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Mesenchymal Stem Cells as A New Approach for the Treatment of Multiple Sclerosis: A Literature Review

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Abstract

Multiple sclerosis (MS) is a high-prevalence autoimmune and neurodegenerative disease that affects young adults. An ideal treatment for MS should have two characteristics. First, its immunosuppression and immunomodulation effects reduce the abnormal immune response, and second, it improves repair by enhancing intrinsic repair processes or even cell replacement. Most available therapies have the first characteristic. Recent studies have proposed mesenchymal stem cells (MSCs) as a new therapeutic candidate for MS. Different clinical trials and animal models of MS have shown the therapeutic effect of MSCs. In the current study, we reviewed the therapeutic effects of MSCs in the animal model and patients with MS.

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Introduction

Multiple sclerosis (MS) is an autoimmune and neurodegenerative disease that affects young adults [1, 2]. Since the prevalence and incidence of MS in developing and developed countries are increasing [3], the exact explanation remains unknown. Different genes and environmental factors are involved in the susceptibility to MS, such as the human leukocyte antigen (HLA) gene (e.g., HLA DRB1*15:01), infection to Epstein–Barr virus (EBV), exposure to ultraviolet B light (UVB), vitamin D deficiency, smoking, and obesity [4, 5]. T-cells are the most important cells that have been responsible for MS pathogenesis. However, B-cells also are involved in the pathogenesis of MS [6]. MS is traditionally a two-phase disease. An early inflammation causes relapsing-remitting disease and delayed neurodegeneration, which is responsible for non-relapsing progression [7]. Neurologists categorize MS

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into four groups based on the stage of the disease [8] as follows: (1) relapsing-remitting MS (RRMS), which is the most prevalent form of MS and influences about 85% of MS patients. It is generally explained by a symptoms flare-up followed by remission intervals. (2) primary progressive MS (PPMS) influences approximately 10% of MS subjects. The symptoms of patients worsen gradually from the beginning of the disease. Relapses or remissions were not seen in this stage, but there may be uncommon plateaus. This form of MS is more resistant to standard drugs commonly used to treat the disease. (3) progressive-relapsing MS (PRMS), a rare form of MS, engages less than 5% of patients. It is progressive from the beginning, with some flare-ups and worsening symptoms. No periods of remission might be seen in this form. (4) secondary progressive MS (SPMS) that some patients with the relapsing-remitting disease may experience this type. In some patients, the progression may delay by treatment with disease-modifying agents. The situation may worsen with or without periods of remission or stabling of symptom severity [8].

Therapeutic methods now focus on treating sudden attacks and easing symptoms. Disease-modifying treatments can alter immune function, which has an anti-inflammatory effect and lowers the frequency of relapses. They have the potential to either stabilize, delay or, sometimes, somewhat enhance impairment [9]. New therapies are required, and stem cell therapy is emerging as a tactic. Mesenchymal stem cells (MSCs) appear promising, while other stem cells, such as hematopoietic stem cells, can also be used [10]. Since MSCs seem to be promising therapeutic agents in neurodegenerative disease, we reviewed the latest studies on the effect of MSC-EVs on MS.

Epidemiology and Etiology of MS

Although it is widely believed that MS has no recognized cause, this is not entirely true. Genetic background, in combination with environmental factors such as vitamin D deficiency, smoking, sunshine (UVB) exposure, and EBV infection, plays pivotal roles in the development of MS [11, 12]. HLA-DRB1*15 is the most genetic risk allele correlated with MS and is in close linkage disequilibrium with this allele [13]. Literature reviews have demonstrated that environmental factors have a critical role in MS [14]. Studies have shown that adult migrants from low-risk countries to Europe develop a low risk for MS; however, a high risk of MS has been seen in children born and migrants in Europe. It has been shown that EBV-negative individuals could be protected from developing MS [15]; patients with EBV infection double the chances of MS occurring [16]. The prevalent explanation for how EBV raises the risk of MS is molecular mimicry [17]. Another theory for disease development is that EBV induces B-cell transformation and/or immortalization [18]. The prevalence of MS rises with latitude [19]. Smoking increases the risk of MS by approximately 50% [20]. It has been shown that smoked tobacco [21] and organic solvents [22] are associated with MS, but oral tobacco or snuff is not [23]. This finding has given rise to the theory that tobacco smoke and organic solvents trigger post-translational alterations in the lungs through antigen presentation. UVB radiation is associated with the latitudinal difference since it increases the skin's ability to produce vitamin D. MS affects women more often than men, and the ratio of MS in females to males is now close to about 3:1 [24].

Pathology and Immunology of MS

In the description of Charcot's pathology related to sclerosing en plaques, they explained that sclerosed plaques affect the spinal cord, pons, and periventricular area [25]. Perivenular inflammatory lesions are the characteristic pathological feature of MS, resulting in demyelinating plaques [26]. The infiltrates inflammatory cells in the area consist of T-lymphocytes, $CD8^+$ cells, B-cells, and plasma cells; however, the number of plasma cells is low [27].

Inflammation could cause oligodendrocyte damage and demyelination. In the early stage of MS, axons are not relatively damaged; however, irreversible axonal damage occurs following disease progress [28]. In both RRMS and SPMS, the inflammatory cells that infiltrate to lesion have a similar makeup; however, in progressive MS, there are more plasma cells and B-cells [29]. In the different clinical stages of the disease, the produced cytokines or stage of B- and T-cell activation is different [27]. Remyelination has been demonstrated to occur in all phases of the disease, particularly in the progressive phase [27]. Patients with SPMS have lower axonal densities in the white matter of their cervical spinal cord and higher degrees of demyelination compared to PPMS patients [30, 31].

Treatment Options for MS

Disease-modifying and symptomatic therapies are two categories of treatments for MS. The first one is specific to MS, and the latter treats symptoms that occur from neurological impairment.

Disease-Modifying Therapies

By expanding the availability and effectiveness of disease-modifying treatments, the desire to treat patients in early-stage has grown. Disease-modifying therapies could be divided as immunosuppressant (such as natalizumab, fingolimod, and ocrelizumab) and immunomodulatory (e.g., glatiramer acetate, interferon beta, and teriflunomide). The closest and most likely treatment for MS is a short course of immune reconstitution therapies like cladribine and alemtuzumab, which can produce long-lasting immunological effects [9, 32].

Symptomatic Treatments

These therapies are a group of physical and pharmaceutical therapies that aim at symptoms of CNS damage; however, they are not specific to MS. They are divided into anticholinergics, which use for bladder dysfunction, and medication for neuropathic pain. The World Health Organization have been approved several symptomatic therapies for MS, e.g., fampridine for walking difficulties and Sativex for spasticity. A critical advantage of symptomatic therapies is their sleep effects. By progressing MS disease, the difficulties with the sleeping increase [32].

MSCs

The MSCs are adult and non-hematopoietic stem cells that could able to multilineage differentiation and self-renewal. They are derived from the mesoderm. MSCs can develop toward ectodermic, endodermic, and mesoderm lineages, including chondrocytes, osteocytes, and adipocytes [33-35]. MSCs were initially discovered in bone marrow but have since been discovered in dental tissues, the umbilical cord, adipose tissue, and other places [36]. Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy (ISCT) states that the following minimum requirements must be met to define human MSCs: (1) the ability to differentiate into chondroblasts, adipocytes, and osteoblasts in vitro; (2) expression of the surface molecules CD73, CD90, and CD105; and the lack of CD14 or CD11b, CD34, CD79α or CD19, CD45, and HLA-DR; (3) plastic adherence in standard culture conditions [37].

The therapeutic potential of MSCs is related to their ability to differentiate and their paracrine actions. Indeed, the so-called extracellular vesicles (EVs), which are made up of various cytokines, microRNAs, and growth factors, can be secreted by MSCs. Also, EVs are divided into exosomes, microvesicles, and apoptotic bodies [38-41].

The ability of MSCs to develop into oligodendrocytes in treating MS has been demonstrated by their expression of oligodendrocyte precursor cell markers like oligodendrocyte transcription factor (Olig2) and A2B5. Myelin basic protein, an oligodendrocyte marker expressed by a smaller proportion of cells, is also present. Only a very small percentage of the

cells displayed the astrocyte marker glial fibrillary acidic protein [42]. Additionally, it was discovered that the condition media produced from MSCs might assist the oligodendrogenesis of hippocampus neural stem cells [43].

The paracrine activity of MSCs or direct interaction with immune cells can exert immunomodulatory effects. More specifically, studies have found that MSCs block Th17 and Th1 cells differentiation while promoting the differentiation of regulatory T (Treg) cells and influencing the polarization of macrophages, leading to the formation of anti-inflammatory M2 macrophages rather than inflammatory M1 macrophages [44, 45].

MSCs as A New Approach to Treatment of MS

In MS patients, immunomodulatory therapies are the most frequently used agents. However, several MS studies evaluate a range of clinically and experimentally therapeutic agents. Pre-clinical data in experimental autoimmune encephalomyelitis (EAE) models suggested that adult stem cell-based therapy would be effective [46, 47]. Among stem cells, MSCs have been evaluated in many autoimmune diseases, including MS, and promising therapeutic results have been achieved for MS [48, 49]. MSCs can potentially differentiate into various cells and could be easily isolated from different tissues [50]. They can typically extract from different tissues such as umbilical cord blood, bone marrow, perivascular, and adipose tissue [51-53] and comprise approximately a low number of the total nucleated adipose tissue and bone marrow cells (0.001%–0.01%) [54, 55]. MSCs can differentiate into osteoblastic, adipogenic, and chondrogenic [48, 56-58]. Due to their biological roles, such as neuroprotection promotion of tissue repair, their multilineage differentiation potential, anti-inflammatory effects, and immunomodulatory effects, MSCs are extensively explored in clinical studies. MSCs were theoretically thought to reside in injured tissues where they may differentiate and replace damaged cells. MSCs extensively studied in clinical trials and MS animal models as a therapeutic agents. Zappia *et al.* [59] have injected MSCs intravenously in EAE mice before and after the onset as a therapeutic protocol. Their results demonstrated that administration of MSCs before disease onset attenuated induced EAE, and the therapeutic effect of MSCs was effective when MSCs were injected at disease onset and the peak of disease [59]. Also, Constantin *et al.* [60] indicated that intravenous administration of MSCs from adipose tissue before disease onset ameliorated the severity of EAE by immunomodulation and decreased demyelination as well as inflammation in the spinal cord [60]. Also, MSCs' therapeutic effects have been shown in other studies on MS animal models. Gerdoni *et al*. showed that MSC-treated mice have milder disease and fewer relapses compared to control mice, with lower leukocyte infiltration, decreased demyelination, and axonal loss [61]. Also, Kassis *et al*. demonstrated that treatment with MSCs ameliorated chronic EAE [46]. The therapeutic effect of MSCs has also been studied in patients with MS. In this regard, Yamout *et al*. [57] evaluated the therapeutic effects and the safety of autologous bone marrow MSCs in seven advanced MS patients. Their results showed the safety of treatment with improvement in Expanded Disability Scale Score (EDSS) in five patients, stabilization in one patient at 3-6 months, and improvement in vision and low contrast sensitivity testing at three months in five patients [57]. Connick *et al*. [62] have investigated the therapeutic effects of autologous MSCs in ten patients with SPMS. Their results showed no adverse effect and improvement in visual evoked response latency and visual acuity with an improvement in the optic nerve area [62]. Cohen *et al*. examined the safety of autologous MSC transplantation in 14 SPMS and 10 RRMS patients and observed no evidence of disease activation or serious adverse events [48]. In a similar study,

Stepien *et al*. [63] investigated the effect of autologous adipose stem cell administration on 16 RRMS and SPMS patients. Their results showed the safety of treatment with no progression of disability or relapses in patients [63]. Bonab *et al*. [64] evaluated the therapeutic effect of autologous MSCs in improving the clinical manifestation of ten patients with MS, and they observed improvement of EDSS in one patient, no change in five patients, and an increase in five patients. Six patients had some degree of improvement in their cerebellar, sensory, and pyramidal functions according to the functional system assessment. The magnetic resonance imaging findings showed no difference in the number of plaques in seven patients [64]. In a clinical trial by Karussis *et al*. [65], the immunological effects and safety of MSCs in patients with MS were studied. Twenty-one patients enrolled in the study that showed no major adverse effects with improvement in EDSS, and immunological results showed an increase in the proportion of Treg cells and a decrease in the proliferative response of lymphocytes [65].

The benefits of MSC therapy in an animal model and patients with MS might be due to the immunomodulatory effects MSCs [66]. MSCs could produce different factors such as transforming growth factor beta (TGF-ß), interleukin (IL)-10, nitric oxide (NO), and indoleamine 2,3-dioxygenase (IDO) that modulate the immune system. Besides, by producing these factors, MSCs could reduce T-cell proliferation and make these cells anergic [67]. They also reduce proliferation and antibody production in B-cells. It has been shown that MSCs induce the generation of Treg cells. The effects of MSCs could be in a cellular or paracrine manner [67].

Conclusion

Current therapies for the treatment of MS are modifying or symptomatic therapies. The need for a new approach to treating MS is undeniable. MSC therapy is a new treatment area for different autoimmune and inflammatory diseases. The most important property of MSCs which make them a suitable candidate for MS is their immunomodulatory effect. These cells secrete anti-inflammatory factors such as TGF-ß, IL-10, NO, and IDO. These factors modulate T-cells, which are the most crucial in the pathogenesis of MS. The therapeutic effect of MSCs has been proved in many animal model studies of MS, and many clinical trials showed the safety and therapeutic effects of these cells in the clinical phase of MS studies. New studies with more patients and more follow-up time are needed to confirm the therapeutic effects of MSCs as a new treatment for MS.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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