stem cell research&therapy

REVIEW

The therapeutic effect of mesenchymal stem cell transplantation in experimental autoimmune encephalomyelitis is mediated by peripheral and central mechanisms

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Abstract

Stem cells are currently seen as a treatment for tissue regeneration in neurological diseases such as multiple sclerosis, anticipating that they integrate and differentiate into neural cells. Mesenchymal stem cells (MSCs), a subset of adult progenitor cells, differentiate into cells of the mesodermal lineage but also, under certain experimental circumstances, into cells of the neuronal and glial lineage. Their clinical development, however, has been significantly boosted by the demonstration that MSCs display significant therapeutic plasticity mainly occurring through bystander mechanisms. These features have been exploited in the effective treatment of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis where the inhibition of the autoimmune response resulted in a significant amelioration of disease and decrease of demyelination, immune infiltrates and axonal loss. Surprisingly, these effects do not require MSCs to engraft in the central nervous system but depend on the cells' ability to inhibit pathogenic immune responses both in the periphery and inside the central nervous system and to release neuroprotective and pro-oligodendrogenic molecules favoring tissue repair. These results paved the road for the utilization of MSCs for the treatment of multiple sclerosis.

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Mesenchymal stem cells are stromal progenitors of the mesodermal lineage

Mesenchymal stem cells (MSCs) are a heterogeneous subset of stromal stem cells that can be isolated from many adult connective tissues. The cells grow as plastic-adherent fibroblast-like cells that proliferate *in vitro*, maintaining pluripotency after prolonged culture. Under appropriate stimulus, MSCs can differentiate *in vitro* and *in vivo* into cells of the mesodermal lineage, such as bone, fat and cartilage cells.

MSCs have mainly been characterized after isolation from the bone marrow, where they are likely to represent the precursor cells for stromal tissue in close physical association with hematopoietic stem cells involved in hematopoiesis and maintenance of the homeostasis of the hematopoietic stem cell niche [1]. In the bone marrow the existence of a population of neural-crest-derived stem cells was also shown, thus providing an explanation for the reported ability of bone-marrow-derived stem cells to also generate, to some extent, neural cells [2].

Despite evidence showing that MSCs can transdifferentiate into multiple cell types *in vitro* and *in vivo*, the real contribution of MSCs to tissue repair – through significant engraftment and differentiation into biologically and functionally relevant tissue-specific cell types – is still elusive [3]. In the bone marrow, MSCs provide a sheltering microenvironment contributing to the preservation of hematopoietic stem cells by shielding them from differentiation and apoptotic stimuli and regulating their quiescence, proliferation and differentiation. Owing to their ability to support hematopoiesis, MSCs were first utilized to enhance immune reconstitution when transplanted together with hematopoietic stem cells. The translation of the capacity of MSCs to differentiate into other tissues was first exploited for reparative purposes, for example, in bone and heart diseases. The observation

that bone-marrow-derived MSCs suppressed T-cell proliferation *in vitro* [4] and *in vivo* [5], however, unexpectedly drove attention to their exploitation for the treatment of immune-mediated diseases; for example, in those diseases where their ability of modulating the immune response could combine with the ability to integrate into damaged tissues and foster repair. Experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis, has been the first experimental autoimmune disease successfully treated with MSCs [6].

Experimental autoimmune encephalomyelitis is an example of immune-mediated disease

EAE can be actively induced in susceptible inbred rodents by immunization with different neural antigens mainly derived from myelin, including myelin basic protein, proteolipid protein (PLP) and myelin oligodendrocyte protein (MOG) in complete Freud's adjuvant. Disease induction with PLP in SJL mice, and likewise MOG in C57BL/6 mice, requires the use of pertussis toxin that facilitates immune cell entry into the central nervous system (CNS) and contributes to T-cell tolerance breaking. EAE can be also induced in naïve mice by the intravenous passive transfer of encephalitogenic myelin-specific T cells. In fact, EAE is considered a prototypical MHC class-II-restricted $CD4^+$ T-cell-mediated disease. During the induction phase, myelin-reactive $CD4^+$ T cells are primed and expanded in the peripheral lymphoid organs. The effector phase involves migration of activated myelin-specific T cells to the CNS, where they cross the blood–brain barrier and require myelin peptides presented by local antigen-presenting cells and dendritic cells for full reactivation [7].

Several lines of evidence indicate that many subsets of T cells play different roles in the onset, maintenance and recovery of EAE, T-helper-type 17 cells and regulatory T cells being among the main contributors to the final outcome [8]. Not only T cells but also B cells producing demyelinating antibodies and macrophages are key effector cells in EAE pathogenesis. Typical EAE lesions resemble patterns of demyelination, inflammatory cell perivascular infiltrates, reactive microgliosis and astrocytosis, observed in multiple sclerosis lesions [9].

Systemic effect of the intravenous delivery of mesenchymal stem cells in experimental autoimmune encephalomyelitis

In the study by Zappia and colleagues we demonstrated that intravenous injection of syngeneic MSCs into C57BL/6 mice immunized with peptide 35 to 55 of MOG significantly improved the clinical severity of EAE, in parallel decreasing CNS inflammation and demyelination [6]. More importantly, we demonstrated that one injection of MSCs at disease onset or at the peak of disease suffices to induce peripheral tolerance, as demonstrated by the inability of T cells isolated from lymph nodes of MSC-treated mice, but not from control animals, to proliferate when stimulated with the immunizing antigen MOG. We also observed a dose-dependent effect that reached maximum efficacy and negligible mortality at the dose of 1×10^6 MSCs. No clinical effect was observed when MSCs were infused during the chronic phase of EAE, suggesting that multiple injections may not provide further advantages if permanent tissue damage has occurred [6]. In another study, Zhang and colleagues demonstrated that intravenous administration of human MSCs could improve the clinical course of PLP-induced EAE in SJL mice through some level of engraftment in the CNS and subsequent release of neurotrophic factors promoting oligodendrogenesis [10]. These results highlighted that MSCs can cross MHC boundaries and exert their therapeutic effect also in the CNS, regardless of a very limited engraftment. Following these pioneer works, in the last years several studies have focused on the mechanisms underlying the therapeutic effect of MSC transplantation on EAE.

The concept that MSCs ameliorate EAE through the induction of peripheral immune tolerance was further nourished by the demonstration that intravenous administration of allogeneic MSCs in PLP-immunized mice inhibits the production of myelin-specific antibodies compared with controls [11]. In addition, the exposition of encephalitogenic T cells to MSCs *in vitro* significantly decreases their ability to passively transfer EAE to healthy syngeneic mice [11]. Many other studies have confirmed that MSCs can modulate the peripheral immune response to myelin antigens [12-19]. These *in vivo* results have been corroborated by detailed *in vitro* studies dissecting the mechanisms of action of MSCs on T lymphocytes, B lymphocytes, dendritic cells, natural killer cells and other immune cells [20].

Mesenchymal stem cells are neuroprotective

It is important to underline that effects of MSCs on EAE are not exclusively due to their immunomodulatory activity, as many groups have shown that MSCs can also protect neurons and spare axons with no or very limited evidence of engraftment and/or transdifferentiation into neural cells [11-13,15,16,21]. These findings posed the question of whether the observed neuroprotection in EAE is due to the peripheral effects suppressing the immune response that damages myelin or to a direct protective and reparative activity that follows their engraftment in the CNS.

Several lines of evidence suggest that, somehow, MSCs have a direct effect on neural cells. They have been shown to enhance remyelination *in vivo* [15,16], provide *in vitro*

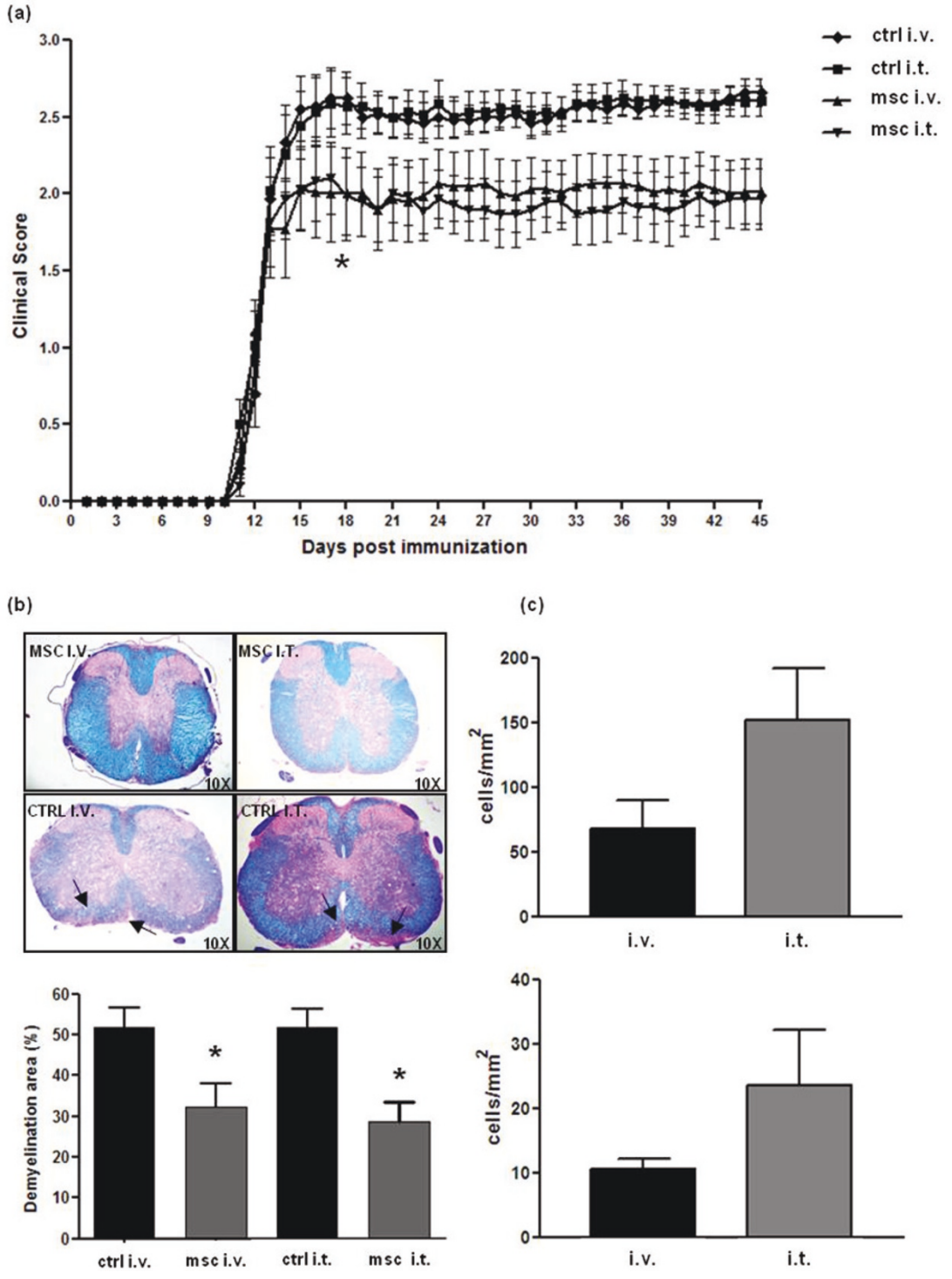

Figure 1. Local mesenchymal stem cell administration does not provide significant advantage compared with systemic infusion. **(a)** Clinical course of peptide 33 to 55 of myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (EAE) in C57Bl6 mice after intrathechal (i.t.) or intravenous (i.v.) mesenchymal stem cell (MSC) injection. Arrow, day of injection. **P* ≤0.05 Mann–Whitney U test. **(b)** Analysis of demyelination in the spinal cord of treated mice; 5 μm sections were stained with Luxol Fast Blue and the demyelinated area was expressed as a percentage of the total surface area. **P* ≤0.01 Mann–Whitney U test. **(c)** Counts of luciferase-labeled MSCs in the central nervous system (CNS) of EAE-affected mice. Luciferase-positive MSCs were detected using a rabbit anti-luciferase monoclonal antibody (Alexa Fluor 488-conjugated) after 24 hours and 40 days from intravenous and intratechal injection. Six CNS tissue sections per mouse were analyzed and in each section the number of positive cells was reported as the number of positive elements/mm^2.

Table 1. Clinical features of experimental autoimmune encephalomyelitis-affected mice

	Disease incidence	Disease onset, days after immunization	Mean maximum neurologic score	Cumulative disease score
EAE control i.v.	14 / 14 (100%)	12 ± 0.8	3 ± 0.5	84.4 ± 13
EAE + MSCs i.v.	14 / 15 (93.4%)	11.5 ± 0.5	2.5 ± 0.9	67.6 ± 28.7*
EAE control i.t.	14 / 14 (100%)	11.6 ± 0.6	3 ± 0.5	85.2 ± 15.3
EAE + MSCs i.t.	14 / 15 (93.4%)	12.3 ± 1	2.4 ± 0.7*	63.7 ± 25.7*

Data presented as *n* / total (%) or mean ± standard deviation. EAE, experimental autoimmune encephalomyelitis; i.t., intrathecally; i.v., intravenously; MSC, mesenchymal stem cell. *$P \leq 0.05$ (Student's *t* test).

soluble cues that influence fate determination of neural cells [16,22], display a potent antioxidant effect *in vivo* [23,24] and display a neuroprotective effect [25] mediated by the release of antiapoptotic molecules *in vitro* [26] and *in vivo* [27]. These neuroprotective effects may well explain the remarkable effect obtained with the administration of MSCs in experimental models of stroke [28] and spinal cord injury [29]. There is uncertainty, however, regarding the ability of MSCs to colonize the CNS after peripheral delivery due to their scarce ability to pass the lung filter following intravenous administration [30] and due to the lack of reliable labels or definitive markers for MSCs [31].

Irrespective of these aspects, the current view suggests that MSCs may exert their neuroprotective effect at distance through the release of trophic molecules, possibly affecting microglia activation [27] and inducing local neurogenesis [15,16,32].

Does local administration provide significant advantage compared with systemic infusion?

To enhance the possibility for MSCs to engraft in the CNS and provide optimal therapeutic effects locally, Kassis and colleagues demonstrated, following intraventricular injection of MSCs, the expression of neural markers by a few transplanted labeled cells mainly in the proximity of inflammatory lesions – suggesting that some level of transdifferentiation was achieved [12]. Similarly, Barhum and colleagues showed that intraventricular administration *in vitro* of MSCs modified to produce neurotrophins successfully attenuated EAE [19].

We therefore evaluated whether local injection of a high number of MSCs may provide some advantage over intravenous systemic administration by comparing two different routes of cell delivery in C57Bl/6 mice following immunization with the myelin antigen, peptide 35 to 55 of MOG. The intratechal delivery of 1×10^6 MSCs at the onset of the first clinical symptoms (around day 10) resulted in a significant amelioration of EAE compared with intratechally PBS-injected animals. No significant difference was observed, however, when we compared the clinical course of mice intravenously injected with those treated intratechally (Figure 1 and Table 1). No significant difference was also observed when the extent of spinal cord demyelinating lesions was compared (Figure 1). As expected, the number of Luciferase-transfected MSCs, detected after 24 hours in the CNS of intratechally injected mice, was higher than in those where MSCs were delivered intravenously. After 40 days, however, the number of Luciferase-positive cells was clearly diminished with no statistical difference between the two groups (Figure 1). These results favor the current hypothesis that MSCs act by different mechanisms, mainly paracrinally on cells both at a distance and at the site of tissue damage, without the requirement of long-term engraftment [33].

Intravenous injection of mesenchymal stem cells also modulates the immune response in the CNS

A major issue still unsolved by the above-described studies was whether intravenously injected MSCs could also impact the immune response inside the CNS. It is well known that, following intravenous administration, MSCs inhibit infiltration of T cells and macrophages in mice with EAE [6]. These results, however, are likely to be an effect of the cells' tolerogenic ability exerted in the periphery on encephalitogenic T cells, as demonstrated by the inhibition of EAE following passive transfer of myelin-specific T cells [11].

To address this question we isolated T cells infiltrating the brain of EAE-affected mice treated either intravenously or intratechally with MSCs and we measured by intracellular flow cytometry and real-time PCR the expression of the transcription factor FOXP3, a specific marker of regulatory T cells previously demonstrated to be expanded in the lymphoid organs of mice with collagen-induced arthritis treated with MSCs [34]. We observed not only that the intratechal delivery of MSCs induced an expansion of $FoxP3^+$ T cells in the brain of EAE-affected mice compared with controls, but also that a similar result was observed in intravenously injected mice (Figure 2). Such a result probably depends on increased recruitment of this subset from the peripheral blood. To our surprise we observed, in the T cells isolated from the brain of both groups of MSC-treated mice compared with controls, an increase in the expression of

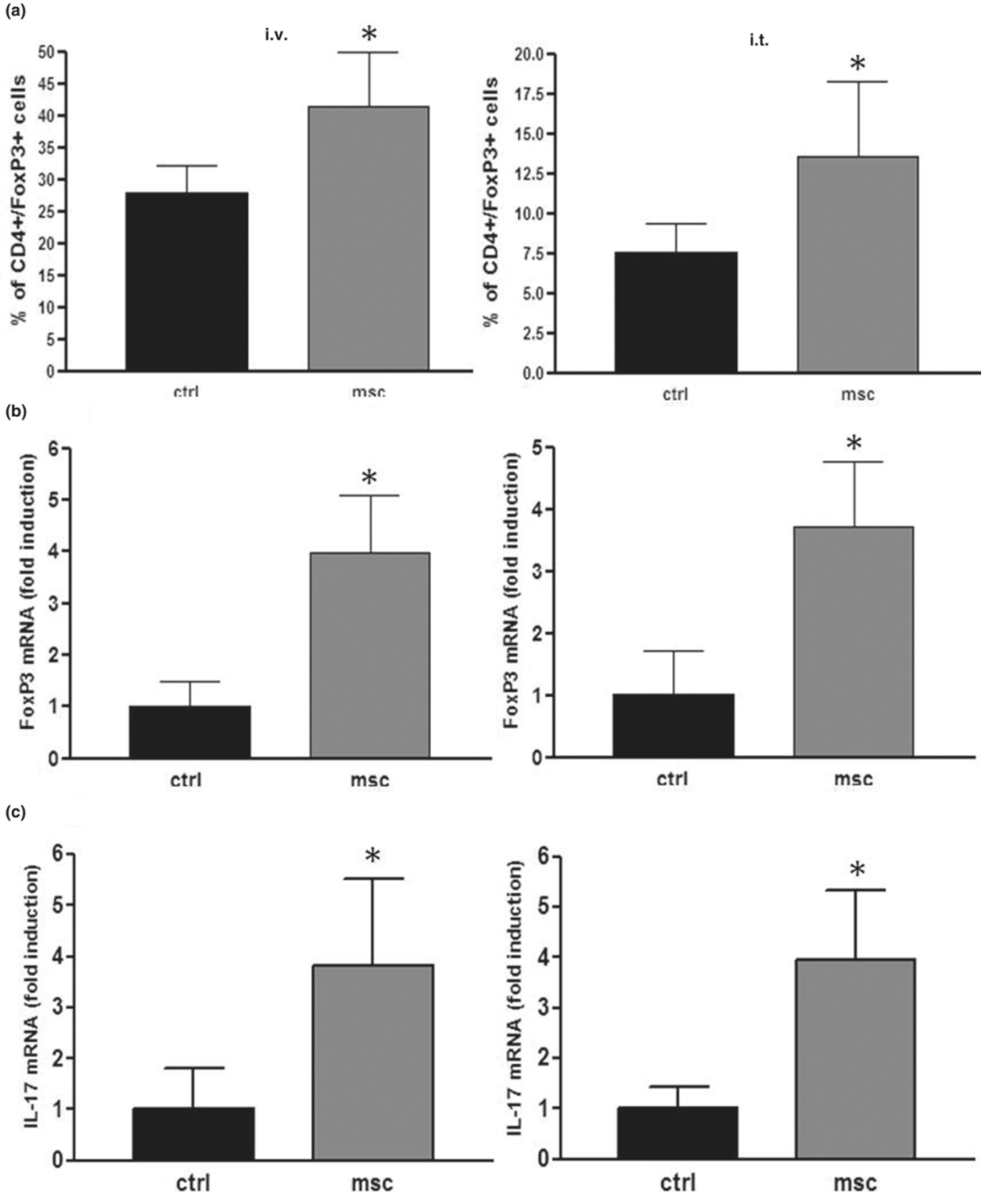

Figure 2. Intratechal and intravenous injection of mesenchymal stem cells modulates immune response in central nervous system. Expression of FoxP3 in T cells infiltrating the central nervous system of experimental autoimmune encephalomyelitis affected mice at the peak of disease: **(a)** at protein level, evaluated by intracellular flow cytometry (FACSCanto II; BD Bioscience, Buccinasco, Milan, Italy); and **(b)** at mRNA level, evaluated by real-time PCR using a LightCycler® 480 (Roche Applied Science, Indianapolis, IN, USA). **(c)** IL-17 mRNA expression from infiltrating T cells, analyzed by real-time PCR. **P* ≤0.05 Mann–Whitney U test. i.v., intravenous; i.t. intrathecal.

IL-17, a cytokine that plays an important role in the pathogenesis of autoimmune diseases (Figure 2). These results may be explained by the recent demonstration that MSCs can induce T-helper-type 17 cells to acquire a regulatory phenotype [35], and may also clarify the observation that human MSCs were shown to increase T-helper-type 17 responses *in vitro* [36].

Conclusions

Overall, many studies have confirmed that MSCs, either from syngenic or xenogeneic sources, are effective in the treatment of EAE and dissected their mechanisms of action, probably in a much deeper fashion than in any other experimental disease. The results discussed in the present article demonstrate that MSCs can repair neural tissues as they display a broad therapeutic activity that acts both on immune and neural cells but feebly involves their transdifferentiation. Interestingly, despite a limited ability to engraft in the nervous system, MSCs can clearly modulate the immune response not only in the peripheral lymphoid organs [6] but also within the CNS.

Based on these studies and the available clinical experience obtained in several human conditions, MSCs can be considered an appealing therapeutic option for multiple sclerosis individuals with ongoing inflammatory disease refractory to conventional therapies [37,38].

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Abbreviations

CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; IL, interleukin; MHC, major histocompatibility complex; MOG, myelin oligodendrocyte glycoprotein; MSC, mesenchymal stem cell; PBS, phosphate-buffered saline; PCR, polymerase chain reaction; PLP, proteolipid protein.

Competing interests

The authors declare that they have no competing interests.

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