Cellular Immunology 293 (2015) 113–121

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Review

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

Tohid Gharibi [a,b], Majid Ahmadi [a,b], Narges Seyfizadeh [a,b], Farhad Jadidi-Niaragh [c,*], Mehdi Yousefi [a,b,*]

[a] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Department of Immunology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 16 November 2014
Accepted 2 January 2015
Available online 10 January 2015

Keywords:
Mesenchymal stem cells
Multiple Sclerosis
Immunomodulation

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

* Corresponding authors at: Department of Immunology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. Fax: +98 4113364665 (M. Yousefi).
E-mail address: Yousefime@tbzmed.ac.ir (M. Yousefi).

http://dx.doi.org/10.1016/j.cellimm.2015.01.002
0008-8749/

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