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Review

Immunomodulatory characteristics of mesenchymal stem cells and their role in the treatment of Multiple Sclerosis

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ABSTRACT

Multiple Sclerosis (MS) is a chronic inflammatory neurodegenerative disease of central nervous system (CNS). Although the main cause of MS is not clear, studies suggest that MS is an autoimmune disease which attacks myelin sheath of neurons. There are different therapeutic regimens for MS patients including interferon (IFN)-β, glatiramer acetate (GA), and natalizumab. However, such therapies are not quite effective and are associated with some side effects. So which, there is no complete therapeutic method for MS patients. Regarding the potent immunomodulatory effects of mesenchymal stem cells (MSCs) and their ameliorative effects in experimental autoimmune encephalopathy (EAE), it seems that MSCs may be a new therapeutic method in MS therapy. MSC transplantation is an approach to regulate the immune system in the region of CNS lesions. In this review, we have tried to discuss about the immunomodulatory properties of MSCs and their therapeutic mechanisms in MS patients.

1. Introduction

Multiple Sclerosis (MS) is a common chronic disease of central nervous system (CNS) that can cause severe physical disability and nervous system defects [1,2]. MS usually occurs between the ages of 20–40 years and is more common in females. General prevalence of MS is 120 people out of 100,000 and the disease complexity has made it difficult to find an appropriate treatment [1,3,4]. MS is characterized by demyelination of nervous cells as well as different degrees of axonal damages [2,5]. The CNS damage in MS is associated with neural clinical manifestation including visual and sensory disorders, weakness, spasticity, acute and chronic pains, tiredness, depression, and organ paralysis [1,6]. The precise etiology of MS is unknown, however there is evidence which implies immune dysregulation, infections, and genetic background as possible etiologic factors in MS [2,7]. Following activation of autoreactive T cells through some infectious agents that are molecular mimicking from proteins of myelin sheath, they pass through the blood brain barrier (BBB) and enter the CNS. These cells demyelinate the neurons through the neuro-inflammatory responses which finally lead to the destruction of myelin and axon of nervous cells and plaques formation in the brain white matter and spinal cord [8–10].

Interferon (IFN)-β and glatiramer acetate (GA) are considered as the first-line therapies for treatment of PRMS. While IFN-β increases the production of anti-inflammatory cytokines, GA goes to resemble myelin and mislead the immune system [4,11]. The teriflunamide and the fingolimod are the other types of treatment that are usually prescribed orally [12]. Triflunomide is a pyrimidine synthesis inhibitor that decreases proliferation and activation of autoreactive T and B cells [13]. Natalizumab monoclonal antibody causes a 60% decrease in recurrence of the disease per year and improves the neurogeneration process. This medication is considered as a second-line treatment [14]. Mitoxantrone which inhibits DNA synthesis is another medication which can be used for the treatment of SPMS and PPMS [15]. However, none of the mentioned treatments showed complete remission in the majority of patients and were also associated with some side effects [14]. Thus, currently it seems that there is no effective treatment for MS [16,17].

Recently application of stem cell therapy and particularly mesenchymal stem cells (MSCs) transplantation for MS therapy has become the center of focus among the researchers. This has created a lot of hopes to treat MS patients [18]. Several studies have been shown that MSCs have immunomodulatory and anti-inflammatory effects in various tissues [19]. These characteristics were also proved when MSCs were used in the treatment of the experimental

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autoimmune encephalomyelitis (EAE), which is considered as MS animal model [20–28]. It has been shown that MSC transplantation modulates immune system at CNS lesions and enhances remyelination and repairing process [29]. Numerous attempts have been made recently to use the immunomodulatory properties of the MSCs as a treatment for MS and satisfying results have been obtained. However, the precise immunomodulatory mechanisms by which these cells exert their regulatory effects have not been clarified yet. In this review, we have described the immunomodulatory properties of MSCs and their role in the treatment of MS disease.

2. MSCs and identification methods

The MSCs were first described as the fibroblast-like cells in the bone marrow by Friedenstein et al. in 1968 [30]. They cultivated the bone marrow cells in the plastic containers to separate the cells that adhered to the container from the hematopoietic cells which did not adhere to the container. These cells were named the colony forming unit fibroblast or CFU-F [30,31]. Later in 1980s, investigations indicated that these cells have the ability to differentiate toward the other lines of the mesodermal cells including myoblastes, tenocytes and chondrocytes. Caplan et al. introduced the term "mesenchymal stem cells" for these cells with respect to such abilities [32]. MSCs constitute about 0.01% to 0.001% of the entire nucleated cells of bone marrow. However, these cells are easily reproducible in culture mediums [33,34]. Unfortunately, there is (are) no precise marker(s) to identify the MSCs. However, the presence or the absence of some markers is used for discrimination of these cells. The International Society for Cell Therapy (ISCT) determined the minimum criteria for the MSCs identification in 2006. These criteria are as follows [35]:

1. The ability of adherence to the plastic culture container.
2. The ability of differentiation into at least 3 cell lines including adipose, cartilage and bone tissue.
3. Having the phenotype of $CD90^+$, $CD73^+$, $CD105^+/CD34^-$, $CD45^-$, $CD14^-$, $CD19^-$, $HLADR^-$, $CD115^-$.

3. Immunomodulatory effects of MSCs on different immune cells

An important characteristic of the MSCs is their ability to suppress and modulate the immune system [19]. The MSCs have inhibitory effect on the different immune cells such as T, B, natural killer (NK), and dendritic cells (DCs).

T cells play a pivotal role in the initiation and formation of several autoimmune and inflammatory diseases. There are several reports regarding the increased levels of different TH1-derived cytokines in the peripheral blood and CNS of EAE animal models [36,37]. Additionally, EAE can be induced in the naive recipient mice by the adoptive transfer of myelin-specific $CD4^+$ TH1 cells [38]. Current data indicates that beside the TH1 cells, TH17 cells play an important role in neuroinflammatory process of MS [39–42]. The immunopathogenic role of $CD8^+$ T cells is also substantiated in the immunopathogenesis of MS and EAE [43,44]. The MSCs affect T cells through several mechanisms, such as inhibition of the T cell proliferation which arrest cell cycle in G_0/G_1 phase [45,46]. There are several reports which indicate human bone marrow derived MSCs(BM-MSCs can suppress the proliferation of *in vitro* pre-stimulated T cells [46,47]. Moreover, it has been reported that while BM-MSCs suppress TH1 (TNF-α and IFN-γ) and TH17 (IL-17) derived cytokines, they enhance the production of anti-inflammatory cytokines such as IL-4 from TH2 cells. Consequently, these cells cause an immune deviation from TH1and TH17 toward TH2 responses [48,49]. The immunosuppressive effects of Adipose derived MSCs on inflammatory cytokines and transcription factors of mouse mononuclear leukocytes such as IL-17, IFN-γ, and T-bet and also stimulatory effects such as upregulation of TGF-β have been reported by other investigators [50]. However, there is a controversial report which implied increased expression of TH17 cytokines and decreased IL-10 production from TH cells following treatment with human derived MSCs [51]. Consistently, there are controversial reports regarding the level of IL-23 production following MSC-therapy in both *in vitro* and *in vivo* studies [52–55]. Interestingly, while MSCs can secrete GM-CSF [56], they inhibit the production of this growth factor from other mononuclear cells such as T cells [57]. MSCs can also affect the regulatory T (Treg) cells. It has been shown that co-culture of MSCs and peripheral blood mononuclear cells (PBMC) leads to the generation of functional Treg cells [49,58]. Moreover, it was reported that, Human MSCs can also suppress proliferation and cytotoxic function of cytotoxic T lymphocytes (CTLs) [59]. Also it has been shown that the human MSCs can suppress the expansion of invariantNKT (iNKT) and γδT cells in part through PGE2 (but not IDO and TGF-β) [60]. It has been reported that MSCs can exert their regulatory effects through both contact dependent and contact independent (via soluble factors) mechanisms. While the expression of inhibitory molecules such as PDL1 and PDL2 on human MSCs can suppress effector T cells [61], the lack of co-stimulatory molecules on these cells induces anergy in T cells [19]. Moreover, it was demonstrated that the soluble factors secreted from BM-MSCs inhibit T cell proliferation in a culture system using a semi-permeable membrane [45,46]. It has been shown that MSCs secrete a wide variety of soluble factors such as IL-1β, hepatocyte growth factor (HGF), transforming growth factor (TGF)-β, prostaglandine (PG)E2, indolamin 2,3 dioxygenase (IDO), hemoxygenase-1 (HO-1), leukocyte inhibitory factor (LIF), insulin growth factor (IGF), SHLAG5, galactin, jagged-1 and IL-10 (Fig. 1) [45,48,62–73]. Most of these factors are not secreted naturally from BM-MSCs; however, the interaction with activated T cells induces their production. Exposure of BM-MSCs with IFN-γ before their therapeutic application increases their immunosuppressive effect. Consequently, it seems that application of MSCs for the treatment of inflammatory diseases such as graft versus host disease (GVHD) in which the higher amounts of IFN-γ is secreted might be rational [67]. In this mechanism, produced IFN-γ by T and NK cells in the inflammatory area induces the production of IDO molecule by MSCs, which suppress the immune system (Fig. 1) [67,74]. Interestingly, it has been demonstrated that low concentrations of IFN-γ are needed for MHC-II expression and antigen presentation by MSCs. Moreover, it is suggested that antigen presentation occur during a narrow period prior to higher levels of IFN-γ [75]. Furthermore, IFN-γ-induced antigen presentation of MSC can be modulated by TGF-β, serum factors, and cell density *in vitro* through their convergent effects on CIITA expression [76]. The cross-presentation of exogenous antigens to an effective $CD8^+$ T cells by MSCs has been also reported [76].

DCs are the professional antigen presenting cells that present the antigens to T cells and activate them. As a result, MS pathogenesis can be also significantly affected by DCs that can infiltrate into CNS [77]. DC maturation plays a key role in initiating T cell responses. In some microenvironmental conditions, immature DCs can be generated which leads to induction of IL-10-producing Treg cells and T cell anergy [78]. Moreover, there are some regulatory DCs which enhance peripheral tolerance and development of the Treg cells [78]. It has been reported that human MSCs not only inhibit conventional DCs, but also induce regulatory DCs [79,80]. The secreted factors from MSCs such as PGE2, IL-6 and monocyte-colony stimulating factor (M-CSF) can significantly inhibit the differentiation, endocytosis and IL-12 secretion in DCs [80]. It

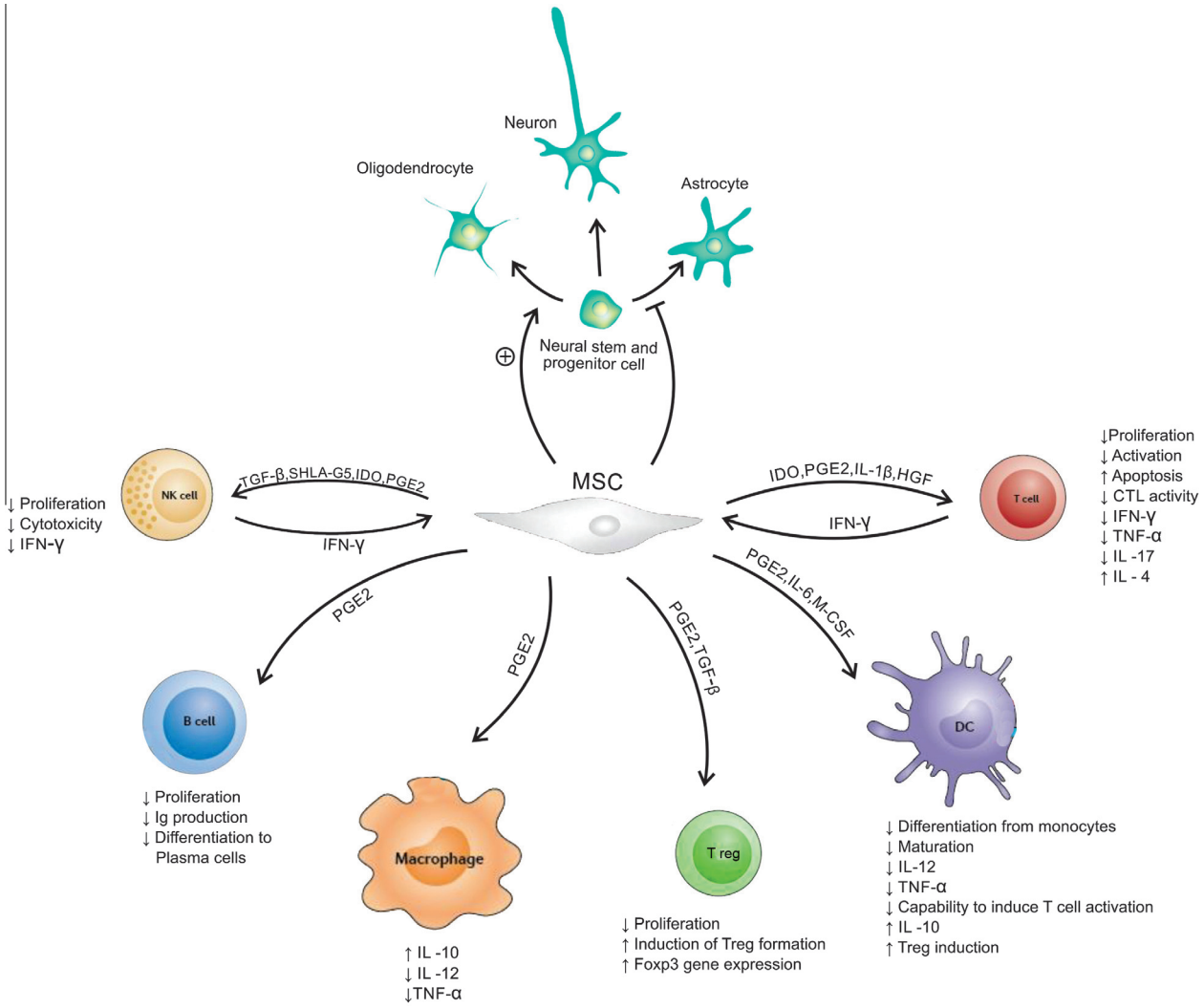

Fig. 1. The effects of MSCs on immune system and neural stem and progenitor cells. IDO: indolamine 2, 3 dioxygenase, PGE2: prostaglandine E2, HGF: hepatocyte growth factor.

has been shown that the DCs induced in the presence of human MSCs, produce a fewer amount of IL-12, TNF-α and MHC class II and higher levels of IL-1β and IL-10 (Fig. 1) [81]. So which, MSCs disrupt the DC maturation which result in production of the non-functional T cells [79]. Recently it has been showed that BM-MSCs express some toll-like receptors (TLRs) such as TLR1, 3, 4, and 5. MSCs stimulated by TLR4, secrete mainly pro-inflammatory cytokines, however, those stimulated by TLR3 secrete the immunomodulatory mediators such as IDO which can suppress DCs [82,83]. So which, MSC function is critically dependent on the inflammatory state of their microenvironment. This is especially important in considering MSCs for immunosuppressive therapies [84–86]. Recently, it is reported that the modulatory effects of TLR ligans on MSCs is through microRNAs (miRNAs) [87]. Surprisingly, TLR2/6-dependent stimulation of MSCs promotes angiogenesis *in vitro* and *in vivo* which implies a novel mechanism for therapeutic angiogenesis [56].

NK cells play an important role in destroying the cells infected by virus and tumor. This cells also secrete significant amount of inflammatory cytokines such as TNF-α and IFN-γ [88,89]. Several studies have been shown that the human MSCs could inhibit the proliferation of NK cells and their cytokine production. This inhibition takes place by the contact-dependent mechanism or soluble factors such as PGE2 and TGF-β [88,89]. The secreted SHLAG5 by human MSCs could inhibit both cytotoxic function and IFN-γ production of NK cells (Fig. 1) [73]. The expression of SHLAG5 receptors including Ig-like transcript (ILT)-2, ILT-4 and CD96 has been detected on some leukocytes and particularly NK cells which can lead to immune suppression [90].

B cells can significantly affect the pathogenesis of MS [91]. It has been demonstrated that autoantibodies were reactive against myelin proteins and neurons and influenced the demyelination process [92]. Recent studies showed that human BMMSCs could suppress the proliferation and immune function of B cells stimulated by anti-CD40 monoclonal antibody or IL-4 [93].

4. The role of MSCs in the treatment of MS and EAE animal models

It has been shown that the systemic injection of the murine MSCs to the EAE animal model could induce immune tolerance and T cell anergy [28]. Moreover, following systemic administration of green fluorescent protein (GFP)-labeled MSCs, they were migrated into CNS lesions and lymph nodes of EAE mice and decreased disease symptoms [22,28]. Gordon and coworkers have been demonstrated that human-derived MSCs injected intraperitonealy exert profound ameliorative effects in EAE model, however,

with little CNS infiltration [94]. Infiltration of MSCs into CNS and their ameliorative effects on EAE animal model have been also demonstrated by other group [95]. It is suggested that human and rodent derived MSCs can fuse in the cerebellum of mice and create heterokaryon [96]. Another group showed that allogeneic MSCs could attenuate EAE. They reported that this ameliorative effect was associated with reduction of neuroinflammatory cytokines such as IFN-γ and IL-17. Interestingly, they observed that prestimulation of MSCs with IFN-γ result in complete loss of their suppressive function and immune rejection, *in vivo* [97]. Accumulation of intravenously administered human MSCs in myelin damaged area of EAE mice and reduction of demyelination have been reported by other investigators [94]. On the other hand, Grigoriadis and coworkers demonstrated that although intracerebroventricular administration of autologous MSCs into mice with mild EAE was associated with ameliorative effect, it could not attenuate severe EAE and was associated with some adverse effects [23]. The intra-cerebrally injected human placental MSCs into EAE mice have also decreased disease severity and increased mice survival [98]. Moreover, intrathecal injection of MSC-derived neural progenitors into EAE mice showed significant ameliorative and neuroprotective effects. These cells are a subtype of bone marrow MSCs with neural progenitor and immunomodulatory characteristics, and a decreased potential for differentiation toward mesoderm [99]. Characterization of these progenitor cells in MS patients showed that they share similar phenotype and immunomodulatory function with those derived from normal individuals [100]. The human umbilical cord-derived MSCs have also exerted anti-inflammatory function in EAE mice [101]. The infusion of adipose-derived MSCs to EAE mice could also maintain glycogen synthase kinase 3β (GSK3β) in inactive form which led to control of neuroinflammation [102]. Yousefi and colleagues have recently been compared the efficacy of intraperitoneal and intravenous injection routs of adipose-tissue MSCs in EAE mice. They observed that intraperitoneal infusion had higher effect on increasing splenic Treg numbers and IL-4 levels, and decreasing IFN-γ and cell infiltration in brain compared to intravenous injection. However, both routs of injections, similarly downregulated splenocyte proliferation, IL-17 generation and disease symptoms [103]. On the other hand, Wang and coworkers compared the therapeutic efficacy of bone marrow-derived MSCs with human embryonic MSCs in treatment of EAE. They showed that the embryonic MSCs had higher therapeutic effects in EAE attenuation and inhibiting demyelination process compared to bone marrow-derived MSCs. Moreover, treatment of EAE mice with bone marrow MSCs was associated with IL-6 upregulation which declines therapeutic efficacy of MSCs [104].

One interesting approach in MS therapy is the using genetic engineered MSCs which can express some therapeutic proteins such as anti-inflammatory cytokines. It is suggested that transfection of MSCs with neurotrophin-3 gene can significantly increase their remyelination potential in animal models [105]. Intraperitoneal injection of MSCs expressing vasoactive intestinal peptide (VIP) has also reduced EAE symptoms [106]. The intraperitoneal injection of IL-10 expressing human adipose-derived MSCs to EAE mice had also beneficial effects [107]. Interestingly, administration of IFN-β secreting bone marrow-derived MSCs to EAE mice alone [108] or in combination with minocycline [109] significantly decreased disease progression, demyelination and inflammation. Furthermore, intranasal administration of myelin oligodendrocyte glycoprotein-specific receptor expressing MSCs to EAE mice was associated with higher CNS infiltration of MSCs and disease regression [110]. Moreover, it is reported that 17β-estradiol increased efficacy of intravenous infusion of adipose-derived MSCs in axon remyelination in mouse cuprizone model of MS [111]. The similar results regarding the ameliorative potential of adipose-derived MSCs in mouse cuprizone model are reported by others [112]. Controversially, it is reported that neither murine nor human bone marrow-derived MSCs entered the damaged area in the CNS of mouse cuprizone model, so which they could not exert protective effects [113]. Coadministration of minocycline and bone marrow-derived MSCs to EAE mice enhanced the ameliorative capacity of stem cells [114]. Moreover, it has been suggested that pharmacological regulation of autophagy process may increase immunosuppressive action of MSCs in EAE mice [115].

Different immunosuppressive and neuroprotective mechanisms are involved in the ameliorative effects of MSCs in the treatment of EAE. It has been shown that the treatment of EAE with the human BM-MSCs could decrease IFN-γ- and increase IL-4-producing cells. Moreover, treatment with MSCs not only decreases TH1 and TH17 derived cytokines (such as IL-17, IL-2, IL-12, IFN-γ and TNF-α), but also enhances the production of TH2 derived cytokines (such as IL-5 and IL-4) [20,116]. It has also been reported that IFN-γ enhances the production of several immunomodulatory factors such as IDO, TGF-β, PGE2, Cox-2 and HGF by accumulated MSCs in inflammatory regions of CNS [117]. Moreover, it has been also shown that human BM-MSCs-derived PGE2 enhances the generation of anti-inflammatory macrophages which produce IL-10 [118]. Moreover, MSCs increase the phagocytic function of macrophages for clearing the apoptotic cells and cause the stimulation of the neurogeneration [119]. Moreover, it has been reported that TLR3-mediated stimulation of MSCs in the CNS, induces anti-inflammatory properties which can be useful in the treatment of EAE and likely MS [82,120]. In a recent study where conditioned medium derived from MSCs (MSC-CM) was infused into EAE mice, it was observed that HGF signaling mediates MSC-CM-induced changes in cytokine expression in EAE. Moreover, inhibition of HGF signaling decreased MSC-mediated functional recovery in EAE [121]. Furthermore, it was reported that splenocytes from the EAE mice treated with MSCs, were less proliferative compared to those treated by other methods [20].

Previous studies have been demonstrated that the frequency and function of Treg cells were decreased in MS patients [122–124]. Interestingly, it has been demonstrated that MSCs could increase the frequency of Treg cells and induce the expression of FoxP3 both *in vitro* and *in vivo* [28,125,126]. Consistently, treatment of EAE mice with MSCs led to reduced disease progression, and increased Treg cells, Foxp3, TGF-β1, and IL-10 mRNA in the spleen and lymph nodes [127]. Intravenous injection of human bone marrow-derived MSCs to EAE mice not only decreased Th17 cells, but also increased the frequency of regulatory B cells [128].

Interestingly, treatment of EAE mice with human BM-MSCs increased oligodendrocytes in the CNS and decreased the number of astrocytes. Considering the fact that the astrocytes disturbs the CNS repair process and oligodendrocytes remyelination, it seems that the application of MSCs will be associated with ameliorative effects in MS patients (Fig. 1) [20]. Consistently, injection of bone marrow-derived MSCs to mice with chronic demyelinated white matter, activated oligodendrocyte progenitors and enhanced remyelination process in the grafted area [129]. On the other hand, it has been shown that MSCs modulate astrocyte response through regulation of apoptosis and inflammation [130]. This modulatory effect is in part through regulation of ciliary neurotrophic factor (CNTF) and the Janus kinase/signal transducer and activator of transcription (JaK/STAT) pathway [131].

It is suggested that the neuroprotective function of MSCs in EAE animal models is related in part to their antioxidative action [132]. Consistently, Kemp and colleagues have recently been showed that human derived MSCs could exert neuroprotective effects in part through secretion of superoxide dismutase 3 as a potent antioxidant biomolecule, *in vitro* [133]. Moreover, it is reported that the secretion of superoxide dismutase 3 was regulated synergistically by the cyto-

kines such as TNF-α and IFN-γ [134]. It has been also reported that the neuroprotective function of MSCs can be exerted in part through decreasing neuronal sensitivity to glutamate receptor ligands [135]. Koning and colleagues have been recently showed that during the acute phase of EAE, the frequency of MSCs in the bone marrow was significantly decreased [136]. This observation suggests that during disease progression MSCs migrate to periphery with higher numbers compared to non-progressive disease stages.

The above mentioned immunomodulatory and neuroprotective characteristics together with the ability of MSCs to migrate into the CNS and differentiation into neuron cells, have suggested the use of MSCs in EAE treatment [137,138]. Recently it was shown that the intravenous administration of adipose-derived MSCs to the EAE mice prior to the beginning of the disease led to MSCs homing in lymphoid organs and CNS. Subsequently, these MSCs were able to reduce the brain and spinal cord inflammation, demyelination, and the severity of EAE [21]. Moreover, intracerebroventricularly administrated human MSCs which induced the secretion of neurotrophic factors in EAE mice had ameliorative effect and prolonged the animal survival through the mechanisms of immunomodulation and neuroprotection [139]. It has also been demonstrated that the administration of adipose-derived MSCs into EAE animal models, not only reduced both demyelination and axonal loss, but also induced TH2-type cytokine production and increased the number of endogenous oligodendrocyte progenitors [21].

In initial human studies, Mohyeddin Bonab and colleagues injected ten progressive MS patients intrathecally with *ex vivo* expanded MSCs. Although they did not reach to fully successful results, however, it was hopeful [140]. Another group has investigated the ameliorative effect of endometrial regenerative cells which are a population of mesenchymal-like stem cells in four MS patients. The intravenously and intrathecally injected cells had ameliorative effects without significant adverse effects [141]. The administration of umbilical cord derived MSCs to MS patients was also associated with immunosuppression and disease attenuation [142]. Yamout et al. have recently been reported that the intrathecal injection of *ex vivo* expanded autologous bone marrow derived MSCs to ten MS patients was associated with ameliorative effects [143]. Karussis and coworkers performed a phase 1/2 open-safety clinical trial in 15 MS patients with using intrathecal and intravenous administration of autologous MSCs and showed immunomodulatory effects of MSCs and their safety in MS therapy [144]. Another phase IIA study has been also confirmed the feasibility, safety and efficacy of autologous MSCs in ten SPMS patients [145]. Moreover, treatment of fifty MS patients in Iraq with intrathecal injections of peripheral blood cells purified via aphaeresis following G-CSF (granulocyte colony stimulating factor) therapy was associated with hopeful outputs [146]. Consistently, Connick and colleagues have recently published the results of a clinical trial study in which ten SPMS patients with optic nerve disabilities were intravenously injected with autologous MSCs and were under supervision for 10 months. It was observed that these patients gained a relative recovery in their optic nerves and no side effect was observed during the use of MSCs [147]. The intravenous infusion of autologous MSCs to eight MS patients was also associated with some positive effects without significant adverse effects [148]. Bonab and colleagues have also been surveyed the ameliorative effects of MSCs transplantation in twenty-five progressive MS patients unresponsive to conventional treatments and showed that a intrathecal infusion of *ex vivo* expanded MSCs attenuates disease symptoms without significant adverse effects [149]. It has also been demonstrated that intrathecal treatment of MS patients with MSCs leads to upregulation of FoxP3 in PBMCs [150]. On the other hand, it is demonstrated that intrathecal injection of MSCs to twenty-five MS patients had no effect on cytokines such as IFN-γ, TGF-β, IL-4, IL-10, IL-6 and also FoxP3 in peripheral blood. The authors have suggested that this variation is due to local function of MSCs in CNS [151]. Moreover, during four years treatment of one progressive MS patient with both allogenic human umbilical cord-derived MSCs and autologous bone marrow-derived MSCs no significant adverse effect was observed and ameliorative effect was also appeared [152].

Several ongoing clinical trials in the different world area are investigating the effectiveness and adverse effects of treatment of MS patients using the MSCs [153]. However, despite performing some phase I/II studies, no significant positive results have been reached until now and further investigations are required (as shown in Table 1) [154].

5. Advantages and disadvantages of the application of MSCs

The main disadvantage of using the immunosuppressive medications is the lack of effective discrimination between the immune

Table 1
Studies related to the role of MSCs in the treatment of MS.

The main claim	Number of patients	Refs.
Intrathecal Infusion of *ex vivo* expanded MSCs was associated with some ameliorative effects	10	[140]
The intravenously and intrathecally injected mesenchymal-like stem cells attenuate disease symptoms	4	[141]
The umbilical cord derived MSCs suppress neuroinflammation in MS patients	ND	[142]
The intrathecal injection of ex vivo expanded autologous bone marrow derived MSCs to MS patients decreased disease symptoms	10	[143]
The intrathecal and intravenous administration of autologous MSCs was safe and modulated immune responses in MS patients	15	[144]
The autologous MSCs are safe and efficient tools in treatment of MS patients	10	[145]
The intrathecal injections of peripheral blood cells purified via aphaeresis following G-CSF therapy was associated with hopeful outputs	50	[146]
The intravenous injection of autologous MSCs to SPMS patients with optic nerve disabilities led to a relative recovery in their optic nerves	10	[147]
The intravenous infusion of autologous MSCs to MS patients attenuates MS symptoms	8	[148]
The treatment of MS patients unresponsive to conventional treatments with intrathecal infusion of ex-vivo expanded MSCs attenuates disease symptoms	25	[149]
The intrathecal injection of MSCs to MS patients leads to upregulation of FoxP3 in peripheral blood mononuclear cells	7	[150]
The intrathecal injection of MSCs to 25 MS patients had no effect on cytokines such as IFN-γ, TGF-β, IL-4, IL-10, IL-6 and also FoxP3 in peripheral blood	25	[151]
Both allogeneic human umbilical cord-derived MSCs and autologous bone marrow-derived MSCs have ameliorative effect in MS patient	1	[152]
The MSCs isolated from MS patients and normal subjects have similar proliferation, differentiation potential and cell surface antigen expression	4	[160]
Autologous and allogeneic human MSCs suppress both antigen specific and antigen non-specific T cells isolated from MS patients in part through secretion of PGE2, similarly.	15	[161]
The MSCs derived from MS patients showed the decreased suppressive function and distinct gene expression profile of compared to those isolated from normal subjects	ND	[162]

ND: not determined.

response against the pathogens and the immune response against the body tissues in the autoimmune disease. Consequently, the suppression of the host immune system through these medications declines the immune system against the infections and pathogens. Fortunately, immunosuppressive function of MSCs is limited to inflammatory regions, because they have ability to migrate into the inflammatory tissues. However, despite the mentioned advantages, there are some concerns about formation of the ectopic tissues by the MSCs and also there is a possibility of their transformation and tumorigenic potential [19,155].

6. Immunogenicity of MSCs

As the MSCs do not express MHC class II molecules and co-stimulatory molecules such as CD80, CD86 and CD40, they are considered as low immunogenic cells. Moreover, MSCs seldom express MHC class I molecules [156]. However, recent studies showed that the MSCs have high number of receptors that enables them to communicate with T cells. These receptors include ALCAM (activated leukocyte cell adhesion molecule), ICAM1 (intracellular adhesion molecule-1) and VCAM1 (vascular cell adhesion molecule-1) that connect to their ligands on the T cells [157]. Although it has been suggested that the MHC class II molecules do not express on MSCs, the western blot experiments have been shown their expressin, likely in cytosol [158]. Moreover, the stimulation of MSCs by IFN-γ induces the expression of MHC class II [159]. Recent studies indicated that although the injected allogeneic MSCs can be identified after a long period of times, most of them are eventually destroyed by the immune system [157].

7. Conclusion

MSCs attracted considerable attention during the past decade. The application of MSCs has emerged a new therapeutic method for autoimmune diseases. Currently MSCs are widely used in the clinical trials and initial promising results are obtained regarding the control and prevention of MS. However, the mechanisms by which MSCs exert their ameliorative effects are elusive. Several studies have been showed that the MSCs are in close relation with various immune cells and mediators in the different inflammatory tissues. So which, they can be worthy tools for the treatment of different inflammatory disease such as MS. However, clarifying their precise mechanisms in the treatment of MS patients is needed. Identification of these mechanisms in the future can be determinant and helpful in selecting the appropriate dose and time of injection and also in selecting the type of MSCs from different source tissues for each state of the MS.

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None.

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