



[Skip to content](#)

Advertisement



Menu

- [Explore journals](#)
- [Get published](#)
- [About BMC](#)
- [Login My Account](#)
- 

Search all BMC articles 



[Stem Cell Research & Therapy](#)

Menu

- [Home](#)
- [About](#)
- [Articles](#)
- [Submission Guidelines](#)

Table of Contents

1. [Abstract](#)
2. [An introduction to mesenchymal stem cell modulation of T cell-mediated immune responses](#)
3. [Mesenchymal stem cell modulation of T helper cell subsets](#)
4. [Mesenchymal stem cell modulation of cytotoxic T lymphocytes](#)
5. [Concluding remarks and future directions](#)
6. [Note](#)
7. [Declarations](#)
8. [References](#)
9. [Comments](#)

We use cookies to personalise content and ads, to provide social media features and to analyse our traffic. We also share information about your use of our site with our social media, advertising and analytics partners in accordance with our [Privacy Statement](#). You can manage your preferences in 'Manage Cookies'.

> [Manage Cookies](#)

- Rhodri Ceredig¹ and
- Matthew D Griffin¹[Email author](#)

Stem Cell Research & Therapy 2011, 2:34

<https://doi.org/10.1186/scrt75>

© BioMed Central Ltd 2011

- **Published:** 11 August 2011

Abstract

Mesenchymal stem (stromal) cells (MSCs) are rare, multipotent progenitor cells that can be isolated and expanded from bone marrow and other tissues. Strikingly, MSCs modulate the functions of immune cells, including T cells, B cells, natural killer cells, monocyte/macrophages, dendritic cells, and neutrophils. T cells, activated to perform a range of different effector functions, are the primary mediators of many autoimmune and inflammatory diseases as well as of transplant rejection and graft-versus-host disease. Well-defined T-cell effector phenotypes include the CD4⁺ (T helper cell) subsets Th1, Th2, and Th17 cells and cytotoxic T lymphocytes derived from antigen-specific activation of naïve CD8⁺ precursors. In addition, naturally occurring and induced regulatory T cells (T_{reg}) represent CD4⁺ and CD8⁺ T-cell phenotypes that potently suppress effector T cells to prevent autoimmunity, maintain self-tolerance, and limit inflammatory tissue injury. Many immune-mediated diseases entail an imbalance between T_{reg} and effector T cells of one or more phenotypes. MSCs broadly suppress T-cell activation and proliferation *in vitro* via a plethora of soluble and cell contact-dependent mediators. These mediators may act directly upon T cells or indirectly via modulation of antigen-presenting cells and other accessory cells. MSC administration has also been shown to be variably associated with beneficial effects in autoimmune and transplant models as well as in several human clinical trials. In a small number of studies, however, MSC administration has been found to aggravate T cell-mediated tissue injury. The multiple effects of MSCs on cellular immunity may reflect their diverse influences on the different T-cell effector subpopulations and their capacity to specifically protect or induce T_{reg} populations. In this review, we focus on findings from the recent literature in which specific modulatory effects of MSCs on one or more individual effector T-cell subsets and T_{reg} phenotypes have been examined *in vitro*, in relevant animal models of *in vivo* immunological disease, and in human subjects. We conclude that MSCs have the potential to directly or indirectly inhibit disease-associated Th1, Th2, and Th17 cells as well as cytotoxic T lymphocytes but that many key questions regarding the potency, specificity, mechanistic basis, and predictable therapeutic value of these modulatory effects remain unanswered.

Keywords

- Th17 Cell
- Experimental Allergic Encephalomyelitis
- Mixed Lymphocyte Culture
- Th17 Cell Activity
- Treg Phenotype

An introduction to mesenchymal stem cell modulation of T cell-mediated immune responses

T lymphocytes (T cells) are the primary cellular effectors of the adaptive immune system and their functional properties are central to antigen specificity and memory associated with cognate immunity [1, 2, 3]. Antigen-specific activation and differentiation of naïve T cells result in the generation of a range of T-cell phenotypes that may be defined by the acquisition of characteristic cytokine secretion profiles, cytolytic mechanisms, or counter-regulatory properties [1, 2, 3]. In the wake of antigen-specific adaptive immune responses, a small proportion of activated T cells persist as memory cells and have the capacity to respond more rapidly and potently to secondary encounters with the same antigen [1, 3]. These memory cells may retain the effector phenotype imprinted upon them during primary activation [1]. When these memory cells are appropriately coordinated and regulated, the diversity of T-cell effector phenotypes allows immune protection against a multitude of pathogenic microorganisms while maintaining self-tolerance and homeostasis [2]. On the other hand, overexuberant pro-inflammatory T-cell responses may lead to auto-immune and allergic diseases, including multiple sclerosis, inflammatory bowel disease, type 1 diabetes mellitus, and asthma [4, 5, 6, 7]. Furthermore, life-saving treatments such as allogeneic bone marrow

(BM) and solid organ transplantation may be complicated by alloantigen-specific T-cell immune responses, resulting in graft-versus-host disease (GvHD) or transplant rejection [8].

Mesenchymal stem (or stromal) cells (MSCs) are a heterogeneous population of fibroblast-like progenitor cells that may be isolated and expanded from BM, umbilical cord, fat, gingiva, and other tissues [9]. They have the capacity to self-renew and differentiate into various mesodermal cell lineages, including adipocytes, osteocytes, and chondrocytes under controlled culture conditions [9]. In the past two decades, MSCs have garnered considerable attention for their potential use as regenerative therapeutic agents in a range of acute and chronic diseases [8, 9, 10, 11]. Mechanistically, the beneficial effects of MSC therapies have been more frequently linked to their 'trophic' (paracrine) effects rather than their ability to transdifferentiate [11]. Specifically, MSCs are now viewed as having potent anti-inflammatory and immune-modulating properties that, in many studies, have been shown to be associated with inhibition of effector T-cell activation with or without a concomitant increase in regulatory T cell (T_{reg}) numbers [4, 6, 10, 11, 12]. The T-cell suppressive effects of MSCs were initially described over a decade ago [13] and have since been reported consistently for both $CD4^+$ T helper (Th) cells and $CD8^+$ cytotoxic T lymphocytes (CTLs) [8, 11, 14]. Suppression of T cells by MSCs may be direct or may occur indirectly via modulatory effects on antigen-presenting cells such as dendritic cells (DCs), resulting in altered cytokine expression and impaired antigen presentation [15, 16, 17]. MSCs themselves demonstrate a lack of stimulatory capacity toward T cells [18, 19]. MSCs isolated from various sources (BM, adipose tissue, and Wharton's jelly) have been reported to equally suppress proliferation of $CD4^+$ and $CD8^+$ T-cell subsets in a dose-dependent fashion [20]. Reported roles for both cell-cell contact and release of soluble factors in MSC-mediated T-cell suppression are evident throughout the literature, and numerous candidate mediators have been reported: prostaglandin E_2 (PGE_2), indoleamine-2,3-dioxygenase, nitric oxide, interleukin (IL)-27, transforming growth factor-beta ($TGF-\beta$), monocyte chemoattractant protein 1 (MCP-1/CCL2), human leukocyte antigen G, and intracellular adhesion molecule 1 among others [8, 10, 11, 12, 17, 21, 22, 23, 24]. The abundance of mediators identified to date suggests that MSCs exploit different immunosuppressive mechanisms under different disease conditions. MSC therapy has been successful in a range of disease models and some clinical conditions known to be associated with damaging effector T-cell responses or failure of T_{reg} -mediated counter-regulation or both [4, 6, 8, 11, 22, 25, 26, 27, 28]. Overall, it is now very well established that MSCs exert diverse and potent modulatory effects on the T-cell compartment of the immune system, most of which are suppressive in nature and of potential therapeutic value. Nevertheless, some significant controversies and a basic lack of information regarding the range of effects that MSCs have on individual T-cell effector subsets remain. In the remaining sections of this review, we focus on the most recent data related to MSC modulation of individual well-defined Th cell and CTL effector phenotypes *in vitro* and *in vivo*. Where possible, we emphasize the relevance of current knowledge on this topic to diseases for which MSC therapy is perceived to be beneficial. We also highlight key gaps in our understanding and important unanswered questions that may be the subject of future studies.

[Mesenchymal stem cell modulation of T helper cell subsets](#)

Th cells are cytokine-producing $CD4^+$ cells that recognize peptides presented to them by major histocompatibility complex (MHC) class II molecules [1, 2, 3]. Differentiation of Th cells into effector cells depends largely on the cytokine milieu present at the time of antigen presentation and activation [1, 2, 3]. In the context of this article, we will focus on reviewing recent progress (summarized in Figure 1) in understanding MSC effects on the well-described subsets Th1, Th2, and Th17 cells, T_{reg} , and CTLs with emphasis, where possible, on mechanistic and disease-specific *in vivo* studies.

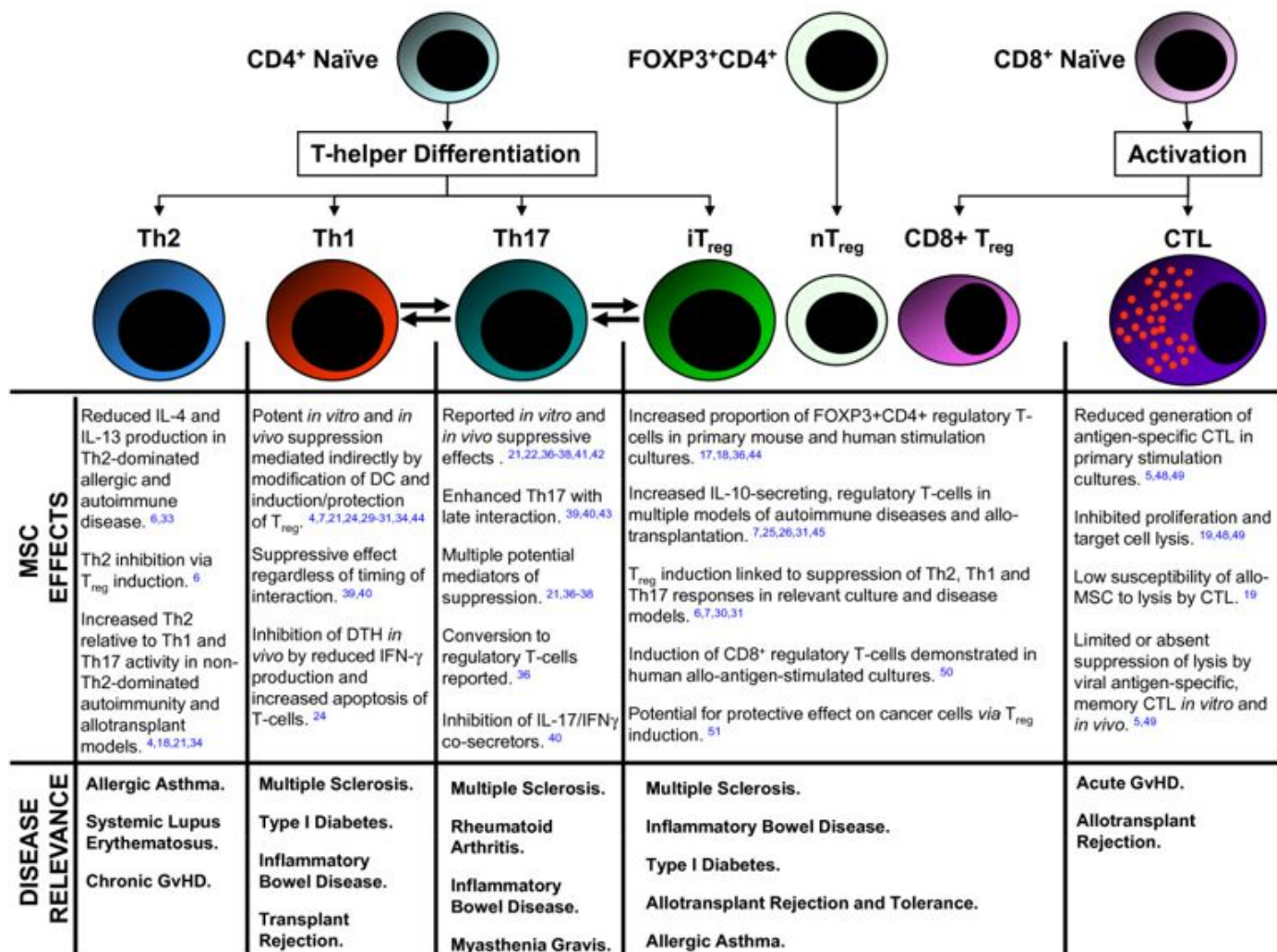


Figure 1

Diagrammatic summary of the major CD4⁺ and CD8⁺ T-cell effector subtypes (as derived from naïve CD4⁺ and CD8⁺ T cells), the reported effects of mesenchymal stem cells (MSCs) on these effectors, and some clinically important disease associations for each. Bidirectional arrows indicate reported inter-conversion (plasticity) between Th1/Th17 phenotypes and Th17/iT_{reg} phenotypes that may be of relevance to MSC immune modulatory effects. Relevant references are indicated numerically for individual statements. CTL, cytotoxic T lymphocyte; DC, dendritic cell; DTH, delayed-type hypersensitivity; FOXP3, forkhead box P3 transcription factor; GvHD, graft-versus-host disease; IFN- γ , interferon-gamma; IL, interleukin; iT_{reg}, induced regulatory T cell; nT_{reg}, natural regulatory T cell; Th1, T helper type 1 cell; Th2, T helper type 2 cell; Th17, T helper type 17 cell; T_{reg}, regulatory T cell.

T helper type 1 cells

Th1 cell induction occurs when CD4⁺ T cells are activated in the presence of IL-12, interferon-gamma (IFN- γ), and IL-27 [29]. IFN- γ is the characteristic cytokine produced by Th1 cells in addition to tumor necrosis factor (TNF). Known effector functions of Th1 cells include activation and recruitment of macrophages to sites of inflammation and induction of immunoglobulin (Ig) G2a production by B cells [2]. Th1 cells are responsible for the clearance of intracellular pathogens and delayed-type hypersensitivity (DTH) reactions by amplifying cellular immunity [29]. DTH reactions are mediated by both Th1 cells and CTLs [25], and, through their role as coordinators of this form of immune response, Th1 cells have the capacity to cause maladaptive tissue damage. Examples of Th1 cell-mediated inflammatory and autoimmune diseases are type 1 diabetes mellitus and Crohn's disease [7]. The literature to date indicates that MSCs exert primarily suppressive effects on Th1 cell differentiation and effector function, and evidence favors predominantly indirect mechanisms. *In vitro*, the generation of Th1 cells is reduced in mixed lymphocyte cultures containing MSCs or MSC-conditioned medium, likely due to inhibition of Th1 cell-stimulating properties of DCs [30]. In the *in vivo* setting, Lim and colleagues [25] recently demonstrated that infusion of MSCs attenuated cutaneous DTH in mice and that this effect was associated with reduced infiltration of CD4⁺ and CD8⁺ T cells at the challenge

site and increased apoptosis of activated T cells in the draining lymph nodes. MSCs were detected close to the germinal center and paracortical region in lymph nodes [25], suggesting that they modulate immune responses directly in the area where DCs are likely to activate T cells. In experimental colitis (an animal model of inflammatory bowel disease), dose-dependent xenogenic, allogenic, and autologous adipose-derived MSCs ameliorated disease activity and were specifically associated with reduced IFN- γ -producing Th1 cells in association with increased numbers of forkhead box P3 (FOXP3)-expressing T cells (T_{reg}) [7]. Furthermore, when treated with either total $CD4^+$ T cells or T_{reg} -depleted $CD4^+$ T cells from mesenteric lymph nodes of MSC-treated colitic mice, mice with induced colitis demonstrated attenuated and enhanced colitis, respectively [7]. These data suggest that the administration of MSCs in experimental colitis dampens Th1 cell responses via induction of T_{reg} but does not eliminate Th1 cells entirely. MSCs have also been used experimentally to effectively prevent or treat Th1 cell-mediated auto-immune diabetes mellitus in streptozotocin-treated rats and in nonobese diabetic (NOD) mice [31, 32]. In the rat model, the protective effects observed following administration of MSCs were shown to be associated with increased IL-10 and IL-13 expression by T cells and with increased frequencies of both $CD4^+$ and $CD8^+$ FOXP3 $^+$ T cells as opposed to a direct reduction of IFN- γ -producing T cells [31]. In NOD mice, a single MSC injection minimized beta-cell destruction following transfer of diabetogenic T cells. Protection was shown to be associated with MSC migration to pancreatic lymph nodes and with induction of IL-10-producing FOXP3 $^+$ T_{reg} [32]. These examples from the recent literature indicate that, in clinically relevant disease settings, MSCs consistently suppress harmful autoimmune Th1 cell responses by predominantly indirect mechanisms, including modulation of antigen-presenting DCs and promotion of naturally occurring or induced FOXP3-expressing T_{reg} .

T helper type 2 cells

Th2 cell differentiation occurs when $CD4^+$ T cells are activated in the presence of IL-4, which itself is produced by Th2 cells in addition to IL-5, IL-9, IL-10, and IL-13 [2, 3, 29]. The role of Th2 cells in adaptive immunity is linked to host defense against extracellular parasites, to antibody class switching to IgG1 and IgE in B cells, and to recruitment of eosinophils [2, 3, 29, 33]. Dysregulated Th2 cell responses are associated with allergic diseases such as asthma [2]. Very few studies have examined MSC effects on immune-mediated diseases in which Th2 cell responses are dominant. However, Kavanagh and Mahon [6] recently reported that allogeneic MSC administration reduced the number of infiltrating eosinophils, suppressed IgE induction, and inhibited IL-13 and IL-4 production in a mouse model of ovalbumin-induced airway inflammation. Additionally, increases in IL-10 and FOXP3 expression were observed in this study, suggesting that MSCs suppress allergen-specific Th2 cell responses in allergic airway inflammation in part via induction of T_{reg} . As further evidence of this, depletion of T_{reg} resulted in reversal of the protective effects of the MSCs [6]. In human subjects with chronic GvHD (which is also characterized by predominant Th2 cell activity), MSC infusion has been reported to result in clinical improvement with a reduction in IL-4- and IL-10-producing T cells and a concomitant increase in IL-2- and IFN- γ -producing cells [34].

In other circumstances, there is evidence that MSCs may favor the emergence of Th2 phenotype T cells. Bai and colleagues [4] demonstrated, for example, that mice treated with human BM-derived MSCs recovered function from limb paralysis in relapsing-remitting and chronic experimental allergic encephalomyelitis (EAE), a model for multiple sclerosis, by induction of Th2 cells. In this study, neurological improvement was associated with reduced $CD45^+$ leukocytic infiltration of the brain and spinal cord, with increased levels of the Th2 cell-related cytokines IL-4 and IL-5, and with potent reduction in the Th1/Th17 cell-related cytokines IL-17, IFN- γ , TNF, and IL-12 [4]. The results suggested that MSC administration in EAE favorably altered the balance between pro-inflammatory Th1/Th17 cell and anti-inflammatory Th2 cell responses. Likewise, Fiorina and colleagues [35] reported a shift in Th1/Th2 cell balance toward Th2 cells following allogeneic MSC administration to NOD mice. Further evidence supporting a shift toward Th2 cell responses is provided by Batten and colleagues [18], who describe the use of human BM-derived MSCs for tissue engineering of a heart valve. $CD4^+$ T cells co-cultured with MSCs expressed lower levels of IL-1- α and - β , TNF, and IFN- γ but higher levels of IL-5, IL-8, and IL-3 in response to allogeneic peripheral blood mononuclear cells. Consistent with the findings of Kavanagh and Mahon [6], those of Batten and colleagues [18] additionally indicated increased expression of FOXP3 in $CD4^+$ T cells co-cultured with MSCs, suggesting the induction of a T_{reg} phenotype. Thus, though relatively limited, the experimental evidence to date suggests that MSCs suppress effector function of Th2 cells in Th2 cell-predominant inflammation. In other T cell-mediated immunological disorders, however, predominant MSC suppression of the Th1 and Th17 cell pathways may result in a relative skewing toward less damaging Th2 and T_{reg} phenotypes. Whether MSCs actively induce the differentiation and expansion of Th2 cells during primary or secondary antigen-specific immune responses has not been well tested but appears less likely.

T helper type 17 cells

The Th17 cell effector phenotype is defined by preferential secretion of IL-17A (IL-17) along with other cytokines, including IL-17F, IL-21, and IL-22. Th17 cells are pro-inflammatory and protect against extracellular pathogens, including fungi, mycobacteria, and Gram-negative bacteria, via recruitment of neutrophils [36]. Th17 cells may also be pathogenic and have

been shown to have an important role in immunological diseases, including rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease [36]. TGF- β and IL-6, with or without IL-21, IL-23, and IL-1, are necessary for the induction and expansion of Th17 cells from naïve CD4⁺ precursors [2, 36]. Recently, MSC effects on the Th17 cell differentiation pathway have been examined in mice and humans. Ghannam and colleagues [37] observed that human MSCs induce regulatory characteristics in Th17 cells in an inflammatory environment by downregulating the Th17 cell-specific transcription factor ROR γ t (retinoid-acid receptor-related orphan receptor gamma t) and up-regulating FOXP3. Moreover, when re-purified, these regulatory-phenotype Th17 cells suppressed proliferation of newly initiated CD4⁺ T cells [37]. *In vivo*, MSC administration has been shown to suppress the development of EAE via a reduction in IL-17 production in the central nervous system along with reduced IFN- γ , TNF, and IL-23 and increased TGF- β and IL-4 [22]. Inhibition of Th17 cell activity in EAE has also been reported by Zappia and colleagues [38] and Rafei and colleagues [39], although the studies to date have identified different mechanisms for the MSC anti-Th17 cell effect, including IL-27 [22], alternatively cleaved MCP-1 [39], and induction of a state of T-cell anergy [38]. In our own hands, MSCs potently suppress the *in vitro* differentiation and re-activation of mouse Th17 cells derived from naïve and memory precursors via cyclooxygenase 2 upregulation and PGE₂ production (MM Duffy, R Ceredig, and MD Griffin, unpublished work).

Although these studies indicate that MSCs have the potential to suppress Th17 cell-mediated immunity and may do so by several mechanisms, some evidence for a Th17 cell-promoting effect of MSCs also exists. For example, Carrión and colleagues [40] observed that MSCs promoted Th17 cells while inhibiting Th1 cells *in vitro* if their addition to mouse T-cell differentiation cultures was delayed by 3 days. Similarly, Darlington and colleagues [41] observed that MSC-conditioned medium suppressed human Th1 cells *in vitro* while having an opposing effect on Th17 cells. In the same study, MSC-conditioned medium was found to reduce numbers of IL-17/IFN- γ double-expressing CD4⁺ T cells; this finding may have clinical implications for patients with multiple sclerosis as this subset was recently described in immune-mediated demyelinating disease [41]. Whether MSCs inhibit or enhance disease-associated Th17 cells *in vivo* is less well understood, although Ghannam and colleagues [37] observed that MSCs suppressed the production of IL-17 and IL-22 by established human Th17 cell clones with a paradoxical increase in IL-10-producing cells. Furthermore, Rafei and colleagues [39] demonstrated amelioration of EAE and inhibition of Th17 cell activity when MSCs were first administered 1 week after the onset of neurological signs of disease, suggesting the inhibition of established T-cell effector responses. Inhibition of Th17 cell-mediated inflammation and autoimmunity by MSC administration has also been reported in models of type 1 diabetes mellitus, collagen-induced arthritis, and experimental autoimmune myasthenia gravis in association with shifts toward increased Th2 or T_{reg} activity or both [23, 42, 43]. Overall, a significant amount of evidence for specific effects of MSCs on the Th17 cell effector pathway is emerging. These effects would appear to be suppressive under diverse conditions but with the potential to enhance Th17 cell activity under some circumstances. In this regard, it is worth noting that MSCs may act as a source of IL-6, which is one of the primary mediators of Th17 cell differentiation [44]. The role of MSC-produced IL-6 is likely to be more complex, however, as MSCs derived from IL-6-deficient mice were less effective than wild-type MSCs in suppressing inflammation associated with collagen-induced arthritis in a study by Bouffi and colleagues [42].

Regulatory T cells

A subset of CD4⁺ T cells have been identified as having regulatory (suppressor) functions that are essential for the prevention of autoimmunity and the resolution of inflammatory processes. These CD4⁺ T_{reg} are best characterized by surface expression of the IL-2 receptor alpha chain (CD25) and, more specifically, by intracellular expression of the transcription factor FOXP3. They can be further subdivided into naturally occurring T_{reg} (nT_{reg}) that develop in the thymus or induced T_{reg} (iT_{reg}) that differentiate from naïve peripheral CD4⁺ T cells in the presence of TGF- β [2]. T_{reg} exert potent immunosuppressive effects via cell-cell contact and production of soluble factors and may negatively regulate the activation of each of the major Th cell subtypes as well as other immune and inflammatory cells [2]. As indicated at several points in the preceding sections, there has been a consistent theme among many *in vitro* and *in vivo* studies in support of MSC enhancement of T_{reg} number and activity [8, 10]. English and colleagues [17] showed that human FOXP3⁺CD25^{high} T_{reg} were induced upon co-culture of allogeneic MSCs and CD4⁺ T cells and exerted suppressive activity when re-purified and added to a newly initiated mixed lymphocyte culture. This was corroborated in a study of human adipose tissue-derived MSCs that, in addition to reducing IL-17, TNF, and IFN- γ production, induced IL-10-producing, FOXP3⁺ T_{reg} *in vitro* among collagen-specific peripheral blood T cells of patients with rheumatoid arthritis [45]. Upon re-isolation, the T_{reg} originally generated in the presence of MSCs had the capacity to inhibit IFN- γ production and proliferation of a subsequent collagen-stimulated T-cell culture [45]. *In vivo* models of kidney, liver, and heart allotransplantation, several laboratories have linked the protective effects observed with MSC therapy directly to the presence of T_{reg} [26, 27, 46]. The importance of the induced T_{reg} populations in such transplant models, as well as in some models of allergic and autoimmune disease, is well illustrated by the induction of graft rejection or loss of therapeutic benefit

following T_{reg} depletion [6, 8, 26]. One concern that requires further investigation regarding MSC-induced T_{reg} relates to the potential for phenotypic plasticity of pro- and anti-inflammatory $CD4^+$ T-cell subsets under varying *in vivo* conditions. For example, as highlighted in a review by Afzali and colleagues [47], T_{reg} may be converted to a Th17 cell phenotype when exposed to inflammatory stimuli. In such circumstances, MSC-induced T_{reg} may exacerbate the disease state. Further human studies will be essential to fully elucidate the clinical relevance and robustness of MSC-induced T_{reg} *in vivo*, as evidenced by the study of Carrión and colleagues [48] in which the presence of MSC-induced T_{reg} did not alter the disease course in two patients with systemic lupus erythematosus.

Mesenchymal stem cell modulation of cytotoxic T lymphocytes

$CD8^+$ CTLs recognize cytosolic antigen-derived peptides presented by MHC class I and thus are essential for the destruction of virus-infected cells and tumor cells. Following their primary activation by professional antigen-presenting cells such as DCs, CTLs induce cell death upon secondary encounter of antigen expressed by any cell type via pro-apoptotic surface receptors or targeted release of cytotoxic granules [3, 19]. CTLs also release $IFN-\gamma$, TNF, and lymphotoxin- α to inhibit viral replication and to recruit macrophages to the site of infection [3]. Death receptor ligands such as TRAIL (TNF-related apoptosis-inducing ligand) and Fas ligand are upregulated on activated CTLs. In patients receiving allogeneic BM or hematopoietic stem cell transplants, activated CTLs mediate GvHD, causing damage to liver, intestine, skin, and other tissues [19]. Therapeutically administered MSCs have the potential to reduce disease severity in GvHD and other immune-mediated diseases via direct effects on CTLs as well as through inhibition of Th cell responses, which are required for full activation of CTLs [3]. For allogeneic MSC administration, the beneficial effects may also be limited by alloantigen-specific CTL-mediated MSC lysis. In a study by Rasmusson and colleagues [19], however, MSCs were resistant to CTL lysis despite the expression of MHC class I on their surface. MSCs were also unable to induce pro-inflammatory cytokine production or CD25 upregulation by CTLs [19]. This same group and others have also demonstrated that MSCs inhibit the formation of CTLs in mixed lymphocyte cultures and prevent CTL-associated lysis of target cells if added during the primary stimulation phase [49, 50]. In contrast, MSCs were unable to suppress activated CTLs at the cytotoxic effector phase [50]. Such findings were corroborated by Karlsson and colleagues [5], who showed that, while MSCs potently suppressed primary alloantigen-induced proliferation and $IFN-\gamma$ production by human peripheral blood leukocytes, they had no effect on cytomegalovirus (CMV)-induced proliferation or $IFN-\gamma$ production. Furthermore, MSCs were unable to suppress proliferation or cytolytic killing in established CMV- or Epstein-Barr virus-specific CTL lines [5]. These observations are of particular clinical relevance to the treatment of GvHD patients who are at high risk from the reactivation of viral infections. However, in this case, administration of MSCs was ineffective toward CMV-mediated $CD8^+$ T-cell effector functions while potently suppressing alloantigen-induced responses [5].

Interestingly, some of the protective effects of MSCs in GvHD may also result from the generation of $CD8^+$ T_{reg} , as demonstrated by Prevosto and colleagues [51]. It is proposed that $CD8^+$ T_{reg} may amplify the immune modulatory effects of MSCs because, when re-purified from peripheral blood leukocytes/MSC co-cultures, these cells potently suppressed subsequent peripheral blood leukocyte proliferation in response to alloantigen and to the non-specific mitogen phytohaemagglutinin [51]. It is also important to note that MSC-associated immune modulation may have detrimental effects in the setting of cancer. In a recent study by Patel and colleagues [52], the addition of MSCs to co-cultures of breast cancer cells and peripheral blood leukocytes resulted in enhanced T_{reg} numbers and Th2 cell-related cytokines as well as inhibited proliferation and release of granzyme B by CTLs, all of which resulted in protection of cancer cells from immune-mediated lysis. *In vivo* studies to examine this phenomenon are essential to fully understand the complex interaction between MSCs, T cells, and cancer cells and to ensure that MSC administration is not associated with recurrence or rapid metastasis of cancer in some patient groups. Overall, the experimental and clinical evidence to date suggests that MSCs exert both direct and indirect suppressive effects on the generation of antigen-specific CTLs and may foster the emergence of $CD8^+$ T_{reg} but do not significantly inhibit the immune surveillance functions of pre-existing $CD8^+$ memory T cells.

Concluding remarks and future directions

The immune suppressive and anti-inflammatory properties of MSCs are now very well established and clearly encompass potent modulatory influences on the generation and disease-associated activity of multiple T-cell effector phenotypes [8, 9, 10, 11, 12]. Preclinical models provide a strong impetus for translating MSC therapy to wide-spread clinical use for a range of common, T-cell-mediated autoimmune diseases and for prevention or treatment of transplant complications such as rejection and GvHD [8, 10]. Despite this, a critical review of our current understanding of these effects and of recent developments in MSC clinical trials [28] indicates that much remains to be learned at both the mechanistic and logistic levels. The dizzying array of potential MSC-associated mediators of T-cell suppression, the many differences between small-animal immunological models and human

immune-mediated diseases, and the lack of uniformity in MSC culture and administration protocols suggest that a more focused experimental pipeline will be required for the therapeutic potential to be realized in the near future. Table 1 summarizes a number of key questions that, on the basis of the literature to date, we believe to be important for translational progress in this field. In particular, we would highlight the need to better understand conditions in which MSC administration has been found to be ineffective or even harmful during T cell-mediated disease. Zappia and colleagues [38] demonstrated, for example, that the time of administration of MSCs was a critical parameter for successful treatment of EAE since MSC administration prior to or during the early disease course was effective whereas MSC benefit was lost once central nervous system inflammation was fully established. Similarly, in experimental arthritis, the timing of MSC administration, the relative effects of MSCs on different Th cell subsets, and the local joint conditions have been reported to critically determine the balance between therapeutic efficacy, lack of benefit, and detrimental effects [40, 42, 44, 53]. These studies should in no way dampen enthusiasm for further preclinical and clinical applications of MSCs in disease conditions in which one or more T-cell effector pathways are known to be the primary cause for acute or chronic tissue damage. Rather, they highlight the complexity of the interactions that occur between stromal cells and cells of the immune system and the wealth of basic and therapeutic insights that can be gained from continued investigation of these interactions.

Table 1

Key unanswered or incompletely answered questions about mesenchymal stem cell effects on T-cell effector functions

1	Is there a true hierarchy of suppressive potency for MSC effects on the three major T helper cell effector pathways (for example, Th1 cells > Th17 cells > Th2 cells)?
2	Are individual T-cell effector phenotypes susceptible to different MSC mechanisms of suppression, or does suppressive mechanism vary by MSC culture condition or by disease pathogenesis (or by both)?
3	How important is cell-cell contact for the <i>in vivo</i> direct and indirect suppression by MSCs of harmful T-cell effector functions?
4	Is the apparent shift from Th1/Th17 to Th2/T _{reg} responses following MSC therapy in some diseases due to true induction and expansion of anti-inflammatory T-cell effector phenotypes or to their preferential survival?
5	What are the relative effects of MSCs on memory and pre-activated T-cell effectors compared with naïve T cells undergoing primary activation?
6	Do immunosuppressive potency and mechanism of action vary among the individual cells within heterogenous MSC cultures and can they be enhanced by MSC cloning or modification?
7	To what extent and under what circumstances are MSCs capable of promoting harmful T-cell effector functions?
8	How long-lasting is MSC modulation of antigen-specific T-cell effectors following single or multiple <i>in vivo</i> administration?
9	How can MSC <i>in vivo</i> immune suppressive potency, mechanism of action, and site of migration be better predicted for a given culture preparation prior to therapeutic administration?
10	Does the <i>in vivo</i> immunogenicity of allogeneic MSCs limit their long-term therapeutic benefit in autoimmune disease and allotransplantation?

11 What are the combined *in vivo* effects of MSC and other anti-T-cell therapies?

MSC, mesenchymal stem cell; Th1, T helper type 1; Th2, T helper type 2; Th17, T helper type 17; T_{reg}, regulatory T cell.

Note

This article is part of a review series on Immunology and stem cells, edited by Christian Jorgensen. Other articles in the series can be found online at <http://stemcellres.com/series/immunology>

Abbreviations

BM:

bone marrow

CMV:

cytomegalovirus

CTL:

cytotoxic T lymphocyte

DC:

dendritic cell

DTH:

delayed-type hypersensitivity

EAE:

experimental allergic encephalomyelitis

FOXP3:

forkhead box P3

GvHD:

graft-versus-host disease

IFN- γ :

interferon-gamma

Ig:

immunoglobulin

IL:

interleukin

MCP-1:

monocyte chemotactic protein 1

MHC:

major histocompatibility complex

MSC:

mesenchymal stem (stromal) cell

NOD:

nonobese diabetic

PGE₂:

prostaglandin E₂

TGF- β :

transforming growth factor-beta

Th:

T helper

Th1:

T helper type 1

Th2:

T helper type 2

Th17:

T helper type 17

TNF:

tumor necrosis factor

T_{reg}:

regulatory T cell(s).

Declarations

Acknowledgements

The authors are funded by grants from Science Foundation Ireland (grant numbers SFI PI 06/IN.1/B652 to MMD and MDG, SFI PI 07/IN.1/B925 to TR, and SFI SRC 09/SRC/B1794 to MDG, TR, and RC), by a Science Foundation Ireland Stokes Professorship to RC, and by grants from the Health Research Board of Ireland (grant numbers HRA_HSR/2010/63 to MDG and RP/2007/60 to TR).

Authors' original submitted files for images

Below are the links to the authors' original submitted files for images.
[13287_2011_75_MOESM1_ESM.pdf](#) Authors' original file for figure 1

Competing interests

The authors declare that they have no competing interests.

Authors' Affiliations

(1)

Regenerative Medicine Institute (REMEDI), National Centre for Biomedical Engineering Science (NCBES) and School of Medicine, Nursing and Health Sciences, Orbsen Building, National University of Ireland Galway, University Road, Galway, Ireland

References

1. Kaech SM, Wherry EJ, Ahmed R: Effector and memory T-cell differentiation: implications for vaccine development. *Nat Rev Immunol.* 2002, 2: 251-262. 10.1038/nri778. [View ArticlePubMedGoogle Scholar](#)
2. Wan YY, Flavell RA: How diverse--CD4 effector T cells and their functions. *J Mol Cell Biol.* 2009, 1: 20-36. 10.1093/jmcb/mjp001. [PubMed CentralView ArticlePubMedGoogle Scholar](#)
3. Janeway C: T-cell mediated immunity. *Janeway's Immunobiology.* Edited by: Murphy K, Travers P, Walport M. 2008, New York: Garland Science, Taylor & Francis Group, 364-368. [7Google Scholar](#)
4. Bai L, Lennon DP, Eaton V, Maier K, Caplan AI, Miller SD, Miller RH: Human bone marrow-derived mesenchymal stem cells induce Th2-polarized immune response and promote endogenous repair in animal models of multiple sclerosis. *Glia.* 2009, 57: 1192-1203. 10.1002/glia.20841. [PubMed CentralView ArticlePubMedGoogle Scholar](#)
5. Karlsson H, Samarasinghe S, Ball LM, Sundberg B, Lankester AC, Dazzi F, Uzunel M, Rao K, Veys P, Le Blanc K, Ringdén O, Amrolia PJ: Mesenchymal stem cells exert differential effects on alloantigen and virus-specific T-cell responses. *Blood.* 2008, 112: 532-541. 10.1182/blood-2007-10-119370. [View ArticlePubMedGoogle Scholar](#)
6. Kavanagh H, Mahon BP: Allogeneic mesenchymal stem cells prevent allergic airway inflammation by inducing murine regulatory T cells. *Allergy.* 2011, 66: 523-531. 10.1111/j.1398-9995.2010.02509.x. [View ArticlePubMedGoogle Scholar](#)
7. Gonzalez MA, Gonzalez-Rey E, Rico L, Buscher D, Delgado M: Adipose-derived mesenchymal stem cells alleviate experimental colitis by inhibiting inflammatory and autoimmune responses. *Gastroenterology.* 2009, 136: 978-989. 10.1053/j.gastro.2008.11.041. [View ArticlePubMedGoogle Scholar](#)
8. English K, French A, Wood KJ: Mesenchymal stromal cells: facilitators of successful transplantation?. *Cell Stem Cell.* 2010, 7: 431-442. 10.1016/j.stem.2010.09.009. [View ArticlePubMedGoogle Scholar](#)
9. Barry FP, Murphy JM: Mesenchymal stem cells: clinical applications and biological characterization. *Int J Biochem Cell Biol.* 2004, 36: 568-584. 10.1016/j.biocel.2003.11.001. [View ArticlePubMedGoogle Scholar](#)
10. Griffin MD, Ritter T, Mahon BP: Immunological aspects of allogeneic mesenchymal stem cell therapies. *Hum Gene Ther.* 2010, 21: 1641-1655. 10.1089/hum.2010.156. [View ArticlePubMedGoogle Scholar](#)
11. Caplan AI: Why are MSCs therapeutic? New data: new insight. *J Pathol.* 2009, 217: 318-324. 10.1002/path.2469. [View ArticlePubMedGoogle Scholar](#)
12. Barry FP, Murphy JM, English K, Mahon BP: Immunogenicity of adult mesenchymal stem cells: lessons from the fetal allograft. *Stem Cells Dev.* 2005, 14: 252-265. 10.1089/scd.2005.14.252. [View ArticlePubMedGoogle Scholar](#)
13. Bartholomew A, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S, Hardy W, Devine S, Ucker D, Deans R, Moseley A, Hoffman R: Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. *Exp Hematol.* 2002, 30: 42-48. 10.1016/S0301-472X(01)00769-X. [View ArticlePubMedGoogle Scholar](#)
14. Gieseke F, Bohringer J, Bussolari R, Dominici M, Handgretinger R, Muller I: Human multipotent mesenchymal stromal cells use galectin-1 to inhibit immune effector cells. *Blood.* 2010, 116: 3770-3779. 10.1182/blood-2010-02-270777. [View ArticlePubMedGoogle Scholar](#)
15. Cutler AJ, Limbani V, Girdlestone J, Navarrete CV: Umbilical cord-derived mesenchymal stromal cells modulate monocyte function to suppress T cell proliferation. *J Immunol.* 2010, 185: 6617-6623. 10.4049/jimmunol.1002239. [View ArticlePubMedGoogle Scholar](#)
16. Wang Q, Sun B, Wang D, Ji Y, Kong Q, Wang G, Wang J, Zhao W, Jin L, Li H: Murine bone marrow mesenchymal stem cells cause mature dendritic cells to promote T-cell tolerance. *Scand J Immunol.* 2008, 68: 607-615. 10.1111/j.1365-3083.2008.02180.x. [View ArticlePubMedGoogle Scholar](#)
17. English K, Ryan JM, Tobin L, Murphy MJ, Barry FP, Mahon BP: Cell contact, prostaglandin E(2) and transforming growth factor beta 1 play non-redundant roles in human mesenchymal stem cell induction of CD4+CD25(High) forkhead box P3+ regulatory T cells. *Clin Exp Immunol.* 2009, 156: 149-160. 10.1111/j.1365-2249.2009.03874.x. [PubMed CentralView ArticlePubMedGoogle Scholar](#)
18. Batten P, Sarathchandra P, Antoniw JW, Tay SS, Lowdell MW, Taylor PM, Yacoub MH: Human mesenchymal stem cells induce T cell anergy and downregulate T cell allo-responses via the TH2 pathway: relevance to tissue engineering human

- heart valves. *Tissue Eng.* 2006, 12: 2263-2273. 10.1089/ten.2006.12.2263. [View ArticlePubMedGoogle Scholar](#)
19. Rasmusson I, Uhlin M, Le Blanc K, Levitsky V: Mesenchymal stem cells fail to trigger effector functions of cytotoxic T lymphocytes. *J Leukoc Biol.* 2007, 82: 887-893. 10.1189/jlb.0307140. [View ArticlePubMedGoogle Scholar](#)
 20. Najjar M, Raicevic G, Boufker HI, Fayyad Kazan H, De Bruyn C, Meuleman N, Bron D, Toungouz M, Lagneaux L: Mesenchymal stromal cells use PGE2 to modulate activation and proliferation of lymphocyte subsets: Combined comparison of adipose tissue, Wharton's Jelly and bone marrow sources. *Cell Immunol.* 2010, 264: 171-179. 10.1016/j.cellimm.2010.06.006. [View ArticlePubMedGoogle Scholar](#)
 21. Tatara R, Ozaki K, Kikuchi Y, Hatanaka K, Oh I, Meguro A, Matsu H, Sato K, Ozawa K: Mesenchymal stromal cells inhibit Th17 but not regulatory T-cell differentiation. *Cytotherapy.* 2011, 13: 686-694. 10.3109/14653249.2010.542456. [View ArticlePubMedGoogle Scholar](#)
 22. Wang J, Wang G, Sun B, Li H, Mu L, Wang Q, Li G, Shi L, Jin L, Kostulas N: Interleukin-27 suppresses experimental autoimmune encephalomyelitis during bone marrow stromal cell treatment. *J Autoimmun.* 2008, 30: 222-229. 10.1016/j.jaut.2007.10.001. [View ArticlePubMedGoogle Scholar](#)
 23. Zhao W, Wang Y, Wang D, Sun B, Wang G, Wang J, Kong Q, Wang Q, Peng H, Jin L, Li H: TGF-beta expression by allogeneic bone marrow stromal cells ameliorates diabetes in NOD mice through modulating the distribution of CD4+ T cell subsets. *Cell Immunol.* 2008, 253: 23-30. 10.1016/j.cellimm.2008.06.009. [View ArticlePubMedGoogle Scholar](#)
 24. Ren G, Zhao X, Zhang L, Zhang J, L'Huillier A, Ling W, Roberts AI, Le AD, Shi S, Shao C, Shi Y: Inflammatory cytokine-induced intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in mesenchymal stem cells are critical for immunosuppression. *J Immunol.* 2010, 184: 2321-2328. 10.4049/jimmunol.0902023. [PubMed CentralView ArticlePubMedGoogle Scholar](#)
 25. Lim JH, Kim JS, Yoon IH, Shin JS, Nam HY, Yang SH, Kim SJ, Park CG: Immunomodulation of delayed-type hypersensitivity responses by mesenchymal stem cells is associated with bystander T cell apoptosis in the draining lymph node. *J Immunol.* 2010, 185: 4022-4029. 10.4049/jimmunol.0902723. [View ArticlePubMedGoogle Scholar](#)
 26. Ge W, Jiang J, Arp J, Liu W, Garcia B, Wang H: Regulatory T-cell generation and kidney allograft tolerance induced by mesenchymal stem cells associated with indoleamine 2,3-dioxygenase expression. *Transplantation.* 2010, 90: 1312-1320. 10.1097/TP.0b013e3181fed001. [View ArticlePubMedGoogle Scholar](#)
 27. Casiraghi F, Azzollini N, Cassis P, Imberti B, Morigi M, Cugini D, Cavinato RA, Todeschini M, Solini S, Sonzogni A, Perico N, Remuzzi G, Noris M: Pretransplant infusion of mesenchymal stem cells prolongs the survival of a semiallogeneic heart transplant through the generation of regulatory T cells. *J Immunol.* 2008, 181: 3933-3946. [View ArticlePubMedGoogle Scholar](#)
 28. Ankrum J, Karp JM: Mesenchymal stem cell therapy: two steps forward, one step back. *Trends Mol Med.* 2010, 16: 203-209. 10.1016/j.molmed.2010.02.005. [PubMed CentralView ArticlePubMedGoogle Scholar](#)
 29. Hermann-Kleiter N, Baier G: NFAT pulls the strings during CD4+ T helper cell effector functions. *Blood.* 2010, 115: 2989-2997. 10.1182/blood-2009-10-233585. [View ArticlePubMedGoogle Scholar](#)
 30. Aksu AE, Horibe E, Sacks J, Ikeguchi R, Breitingner J, Scozio M, Unadkat J, Feili-Hariri M: Co-infusion of donor bone marrow with host mesenchymal stem cells treats GVHD and promotes vascularized skin allograft survival in rats. *Clin Immunol.* 2008, 127: 348-358. 10.1016/j.clim.2008.02.003. [View ArticlePubMedGoogle Scholar](#)
 31. Boumaza I, Srinivasan S, Witt WT, Feghali-Bostwick C, Dai Y, Garcia-Ocana A, Feili-Hariri M: Autologous bone marrow-derived rat mesenchymal stem cells promote PDX-1 and insulin expression in the islets, alter T cell cytokine pattern and preserve regulatory T cells in the periphery and induce sustained normoglycemia. *J Autoimmun.* 2009, 32: 33-42. 10.1016/j.jaut.2008.10.004. [View ArticlePubMedGoogle Scholar](#)
 32. Madec AM, Mallone R, Afonso G, Abou Mrad E, Mesnier A, Eljaafari A, Thivolet C: Mesenchymal stem cells protect NOD mice from diabetes by inducing regulatory T cells. *Diabetologia.* 2009, 52: 1391-1399. 10.1007/s00125-009-1374-z. [View ArticlePubMedGoogle Scholar](#)
 33. Coffman RL: The origin of TH2 responses. *Science.* 2010, 328: 1116-1117. 10.1126/science.1192009. [View ArticlePubMedGoogle Scholar](#)
 34. Zhou H, Guo M, Bian C, Sun Z, Yang Z, Zeng Y, Ai H, Zhao RC: Efficacy of bone marrow-derived mesenchymal stem cells in the treatment of sclerodermatous chronic graft-versus-host disease: clinical report. *Biol Blood Marrow Transplant.* 2010, 16: 403-412. 10.1016/j.bbmt.2009.11.006. [View ArticlePubMedGoogle Scholar](#)
 35. Fiorina P, Jurewicz M, Augello A, Vergani A, Dada S, La Rosa S, Selig M, Godwin J, Law K, Placidi C, Smith RN, Capella C, Rodig S, Adra CN, Atkinson M, Sayegh MH, Abdi R: Immunomodulatory function of bone marrow-derived mesenchymal stem cells in experimental autoimmune type 1 diabetes. *J Immunol.* 2009, 183: 993-1004. 10.4049/jimmunol.0900803. [PubMed CentralView ArticlePubMedGoogle Scholar](#)
 36. Awasthi A, Kuchroo VK: Th17 cells: from precursors to players in inflammation and infection. *Int Immunol.* 2009, 21: 489-498. 10.1093/intimm/dxp021. [PubMed CentralView ArticlePubMedGoogle Scholar](#)
 37. Ghannam S, Pene J, Torcy-Moquet G, Jorgensen C, Yssel H: Mesenchymal stem cells inhibit human Th17 cell differentiation and function and induce a T regulatory cell phenotype. *J Immunol.* 2010, 185: 302-312. 10.4049/jimmunol.0902007. [View ArticlePubMedGoogle Scholar](#)
 38. Zappia E, Casazza S, Pedemonte E, Benvenuto F, Bonanni I, Gerdoni E, Giunti D, Ceravolo A, Cazzanti F, Frassoni F, Mancardi G, Uccelli A: Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell

- anergy. *Blood*. 2005, 106: 1755-1761. 10.1182/blood-2005-04-1496. [View ArticlePubMedGoogle Scholar](#)
39. Rafei M, Campeau PM, Aguilar-Mahecha A, Buchanan M, Williams P, Birman E, Yuan S, Young YK, Boivin MN, Forner K, Basik M, Galipeau J: Mesenchymal stromal cells ameliorate experimental autoimmune encephalomyelitis by inhibiting CD4 Th17 T cells in a CC chemokine ligand 2-dependent manner. *J Immunol*. 2009, 182: 5994-6002. 10.4049/jimmunol.0803962. [View ArticlePubMedGoogle Scholar](#)
40. Carrión F, Nova E, Luz P, Apablaza F, Figueroa F: Opposing effect of mesenchymal stem cells on Th1 and Th17 cell polarization according to the state of CD4(+) T cell activation. *Immunol Lett*. 2011, 135: 10-16. 10.1016/j.imlet.2010.09.006. [View ArticlePubMedGoogle Scholar](#)
41. Darlington PJ, Boivin MN, Renoux C, Francois M, Galipeau J, Freedman MS, Atkins HL, Cohen JA, Solchaga L, Bar-Or A: Reciprocal Th1 and Th17 regulation by mesenchymal stem cells: implication for multiple sclerosis. *Ann Neurol*. 2010, 68: 540-545. 10.1002/ana.22065. [View ArticlePubMedGoogle Scholar](#)
42. Bouffi C, Bony C, Courties G, Jorgensen C, Noël D: IL-6-dependent PGE2 secretion by mesenchymal stem cells inhibits local inflammation in experimental arthritis. *PLoS ONE*. 2010, 5: e14247-10.1371/journal.pone.0014247. [PubMed CentralView ArticlePubMedGoogle Scholar](#)
43. Kong QF, Sun B, Wang GY, Zhai DX, Mu LL, Wang DD, Wang JH, Li R, Li HL: BM stromal cells ameliorate experimental autoimmune myasthenia gravis by altering the balance of Th cells through the secretion of IDO. *Eur J Immunol*. 2009, 39: 800-809. 10.1002/eji.200838729. [View ArticlePubMedGoogle Scholar](#)
44. Chen B, Hu J, Liao L, Sun Z, Han Q, Song Z, Zhao RC: Flk-1+ mesenchymal stem cells aggravate collagen-induced arthritis by up-regulating interleukin-6. *Clin Exp Immunol*. 2010, 159: 292-302. 10.1111/j.1365-2249.2009.04069.x. [PubMed CentralView ArticlePubMedGoogle Scholar](#)
45. Gonzalez-Rey E, Gonzalez MA, Varela N, O'Valle F, Hernandez-Cortes P, Rico L, Buscher D, Delgado M: Human adipose-derived mesenchymal stem cells reduce inflammatory and T cell responses and induce regulatory T cells in vitro in rheumatoid arthritis. *Ann Rheum Dis*. 2010, 69: 241-248. 10.1136/ard.2008.101881. [View ArticlePubMedGoogle Scholar](#)
46. Wang Y, Zhang A, Ye Z, Xie H, Zheng S: Bone marrow-derived mesenchymal stem cells inhibit acute rejection of rat liver allografts in association with regulatory T-cell expansion. *Transplant Proc*. 2009, 41: 4352-4356. 10.1016/j.transproceed.2009.08.072. [View ArticlePubMedGoogle Scholar](#)
47. Afzali B, Mitchell P, Lechler RI, John S, Lombardi G: Translational mini-review series on Th17 cells: induction of interleukin-17 production by regulatory T cells. *Clin Exp Immunol*. 2009, 159: 120-130. [View ArticlePubMedGoogle Scholar](#)
48. Carrión F, Nova E, Ruiz C, Diaz F, Inostroza C, Rojo D, Monckeberg G, Figueroa FE: Autologous mesenchymal stem cell treatment increased T regulatory cells with no effect on disease activity in two systemic lupus erythematosus patients. *Lupus*. 2010, 19: 317-322. 10.1177/0961203309348983. [View ArticlePubMedGoogle Scholar](#)
49. Maccario R, Podestà M, Moretta A, Cometa A, Comoli P, Montagna D, Daudt L, Ibatìci A, Piaggio G, Pozzi S, Frassoni F, Locatelli F: Interaction of human mesenchymal stem cells with cells involved in alloantigen-specific immune response favors the differentiation of CD4+ T-cell subsets expressing a regulatory/suppressive phenotype. *Haematologica*. 2005, 90: 516-525. [PubMedGoogle Scholar](#)
50. Rasmusson I, Ringden O, Sundberg B, Le Blanc K: Mesenchymal stem cells inhibit the formation of cytotoxic T lymphocytes, but not activated cytotoxic T lymphocytes or natural killer cells. *Transplantation*. 2003, 76: 1208-1213. 10.1097/01.TP.0000082540.43730.80. [View ArticlePubMedGoogle Scholar](#)
51. Prevosto C, Zancolli M, Canevali P, Zocchi MR, Poggi A: Generation of CD4+ or CD8+ regulatory T cells upon mesenchymal stem cell-lymphocyte interaction. *Haematologica*. 2007, 92: 881-888. 10.3324/haematol.11240. [View ArticlePubMedGoogle Scholar](#)
52. Patel SA, Meyer JR, Greco SJ, Corcoran KE, Bryan M, Rameshwar P: Mesenchymal stem cells protect breast cancer cells through regulatory T cells: role of mesenchymal stem cell-derived TGF-beta. *J Immunol*. 2010, 184: 5885-5894. 10.4049/jimmunol.0903143. [View ArticlePubMedGoogle Scholar](#)
53. Tso GH, Law HK, Tu W, Chan GC, Lau YL: Phagocytosis of apoptotic cells modulates mesenchymal stem cells osteogenic differentiation to enhance IL-17 and RANKL expression on CD4+ T cells. *Stem Cells*. 2010, 28: 939-954. [PubMedGoogle Scholar](#)

Copyright

© BioMed Central Ltd 2011

[Download PDF](#)

Export citations

Papers, Zotero, Reference Manager, RefWorks (.RIS)

- [↓ Download Citations](#)
- [↓ Download References](#)
- [↓ Download Both](#)

EndNote (.ENW)

- [↓ Download Citations](#)
- [↓ Download References](#)
- [↓ Download Both](#)

Mendeley, JabRef (.BIB)

- [↓ Download Citations](#)
- [↓ Download References](#)
- [↓ Download Both](#)

In these collections

- [Immunology and stem cells](#)

Metrics

- Article accesses: 14030
- Citations: 151 [more information](#)

Share this article

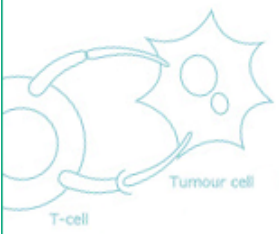
- [Share on Twitter](#) 
- [Share on Facebook](#) 
- [Share on LinkedIn](#) 
- [Share on Weibo](#) 
- [Share on Google Plus](#) 
- [Share on Reddit](#) 

Other Actions

- [Order reprint](#)

Advertisement


Immune Checkpoint Protein



T-cell Tumour cell

- ▶ Validated bioactivity
- ▶ High purity
- ▶ His-/Fc-tagged and tag free
- ▶ Multiple species

[Learn more](#)



Sino Biological
Biological Solution Specialist



Stem Cell Research & Therapy

ISSN: 1757-6512

Contact us

- Submission enquiries: [Access here and click Contact Us](#)
- General enquiries: info@biomedcentral.com

BMC



- [Explore journals](#)
- [Get published](#)
- [About BMC](#)

- [Read more on our blogs](#)
- [Receive BMC newsletters](#)
- [Manage article alerts](#)
- [Language editing for authors](#)
- [Scientific editing for authors](#)

- [Policies](#)
- [Accessibility](#)

- [Press center](#)
- [Contact us](#)
- [Leave feedback](#)
- [Careers](#)

Follow BMC

- [BMC Twitter page](#) 
- [BMC Facebook page](#) 
- [BMC Google Plus page](#) 
- [BMC Weibo page](#) 

By using this website, you agree to our [Terms and Conditions](#), [Privacy statement](#) and [Cookies](#) policy. [Manage the cookies](#) we use in the preference centre.

SPRINGER NATURE

© 2018 BioMed Central Ltd unless otherwise stated. Part of [Springer Nature](#).