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REVIEW

Interactions between mesenchymal stem cells and the immune system

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Abstract In addition to being multi-potent, mesenchymal stem cells (MSCs) possess immunomodulatory functions that have been investigated as potential treatments in various immune disorders. MSCs can robustly interact with cells of the innate and adaptive immune systems, either through direct cell–cell contact or through their secretome. In this review, we discuss current findings regarding the interplay between MSCs and different immune cell subsets. We also draw attention to the mechanisms involved.

Keywords Mesenchymal stem cell · Inflammation · Immune regulation · Plasticity

Abbreviations

MSCs	Mesenchymal stem cells;
Sca-1	Stem cell antigen-1
ESCs	Embryonic stem cells
iPSCs	Induced pluripotent stem cells
Th	T-helper
TGF-β	Transforming growth factor beta
HGF	Hepatocyte growth factor
IFN	Interferon
Treg	Regulatory T cell
NK	Natural killer
DC	Dendritic cell
EAE	Experimental autoimmune encephalomyelitis
SLE	Systemic lupus erythematosus
GVHD	Graft-versus-host disease
TNF	Tumor necrosis factor
IL	Interleukin
iNOS	Nitric oxide synthase
COX	Cyclooxygenase
NO	Nitric oxide
PGE2	Prostaglandin E2
CXCR3	CXC chemokine receptor3
CCR5	C-C chemokine receptor type 5
ICAM-1	Intercellular adhesion molecule 1
VCAM-1	Vascular cell adhesion molecule 1
IDO	Indoleamine 2,3-dioxygenase
HLA-G5	Human leukocyte antigen class I molecule G5
EV	Extracellular vesicle
TSG6	Tumor necrosis factor-induced protein 6
Breg	Regulatory B cell
STAT3	Signal transducer and activator of transcription 3
Blimp1	B lymphocyte-induced maturation protein 1
IL-1Ra	IL-1 receptor antagonist
APC	Antigen-presenting cell
MIF	Macrophage migration inhibitory factor.

Introduction

Mesenchymal stem cells (MSCs) are multi-potent cells that can be isolated from various adult tissues, such as the bone marrow, umbilical cord, adipose, peripheral blood, liver, and tooth root [1, 2]. In vitro, these cells are adherent to plastic dishes and can be passaged consecutively for 30–40 generations while retaining their multipotency [3, 4]. They can be induced to differentiate into cells of mesodermal lineages, such as adipocytes, chondrocytes, and osteoblasts [3]. Interestingly, they also have the potential to trans-differentiate into ectodermal or endodermal cell lineages [5].

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Phenotypically, MSCs are positive for cell surface antigens, including stem cell antigen-1 (Sca-1), CD105, CD73, and CD90, and they do not express markers of hematopoietic cell lineage, such as CD34, CD45, CD11b, major histocompatibility complex class II (MHCII), and endothelial marker CD31 [6–9] (Fig. 1).

Stem cell-based investigations have increased hope for the treatment of many diseases. Nevertheless, the clinical applications of embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are hindered by their teratoma-generating ability in vivo [10, 11] and, most importantly, ethical concerns [12]. MSCs bring new enthusiasm for regenerative medicine and immune disorder-related diseases, because they are convenient to isolate, have strong self-renewal abilities, and have multi-potent differentiation abilities. Moreover, MSCs are free of the complications that can emerge with the use of ESCs and iPSCs. Much has been learnt about the functions of MSCs during tissue repair and in the control of immune disorders. They can directly replace damaged tissues through differentiation, even though this is less effective than that of ESCs or iPSCs. Several studies have reported the successful promotion of tissue regeneration, including the liver [13], kidney [14], heart [15], and pancreas [16] through the administration of MSCs. Most importantly, MSCs modulate tissue regeneration and various immune disorders through their immunoregulatory properties. These cells are capable of interacting with various types of immune cells, including T cells, B cells, natural killer (NK) cells, macrophages, dendritic cells (DCs), neutrophils, and mast cells. These interactions occur through direct cell–cell contact or their specific secretome, which consists of various growth factors and immunomodulatory factors. This balances the immune response and regulates inflammation profiles, thus promoting the successful treatment of various immune cell-associated diseases, as reviewed in detail elsewhere [17–19]. In this study, we primarily discuss the current findings on the immunomodulatory properties of MSCs and the associated mechanisms.

T cells

T cells are extensively distributed throughout tissues. In the thymus, hematopoietic stem cell-derived progenitors develop into T cells through a series of distinct developmental stages [20]. Activation of naïve T cells requires two signals, namely, T cell receptor signaling and co-stimulatory signaling [21, 22]. Upon activation, $CD4^+$ T cells can differentiate into T-helper 1 (Th1), Th2, Th9, Th17, or

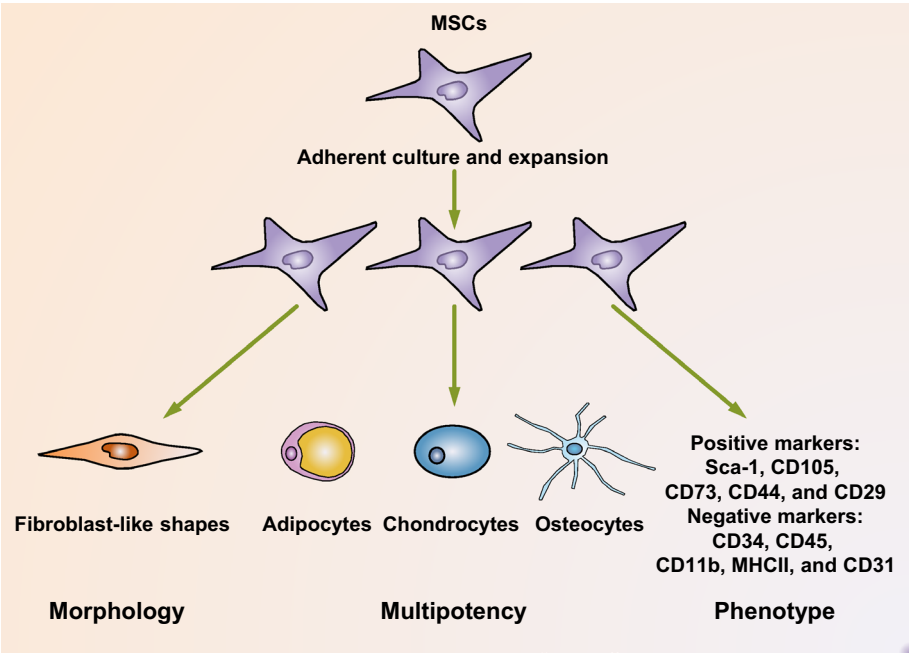

Fig. 1 Multiple criteria for the definition of MSCs. MSCs can be isolated from various origins, such as the bone marrow, adipose tissues, and peripheral blood. In culture, they are adherent to plastic dishes, thus can be purified and expanded by consecutive passaging. Usually, MSCs exhibit heterogeneous population of fibroblast-like shapes. MSCs are multi-potential which can differentiate into cells of mesenchymal tissues, including adipocytes, chondrocytes, and osteocytes. These cells can also trans-differentiate into cells of non-mesenchymal tissues. Usually, mouse and human MSCs are positive for such markers as Sca-1, CD105, CD73, CD44, and CD29, while they are negative for such markers as CD34, CD45, CD11b, MHCII, and CD31. These criteria combined to form a strict definition of MSCs

regulatory T cell (Treg) subsets, depending on the strength of the stimulation and the cytokine milieu [23–26]. Various infections also activate and promote the differentiation of $CD8^+$ T cells into cytotoxic T lymphocytes that secrete granzymes, perforins, and various cytokines to kill infected cells [27]. T-cell-mediated immunity is the key component of the adaptive immune system, protecting against infections and malignancies but also mediating a number of autoimmune diseases [28].

The interplay between MSCs and T cells has been intensively studied. It was found that MSCs potently inhibited T cell proliferation in several models. A study investigating baboon MSCs highlighted their proliferation-suppressive feature, which could also be applied to an in vivo graft-versus-host disease (GVHD) model [29]. Moreover, human bone-marrow-derived MSCs efficiently inhibited the proliferation of T lymphocytes in vitro. The proliferation-inhibiting effect of MSCs on T cells is thought to be mediated by the release of transforming growth factor beta (TGF-β) and hepatocyte growth factor (HGF), which leads to the decrease of cyclin D2 and the increase of $p27^{kip1}$ expression in T cells, resulting in arrest of proliferation in the G1 phase [30, 31]. MSCs are also capable of inducing apoptosis of activated T cells, a process associated with the conversion of tryptophan into kynurenine [32], and with the Fas/Fas ligand-dependent pathway [33].

In addition to affecting T-cell proliferation and apoptosis, MSCs can also alter the activation and differentiation process of T cells. Several lines of evidence have exhibited that MSCs suppressed interferon (IFN)-γ and IL-17 secretion but promoted IL-10 production of T cells by antagonizing the differentiation of Th1 and Th17 cells, thereby inducing the generation of Tregs [34, 35]. MSCs also suppressed effector T-cell priming indirectly through the regulation of DCs and NK cells [36]. These findings were applicable to several in vivo models, as MSC transplantation efficiently improved several inflammatory diseases, such as experimental autoimmune encephalomyelitis (EAE) [34], arthritis [37], experimental autoimmune uveitis [38], transplant arteriosclerosis [39], acute hepatitis [40], systemic lupus erythematosus (SLE) [41], and GVHD [42].

Interestingly, MSCs are not capable of suppressing T cells unless they are pre-stimulated by certain inflammatory cytokines, such as IFN-γ and at least one other cytokine, specifically tumor necrosis factor (TNF)-α, interleukin (IL-)1α, or IL-1β [43, 44]. In response to stimulation by these inflammatory cytokines, MSCs upregulated their inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 expression levels, which resulted in robust production of the immunosuppressive molecules nitric oxide (NO) and prostaglandin E2 (PGE2) to modulate immune responses [43, 45]. In addition, these MSCs produced a variety of chemokines and adhesion molecules, such as CXC chemokine receptor 3 (CXCR3) ligands, C-C chemokine receptor type 5 (CCR5) ligands, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1). These chemokines are critical for lymphocyte recruitment to injured sites in close proximity, thus ensuring their optimum suppressive function [17, 43, 44, 46]. The induced expression of soluble immunoregulatory molecules and adhesion molecules was both indispensable for effective T-cell inhibition, since blocking either of them would greatly reverse the suppressive effects of MSCs [43, 44].

However, the immunosuppressive ability of MSCs is not always achieved, as several contradictory findings showed that MSCs were unable to suppress or even enhance T cell responses under several conditions. Indeed, the immunomodulatory capacity of MSCs is dependent upon the types and strengths of the inflammatory signals they receive. This plasticity of MSCs in immunomodulation was demonstrated in a study investigating how different concentrations of IFN-γ and TNF affected the functions of MSCs in immune regulation [47]. In this study, low proinflammatory cytokine levels led to inadequate production of NO from murine MSCs, whereas high proinflammatory cytokine levels resulted in adequate production of NO and guaranteed their inhibitory effects on T cells. The plasticity of murine MSCs was also applicable in human MSCs [47] (Fig. 2). This was confirmed in vivo in several murine models, including models for delayed-type hypersensitivity response, tumor growth, and heart transplantation [47, 48].

Notably, the key molecules mediating the immunosuppressive function of MSCs are species dependent, with iNOS being a key molecule in mice, whereas indoleamine 2,3-dioxygenase (IDO) is a key molecule in humans [49, 50]. iNOS is a synthase that catalyzes the production of NO in vivo, which is highly immunosuppressive at high concentrations [51]. In murine models of GVHD and experimental arthritis, $iNos^{-/-}$ or iNOS inhibitor treated MSCs failed to suppress T cells and thus did not exert therapeutic effects [43, 52]. IDO strongly inhibited immune responses by depleting tryptophan and promoting the accumulation of tryptophan metabolites [53, 54]. Similar to iNOS, IDO in human MSCs exerted immunosuppressive functions in a few models [50, 54, 55]. Human MSCs also secreted a considerable amount of soluble human leukocyte antigen class I molecule G5 (HLA-G5) to mediate their immunosuppressive functions [35]. Nevertheless, murine and human MSCs also share some common molecules in mediating T-cell immunosuppression. One of the most important molecules may be PGE2, whose role was highlighted in a number of studies. Mouse bone-marrow MSCs secrete large amounts of PGE2, which is correlated with higher efficacy to EAE inhibition, collagen-induced arthritis mitigation, and mixed lymphocyte reaction suppression [39, 52, 56]. In addition,

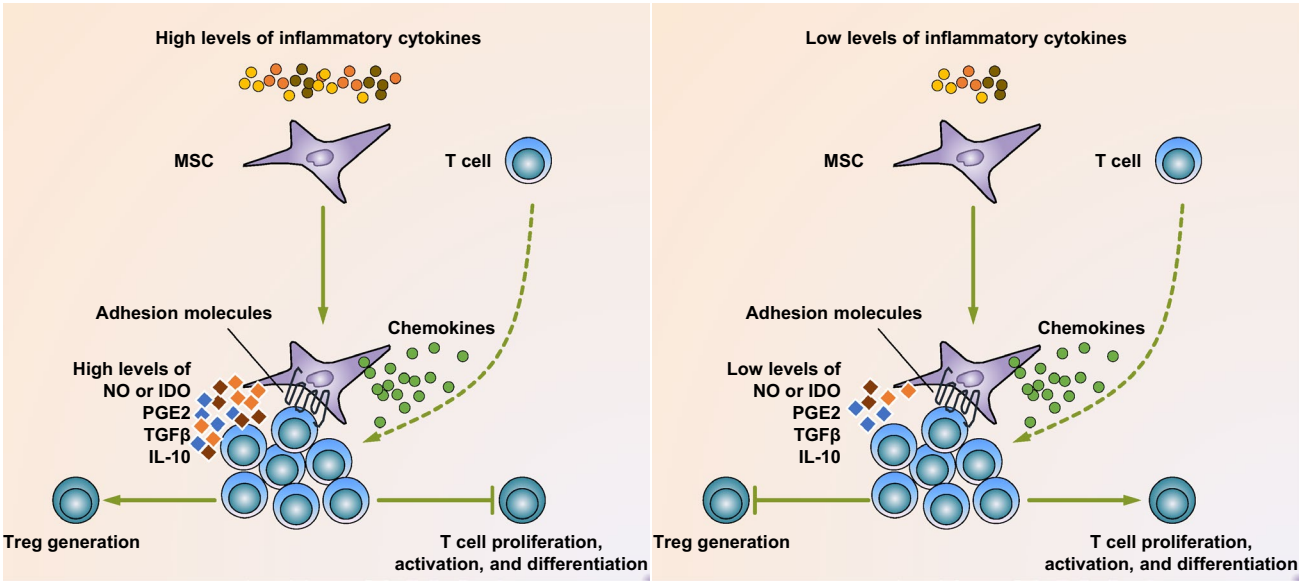

Fig. 2 MSC plasticity in immuno-modulation. In response to high levels of proinflammatory cytokines that exist in the acute phase of inflammatory diseases, MSCs are licensed to secrete large amounts of immuno-suppressive factors, such as NO (mice) or IDO (humans), PGE2, TGFβ, and IL-10. In addition, these MSCs also produce various chemokines and express adhesion molecules that are responsible for T-cell recruitment and keeping T cells in close proximity with them. As a result, T cells are suppressed in proliferation, activation, and differentiation. Moreover, $CD4^+CD25^+Foxp3^+$ Tregs can also be generated by these suppressive MSCs (*left panel*). In response to low levels of proinflammatory cytokines that exist in various chronic diseases, MSCs still produce considerable amounts of chemokines and adhesion molecules that recruit T cells in close proximity with them. However, they produce only low levels of the immuno-suppressive factors. Thus, the recruited T cells are unchecked and become activated (*right panel*)

the emerging roles of MSC-derived extracellular vesicles (EVs) in T-cell suppression are attracting increasing interest [57–61]. Similar to the functions of MSCs, EVs may also inhibit effector T cell differentiation, activation, and proliferation [62–66], induce T cell apoptosis [66, 67], and promote Treg generation [65–68]. Other soluble factors, such as TGF-β, HGF, tumor necrosis factor-induced protein 6 (TSG6), and IL-10, have also been implicated in suppression of T cells [30, 69–71]. However, the role of TGF-β has not been completely defined, since TGF-β may act directly on MSCs by inhibiting iNOS expression, thus antagonizing their immunosuppressive effects [69].

B cells

B cells are another hallmark effector cells of the adaptive immune system. These cells are differentiated from hematopoietic stem cells through a series of coordinated stages [72]. Following the recognition of specific antigens by B cell receptors, naïve B cells will proliferate and differentiate into activated antibody-producing cells and memory cells to mediate and sustain protection against foreign pathogens [73–75]. Distinct from the conventional B cells which are termed B2 cells, there is a population of B1 cells enriched in the pleural and peritoneal cavities in mice. These cells respond effectively to innate immune signals and play a role in the elimination of pathogens and in providing long-term protection for the host [76]. Regulatory B cells (Bregs) are another subset of B cells; they produce IL-10 and exert immunomodulatory functions in several models [77].

Both human and murine MSCs are capable of suppressing the proliferation, differentiation, and activation of B cells. Several lines of evidence demonstrated that B cells co-cultured with MSCs exhibited cell cycle arrest, impaired plasma cell generation, compromised immunoglobulin-secreting ability, and reduced chemotactic properties [78–81]. Soluble factors are of critical importance to exert this suppressive function [78, 81–83]. CCL2 is one such factor mediating these actions, as metalloproteinase-processed CCL2 derived from MSCs inhibited signal transducer and activator of transcription 3 (STAT3) activation in plasma cells, leading to PAX5 expression and thus suppression of immunoglobulin synthesis [80, 82]. In a recent study, IL-1 receptor antagonist (IL-1Ra) derived from MSCs was shown to control B-cell differentiation and arthritis progression [83]. In addition, EVs derived from MSCs were also important in suppressing B-cell proliferation, differentiation, and antibody production, which were observed in a dose-dependent manner [60, 84]. In addition, cell–cell contact was also crucial, and was associated with

the PD-1/PD-L1 pathway [85]. In addition to these findings, the modulation of several other signaling pathways, such as Akt, extracellular response kinase 1/2, p38, and B lymphocyte-induced maturation protein 1 (Blimp1) signaling, was highlighted in other studies [79–81].

There is evidence that MSCs also regulate B-cell responses through the induction of Bregs, which are $CD19^{+}CD24^{high}CD38^{high}$ in humans and $CD19^{+}CD1d^{high}CD5^{+}$ in mice. These cells secrete a considerable amount of anti-inflammatory cytokine IL-10, resulting in suppressed immune responses [86]. Indeed, the induction of Bregs by MSCs was shown to be efficient in treating several diseases in mouse models, such as GVHD, SLE, and EAE [86–89].

As in T cells, inflammatory stimulation of MSCs enhances their inhibitory effects on B cells. Potent IFN-γ signaling is crucial to stimulate the suppressive function of MSCs [85]. Moreover, sufficient inflammatory signals, such as signals from the bacterium *Mycoplasma arginini*, efficiently enhanced the ability of MSCs to suppress the antibody secretion of B cells [90]. In contrast, insufficient inflammatory signal-stimulated MSCs, such as those derived from lupus-like mice or SLE patients, are compromised in suppressing B-cell proliferation and differentiation, or can even increase the number of antibody-secreting B cells [91, 92]. Thus, it is understandable that several conflicting results have been observed, as some researchers report that the proliferation, activation, differentiation, and antibody production of B cells could be enhanced through the addition of MSCs [93, 94]. Although it is suggested that these disparities might result from variances in B cell purity, stimuli, source of MSCs, and the MSC-to-B cell ratio [95], the plasticity of MSCs as a result of the different intensities of the inflammatory signals they receive should also be carefully considered.

DCs

DCs play crucial roles in the acquisition, processing, transporting, and presentation of various antigens and comprise the most potent antigen-presenting cells (APCs) in the body [96]. These cells are specialized in antigen presentation and, therefore, are of critical importance in directing the responses of the adaptive immune system [4].

Increasing evidence demonstrates that MSCs have potent immunosuppressive effects on DCs. In an in vitro study, it was found that both MSCs and their culture supernatants inhibited the activation of DCs, down-regulated their endocytosis and IL-12 secreting ability, prevented their maturation, and decreased their ability to activate alloreactive T cells [97]. Similar findings were obtained in another in vitro study, which demonstrated that MSCs strongly inhibited the differentiation of monocytes to DCs, and skewed mature DCs to an immature state by suppressing their expression of MHCII, CD1-α, CD80, and CD86, and by inhibiting their IL-12 production [98]. In addition to inhibiting the differentiation of DCs from monocytes, MSCs also profoundly inhibit the differentiation and function of CD34-positive hematopoietic progenitor cell-derived DCs [99, 100]. Similar findings have also been demonstrated by several other studies [101–103]. MSCs can also skew mature DCs into a regulatory phenotype dependent on Jagged1, Jagged2, or IL-10-SOCS3 signaling [104–106]. In addition, the migration of DCs can be impaired by MSCs, which downregulated molecules associated with DC migration, such as CCR7 and CD49dβ1, and decreased their antigen presentation and inflammatory cytokine secretion ability, making them less efficient in activating T cells [36, 103, 107, 108]. In accordance with these in vitro findings, it was found that administration of MSCs effectively improved fulminant hepatic failure induced by *Propionibacterium acnes* and LPS by inducing the generation of regulatory liver DCs and Tregs [109]. In addition, infusion of ex-vivo MSC-stimulated DCs alleviated colitis in mice by increasing Treg amounts and decreasing lymphocyte proliferation [110]. The suppressive effects of MSCs on DCs also resulted in mitigation of several other immune disorders, including acute GVHD [108], allograft rejection [111], and type 1 diabetes [65].

In exploring possible mechanisms, it was found that IL-6 was involved in the suppressive effects of MSCs on DC differentiation, even though its strength was controversial [100, 112–114]. M-CSF was another candidate in this process, but was tested in combination with IL-6 [99]. Further mechanistic studies indicated that MSC-derived PGE2 and its receptor EP4 played a major role in the inhibitory effects of MSCs on DCs [109]. Notably, PGE2 levels were upregulated in MSC-monocyte co-cultures, and the addition of PGE2 inhibitor NS-398 restored DC function and differentiation, whereas direct addition of PGE2 blocked monocyte differentiation toward DCs [114]. In addition, EVs derived from MSCs were also shown to promote the induction of immature IL-10-secreting DCs, which were indicated in suppression of inflammatory T-cell responses to islet antigens [65]. Importantly, direct cell–cell contact of MSCs and DCs was also suggested in the suppression of DC generation, a process mediated by activation of Notch signaling in DCs [100]. Another finding showed that MSCs blocked cell cycle progression of DCs which may account for the impaired differentiation and function of DCs co-cultured with MSCs [115]. Interestingly, in certain circumstances, the survival of MSCs is dependent on DCs, which has been emphasized in a recent study showing that lymphotoxin-β expression in DCs assisted adipose-derived MSC survival in mouse models of scleroderma skin fibrosis [116].

Macrophages

It is well known that macrophages are critical cells within the innate immune system [117]. Contrary to the long-held view that all macrophages are derived from monocytes in the bone marrow, recent studies have suggested the distinct origins of tissue resident macrophages and circulating macrophages; the former are derived from the yolk-sac and self-maintain independently of the bone marrow contribution during adulthood, whereas the latter are differentiated and replenished from bone-marrow monocytes [118, 119]. Macrophages have prominent plasticity and can be polarized into classically activated M1 or alternatively activated M2 macrophages, depending on the specific micro-environment they are in. In general, M1 macrophages are proinflammatory and possess remarkable antimicrobial abilities via the secretion of various inflammatory cytokines and chemokines, whereas M2 macrophages are immunomodulatory by releasing IL-10 and trophic factors to promote tissue repair and resolve inflammation [120].

Various in vitro studies have demonstrated that co-culture of macrophages with MSCs led to the generation of M2 macrophages, which secreted high levels of IL-10, and low levels of various inflammatory cytokines, such as IL-12, TNF-α, IL-1β, and IL-23, had increased phagocytic ability while displaying decreased co-stimulatory molecule CD86 and MHCII expressions [121–124]. Moreover, pro-inflammatory stimulation-licensed MSCs promoted further M2 macrophage polarization [123, 125]. The biological relevance of these in vitro findings has been investigated in vivo in several recent studies. In an elegant study investigating sepsis, it was demonstrated that administration of bone-marrow MSCs effectively improved organ function and reduced mortality. This beneficial effect was eliminated by macrophage depletion or IL-10 signaling abrogation [125]. In a model of cutaneous wound healing, the transplantation of human gingiva MSCs formed a spatial interaction with macrophages in the wound site, thus suppressing their TNF-α and IL-6 secretion while promoting IL-10 production to mitigate local inflammation [121]. Similar effects of MSCs were observed in several other immune disorders, such as peritonitis [126], ischemia–reperfusion injury [127], acute liver injury [128], atherosclerosis [128], endotoxemia [129], type 2 diabetes [130], asthma [131], and arthritis [83]. MSCs are also capable of enhancing recruitment of macrophages to injured sites, thus promoting tissue regeneration or improving immune disorders [132, 133].

In investigating the mechanisms, it was found that this effect resulted from a combination of soluble factor-dependent signaling, including the release of PGE2 functioning through the EP2 and EP4 receptors on macrophages, and cell-contact-mediated signaling [125]. Inflammatory signals, such as IFN-γ, TNF-α, and LPS, stimulated the expressions of IDO and COX2 in MSCs, which further enhanced the suppressive functions of MSCs [95, 134, 135]. IL-1Ra was another factor mediating the immunomodulatory effect [83, 128]. IL-1Ra-deficient MSCs were less effective than wild-type MSCs in inducing M2 macrophage polarization and were unable to mitigate arthritic progression in a collagen-induced arthritis model [83]. In addition, MSC-derived exosomes were shown to induce generation of IL-10- and TGF-β-secreting M2-like macrophages from primary human and mouse monocytes [68]. TGF-β signaling was indicated in the mediation of M2 polarization of macrophages in a mouse model of asthma [136]. In a model of zymosan-induced peritonitis, inflammation-activated MSCs secreted TNF-stimulated gene 6 (TSG-6), which interacted through CD44 on macrophages to decrease zymoson/TLR2-mediated nuclear translocation of NF-κB, creating a negative feedback loop to attenuate macrophage activation [126].

NK cells

Natural killer (NK) cells are the key effector cells of the innate immune system; they are developed from a common lymphoid progenitor that is capable of giving rise to all lymphocyte subsets in or outside of the bone marrow [137, 138]. The activities of NK cells are finely regulated by the interaction of various activating and inhibitory receptors expressed on their surfaces with cognate ligands [139]. NK cells are critically involved in the control of various types of microbial infections and tumors by inducing direct cytotoxicity of target cells and/or proinflammatory cytokine production [140, 141].

A number of studies have demonstrated that MSCs are potent inhibitors of NK cells, as they are capable of suppressing the proliferation, cytokine production, and cytotoxicity of NK cells under specific circumstances [142–147]. For this, the ratio of MSCs and NK cells is important, since such suppressive effects could only be exerted at high MSC-to-NK ratios [144]. The significance of these findings was investigated in vivo, in which MSC administration hindered the trafficking and activation of NK cells in the liver, thus ameliorating Poly(I:C)-induced liver injury [146]. To clarify the mechanisms, soluble factors, such as IDO, PGE2, HLA-5, and EVs, have been shown to play critical roles [35, 60, 145]. Notably, blocking the synthesis or activities of either IDO or PGE2 significantly reversed the suppressive effect, with the two factors acting synergistically in this process [144, 145]. CD73 can dephosphorylate AMP into adenosine, and is crucial in the induction of an anti-inflammatory environment mediated by adenosine [148]. It was found that up-regulation of

CD73 on NK cells by MSCs led to such inhibition [149, 150]. In addition, direct cell–cell contact is also necessary for the inhibition of NK cells, which is involved in expression of TLR4 on MSCs [147, 151]. Nevertheless, disparities concerning the role of MSCs in modulating NK cells have been noted, as several studies reported opposite effects. It was shown that MSCs, when irradiated as a feeder layer, stimulated the proliferation of NK cell progenitors significantly [152]. Another study observed that MSCs efficiently enhanced the IFN-γ levels secreted by NK cells when stimulated by IL-12/IL-18 [153]. Moreover, NK cells and MSCs interacted in a positive feedback manner, in which NK cell-derived IFN-γ stimulated the CCL2 synthesis of MSCs, which in turn primed NK cells for the further release of IFN-γ [154]. NK cells also stimulated MSC recruitment, a process dependent on chemokines CCL5 and CXCL7 secreted by NK cells [155]. In addition to these findings, MSCs are lysis-sensitive targets for activated NK cells. It has been shown in several studies that MSCs could be efficiently lysed by activated NK cells, which was involved with the various activating receptors on NK cells [144, 156].

Taken together, these findings suggest that the interplay between MSCs and NK cells strongly depends on the stimulation of both cells, their microenvironment, and their ratios. Even so, more in vivo investigations should be conducted to determine the significance of these observations.

Neutrophils

Neutrophils are polymorphonuclear leukocytes and are recognized as one of the key players during acute inflammation [157]. They are abundantly found in the bloodstream and can be recruited to sites of injury within minutes. Neutrophils eliminate pathogens through multiple mechanisms, such as phagocytosis, secretion of bactericidal molecules, and neutrophil extracellular traps [4, 157, 158].

In 2008, it was first reported that MSCs had beneficial effects on neutrophils. Human bone-marrow MSCs from healthy donors, even at very low MSC to neutrophil ratios, significantly suppressed the apoptosis of resting or IL-8-activated neutrophils, a process largely dependent on IL-6 secretion [159]. Similarly, MSCs pre-treated with TLR3 stimulator Poly (I:C) exerted potent anti-apoptotic effects on neutrophils, primarily mediated by the combined action of IL-6, IFN-β, and GM-CSF [160]. In addition to their anti-apoptotic functions, MSCs also secreted IL-8 and macrophage migration inhibitory factor (MIF) to recruit neutrophils in vitro [161]. These findings were corroborated by several in vivo assays [162–164]. It was reported that neutrophils were effectively recruited by subcutaneously injected LPS-stimulated MSCs [162]. In addition, TNF-α-stimulated or gastric cancer-derived MSCs strikingly recruited neutrophils into the tumor, fostering tumor metastasis, and angiogenesis [163]. Through these mechanisms, it is speculated that MSCs may help preserve the storage pool of neutrophils in the bone marrow, and can also facilitate neutrophil migration to inflammatory sites, contributing to the resolution of infection and inflammation [165]. Nevertheless, conflicting findings also exist. In a murine vasculitis model, MSCs inhibited neutrophil activation, prevented neutrophil extracellular trap formation and excessive spillage of tissue-damaging proteases, thus dampening unrestrained inflammation and attenuating tissue damage. In this model, the therapeutic effect of MSCs was mediated by the constitutive release of superoxide dismutase-3 [166]. In another model of neutrophil recruitment induced by cytokine-stimulated endothelial cells, MSCs from various origins suppressed neutrophil recruitment effectively [167]. Moreover, MSC-derived EVs were also shown to inhibit the influx of neutrophils to the lung in an endotoxin-induced lung injury model [168]. It would be of interest to explore why these discrepancies exist, whether this is model-specific or is due to a different MSC dose or other aspects.

Mast cells

Mast cells are generally considered as the major effector cells in allergic reactions [169]. Several lines of evidence also implicated their role in inflammatory diseases, where they are activated by non-allergic triggers to contribute to hose defense or autoimmunity [170, 171].

When mast cells were co-cultured with bone-marrow-derived MSCs, their degranulation, inflammatory cytokine secretion, and chemotaxis abilities were suppressed, an effect dependent on the upregulation of COX2 in MSCs. This finding was confirmed in vivo as MSC administration significantly hindered mast cell degranulation in mouse skin and the peritoneal cavity [172]. In a murine model of atopic dermatitis, administration of MSCs suppressed both the infiltration and degranulation of mast cells, which was mediated by the production of PGE2 and TGF-β1 from the MSCs [173]. Similar findings were noted in several other studies [174–176]. MSC-produced PGE2 also suppressed mast cell infiltration and de novo synthesis of inflammatory cytokines in a murine contact hypersensitivity model [177]. Interestingly, MSCs could also in turn be activated by IgE-stimulated mast cells, thus releasing thymic stromal lymphopoietin and hematopoietic growth factors, regulating the lineage commitment and proliferation of $CD34^+$ precursor cells [178]. In addition, mast cells also affected MSCs by promoting their proliferation and accumulation while inhibiting their differentiation via the activation of

platelet-derived growth factor, which may play a role in improving the process of cardiac regeneration [179].

Conclusions and future perspectives

We have discussed our current understanding of the interactions between MSCs and the immune system and the underlying mechanisms (Fig. 3; Table 1). MSCs possess potent immunomodulatory properties, which is dependent on the types and intensities of inflammatory stimulus present in the microenvironment. However, human and murine MSCs may utilize distinct effector molecules to exert their functions (see Table 2 for a detailed comparison of human and murine MSCs). Through the immunomodulatory properties, MSCs are capable of interacting with cells of both the innate and adaptive immune systems and can affect the progression of various inflammatory diseases.

The immunomodulatory capabilities of MSCs have provided considerable possibilities to improve tissue regeneration and to treat immune disorders. In fact, the clinical virtues of MSC therapy have been tested in a variety of clinical trials for diseases, such as GVHD, SLE, rheumatoid arthritis, Type 1 diabetes, and Crohn's disease, as reviewed by Paul S. et al. and Hafsa et al. [18, 19], with effective outcomes in several cases [41, 181–184]. Moreover, MSC-based products, such as Prochymal and Cupistem, have also been commercially used for treatment of various diseases [185, 186]. Nevertheless, there are still challenges in the application of MSC therapy, as the clinical outcome varies between trials and reports exist that show the therapeutic effects of MSCs cannot be obtained in some cases [187, 188]. However, given the potent plasticity nature of MSCs, these discrepancies may result from the timing, dose, infusion route, and pretreatment of MSCs in different trials. Thus, establishing standardized methods is necessary to avoid such discrepancies and guarantee the efficacy of MSC therapy.

Choosing the most appropriate type of MSC is also important for positive clinical effects. Even though human MSCs are primarily isolated from bone marrow [54, 63, 182, 188, 189], there are increasing publications highlighting the function of MSCs from other tissues, such as the umbilical cord [130, 173], gingiva [121, 189], or adipose tissues [37, 86]. How these MSCs differ in terms of repair capacities and immunomodulatory properties are largely unknown, and whether MSCs from certain source(s) are more efficient in treating specific diseases remains unexplored. Thus, we suggest that future efforts should be made to fully define the range of sources from which human MSCs can be isolated and suggest further works to identify

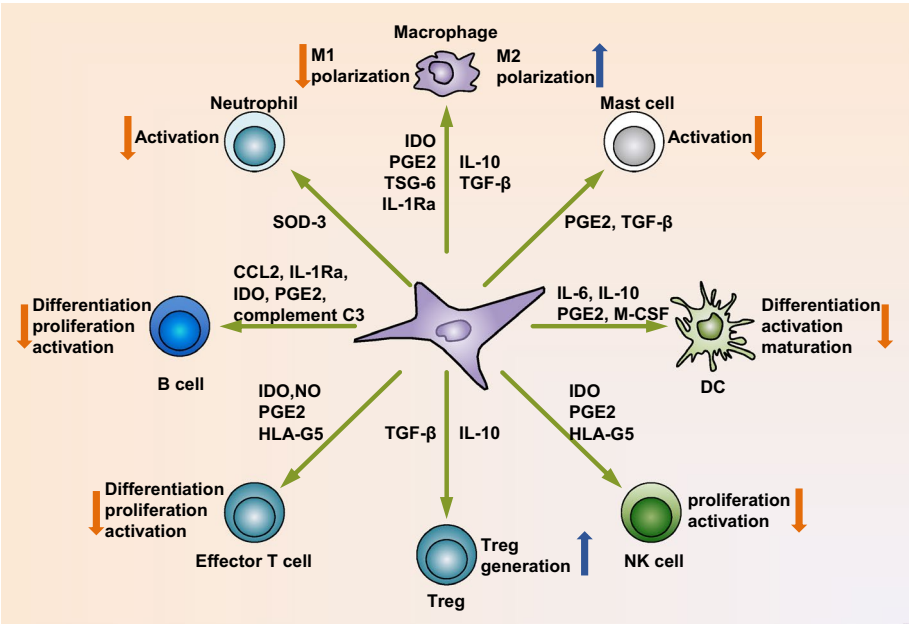

Fig. 3 Mechanisms of immunomodulatory functions of MSCs. MSCs possess broad immunomodulatory properties. After activation, MSCs can secrete a variety of soluble factors, such as NO (mice) or IDO (humans), PGE2, TGF-β, HLA-G5, TSG-6, CCL2, IL-1Ra, and IL-10. Production of these factors can suppress the differentiation, proliferation, activation of various immune cell subsets, including T cells, B cells, DCs, macrophages, NK cells, neutrophils, and mast cells. In addition, Tregs may be generated in response to TGF-β and IL-10 production from MSCs. As a result, the immune response will be inhibited and local inflammation is suppressed by MSCs (also refer to Table 1 for more detailed information regarding the mechanisms of immunomodulatory functions of MSCs)

Table 1 The functions of MSCs in regulating different immune cells and the related mechanisms

Immune cell type	MSC function	Mechanism	References
T cell	Suppressing T cell differentiation, proliferation, activation, and survival	TGF-β, HGF, IDO, NO, PGE2, HLA-G5, TSG6, IL-10, EVs	[30, 31, 34, 35, 43, 62–66, 69–71, 180]
		Cell–cell contact: Fas/FasL signaling	[33]
	Promoting T cell recruitment	CXCR3 ligands, CCR5 ligands, ICAM-1, VCAM-1	[17, 43, 44, 46]
B cell	Suppressing B cell differentiation, proliferation, activation, and chemotaxis; Breg induction	CCL2, IL-1Ra, IDO, PGE2, complement C3, EVs	[60, 78, 81–84, 87, 90, 180]
		Cell–cell contact: PD-1/PD-L1	[85]
	Promoting B cell differentiation, proliferation, and activation	VEGF	[93, 94]
DC	Suppressing DC differentiation, activation, endocytosis, migration, and maturation	IL-6, IL-10, M-CSF, PGE2, EVs	[36, 65, 99, 101–103, 107–109, 113, 114]
		Cell–cell contact: notch pathway activation	[100]
Macrophage	Suppressing M1 while inducing M2 polarization	PGE2, IDO, IL-1Ra, IL-10, TSG-6, TGF-β, exosomes	[68, 83, 123, 125, 126, 131, 135, 136]
NK cell	Suppressing NK cell proliferation, migration, and activation	IDO, PGE2, HLA5, EVs	[35, 60, 142–147]
		Cell–cell contact: CD73, TLR4	[147, 149–151]
	Promoting NK cell progenitor proliferation and NK activation	CCL2	[152–154]
Neutrophil	Suppressing neutrophil activation, recruitment, neutrophil extracellular trap formation, and protease secretion	Superoxide dismutase-3, EVs	[166–168]
	Promoting survival and recruitment	IL-6, IL-8, MIF, IFN-β, and GM-CSF	[159–162]
Mast cell	Suppressing mast cell degranulation, inflammatory cytokine secretion, and chemotaxis	PGE2 and TGF-β1	[172–177]

Table 2 Comparison of human and murine MSCs

Items	Human MSCs	Murine MSCs
Differences in specific markers	Stro-1, CD146, alkaline phosphatase, CD49a, CD271, and HLA-DR [3, 8]	Nestin, CD105, vascular cell adhesion protein, CD90, MHCII [5, 19, 46]
Common markers	Positive: Sca-1, CD105, CD73, CD29, and CD44 Negative: CD45, CD34, CD11b, CD31, and MHCII [3, 5, 8, 19, 46]	
Differences in effector molecules for immune regulation	IDO, HLA-G5 [35, 47, 50]	NO [47, 50]
Common effector molecules for immune regulation	PGE2, IL-6, IL-10, TGFβ, TSG-6, CCL2, IL-1Ra [30, 39, 69–71, 80, 82, 83]	
Key cytokines for induction of immunosuppressive capacity	IFN-γ and TNF-α [43, 47]	IFN-γ [43]

the most appropriate types of MSCs for specific disease treatment.

Naturally, there are concerns from the scientific community about the efficacy and safety of MSC-based therapies. However, MSC-based therapy still merits further investigation due to the advantages discussed above. Undoubtedly, we are now bridging the translational gap between the basic research of MSCs and their clinical applications for disease treatment. With the increasing explorations in MSCs, we may expect that all these concerns will be addressed over time once a better understanding of the immunomodulatory properties of MSCs is achieved and when MSCs can be exploited appropriately to optimize their therapeutic effects.

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Compliance with ethical standards

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

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