# Cellular and molecular interactions of mesenchymal stem cells in innate immunity

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## Abstract

In recent years, human mesenchymal stem/stromal cells (MSC) have attracted major attention for their possible clinical applications. In addition to their tissue regenerative capacity, they display immune-modulatory properties for which they have been used in the treatment of acute graft-versus-host disease and autoimmune diseases. Various studies have analyzed the inhibitory effect exerted by MSC on cells belonging to acquired or to innate immunity. In this context, MSC have been shown to inhibit proliferation and function of natural killer (NK) cells and to hinder the generation of dendritic cells and macrophages, thus interfering with inflammatory processes and with the generation of type I immune responses. In addition, MSC promote the differentiation of regulatory cells and participate in the regeneration of tissues damaged as a consequence of the inflammatory process. Different molecular mechanisms are involved in the immunosuppressive effect. Further investigation on the biology of MSC and on the regulatory events involved in their functional activities can help to optimize their use in clinical practice.

**Keywords:**

dendritic cells; immumodulation; macrophages; mesenchymal stem cells; natural killer cells.

## Introduction

After more than a decade of investigation, it is now evident that the clinical use of mesenchymal stem/stromal cells (MSC) represents an important reality in the treatment of several pathologic conditions in which inflammation and immunopathologic reactions have a fundamental role. Indeed, both *in vitro* and *in vivo* studies, including phase I, II and also III clinical trials, have established the therapeutic potential of MSC and the safety of their infusion even in an allogeneic setting.[1] In particular, MSC have been successfully used in the treatment of immune-related disorders including autoimmune diseases or graft-versus-host disease (GvHD) in patients receiving allogeneic hematopoietic stem cell transplantation (HSCT). The clinical benefit of MSC infusion can be ascribed to two major biological activities, namely the immunomodulatory effect on different cells involved in the immune response and the capability of promoting tissue regeneration. The first reports describing the immunomodulatory activity of MSC were focused on their capacity to inhibit proliferation and function of T cells.[2] Subsequently, it became evident that suppression of T-cell activities was mediated not only by a direct effect, but also through the inhibition of the differentiation and function of cells involved in the regulation of adaptive immune responses. Thus, MSC were shown to block the generation of functional antigen-presenting cells, including myeloid dendritic cells (DC)[3, 4, 5] and macrophages.[6, 7] This effect results in the generation of cells unable to efficiently stimulate type I immune responses. In some cases, such MSC-conditioned cells display phenotypic and functional features of regulatory cells, capable of further inhibiting even ongoing inflammatory/immune

responses. In the case of macrophages, MSC can induce polarization towards M2 cells.[8] M2 cells represent the so called ‘alternatively activated’ macrophages, which not only have regulatory activity but also participate in wound healing.[9] Thus, in the case of severe tissue injury due to drug-resistant harmful immune responses (for example, GvHD), the MSC-mediated induction of M2 macrophages may contribute at the same time to immunosuppression and tissue regeneration. Natural killer (NK) lymphocytes are cells of the innate immunity characterized by a strong cytolytic activity against tumor or virally-infected cells.[10, 11] Their function is finely regulated by a series of surface receptors transducing either inhibitory[12] or activating signals.[13] More recently, NK cells have been shown to have a role in the regulation of both innate and adaptive immune responses by interacting with DC both in inflamed peripheral tissues and in secondary lymphoid compartments.[14, 15] In particular, NK cells have been shown to be capable of either killing DC or promoting their maturation.[16, 17] In addition, NK cells can respond to cytokines such as interleukin (IL)-2 and IL-15 or pathogen-associated TLR ligands and produce interferon-γ (IFN-γ), which, in turn, primes macrophages to secrete pro-inflammatory cytokines, to produce increased amounts of superoxide anions, and oxygen and nitrogen radicals, thus increasing their killing ability against pathogens.[18] By inhibiting NK-cell activation and effector function, MSC affect the ability of NK cells to sustain type I immune response. On the other hand, in the scenario of using MSC in allogeneic HSCT, one should consider that the inhibition of ‘alloreactive’ NK cells may compromise their graft-versus-leukemia effect, which has a central role in the positive outcome of haploidentical HSCT in the treatment of high-risk leukemias.[19]

In spite of the general evidence that MSC can affect both the generation and function of innate immune cells, data are partially contradictory and further investigation is needed to clarify the mechanisms involved in their inhibitory effect. In this review, we provide an overview of the most relevant studies on the interactions between MSC and cells of the innate immunity in humans.

## MSC interaction with NK cells

In most studies, the relevance of the results of the interaction between MSC and NK cells has been focused on the consequences that such interaction may have on the therapeutical benefit of both MSC and NK cells in the context of allogeneic HSCT. MSC have been employed in clinical trials aimed at improving engraftment of hematopoietic stem cells and at preventing or treating acute GvHD.[20] NK cells have been shown to have a fundamental role in haploidentical HSCT, having a central role in the eradication of leukemia and in the prevention of GvHD.[21] Infusion of MSC as immunosuppressive treatment for T-cell response has a positive effect on GvHD. However, it may also inhibit NK-cell activity. In this context, *in vitro* studies have investigated the results of the interaction between MSC and NK cells. Indeed, it has been shown that NK/MSC interaction can lead to relevant effects on the function of both cell types.

MSC were able to inhibit proliferation and effector function of freshly isolated peripheral blood NK cells. On exposure to cytokines such as IL-2 and IL-15, NK cells become activated and undergo proliferation. In the presence of MSC, the cytokine-induced NK-cell proliferation was strongly impaired, with no evidence of apoptosis or cell death.[22, 23] The inhibition was dose-dependent, being detected at NK/MSC ratios ranging from 1:1 to 10:1 and decreasing at higher NK/MSC ratios. The inhibitory effect was mediated by MSC-derived soluble factors. This was revealed by transwell experiments in which the inhibitory effect occurred in the absence of cell contact.[22] In addition to inhibition of NK-cell proliferation, MSC could also impair their lytic potential. Notably, the NK-mediated cyotoxicity represents an important mechanism by which virus-infected and tumor cells are eliminated. Moreover, it has been shown to represent a quality control step during the generation of functionally mature DC as the result of the removal of DC that do not express adequate levels of HLA class I molecules (DC editing).[24] Resting NK cells are characterized by a low cytolytic activity. In *in vitro* experiments, induction of NK-cytotoxicity was strongly affected by MSC. Interestingly, different from the case of NK-cell proliferation, inhibition of cytotoxicity induction appears to require cell-to-cell contact.[22] MSC inhibited lysis of both HLA-class $I^+$ (various tumor cell lines and immature DC) and HLA-class $I^-$ target cells.[25]

Under normal conditions, the cytokine-induced activation of NK cells leads to *de novo* or increase of surface expression of activating receptors including NKp44, NKp30, NKG2D. These molecules, together with NKp46 and DNAM-1, and several coreceptors, are primarily involved in NK-cell activation and induction of effector functions, such as cytotoxic activity and cytokine production.[26] MSC have been reported to inhibit the expression of NKp44, NKp30 and NKG2D and of other important functional molecules, such as the coreceptor 2B4 and CD132 (IL-2Rγ chain).[25] Notably, low expression of CD132 renders NK cells less responsive to cytokine activation, thus representing an additional mechanism possibly involved in the inhibitory effect.

As mentioned above, cytokine production represents a major effector function of NK cells. Upon stimulation by triggering signals, NK cells can produce a number of cytokines, including IFN-γ, Tumor necrosis factor-α (TNF-α), and IL-10. When cultured with MSC, NK cells display a decreased capability of secreting these cytokines independently of the activating stimulus (represented by cytokines such as IL-15, IL-12 and IL-18, or the interaction with tumor cells).[22, 23] Notably, as in the case of NK-cell proliferation, inhibition occurred also under transwell conditions, thus suggesting a role for soluble mediators.

Indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2) and soluble HLA-G5 (sHLA-G5) have been shown to have a major role in the inhibition of cytokine-induced NK-cell proliferation and effector function. A partial, but significant restoration of NK-cell proliferation and cytotoxicity was observed when PGE2 synthesis was inhibited, suggesting that PGE2 was involved in the inhibitory effect.[22] Moreover, MSC were reported to release sHLA-G5 molecules, which inhibit the NK-cell cytotoxicity.[27] Spaggiari *et al.*[25] showed that blocking of IDO activity could significantly restore NK-cell proliferation, whereas the PGE2 synthesis inhibitor NS-398 had a positive effect on cytotoxicity. Interestingly, when both inhibitors were added simultaneously to NK/MSC cocultures, an almost complete restoration of both NK-cell proliferation and cytotoxicity was obtained. These data indicate that PGE2 and IDO are fundamental mediators of the MSC-mediated inhibitory effect on NK cells and that they may act synergistically.

In addition, one or another soluble factor may be mostly involved in the inhibition of NK-cell proliferation or cytolytic activity. In particular, triptofan depletion due to IDO degradation may have a more prominent impact on cell proliferation, whereas PGE2 may predominantly interfere with cytolytic activity and cytokine production. Notably, PGE2 is constitutively produced by MSC, whereas IDO is *de novo* expressed upon cell exposure to IFN-γ or TNF-α. It is conceivable that during NK/MSC interactions, NK cells rapidly secrete IFN-γ and TNF-α, which, in turn, upregulate PGE2 production and IDO synthesis. It is now well established that IFN-γ represents a crucial factor for the induction of the MSC-mediated immunoregulatory activity. Meisel *et al.*[28] first described that IDO expression is induced by IFN-γ. In addition, Krampera *et al.*[29] reported that neutralization of IFN-γ, produced by NK cells, partially restored NK-cell proliferation in NK/MSC cocultures. Aggarwal *et al.*[30] showed that PGE2 synthesis was increased by exposing MSC to IFN-γ. Also sHLA-G5 production can be increased by IFN-γ.[31]

A most relevant finding regarding the MSC/NK-cell interaction is the fact that NK cells can kill both autologous and allogeneic MSC. MSC express low/intermediate levels of HLA-class I molecules, rendering them virtually undetectable by alloreactive cytolytic T cells. On this basis, clinical trials have employed allogeneic (HLA-mismatched) MSC with no evidence of a response by recipient's T cells. However, MSC express low levels of HLA class I molecules rendering them susceptible to NK-cell lysis. In this context, MSC also express some ligands of activating NK receptors, including ULBP1–4 and MICA (NKG2D ligands), PVR and Nectin-2 (DNAM-1 ligands), and other still unidentified ligands, as the NKp30 ligand(s) (as revealed indirectly, by masking experiments in cytotoxicity assays).[23] Thanks to their phenotypic profile, MSC are susceptible to NK-mediated lysis, independently of whether they are autologous or allogeneic. However, it should be considered that killing of MSC is possible only when NK cells are activated, for example, by cytokines such as IL-2 and IL-15,[22, 23] which up-regulate the expression of NKp30 and NKG2D activating receptors and

potentiate their lytic machinery. In contrast, freshly-isolated, resting NK cells are not capable of killing MSC, even at high effector/target ratios. It is of note that killing of MSC has been shown to be mediated not only by intracellular calcium increase with subsequent release of perforins,[32] but also by the interaction of TRAIL and FasL with their specific receptors DR4, DR5 and Fas expressed by fetal and adult MSC, respectively.[33]

During infection or, more generally, during inflammatory responses, cells are exposed to proinflammatory cytokines, such as IFN-γ that up-regulate the surface expression of HLA-class I and HLA-class II on MSC.[34] This may impact on the susceptibility of MSC to NK-mediated lysis, owing to the interaction between HLA-class I and inhibitory NK receptors. These are represented not only by killer Ig-like receptors, specific for allotypic determinants of classical HLA class I molecules, but also by NKG2A, specific for non classical HLA-E molecules. Indeed, monoclonal antibody-mediated disruption of these inhibitory interactions could restore efficient NK-cell-mediated killing of MSC.[23]

## Interaction with DC

DC have a critical role in initiating and regulating immune responses by promoting antigen-specific T-cell activation. Moreover, they are involved in relevant functional interactions with different cells of the innate immune system. DC are the most effective antigen-presenting cells and prime naive T cells to initiate adaptive immune responses including those against allogeneic cells or self antigens, as in the case of GvHD and autoimmune diseases, respectively. A large body of evidence accounts for the ability of MSC to strongly inhibit DC generation from both monocytes and CD34$^{+}$cell precursors. However, in spite of the general evidence that MSC can inhibit the generation of functional DC, results on the mechanisms involved are often contradictory, possibly reflecting differences in the experimental setting. In 2005, Aggarwal and Pittenger first reported that bone marrow-derived MSC inhibited TNF-α secretion by CD1c$^{+}$ myeloid DC, while they increased IL-10 production by BDCA-4$^{+}$ plasmacytoid DC.[30] Thereafter, MSC were shown to inhibit T cells indirectly, as a result of the induction of regulatory APC with T-cell suppressive properties.[6] It is conceivable that impairment of DC function may be ascribed to MSC-mediated interference with the normal process of DC differentiation from cell precursors. Indeed, in the presence of MSC, monocytes induced to differentiate towards DC with granulocyte-macrophage colony-stimulating factor (CSF) and IL-4 did not acquire the expression of CD1a nor down-regulate expression of the monocyte marker CD14. Moreover, upon lipopolysaccharides (LPS) stimulation (inducing full DC maturation), monocytes expressed low levels of the costimulatory molecules, CD80 and CD86, and of the DC maturation marker CD83.[3,4,5] Notably, inhibition of DC differentiation was not accompanied by substantial cell loss. Thus, Jiang *et al.*[3] reported that cell viability was not affected by MSC, and that cell recovery was comparable in control cultures and Mo-MSC co-cultures. Importantly, the inhibition exerted by MSC was reversible. Thus, monocyte-derived cells cocultured with MSC and replated with fresh cytokines in the absence of MSC acquired the DC phenotype, that is, loss of CD14, acquisition of CD1a and CD83.[3] However, these co-culture experiments were performed under transwell culture conditions. This may explain why different results were obtained by Nauta *et al.*,[4] who cultured MSC and monocytes in direct contact. When MSC were removed from monocyte cultures after 2 days, cells down-regulated CD14 expression, but did not express CD1a, thus suggesting that inhibition may not be completely reversible and that early conditioning by MSC is likely to be essential for the inhibitory effect.

In addition to monocytes, MSC can prevent the generation of DC also from CD34$^{+}$ precursors. Indeed, MSC were shown to interfere with the differentiation of dermal/interstitial DC from umbilical cord blood-derived CD34$^{+}$ cells, by blocking the transition of CD14$^{+}$CD1a$^{-}$ intermediate precursors to CD14$^{-}$CD1a$^{+}$ cells, while they did not prevent the generation of CD14$^{-}$CD1a$^{+}$ Langerhans cells. Moreover, the CD14$^{+}$CD1a$^{-}$ subset expressed low levels of CD80, CD86, CD83 and CD40 after LPS stimulation.[4] In contrast, another group reported that MSC could inhibit the differentiation of both dermal/interstitial and Langerhans cells.[35] In addition, they showed that MSC could inhibit proliferation of DC precursors, with a threefold decrease of the proliferation rate. Variability of results

may be in part explained by the use of different DC precursors (that is, cord blood- versus adult bone marrow-derived $CD34^+$ cells) and by differences in the experimental setting.

Another relevant question concerning DC-MSC interactions is whether MSC can interfere not only with the early steps of DC differentiation, but also with later stages, such as the progression from immature to mature DC. Contradictory results were obtained by different groups on this issue. Jiang *et al.*[3] reported that MSC could moderately suppress LPS-induced maturation of monocyte-derived DC. Thus, the resulting cells displayed decreased ability to stimulate allogeneic T-cell proliferation in mixed lymphocyte reaction, associated with lower levels of IL-12 production and IFN-γ induction as compared with control mature DC. On the other hand, Spaggiari *et al.*[5] showed that MSC fail to interfere with LPS-induced maturation of DC. In these experiments, DC undergoing final differentiation in the presence of MSC displayed a normal phenotype and were even more efficient stimulators in mixed lymphocyte reaction than mature DC obtained under standard conditions. Recently, a new pathway of MSC-mediated regulation of DC function was proposed by Aldinucci *et al.*,[36] who showed that immature DC, stimulated with LPS in the presence of MSC, are unable to form active immune synapses with lymphocytes, despite the expression of a mature phenotype and a normal IL-12/IL-10 production profile. In addition, MSC-treated DC retained endocytic activity and podosome-like structures, typical of immature DC. The inability of DC to establish synapses was associated with alteration of cytoskeleton rearrangement, including an absence of actin redistribution, which normally occurs in immature DC upon stimulation with LPS. As a consequence, DC, while undergoing some sort of differentiation, retained features of immaturity, thus becoming unable to efficiently activate alloreactive T cells.

Regarding the functional capability of DC generated in the presence of MSC, there is general consensus that these DC are characterized by a sharply impaired ability to stimulate allogeneic T-cell proliferation as compared with control DC generated in the absence of MSC. Moreover, they produce very low levels of IL-12 upon stimulation with LPS[3, 5] or CD40L.[4] However, the precise nature of DC generated in the presence of MSC is not yet clear. They could be either altered DC with an impaired function or 'educated' DC with regulatory activity. In the work by Li *et al.*,[35] secondary allostimulation of T cells by DC generated in the presence of MSC induced the generation of FoxP3-expressing alloantigen-specific T cells, indicating that MSC could promote the generation of tolerogenic DC, capable of stimulating expansion of Treg cells.

MSC exert their immune-modulatory/anti-inflammatory activity by secreting inhibitory mediators and/or by establishing cell-contact interactions with immune cells. In the case of DC, most studies support a major role of soluble factors, as suggested by the blocking effect of specific inhibitors.[37] In this context, IL-6 and macrophage-CSF were shown to be involved, at least in part, in the MSC-mediated inhibition of DC differentiation from monocytes.[3, 4] Thus, anti-IL-6 and anti-macrophage-CSF neutralizing antibodies induced loss of CD14, but could not restore the expression of CD1a. Another MSC product, PGE2, known to represent a major mediator of the inhibitory effect of different immune cells, was shown to strongly inhibit DC differentiation.[5] Indeed, PGE2 levels were highly increased in the supernatants of monocyte-MSC co-cultures as compared with those of monocytes alone. Moreover, the selective inhibition of cyclooxigenase-2 activity and thereby of PGE2 synthesis almost completely reverted the inhibitory effect as confirmed by the restoration of both DC phenotype and function. Notably, this effect was achieved in spite of the presence of high levels of IL-6 in co-culture supernatants, thus suggesting that PGE2 and not IL-6 was predominantly involved in the inhibitory effect.[5] Importantly, a substantial role of cell-to-cell interactions occurred in experiments in which bone marrow-derived $CD34^+$ cells (and not peripheral blood monocytes) were used as DC precursors, thus suggesting that different mechanisms may be responsible for the interference with distinct differentiation pathways. Indeed, Li *et al.*[35] showed that, in co-culture experiments performed using transwell chambers to maintain separate MSC and $CD34^+$ cells, inhibition of DC differentiation was significantly inhibited. On this basis, the inhibitory mechanism proposed was an MSC-induced expression and subsequent signaling through the Notch-2 receptor in

CD34$^{+}$-derived DC. The inhibition of Notch-2 signaling resulted in complete restoration of DC phenotype and function.

## Interaction with monocytes/macrophages

A limited number of studies have been performed to investigate the effects of MSC on the generation of pro-inflammatory macrophages. However, all these studies indicated that MSC would interfere with the acquisition of M1 phenotype, while promoting M2 polarization. Kim and Hematti[8] first reported that human bone marrow-derived MSC could promote the generation of alternatively activated macrophages, characterized by a high expression of CD206 and a cytokine profile typical of M2 macrophages, with increased IL-10 and lower IL12 and TNF-α production. By using the same experimental protocol, Zhang *et al.*[38] showed that human gingiva-derived MSC could induce polarization of M2 macrophages *in vitro*. Interestingly, by using an excisional skin-healing model in mice, they also reported that repeatedly infused human gingiva-derived MSC could home to the wound site in close proximity with host macrophages and promote their polarization toward M2 phenotype. Thus, gingiva-derived MSC could mitigate local inflammation by suppressing the infiltration of inflammatory cells, the production of IL-6 and TNF-α, and by increasing the production of IL-10. A significant enhancement of wound healing was observed consisting of increased re-epithelialization, collagen deposition and angiogenesis.

In another study by Cultler *et al.*,[7] umbilical cord-derived MSC (UC-MSC) were shown to suppress alloantigen-induced T-cell proliferation in peripheral blood mononuclear cell (PBMC) cultures. Notably, in these experiments, monocytes isolated from PBMC/UC-MSC co-cultures displayed increased expression of CD206, lower levels of surface HLA-DR and reduced capability of stimulating alloreactive T-cell response in mixed lymphocyte reaction experiments. Removal of monocytes from PBMC cultures reduced the immunosuppressive effect of UC-MSC, thus suggesting that these cells may represent an essential intermediary of UC-MSC-mediated inhibition of T-cell proliferation. The important role of MSC-conditioned monocytes has been confirmed by another study by François *et al.*,[39] who showed that monocyte depletion from PBMC stimulated with anti-CD3/CD28 antibodies resulted in a decrease of the percentage of CD4$^{+}$CD25$^{+}$Foxp3$^{+}$ Treg cells induced by the presence of bone marrow-MSC. Also in these experiments, monocytes expressed the M2 marker CD206 and produced higher levels of IL-10 compared with monocytes of PBMC cultured in the absence of MSC.

Concerning the mechanisms underlying the M2 polarizing effect exerted by MSC on macrophages, an essential role of different soluble factors has been demonstrated. In particular, by the use of specific neutralizing antibodies, Zhang and colleagues showed an involvement of IL-6 and granulocyte-macrophage-CSF in the induction of M2 phenotype by gingiva-derived MSC.[38] In the case of UC-MSC, Cutler *et al.*[7] reported that PGE2 synthesis was increased in PBMC-UC-MSC co-cultures compared with cultures of UC-MSC alone. Moreover, pretreatment of UC-MSC with the PGE2 inhibitor indomethacin partially reverted their ability to modulate the monocyte phenotype and function. In the study by François *et al.*[39] the IDO activity was primarily involved in the induction of IL-10-secreting CD14$^{+}$CD206$^{+}$ immunosuppressive macrophages. However, in this case, it must be considered that bone marrow-MSC used in the experiments had been previously “activated” with IFN-γ and TNF-α. It is well known that human MSC do not express IDO mRNA constitutively and that stimulation by inflammatory cytokines such as IFN-γ and TNF-α can induce IDO expression and activity. Thus, a role of IDO is conceivably possible if MSC have been previously exposed to a pro-inflammatory environment.

## Concluding remarks

The immunoregulatory activity of MSC offers a valuable, novel strategy in the design of therapeutic protocols aimed at suppressing pathologic immune responses, such as GVHD and autoimmune disorders. In this context, it has been shown that MSC can exert their inhibitory effect at multiple

levels. Indeed, not only adaptive immune cells, but also cells of the innate immunity, including DC, macrophages and NK cells can undergo MSC-mediated regulation. A number of studies have analyzed the effects of the presence of MSC on the differentiation and function of these cells. A general conclusion that can be drawn is that inhibition is not always a predictable event and it may depend on the activation state and/or differentiation stage of target cells. For example, in the case of NK cells, different outcomes of MSC–NK-cell interaction may occur. Thus, the activation of resting NK cells can be hindered by MSC, and the resulting cells are impaired in their effector functions.[22, 25] On the other hand, activated NK cells are capable of efficiently killing both autologous and allogeneic MSC.[23] This largely depends on different molecular interactions occurring between the two cell types in one or another condition. Thus, upon cytokine-induced activation, NK cells up-regulate the surface expression of activating NK receptors and acquire full lytic potential. Regarding DC, most results support the notion that DC at early stages of differentiation are sensitive to the inhibitory effect, while at later stages are resistant. This probably reflects a different responsiveness to factors mediating the inhibition (such as PGE2, IL-6 and macrophage-CSF).

Another important aspect of MSC function is that the immunosuppressive activity is not a constitutive property of MSC, but it depends on a process of activation or 'licensing'.[40] In this context, it must be considered that microenvironmental stimuli represent an additional variable that can greatly influence MSC function. Activation of MSC is mostly consequent to exposure to inflammatory cytokines, such as IFN-γ, TNF-α and IL-1α/β, which are produced by different cell types following induction of an inflammatory or immune response. For example, IFN-γ and TNF-α are produced by NK cells rapidly upon cytokine activation or crosslinking of activating receptors. Monocyte-derived IL-1β has a promoting effect on the MSC-mediated inhibition of T-cell proliferation by enhancing PGE2 secretion.[41] These soluble activators can induce changes in both MSC phenotype and gene expression, thus allowing cells to act as immune regulators.

Future studies aimed at further clarifying the molecular mechanisms involved in the interaction between MSC and immune cells will contribute to a better understanding of MSC biology and, hopefully, to the optimal use of MSC in the clinical practice.

### *Conflict of interest*

The authors declare no conflict of interest.

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