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Stem Cell Therapies for Multiple Sclerosis: Promising Approaches and Future Directions

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ABSTRACT

Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by inflammation, demyelination, and neurodegeneration. While current treatments focus on symptom management and disease modification, they often have limitations such as incomplete efficacy and variable response rates among patients. Stem cell therapies, including mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and induced pluripotent stem cells (iPSCs), have emerged as promising approaches to address the complex pathophysiology of MS. Animal studies have shown that these stem cells can modulate the immune response, promote remyelination, and support neuronal repair in the EAE model. Human clinical trials have demonstrated the safety and potential efficacy of MSCs and HSCs in reducing disease progression and improving neurological function in MS patients. Whereas therapies based in iPSCs have not reached clinical applications due to complications regarding tumorigenicity and immunogenicity Additionally, continued challenges such as optimizing stem cell sources, understanding the mechanisms of action, and conducting robust long-term clinical trials stand as barriers to treatment application. Closing the gap between preclinical research and clinical implementation requires determination of protocols, understanding regulatory pathways, and efficient manufacturing of stem cell sources. Overall, stem cell therapies represent a promising avenue for improving the treatment of MS, but further research and clinical development are needed to fully realize their potential.

Keywords

Multiple Sclerosis, Stem Cell Therapy, Mesenchymal Stem Cells, Hematopoietic Stem Cells, Induced Pluripotent Stem Cells.

List of Abbreviations

AD-MSCs: Human Adipose-Derived Mesenchymal Stem Cells, BM-MSCs: Bone Marrow-Derived Mesenchymal Stem Cells, CNS: Central Nervous System, DMTs: Disease-Modifying Therapies, EAE: Experimental Autoimmune Encephalomyelitis, EDSS: Expanded Disability Status Scale, HSCs: Hematopoietic Stem Cells, HSCT: Hematopoietic Stem Cell Transplantation, iPSCs: Induced Pluripotent Stem Cells, MSCs: Mesenchymal Stem Cells, MS: Multiple Sclerosis, NSCs: Neural Stem Cells, OPCs: Oligodendrocyte Precursor Cells, UCMSCs: Umbilical Cord Mesenchymal Stem Cells.

Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS). MS is the most frequent demyelinating disease of the central nervous system. The disease is characterized by inflammation, demyelination, and neurodegeneration. While the exact cause of MS is not clearly understood, it is believed to be caused by a combination of genetic, environmental, and immunological factors [1]. To understand MS, it is important to understand the basic anatomy of the central nervous system and the important components that relate to MS. Myelin is the protective sheath that surrounds nerve fibers in the CNS. The myelinating cells in the CNS are known as oligodendrocytes [2]. Myelin, while protecting the nerve fibers, also contributes to facilitating transmission of nerve impulses in the CNS and maintaining the integrity and function of the

nervous system. Myelin acts as an insulating layer surrounding the axons of the nervous system. They allow for efficient and rapid transmission of electrical impulses [2]. Myelin contributes to the efficiency of conduction through allowing the impulses to have saltatory conduction. This is essentially where signals "jump" from one node of Ranvier, which are the gaps between the myelinated sections, to the next. Rapid transmission of signals is crucial for baseline motor and cognitive functions [3]. Lastly, oligodendrocytes also provide metabolic functions to support the axons through supplying essential growth factors and nutrients [4]. When an individual has MS, their immune system mistakenly targets and attacks the myelinated sections of the CNS. Therefore, leading to inflammation, demyelination, leading to axonal damage. As described through the function of myelin, destruction of myelin disrupts the efficiency of electrical impulse conduction. This impairs neuronal communication and leads to issues with functionality of the CNS [5]. To delve into the pathophysiology of the disease, there are multiple occurrences that contribute to the progression of MS. MS is characterized by inflammatory attacks in the CNS. Inflammatory attacks in the CNS occur when immune cells, mainly T lymphocytes, enter the blood-brain barrier and place an attack on the myelin. Inflammatory attacks subsequently lead to the formation of focal lesions, also known as plaques along axons in the brain and spinal cord. These lesions have the potential to develop anywhere in the CNS, mainly affecting the brain stem, spinal cord, optic nerve, and periventricular areas [2]. Prolonged inflammation and demyelination in MS contribute to neurodegeneration overtime and can result in the loss of nerve cells. Neurodegeneration is the result that contributes to the progression of the disease [2]. In response to the described injury to the CNS, astrocytes and microglia cells undergo a process known as reactive gliosis [6]. This condition is characterized by the activation and proliferation of glial cells, as well as glial scar formation. Additionally, reactive gliosis may lead to the release of pro-inflammatory cytokines, which contribute further to tissue damage and progression of the condition [7]. The described injuries to the CNS due to MS are a result of a complex interplay between several factors. Including immune-mediated inflammation, demyelination, reactive gliosis, all contributing to neurodegeneration events, which in turn lead to the progressive nature of the disease. There is currently no cure for MS and the highly variable nature in the causes of the disease make treatment a challenge clinically.

Clinical challenges arise with MS treatment due to the range of symptoms and presentations that are involved with the disease. Typical treatment involves symptom management, reducing relapses, and slowing disease progression [8]. Currently, there are several categories of treatment options that are employed when targeting MS. These categories include disease-modifying therapies, symptom management, and rehabilitation strategies. Disease-modifying therapies (DMTs) are the hallmark treatment option for MS. DMTs are employed to reduce disease activity, prevent relapse, and slow disease progression. While DMTs have shown to be efficient in reducing rate of relapse and slowing further development of disease in some patients, these treatments do not prove to be successful for all individuals diagnosed with MS. DMT's may have negative side effects associated with certain medications. Including flu-like symptoms, increased risk of injection, and injection site reactions [9]. Another method of treatment includes symptom management. Since MS symptoms can vary widely among individuals, highly specified actions are taken by clinicians to aid patients manage the variable manifestations of MS. Symptoms of MS may include muscle weakness, spasticity, pain, cognitive impairment, and depression. Clinical symptom management strategies include medications, such as muscle relaxants and antidepressants, physical therapy, occupational therapy, speech therapy, and cognitive rehabilitation [10]. While symptom management may improve the quality of day-to-day functioning for the patient, these methods do not target the root of the cause in MS. Therefore, the underlying condition still resides, and the individual may continue to see progression of disease and presence of symptoms. Lastly, rehabilitation strategies may be used to improve overall function in the patient. Typically employed in early stages of the disease professional rehabilitation treatment may reduce the stage of disease progression and functional dysfunction of MS patients. Also, there may be improvements in neurological function and reduced family and social burdens [11]. Rehabilitation strategies include programs designed to strengthen muscles, improve balance and coordination, and enhance the overall quality of life for patient. While rehabilitation programs may be beneficial for some disease progressions, the neurodegeneration is not targeted and thus these treatments do not alter the course of disease or prevent progression of the condition long term.

These three categories of treatment represent major advancement in improving the functionality and quality of life for those affected by MS. However, current therapies have limitations. These limitations including incomplete efficacy, variable response rates among patients, negative side effects, and the requirement of lifelong treatment. These limitations present due to treatments neglecting to adequately address the neurodegeneration and demyelination of CNS axons. Stem cell therapies have emerged as a promising approach for treating MS through addressing both inflammatory and neurodegenerative sectors of the disease. Stem cells have the capability to modulate the immune response, induce remyelination of axons, and support neuronal repair and regeneration of the CNS [1]. Several types of stem cells have shown promise in MS treatments. These stem cell types include mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and induced pluripotent stem cells (iPSCs). Broadly, the application of these stem cells aims to revolutionize MS treatment through addressing the underlying pathophysiology of the disease with a goal of offering an improved outcome for patients diagnosed with MS. MSCs are stromal cells residing in many tissues including bone marrow, adipose tissues, and umbilical cord tissues. They contain numerous cytokines, mediators, and signaling molecules which give these cells certain immunomodulatory properties and suppress aberrant immune responses in MS. These specific properties work to reduce inflammation and prevent further damage to myelin and axons [12]. HSCs can be transplanted through HSC Transplantation

(HSCT) or Bone Marrow Transplantation (BMT) are considered an avenue for patients with severe cases of MS who have shown resistance to DMTs. HSCs can be obtained from peripheral blood, bone marrow, and umbilical cord blood [13]. HSCs aim to reset the immune system by replacing autoreactive immune cells with healthy cells. These can be autologous (derived from the patient's own stem cells) or allogenic (compatible donor) [14]. Lastly, iPSCs aim to modulate the autoimmune response in the central nervous system and promote immunomodulatory and regenerative effects. IPSCs are stem cells that are generated by reprogramming adult somatic cells into a pluripotent state. Since pluripotent stem cells can differentiate into any cells type in the body, they are suggested to be useful in MS treatment due to this capacity to differentiate into neurons and glial cells [15].

The clinical application of stem cell therapies in multiple sclerosis (MS) represents a promising avenue for addressing the complex pathophysiology of the condition. These treatment options offer multifaceted approaches to modulate the immune response, promote remyelination, and support neuronal repair and regeneration in the central nervous system. This paper will explore the current climate of stem cell research in MS treatment, highlighting various stem cell types, transplantation techniques, and emerging strategies, while also considering their potential clinical efficacy, safety profiles, and long-term outcomes.

Methods

A comprehensive literature search was conducted using electronic databases. Keywords such as "multiple sclerosis," "stem cells," "mesenchymal stem cells," "hematopoietic stem cells," "induced pluripotent stem cells," and "clinical trials" were used to identify relevant information within published peer-reviewed journals. Both experimental and review articles were considered relevant and reviewed. The types of stem cells investigated include Mesenchymal Stem Cells (MSCs), Hematopoietic Stem Cells (HSCs), and Induced Pluripotent Stem Cells (iPSCs). Therefore, the studies examining the therapeutic potential of these sources in relation to MS were reviewed and relevant data was extracted. Data was compiled and summarized, details regarding study design, stem cell type, transplantation method, outcomes, and key results were included. Considerations and a quality assessment was made. The quality of the included studies was assessed using relevant criteria. This pertained to study design, sample size, control groups, and experimental limitations. Finally, synthesis was conducted, the findings of included studies were synthesized and discussed. Overall, the methods employed in this review aim to provide a comprehensive overview of current stem cell therapy applications in multiple sclerosis.

Animal Studies

Animal models provide crucial insight into the understanding of the pathophysiology of MS, as well as into the evaluation of therapeutic intervention. Since MS is complex condition, there is no single animal model that can capture all nuances and variation of the human condition [16]. However, animal models can be used to indicate critical aspects of the disease studied. The experimental autoimmune encephalomyelitis (EAE) is one of the most widely used animal models of MS because it shares key pathological features with human MS. These features being inflammation, demyelination, and neurodegeneration. In EAE, autoimmunity to CNS components is induced in susceptible mice through immunization with self-antigens derived from basic myelin protein. This leads to the infiltration of autoreactive T cells into the CNS, resulting in inflammation, demyelination, and neurological defects that resemble complications seen in human MS [16]. A study employed the use of EAE to study aspects of MS when treated with MSCs. Specifically, the study investigated the therapeutic efficacy of MSCs and MSCs-derived neural progenitor cells (MSCs-NPs) in treating experimental autoimmune encephalomyelitis (EAE). MSCs and MSCs-NPs were derived from mouse bone marrow and characterized through immunophenotyping and differentiation assays. EAE was induced in mice, and three intravenous injections of MSCs, MSCs-NPs, or a combination were administered at the onset of the chronic phase of the disease. Clinical disability was monitored, and various assays were performed to evaluate immunomodulatory effects, cytokine production, and proliferation of MOG35–55-specific splenocytes [16]. In terms of clinical efficacy, this study found that both MSCs and MSCs-NPs significantly reduced EAE clinical scores when compared to untreated mice. Additionally, MSCs-NPs showed a more profound reduction in clinical scores when compared to MSCs. Additionally, combination therapy, meaning treatments including both MSCs and MSCs-NPs did not provide any additional benefits. As for immunomodulatory effects, MSCs-NPs exhibited higher potency in slowing proliferation of pathogenic T cells and reducing IFN-γ (major cytokine found in MS lesions) production as compared to MSCs. Additionally, MSCs and MSCs-NPs significantly decreased levels of IFN-γ and IL-17 while increasing IL-10 production in MOG35–55-stimulated splenocytes. The decrease in FN-γ and IL-17 levels, along with the increase in IL-10 production observed in MOG35–55-stimulated splenocytes treated with MSCs and MSCs-NPs, indicates a shift towards an anti-inflammatory immune response. This study did not report adverse effects associated with MSCs or MSCs-NP treatments. Long-term outcomes were not evaluated in this study.

Looking at the effects of HSCs in the EAE model, this study aimed to evaluate the efficacy of nonmyeloablative conditioning and syngeneic bone marrow transplantation (BMT) in EAE. Looking at study design, EAE was induced in C57BL/6 mice, which were then divided into four groups. First, the conditioning group (received conditioning regimen), normal-EAE BMT group (received conditioning and bone marrow grafts from normal mice), EAE-EAE BMT group (received conditioning and bone marrow grafts from EAE mice), and EAE control group (received no therapy) [17]. Looking at the results, treatment with BMT displayed significant clinical improvement on day 80 after BMT compared to untreated EAE. However, by day 120, the clinical score of the Conditioning group was not significantly different from the EAE control group. In terms of clinical efficacy, complete and long-term remission of EAE required transplantation with bone marrow cells from healthy or diseased donors. This study displayed those treated with

BMT resulted in sustained improvement in symptoms, indicating a possible initiation of long-term immune tolerance. Essentially, this study demonstrates the efficacy of syngeneic BMT in inducing long-term remission of EAE; however, further research must be conducted to understand the mechanisms underlying these effects. This will enable evaluation of long-term safety and efficacy of BMT in MS.

IPSCs also present a promising avenue for treating MS and other demyelinating disorders. iPSCs can differentiate into various cell types and iPSC-derived cells have shown to have the ability to offer potential therapeutic benefits in the EAE model. Studies have investigated the effects of iPSC-derived neural stem cells (NSCs) and oligodendrocyte precursor cells (OPCs) in. the EAE model. Additionally, transplantation of iPSC derived NSCs into EAE mice resulted in reduced symptoms, decrease in demyelinated axons, and overall improved spinal conditions. While transplanted NSCs did not show to participate in remyelination of axons, they have shown to play a role in survivability and differentiation of endogenous myelinating cells through the section of neurotrophins [18]. iPSC derived OPCs have shown to have myelin-forming abilities when injected into EAE models. When demyelinated areas have been treated with these stem cells, they have shown the ability to differentiate into mature oligodendrocytes. Therefore, contributing to the remyelination of axons and promoting functional recovery. The transplantation of iPSC-derived cells in EAE models has shown promising clinical efficacy, including reduced demyelination, improved nerve function, and increased survival rates. Furthermore, iPSC-derived cells have demonstrated the ability to integrate into host tissues and contribute to long-term myelin repair [18].

Long-term studies are essential to assess the sustained therapeutic effects and safety profile of iPSC-derived cell therapies in EAE and MS. Monitoring for potential adverse effects, such as tumorigenicity and immunogenicity, are crucial in assessing the long-term benefits and risks of treatments applying iPSCs.

Human Studies – Clinical Trials

Clinical applications of these therapies have shown promise in both safety and clinical efficacy. Clinical applications of MSCs in human clinical trials have involved a few variations of MSCs. Autologous MSCs therapy, referring to MSCs derived from the patient, have shown promising clinical applications. In terms of efficacy, some trials have displayed instances of reducing the number of lesions in MRI scans, improving clinical scores, and enhancing neurological function. In terms of long-term outcomes, some trials have mostly only displayed short-term improvement. Further investigation must be done to determine long-term effects. As for safety, most trials reported no significant adverse events associated with autologous MSC transplantation [19]. Another derivative of MSCs are Bone Marrow-Derived MSCs (BM-MSCs). Treatments derived from BM-MSCs have clinically shown improvements in immunological responses, neurological function, and disability scores. As for long-term outcomes, BM-MSCs did display some patients with long-term benefits. Some individuals showed stability in disease progression; however, more research must be done to make conclusive claims. Finally, most transplantations of BM-MSCs reported to be done without any significant adverse effects [19]. Human Adipose-Derived MSCs (AD-MSCs) showed improvements in MS disabilities, specifically including managing sexual and social issues. No evidence of long-term effects was supported by clinical trials. AD-MSCs appeared to not cause adverse effects in patients. Finally, Umbilical Cord MSCs (UCMSCs) showed improvements in neurological parameters, disability scores, and quality of life. Long-term benefits were seen with reduced lesion activity in MRI scans and sustained improvements in the expanded disability status scale (EDSS). There were no major adverse effects reported with UCMSCs [19]. Overall, MSCs derived from various sources, appear to be safe when applied clinically. MSCs are also growing in popularity due to their practicality. MSCs are relatively easy to isolate, they are safe to administrate, and have shown to not need immunosuppressive therapy to prevent rejection [20]. These stem cells may even offer potential benefits for MS patients in terms of reducing disease activity, improving neurological function, and enhancing quality of life. However, further research, including expanded clinical trials with longer follow-up periods, is necessary to fully understand the safety, efficacy, and long-term outcomes of MSC therapies in MS treatment.

Compared to MSCs, HSCs have been studied to a much lower degree clinically. In a clinical trial that compared nonmyeloablative hematopoietic stem cell transplantation (HSCT) with disease-modifying therapy (DMT) in 110 patients with relapsing-remitting multiple sclerosis (MS). Among 926 patients screened, 110 were enrolled, with 55 in each group. The primary endpoint was disease progression, defined as an increase in Expanded Disability Status Scale (EDSS) score of ≥1.0 point [21]. Disease progression occurred in 3 patients in the HSCT group and 34 patients in the DMT group. In the HSCT group, mean EDSS score decreased from 3.38 to 2.36 at 1 year, while in the DMT group, it increased from 3.31 to 3.98. Additionally, secondary endpoints showed a significant reduction in relapses in the HSCT group compared to the DMT group. Finally, improvement in neurological and quality-of-life measures was observed in the HSCT group compared to the DMT group. This trial demonstrated that HSCT was more effective at preventing disease progression and reducing rates of relapse in MS patients. While the results of this study may be indicative of the possibility of HSCT to aid patients with MS in mitigating disease progression, more research must be done to confidently assess the impact of HSCT as an effective, safe, and long-term MS therapy.

IPSCs have not seen widespread clinical applications due to some limitations. IPSCs are generated *in vitro* from a patient's own fully differentiated somatic cells through the process of reprogramming. iPSCs can be differentiated into both neural stem cells (NSCs) and oligodendrocyte precursor cells (OPCs). These options have opened avenues for pathophysiological research and methods of stem cells therapy using iPSCs. While there is promise, iPSCs-derived cells have not yet been applied to a clinical setting.

There is evidence that the epigenetic signature of cells can be maintained after induction into iPSCs, contributing to issues of immune rejection of graphs [20]. There have also been instances of unexpected functions of iPSCs. In one case, iPSC-NSCs grown from patients with Primary-progressive multiple sclerosis (PPMS), when transplanted into models of cuprizone-demyelinated mice, showed inherent defects [20]. Additionally, the methods of retrieval have contributed to issues with efficacy. The induction process required for generation of NSCs from iPSCs and the expansion to produce enough cells for the transplantation process is time consuming. This time element has led to an increase in the likelihood of genetic instability, leading to oncogenesis following transplantation. While there are issues to be resolved prior to further clinical application, with rapid progress in the field of iPSCs, these complications may be addressed and solved.

Future Directions

The landscape of stem cell therapy in MS is continually evolving. These treatment methods present a promising avenue for exploration and advancement. While progress has been made in understanding therapeutic potential of various stem cell types, there are several key areas for future research and clinical development. Exploring how stem cell therapies and stem cell sources can be optimized will be key when looking to future research. Continued investigation into the most effective types and sources of stem cells for MS treatment is warranted. While mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and induced pluripotent stem cells (iPSCs) have shown promise, further refinement of protocols for isolation, expansion, and differentiation of these cells is necessary. Additionally, exploring novel sources of stem cells and innovative approaches to enhance their therapeutic efficacy will be crucial.

To understand this optimization, it will be crucial to have an improved mechanistic understanding of the disease of MS and how stem cells specifically fit into treatment methods. Once an understanding the "how" of stem cell therapy will provide insight into optimizing treatment strategies and predicting long-term outcomes for patients. Comprehensive studies are essential to dissect the precise roles of stem cells in modulating the immune response, promoting remyelination, and supporting neuronal repair and regeneration. Once clinicians and researchers understand the mechanism of action, there will be increased confidence in safety and efficacy during treatment applications. Finally, this mechanistic understanding will inform the development of targeted interventions and personalized treatment approaches.

Among all three of the discussed stem cell types, the conduction of robust and long-term clinical trials is essential to assess the safety and efficacy of stem cell therapies in MS. Studies documenting the adverse effects, including tumorigenicity and immunogenicity is essential to structuring a safety profile for these stem cell therapies. Also, long-term studies are needed to evaluate the durability of therapeutic effects and the potential disease-modifying capabilities of stem cell therapies in MS. Additionally, with MS being a disease defined by heterogeneity and variability, tailored treatment plans are essential in proactive treatment. Thus, moving towards a paradigm of precision medicine in MS involves patient-specific therapeutic interventions targeting individual characteristics and disease subtypes. Integrating biomarkers, genetic profiling, and imaging techniques into clinical practice can facilitate patient stratification and enable personalized treatment strategies [22]. This approach may optimize treatment response rates and minimize adverse effects by treating patients with the most appropriate therapies based on their specific disease profile. Bridging the gap between preclinical research findings and clinical implementation remains a challenge in stem cell therapy for MS. Outlining regulatory pathways, fostering interdisciplinary collaborations, and establishing standardized protocols for stem cell transplantation and manufacturing are critical steps in the direction of implementing these therapies into clinical settings.

Conclusion

The exploration of stem cell therapy in MS represents a dynamic and promising field in the journey for effective treatment applications. Stem cells offer several avenues for approaching the complex pathophysiology of MS through the modulation of the immune response, promoting remyelination of axons, and supporting neuronal repair and overall regeneration of the immune system. This comprehensive review delves into the mechanisms underlying MS pathology and the various stem cell types that aim to provide regenerative therapy to the disease. The types of stem cells analyzed include Mesenchymal Stem Cells (MSCs), Hematopoietic Stem Cells (HSCs), and Induced Pluripotent Stem Cells (iPSCs), and their clinical applications. Animal studies have provided crucial insights into stem cell therapies, demonstrating their efficacy in reducing inflammation, promoting remyelination, and improving clinical outcomes in models of MS such as experimental autoimmune encephalomyelitis (EAE). Human clinical trials have shown promising results, particularly with MSCs and HSCs. Treatments based in these stem cells have shown to improve neurological function, reduce disease progression, and enhance quality of life for MS patients. However, challenges such as variability in treatment response, long-term safety, and the need for personalized therapeutic approaches remain to be addressed. Future directions in stem cell therapy for MS include optimizing stem cell sources and mechanisms of action. Therefore, understanding the process of the disease is essential in efficient treatment. Additionally, conducting comprehensive clinical trials is essentially to determine long term efficacy of treatment. Increased data on clinical applications will also aid in bridging the gap between preclinical research and clinical application for analyzing the full potential of stem cell therapies targeting MS.

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