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CELLULAR TRANSPLANTS (J GRINYO, SECTION EDITOR)

Immunosuppressive Properties of Mesenchymal Stem Cells

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Abstract The properties of mesenchymal stem cells (MSCs) have become better known over the past decade and show potentially attractive new capabilities in solid-organ transplantation. After systemic administration, MSCs migrate to the damaged tissues, engraft, and then display potent anti-inflammatory and immunomodulatory properties through cell-to-cell interactions and secretion of soluble factors. They are weakly immunogenic and influence the differentiation and function of both innate and adaptive immune cells, thus promoting a tolerogenic response. Moreover, the results of the preclinical studies and the initial clinical trials support the evidence that MSCs can, at least partially, induce allograft tolerance. This review describes the immunosuppressive properties of MSCs on cells involved in alloimmune response and the current understanding of their underlying mechanisms, which is a prerequisite for an optimal clinical use.

Keywords Mesenchymal stem cells · Immunosuppression · Molecular mechanisms · Transplantation · Cell therapy

Introduction

Mesenchymal stem cells (MSCs) are multipotent non-hematopoietic progenitor cells capable of self-renewing and differentiating into multiple mesodermal lineages, including bone, cartilage, fat, tendon, and muscle [1]. Human MSCs were originally identified in the 1960s as a subpopulation of bone-marrow stromal cells with the potential to regenerate a bone-marrow environment in vivo [2]. Indeed, MSCs secrete cytokines, growth factors, and matrix molecules that influence homing, proliferation, and maturation of hematopoietic progenitor cells [3, 4]. Since then, MSCs have been isolated from various adult and fetal tissues, such as adipose tissue, amniotic fluid, placenta, umbilical-cord blood, dental pulp, and fetal liver [5–8]. All these types of MSCs have equivalent capacities of regeneration and differentiation but express no specific markers. In order to compare the study outcomes, the International Society for Cellular Therapy (ISCT) proposed minimal criteria to define human MSCs, i.e., (i) plastic-adherence under standard culture conditions; (ii) expression of CD73, CD90, and CD105, and no expression of CD45, CD34, CD14, CD11b, CD79a, CD19, or major histocompatibility complex (MHC) class-II antigens; and (iii) an ability to differentiate into osteoblasts, adipocytes, and chondroblasts in vitro [9].

Over the past decade, the properties of MSCs have become better known and show potentially attractive new capabilities in solid-organ transplantation. Firstly, MSCs are easily expanded ex vivo without any loss of function. After systemic administration, they migrate to the damaged tissues, engraft, and then differentiate under the appropriate conditions [10]. Moreover, MSCs display potent anti-inflammatory and immunomodulatory properties in vitro and in vivo. They are poorly immunogenic and influence the differentiation and function of both innate and adaptive immune cells. Thus, MSCs are promising candidates for cell-based therapies in the field of transplantation and also for all immune-mediated disorders. This review describes the immunosuppressive properties of MSCs on both innate and adaptive immune cells, our current

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understanding of their underlying mechanisms, the results from preclinical animal studies, and the first clinical trials involving solid-organ transplantation.

MSCs and Adaptive Immunity

T Cells

Interactions between MSCs and T cells have been extensively studied over the past decade. T cells are the major cellular effectors of the adaptive immune response and play a central role in cellular-mediated immunity. Human MSCs share several adhesion molecules with thymic epithelium that are essential for interactions with T cells. They express constitutively vascular-cell adhesion molecule-1 (VCAM-1), leukocyte function-associated antigen-3 (LFA-3), and MHC class-I antigens. They can also express intercellular adhesion molecule-1 (ICAM-1) and MHC class-II antigens when exposed to interferon (IFN)-γ. However, they do not express the costimulation molecules CD80, CD86, CD40, or CD40L, even after IFN-γ stimulation [11]. Due to this peculiar immunophenotypic profile, MSCs are immunoprivileged and therefore fail to behave as antigen-presenting cells (APCs) or to elicit an allogeneic T cell proliferative response in vitro. Moreover, rodent, baboon, and human MSCs inhibit T cell proliferation triggered by allogeneic lymphocytes, nonspecific mitogens, and antigenic peptides in vitro [12–15]. This suppressive effect is dose-dependent and concerns both naïve and memory $CD4^+$ and $CD8^+$ T cells. It is not MHC-restricted because it occurs regardless of the source of MSCs, including "third-party" MSCs. In vivo administration of MSCs prolongs MHC-mismatched skin-allograft survival in baboons [13] and reduces steroid-resistant acute graft-versus-host disease in humans [16, 17].

Three fundamental mechanisms account for the unresponsiveness of T cells: peripheral deletion, anergy, and suppression/regulation. Some reports suggest that inhibition of T cell proliferation is not caused by induction of apoptosis but rather by the anergy state, which is reversible after MSC removal or administration of exogenous interkeukin-2 (IL-2), both in vitro and in a mouse model of experimental autoimmune encephalomyelitis [12, 18]. This anergy state may not be secondary to the lack of a costimulatory signal because the addition of the anti-CD28 antibody fails to restore an allogeneic T cell response [11]. Expression and phosphorylation patterns of molecules involved in T cell signaling pathways are regulated differently in T cells that are activated or anergized. Thus, T cells that are stimulated in the presence of MSCs are arrested in the early G_1 phase due to inhibition of cyclin D2 and upregulation of the inhibitory protein p27kip1, which is consistent with arrest anergy [19].

The mechanisms underlying the immunosuppressive effects of MSCs on T cells involve both soluble factors and cell-to-cell contact. Until now, many soluble factors have been reported, including hepatocyte growth factor, transforming growth factor $\beta 1$ (TGF-$\beta 1$), prostaglandin E2 (PGE_2), human leukocyte antigen (HLA)-G, inducible nitric-oxide synthase (iNOS), heme oxygenase-1 (HO-1), and galectin-1 [12, 20–24]. MSCs also express membranous markers that can modulate the expression of cytokine receptors and signal transducers in T cells, such as the inhibitory molecule for programmed death 1 (PD-1) [25]. Finally, MSCs express indoleamine 2,3-dioxygenase (IDO), which catalyzes conversion from tryptophan to kynurenine. Intracellular tryptophan depletion prevents T cell entry into the S phase, and thus induces cell cycle arrest in the G_1 phase [26]. Altogether, most of these mechanisms are probably redundant because blocking one of them does not completely abrogate the immunosuppressive functions of MSCs.

Human and murine MSCs can impair the activity of $CD4^+$ and $CD8^+$ effector T cells. After antigenic stimulation, T-helper cells are induced to differentiate into Th1, Th2, and Th17 or regulatory T cells (Tregs). MSCs cause effector T cells to decrease IFN-γ and tumor necrosis factor (TNF)-α production and to increase IL-4 both in vitro and in vivo, supporting the inhibition of the Th1 response [18, 20]. MSCs inhibit differentiation of naive T cells into Th17 cells in vitro and impair the production of the inflammatory cytokines IL-17 and IL-22 by differentiated Th17 cells. Moreover, MSCs induce the production of IL-10 and reciprocally modulate the expression of the transcription factors, retinoid-related orphan receptor (ROR)-C and forkhead box p3 (FOXP3), through epigenetic changes. Thus, Th17 cells acquire the capability of inhibiting in vitro proliferative responses of activated $CD4^+$ T cells through the induction of a regulatory phenotype [27]. In vivo, MSCs inhibit naturally occurring Th17 cells derived from unilateral ureteral obstruction in mice [28]. These effects on Th17 cells seem to be mediated by both direct cellular contact and by the production of PGE_2 and IL-10 [27, 29, 30].

Tregs play a major role in the maintenance of self-tolerance through the negative regulation of immune responses. In vitro, human MSCs increase the proportion of T cells with a regulatory phenotype that possesses a methylated *FOXP3* gene with a Treg-specific demethylated region (TSDR) specific to induced Tregs [20, 31, 32]. More precisely, MSCs induce three major Treg subsets corresponding to $IL\text{-}10^+$ T regulatory 1 (Tr1), TGF-β^+ T helper 3 (Th3), and $CD25^+FOXP3^+$ natural Treg-like $CD4^+$ cells [33]. These Tregs are functional and can efficiently suppress T-cell proliferation triggered by antigenic peptides [32, 34]. Activation of the Notch1 pathway in $CD4^+$ T cells cocultured with MSCs could be responsible for Treg differentiation, especially as FOXP3 is a downstream target for Notch signaling [35]. In vivo, murine MSCs prevent

autoimmune diabetes in NOD mice [36] and prolonged cardiac allograft survival in a semiallogeneic heart transplant mouse model [37] through the generation of Tregs. This effect requires both direct contact between MSCs and allogeneic T cells and soluble factors such as PGE_2, TGF-β, and HO-1 [33, 34]. Taken together, these results suggest that MSCs induce a more anti-inflammatory or tolerant response after $CD4^+$ T cell activation.

Finally, human MSCs inhibit the initial formation of cytotoxic T lymphocytes [38] and suppress proliferation of naive and memory T cells in response to allogeneic dendritic cells (DCs) or non-specific mitogens in vitro. In contrast, MSCs have little inhibitory effect on T cell responses to viruses, such as Epstein–Barr virus and cytomegalovirus, in vitro and in vivo [39]. Murine MSCs affect antigen-specific proliferation, IFN-γ production, and cytotoxic activity of naive and memory T cells [40]. In vivo, allogeneic MSCs have promoted tumor growth in a murine melanoma model, possibly through the generation of $CD8^+$ regulatory T cells [14].

B Cells

Although the effects of MSCs on T cells have been extensively analyzed, the interactions between MSCs and B cells are less well documented and the results are controversial. B cells play a major role in humoral-mediated immunity. They differentiate into immunoglobulin [Ig]-secreting plasmablasts after antigenic stimulation and are potent APCs. Discrepancies found between published reports may be explained by differences between the B cell subset population studied (purified versus enriched B cells) and the stimuli used to trigger B cell proliferation and differentiation [41]. Using enriched B cells, Rasmusson et al. have shown that human MSCs do not improve B cell survival but can either stimulate or inhibit IgG secretion in peripheral and spleen-derived B cells, depending on the strength of stimulation with lipopolysaccharide (LPS) or virus antigens [42]. Comoli et al. consistently report that MSCs suppress antibody production after a strong stimulus such as alloantigens. Interestingly, this inhibition is abrogated when anti-CD40 is present, suggesting that MSC-mediated inhibition of B cell function is mainly indirect due to a suppressive effect on $CD4^+$ T cells [43]. Both secreted factors (e.g., TGF-β, PGE_2) and cell–cell contact seem to be involved in this process.

In contrast, some authors have focused on the direct effects of MSCs on B cells using a purified $CD19^+$ population [44, 45]. Human MSCs increase B cell viability while also inhibiting proliferation after polyclonal stimulation mimicking the three signals of B cell activation (i.e., B cell receptor engagement, costimulation, and cytokine- or toll-like receptor [TLR]-activation). In the presence of MSCs, B cells are arrested in the G_0/G_1 phases of the cell cycle. MSCs also inhibit B cell differentiation, as shown by a decrease in $CD38^+/CD138^+$ expression after exposure to DCs, and impaired antibody production. Finally, MSCs downregulate CXCR4, CXCR5, and CCR7 expressions, as well as chemotaxis to their respective ligands, CXCL12 and CXCL13, which control homing to secondary lymphoid organs. These effects are associated with activation of the mitogen-activated protein kinase (MAPK) pathways, i.e., extracellular-response kinase (ERK) 1/2 and p38. In contrast, Traiggiai et al. found that MSCs supported both polyclonal expansion and differentiation of transitional, naive, and memory B cells isolated from healthy donors and total B cells from patients with systemic lupus erythematosus. In this particular case, B cells were stimulated with an agonist of TLR-9 without triggering the B cell receptor [46]. Underlying mechanisms appear to be primarily dependent on cell–cell contact despite that IL-6, a potent B cell growth factor, is produced by MSCs after stimulation with the TLR-9 agonist. These findings are in-line with the postulated role of MSCs in supporting stages of B-cell development in vivo.

In addition, two studies have used splenic B cells, purified by negative selection (CD43 depletion), to avoid inadvertent activation of B cells and have consistently reported that MSCs inhibit B cell proliferation and terminal differentiation into plasma cells [47, 48]. This suppressive effect is associated with downregulation of the transcription factor B-lymphocyte-induced maturation protein-1 (Blimp-1) and upregulation of the transcription factor PAX5 [47, 49]. Various mechanisms of action have been described, such as matrix metalloproteinase-processed CCL-2 or PD-1/PD-L1 interactions [48, 49].

In vivo, soluble factors released by MSCs reduce antigen-specific IgM and IgG1 secretion in mice immunized with T-independent or T-dependent antigens [47]. In murine models of systemic lupus erythematosus, a B cell-driven autoimmune disease, there are contradictory reports on the effect of MSCs. Youd et al. found that MSCs worsen disease-enhancing autoantibody production, the number of plasma cells, glomerular immune-complex deposition, and proteinuria [50]. In contrast, Schena et al. reported that MSCs do not affect autoantibody production but only reduce glomerular immune-complex deposition, lymphocytic infiltration, and glomerular proliferation [48]. Finally, Choi et al. showed that human adipose-derived MSCs (ADSCs) have a beneficial effect on systemic lupus erythematosus during the early stages of disease, by improving survival rate, histologic and serologic abnormalities, and immunologic function [51]. In solid-organ transplantation, infusion of MSCs reduces alloantigen-specific antibodies and improves long-term survival of heart and kidney allografts [52, 53••].

Regulatory B cells (Bregs) are a peculiar subset of B cells that express the surface markers CD24 and CD38, and produce IL-10 ($CD19^+CD24^{high}CD38^{high}IL\text{-}10^+$). Franquesa et al. recently reported that coculture of B cells with MSCs, anti-IgM, anti-CD40, and IL-2 significantly increased the percentage of Bregs secreting IL-10 [54]. Expansion of Bregs is

an emerging approach in the treatment of autoimmune disorders; thus, the in vivo induction of Bregs secondary to MSC infusion seems an interesting option to consider.

Dendritic Cells

DCs are the most potent APCs that can initiate and regulate the adaptive immune responses by promoting antigen-specific T cell activation. Human MSCs strongly inhibit the initial differentiation of both $CD34^+$ cells and monocytes into DCs. These cells, instead, develop macrophage morphology with numerous vacuoles; they retain high $CD14^+$ expression and do not acquire CD1a expression [55–58]. Monocytes have been shown to enter into the cell cycle before differentiating into functional DCs. Similar to that observed in T cells, monocytes are arrested in the G_0 phase of the cell cycle due to downregulation of cyclin D2 [59].

In addition, human MSCs impair DC maturation, as shown by the reduced expression of CD83, HLA-DR, and the costimulatory molecules CD80/CD86 and a decreased secretion of IL-12 [55–58]. MSCs also suppress the chemotactic activity of DCs in response to CCL21, an important chemokine that regulates DC migration into the T cell area of lymph nodes [60]. These suppressive effects are mediated via either soluble factors (M-CSF, IL-6, TGF-β, PGE_2) or intercellular contact. In particular, MSCs have been shown to interfere with the DC-activation process by altering cytoskeleton organization, resulting in an inability to form active immune synapses with T cells [61]. DCs generated in the presence of MSCs fail to express proinflammatory cytokines (such as TNF-α and IL-12), class-II MHC, and costimulatory molecules but secrete large amounts of anti-inflammatory cytokine IL-10. Accordingly, DCs generated in coculture with MSCs fail to induce T cell activation or proliferation but promote alloantigen-specific Tregs that express both TGF-β and FOXP3 [62, 63].

In vivo, murine MSCs impair TLR4-induced activation of DCs, resulting in inhibition of cytokine secretion, downregulation of molecules involved in the migration to lymph nodes, antigen presentation to $CD4^+$ T cells, and cross-presentation to $CD8^+$ T cells. These effects are associated with inhibition of the MAPK pathways [64•]. Taking these findings together, the results indicate that human MSCs can inhibit T cell activation indirectly by inducing regulatory APCs.

MSCs and Innate Immunity

Macrophages

Macrophages are key effector cells in innate immunity and are involved in tissue defense, homeostasis, and repair. They can exhibit either a proinflammatory or an anti-inflammatory phenotype according to the microenvironment associated with the successive phases of the inflammatory response. In vitro, both human and murine MSCs can switch activated macrophages into a regulatory phenotype characterized by high expression of CD206 and IL-10, low expression of inflammatory cytokines (TNF-α, IL-6, IL-12p70, IFN-γ), and high phagocytic activity of apoptotic cells. MSCs also inhibit the upregulation of CD80 and CD86 costimulatory molecules and of MHC class-II molecules, while increasing the expression of inhibitory receptors ILT-3 and ILT-4 in macrophages. Thus, MSCs polarize proinflammatory M1 macrophages into anti-inflammatory M2 macrophages but also impair their capacity to activate antigen-specific $CD4^+$ T cells [65–68].

In vivo, MSCs have been shown to improve mouse survival and attenuate organ injuries in models of acute lung injury and peritonitis by specific reprogramming of IL-10-secreting macrophages [69–71]. Similarly, MSCs also promote repair and tissue remodeling, as demonstrated by the increased proliferation of tubular epithelial cells and a reduction in total collagen deposition in a mouse model of ischemia-reperfusion with acute kidney injury [72]. Furthermore, MSCs produce CCR2 ligands that are responsible for macrophage recruitment. This secretion was associated with accelerated wound closure in a mouse model of excisional skin healing but has also promoted tumorigenesis in mouse models of lymphoma, melanoma, and breast carcinoma [73, 74]. In addition, injection of MSC recruits alveolar macrophages, which led to decreased airway hyperresponsiveness, eosinophilic infiltration, and Th2 cytokine production in a mouse model of allergic asthma [75]. As engraftment of MSCs is limited in vivo, despite tissue-specific homing, macrophage polarization could be a key step in explaining their persistent effects after elimination. In addition, Melief et al. demonstrated that MSCs promote the generation of Tregs, both directly [see above] and indirectly, in skewing monocytes toward IL-10-secreting macrophages [76•]. In the same way, Akiyama et al. reported that infusion of allogeneic MSCs induced transient T cell apoptosis via the FAS pathway in mice with systemic sclerosis or experimental colitis. Apoptotic T cells trigger TGF-β production by macrophages loaded with apoptotic bodies, which in turn upregulated Tregs and led to immune tolerance in vivo [77••].

Contrary to what has been observed with other cell types, MSC immunoregulation of macrophages is mostly mediated by soluble factors. Two main mechanisms have been reported in mouse models of peritonitis [70, 71]. Nemeth et al. showed that inflammatory signals such as LPS or TNF-α activate MSCs that reprogram resident macrophages through the secretion of PGE_2, which acts on EP2 and EP4 receptors on macrophages to induce secretion of IL-10. In addition, Choi et al. reported that activated MSCs secrete the anti-inflammatory protein TNF-α-stimulated gene-6 protein (TSG-6), which interacts through the CD44 receptor on

resident macrophages. The CD44 molecule is dissociated from TLR-2, leading to impairment of TLR-2-induced NF-κB signaling [71]. Finally, IDO activity has also been implicated in the differentiation of monocytes into IL-10-secreting macrophages [78]. Altogether, MSCs induce an anti-inflammatory response and may involve macrophages in Treg expansion.

NK Cells

NK cells play a critical role in the defense against virus-infected cells and tumor cells. They are divided into two subtypes: CD56dim, which exerts cytolytic activity, and the CD56bright-producing cytokines, such as IFN-γ, TNF-α, IL-10, and GM-CSF. In vitro, human MSCs exert opposite effects on peripheral blood NK cells depending on the culture conditions. Interactions between fresh NK cells and MSCs lead to NK-cell activation, as shown by upregulation of CD69, whereas downregulation of CD69 is observed after interaction of IL-2-stimulated NK cells and MSCs [79, 80]. In addition, MSCs inhibit both IL-2- and IL-15-induced NK-cell proliferation without enhancing cell death [81–83]. This suppressive effect is dose-dependent and requires the presence of IFN-γ produced by activated NK cells, which in turn enhances the IDO activity by MSCs [82]. MSCs also influence NK-cell cytokine production. In standard media, NK cells release high amounts of IFN-γ and TNF-α upon binding with MSCs, via interactions with NKp30 and LFA1/ICAM1 [79]. Conversely, MSCs inhibit IFN-γ secretion by IL-2- or IL-15-activated NK cells [20, 81, 82] suggesting that MSC regulates NK cells in an inflammatory context.

In addition, MSCs have been shown to downregulate the natural cytotoxicity receptors NKp30 and NKp44 and the NK group 2D (NKG2D), which correlate with impaired cytotoxic activity [81, 84]. These effects are mediated by cell-to-cell contact and soluble factors, such as TGF-β, PGE_2, IL-10, or HLA-G5 [81, 84, 85]. NK cells seem able to kill both autologous and allogeneic MSCs through LFA1/ICAM1 interaction and NKG2D engagement by MHC class I-related chain A/B (MICA/B) and UL16-binding proteins (ULBPs) expressed in MSCs [38, 79, 81]. However, in a proinflammatory environment, the cytotoxic effect of NK cells on MSCs may be partially neutralized in the presence of IFN-γ, which induces upregulation of HLA class-I molecules at the surface of MSCs, thus providing a strong inhibitory signal for NK cell activation [83]. Moreover, TLR3-primed MSCs are more resistant to IL-2-activated NK cells because of modulation of surface expression and secretion of MICA molecules [86]. Thus, MSCs could modulate their behavior in a proinflammatory environment to decrease their susceptibility to NK cell cytotoxicity.

iNKT and γδ T Cells

Invariant natural killer T (iNKT) and γδ T cells are two unconventional T cell populations involved in the defense against infections and cancers, autoimmune disease pathogenesis, and the maintenance of transplant tolerance. Similar to that observed with conventional αβ T cells, MSCs inhibit iNKT and γδ T cell proliferation from peripheral blood mononuclear cells in vitro via both cell-to-cell contact and soluble factors, such as PGE_2. In contrast, MSCs only partially affect iNKT and γδ T cell cytokine production and cytotoxic activity and do not alter antigen presentation by activated γδ T cells to naive $CD4^+$ T cells. Finally, activated γδ T cells can lyse MSCs through a TCR-dependent mechanism [87].

MSCs in Solid-Organ Transplantation

Transplantation still remains the only therapeutic solution for end-stage failure of several organs. However, the long-term use of immunosuppressive drugs can cause life-threatening infections, malignancies, and metabolic side effects and cannot prevent chronic allograft injury, which limits the survival of transplanted organs and patients. MSCs have already been tested in various preclinical studies and some clinical studies to assess their ability to prevent antibody-mediated and cellular acute rejection after solid-organ transplantation (Table 1). In rodent models, most studies show that MSC infusion prolongs allograft survival [23, 37, 52, 88–91]. Both recipient and donor-derived MSCs are able to prevent acute rejection after heart or kidney transplantation [37, 90••, 91], but the possibility of using third-party MSCs is still unclear [52, 89]. The timing of a MSC injection (pretransplant vs. posttransplant) appears to be crucial. In vivo distribution of infused MSCs and their consequences on MSC-induced immunomodulation are mainly influenced by tissue injury or inflammatory signals. Pretransplant-infused MSCs preferentially migrate into the recipient's spleen and lymph nodes, where they interact with immune cells at sites of initial T cell priming, thus promoting a tolerogenic response. In contrast, posttransplant-infused MSCs migrate into allografts where they can induce early graft dysfunction. This "engraftment syndrome" has been documented in both rats and humans [90••, 92]. Eventually, MSCs are cleared from the recipient; therefore, the risk of side effects should be low. Although MSC infusion alone prolongs allograft survival, some studies have reported a synergistic effect between MSCs and mycophenolate mofetil or sirolimus, thereby inducing a donor-specific tolerance [52, 89]. Because MSCs modulate immune cells, they need time to initiate their immunosuppressive properties in vivo. Their infusion with immunosuppressive drugs appears necessary to blunt the allogeneic immune response and, thus, to enable successful MSC engraftment. The discrepancies between outcomes in the different rodent transplantation models can be

Table 1 In vivo evaluation of MSCs in solid organ transplantation

Species	Model	MSC source	MSC dose	MSC injection	IS drugs	MSC effect	Ref.
Rat (Wistar-Fisher344)	Fully allogeneic heart transplantation	Donor BM-MSCs	4 infusions 2×10^6 cells	Intravenous Days −7 and 0–3	None	Prolonged graft survival shift of the Th1/Th2 balance toward a Th2-type response	[88]
Mouse (B6C3-C57BL/6)	Semi-allogeneic heart transplantation	Recipient or donor BM-MSCs	2 infusions 0.5×10^6 cells	Intravenous Days −7 and −1	None	Prolonged graft survival with both types of MSCs expansion of donor-specific Tregs	[37]
Rat (LEW.1W–LEW.1A)	Fully allogeneic heart transplantation	Donor BM-MSCs	1 or 2 infusions $5 \pm 7 \times 10^6$ cells	Intravenous Days −7 and −1	None	Prolonged graft survival with 2 MSC infusions involvement of iNOS and HO-1 expression	[23]
Rat (Lewis-ACI)	Fully allogeneic heart transplantation	Recipient or donor BM-MSCs	2 infusions 2×10^6 cells	Intravenous day 0 and +3	CsA (0.5 mg/kg) Days 5–9	No improvement of graft survival with MSC infusion alone accelerated graft rejection with CsA and MSC infusion	[92]
Rat (Lewis-ACI)	Fully allogeneic heart transplantation	Recipient, donor, and third-party BM-MSCs	1 infusion 2×10^6 cells	Intravenous Day −4	MMF (20 mg/kg) Days 0–7	Prolonged graft survival with MMF and donor MSC infusion involvement of IDO expression and tolerogenic DCs	[89]
Mouse (C57BL/6-Balb/c)	Fully allogeneic heart transplantation	Recipient, donor, and third-party BM-MSCs	1 Infusion 1×10^6 cells	intravenous Day +1	Rapa (2 mg/kg) Day 0–13	Prolonged graft survival, reduction of alloreactive antibodies expansion of donor-specific Tregs and tolerogenic DCs	[52]
Mouse (Balb/c-C57BL/6)	Fully allogeneic heart transplantation	Donor BM-MSCs	1 or 2 infusions 0.5×10^6 cells	Intravenous Days −7, −1, or +2	None	Prolonged graft survival with pre-transplant MSC infusion expansion of donor-specific Tregs	[90••]
Mouse (C57BL/6-Balb/c)	Fully allogeneic kidney transplantation	Donor BM-MSCs	1 infusion 1×10^6 cells	Intravenous Day +1	None	Prolonged graft survival, reduction of alloreactive antibodies, expansion of donor-specific Tregs, Th2 shift, IDO involved	[91]
Rat (Fisher344-Lewis)	Fully allogeneic kidney transplantation	Third-party BM-MSCs	1 infusion 0.5×10^6 cells	Intravenous week +11	CsA (5 mg/kg) day 0–15	Improved renal outcome, decreased proteinuria rate, reduced interstitial fibrosis and tubular atrophy at 24 weeks	[53••]
Human	Fully allogeneic kidney transplantation	Syngeneic BM-MSCs	2 infusions $1–2 \times 10^6$/kg	Intravenous Days +1 and +15	Normal or low-dose CNI, MMF, steroids	Lower acute rejection rate at 6 months, less opportunistic infections, improved renal outcome at 1 year	[93••]

BM-MSCs bone-marrow mesenchymal stem cells, *CNI* calcineurin inhibitors, *CsA* cyclosporine A, *DCs* dendritic cells, *HO-1* heme oxygenase-1, *IDO* indoleamine-2,3-dioxygenase, *iNOS* inducible nitric-oxide synthase, *IS drugs* immunosuppressive drugs, *MMF* mycophenolate mofetil, *Rapa* rapamycin, *Tregs* T regulatory cells

partially explained by the fact that immune responses in kidney allografts are weaker than in cardiac allografts.

In humans, syngeneic MSC infusion has been evaluated as a replacement for basiliximab induction therapy in living-related donor kidney transplantation for patients with low immunological risk [93••]. An induction therapy with MSCs, compared to basiliximab, resulted in a lower rate of acute rejection episodes at 6 months, less opportunistic infections, improved renal outcomes at 1 year, and no adverse events. However, the benefit of MSCs to reduce acute rejection at 1 year is less pronounced. This suggests that additional injection of these cells have to be evaluated to prevent acute rejection.

Due to their regenerative properties, MSCs may also help prevent and treat chronic allograft dysfunction. Thus, Franquesa et al. assessed the effect of a single delayed infusion of MSCs in a rat-kidney transplantation model of chronic allograft dysfunction. Interestingly, this treatment was associated with stabilization of renal function and a decreased proteinuria rate, as well as reduced interstitial fibrosis and tubular atrophy at 24 weeks [53••]. These results suggest that MSCs may modulate the mechanisms involved in chronic allograft dysfunction, thereby opening up new opportunities to treat patients with a chronic rejection.

Conclusion

The induction of allograft tolerance defined as drug-free acceptance with preserved immunocompetence has long been a dream in solid-organ transplantation. MSCs are multipotent non-hematopoietic progenitor cells capable of self-renewing and differentiating into multiple mesodermal lineages. They inhibit the activation and function of both adaptive and innate immune cells involved in allogeneic rejection (Fig. 1). In rodent models of heart and kidney transplantation, MSCs induce donor-specific tolerance in combination with immunosuppressive drugs, and they allow drug minimization in human renal transplantation indicating their immunosuppressive properties. However, the adequacy between immunosuppressive therapies and MSCs still need to be determined. Finally, the recent reports evaluating the use of MSCs in tissue repair and/or treatment of chronic rejection open new perspectives for the long-term benefits of MSCs on allograft function and survival but safety also has to be ascertained.

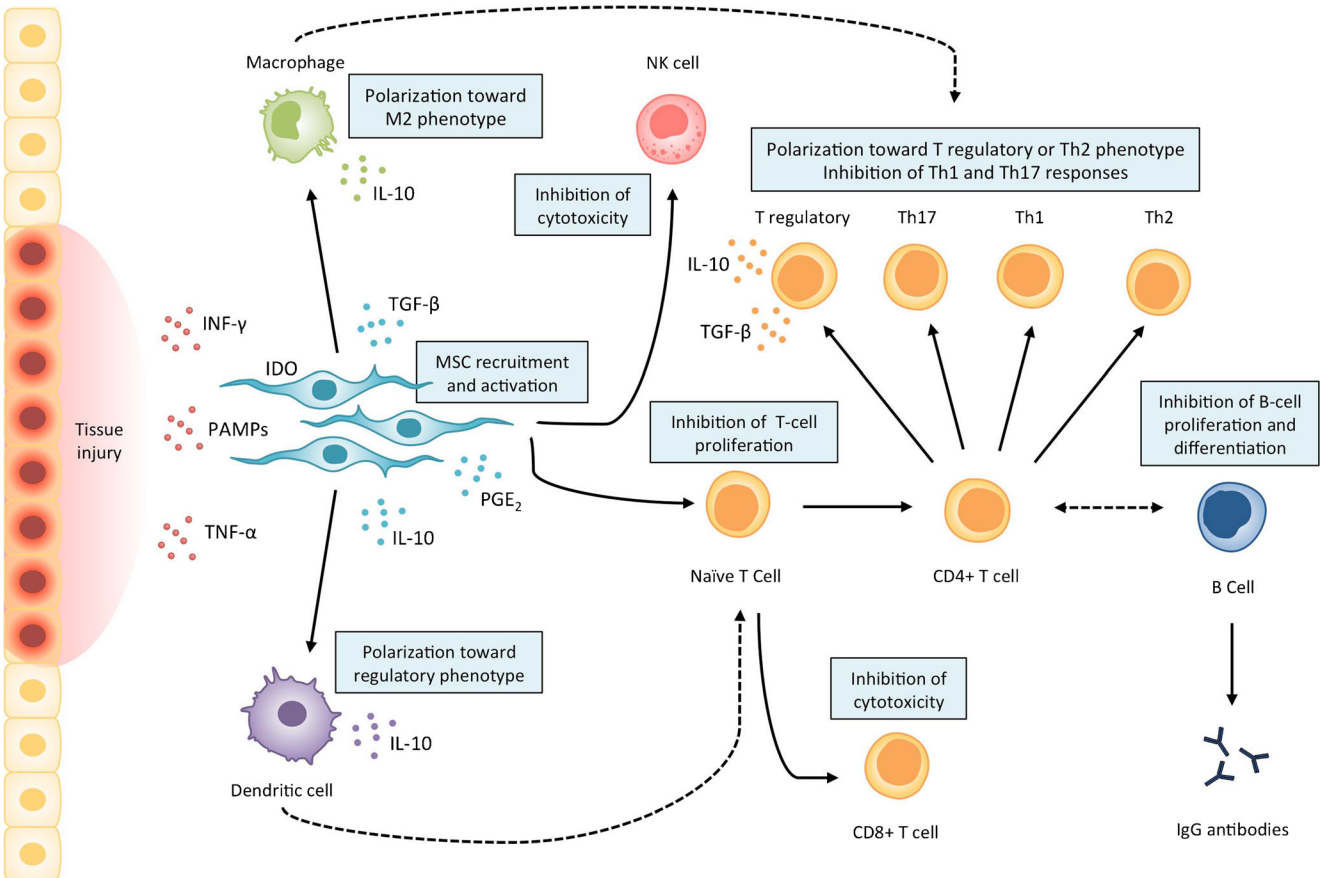

Fig. 1 Immunosuppressive properties of MSCs. When tissue is damaged, MSCs migrate into the injury site and are activated by inflammatory stimuli. Then, MSCs influence the differentiation and function of both innate and adaptive immune cells, and promote tolerogenic immune response. *IDO* indoleamine-2,3-dioxygenase, *IFN-γ* interferon-γ, *IL* interleukin; *Ig* immunoglobulin, *PAMPs* pathogen-associated molecular patterns, *TGF-β* transforming growth factor-β, *TNF-α* tumor necrosis factor-α

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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