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REVIEW

Biological functions of mesenchymal stem cells and clinical implications

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Abstract

Mesenchymal stem cells (MSCs) are isolated from multiple biological tissues—adult bone marrow and adipose tissues and neonatal tissues such as umbilical cord and placenta. In vitro, MSCs show biological features of extensive proliferation ability and multipotency. Moreover, MSCs have trophic, homing/migration and immunosuppression functions that have been demonstrated both in vitro and in vivo. A number of clinical trials are using MSCs for therapeutic interventions in severe degenerative and/or inflammatory diseases, including Crohn's disease and graft-versus-host disease, alone or in combination with other drugs. MSCs are promising for therapeutic applications given the ease in obtaining them, their genetic stability, their poor immunogenicity and their curative properties for tissue repair and immunomodulation. The success of MSC therapy in degenerative and/or inflammatory diseases might depend on the robustness of the biological functions of MSCs, which should be linked to their therapeutic potency. Here, we outline the fundamental and advanced concepts of MSC biological features and underline the biological functions of MSCs in their basic and translational aspects in therapy for degenerative and/or inflammatory diseases.

Keywords Mesenchymal stem/stromal cells · Cell identity · Cell functions · Cell therapy

Introduction

Hundreds of clinical trials are now using mesenchymal stem cells (MSCs) to test therapeutic interventions for numerous severe diseases, alone or in combination with other drugs [1–4]. These trials are designed mostly (Fig. 1) for treatment in (1) orthopedics (e.g., non-union bone fracture, craniofacial trauma); (2) degenerative diseases of the skeletal system (e.g., osteonecrosis, osteogenesis imperfecta), eyes (e.g., glaucoma, macular degeneration, retinitis pigmentosa), heart (e.g., ischemic cardiomyopathy), kidney (e.g., acute kidney injury), liver (e.g., liver cirrhosis), lung (e.g., pulmonary fibrosis) or multiple organs (e.g., diabetes complications); (3) autoimmunity affecting the skeletal system (e.g., osteoarthritis, rheumatoid arthritis), brain and spinal cord (e.g., multiple sclerosis), gastrointestinal tract (e.g., Crohn's disease, ulcerative colitis), pancreas (e.g., diabetes type 1) or multiple organs (e.g., systemic lupus erythematosus); (4)

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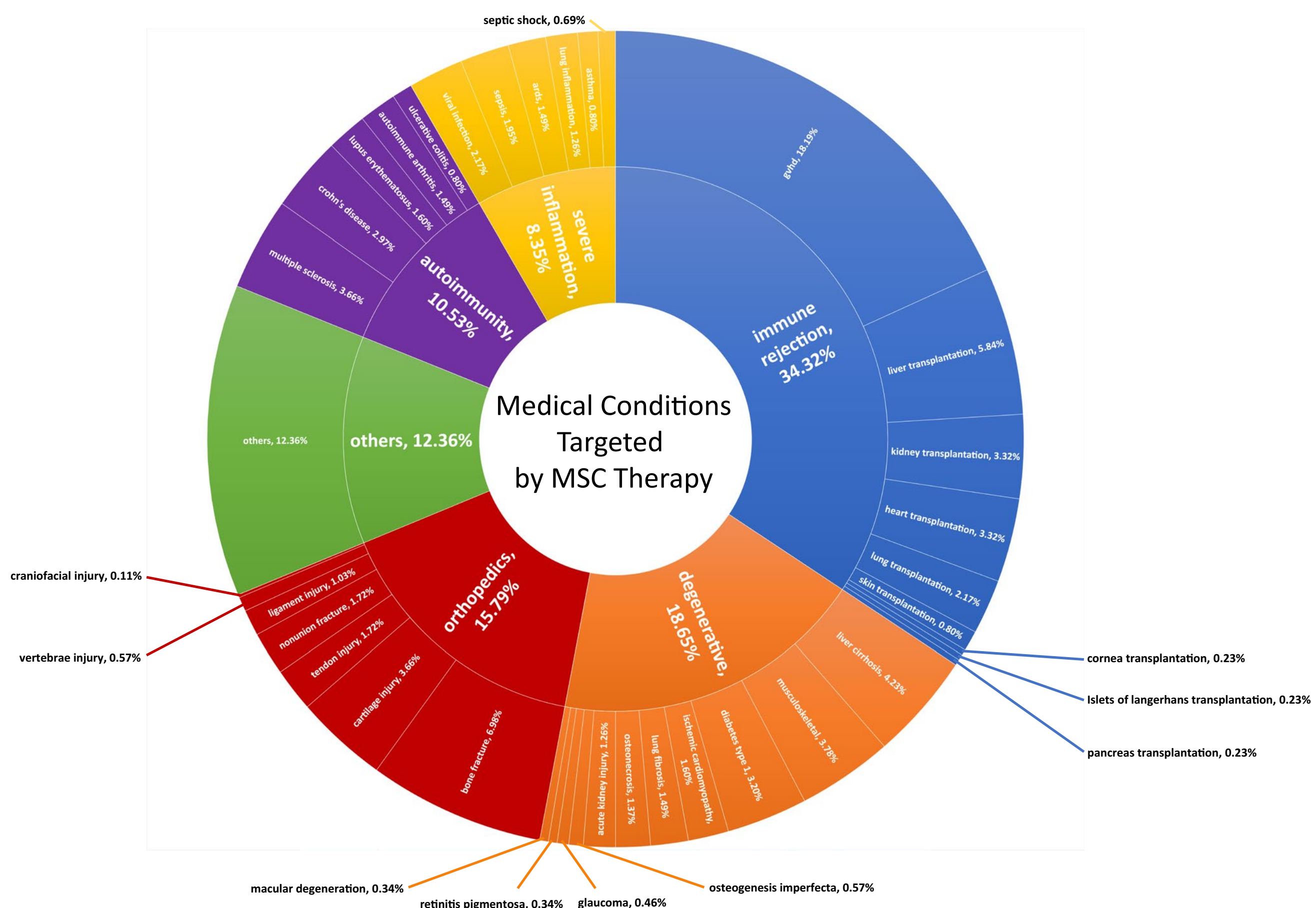

Fig. 1 Medical conditions targeted by MSC therapy. Diagram of the conditions targeted by MSCs by proportion of trials. Data were obtained using a recurrent search of keywords for medical conditions (appearing in the diagram) associated with mesenchymal stem/stromal cells at ClinicalTrials.gov. The search was completed on April 2019. The group "medical conditions for degenerative disorders" represents about 18% of total trials, and inflammatory disorders combined (autoimmune diseases, transplant immune rejection, severe inflammatory diseases) represent about 45% of all trials and most of the clinical trials of MSCs for treatment

inflammatory diseases of the lung (e.g., acute respiratory distress syndrome, chronic obstructive pulmonary disease) or multiple organs (e.g., sepsis); as well as (5) immune rejection in allogeneic transplantation [e.g., graft-versus-host disease (GvHD), solid organ rejection] [1–3, 5].

Most clinical studies are registered in the database of the US National Institutes of Health (NIH) (https://clinicaltrials.gov/). Such clinical assays are undertaken worldwide in university hospitals and biomedical institutions, principally in China, the European Union and the United States (Fig. 2a). Of note, most studies are in the early phases, typically phase 1 or 1/2; fewer are in phase 2 and even fewer in more advanced phases (Fig. 2b).

The available data support the safety of MSC therapy with both autologous and allogeneic MSCs, but actual data on the efficacy of MSC therapy are often preliminary [2]. However, MSCs embody a biological material for cell therapy that is safe, barely immunogenic and of immediate applicability in diseases [1–3, 5, 6]. Regardless, clinical practice requires better coordination of the characterization, production, and delivery of MSCs [2, 7–11]. Advanced-phase clinical trials expect to develop MSC therapy (Fig. 2c), which implies an increasing number of pharmaceutical biotechnologies [2, 12]. Yet, there are obstacles to the development of MSC therapy [1–4, 6, 8–11]; indeed, substantial clinical assays, with publicly disclosed results, have shown insufficient outcomes, with inconstant therapeutic benefits in diseases such as acute GvHD [1–3]. Recent research has progressed to further define MSC functions and modes of actions that should reflect therapeutic potentials of MSCs [13–17]. In this review, we attempt to outline the essential and advanced concepts in the biology of MSCs, especially MSC biological functions in their fundamental and translational aspects in degenerative and/or inflammatory diseases.

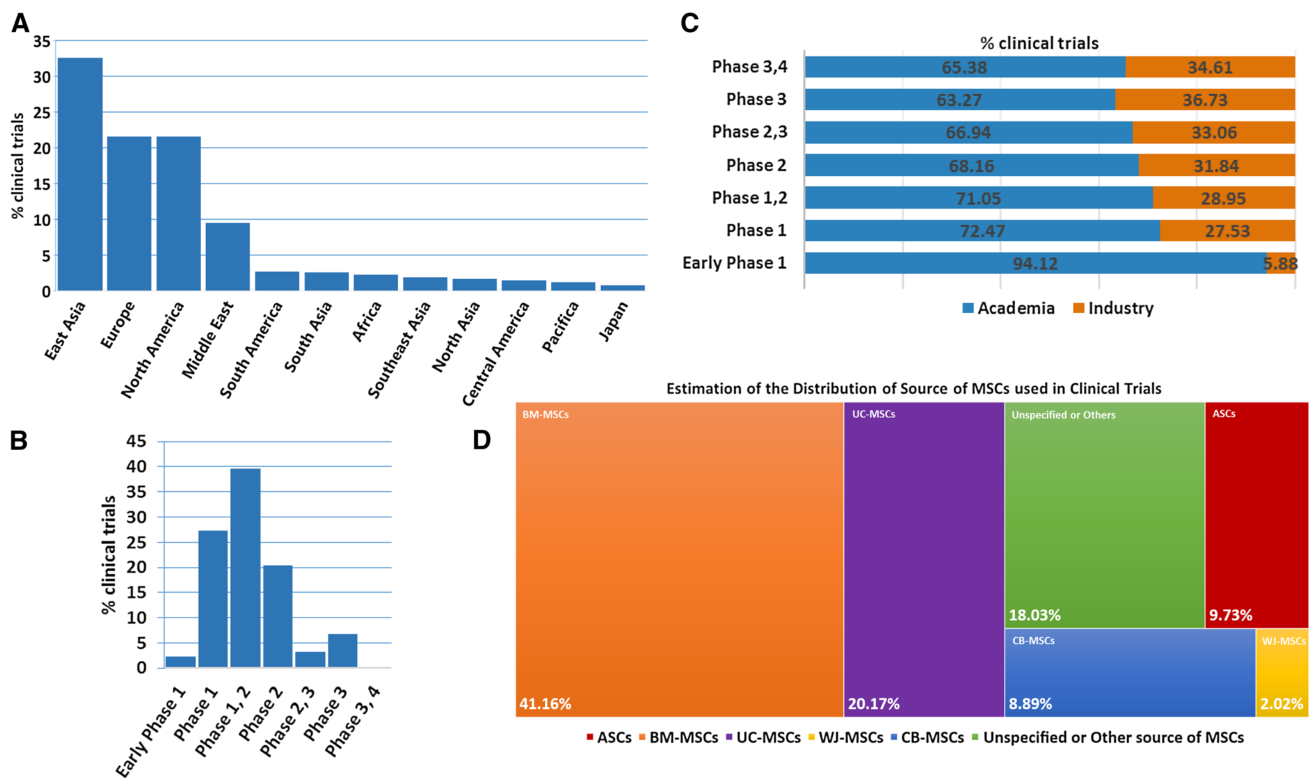

Fig. 2 Worldwide usage and progress of MSC therapy. Proportion of clinical trials of MSCs by location. Data were obtained by a search of ClinicalTrials.gov completed on June 2018. **a** East Asia (mostly China) followed by Europe and North America (mostly United States) are the locations of 70% of all clinical trials investigating MSCs as treatment. **b** Phase 1 and 2 clinical trials of MSCs as treatment represent about 85% of the total number, whereas more advanced clinical trials in phases 3 and 4 represent less than 10%. **c** Increased proportion of pharmaceutical industry-sponsored clinical trials investigating MSCs as treatment progressing to the advanced phase. Academia-sponsored clinical trials represent most of the clinical trials of MSCs as treatment, about 60% at least. **d** Sources of MSCs by proportion of clinical trials. Data were obtained using a recurrent search of keywords for sources of MSCs in trials (appearing in the diagram) at ClinicalTrials.gov. The search was completed on June 2018. Bone marrow-derived MSCs (BM-MSCs) are investigated in about 40% of total trials, followed by umbilical cord-derived MSCs (UC-MSCs) at 20% and adipose tissue-derived MSCs (ASCs) at 10%

MSC biological concept

The Friedenstein group, in the 1960s and 1970s, demonstrated that only a marginal cell subset residing among rodent bone marrow cells had osteogenic abilities [18–23]. This bone marrow cell subset was defined as adherent colony-forming unit fibroblasts (CFU-Fs) in vitro in contrast to non-adherent hematopoietic CFU cells (CFU-Cs) [18, 21, 24–26]. CFU-Fs were initially considered to produce cells associated with skeletal tissue, that is, stem/progenitor cells [18, 22, 23, 27–29], but were also considered feeder cells for ex vivo culture of hematopoietic stem cells (HSCs), or stroma cells [19, 28–33]. The CFU-F designation then evolved into other terms that were supposed to best define the biology of the cells, based on cell functions, such as "osteogenic stem cells" or "bone-marrow stromal cells" [29, 34]. Furthermore, these biological concepts were substantiated in other species, including in humans [24, 27, 35–41]. Later, the general notion of adult "mesenchymal stem cells", first proposed by Caplan et al., emerged by accommodating the concept of cells originating from the embryonic mesoderm [42, 43]. Of note, the appellation adult "mesenchymal stem cells" is still imprecise from strict biological opinion [13, 44, 45] but has endured and is widely used by scientists and clinicians [44–46]. However, the designation MSCs are often debated and/or further described with the terms "stem" and "stromal" combined, whereas the term "multipotent" is sometimes preferred to "mesenchymal", for "mesenchymal stem/stromal cells" or "multipotent stem/stromal cells". The hesitancy on strict denomination attests to the uncertainties of MSC identity and functions [13, 45, 47–49].

The concept of MSCs suggests the existence in vivo of stem and/or progenitor subsets within adult or neonatal tissues that sustain the homeostasis of other stem and/or progenitor cells while being able to provide de novo-specialized cells of mesodermal lineage [13, 48, 50]. MSC functions in vivo were believed to regulate the homeostasis of HSCs by producing trophic factors and favoring wound healing by differentiating into tissue-specific cells [13, 50–52]. In 1995, Lazarus et al. envisioned the use of MSCs as cell therapy

similar to bone marrow transplant [48]. Later, in the 2000s, other studies drew attention to further MSC functions, namely homing/migration [53–62] and immunosuppression [63–68]. Thereafter, MSC therapy has been investigated extensively in both preclinical and clinical settings to evaluate its therapeutic effect in degenerative and/or inflammatory diseases lacking appropriate treatments [1–3, 5, 11, 69].

Here, we discuss the fundamental biology and translational advances regarding MSCs isolated from human adult or neonatal tissues, expanded in vitro and used as therapeutics directly after thawing MSCs from frozen batches or indirectly by harvesting "fresh" cells after continuous culture of MSCs that are delivered by topical or systemic adoptive transfer in autologous, allogeneic or xenogeneic contexts. First, we briefly consider elements of sources of human MSCs.

Adult and neonatal tissue source of MSCs

MSCs are typically obtained from adult bone marrow and adipose tissue (Fig. 2d); neonatal tissue such as umbilical cord is also commonly used to obtain MSCs [70]. MSCs in vivo may be confined to a marginal cell population that supposedly exists in all organs containing a perivascular niche because of the expression of stromal cell surface marker 1 (Stro-1) and/or α-smooth muscle actin (α-SMA) in all MSCs regardless of their source [71]. This population represents an estimated 0.00001% of bone marrow cells and up to 1% or more of adipose tissue cells [70, 72–82]. MSCs in umbilical cord likely represent a cell frequency comparable to or below that found among adult bone marrow cells but with better expandability in vitro as compared with their adult counterparts because of their fetal nature [80]. Still, bone marrow as a source of MSCs remains the most valued because this source is better documented and largely used in both preclinical and clinical research [83]. Therefore, MSCs derived from bone marrow (BM-MSCs) are considered a paragon of MSCs [72, 84].

BM-MSCs are isolated from total marrow obtained from the iliac crest of the pelvic bone of healthy donors. This is an invasive method that requires anesthesia and implies nosocomial infection hazards; it is now used mostly for BM-MSCs intended for clinical use [73, 81, 85, 86]. Total bone marrow from femoral heads obtained during orthopedic surgery with femur head and neck osteotomy is also a source of BM-MSCs but solely for preclinical research use [81, 85, 86]. Isolation of MSCs from total bone marrow involves density gradient centrifugation, with collection of the mononuclear cell fraction. To isolate MSCs by adherence and expansion, the mononuclear cells are seeded in culture dishes at low density, about 10^3–10^4 cells/cm^2, but more commonly at 10^5 cells/cm^2 and can reach up to 10^6 cells/cm^2 [74, 81, 87].

MSCs from adipose tissue (ASCs) are isolated from tissue samples obtained after medical interventions involving liposuction or lipectomy. Adipose tissues are obtained from patients by aspirating or excising visceral or subcutaneous fat tissue located in the abdomen, brachium, femoral, or gluteal areas [88]. Furthermore, ASC isolation involves enzymatic digestion of fat tissue samples with collagenases, then red blood cell (RBC) removal with specific RBC lysis followed by cell filtration. Of note, methods for expanding ASCs are similar to those used for BM-MSCs. Today, adipose tissue is increasingly used as a source for MSCs, mostly because of its natural abundance of MSCs and also the less invasive surgical measures for obtaining adipose tissue as compared with bone marrow tissue and so is ideal for clinical use [72, 81, 82, 86, 87, 89].

MSCs may be isolated from neonatal tissues, especially umbilical cord, which is easily accessible. Whole umbilical cord or its individual biological compartments can be a source of MSCs [70, 90]. MSCs can be isolated from whole umbilical cord, containing conjunctive tissue, Wharton's jelly tissue and vasculature. Conversely, they can be isolated from Wharton's jelly after removal of blood vessels and residual conjunctive tissues from umbilical cord. Alternatively, MSCs can be isolated specifically from umbilical cord blood (i.e., fetal blood within umbilical vasculature [90]). Cell biology methods used for isolating MSCs from umbilical cord vary depending on the umbilical cord compartment chosen as a source. Typically, these methods may include enzymatic digestion of umbilical-cord tissue samples, RBC-specific lysis, cell filtration, and/or density gradient separation [74, 86, 90]. The procedures for isolation/expansion are similar for adult and neonatal MSCs. The existence of various umbilical compartments for sourcing MSCs suggests differences in MSC yield, and in fact whole umbilical cord and Wharton's jelly tissue are superior to umbilical cord blood in terms of quantity of obtainable MSCs [70, 91].

The tissues described above for sources of MSCs seem somewhat disparate, but they are not entirely unlike each other because bone marrow, adipose tissue, and umbilical cord share biological similarities [80]. To exemplify, bone marrow resembles adipose tissue because in adults, bone marrow consists of nearly 30–70% adipose tissue, known as yellow marrow or marrow adipose tissue (MAT), but adipose tissue in other anatomical areas typically consists of white adipose tissue (WAT) [92]. The function of MAT is not yet definitively established. However, although MAT and WAT have unique specificities [92], MAT exhibits certain WAT properties such as lipid-storage and endocrine functions [92]. Moreover, MSCs are derived from both bone marrow (containing MAT) and WAT, and both derived MSCs fit ISCT criteria. Thus, MAT and WAT could be considered tissues sharing certain biological features and likely cellular contents, including MSCs. Moreover, bone marrow, adipose

tissue, and umbilical cord consist of connective tissues with perivascular niches where MSCs are thought to reside [93].

Furthermore, MSCs have been isolated from multiple other adult tissue including bursa [94], dental pulp [77], dermis [95], gingival tissue [96], ligaments [97], peripheral blood [98], and synovium [99] as well as other neonatal tissue such as placenta [100]. Of note, MSCs may be obtained via in vitro differentiation of human induced pluripotent stem cells [101]. However, these last MSC sources are not much used for MSC therapy.

MSC culture methods, cryopreservation and standardization needs

Unrelated to sourcing, MSCs are produced in vitro with rather similar culture methods. Mononuclear cells isolated from biological tissues are suspended in derivatives of Eagle's medium (α-MEM or DMEM) supplemented with fetal bovine serum (FBS)- or human-derived supplement such as serum AB or platelet derivatives such as platelet lysates or platelet-rich plasma with or without additional factors. Of note, the composition of serum and their derivatives are ill defined and, therefore, these products must often be screened for their efficacy in MSC culture, for sustaining and promoting cell proliferation of MSCs without affecting their undifferentiated state [102].

Importantly, to meet standards of good manufacturing production and to satisfy demands for the highest safety, quality and quantity of MSCs, MSC culture systems must be optimized and standardized [2, 5, 103]. Especially, attempts to improve MSC culture include (1) privileging advanced stringent aseptic methods, (2) using hypoxic conditions mimicking the native microenvironment of MSCs, (3) avoiding non-human products (i.e., xenogeneic-free medium) and (4) restraining undefined medium composition (e.g., by promoting the use of serum-free medium) [2, 87, 104–108]. Furthermore, MSCs are subcultured using standard cell culture systems or by large-scale bioprocessing with high-capacity bioreactors intended for extensive cell production yield to meet therapeutic demands [86, 104, 105, 109–112]. Especially, bioprocesses with large-scale bioreactors are culture methods used for producing MSCs with pharmaceutical biotechnologies conferring improved yield and reduced production costs [103, 106, 112]. Yet, this large-scale production of MSCs needs to be standardized for reliability and require even more stringent post-production quality controls of MSC products for consistency, efficacy, and safety [103, 106].

In addition, various cryopreservation procedures for MSCs used in academic and pharmaceutical laboratories require further optimization and standardization [113]. Concerns exist about the therapeutic capabilities of extemporaneous freeze–thawed MSCs and MSCs harvested from continuous cultures [8]. Thus, immediately thawed MSC products might show attenuated therapeutic effects as compared with freshly cultured MSCs [8]. Currently, no clear consensus has emerged for the MSCs used in therapy [114], but the trend is to use immediately thawed MSC products in the clinic because of the ease of use and readiness of frozen off-the-shelf MSC products [2, 115].

Practices in culture, cryopreservation and clinical usage of MSC products require standards because current practices among laboratories remain inconsistent, in both preclinical and clinical settings, and these fluctuating practices may affect the identity and functions of MSCs [2, 8].

MSC identity and functions

MSCs in culture are thought to contain diverse cell subsets resulting from intrinsic and extrinsic influences in addition to inherent disparities related to different sources and donors [16, 116–119]. Cell heterogeneity is expected in MSC cultures for use in preclinical and clinical settings [116, 118–123]. MSCs in culture include multipotent cells and/or diverse but coherent committed progenitors [21]. MSCs from different sources may not be all alike, but MSC cultures might share common features in agreement with the International Society of Cell Therapy (ISCT) criteria established in 2006 [11, 119, 124]. Of note, ISCT proposed minimal criteria to define MSCs: (1) MSCs must be adherent cells showing a spindle-shape morphology in standard culture conditions; (2) MSCs must show cell surface expression of cluster of differentiation (CD)105, CD73 and CD90 but not CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR antigens; and (3) MSCs must differentiate to osteoblasts, adipocytes and chondroblasts in vitro following a definite stimulation [124]. Originally, these nominal principles were intended to homogenize the depiction of MSCs among research laboratories. Today, these criteria require modification with new knowledge of MSCs [1, 10, 49, 125]. Particularly, surface antigens that identify MSCs in vivo and/or in vitro remain to be elucidated. Indeed, surface antigens that conceivably relate to stemness, including Stro-1, stage-specific embryonic antigen (SSEA)-1, SSEA-4, CD271, and CD146, have been examined but are not satisfactory because of the wide variation in expression of these antigens depending on the source of MSCs [75, 126]. Meanwhile, thorough transcriptomic and functional analysis of MSCs from different biological sources have revealed transcriptional signatures that differ among cultures of MSCs from different sources, with close but nonetheless different differentiation abilities [11, 16, 119–123, 127]. The identity of MSCs is not yet clear; thus, defining the biological functions of MSCs that would support identification of MSCs with therapeutic

interests is vital. Hereafter, we discuss MSC functions (Fig. 3) including proliferation, multipotency, trophic ability, homing/migration and immunosuppression in fundamental aspects and their clinical implications.

Mesenchymal stem cell proliferation function

A cell must be able to proliferate for self-renewal and cell expansion, which is related to “stemness” [108, 128]. MSCs are proliferative in vitro but retain a fibroblast-like morphology. Early in culture, the proliferation function of MSCs (Table 1) seems tightly controlled under low activity of wingless type (Wnt)/β-catenin signaling [129]. Moreover, the availability of O_2 regulates MSC proliferation by modulating the transcription factor (TF) hypoxia-inducible factor 1, which permits the expression of genes controlling cell cycle progression [130, 131]. Hence, hypoxic culture conditions in vitro ($O_2 < 10\%$) improve MSC proliferation by mirroring the usual O_2 strain conditions in vivo. Furthermore, in vivo hypoxic conditions protect mitochondria physiology by decreasing the oxidative metabolism needs of MSCs in contrast to atmospheric normoxia ($O_2 > 20\%$), with in vitro-expanded MSCs subjected to elevated oxidative stress, thereby impeding MSC proliferation [131].

MSCs are proliferative in vitro, but their proliferation ability decreases with time of culture along with a lack of telomerase activities and modifications in cell morphology [132, 133]. Decreased cell proliferation abilities of MSCs

Table 1 Pathways of MSC proliferation function

Molecular pathways	Mesenchymal stem cell (MSC) proliferation function	References
Wnt-3a/β-catenin	–	De Boer et al. [129]
HIF-1	+	Fehrer et al. [130], Estrada et al. [131]
Telomerase	+	Zimmerman et al. [132], Bernardo et al. [133]

The activity status of molecular pathways critical in the proliferation function of MSCs. Data are summarized from references [129–133]

HIF-1 hypoxia-inducible factor 1, *Wnt-3a* wingless type 3a

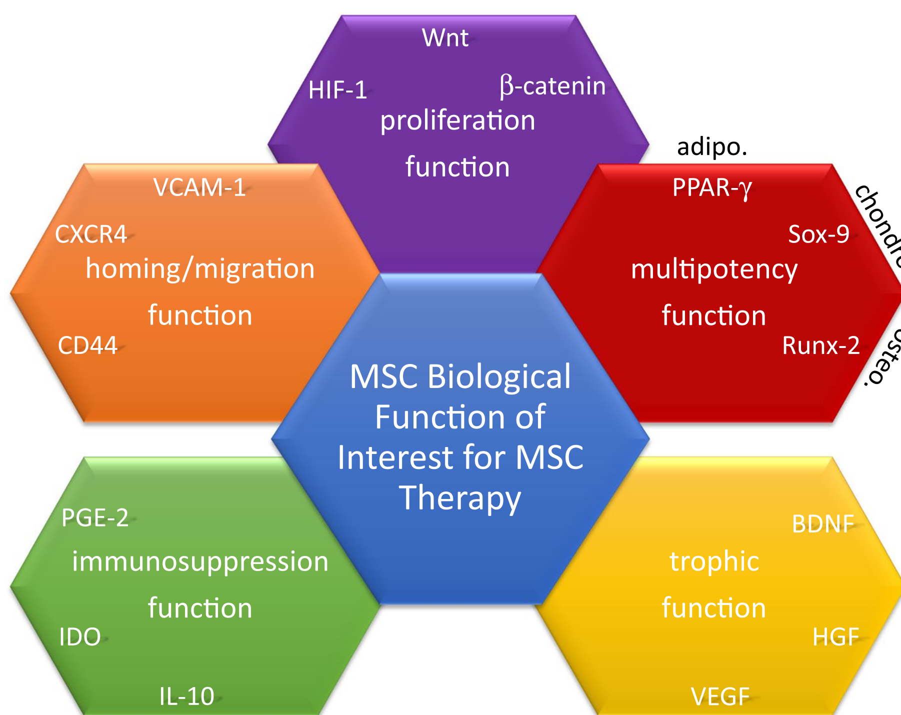

Fig. 3 Biological functions of MSCs. The five biological functions of MSCs with interest in therapeutics: (1) proliferation function, (2) multipotency function, (3) homing/migration function, (4) trophic function, and (5) immunosuppression function. The diagram gives three representative molecules involved in each of these functions. *HIF-1* hypoxia-inducible factor 1, *Wnt* wingless type, *PPAR-γ2* peroxisome proliferator-activated receptor 2, *SOX9* sex-determining region of the Y chromosome-box 9, *RUNX-2* runt-related transcription factor 2, *Adipo* adipocyte, *Chondro* chondroblast, *Osteo* osteoblast, *BDNF* brain-derived neurotrophic factor, *HGF* hepatocytes growth factor, *VEGF* vascular endothelial growth factor, *IL* interleukin, *IDO* indoleamine 2,3 dioxygenase, *PGE2* prostaglandin E2, *CD* cluster of differentiation, *CXCR* CXC chemokine receptor, *VCAM-1* vascular cell adhesion molecular 1

appear as an archetypical cell senescence, with progressive loss of proliferation and cell cycle arrest [134]. Even with senescence, the phenotype of MSCs remains rather unchanged and with virtually no genetic disturbance or chromosomal instability [133]. Yet, senescence-associated DNA methylations are identified on specific CpG sites and seem to be the typical epigenetic signature of senescent MSCs [135]. MSCs exposed to overwhelming stimuli, including metabolic stress and/or attempts to repair genomic DNA damage during in vitro expansion, might promote senescence, which is likely a defense against cell death or genetic subversion [133, 135]. Of note, the frequency of senescence occurring in MSCs can be intrinsically influenced by the origin of MSCs from different tissues and different donors [133, 135]. Other than the expansion concerns of MSCs, the significance of senescence in terms of further upheaval of other MSC functions and therapeutic potency of MSCs are unclear but are drawing increasing interest [136].

Mesenchymal stem cell multipotency function

MSCs differentiate into adipocytes, chondroblasts and osteoblasts under a definite stimulation in vitro (Table 2); the differentiation is perceived morphologically and/or with specific expression of biomarkers [73, 124, 137]. MSCs undergo an overhaul of intracellular signaling and transcriptional modifications, possibly in vivo depending on the biological conditions or during in vitro manipulations [15]. Manipulation of MSCs in vitro includes use of diverse molecules such as chemicals, cytokines, hormones, vitamins and/or mechanical/physical supports by means of scaffold biomaterials [40, 73, 124, 137, 138].

Adipogenesis is typically achieved by stimulating MSCs with dexamethasone, insulin, isobutylmethylxanthine, and indomethacin in vitro [73, 139]. MSCs differentiating into adipocytes is revealed by lipid vacuoles that gradually form a single large vacuole in terminally differentiated adipocytes [73, 139]. Furthermore, adipogenesis can be assessed by enzyme expression and/or activity of lipoprotein lipase and the accumulation of fatty acid-binding protein adipocyte P2 in mature adipocytes [73, 139].

Table 2 Pathways of MSC multipotency function

MSC multipotency function	Adipocyte	Chondroblast	Osteoblast	References
Upstream molecular pathways				
BMP-2, -4, -6	−	+	+	Sekiya et al. [151], Friedman et al. [149]
EGF	−	−	+	Kratchmarova et al. [303], Platt et al. [304]
FGF-2	−	+	+	Chiou et al. [143], Miraoui et al. [305]
IGF-1	+	+	−	Scavo et al. [306], Indrawattana et al. [148]
TGF-β1, -β3	−	+	−	Roelen et al. [307], Maeda et al. [308]
Intracellular signaling pathways				
HH	−	+	+	Fontaine et al. [156], Oliveira et al. [309]
MAPK	−	+	+	Chang et al. [310], Celil et al. [152]
Notch	−	−	+	Oldershaw et al. [157], Ugarte et al. [314]
Smad-3, -4	−	+	+	Furumatsu et al. [147], Zhou et al. [312]
Wnt-3a, -7a/β-catenin	+	+	+	Tuli et al. [142], De Boer et al. [129]
Downstream transcription factor				
C/EBP-α/β	+	−	−	Qian et al. [313], Cristancho et al. [140]
Osterix/Sp7	−	−	+	Celil et al. [152], Zhu et al. [317]
PPAR-γ2	+	−	−	Cristancho et al. [140], Yu et al. [316]
RUNX-2	−	−	+	Xu et al. [315], Thiagarajan et al. [314]
SOX9	−	+	−	Indrawattana et al. [148], Furumatsu et al. [147]

The activity status of most critical upstream molecular pathways, intracellular signaling and downstream transcription factors essential for the multipotency function of MSCs differentiating into adipocytes, chondroblasts and osteoblasts. Data are summarized from references [129, 140, 142, 143, 147–149, 151, 152, 156, 157, 303–317]

EGF epidermal growth factor, *FGF-2* fibroblast growth factor 2, *IGF-1* insulin-like growth factor 1, *TGF-β1 or -β3* transforming growth factor β1 or β3, *HH* hedgehog, *MAPK* mitogen-activated protein kinase, *Wnt-3a or -7a* wingless type 3a or 7a, *PPAR-γ2* peroxisome proliferator-activated receptor 2, *C/EBP-α/β* CCAAT/enhancer-binding protein α, *RUNX-2* runt-related transcription factor 2, *SOX9* sex-determining region of the Y chromosome-box 9

Mainly, the action of Wnt/β-catenin signaling is required for commitment of MSCs into preadipocytes, whereas in later stages, the inactivation of the Wnt/β-catenin pathway seems necessary to complete the maturation of adipocytes [139]. Thus, the Wnt/β-catenin pathway affects the downstream action of specific TFs such as CCAAT/enhancer-binding protein α/β (C/EBP-α/β) and peroxisome proliferator-activated receptor γ2 (PPAR-γ2). Both C/EBP-α/β and PPAR-γ2 activities are essential during early and late stages of adipogenesis [139, 140].

Chondrogenesis in vitro ensues usually with MSCs placed in aggregate or pellet cultures and stimulated with transforming growth factor-β1 or -β3 (TGF-β1 or -β3), and/or insulin-like growth factor 1 (IGF-1), fibroblast growth factor 2 (FGF-2), or bone morphogenic protein 2 (BMP-2) [73, 141–145]. FGF-2 facilitates chondrogenesis of aggregated MSCs stimulated with TGF-β1 or -β3 and/or IGF-1 [143, 144]. Particularly, FGF-2 alone does not induce chondrogenesis; rather, FGF-2 enables chondrogenesis by upregulating FGF-R2 and transcription factor SOX9 [143]. During chondrogenesis, progenies gradually produce sulfated proteoglycans such as aggrecan and type II and IX collagen, with the development of a distinctive chondroblast cell morphology [73, 141]. MSC differentiation into chondroblasts is regulated by molecular pathways including Wnt/β-catenin, TGF-βs, hedgehog (HH), BMPs, and FGFs [139, 146]. Together, activation of these upstream signaling pathways converges to dictate the proper action of TFs belonging to the sex-determining region of the Y chromosome-box (SOX) family, notably not only SOX9, but also SOX5 and SOX6, which are required for completion of chondrogenesis [146–148].

Osteogenesis can be achieved in vitro by stimulating MSCs with ascorbic acid, β-glycerophosphate, vitamin D3 and/or BMP-2, -4, -6 and -7 [73, 149]. MSCs commit to osteoblast progenies with increasing activity of alkaline phosphatase L (ALPL) isoform (also known as tissue non-specific isoform or liver, kidney, or bone isoform) and calcium deposition, progressively assuming the morphology and phenotype of osteoblasts [73, 150, 151]. Osteogenic differentiation of MSCs implies multiple signaling pathways, which ultimately depends mostly on the action of the TF runt-related transcription factor 2 (RUNX-2) associated with other specific TFs such as Osterix/SP7 [152–154]. RUNX-2 acts to modify transcription in favor of bone-related gene expression and is regulated by upstream pathways, especially Wnt/β-catenin, HH, Notch and BMPs [142, 151, 155–157].

Other studies suggested that MSCs may also differentiate into endothelial progenitors and myoblasts as well as specialized cells beyond the mesoderm lineage, notably neuroblasts [158–160]. Such differentiation potential of MSCs remains not well substantiated, and findings of their signaling pathways are still lacking, especially if they are to be considered events of cell transdifferentiation [161].

The MSC multipotency function was long thought to be therapeutically practical for tissue regeneration with the adoptive transfer of MSCs to improve conditions in degenerative disorders [162]. Early initiatives evaluated the therapeutic effects of MSC adoptive transfer in patients with osteogenesis imperfecta (OI), a congenital disease with altered expression of collagen genes leading to skeletal malfunctions. Some results from preliminary clinical studies showed bone tissue reinforcements after adoptive transfer of MSCs in children with severe OI symptoms, including recovery of skeletal growth and strength [163]. However, MSCs in the host bone tissue accounted for less than 1% of the total MSCs given to these patients, which suggests that the multipotency function is probably not essential in ameliorating OI symptoms [163, 164]. Likewise, suggestions that MSCs could differentiate into neurons led some investigators to consider MSC therapy in patients with eye diseases such as glaucoma, macular degeneration and retinitis pigmentosa [165]. Preclinical studies have shown a certain therapeutic benefit of MSC adoptive transfer in improving conditions in experimental models of retina diseases [165, 166], yet evidence showing MSC engraftment into the retina has not been clearly established [166]. Similarly, clinical studies showing reduced symptoms of retinal degeneration in patients after MSC adoptive transfer [167–169] supported that the beneficial effects are not likely related to MSC engraftment and that the therapeutic effect results from a transient presence of MSCs into damaged tissue [170, 171]. Furthermore, amelioration of disease after MSC adoptive transfer has been substantiated in experimental models of acute kidney injury [172], cardiomyopathy [173], diabetes complications [174], and liver cirrhosis [175]. Yet again, any permanent engraftment of MSCs into these diseased tissues has not been verified, which suggests that the multipotency function does not likely explain the therapeutic ability of MSCs in degenerative diseases [164, 176]. Overall, both preclinical and clinical studies have provided indications supporting MSC therapy in degenerative diseases, but the mechanism leading to the observed therapeutic effects is considered solely executed via a brief "hit-and-run" mode of action of MSCs [17, 164, 177, 178].

By contrast, the multipotency function of MSCs may be exploited in tissue engineering for therapeutic needs in trauma and/or in malfunctioning or loss of an organ [179, 180]. Particularly, tissue engineering based on MSCs may be used in orthopedics to attempt to improve the formation of organs related to the skeletal system that are deficient [179]. Tissue engineering combining innovative biomaterials with MSCs offers interesting alternatives that allow for producing advanced prosthetics to align biological functionality and mechanical compliance [181]. MSCs seeded on 3-D

biomaterial scaffolds facilitate cell differentiation toward the formation of skeletal-related tissues [181, 182]. Hence, 3-D culture systems have been found to augment cell–cell interactions, favoring organized tissue formation while being compliant for transplantation [182, 183]. Biomimetic porous materials resembling the composition of bones, including hydroxyapatite and β-tricalcium phosphate, or biodegradable polymers such as polylactic acid, are regularly used as scaffolds for MSCs for tissue-engineering organs related to the skeletal system [183]. As well, pioneering research is focusing on advanced 3-D microfluidic bioprinting technologies based on MSCs and are currently being developed for clinical practice [184]. Tissue engineering using MSCs is rapidly evolving and is still in its infancy. Nonetheless, some clinical studies have shown therapeutic benefits with use of tissue engineering based on MSCs, remarkably in healing of femoral osteonecrosis [185] as well as for aiding the functional restoration of mandibles in severely atrophied mandibular defects [186].

Mesenchymal stem cell trophic function

MSCs are considered to regulate homeostasis within hematopoietic niches in vivo by supporting the maintenance, expansion and/or differentiation of HSCs. Also, MSCs may support the in vivo homeostasis of other progenitors [67, 179, 187, 188]. The MSC trophic function toward HSCs could be attributed to MSCs producing: (1) growth factors such as stem cell factor, platelet-derived growth factor, macrophage-colony stimulating factor (M-CSF), granulocyte-CSF (G-CSF), FMS-like tyrosine kinase-3 ligand, thrombopoietin, erythropoietin (EPO), angiopoietin 1 (Ang-1); (2) chemokines such as CXCL12, also known as stromal-derived factor 1, and CCL5, also known as regulated on activation normal T cell expressed and secreted (RANTES); (3) interleukins (ILs) including IL-3 and IL-6; and (4) extracellular matrix molecules such as hyaluronans [47, 189–191]. Hence, HSCs co-transplanted with MSCs enable HSC transplant success in vivo, which was revealed in a phase 1/2 clinical trial showing both amelioration of HSC engraftment in bone marrow and improvement in hematopoietic function recovery [192].

Beyond the ability to sustain homeostasis of HSCs and bone tissue, the MSC trophic function (Table 3) might be beneficial in favoring tissue healing and regeneration in different organs [47, 69]. To exemplify, Ang-1 and CXCL12 produced by MSCs have a significant impact on angiogenesis by recruiting adjacent endothelial progenitor cells in vivo [193, 194], whereas brain-derived neurotrophic factor (BDNF) or neurotrophin-3 (NT-3) released by MSCs acts on neural progenitors in the lesion area, thereby improving neurogenesis [195, 196]. Hence, the therapeutic effects of MSCs in preclinical models of neurodegenerative diseases were revealed particularly in amyotrophic lateral sclerosis (ALS), Huntington disease, multiple sclerosis, Parkinson disease, and spinal cord injury [197]. The benefits of MSC therapy are alleged to occur via neurotrophic factors produced by MSCs, such as BDNF, ciliary neurotrophic factor, glial cell-derived neurotrophic factor (GDNF), nerve growth

Table 3 Fundamental molecules of MSC trophic function

Growth factors	Biologic effect on progenitors	References
MSC trophic function		
Ang-1	Angiogenesis	Pedersen et al. [318], Kingham et al. [319]
EGF	Pleiotropic	Li et al. [320], Ding et al. [321]
EPO	Angiogenesis	Zwezdaryk et al. [322], Hu et al. [323]
FGF-1, -18	Pleiotropic	Wu et al. [324], Zhang et al. [325]
GDNF	Neurogenesis	Horita et al. [326], Ding et al. [327]
BDNF	Neurogenesis	Jeong et al. [328], Pollock et al. [195]
HGF	Pleiotropic	Neuss et al. [329], Kennelly et al. [220]
IGF-1	Neurogenesis	Zhang et al. [330], Tfilin et al. [331]
KGF	Epithelialization	Casey et al. [332], Zhu et al. [333]
PDGF-AB	Pleiotropic	Ding et al. [334], Osborne et al. [335]
SDF-1 (CXCL12)	Angiogenesis, neurogenesis	Mishra et al. [336], Lin et al. [200]
VEGF	Angiogenesis	Mayer et al. [337], Beckermann et al. [338]

The most critical molecules produced and secreted by MSCs for their trophic function. Data are summarized from references [195, 200, 220, 318–338]

Ang-1 angiopoietin-1, *EGF* epidermal growth factor, *EPO* erythropoietin, *FGF-1 or -18* fibroblast growth factor 1 or 18, *GDNF* glial cell line-derived neurotrophic factor, *BDNF* brain-derived neurotrophic factor, *HGF* hepatocyte growth factor, *IGF-1* insulin-like growth factor 1, *KGF* keratinocyte growth factor, *PDGF-AB* platelet-derived growth factor AB, *SDF-1* stromal cell-derived factor 1, *VEGF* vascular endothelial growth factor

factor, and NT-3 [196–202]. Furthermore, in experimental models of neurodegenerative diseases, MSC production of other growth factors including vascular endothelial growth factor (VEGF) acted synergistically with neurotrophic factors to improve conditions [197, 203]. Furthermore, in a clinical study of 37 patients with ALS, organ improvements were correlated with the paracrine actions of the neurotrophic factor BDNF and growth factors including VEGF [204]. Consistently, in a clinical trial of ten patients with secondary progressive MS treated with MSC adoptive transfer, the benefits were assessed by functional and physiological amelioration, including some visual endpoints that suggested neuroprotection [171].

The clinical use of culture-conditioned or genetically engineered MSCs with enhanced aptitude to produce neurotrophic factors has been considered to improve the efficacy of MSC therapy in neurodegenerative disorders [195, 197]. For instance, in a phase 1/2 clinical trial, investigators examined MSCs overexpressing neurotrophic factors (MSC-NTFs) induced by a culture stimulation method before adoptive transfer in patients with ALS [205]. The results suggested that intratracheal and intramuscular adoptive transfer of MSC-NTFs in patients with ALS is safe, with significant enhancement of clinical benefits, to be confirmed in an upcoming phase 3 clinical trial (ClinicalTrials.gov: NCT03280056).

The MSC trophic function has been assessed in experimental models of degenerative diseases affecting the kidney (acute kidney injury), liver (liver cirrhosis), or multiple organs (diabetes complications) [172, 206, 207]. Organ condition and/or function improvements with MSC therapy in those diseases are associated with MSC production of growth factors, notably hepatocyte growth factor (HGF), IGF-1, and sometimes growth factors related to angiogenesis and neurogenesis such as VEGF, EPO, and GDNF [208–212]. Likewise, in degenerative diseases affecting the heart such as myocardial infarction, preclinical and clinical findings support the therapeutic benefit via a paracrine action of various growth factors after MSC adoptive transfer, to improve heart condition and function [213–215]. Remarkably, often this amelioration is associated with neovascularization into damaged myocardium, which suggests a role for growth factors associated with angiogenesis in the therapeutic effect of MSCs [216–218]. Other investigators suggested a broader role for growth factors involved in myocardium remodeling, including IGF-1 and HGF, produced by MSCs [218]. Similarly, preclinical studies associated the beneficial therapeutic effects of MSCs in lung emphysema and chronic obstructive pulmonary disease (COPD) with production of HGF and VEGF by MSCs [219, 220]. Consistently, in phase 1 clinical trials, adoptive transfer of MSCs in patients with COPD facilitated functional recovery of respiratory capacities, and the therapeutic benefits of MSCs may involve trophic factors [221, 222]. Moreover, a clinical assay undertaken on a compassionate basis involving two patients with severe acute respiratory distress syndrome (ARDS) receiving MSC adoptive transfer reported some positive outcomes with recovery of respiratory capacities concomitant to a lessening in lung tissue damage [223]. Especially, the investigators suggested that the MSC mode of action in ARDS may involve at least in part the action of a number of growth factors, and a further phase 1/2 clinical trial is ongoing [223].

Mesenchymal stem cell homing/migration function

The MSC fate resulting from systemic adoptive transfer might occur with (1) passage/location in non-specific tissues, (2) homing into native niches or (3) migration into damaged and/or diseased tissues [224]. Whatever the MSC fate within a short time after systemic adoptive transfer, how and under which conditions MSCs might survive or be eliminated from the host is not well established [177, 225]. This situation has critical significance both in terms of pharmacokinetics and pharmacodynamics of a given MSC therapy [226, 227]. The MSC function of homing/migration (Table 4) has been documented in preclinical studies, but the actual biodistribution of MSCs after systemic adoptive transfer in humans is just being revealed [227, 228]. Of note, some preclinical studies gave clues to the prospective mode of action of MSC homing/migration including for chemotaxis, rolling/adhesion, diapedeses and interstitial migration [53, 55, 56, 58, 60–62, 229, 230]. After adoptive transfer, MSCs may move along blood vessels, pass through the endothelial wall, and home into niches where they naturally reside or further migrate into tissues that are damaged and/or diseased [231, 232]. The expression and functionality of adhesion molecules, chemokine receptors, and enzymes belonging to the molecular class of metalloproteinases (MMPs) are indispensable for enabling trafficking of MSCs from peripheral blood toward specific target organs [231, 233].

The interaction of MSCs with endothelial cells (ECs) requires adhesion molecules, most being integrins. However, recent findings indicate that MSCs show a deficit in expression and/or functionality of adhesion molecules implicated in homing/migration as compared with HSCs or leukocytes [234]. Hence, P-selectin (CD62P) glycoprotein ligand 1 (PSGL-1) is not found to be expressed on MSCs [59]. Yet, adhesion of MSCs onto microvasculature seems to remain fully dependent on a CD62P receptor expressed on ECs. Actually, MSCs interact with CD62P but via at least another glycoform ligand of CD62P that is dissimilar to the natural ligand PSGL-1 [59, 229]. In addition, firm adhesion of MSCs with ECs is mediated by integrins,

Table 4 Fundamental molecules of MSC homing/migration function

Molecule class	MSC homing/migration function	References
Adhesion molecules	CD44	Herrera et al. [339], Sackstein et al. [59]
	Integrin α1	Popov et al. [340]
	Integrin α3	Frith et al. [341]
	Integrin α4	Semon et al. [237]
	Integrin α5	Veevers-Lowe [342]
	Integrin β1	Semon et al. [237]
Chemokine receptors	CCR2	Ringe et al. [238]
	CCR7	Sordi et al. [61]
	CCR10	Von Lüttichau et al. [343]
	CXCR4	Ringe et al. [238], Baek et al. [344]
	CXCR5	Baek et al. [344]
	CXCR6	Baek et al. [344], Jung et al. [345]
Metalloproteinases	MT1-MMP	Lu et al. [346]
	MMP-1	Ho et al. [245]
	MMP-9	Kim et al. [246]
Protease inhibitors	TIMP-1	Egea et al. [347]
	TIMP-2	Ries et al. [244]
	TIMP-4	Chelluboina et al. [348]

The most critical molecules—adhesion molecules, chemokine receptors and metalloproteinases—involved in the MSC homing/migration function. Data are summarized from references [59, 61, 237, 238, 244–246, 339–348]

CD cluster of differentiation, *CCR* CC chemokine receptor, *CXCR* CXC chemokine receptor, *MMP* matrix metalloproteinase, *MT1-MMP* membrane type 1-MMP, *TIMP* tissue inhibitor of metalloproteinases

including heterodimeric integrin α4β1, also known as very late antigen-4 (VLA-4), which interacts with its receptor vascular cell adhesion molecule 1 (VCAM-1) expressed on ECs [229, 235–237]. Both CD62P and VCAM-1 expressed on ECs are required for MSCs in rolling/adhesion processes, which has been verified in vivo in preclinical studies [230, 231]. Similarly, MSCs showed a weak aptitude to interact with E-selectin (CD62E) [230]. CD62E is expressed constitutively by cells of blood vessels irrigating bone marrow and is expressed on any ECs when activated by inflammatory cytokines [230, 231]. Although MSCs express CD44, an adhesion molecule that interacts with selectins, CD44 on MSCs lack proper posttranslational glycosylation modifications, so it is unable to interact well with CD62E [59, 230, 235]. Especially cell homing into bone marrow requires the expression of a ligand to CD62L/CD62E, also known as hematopoietic cell E-/L-selectin ligand (HCELL), a competent glycoform of CD44, and although HSCs express HCELL, MSCs do not [59, 230]. Thus, modifying CD44 expressed on MSCs in vitro to enhance in vivo trafficking of MSCs to bone marrow has been considered [59, 230]. A preclinical study showed that converting the native CD44 glycoform on MSCs into molecules resembling HCELL using enzymatic glycosylation procedures could significantly improve MSC homing to bone marrow [59].

Chemokine receptors that are expressed variably on the cell surface of MSCs include CCR2, 3, 4, 7, 10, and CXCR4, 5, and 6 [238–240]. Notably, CXCR4 is an important molecule regulating homing/migration of HSCs and is likely involved in MSC homing/migration as well [240]. However, CXCR4 is expressed sporadically on the cell surface of MSCs as compared with HSCs [240]. Still, the expression of CXCR4 on MSCs could be upregulated with inflammatory cytokine stimulation such as tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β) [241, 242]. Moreover, MSCs with enhanced production of CXCR4 enabled by genetic engineering showed better homing/migration in vivo in preclinical studies [243].

The activity of proteolytic enzymes belonging to the molecular class of MMPs enables diapedeses and interstitial migration of MSCs toward tissues [231]. Notably, MMP-2 and its activator membrane type-1-MMP and tissue inhibitor of metalloproteinases 2 have been found critical for diapedesis of MSCs [244]. Other MMP pathways with various collagenase activities such as MMP-1, -3 and -9 were also found positively associated with MSC homing/migration [245, 246].

Research of the MSC homing/migration function has involved mostly preclinical models, but in certain aspects, some results agree with clinical findings, especially regarding the biodistribution of MSC post-adoptive transfer [192,

231, 234, 247]. Thus, modification of MSCs by biological manipulations with enzymatic procedures or genetic methods to reinforce MSC homing/migration is envisaged to improve MSC therapy [231, 234].

Considered routes for adoptive transfer of MSCs may be topical into damaged/diseased tissue or systemic into peripheral blood. In this context, preclinical studies compared the therapeutic effects of MSCs with topical or systemic delivery of MSCs [164, 225, 231]. When adoptive transfer of MSCs is topical, that is, by intra-articular, intracoronary, intramuscular, intrathecal, or intratracheal routes, the therapeutic effects of MSCs are expected to be exerted locally. Therefore, MSC homing/migration is rather less indispensable, except from essential interstitial migration of MSCs within damaged/diseased tissue itself [164]. If delivery of MSCs is systemic, using intravascular adoptive transfer via intraarterial or intravenous routes, MSC homing/migration is absolutely required for MSCs to reach their target [164, 231]. Of note, MSC homing/migration may be also affected by whether adoptive transfer of MSCs is by intra-arterial or intravenous means [164, 225, 231]. MSCs delivered via the intraarterial route may avoid the lung first-pass effect inherent to any intravenous injection that considerably reduces the pharmacodynamics of MSCs. After an adoptive transfer of MSCs via an intra-arterial route, MSC entrapment into the lung is virtually absent as compared with the intravenous route [248]. However, intra-arterial injection is a complex procedure that requires medical expertise and has health risks [248, 249]. Therefore, intravenous delivery of MSCs, despite its disadvantages, is regularly used in both preclinical and clinical settings.

Further investigations are needed to properly define MSC homing/migration in vivo in humans and to determine whether findings from preclinical studies could be valuable to enhance the efficacy of MSC therapy.

Mesenchymal stem cell immunosuppression function

MSCs expanded in vitro are rather hypoimmunogenic because they do not express HLA-class II molecules or costimulatory molecules including CD40, CD80, CD83, CD86 and CD154. Yet, MSCs express HLA-class I molecules, and MSCs stimulated with interferon γ (IFN-γ), IL-1β, and/or TNF-α showed upregulated HLA-class I molecules and promoted the expression of HLA-class II and adhesion molecules [14, 68, 250]. Under these conditions, MSCs remain unable to express costimulatory molecules, but the capacity for co-stimulation is critical for activating T lymphocytes [68, 250]. Counterintuitively, inflammation enhances the immunosuppression function of MSCs. Indeed, inflammation upregulates HLA-class II molecules on MSCs and thus their interaction abilities with T lymphocytes. The absence of costimulatory molecules on MSCs, despite the inflammatory signals, will result in suboptimal activation of T lymphocytes and clonal anergy [251–253]. Of note, MSCs do not induce allogeneic proliferation of T lymphocytes in vitro, even when HLA class II molecules are upregulated on MSCs and co-stimulatory signaling is delivered by an anti-CD28 monoclonal antibody [68]. This finding strongly suggests an active MSC immunosuppression function, whereas enhancement of this function would require a "licensing" signal delivered by inflammatory factors [14, 251]. Hence, some investigators attributed failures in MSC therapy to inappropriate "licensing" of the MSCs used, whereas others suggested optimizing MSC therapy with a preconditioning treatment, that is, a prior in vitro stimulation of MSCs with appropriate inflammatory factors, to obtain optimal therapeutic effects in vivo [254, 255].

The MSC immunosuppression function was interpreted mostly by preclinical studies, both in vitro and in vivo, but substantial results are also sustained in clinical findings [256]. MSCs suppress a broad range of immune cells, including T, B, and natural killer (NK) lymphocytes, and affect functions of myeloid cells such as monocytes, dendritic cells (DCs) and macrophages [68, 257–262]. MSCs modulate both innate and adaptive immune cells by disrupting their activation, proliferation, maturation, cytokine production, cytolytic activity, or antibody production [256]. Specifically, MSCs impede effector T-lymphocyte functions such as T helper 17 (Th17) cytokine production [263, 264] while favoring tolerogenic $CD4^+$ Th2 lymphocyte differentiation, at the expense of immunity mediated by $CD4^+$ Th1 lymphocytes [265]. Furthermore, MSCs obstruct B lymphocytes from further differentiating into plasma cells and impede their ability to secrete immunoglobulins [257]. MSCs inhibit the cytotoxic potential of NK lymphocytes as well as their ability to secrete INF-γ [258, 259]. Moreover, MSCs prevent the differentiation of $CD14^+$ monocytes and $CD34^+$ progenitors into mature DCs [266]. Also, MSCs can diminish the DC ability to express HLA-class II as well as CD80 and CD86 costimulatory molecules [260, 266]. Notably, MSCs promote the emergence and/or recruitment of regulatory/suppressive immune subsets, including $CD4^+CD25^+FOXP3^+$ T lymphocytes [258, 267], $CD8^+CD28^-$ T lymphocytes [268], IL-10-producing B lymphocytes [269], IL-10-producing DCs [270], and alternatively activated M2-macrophages [262, 271]. Such MSC abilities facilitate the amplification of their immunosuppression effects by reinforcing the host's own regulatory/immunosuppressive immune subsets [256].

The MSC immunosuppression function (Table 5) is mostly executed via production of soluble factors and their paracrine actions on immune cells. Direct cell–cell contacts between MSCs and immune cells are also involved,

Table 5 Fundamental molecules of MSC immunosuppression function

Molecule	Molecule class	MSC immunosuppression function	References
Soluble	Interleukins	IL-6	Najar et al. [349]
		IL-10	Beyth et al. [350], Rasmusson et al. [351]
		LIF	Nasef et al. [352]
		TGF-β	Sotiropoulo et al. [353], Patel et al. [354]
		TSG-6	Choi et al. [355]
	Enzymes	HO-1	Mougiakakos et al. [356]
		IDO	Francois et al. [357]
		iNOS	Ren et al. [358]
	Hormones	PGE2	Spaggiari et al. [259, 359]
	Others	Galectin-1	Gieseke et al. [360]
		HLA-G	Selmani et al. [258]
		Semaphorin-3A	Lepelletier et al. [361]
Membrane bound	Adhesion molecules	ICAM-1	Espagnolle et al. [362]
		VCAM-1	Yang et al. [363]
	B7-family members	B7-DC	Davies et al. [364]
		B7-H1	Tipnis et al. [365]
		B7-H4	Xue et al. [366]
	TNF-family members	FasL	Gu et al. [367]

The most critical soluble and membrane-bound molecules involved in the MSC immunosuppression function. Data are summarized from references [258, 259, 349–367]. Inducible nitric oxide synthase (iNOS) is shown in this table because it can be expressed in human MSCs but seems less active than indoleamine 2,3 dioxygenase (IDO) in the immunosuppression function of human MSCs [358]

IL interleukin, *TGF* transforming growth factor, *TSG-6* TNF-stimulated gene 6, *HO-1* heme oxygenase 1, *PGE2* prostaglandin E2, *HLA-G* human leucocyte antigen G, *ICAM-1* intercellular adhesion molecule 1, *VCAM-1* vascular cell adhesion molecular 1, *B7-DC* also known as programmed death-ligand 2, *B7-H1* also known as programmed death-ligand 1, *B7-H4* also known as V-set domain-containing T-cell activation inhibitor 1, *FasL* Fas ligand, *TNF* tumor necrosis factor

although seemingly occasional as compared with actions obtained by soluble factors [14, 256, 272]. MSCs produce and release various soluble factors that are accountable for the immunosuppression function; among them are a diverse class of molecules comprising ILs, such as IL-6, leukemia inhibitory factor, IL-10, TGF-β, and TNF-stimulated gene 6 (TSG-6) but also metabolic enzymes including heme oxygenase 1 (HO-1), indoleamine 2,3 dioxygenase (IDO), and inducible nitric oxide synthase (iNOS) as well as pleiotropic hormones such as prostaglandin E2 (PGE2) and other proteins such as galectin-1, non-classical HLA-class Ib HLA-G, and semaphorin-3A. Relating to membrane-bound molecules expressed on MSCs and implicated in their immunosuppressive function are immunoregulatory B7 family member proteins such as B7-H4, also known as V-set domain-containing T cell activation inhibitor 1; but also B7-H1 and B7-DC, also known as programmed death-ligand 1 (PD-L1) and PD-L2; and TNF family member protein fas ligand, also known as CD95L; as well as intercellular adhesion molecule 1, also known as CD54; and VCAM-1, also known as CD106 [4, 14, 66, 256, 272, 273]. Hence, MSCs are multiarmed for immunosuppression, which, therefore, validates an assessment of their therapeutic value in various immune disorders [256].

MSC therapy is used for immunomodulation mostly in immune rejection and autoimmunity, including conditions such as in HSC transplantation, solid organ transplantation, Crohn's disease (CD), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [256, 274]. Nevertheless, the mode of action of the MSC immunosuppression function in vivo is still not known in all aspects [2, 256]. Typically, in experimental models, the efficacy of MSC therapy is associated with the action of soluble factors such as IL-10, IDO, PGE2, TGF-β, TSG-6 and expansion of $CD4^{+}CD25^{+}FOXP3^{+}$ regulatory T cells [256]. The first translational attempts used MSCs for immunomodulation purposes, especially for severe GvHD in patients unresponsive to available treatments [66, 273, 275, 276]. The proof-of-concept was shown in a pilot study reporting the practicability of adoptive transfer of MSCs in a 9-year-old patient with acute GvHD grade IV [276]. Adoptive transfer of MSCs in this patient resulted in overall improvement of his condition, with outcomes observed within few days and

lasting for at least up to 1 year post-treatment [276]. Later, the investigators reported promising results for MSC therapy in a population of 55 patients with acute GvHD refractory to steroid treatments [275]. Notably, patients responded to MSCs with higher survival rate, which reached 52% at 2 years post-treatment, as compared with just 10% in control patients who did not receive MSCs [275]. Altogether, in this phase 2 clinical study, the authors interpreted their results positively and suggested that adoptive transfer of MSCs might be a suitable therapeutic approach in patients with acute GvHD [275]. Meanwhile, a phase 3 clinical trial (ClinicalTrials.gov: NCT00366145), explored an MSC product (Prochymal®) produced on an industrial scale by Osiris Therapeutics and tested for treatment of steroid-resistant GvHD in 240 patients [8]. However, the company reported non-positive outcomes for Prochymal®, with failure to ameliorate the clinical conditions of GvHD as compared with placebo [8]. This non-success was found to contrast with results observed in a clinical assay led by academic institutions, with use of adoptive transfer of MSCs from different donors and sources [8, 275, 276]. MSC product uncertainties including the quality of MSCs produced with industrial-scale methods and cryopreservation have been discussed as possible causes for the failure of Prochymal® [8]. However, an amended type of Prochymal, namely MSC-100-IV (Remestemcel-L®), produced by Mesoblast, has been tested in children with severe GvHD resistant to steroids in a clinical trial (ClinicalTrials.gov: NCT02336230). Early in 2018, data from a press release on this clinical trial described significant therapeutic benefits in pediatric steroid-resistant GvHD, with an overall response of up to 69% at day 28 after MSC therapy with Remestemcel-L® as compared with the protocol-defined control rate of 45% [2]. Furthermore, in solid organ transplantation, clinical assays to evaluate therapeutic efficacy of MSCs in acute allogeneic rejection in kidney transplantation and liver transplantation showed that MSC therapy combined with low-dose anticalcineurin reduced kidney or liver allograft pathology, with decreased rejection episodes [277–284]. Moreover, biological analyses in clinical studies have shown a link between observed therapeutic benefits and an increase in regulatory/suppressive subsets in peripheral blood, particularly $CD4^{+}CD25^{+}FOXP3^{+}$ regulatory T cells, which is consistent with most preclinical findings [277, 278, 280–284].

The benefits of MSC therapy have been evaluated in clinical studies for autoimmune diseases, including CD, RA, and SLE [285–293]. A phase-2 clinical trial aiming to assess both the safety and efficacy of adoptive transfer of MSCs for patients with luminal CD has been undertaken [288]. Promisingly, results showed that MSC therapy diminished both the CD Activity Index and CD Endoscopic Index of Severity in patients unresponsive to any available treatment [288]. Furthermore, an MSC product (Cx601) from Tigenix (Alofisel®) recently demonstrated long-term therapeutic efficacy in CD perianal fistula complications in 212 patients in a phase 3 clinical trial, with remission in 51.5% of patients given Cx601 versus 35.6% given placebo [292]. Similarly, in patients with RA, MSC therapy seems to be pertinent to modulate inflammation and ameliorate conditions of RA [290, 291]. A phase 1/2 clinical trial evaluated another MSC product (Cx611) from Tigenix: results showed a predisposition for therapeutic efficacy of Cx611 in patients with RA that needs further assessment [289]. In addition, a 5-year follow-up study of MSC therapy in 81 patients with severe SLE lacking other therapeutic options showed a remarkable alleviation of conditions with MSC therapy [293]. The survival rate was 84% ($n = 68/81$) after MSC therapy; 34% achieved long-term clinical remission with better outcomes than controls [293].

Conclusion

MSC identity is still being questioned, and practices in culture, cryopreservation and clinical use of MSCs require standardization, both in preclinical and clinical settings, because these unknowns certainly affect the functions of MSCs used in cell therapy. Here, we attempted to delineate MSC functions that are essential in therapeutic effects of MSCs, including (1) proliferation, (2) multipotency, (3) trophic ability, (4) homing/migration, (5) and immunosuppression. Each of these functions may alone and/or when combined remain essential to the therapeutic ability of MSCs for various diseases.

MSC proliferation function (Table 1) is vital for MSC therapy, because the number of MSCs obtainable after isolation from biological sources is scarce, but an elevated number of MSCs is often required in clinical settings. Typically, a dose for MSC therapy represents about $1–10 \times 10^{6}$ MSCs/kg body weight [162]. The ability of MSCs to expand vigorously in vitro to yield a significant number of MSCs is critical to ease the development of MSC therapy. Thus, considerable efforts are made both in academia and industry to better address MSC proliferation function to improve their production while preserving the safety and therapeutic potency of MSC products [162].

Furthermore, permanent engraftment of MSCs into diseased tissues does not seem to occur, so the multipotency function of MSCs is not likely involved in the therapeutic ability of MSCs in degenerative diseases [164, 176]. Although current research has provided indications supporting MSC therapy in degenerative diseases, the modes of actions are considered to occur by a brief "hit-and-run" mechanism via the MSC trophic function and/or immunosuppression function [17, 164, 177, 178, 294]. However, the multipotency function of MSCs (Table 2) is of particular

interest in tissue engineering for rebuilding organs to correct malfunctioning or replace lost organs following disease or trauma, especially in orthopedics [179, 180].

By contrast, the MSC trophic function appears to have a critical role in mediating the beneficial effect of MSC therapy for degenerative and/or inflammatory diseases and is currently a matter of intensive research [47, 125, 190]. Furthermore, the MSC production of trophic factors (Table 3) at lesions close to tissue damage in degenerative diseases could be enforced via a paracrine action targeted to specific tissue-resident progenitor cells and/or parenchymal cells by enhancing their own ability to metabolize, proliferate, differentiate and/or migrate, thus limiting further tissue damage [47, 69, 179].

To allow MSCs to exert their therapeutic effects after systemic adoptive transfer, the MSC homing/migration function (Table 4) is absolutely required. The MSC function of homing has been envisaged as comparable to the HSC ability to home into bone marrow after the adoptive transfer of HSCs into peripheral blood [54, 57, 224, 228, 231]. MSCs may also migrate into damaged and/or diseased tissues, where allegedly they can deploy their therapeutic effects [224, 228, 231]. The migration function of MSCs has been considered to have similarities to the migration function of leukocytes in diseases but, in contrast to leukocytes, MSCs migrate for a longer time, with specific modes of action [224, 228, 231]. Here, we considered together the function of homing/migration of MSCs because the fate of homing or migration of MSCs is solely determined by in vivo pathophysiological conditions [231, 295]. MSC homing/migration is required in therapeutics but is not sufficient to ensure that MSCs would reach damaged and/or diseased organs. Indeed, administration routes for adoptive transfer of MSCs may also significantly affect MSC homing/migration abilities [164]. Hence, selection of MSC delivery routes is critical because it ultimately affects the pharmacokinetics and pharmacodynamics of a given MSC therapy [164, 225, 231].

Most importantly, the MSC immunosuppression function (Table 5) is thought to mediate most of the therapeutic effects in the treatment of severe inflammatory diseases with limited medical options, including GvHD, immune rejection in allogeneic solid organ transplantation, sepsis, ARDS, CD, RA, and SLE [10, 69, 256, 258, 272, 273]. Significantly, the immunosuppression function of MSCs currently serves in functional in vitro assay approaches as release criterion for MSC products intended for clinical use [9]. The ISCT has proposed novel guidance for therapeutic potency assessment of MSCs intended for clinical release on the basis of their immunosuppression function in vitro [1, 10, 115, 125]. The recommendation is motivated by the need to improve consistency and effectiveness of MSC therapy and is based on the assumption that ensuring in vitro robustness of the immunosuppression function of MSCs would be associated with the therapeutic effect in vivo [2, 8–11]. Thus, use of easy-to-implement in vitro potency assays imply co-culture of MSCs with activated peripheral blood leukocytes in conditions under which lymphocyte proliferation inhibition is measurable concurrent with the secretome and transcriptome dynamic response of MSCs [223]. These in vitro immunopotency assay matrices are now being developed and the first clinical results seem relevant to help define release criterion for MSC products, with anticipation to bring more stringent consistency in MSC therapy [2, 10].

However, the biological functions of MSCs might remain incompletely defined. Indeed, the trophic function and the immunosuppression function could be associated with their function to modulate uncontrolled cell death occurring during diseases [6, 187, 296–302]. Therefore, further investigations are needed to understand the biological functions of MSCs, to improve and facilitate the use of MSC therapy in the clinic.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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