative disease characterized by progressive motor loss and involuntary movements, memory loss, cognitive decline, and psychological issues.[1] Huntington's disease is an inherited disease that causes neurons to break down, leading to their death.[1] The CAG expansion in the Huntingtin gene leads to the production of a toxic protein, known as mHTT, that damages nerve cells in the brain, specifically the striatum and cortex.[1] Along with physical decline, mental deterioration, and changes in eating habits are found in HD patients.[2] Currently, there is no cure available, and treatments focus on relieving symptoms, instead of treating the cause. However, there is a growing interest in the use of mesenchymal stem cells for a potential treatment for this fatal disease.

Mesenchymal stem cells are known for their ability to promote tissue repair, secrete immunomodulatory cytokines, and various neurotropic factors.[4] MSCs are relatively accessible and are found in various adult tissues, such as dental pulp and bone marrow.[3] Additionally, there are no ethical concerns associated with the use of MSCs.[3] Preclinical studies using rodent HD models demonstrated an increase in muscular

strength, neuromuscular electromyography activity, cortex-related and striatum-related motor function, although there was a poor graft survival rate.[4] Human mesenchymal stem cells genetically engineered to overexpress brain-derived neurotrophic factor (BDNF) have been shown to enhance neuroprotection, improve motor function, and slow disease progression in Huntington's disease mouse models, highlighting the therapeutic potential of MSC-based gene-enhanced approaches.[4]

This research paper aims to explore the potential therapeutic effects of MSC therapy in HD rodent models. In order to evaluate the potential therapeutic benefits and limitations, this paper analyzes various studies that focus on previously experimented with MSC use in HD models and outcomes.

MSC therapy represents an emerging area of interest in treatment for Huntington's disease research. Along with this growing interest, there is an increase in preclinical studies and trials in HD rodent models. Different variations of preclinical studies exist, and administration routes, objectives, dosages, and cell sources vary across studies. As HD continues to lack a definitive cure and MSCs show potential in treating this disease, this calls for a literature review describing previously conducted research. This study explores previously conducted research. The reason behind this research paper is deeply personal, with the author having a growing passion for neuroscience and stem cell treatments.

Methodology

The purpose of this study is to evaluate the therapeutic effects of MSC therapy in HD rodent models. This paper is a comprehensive literature review of previously conducted research. Peer-reviewed articles and online credible resources such as PubMed, National Institute of Neurological Disorders and Stroke, and Mayo Clinic.

A systematic literature search was conducted using search words including mesenchymal stem cells, rodent models, Huntington's disease, stem cell therapy, and neurotrophic factors. The author selected studies that examined mesenchymal stem cells derived from multiple sources and involved bioengineering the stem cell variants. Inclusion criteria were peer-reviewed studies involving MSC therapy in HD rodent models, original research conducted between 2010 and 2025, and studies including standard lab rodents. The use of standard rodent models supported consistency and comparability throughout the paper. The author relied entirely on online and published sources, and no physical tools, experiments, or lab materials were involved. The reviewed literature posits that MSC therapy in HD has therapeutic potential, although it is still in its early clinical stages.

Review of Related Literature

Pathophysiology of Huntington's and MSCs

Huntington's disease is a progressive, inherited neurodegenerative disease that most commonly affects individuals of European descent.[5] Mutation of the HTT gene, which normally contains 10-36 CAG repeats, causes people to have 36-120 CAG repeats (as shown in Figure 1).[6] The Huntington gene is comprised of cytosine, guanine, and thymine, three of the four bases that make up the DNA. The HTT gene is located on the non-sex chromosome 4, although the literature is still limited regarding the function of the HTT gene.[7] The expanded CAG gene found in Huntington's patients causes neurons to break down, specifically in the striatum and cerebral cortex.[8] The striatum and cerebral cortex serve important roles in controlling movement, cognition, emotions, and coordination.[9] Neurons in these places are particularly affected by the mutation in the HTT gene.[10] Symptoms of Huntington's disease include memory problems, mood swings, twitching and movement problems, lower cognitive function, and clumsiness.[11] These symptoms typically emerge within an individual's thirties to forties; while an earlier onset is classified as juvenile Huntington's Disease.[12]

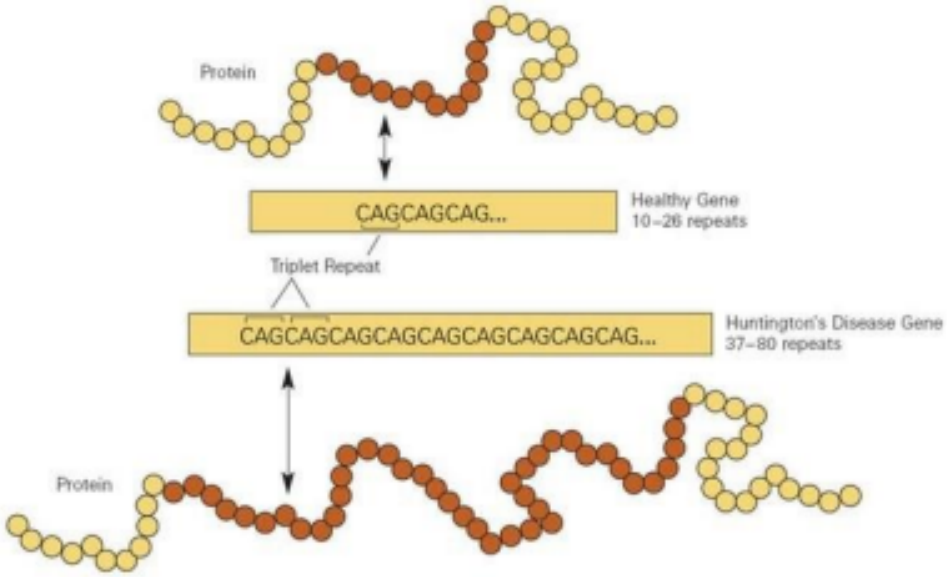

Figure 1. *Huntington's disease (Elliott, 2010). Diagram of the mHTT mutation, causing CAG repeats in Huntington's Disease. Note. Reprinted under a Creative Commons Attribution-ShareAlike 2.0 Generic license from Wikimedia Commons.* https://commons.wikimedia.org/wiki/File:Huntington%27s_disease_(5880985560).jpg

Mesenchymal stem cells are adult stem cells, often found in adipose tissues and bone marrow. These stem cells are multipotent and are capable of differentiating into cells of multiple lineages.[4] Unlike embryonic stem cells, mesenchymal stem cells are not associated with any significant ethical concerns. Additionally, MSCs make and repair skeletal tissues such as cartilage, bone, and fat found in bone marrow.[13] As shown in Figure 2, MSCs can differentiate into various types of cells. In Huntington's disease, MSCs can replace neurons.

While numerous studies have reported that mesenchymal stem cells possess tumorigenic potential, other investigations suggest that MSCs may instead contribute to tumor progression by enhancing growth and metastasis (as shown in Table 1).

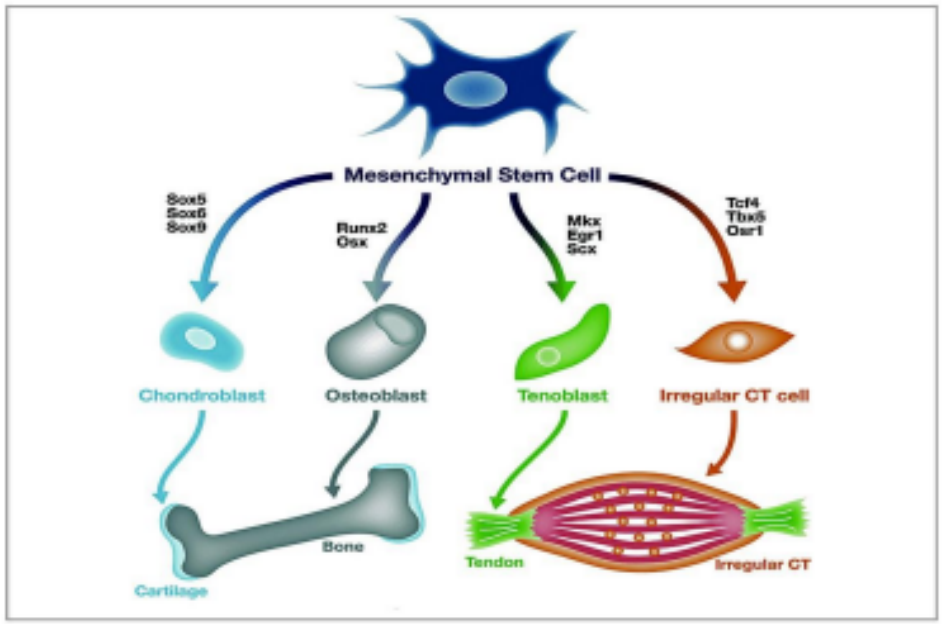

Figure 2. *From mesenchymal stem cells to specific connective tissue cell types. Diagram illustrating the differentiation of mesenchymal stem cells into various connective tissue cell types. Note. Reprinted under a Creative Commons Attribution-ShareAlike 4.0 International license from Wikimedia Commons.*

Table 1*. Advantages and Disadvantages of MSCs*

Author/Researcher	Advantages of using MSCs	Disadvantages of using MSCs
Wysoka	Enhanced apoptotic resistance[14]	Risk associated with tumorigenesis[14]
	Many traits are not thoroughly investigated[14]	Genetic instability and chromosomal aberrations[14]
Baranovskii	Numerous clinical studies have shown a wide clinical potential of MSCs[15]	Thromboembolism and fibrosis are associated risks[15]
	Secretion of growth factors and cytokines suppresses inflammation and improves vascularization and tissue healing[15]	May be affected by viruses[15]
Zhou	MSCs express low levels of MHC class I and little to no MHC class II, which means they are less likely to be rejected[16]	Inconsistent characteristics of MSCs, such as immunocompatibility, stability, heterogeneity, differentiation, and migratory capacity[16]
Gopalarethinam	Lack of demanding cell culture conditions and proven to be effective transducers of cDNA for certain proteins whose expression is sought in a patient, as well as viral vectors harboring therapeutic genes[17]	Maldifferentiation, immunosuppression and cancerous tumor growth[17]
Afkhami	Can limit tumor growth and produce significant antitumorigenic properties via blocking AKT signaling[18]	Risk of enhancing drug resistance[18]

Kim	Both the autograft and allograft are possible[19]	Limited replicative lifespan (alteration of various functions, including multipotency)[19]
Hildreth	MSCs lack the co-stimulatory molecules of the B7 family that are required to initiate an immune response[20]	Clinical outcomes often fall short of pre-clinical expectations[20]

Table 1 displays a concise comparison of the key advantages and limitations of mesenchymal stem cells reported across multiple studies, which is essential for evaluating their therapeutic role in Huntington's rodent models. While MSCs demonstrate promising properties such as immunomodulation, low immunogenicity, secretion of anti-inflammatory and regenerative factors, and potential antitumor effects, they also present significant concerns, including tumorigenesis, genetic instability, heterogeneity, and limited replicative lifespan. Presenting both the benefits and risks in one structured summary allows for a more balanced interpretation of preclinical findings and helps contextualize therapeutic outcomes within the broader challenges of safety, consistency, and translational applicability.

Preclinical Evidence of MSC Therapy in HD Rodent Models

In 15 studies incorporating 346 HD rodent models, larger striatal and smaller ventricular volumes were observed in the models compared to the controls.[21] Additionally, MSCs that were implanted before motor dysfunction resulted in enhanced motor coordination.[21] MSC therapy in the models improved muscular strength, neuromuscular electromyography activity, cortex-related motor function, and striatum-related motor function, while cognition was unchanged.[21] The weight of the male HD rodents increased after transplantation, while the weight of the female HD rodents remained unchanged.[22] Stem cell-based therapies in HD animal models improved both neurological and behavioral function.[22] These findings suggest that stem-cell therapies for neurodegenerative diseases, such as Huntington's, may be effective in alleviating and/or halting the pathophysiological mechanisms underlying HD.[22] Mice that were given the treatment displayed enhanced motor coordination and reduced deficits in tests such as the rotarod test.[22] The rotarod test is a behavioral assessment used to evaluate motor coordination and balance in animal models, primarily with rodents.[24] The transplanted MSCs led to a decrease in neurodegenerative symptoms, which improved behavioral outcomes compared to the controls.[23] Collectively, the reviewed literature reports consistent and significant improvements in behavioral and motor function of the models after MSC transplantation increased.

Mesenchymal stem cells can be derived from many sources, with the most common area of extraction being the bone marrow (BMSC).[25] In these studies, quinolinic acid (QA) lesions were applied to the striatum, which mimicked the symptoms of Huntington's.[26] The QA lesioning caused motor dysfunction, and the following week, they inserted BMSCs. The BMSCs were grown in a lab and were marked with a dye, DAPI, before transplantation. The transplanted BMSCs survived transplantation and exhibited neuronal growth.[26] The rodents that were administered the BMSCs had larger striatal growth, suggesting that the treatment given had less damage compared to before the treatment.[19] This was revealed using stereological striatal volume tests, which are a way to assess changes in striatal volume.[19] Additionally, the authors noted that there was less motor dysfunction present in rodents that were given the transplants[26]. The cultured BMSCs produced neurotrophic factors, which are helpful proteins, such as NGF (nerve growth factor), BDNF (brain-derived neurotrophic factor), GDNF (glial-derived neurotrophic factor), and CNTF (ciliary neurotrophic factor). These proteins support and protect neurons, and the authors found that the genes for these proteins were more active in the rodents that were given the treatment.[26,27] Overall, the authors found that injecting bone marrow-derived MSCs into the lesioned striatum improved brain structure and behavioral changes.[26]

Researchers also studied human bone marrow-derived MSC (hBM MSC) transplantation into QA lesion mice and R6/2-J2 mice.[26] R6/2-J2 mice are genetically modified mice that carry the genetic mutation found in patients who have HD[26]. The authors injected the hBM-MSCs directly into the striatum of the mice.[26] Ten weeks later, the QA mice displayed improved motor function, and it delayed disease progression.[26] On the other hand, the genetically modified mice displayed increased survival, but it did not improve motor function.[26] The transplanted hBM-MSCs lowered levels of cell death in the striatum as well as promoted cell survival and growth, tissue repair, and supported new blood vessels.[26] These findings show that hBM-MSCs could be a promising treatment for MSCs because of their ability to prevent neuronal death, promote brain repair, and support new blood vessel and tissue growth. However, the treatment only improved motor function in the QA model, while motor function remained unchanged in the R6/2-J2 model. This suggests that the hBM-MSC treatment can be more effective in certain types and stages of HD.

Huntington's disease causes striatal neurons to die, and in a 2016 study, researchers genetically engineered MSCs to produce BDNF.[2] BDNF, which stands for brain-derived neurotrophic factor, has been shown to prevent cell death and support the growth of neurons in transgenic mouse models[28]. The engineered MSCs, also known as MSC/BDNF, were injected into the striata of two HD model mice, the YAC128 and R6/2, along with unmodified MSCs.[2] One group received unmodified MSCs, and another group received MSC/BDNF.[28] YAC128 mice are genetically engineered (transgenic) mice that carry the full human HTT gene on a yeast artificial chromosome (YAC).[2] Their purpose is to mimic a slower, more human-like progression with around 128 CAG repeats.[29] On the other hand, R6/2 mice are genetically engineered to carry a fragment of the human HTT gene.[30] They carry around 150 CAG repeats, and these mice are meant to mimic a faster disease progression with a shorter lifespan.[31] In the study, the mice had weakened immune systems.[2] In YAC128 mice, MSC/BDNF therapy slowed brain shrinkage and caused reduced anxiety.[2] In R6/2 mice, both MSC and MSC/BDNF therapy caused neuronal growth; however, only MSC/BDNF therapy increased the lifespan of the mice.[2] This study shows that engineering MSCs to produce BDNF and other neurotrophic factors can enhance the ability of MSCs to protect neurons and slow down HD progression.

This treatment can also be modified to fit with other neurodegenerative diseases. Another 2024 study administered the treatment intravenously, focusing on liver pathology and how HD affects other organs.[31] The authors noted that HD models and patients experience inflammation throughout the body.[31] Researchers examined liver tissue in R6/2 mice to look for liver enzyme changes and inflammatory markers.[31] They found signs of liver inflammation and gave IV infusions of MSCs to the mice.[31] The authors concluded that inflammation in the liver decreased after treatment, since liver enzymes went back closer to normal levels.[31] Motor function and brain pathology improved after treatment, even though MSCs were not found in postmortem brains.[31] These findings emphasize the importance of treating the body and not solely the brain, since it can still improve neurological function. Additionally, these findings raise the possibility of treating liver inflammation as a therapeutic angle and using blood biomarkers related to the liver as a way to monitor progression and response to therapy.

Discussion

The findings of this review indicate that MSC therapy holds much potential for treatment in HD by improving motor coordination, neuronal survival, and slowing neurodegeneration. In several studies mentioned, bone marrow-derived or genetically modified MSCs increased striatal volume, improved behavioral and motor performance, and promoted neurogenesis along with angiogenesis. Together, these findings address the research question of whether MSC therapy can represent an effective approach for the treatment of HD. Overall, MSC transplantation exerts robust neuroprotection and could form the basis for novel regenerative therapies in neurological disorders.

These findings confirm that MSC treatment is consistent with previous evidence of the regenerative capabilities of stem cells in neurological diseases. For instance, studies involving rodent models of Alzheimer's disease have shown that MSCs modulate inflammation, secrete neurotrophic factors, and support tissue repair. All effects that were also found in HD models.[32] The research extended these

observations by specifically correlating MSC treatment with improved striatal regeneration and motor performance in HD.

Furthermore, evidence that genetically modified MSCs overexpressing BDNF enhance neuronal survival supports prior findings for the neuroprotective action of BDNF. This correlation illustrates the fact that MSCs serve not only as cell replacements but also as therapeutic molecules that secrete neuroprotective effects.

Several of the results showed that the outcomes of MSC treatment depend on the model of HD and the stage of the disease. For example, the hBM-MSC treatment improved motor function in QA lesioned mice but did not affect genetically modified R6/2-J2 mice. These findings indicate that this therapy may be more effective in acute or chemically induced models than in genetic models of HD. The second unexpected finding came from the study using intravenous administration of MSCs, in which improvements in motor functions occurred in the absence of MSCs in postmortem brain tissue. These observations suggest that MSCs act systemically with anti-inflammatory effects, indirectly benefiting the health of the brain. These results expand the understanding of how stem cell therapies might act beyond localized neural repair, emphasizing the role of body-wide inflammation in HD pathology.

However, several limitations should be pointed out. First, many of the reviewed studies were conducted using rodent models, which cannot fully represent the complexity of human HD. Moreover, the difference between QA lesioned and transgenic models underlines the variability in how these models actually reflect human disease processes. In addition, while short-term efficacy was clear, long-term safety and effectiveness are not well known, especially with respect to possible immune responses or tumorigenicity. Another limitation is that cognitive benefits were not consistently observed, suggesting that MSC therapy may mainly address motor symptoms rather than the full spectrum of HD impairments. Finally, many studies involved small sample sizes and did not apply standardized MSC sources or dosages, limiting generalizability. Further research is needed to understand how MSCs can best be used as a treatment in humans, including their routes of administration, the timing of treatment in the course of a neurodegenerative disease, and the possible use of genetically engineered MSCs for safe delivery of neurotrophic factors such as BDNF or GDNF. Most of the studies reviewed have focused on systemic inflammation; further research on this subject may provide biomarkers and expand therapeutic benefits beyond the brain. Clinical trials in humans will be critical to establish safety, dosing, and efficiency over time.

Conclusion

The review presents that mesenchymal stem cell therapy for Huntington's disease leads to new methods of understanding and treating neurodegenerative diseases. Neurodegeneration research has historically focused on two methods, which include managing symptoms and developing drugs that target specific symptoms. Huntington's disease exhibits multiple systems that interact through genetic mutations and protein toxicity, neuroinflammation, metabolic disruption, and the ongoing deterioration of neuronal networks. The multiple causes of the disease require that effective treatments must have multiple treatment methods. The treatment of MSC therapy provides an active biological treatment that connects to various biological processes instead of targeting one specific molecular component. The research reviewed shows that the main theme of neuroprotection exists because complete neuronal replacement remains unattainable. The current scientific evidence shows that safeguarding delicate neurons from degeneration, which leads to their death, is as vital as neuron duplication, which was the main goal of early stem cell studies. MSCs establish their primary function through their role in maintaining stable neural environments, which involve decreasing inflammation, supporting current cells, and enabling tissue restoration. The progressive degeneration of Huntington's disease, which takes place over multiple years, can be mitigated by this protective method.

The patients will experience a better quality of life and extended periods of independence when that process achieves even its smallest slowing. The timing of the intervention establishes another crucial result. The diagnostic process for neurodegenerative diseases begins after patients have lost a substantial number of neurons. The effectiveness of MSC therapy will decline after the initial stages of disease progression because research shows that it produces its best results during these early periods.

This supports the need for early detection approaches, genetic screening, and dependable biomarkers that can flag disease onset before major neuronal damage occurs. Starting treatment before major degeneration occurs gives a better chance of keeping neural circuits working, rather than trying to rebuild systems that have already broken down. This framing places MSC therapy within a preventive or early-intervention model of care, rather than treating it as a last-resort option in advanced disease. Such a shift reflects a wider change in neurodegenerative medicine: rather than waiting to treat symptoms after they appear, the aim is to protect neurons earlier and slow their loss. Hence, these results also suggest that Huntington's disease should not be treated as only a disorder limited to one part of the brain.

As the scientific community learns more about how immune changes and metabolic problems affect the whole body, it becomes clear that treatments for neurodegeneration should address the broader biological setting in which the disease develops. MSC therapy fits within this broader framework because it can act through several pathways, not only by affecting neurons directly. By adjusting inflammatory pathways and supporting blood vessel and tissue health, MSCs may strengthen neural resilience indirectly. Taking a whole-body view broadens how we think about treatment and supports multidisciplinary research that brings together neurology, immunology, and regenerative biology. MSC therapy also shifts how we think about what counts as meaningful treatment success in neurodegenerative disease. Even if full reversal of the underlying pathology is the long-term aim, outcomes like a measurable reduction in the rate of progression, stable symptoms, or a small amount of preserved motor coordination can still be meaningful clinical results. In a progressive, fatal condition like Huntington's disease, even small gains can mean more time living independently, keeping the ability to communicate, and maintaining better mental health.

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