Multiple Sclerosis and Related Disorders 35 (2019) 233–238

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

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

Clinical trial

# Circulating mesenchymal stem cells, stromal derived factor (SDF)-1 and IP-10 levels increased in clinically active multiple sclerosis patients but not in clinically stable patients treated with beta interferon

Rahimeh Emamnejad[a,d], Mohammadali Sahraian[b], Yadollah Shakiba[c], Zahra Salehi[d], Ahmad Masoomi[e], Danyal Imani[d], Farangis Najafi[d], Bahareh Laribi[d], Hedayatollah Shirzad[a,**], Maryam Izad[b,d,*]

[a] Cellular and Molecular Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran
[b] MS Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Immunology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran
[d] Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[e] Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

*Keywords:*
Multiple Sclerosis
MSCs
SDF-1
IP10
IFNβ

ABSTRACT

*Background:* Mesenchymal stem cells (MSCs) have the capacity to migrate into the inflammatory regions in response to chemokines such as, IP-10 and SDF-1α and function as anti-inflammatory and immunomodulatory cells.

*Methods:* In this study we investigated the MSCs frequency in peripheral blood of Relapsing-Remitting Multiple Sclerosis (RRMS) patients in clinically active and not on disease-modifying therapy (DMT) ($n = 22$) and clinically stable on DMT (Interferon-β (IFN-β) therapy) for at least 6 months ($n = 22$) in comparison to sex and age-matched healthy controls ($n = 25$) using flow cytometry. The serum and gene expression levels of IP-10 and SDF-1a were also measured in studied groups by ELISA and Real time- PCR.

*Results:* We obtained significant high levels of circulating $CD45^-CD34^-$ $CD90^+$ and $CD45^-CD34^-$ $CD105^+$ cells in clinically active patients, not on DMT and patients under IFNβ therapy compared with control group. Furthermore, a significant increase in the percentage of circulating $CD45^-CD34^-$ $CD105^+$ $CD90^+$ cells was found in clinically active patients and not on DMT compared with control group. Serum analysis of IP-10 and SDF-1α showed a significant increase in IP10 concentration in both clinically active not on DMT ($P = 0.02$) and on DMT ($P = 0.005$) RRMS patients in comparison with controls.

The expression level of SDF-1α mRNA significantly increased in clinically active not on DMT ($P = 0.03$), while decreased in patients under IFNβ therapy ($P = 0.04$). The mRNA expression of IP-10 only increased in patients on DMT compared with controls ($P = 0.05$).

*Conclusion:* Circulating MSCs, IP-10 and SDF-1α levels, increased in RRMS patients with clinically active not on DMT and IFN-β therapy reduced circulating MSCs and SDF-1α levels.

## 1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) with an unknown etiology identified by demyelination, and irreversible axonal injury (Alvarez et al., 2011). More than 2.3 million people worldwide are suffering from MS, mostly young people (Bezzini et al., 2015). Prevalence of MS in Iran is also high (54.51 per 100,000 (in 2013)) (Etemadifar et al., 2014). About 85% of patients demonstrate a relapsing-remitting multiple sclerosis pattern (RRMS) (Jacques and Lublin, 2015). Dysregulation of immune system and development of auto reactive CD4+ and CD8+ T Cells, are believed to involve in the pathogenesis of the disease (Friese and Fugger, 2009; Fletcher et al., 2010; Nylander and Hafler, 2012).

Mesenchymal stem cells (MSCs) are multipotent and heterogeneous

* Corresponding author at:Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Poorsina St, 16 Azar St, Enghlab Ave, Tehran, Iran.
** Co-corresponding author at: Shahrekord University of Medical Sciences, Rahmatieh, Shahrekord, Iran.
*E-mail addresses:* shirzad1951@yahoo.com (H. Shirzad), izadm@sina.tums.ac.ir (M. Izad).

https://doi.org/10.1016/j.msard.2019.08.013
Received 15 October 2017; Received in revised form 27 June 2019; Accepted 11 August 2019

population of adult Bone Marrow Stem Cells (BMSCs) with high self-renewal capacities (Murphy et al., 2013; Baksh et al., 2004; Karussis and Kassis, 2008). MSCs enter the blood stream after injury and transmigrate to the damaged tissue to participate in immunomodulatory and restoration processes (Kucia et al., 2005). Mesenchymal stem cells may also regenerate nervous cells in the CNS, that is the cause of wide attention to its application in treating neurological diseases such as MS, Parkinson's disease and spinal cord injury (Buzhor et al., 2014). Human MSCs decrease peripheral blood mononuclear cells (PBMC) proliferation, IFN-γ production by T helper-1 (Th1) cells, TNF-α secretion by dendritic cells (DC) and monocytes, and also increase regulatory T cells and IL-10 production (Aggarwal and Pittenger, 2005). Mesenchymal stem cells inhibit the development of Th1, Th17 and Tc17 (IL-17-producing $CD8^+$ T cells) cells in vitro as well (Luz-Crawford et al., 2013; Glenn et al., 2014). In mice with experimental allergic encephalomyelitis (EAE) have been shown that MSCs were able to decrease Th17 and increase CD4 + CD25 + FOXP3 + cells (Luz-Crawford et al., 2013; Glenn et al., 2015).

IP-10/CXCL-10 and SDF/CXCL-12 are chemotactic factors for human MSCs. IP-10 from the Synovial fluid of normal and rheumatoid arthritis (RA) donors significantly recruit human subchondral mesenchymal progenitors (Li et al., 2010; Endres et al., 2010). A number of Studies have shown that the expression of SDF-1 and IP-10 upregulated at damaged tissues and inflammatory conditions and facilitate the homing of MSCs to the injured sites in the brain (Ji et al., 2004; Donega et al., 2014; Gruol, 2016). Human MSCs migrate to demyelinated lesions in response to chemokines including SDF-1, MCP-1, RANTES, MIP-1α and IP-10 (Rice and Scolding, 2010). The chemokine SDF-1α is an isoform of SDF that expresses by neurons (Stumm et al., 2002). IP-10 and SDF-1 are among chemokines which increase in CSF and serum of MS patients. It was also reported that IP-10 expressed in CNS lesions of MS patients and EAE (Szczuciński and Losy, 2007; Matsushita et al., 2013). IP-10 expression also increased in both circulating monocytes and BMSCs isolated from RRMS and secondary progressive (SP) MS patients when stimulated by lipopolysaccharide (LPS) (Bonechi et al., 2014). Astrocytes in both silent and active brain lesions of MS patients express SDF-1 (Calderon et al., 2006).

Interferon-beta (IFN-β) with Anti-inflammatory and immunomodulatory effects is used as the first-line therapy for the treatment of RRMS (Clanet, 2001). IFN-β decreases the relapse rate and severity of the disease and inhibits the development of new brain lesions and disability progression (Clanet, 2001). It also increases expression of IL-10 by monocytes and $CD4^+$ T cells (Liu et al., 2001), the percentage and suppressive function of Regulatory T cells (Namdar et al., 2010), and inhibits leukocyte transmigration across the blood-brain barrier (BBB) (Dhib-Jalbut and Marks, 2010). A study showed that IFN-β transiently increased plasma level of IP-10 in MS patients (Buttmann et al., 2004). Otherwise, MSCs produce different chemokines including IP-10 and SDF-1 and also express many chemokine receptors (CCR2, CCR3, CXCR3, CXCR4, CXCR6, CX3CR1) which lead to their migration (Croitoru-Lamoury et al., 2007). Interferon-β may alter the migration of MSCs from BBB via increasing chemokines receptor expression, including IP-10 and SDF-1 receptors, which are the therapeutic approach to the management of MS (Buttmann et al., 2004; Croitoru-Lamoury et al., 2007).

Because of immunomodulatory properties of MSCs, alteration of peripheral MSCs frequency in MS patients could be involved in the pathogenesis of the disease. In this study, we investigated whether the frequency of MSCs changed in clinically active but not on DMT/or clinically stable RRMS patients after IFN-β therapy. We also measured serum and PBMCs expression levels of IP-10 and SDF-1α.

## 2. Materials and methods

### 2.1. Patients and controls

Forty-four RRMS patients with clinically definite MS were enrolled in this study All patients evaluated with physical and neurological examination by a neurologist according to the revised McDonald's criteria (McDonald et al, 2011) (Polman et al., 2011). Twenty-Two patients were clinically stable on disease-modifying therapy (DMT) (16Female, 6Male; mean age: 35 ± 8.06 years, EDSS: 1.24 ± 0.69). These patients were under IFN-β therapy for at least 6 months (from 6 month up to 10 years). Patients on DMT have no symptoms at the time of sampling. Twenty-Two Patients were clinically active and not on DMT (18Female, 4Male; mean age: 29.71 ± 5.19 years, EDSS: 3.1 ± 0.8). They met our assumed inclusion criteria of not being treated with any kind of IFN-β or other immune modulatory drugs and/or corticosteroid for at least 3 prior months. These patients discontinue medication themselves, because their illness was not deemed severe enough and not have any symptoms until relapse.

The expanded disability status scale (EDSS) of all patients was also assessed by a neurologist. Samplings were done in 1 or 2 days after having symptoms. Fifty percent of patients showed visual impairment (blurred vision, diplopia) and 45.4% of them showed paresthesia symptoms at onset of the disease. All of the patients were referred to Iranian Center of Neurological Research in Sina General Hospital, Tehran University of Medical Sciences (TUMS). Twenty-Five ethnically, sex and age matched healthy controls (19 Female, 6male, age: 30.97 ± 6.1 years), who had no history of MS or other autoimmune and inflammatory diseases themselves and in their families, were also enrolled in this study. All patients and controls were of Iranian origin. The study was conducted according to the ethical guidelines of our institution. Informed consent was obtained from all participants prior to the study. The exclusion and inclusion criteria of studied subject are listed in Supplementary Table 1.

### 2.2. MSCs frequency determination using flow cytometry

Peripheral Blood Mononuclear Cells were isolated from blood by density gradient centrifugation over Lymphodex (inno-Train, Diagnostic Gmbh, Germany). The cells were stained with Anti-CD34-FITC, CD45-APC, CD90-PECY5 and CD105-PE monoclonal antibodies. All monoclonal antibodies were purchased from eBioscience, US. Samples were analyzed using flow cytometer (BD FACS Calibur, US). At least 50,000 events were counted for each sample.

### 2.3. Measurement of IP10 and SDF-1α gene expression levels by Real-time PCR

In order to determine chemokines gene expression levels, total RNA from PBMC of RRMS patients and controls were isolated using BIOZOL-total RNA extraction kit (Bioer, China) according to manufacturer's instruction. To remove genomic DNA contamination, the extracted RNA was first treated with RNase free DNase I and then reverse-transcribed to cDNA by cDNA synthesis kit (Thermo Fisher Scientific, US). Eva Green PCR Master Mix (Solis Bio Dyne, Estonia) was used for doing real-time PCR following the instructions of the supplier (Applied Bio systems, CA). Relative expression levels of chemokines mRNA were normalized by βeta-actin (ACTB) as a housekeeping gene and calculated by the $2^{-\Delta\Delta Ct}$ method. The primer sequences are showed in Supplementary Table 2.

### 2.4. Measurement of IP-10 and SDF-1α by ELISA

Sera were collected from clotted blood samples and frozen at –70 °C for chemokine assays using human IP10 Instant Elisa Kit (eBioscience, US) and human SDF-1a (CXCL12A) Elisa Kit (Thermo scientific,

**Table 1**
Demographic and clinical characteristics of patients and controls.

| Subjects | Sex female/male | Age (years) | Disease duration (years) | Treatment duration; (years) | EDSS score |
|---|---|---|---|---|---|
| Clinically active RRMS patients, not on DMT ($n$ = 22) | 18/4 | 29.7 ± 5.19 | 0–7 | Not on any kind of IFN-β or other immune modulatory drugs and/or corticosteroid 3 months prior to sampling. 1 - 2 days elapsed after the onset of relapse to the sampling. No corticosteroids were administered during the elapsed time | 3.1 ± 0.80 |
| Clinically stable RRMS, on DMT (**IFN-β treated**) ($n$ = 22) | 16/6 | 35 ± 8.06 | 0.5–12 | 0.5–10 | 1.24 ± 0.69 |
| **HCs** ($n$ = 25) | 19/6 | 30.9 ± 6.1 | – | – | – |

Values are expressed as mean ± SD. RRMS: relapsing-remitting multiple sclerosis; DMT: disease-modifying therapy; HC: healthy controls; EDSS: expanded disability status scale.

US).The detection limit for IP10 and SDF-1a were 1 pg/ml and 80 pg/ml respectively.

### 2.5. Statistical analysis

All analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 21.0 (SPSS Inc; Chicago, IL, US). Data are expressed as mean ± SD. Results with P value less than 0.05 were statistically considered significant. Variables between RRMS clinically active patients and not on DMT, IFN-β treated and controls were compared using One-way ANOVA. The post hoc test (Tukey's) was used to identify sample means that were different from others. Correlations between serum and gene expression levels of IP-10 and SDF-1α and the MSCs frequencies were assessed using the Pearson test.

## 3. Results

### 3.1. Patients and controls

Forty-Four RRMS patients and 25 healthy subjects were investigated in this study. Demographic characteristics of the subjects are given in Table 1.

### 3.2. The percentage of circulating MSCs decreased after IFNβ therapy

In this study, three populations of MSCs, $CD45^-CD34^-$ cells, expressing CD90 and/or CD105 markers, were identified according to previous studies (Fortini et al., 2011; Marketou et al., 2014). Lymphocytes and monocytes were first gated on a forward vs. side scatter dot plot and then the percentage of CD90+, CD105+ and CD90+ CD105+ cells were analyzed in CD34- CD45- population as MSCs. Supplementary Figure1 shows a typical example of our analytical gating strategy to analyze the circulating MSCs.

The results of flow cytometry analysis showed that there was a significant difference in the frequency of MSCs between the groups, Clinically active and not on DMT RRMS Patients were shown to have significantly higher proportions of circulating $CD45^-CD34^-CD90^+$ ($P = 0.0001$) and $CD45^-CD34^-$ $CD105^+$ ($P = 0.001$) compared to healthy controls. These cells decreased in patients under IFN-β therapy ($P \leq 0.01$) although the percentage of CD45-CD34-CD90+ cells was significantly higher than controls yet ($P = 0.03$). Furthermore, a significant increase in the number of circulating $CD45^-CD34^-$ $CD105^+$ $CD90^+$ cells was found in clinically active patients compared to control group ($P = 0.02$) (Fig. 1).

### 3.3. IFNβ alters the expression levels of IP10 and SDF-1α in RRMS patients

Analysis of IP10 and SDF-1α mRNA expression levels in PBMC of MS patients showed that the expression of SDF-1α mRNA significantly increased in clinically active patients compared with controls ($P = 0.03$) and significantly decreased in patients under IFNβ therapy and reached to controls' level ($P = 0.04$) (Fig. 2A). The mRNA expression of IP-10 also increased in clinically stable patients compared to controls ($P = 0.05$) (Fig. 2B). Additionally, we observed a positive correlation between the frequency of $CD105^+90^+$ MSCs and expression of SDF-1α ($P = 0.037$) and IP10 ($P = 0.004$) in RRMS patients on DMT (Fig. 2C and D respectively).

### 3.4. Elevated levels of IP10 and SDF-1α in sera of RRMS patients

Serum analysis of IP10 and SDF-1α chemokines showed that IP10 concentration significantly increased in sera of clinically active patients and patients under IFN-β therapy in comparison to controls (P = 0.02 and P = 0.005 respectively). However, no significant difference in IP-10 was seen between patients in clinically active but not on DMT and patients on DMT ($P = 0.2$) (Fig. 3A). Serum concentration of the SDF-1

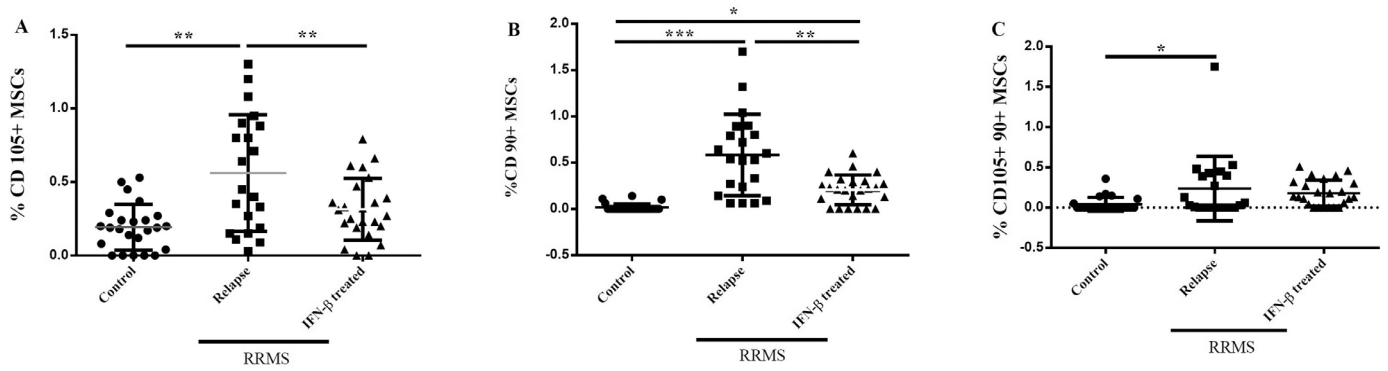


**Fig. 1.** The percentage of $CD45^{-}$ $CD34^{-}/CD105^{+}$(A), CD $90^{+}$ (B) and CD $105^{+}$ $CD90^{+}$ (C) MSCs in gated lymphocytes and monocytes of healthy controls (n = 25), clinically active RRMS patients but not on DMT (n = 22) and clinically stable on DMT (IFN-β treated) (n = 22). One-way ANOVA was used to show the differences between groups. *P*-value <0.05 was considered statistically significant. * *P*-value < 0.05; ** *P*value < 0.01; *** *P*value < 0.001.

in clinically active RRMS patients also increased in comparison to other groups, although it was not significant (Fig. 3B). Interestingly, there was a positive correlation between serum and expression level of IP10 in clinically active RRMS patients ($P = 0.023$) (Fig. 3C). There were not such correlations in other groups.

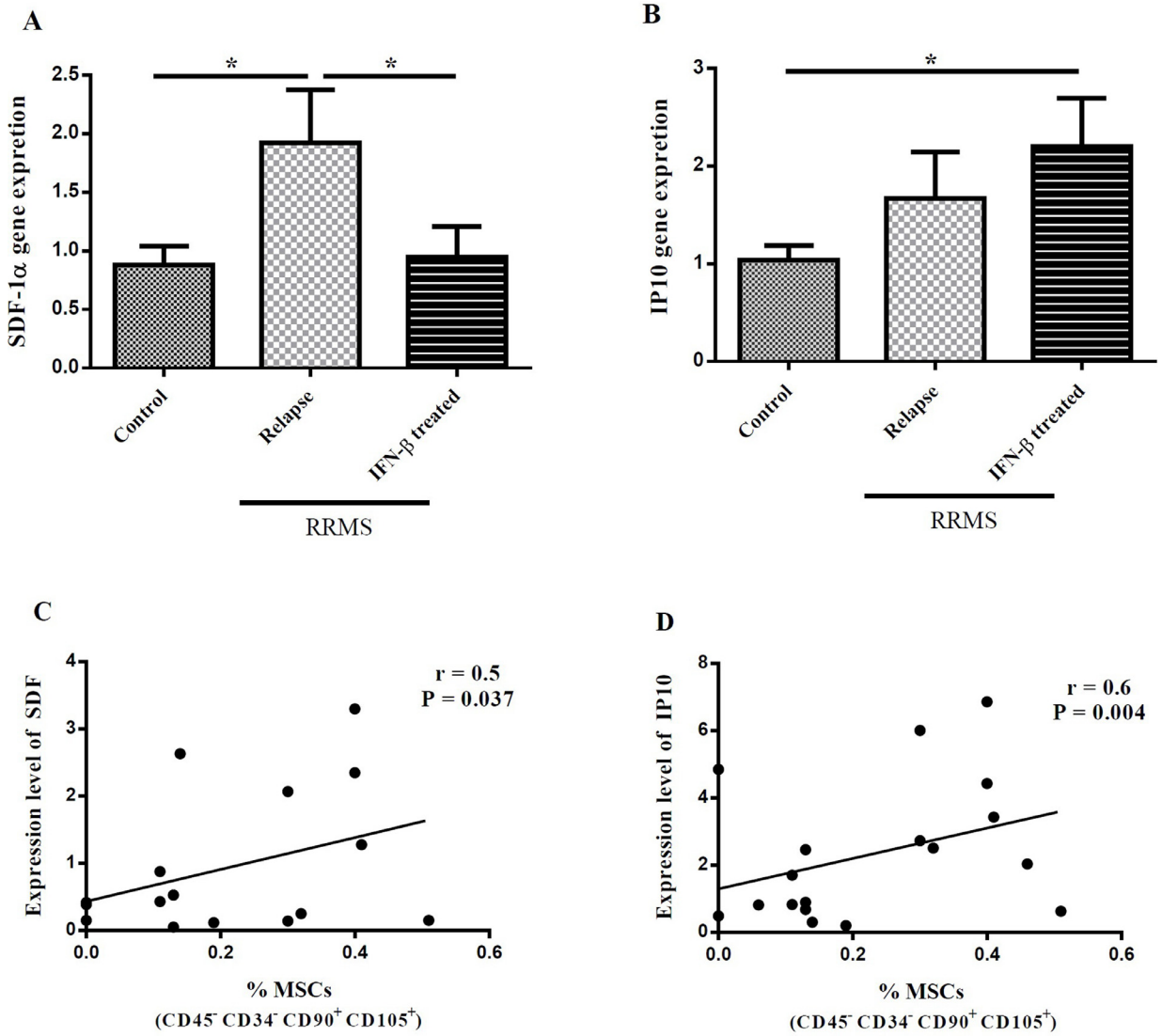


**Fig. 2.** The mRNA expression level of SDF-1α (A) and IP10 (B) were measured by qPCR in RRMS patients and healthy controls. One-way ANOVA was used to test the differences between the groups. Correlation between MSCs frequencies and SDF-1α (C) and IP10 (D) expression levels analyzed using Pearson's Correlation Coefficient. *P*-value ≤ 0.05 was considered statistically significant. * *P*-value < 0.05; ** *P* value < 0.01.

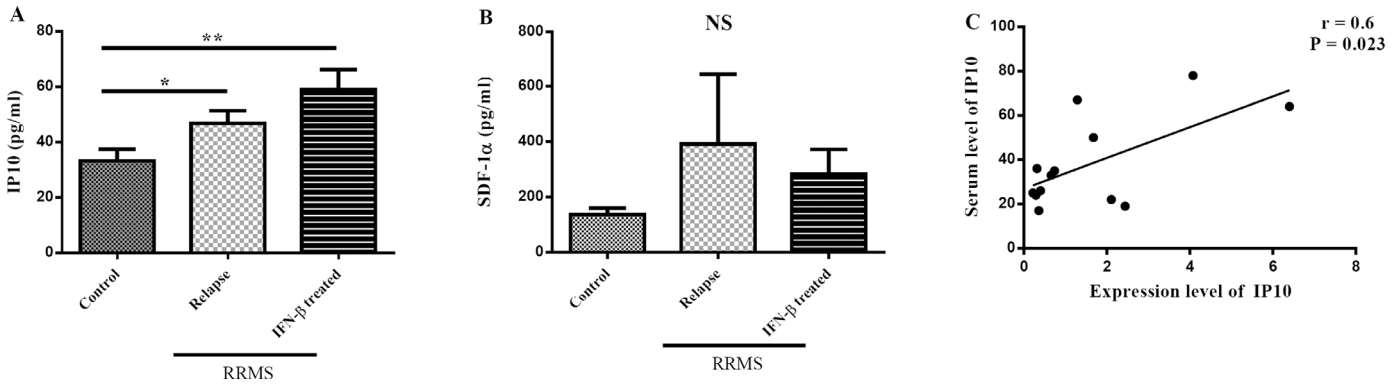


**Fig. 3.** The levels of IP10 (A) and SDF-1α (B) were measured by ELISA in serum of RRMS patients and healthy controls. One-way ANOVA was used to test the differences between groups. Correlation between serum and expression level of IP10 (C) analyzed using Pearson's Correlation Coefficient. *P*-value $\leq 0.05$ was considered statistically significant. * *P*-value $< 0.05$; ** *P*value $< 0.01$.

## 4. Discussion

Mesenchymal stem cells with immunomodulatory functions have been shown to migrate into injured and inflamed sites in response to inflammatory cytokines and chemokines to reduce inflammation (Wojakowski and Tendera, 2005; Castillo-Melendez et al., 2013). In acute phase of MS, inflammation and demyelination could induce migration of MSCs from BM to blood stream and then into the damaged CNS (Karussis and Kassis, 2008). The lack of or decreased MSCs in PB of healthy individuals can explain the absence of injury or inflammation (Hoogduijn et al., 2014).

In EAE, injection of MSCs reduced disease severity and pro-inflammatory cytokines, IFN-γ, IL-17, TNF-α, IL-2, and IL-12p70, and improved demyelination (Bai et al., 2012). Recently, de Oliveira GL et al, also showed a defect in immunomodulatory and immunosuppressive activities of MSCs isolated from patients with multiple sclerosis (de Oliveira et al., 2015).

In this study, we examined the frequency of MSCs in peripheral blood of RRMS patients. Our data showed significant higher level of circulating $CD45^-CD34^-$- $CD90^+/CD105^+$ and $CD90^+$ $CD105^+$ cells in clinically active RRMS patients, not on DMT and IFN-β decreased them. To our knowledge, this is the first study to evaluate circulating MSCs in RRMS patients.

Chemotaxis assays revealed that IP10 and SDF-1α had a critical role in the migration of MSCs (Croitoru-Lamoury et al., 2007). A number of studies showed elevation of IP10 and SDF in MS lesions, CSF and serum of RRMS in active phase (Calderon et al., 2006; Trebst and Ransohoff, 2001; Sørensen et al., 2002; Franciotta et al., 2001). This up-regulation of chemokines seemed to have an important role to regulate the circulation and homing of MSCs to the damaged sites in the brain (Song et al., 2011). Consistent with previous studies, we also found that the mRNA expression and serum level of SDF-1α and IP-10 significantly increased in clinically active RRMS patients, not on DMT. While, IFN-β decreased SDF-1. On the other hand MSCs increased in circulation of clinically active patients and decreased after IFN-β therapy. This result could suggest that SDF-1α cause elevation of circulating MSCs at clinically active phase which needs more exploration.

IFN-β therapy slightly increased IP-10, which is significantly different when compared with healthy individuals (Fig. 2b and 3). In a previous study, it was also shown that IFN-β could cause a transient increase of expression and plasma level of IP-10 in MS patients (Buttmann et al., 2004). Overally, both type I and type II INFs as well as LPS can induce the expression of IP-10. In LPS-stimulated macrophages, the IP-10 express through production of IFN-β (Hamilton et al., 1989; Toshchakov et al., 2002; Groom and Luster, 2011; Fukumoto et al., 2012).

Interestingly, transplantation of pluripotent stem cells in a mouse model of acute liver injury increased the expression of IP-10 in injured liver to repair damage and promote liver regeneration (Chan et al., 2012).

Additionally, the CXC chemokine receptor 3 (CXCR3), a receptor for IP10, was previously reported to express on activated human CD4+ T cells (Melter et al., 2001). Paradoxically, previous studies have reported that CXCR3 also expressed on $FOXP3^+CD4^+$ Tregs and IFN-γ was required for the optimal expression of CXCR3 by Treg cells and these cells had a marked chemotactic response toward IP-10 (Hoerning et al., 2011; Koch et al., 2009). Otherwise, it was shown that a deficiency of IP-10 resulted in increased IFN-γ-producing CD8+ T cells (Rosenblum et al., 2010). In this way, elevation of IP-10 after IFN-β therapy could be an immunomodulatory effect of IFN-β. However, more investigation requires exploring the frequency, phenotype and also functions of MSCs in CNS and PB after IFN-β therapy.

## 5. Conclusion

This study suggests that MSCs with Immunomodulatory and regenerative capacities might release into peripheral blood under inflammatory situation and subsequently migrate to damage CNS in response to IP-10 and SDF-1.

## Declaration of Competing Interest

None.

## Acknowledgment

We are grateful to personnel of, Sina General Hospital, Tehran University of Medical Sciences and patients as well for their help to collect samples.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.08.013.

## References

Aggarwal, S., Pittenger, M.F., 2005. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 105 (4), 1815–1822.
Alvarez, J.I., Cayrol, R., Prat, A., 2011. Disruption of central nervous system barriers in multiple sclerosis. Biochim. Biophys. Acta 1812 (2), 252–264.
Bai, L., et al., 2012. Hepatocyte growth factor mediates mesenchymal stem cell-induced recovery in multiple sclerosis models. Nat. Neurosci. 15 (6), 862–870.
Baksh, D., Song, L., Tuan, R., 2004. Adult mesenchymal stem cells: characterization, differentiation, and application in cell and gene therapy. J. Cell. Mol. Med. 8 (3), 301–316.
Bezzini, D., et al., 2015. Prevalence of multiple sclerosis in Tuscany at 2011: a study based on validated administrative data. Eur. J. Public Health 25 (suppl 3), ckv172 039.

Bonechi, E., et al., 2014. Increased CXCL10 expression in MS MSCs and monocytes is unaffected by AHSCT. Ann. Clin. Transl. Neurol. 1 (9), 650–658.
Buttmann, M., Merzyn, C., Rieckmann, P., 2004. Interferon-β induces transient systemic IP-10/CXCL10 chemokine release in patients with multiple sclerosis. J. Neuroimmunol. 156 (1), 195–203.
Buzhor, E., et al., 2014. Cell-based therapy approaches: the hope for incurable diseases. Regen. Med. 9 (5), 649–672.
Calderon, T.M., et al., 2006. A role for CXCL12 (SDF-1alpha) in the pathogenesis of multiple sclerosis: regulation of CXCL12 expression in astrocytes by soluble myelin basic protein. J. Neuroimmunol. 177 (1-2), 27–39.
Castillo-Melendez, M., et al., 2013. Stem cell therapy to protect and repair the developing brain: a review of mechanisms of action of cord blood and amnion epithelial derived cells. Front. Neurosci. 7, 194.
Chan, C.C., et al., 2012. The role of interferon-gamma inducible protein-10 in a mouse model of acute liver injury post induced pluripotent stem cells transplantation. PLoS ONE 7 (12), e50577.
Clanet, M., 2001. Interferon-beta in the treatment of multiple sclerosis. Clin. Drug. Investig. 21 (4), 307–318.
Croitoru-Lamoury, J., et al., 2007. Human mesenchymal stem cells constitutively express chemokines and chemokine receptors that can be upregulated by cytokines, IFN-β, and copaxone. J. Interf. Cytokine Res. 27 (1), 53–64.
de Oliveira, G.L., et al., 2015. Bone marrow mesenchymal stromal cells isolated from multiple sclerosis patients have distinct gene expression profile and decreased suppressive function compared with healthy counterparts. Cell Transpl. 24 (2), 151–165.
Dhib-Jalbut, S., Marks, S., 2010. Interferon-β mechanisms of action in multiple sclerosis. Neurology 74 (1 Supplement 1), S17–S24.
Donega, V., et al., 2014. Intranasal administration of human MSC for ischemic brain injury in the mouse: in vitro and in vivo neuroregenerative functions. PLoS ONE 9 (11), e112339.
Endres, M., et al., 2010. Chemokine profile of synovial fluid from normal, osteoarthritis and rheumatoid arthritis patients: CCL25, CXCL10 and XCL1 recruit human subchondral mesenchymal progenitor cells. Osteoarthr. Cartil. 18 (11), 1458–1466.
Etemadifar, M., et al., 2014. Estimated prevalence and incidence of multiple sclerosis in Iran. Eur. Neurol. 72 (5-6), 370–374.
Fletcher, J., et al., 2010. T cells in multiple sclerosis and experimental autoimmune encephalomyelitis. Clin. Exp. Immunol. 162 (1), 1–11.
Fortini, C., et al., 2011. Circulating stem cell vary with NYHA stage in heart failure patients. J. Cell. Mol. Med. 15 (8), 1726–1736.
Franciotta, D., et al., 2001. Serum and CSF levels of MCP-1 and IP-10 in multiple sclerosis patients with acute and stable disease and undergoing immunomodulatory therapies. J. Neuroimmunol. 115 (1), 192–198.
Friese, M.A., Fugger, L., 2009. Pathogenic CD8+ T cells in multiple sclerosis. Ann. Neurol. 66 (2), 132–141.
Fukumoto, S., et al., 2012. Suppression of IP-10/CXCL10 gene expression in LPS- and/or IFN-gamma-stimulated macrophages by parasite-secreted products. Cell. Immunol. 276 (1-2), 101–109.
Glenn, J.D., et al., 2014. Mesenchymal stem cells differentially modulate effector CD8+ T cell subsets and exacerbate experimental autoimmune encephalomyelitis. Stem. Cells 32 (10), 2744–2755.
Glenn, J.D., et al., 2015. Disparate effects of mesenchymal stem cells in experimental autoimmune encephalomyelitis and cuprizone-induced demyelination. PloS ONE 10 (9), e0139008.
Groom, J.R., Luster, A.D., 2011. CXCR3 ligands: redundant, collaborative and antagonistic functions. Immunol. Cell. Biol. 89 (2), 207–215.
Gruol, D.L., 2016. Impact of increased astrocyte expression of IL-6, CCL2 or CXCL10 in transgenic mice on hippocampal synaptic function. Brain Sci. 6 (2), 19. https://doi.org/10.3390/brainsci6020019.
Hamilton, T.A., et al., 1989. IFN-gamma and IFN-beta independently stimulate the expression of lipopolysaccharide-inducible genes in murine peritoneal macrophages. J. Immunol. 142 (7), 2325–2331.
Hoerning, A., et al., 2011. Subsets of human CD4(+) regulatory T cells express the peripheral homing receptor CXCR3. Eur. J. Immunol. 41 (8), 2291–2302.
Hoogduijn, M.J., et al., 2014. No evidence for circulating mesenchymal stem cells in patients with organ injury. Stem Cells Dev. 23 (19), 2328–2335.
Jacques, F.H., Lublin, F.D., 2015. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 84 (9), 963 -963.
Ji, J.F., et al., 2004. Interactions of chemokines and chemokine receptors mediate the migration of mesenchymal stem cells to the impaired site in the brain after hypoglossal nerve injury. Stem Cells 22 (3), 415–427.
Karussis, D., Kassis, I., 2008. The potential use of stem cells in multiple sclerosis: an overview of the preclinical experience. Clin. Neurol. Neurosurg. 110 (9), 889–896.
Koch, M.A., et al., 2009. The transcription factor T-bet controls regulatory T cell homeostasis and function during type 1 inflammation. Nat. Immunol. 10 (6), 595–602.
Kucia, M., Ratajczak, J., Ratajczak, M.Z., 2005. Bone marrow as a source of circulating CXCR4+ tissue-committed stem cells. Biol. Cell 97 (2), 133–146.
Li, M., et al., 2010. CXCR4 positive bone mesenchymal stem cells migrate to human endothelial cell stimulated by ox-LDL via SDF-1α/CXCR4 signaling axis. Exp. Mol. Patholo. 88 (2), 250–255.
Liu, Z., et al., 2001. Immunomodulatory effects of interferon beta-1a in multiple sclerosis. J. Neuroimmunol. 112 (1), 153–162.
Luz-Crawford, P., et al., 2013. Mesenchymal stem cells generate a CD4+CD25+Foxp3+ regulatory T cell population during the differentiation process of Th1 and Th17 cells. Stem. Cell. Res. Ther. 4 (3), 65.
Marketou, M.E., et al., 2014. Increased mobilization of mesenchymal stem cells in patients with essential hypertension: the effect of left ventricular hypertrophy. J. Clin. Hypertens. 16 (12), 883–888.
Matsushita, T., et al., 2013. Characteristic cerebrospinal fluid cytokine/chemokine profiles in neuromyelitis optica, relapsing remitting or primary progressive multiple sclerosis. PLoS ONE 8 (4), e61835.
Melter, M., et al., 2001. Expression of the chemokine receptor CXCR3 and its ligand IP-10 during human cardiac allograft rejection. Circulation 104 (21), 2558–2564.
Murphy, M.B., Moncivais, K., Caplan, A.I., 2013. Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Exp. Mol. Med. 45 (11), e54.
Namdar, A., et al., 2010. Effect of IFN-ß therapy on the frequency and function of CD4+CD25+ regulatory T cells and Foxp3 gene expression in relapsing–remitting multiple sclerosis (RRMS): a preliminary study. J. Neuroimmunol. 218 (1), 120–124.
Nylander, A., Hafler, D.A., 2012. Multiple sclerosis. J. Clin. Invest. 122 (4), 1180–1188.
Polman, C.H., et al., 2011. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 69 (2), 292–302.
Rice, C.M., Scolding, N.J., 2010. Adult human mesenchymal cells proliferate and migrate in response to chemokines expressed in demyelination. Cell. Adh. Migr. 4 (2), 235–240.
Rosenblum, J.M., et al., 2010. CXC chemokine ligand (CXCL) 9 and CXCL10 are antagonistic costimulation molecules during the priming of alloreactive T cell effectors. J. Immunol. 184 (7), 3450–3460.
Song, C.H., et al., 2011. Identification of chemoattractive factors involved in the migration of bone marrow-derived mesenchymal stem cells to brain lesions caused by prions. J. Virol. 85 (21), 11069–11078.
Sørensen, T.L., et al., 2002. Multiple sclerosis: a study of CXCL10 and CXCR3 co-localization in the inflamed central nervous system. J. Neuroimmunol. 127 (1), 59–68.
Stumm, R.K., et al., 2002. A dual role for the SDF-1/CXCR4 chemokine receptor system in adult brain: isoform-selective regulation of SDF-1 expression modulates CXCR4-dependent neuronal plasticity and cerebral leukocyte recruitment after focal ischemia. J Neurosci. 22 (14), 5865–5878.
Szczuciński, A., Losy, J., 2007. Chemokines and chemokine receptors in multiple sclerosis. Potential targets for new therapies. Acta Neurol. Scand. 115 (3), 137–146.
Toshchakov, V., et al., 2002. TLR4, but not TLR2, mediates IFN-beta-induced STAT1alpha/beta-dependent gene expression in macrophages. Nat. Immunol. 3 (4), 392–398.
Trebst, C., Ransohoff, R.M., 2001. Investigating chemokines and chemokine receptors in patients with multiple sclerosis: opportunities and challenges. Arch. Neurol. 58 (12), 1975–1980.
Wojakowski, W., Tendera, M., 2005. Mobilization of bone marrow-derived progenitor cells in acute coronary syndromes. Folia Histochem. Cytobiol. 43 (4), 229.