Adv Exp Med Biol – Cell Biology and Translational Medicine (2018) 2: 115–141
https://doi.org/10.1007/5584_2018_213

Published online: 17 May 2018

Regenerative Medicine Applications of Mesenchymal Stem Cells

Samaneh Hosseini, Leila Taghiyar, Fatemeh Safari, and Mohamadreza Baghaban Eslaminejad

Abstract

A major research challenge is to develop therapeutics that assist with healing damaged tissues and organs because the human body has limited ability to restore the majority of these tissues and organs to their original state. Tissue engineering (TE) and regenerative medicine (RM) promises to offer efficient therapeutic biological strategies that use mesenchymal stem cells (MSCs). MSCs possess the capability for self-renewal, multilineage differentiation, and immunomodulatory properties that make them attractive for clinical applications. They have been extensively investigated in numerous preclinical and clinical settings in an attempt to overcome their challenges and promote tissue regeneration and repair. This review explores the exciting opportunities afforded by MSCs, their desirable properties as cellular therapeutics in RM, and implicates their potential use in clinical practice. Here, we attempt to identify challenges and issues that determine the clinical efficacy of MSCs as treatment for skeletal and non-skeletal tissues.

Keywords

Mesenchymal stem cells · Regenerative medicine · Clinical setting · Skeletal tissues · Non-skeletal tissues

Abbreviations

AKI	Acute kidney injury
ALS	Amyotrophic lateral sclerosis
ABGs	Autologous bone grafts
ACI	Autologous chondrocyte implantation
BM	Bone marrow
BMMC	Bone marrow mononuclear cells
BMT	Bone marrow transplantation
CPCs	Cardiac progenitor cells
CCR	C-C chemokine receptor type
CKD	Chronic kidney disease
CXCR	C-X-C chemokine receptor type
DCM	Dilated cardiomyopathy
DMD	Duchenne muscular dystrophy
ESCs	Embryonic stem cells
EPCs	Endothelial progenitor cells
ECM	Extracellular matrix

S. Hosseini, L. Taghiyar,
and M. Baghaban Eslaminejad (✉)
Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
e-mail: eslami@royaninstitute.org

F. Safari
Bone Biology & Orthopaedic Research, Department for BioMedical Research, University of Bern, Bern, Switzerland

FTSW	Full-thickness skin wounds
GVHD	Graft versus host disease
GFP	Green fluorescence protein
HF	Heart failure
HCELL	Hematopoietic cell E-/L-selectin ligand
HGF	Hepatocyte growth factor
hAD-MSCs	human adipose derived-MSCs
HA	Hydroxyapatite
iPSCs	induced pluripotent stem cells
IGF-1	Insulin-like growth factor 1
ISCT	International Society for Cellular Therapy
IA	Intra-arterial
IC	Intracoronary
IV	Intravenous
MHC	Major histocompatibility complex
MSCs	Mesenchymal stem cells
MMPs	Metalloproteinases
MSC-CM	MSCs-conditioned medium
MS	Multiple sclerosis
MI	Myocardial infarction
NIH	National Institute of Health
NYHA	New York Heart Association
NO	Nitric oxide
OA	Osteoarthritis
OI	Osteogenesis imperfecta
PDGF	Platelet-derived growth factor
PSCs	Pluripotent stem cells
PCL	Poly-ε-caprolactone
ciPTEC	Proximal tubule epithelial cells
RM	Regenerative medicine
SCs	Satellite cells
SECs	Sinusoidal endothelial cells
SDF-1	Stromal derived factor-1
TA	Tibialis anterior
TE	Tissue engineering
TGF-β	Transforming growth factor-beta
UC	Umbilical cord
VCAM-1	Vascular cell adhesion molecule 1
VEGF	Vascular endothelial growth factor

1 Introduction

Damaged or lost organs, diseased and injured tissues, and tumor resections present urgent circumstances that necessitate the use of therapeutic approaches. The clinical strategies for treatment of tissues and organs to restore them to fully functional structures are basically classified into three main categories – drug therapy; surgery (autograft and allograft); and novel therapeutic approaches such as gene therapy, cell therapy, and tissue engineering (TE). The complicated healing process in most diseases, requires the simultaneous use of two or more approaches to achieve desired outcomes. Drug therapy, a traditional approach for all disease types, is normally used as a co-treatment with other strategies. For example, administration of immunosuppressive drugs following organ/tissue engraftment (e. g., kidneys, lungs, skin, or liver transplant) is necessary throughout the patient's life (van Gelder et al. 2014). In some cases, drug therapy merely results in a promising outcome. Pharmacologics that target mitochondrial-associated protein kinase C and its substrates, such as aldehyde dehydrogenase 2, reduce ischemic damage and induce cardioprotection (Chen et al. 2008). Advances in nanotechnology, bioinformatics, and biology have increased novel drug designs and delivery systems for effective drug therapy; however, additional attempts are needed to address diseases and chronic conditions such as spinal cord and brain injuries.

Surgery is a second approach that attempts to revive and repair damaged tissues. Surgeons frequently perform tissue reconstruction in cases of tumor resection, trauma injuries, and allotransplantations. For example, autologous bone grafts (ABGs) are the current gold-standard for repair and reconstruction of critical-sized bone defects (Roberts and Rosenbaum 2012). Annually, more than 2 million bone grafts are used in orthopedic procedures worldwide in both adolescents and adults (Blank et al. 2017). Although surgical

approaches are being adapted for skeletal tissues (bone and cartilage), the benefits must be carefully weighed against the risks that include lifelong immunosuppressive therapy. In addition, despite the increased success rates of surgical repair and reconstruction of injured tissue along with technological advances and improved modern surgical tools, repair of some injured non-skeletal tissues (brain, kidneys, and liver) remain challenging.

Limitations with traditional therapeutic approaches have urged scientists to develop novel, effortless, efficient strategies for tissue regeneration. Recently, a new branch of medicine, regenerative medicine (RM), has emerged with the intent to restore normal function of damaged tissues and organs by stimulation of endogenous repair processes. RM may use progenitor cells, stem cells, or therapeutic agents such as genes and trophic factors. Among these, extensive attention has focused on stem cells. Stem cells have greatly improved the disciplines of TE, gene therapy, developmental biology, cell therapy, and nanotechnology. The presence of regenerative cells was first hypothesized in the late nineteenth century by Cohnheim (1867). Currently, we know that most adult tissues possess progenitor and stem cells that are employed to repair minor tissue lesions. Stem cells deliver multiple agents in contrast to the single agent delivery of pharmaceutical drugs. They have the ability to respond to local micro-environmental clues or signals by secretion of bioactive factors. Stem cells can be engaged by gene therapy and material science to revolutionize the regenerative potential of each approach (Taghiyar et al. 2017). Insertion of a relevant gene sequence into a target cell and seeding the cells onto an appropriate natural or artificial material may result in the desired biological effect. The regenerative potency of stem cells, particularly mesenchymal stem cells (MSCs), is taken into consideration in this review. We discuss the numerous basic, translational and clinical studies in skeletal and non-skeletal tissues in an attempt to address current advancements and challenges of MSCs used for clinical applications.

2 Stem Cells and Regenerative Medicine (RM)

Cellular therapy has shown great progress in both preclinical research and the clinical setting. The initial cell transplantation attempts involved intravenous (IV) transfusion of whole blood (Giangrande 2000). Cell therapy, particularly stem cell therapy, was predominantly confined to bone marrow (BM) transplantation for hematological diseases as well as epidermis transplantation for massive burns (Atiyeh and Costagliola 2007). Today, various stem cell sources of adult and pluripotent stem cells (PSCs) such as embryonic stem cells (ESCs) and induced PSCs (iPSCs) have been introduced for tissue repair. Adult stem cells can only differentiate into a limited number of cell types, whereas ESCs and artificially generated iPSCs develop into all three germ layers and are referred to as PSCs (Hosseini and Baghaban Eslaminejad 2017). ESCs derived from the inner-cell mass of the blastocyst provide potent cell sources for clinical applications (Thomson et al. 1998). Pluripotency and the ability for self-renewal make ESCs appropriate for treatment of diseases whereas adult stem cells or progenitor cells have not been clearly identified or are difficult to expand in culture. However, ethical issues exist with harvesting the cells from embryos. In addition, the possibility exists for immunogenicity and tumorigenicity, both of which have delayed clinical translation of ESC research. iPSCs preserve the pluripotency and self-renewal ability of ESCs, yet overcome the ethical concerns associated with ESCs. They can be maintained in culture where they self-renew indefinitely and produce an infinite number of progeny (Takahashi and Yamanaka 2006). Autologous cells can be served even from patients with specific mutations to create iPSCs (Wiley et al. 2015). Kawamata's group evaluated the safety and regenerative capacity of iPSCs in preclinical setting and performed the first clinical trial for treatment of age-related macular degeneration (Kanemura et al. 2014; Souied et al. 2017). Nevertheless, the tumorigenicity risk remains unsolved.

MSCs, a promising cell source, can be harvested from various sources such as BM, adipose tissue, umbilical cord (UC), and dental tissues (Baghaban Eslaminejad et al. 2011; Eslaminejad et al. 2010). MSCs have been studied in clinical trials and there is accumulating evidence regarding their robust potential to treat numerous diseases (Tables 1 and 2). By June 15, 2015, there were 493 MSC-based clinical trials for a wide range of therapeutic applications. Despite clinical success in MSC cell therapy, the long-term safety of MSC-based therapies is poorly established (phase III clinical trials) and continues to pose a major limitation to translating MSCs into clinical practice. Of note, the majority of cell therapy clinical trials have used non-ESCs (postnatal stem cells that included cord blood and MSCs) that were isolated from patients or donor tissues. Most were phase I and phase II, or a mixture of phase I/II studies to explore the safety and efficacy of stem cells in human being. Only a small number were phase III or phase II/III trials.

3 Properties of Mesenchymal Stem Cell (MSC) Related to Their Therapeutic Effects in Regenerative Medicine (RM)

The biological properties of MSCs were unknown when initially isolated from BM by Friedenstein et al. in 1970 (Friedenstein et al. 1970). Numerous attempts have been made to isolate MSCs from various sources to determine their molecular and cellular properties. Understanding the biological characteristics of MSCs would provide clear insight for their prospective clinical applications. In 2006, the International Society for Cellular Therapy (ISCT) defined MSCs on the basis of the following criteria: adherence to plastic substrate under standard tissue culture conditions; ability to express cell surface markers CD73, CD90, and CD105; do not express CD45, CD34, CD14, or CD11b, CD79 alpha or CD19 and HLA-DR surface molecules; and have the capability to differentiate into osteoblast, adipocyte, and chondroblast lineages under external stimuli (Dominici et al. 2006).

Currently, four paramount features of MSCs make them promising for RM, including their self-renewal and multi-lineage differentiation potential. In addition, intravenously injected MSCs have the capability to migrate and home to the sites of injury in response to inflammatory factors. They exert anti-inflammatory effects through secretion of multiple bioactive molecules, which in turn stimulates the recovery of injured cells. Finally, MSCs lack immunogenicity and exhibit immunomodulatory properties (Fig. 1). Here, we provide a brief description of each property.

3.1 Differentiation Potential

The multi-lineage differentiation capability of MSCs has been extensively studied in vitro and in vivo (Nadri et al. 2013a, b). MSCs have the potential to give rise to myogenic, adipogenic, osteogenic, and chondrogenic mesodermal lineages (Galli et al. 2014). It has also reported that MSCs can commit to ectodermal and endodermal cell fates. Our group succeeded in differentiation of MSCs to photoreceptor cells on nanofibrous scaffolds (Nadri et al. 2013a, b). Kopen et al., for the first time, have demonstrated the ability of MSCs to commit to astrocytes and neuron-like cells after they were injected into the central nervous systems of newborn mice (Kopen et al. 1999). In a clinical study, human MSCs (hMSCs) were transplanted into the spinal cord of amyotrophic lateral sclerosis (ALS) patients. This study showed that transplantation of hMSCs were safe and well-tolerated by ALS patients (Mazzini et al. 2003). Recently, several research groups used MSCs in combination with nanomaterials as a promising therapeutic strategy for skin TE both in vitro and in the clinical setting. Wu et al. injected green fluorescence protein (GFP^+) allogeneic BM-derived MSCs (BM-MSCs) around a wound in normal and diabetic mice. They observed significantly enhanced wound healing in both experimental groups compared to control mice (Wu et al. 2007). Another study used biomimetic nanofiber scaffolds (NFSs) seeded with BM-MSCs to treat acute

Table 1 Clinical trials related to mesenchymal stem cell (MSC)-based therapy of skeletal tissues

No.	Disease	Type of cells	Type of injection	Result	References
1	Limb ischemia	AD-MSCs	Multiple intramuscular	At 6 months, a significant improvement was observed in pain rating scales and claudication walking distance. Numerous vascular collateral networks was formed across affected arteries as evidenced by digital subtraction angiography 6 months post MSC implantation.	Lee et al. (2012)
2	Femoral head osteonecrosis	AD-MSCs	Local	The results showed the long-term reduction in hip pain and improvement in MRI scan.	Pak (2012)
3	Long bone non-union	BM-MSCs	Local	The results confirmed the safety of MSC implantation combined with platelet lysate during 12 months and bony union had occurred in four patients.	Labibzadeh et al. (2016)
4	Femoral head osteonecrosis	BM-MSCs	Implantation	Increased Harris hip score along with the reduced volume of the necrotic lesion was observed in group treated by BMMSC.	Zhao et al. (2012)
5	Femoral head osteonecrosis	BM-MSCs	Perfusion via medial circumflex femoral artery	92.31% of hips showed a satisfactory clinical outcome. Only 6 hips (7.69%) progressed to clinical failure.	Mao et al. (2013)
6	OA	AD-MSCs	Intra-articular	An improved knee function and reduced knee pain was observed in cell treated groups particularly high-dose group.	Jo et al. (2017)
7	OA	AD-MSCs	Intra-articular	During 2 years follow-up, none of the patients underwent total knee arthroplasty. But 87.5 % of elderly patients (14/16) improved or maintained cartilage status at least 2 years postoperatively	Koh et al. (2015)
8	OA	BM-MSCs	Intra-articular	Therapeutic benefits such as increased walking distance and decreased visual analog scale (VAS) with no evidence of tumor or neoplastic changes in the patients observed during the 30-month follow-up.	Emadedin et al. (2015)
9	OA	AD-MSCs	Intra-articular	All clinical outcome parameters that include pain, function, and mobility were improved, particularly in low-dose AD-MSCs. Four patients experienced transient knee joint pain and swelling after local injection	Pers et al. (2016)
10	OA	BM-MSCs	Intra-articular	No local or systemic adverse events detected after 1 year. MRI confirmed an increase in cartilage thickness. Pain, knee function, and walking distance were getting improved up to 6 months post-injection.	Emadedin et al. (2012)
11	OA	AD-MSCs	Intra-articular	AD-MSCs treated group showed significant improvement in four clinical scores. Radiography showed neither improvement, no further joint degeneration.	Spasovski et al. (2018)
12	Osteoarthritic knees	BM-MSCs	Intra-articular	MRI revealed better Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scores in the patients received BM-MSCs.	Wong et al. (2013)
13	Osteogenesis imperfecta (OI)	BM-MSCs	Transplantation	Total body bone mineral content of all cell-recipient patients increased. And frequencies of bone fracture. Reduced.	Horwitz et al. (1999)

Table 2 Clinical trials related to mesenchymal stem cell (MSC) based therapy of non-skeletal tissues

No.	Disease	Type of cells	Type of injection	Result	References
1	Grade II to IV graft-versus-host disease (GVHD)	BM-MSCs	Intravenous	86 adverse events and serious adverse events most of which (72.1%) were of infectious nature are reported. Overall survival at 1 and 2 years from the first MSC administration was 50.0% and 38.6%, with a median survival time of 1.1 years.	Introna et al. (2014)
2	Chronic GVHD (cGVHD)	BM-MSCs	Infusion	Patients experienced no adverse effects post MSC infusion. The 2-year survival rate was 77.7%. Clinical improvement was accompanied by the increasing ratio of CD5+CD19+/CD5-CD19+ B cells and CD8+CD28-/CD8+CD28+ T cells.	Weng et al. (2010)
3	Myocardiopathy	UC-MSCs	Left ventricular	Patients treated with UC-MSCs showed improvements in left ventricular function, functional status, and quality of life.	Bartolucci et al. (2017)
4	Autosomal dominant polycystic kidney disease (ADPKD)	BM-MSCs	Cubital vein	No adverse and serious adverse events observed in cell- treated patients and the mean serum creatinine level increased after a 12-month follow-up.	Makhlough et al. (2017)
5	Acute-on-chronic liver failure (ACLF)	UC-MSC	Intravenously through the cubital vein of the arm	The UC-MSC treatment resulted in increased survival rates in ACLF patients; and reduced the end-stage liver disease scores. Liver function was improved as indicated by increased serum albumin, cholinesterase, and prothrombin activity; and increased platelet counts. Serum total bilirubin and alanine aminotransferase levels were significantly decreased in the UC-MSC group.	Shi et al. (2012)
6	Decompensated hepatitis B cirrhosis	hUC-MSCs	Intravenous infusion	The results indicated significant reductions in the serum levels of inflammatory cytokines (IL-6 and TNFα) while the level of immunosuppressive cytokines (IL-10 and TGFβ) increased. Moreover, percentages of T4 cells and Treg cells were increased and T8 cells and B significantly reduced.	Fang et al. (2016)
7	Spinal cord injury (SCI)	AD-MSCs	Intrathecal	There was no sign of tumorous conditions or calcification as evidenced by MRI. Motor recovery was observed in 5 patients at 8 months follow-up. Voluntary anal contraction improvement was seen in 2 patients. ASIA sensory score recovery was seen in 10, although degeneration was seen in one. In somatosensory evoked potential test, one patient showed median nerve improvement.	Hur et al. (2016)
8	Spinal cord injury (SCI)	BM-MSCs	Direct injection into lesion sites	It confirmed the safety of allogenic hMSCs in patients with SCI, however, it might not be efficacious; especially in patients with chronic SCI.	Bhanot et al. (2011)

(continued)

Table 2 (continued)

No.	Disease	Type of cells	Type of injection	Result	References
9	Spinal cord injury (SCI)	BM-MSCs	Direct injection into lesion sites	Total of 75% patients improved with grade A SCI, three with grade B injury and eight patients (100%) with grade C injury, 1 month post transplantation.	Jiang et al. (2013)
10	Secondary progressive multiple sclerosis (SPMS)	BM-MSCs	Intravenous infusion	No serious adverse events were detected. An increase in optic nerve area was observed after treatment in visual acuity. They found no substantial effects on color vision, visual fields, macular volume, retinal nerve fiber layer thickness, or optic nerve magnetization transfer ratio. Bacterial infection was observed in 20% of patients.	Connick et al. (2012)
11	Multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS)	BM-MSCs	Intrathecal and intravenous	MRI of the brain and whole spine did not reveal any significant unexpected pathology and confirmed the existence of MSCs in the occipital horns of the ventricles. Immunological analysis showed a 72% increase in the proportion of $CD4^+$ $CD25^+$ regulatory T cells and a reduction in expression of $CD40^+$, $CD83^+$, $CD86^+$, and HLA-DR on myeloid dendritic cells.	Karussis et al. (2010)
12	Severe emphysema	BM-MSCs	Intravenous	There was no evidence of induction of fibrotic responses in the lung by MSCs. Expression of the endothelial cell marker CD31 in the alveolar septa of emphysematous lung tissue increased after lung volume reduction surgery (LVRS) and MSC infusions.	Stolk et al. (2016)
13	Idiopathic pulmonary fibrosis (IPF)	BM-MSCs	Infusion	The results confirmed the safety of a single infusion of hMSCs in patients with mild-moderate IPF.	Glassberg et al. (2017)
14	Acute respiratory distress syndrome (ARDS)	BM-MSCs	Infusion	The safety of a single dose of allogeneic BM-MSCs in patients with moderate-to-severe ARDS was observed.	Wilson et al. (2015)

full-thickness skin wounds (FTSW) in a rat model. This construct resulted in epithelialization and normal skin formation with hair follicles and sebaceous glands, as well as collagen deposition over 10 days (Ma et al. 2011). Regarding the differentiation potential of MSCs to endodermal lineages, it has been shown that hBM-MSCs and human adipose derived-MSCs (hAD-MSCs) have the ability to transdifferentiate into lung epithelial cells (Mendez et al. 2014). Likewise, MSCs that were systemically injected into C57BL/6 mice after a radiation-induced injury immediately gave rise to functional (epithelial and endothelial) lung cells (Yan et al. 2007). Various in vivo and in vitro experiments reported similar findings (Wang et al. 2018). Transplantation of BM-MSCs into chimeric mice that expressed GFP with ischemically injured renal tubules resulted in differentiation toward renal tubular epidermal cells (Duffield et al. 2005). Although there has been an increase in the therapeutic use of MSCs, direct differentiation and paracrine effects of MSCs used to treat diseases are completely unknown.

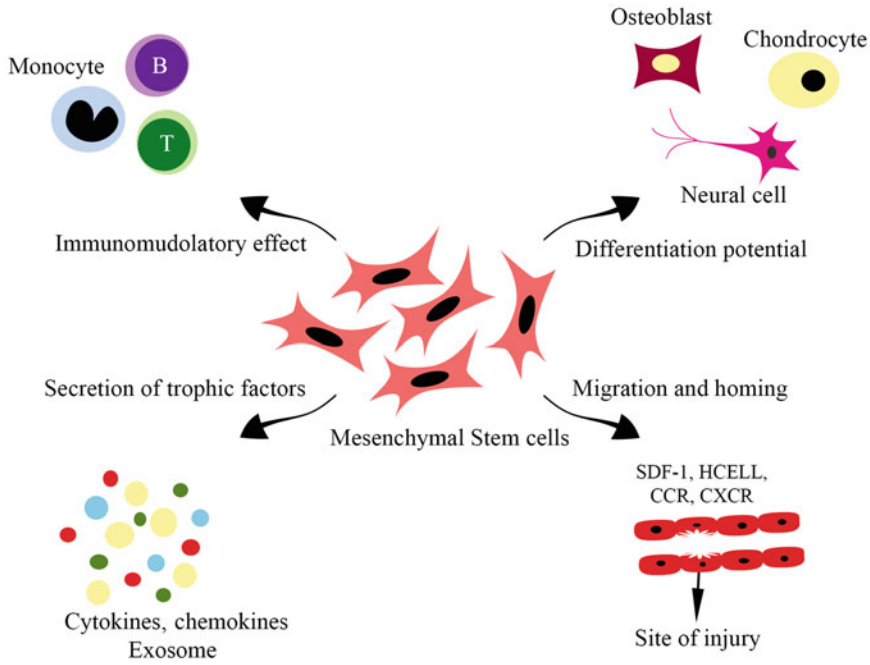

Fig. 1 The paramount features of MSCs related to their therapeutic effects in regenerative medicine (RM) including their multi-lineage differentiation potential, homing and migration capacity, secretion of trophic factors and immunomodulatory effects

3.2 Migration and Homing Capacity

MSCs are therapeutically capable of homing to inflammation sites via systemic infusion routes, such as IV infusions, intra-arterial (IA) injections, and intracoronary (IC) local administration. They exert their functional effects locally in the resident tissue. Regardless of the tissue, MSCs migrate to the injury sites under a variety of pathologic conditions. Ortiz et al. have shown that MSCs attenuated inflammation in lung tissues of bleomycin-challenged mice following homing to the lung in response to an injury (Ortiz et al. 2003). Similarly, transplanted MSCs migrated towards injured muscle tissues in mdx mice (Liu et al. 2007). Agematsu et al. conducted a study to address the origin of MSCs following allogeneic BM transplantation (BMT). They demonstrated that stromal fibroblasts cells in long-term cultures originated from the recipients as evidenced by in situ hybridization using a Y-chromosome specific cDNA probe (PHY10) (Agematsu and Nakahori 1991). However, the number of MSCs in injection site differed in various systemic infusions. Various in vitro and in vivo studies have reported that MSC selectively migrate to the injured site by mediation of numerous cytokines such as receptor tyrosine kinase-dependent growth factors [e.g., platelet-derived growth factor (PDGF) and insulin-like growth factor 1 (IGF-1)] and chemokines (e.g., CCR2, CCR3, CCR4 or CCL5) (Ponte et al. 2007). These homing signals are secreted by injured cells and/or respondent immune cells. Baek et al. have reported that C-C chemokine receptor type 1 (CCR1), CCR7, C-X-C chemokine receptor type 4 (CXCR4), CXCR5, CXCR6, EGF receptor, fibroblast growth factor receptor 1, transforming growth factor-beta (TGF-β) receptor 2, TNF receptor superfamily member 1A, PDGF receptor A, and PDGF receptor B regulate the migration capacity of hAD-MSCs (Baek et al. 2011). Besides these homing signals, other molecules are implicated in different steps of the homing process. For example, CXCR4-stromal derived factor-1 (SDF-1) is of crucial

importance for BM homing (Wynn et al. 2004). Hematopoietic cell E-/L-selectin ligand (HCELL), a specialized glycoform of CD44, is involved in cell migration (Sackstein 2011). G-protein coupled receptors, integrins as adherent molecules such as integrin β1 and integrin α4, which interact with vascular cell adhesion molecule 1 (VCAM-1) are functionally involved in MSC homing. Since efficient cell delivery is the major challenge in RM, the presence of these factors would be a promising strategy to facilitate therapeutic delivery of MSCs and target the injured tissue. Yun et al. showed that prostaglandin E_2 (PGE_2) stimulation facilitated MSCs migration to the injured tissue (Yun et al. 2011) .

3.3 Secreting Multiple Bioactive Molecules

Therapeutic applications of MSCs are associated with direct differentiation of MSCs at the injury site and largely related to an indirect capacity in suppressing immune and inflammatory reactions, activation of normal tissue repair processes, fibrosis and apoptosis inhibition, and enhancement of angiogenesis. MSCs exert these roles by secretion of trophic factors – a variety of paracrine and autocrine factors as well as extracellular vesicles such as exosomes and microvesicles. Various studies have demonstrated that cytokines secreted by MSCs contributed to functional improvement of an infarcted heart (Timmers et al. 2011), spinal cord injury (Cantinieaux et al. 2013), and ischemic limb regeneration (Bhang et al. 2014) models. Ulivi et al. reported that MSCs turned the pro-inflammatory phenotype of macrophages into a phenotype with the ability to inhibit production of inflammatory cytokines (Ulivi et al. 2014). Moghadasali et al. showed the MSCs-conditioned medium (MSC-CM) recovered cell viability and migration of human proximal tubule epithelial cells (ciPTEC) after drug-induced nephrotoxicity (Moghadasali et al. 2013). Systemic infusion of MSCs-CM reduced the expression levels of pro-inflammatory cytokines, which resulted in enhanced survival of hepatocytes and sinusoidal endothelial cells (SECs) in reduced-size liver transplantation (RSLT) in a rat model. (Du et al. 2013). A comprehensive expression profile of BM-MSCs that used an antibody array revealed 120 cytokines and chemokines with 6 highly secreted cytokines (IL-6, IL-8, TIMP-2, MCP-1, VEGF, and OPG) (Park et al. 2009). However, the functional roles of these cytokines have yet to be determined.

3.4 Immunomodulatory Functions of Mesenchymal Stem Cells (MSCs)

The immunosuppressive feature of MSCs was first reported in the early 2000s (Bartholomew et al. 2002). Since then, MSCs have attracted great attention for therapeutic applications. Liechty et al. designed a xenogeneic system to address the fate of MSCs after cell injection/transplantation. They transplanted hBM-MSCs into fetal sheep in the early phase of pregnancy and observed that hBM-MSCs gave rise to multiple tissues (cartilage, heart, adipose tissue, muscle, BM, and thymic stroma). MSCs existed in a xenogeneic environment due to unique immunologic characteristics along with preservation of their multipotential capacity post-transplantation (Liechty et al. 2000). Various studies have shown that MSCs have the ability to affect almost all cells of both the innate and adaptive immune systems and induce an anti-inflammatory phenotype. MSCs modulate the immune response by soluble factors (e.g., IL-6, M-CSF, IL-10, TGF-β, HGF, and PGE2) and cell-cell contact (Xu et al. 2007). Adhesion molecules that include VCAM-1, ICAM-1, and LFA-3 are involved in T-cell interaction and play an important role in MSC-mediated immunosuppression (Xu et al. 2007). Nicola et al. have shown that co-culture of BM-MSCs and T cells led to a significant, dose-dependent reduction of T-cell proliferation (Di Nicola et al. 2002). Apparently, MSCs suppress subpopulations of T-cells such as CD8+ (Chen et al. 2002). It has been demonstrated MSCs have naturally low immunogenic properties due to low expression level of major histocompatibility complex (MHC) class I

antigens and lack of MHC class II and co-stimulatory molecules such as CD80, CD86, and CD40 (Krampera et al. 2003). Recent studies revealed that MSCs-CM exhibited a similar immunomodulatory effect as MSCs. Hashemi et al. compared AD-MSCs-CM derived from BALB/c, C57BL/6, and DBA mouse strains. The immunological assays showed some variation among the strains in the cytokines, nitric oxide (NO), and indoleamine 2,3-dioxygenase production as well as immunomodulatory effects on splenocyte functions. There was suppression of splenocyte proliferation in the presence of ADMSC-CM in the three inbred mouse strains, though, BALB/c CM caused a stronger immunosuppressive effect (Hashemi et al. 2013). Determining MSCs suppressive immune response mediatory role would improve prospective clinical applications of MSCs.

4 Mesenchymal Stem Cells (MSCs) in Skeletal Tissues

Advances in MSC therapy for bone, cartilage, tendons, and muscles will be reviewed in this section. Table 1 lists the clinical studies that employed MSCs as treatment of skeletal diseases.

4.1 Bones

Bones have self-healing capability for small, non-intensive and uncomplicated injuries. Bone healing is a complicated process that consists of overlapping phases – inflammation, repair, and remodeling. Numerous intracellular signaling pathways play a role in bone healing. Newly formed bone is indistinguishable from the surrounding native bone in both its micro structure and macro structure. However, this ability for self-healing is unable to repair large-sized bone defects, which lead to formation of malunions, delayed unions, nonunions, osteomyelitis, necrosis, and tumors. Therefore, an efficient therapeutic approach is of crucial importance for treatment of bone lesions. ABG are the current gold-standard procedure. Annually, more than 2 million ABG are performed as orthopedic procedures worldwide (Blank et al. 2017). Allografts and xenografts are considered to be alternative strategies for bone treatment. Despite the satisfactory results of the aforementioned methods, a number of shortcomings and complications limit their availability and application. Administration of MSCs alone or in combination with biomaterials has emerged as a promising strategy for bone repair and is currently under intensive investigation.

The capability of MSCs to undergo osteogenic differentiation was identified in 1976 (Friedenstein et al. 1976). This finding encouraged scientists to exploit this new technology in the preclinical and clinical settings. The successful outcome of intravascular injection of complete BM and/or BM-MSCs has been reported for regeneration of maxillofacial defects, osteonecrosis, and distraction osteogenesis (Zamiri et al. 2013). According to the official database, the most reported translational use of cell therapy is related to non-union bone defects (Ballini et al. 2017). Healey et al., in 1990, have reported desirable outcomes in 8 patients with delayed union who were treated by percutaneous engraft of autologous BM (Healey et al. 1990). Percutaneous BM grafting in patients with tibial non-union resulted in union treatment in 15 of 20 patients at 4 months after treatment (Goel et al. 2005). Another group injected concentrated autologous BM in patients with tibia nonunion and observed good clinical outcomes (Hernigou et al. 2005).

Direct injection of MSCs is an ineffective delivery method in large bone defects where a significant amount of the bony tissue is lost. Acceleration of the bone healing process of critical size defects fails due to lack of angiogenesis, which would enhance repair capacity. Recently, it has been suggested that the controlled delivery of MSCs and growth factors within biomaterial substrates (hydrogel, scaffold) promotes healing and accelerates functional new bone formation (Khojasteh et al. 2013). Khojasteh et al. delivered MSCs and endothelial progenitor cells (EPCs) in β-tricalcium phosphate scaffolds that contained vascular endothelial growth factor (VEGF)-

loaded microspheres and implanted them in bilateral mandibular bone defects in dogs. Their results showed the most bone formation in the VEGF/MSC scaffold compared with the other groups. The amount of new bone regeneration was highest in the MSCs/EPC/VEGF group (Khojasteh et al. 2017). In clinical settings, Quarto successfully treated a 4 cm tibial critical size defect with autologous BM-MSCs in combination with hydroxyapatite (HA). The injury healed within 6 months (Quarto et al. 2001). Subsequently, Bajada et al. used BM-MSCs combined with calcium sulfate carriers to treat a non-union tibial fracture and the fracture healed 2 months after surgery (Bajada et al. 2007).

Osteonecrosis (avascular necrosis) is a bone and cartilage distraction caused by disease or severe trauma, such as a fracture or dislocation that affects the blood flow to a bone. The National Institute of Health (NIH) considered surgical core decompression technique as the only treatment option for early stage osteonecrosis (Helbig et al. 2012). However, concurrent cell therapy and core decompression approaches have successfully prevented progression of osteonecrosis. In a pilot clinical study, patients with ostenecrotic hips simultaneously underwent treatment with implantation of an autologous BM concentrate and core decompression that resulted in pain reduction and joint symptoms 24 months after the procedure. Only one out of 10 patients in this group progressed to the final stage. In contrast, 62% of the control hips that only received core decompression had evidence of end-stage avascular necrosis (Gangji et al. 2004). Similarly, Sen et al. observed better clinical outcome and hip survival following MSCs transplantation and core decompression (Sen et al. 2012). Numerous studies have incorporated BM aspirated-MSCs or expanded-MSCs into tissue-engineered scaffolds for treatment of non-traumatic osteonecrosis (Centeno et al. 2011). Long-term follow-up of autologous BM-engrafted patients revealed slow (rare) deterioration to the fracture stage over 60 months (Gangji et al. 2011). Use of the same therapeutic approach confirmed decreased pain in all the patients postoperatively, and delayed the progression of the disease to collapse during 17–20 years of follow-up (Hernigou et al. 2003). A recent study reported autologous BM grafting for advanced osteonecrosis of the humeral head and observed disparate outcomes among patients. This finding was most probably related to differences in the amount of BM and varied number of transplanted MSCs (Makihara et al. 2017).

A number of scientists assessed allograft MSCs after reports of their safety and immunosuppressive properties. Horwitz et al., for the first time, reported the feasibility of simultaneous allogeneic BM and MSC transplantations in children with severe osteogenesis imperfecta (OI) (Horwitz et al. 1999). In 2005, Le Blanc et al. conducted a novel clinical trial that used in utero transplantation of allogeneic MSCs into a female fetus with severe OI. After birth, the infant showed no immunoreactivity against the donor and only three fractures occurred during the first 2 years. Both normal psychomotor development and correct growth tendencies were observed in long-term follow-up (Le Blanc et al. 2005). In another study, allogeneic AD-MSCs healed cranial critical-sized defects in a canine model without inducing an immune response by the host (Liu et al. 2013). Similarly, implantation of allogeneic BM-MSCs with hydroxyapatite-tricalcium phosphate (HA-TCP) scaffolds has resulted in bone regeneration of femoral diaphysis defects with no adverse immune response (Arinzeh et al. 2003). However, there is still insufficient data to argue that allogeneic MSCs are safe for clinical applications.

Despite the numerous reports of successful bone healing with BM-MSCs, determining the proper cell sources is a challenge for cell therapy of bone disorders. Numerous in vitro and preclinical studies have been conducted to examine the potential of MSCs derived from various sources such as periosteum, muscle, adipose, and UC on osteogenesis and bone regeneration (Hosseini and Baghaban Eslaminejad 2017). Linero et al. showed that AD-MSCs induced bone regeneration in critical size jaw defects in rabbits. They observed similar results between AD-MSCs and BM-MSCs in terms of amount and quality of neo-formed bone, bone thickness, collagen fiber structure, maturation, and mineral matrix

calcification. For the first time, they have demonstrated that ADSCs have a paracrine effect in bone regeneration and can be a therapeutic alternative for MSCs therapy (Linero and Chaparro 2014). Tawonsawatruk et al. evaluated the ability of human ADSCs (hADSCs) to prevent fracture nonunion in rat models. Cells were injected percutaneously at the fracture site. At 8 weeks, 80% of the animals in the hAD-MSCs treatment group showed evidence of bone healing with substantial improvement in bone mineralization and maturity of bone tissues at the fracture gap compared to only 14% of those in the control group (Tawonsawatruk et al. 2016). Stockmann et al compared the ability of various cell populations for bone regeneration in a pig calvaria defect and observed no significant differences among implanted collagen scaffold seeded with AD-MSCs, PMSCs, and BM-MSCs (Stockmann et al. 2012). In a recent work, Cell tracing or mapping strategies showed that neural-crest stem cells were recruited to the jaw and skull bone defects during the healing process (Lombard et al. 2016). These findings showed the value of NCSCs and/or stem cells from the head and neck area such as dental pulp-derived MSCs as new, relevant cell sources for therapeutic applications. Giuliani et al. seeded human dental pulp-derived MSCs onto collagen I scaffolds to treat human mandible defects. A fully compact bone that had higher matrix density was observed compared to the control, human alveolar spongy bone. The regenerated bone, being entirely compact, completely differed from normal alveolar bone. Long-term follow up showed regeneration of the mandible (Giuliani et al. 2013).

A literature search and database have shown that most clinical trials of bone regeneration administered BM-MSCs; a few have used MSCs from other sources. Of note, these trials are mostly phase I or II. These studies show that MSCs are a prosperous treatment, even in long-term follow-up. However, the mechanisms underlying stem cell therapy are still largely unknown and should be addressed.

4.2 Cartilage

Cartilage is as an avascular, aneural tissue present in the joints, intervertebral disks, and nose, among other locations. There are three different types of cartilage – hyaline cartilage, elastic cartilage, and fibrocartilage. Each has its own chemical and mechanical properties. Articular cartilage is a hyaline cartilage mainly composed of water, extracellular matrix (ECM) components, and chondrocytes (2% of total volume). Chondrocytes are responsible for the synthesis of ECM as well as repair of cartilage defects. Collagen type II is the major constituent of the ECM, which provides high strength and low friction in joints (Camarero-Espinosa et al. 2016). Owing to the absence of a vascular network and low cellularity, cartilage displays a limited intrinsic regeneration capacity when injured. The absence of pain in the damaged aneural cartilage leads to continued loading of the joint, which eventually results in an osteochondral defect and osteoarthritis (Camarero-Espinosa et al. 2016).

Osteoarthritis, a debilitating disease, is the most common chronic joint disorder, which frequently occurs in elderly individuals and athletes as a result of overuse or stress on the joints (Ruiz et al. 2016). Various surgical and non-surgical methods have been employed to treat osteoarthritis, though these approaches are unable to regenerate articular cartilage. These techniques mostly relieve pain and reduce inflammation in the damaged joint (Jo et al. 2014). Total joint replacement is the only definitive therapeutic option for patients with severe arthritis, though this method is invasive and may result in infection and thrombosis (Ruban et al. 2000).

Cellular therapies and TE have been developed to overcome these limitations and promote cartilage regeneration. Given the essential role of chondrocytes in ECM synthesis, autologous chondrocyte implantation (ACI) has been considered to repair cartilage lesions. However, chondrocyte dedifferentiation and two-stage surgical procedure may result in further cartilage damage and degeneration (Knutsen et al. 2007). RM thus offered MSCs as a powerful approach for cartilage repair.

As mentioned above, MSCs can be simply isolated from various tissues and expanded to provide off-the-shelf products for therapeutic applications. Given the fact that epigenetic memory has a significant impact on chondrogenic potential of MSCs, the source of MSCs plays an important role in treatment efficacy. According to recent researches, synovium-derived MSCs and BM-MSCs have exhibited the highest chondrogenic differentiation potential compared to other sources (Li et al. 2011). In contrast, AD-MSCs have a very low chondrogenic capacity (Barry and Murphy 2013). Thus, 68% of clinical trials have used BM-MSCs in cartilage TE and RM (Goldberg et al. 2017).

Numerous studies have proven the crucial role of the TGF-β superfamily to achieve efficient chondrogenic differentiation in vitro (Kim et al. 2014). Nevertheless, multiple factors control the process of chondrogenesis in vivo such as growth factors, mechanical loads, and cell interactions (Sekiya et al. 2002). Providing MSCs with these factors under in vitro conditions would more likely result in fully functional chondrocytes. However, important issues such as hypertrophy and ossification following differentiation are controversial in terms of in vitro chondrogenesis.

MSC transplantation for cartilage repair by direct injection or within different scaffolds at the site of injury have been widely reported and showed promising results (Giannini et al. 2010). In most animal models, MSCs were transplanted into joints and followed up to 6 months after the surgery or injection. Most likely, MSCs' immunomodulatory effects at the damaged site led to improvements rather than their differentiation into chondrocytes. Local MSCs and resident articular chondrocytes have the capability to migrate into the defect site and synthesize a reparative matrix (Davatchi et al. 2016).

Various scaffolds have been developed to promote chondrogenic potential of MSCs after transplantation. Use of collagen gel in some clinical trials improved cartilage regeneration; two separate studies – one reported benefit after 6 months and the other after 5 years after transplantation in osteoarthritis (OA) patients (Davatchi et al. 2016; Wakitani et al. 2004). Other studies reported promising results after 12 months when they used hydroxyapatite ceramic and platelet fibrin glue scaffolds for transplantation of MSCs (Adachi et al. 2005)

The first clinical trial that used an intra-articular injection of autologous BM-MSCs in a patient with OA was reported in 2008. At the 6-month follow-up, the patient reported pain relief, improvement in walking distance and other physical activities (Centeno et al. 2008). After this study, other trials that had 1–2 year follow-up periods reported that the improvements were only limited to the first 6 months after cell treatment. In the second 6 months, patients noticed an increase in symptoms (Davatchi et al. 2011). After these contradictory results, a 5-year follow-up of MSCs therapy for OA was reported in 2016 (Davatchi et al. 2016). It was noted that while symptoms deteriorated after 1 year of treatment, the treated knees were still better compared to untreated knees after 5 years. Although it was unclear why the improvements declined after 1 year, MSCs' behavior supposedly would change in response to the new microenvironment. Inflammation in the defect area causes local MSCs to produce metalloproteinases (MMPs) instead of ECM, which leads to further cartilage degeneration (Richardson et al. 2016).

Over past 16 years, autologous MSCs have been frequently used in trials rather than allogeneic MSCs to eliminate immunogenic responses. However, allogeneic MSCs combined with autologous chondrocytes revealed more promising results than the group without MSCs. Although the therapeutic mechanism of MSCs has yet to be identified, it seemed that suppression of inflammation was more likely to be responsible for the major healing efficacy of MSCs at the transplantation site (Davatchi et al. 2016). Given the short life span of transplanted MSCs, chondrogenic differentiation would hardly be a decisive factor in the healing process.

An important issue in using MSCs for cartilage regeneration is the formation of fibrocartilage

instead of hyaline cartilage, which has an inferior therapeutic outcome. Additionally, hypertrophy occurs upon chondrogenic differentiation. The biomechanical properties of the chondrocytes change after production of collagen type II. Although different techniques have been used to address this issue, there is a need to develop more effective methods to generate hyaline cartilage at the defect site.

4.3 Muscles

Skeletal muscle is a highly organized tissue composed of numerous myofibers as basic structural units, in addition to blood vessels, nerves, and extracellular connective tissue. It attaches to the bone via tendons and generates forces for voluntary movement and locomotion. In adulthood, skeletal muscle has an inherent ability to regenerate minor injuries. This ability is mainly allocated to the existence of a population of undifferentiated mononuclear cells, known a satellite cells (SCs) (Yin et al. 2013). During postnatal muscle development, these cells reside in a quiescent state and activate in response to environmental cues such as injury and inflammatory factors (cytokines). They subsequently proliferate, undergo terminal differentiation and form myofibers, and eventually integrate into the muscle tissue (Collins et al. 2005). On the other hand, muscle does not have the capability to regenerate severe injuries, such as myopathies, large traumatic injuries, muscle tumors, and chronic denervation. Lack of regeneration frequently leads to fibrous scar tissue formation and fatty degeneration of muscle causes volumetric muscle loss.

Current treatments for severe muscle trauma and myopathy include engraftment of intact, vascularized, and innervated autologous muscle and injection of myoblasts. Although myoblasts are the first natural cell sources for cell therapy of skeletal muscle, they have not shown a favorable outcome (Mendell et al. 1995). Myoblasts derived from patients who suffer from Duchenne muscular dystrophy (DMD) poorly expand under in vitro conditions and rapidly undergo senescence (Gussoni et al. 1997). Muscle SCs are an alternative cell sources for muscle treatment. However, various clinical and preclinical studies have reported the shortcomings of SCs transplantation (Boldrin et al. 2015). In addition to the need for a large numbers of injected SCs to treat a complete muscle, they provoke immune responses in the host body and most die during the early hours after the injection.

Muscle-derived stem cells were examined to determine if they could contribute to muscle repair. BM-MSCs were the first that underwent myogenic differentiation and participated in muscle repair (Bossolasco et al. 2004). However, Gang et al. reported contradictory results and observed that BM-MSCs could not regenerate muscle in dystrophin-deficient mice (Gang et al. 2009). Overexpression of PAX3, the master regulator of the embryonic myogenic program, in BM-MSCs was performed to evaluate the ability of these cells to restore dystrophin expression in immunodeficient mice. Transplantation of PAX3-transduced MSCs resulted in more clusters of dystrophin+ myofibers, but there was no functional improvement observed compared to untransduced MSCs (Gang et al. 2009). Dezawa efficiently induced BM-MSCs to differentiate into mature myotubes that were PAX7+ and caused muscle regeneration in mdx-nude mice (Dezawa et al. 2005). To achieve the best outcome, a number of research groups examined the potential cells from adipose, UC, and synovial membrane sources (De Bari et al. 2003; Fukada et al. 2002; Goudenege et al. 2009). The safety and efficacy of muscle-derived CD133+ stem cells in patients with DMD was also assessed in a phase I clinical trial which resulted in positive outcomes with no observed adverse effects (Torrente et al. 2007). Another study compared the regenerative capacity of intramuscular injection of human muscle–derived CD133+ cells and myoblasts to cryoinjured tibialis anterior (TA) muscle in a mouse model. There was efficient muscle regeneration in the group that received muscle-derived CD133+ cells in terms of the numbers of fibers that expressed human proteins and the numbers of human cells in a SC position compared to the myoblast group (Negroni et al. 2009). Despite the apparent

success of MSCs, generation of functional, large-scale muscle tissues is a tremendous clinical challenge. Cells, as therapeutic agents, combined with TE approaches would provide an integrated system whereby the cells could interact with their environment to have a fully functional, mature skeletal muscle. Vandenburgh et al., for the first time, have described the use of tissue engineered constructs for muscle regeneration (Vandenburgh et al. 1988). They cultured myotubes in collagen matrix in vitro and observed that the cells highly preserved their contractile state during expansion Another group developed a poly-ε-caprolactone (PCL)/collagen based nanofiber scaffold to guide morphogenesis of skeletal muscle cells (Choi et al. 2008). Recent attempts have been undertaken to create functional, engineered skeletal muscle with enhanced vascularization, increased innervation, and morphology similar to native muscle (Chan et al. 2006). Witt et al. co-cultured MSCs with myoblasts. Under stimulation with hepatocyte growth factor (HGF) and IGF-1, the three-dimensional (3D) cultivation in fibrin-collagen I gels induced higher levels of myogenic differentiation compared with the two-dimensional experiments (Witt et al. 2017). For the most part, the in vivo applications of muscle TE technologies are in the early stage of pre-clinical development.

4.4 Tendons

Tendons, as specialized connective tissues, are joint stabilizers that curb skeletal muscle damages by transmitting mechanical forces from muscle to bone. Tendons are mainly composed of collagen type I (approximately 80%-95%) and small amounts of other types of collagen (III,V,VI,XII, XIV), glycosaminoglycans, and proteoglycans. Collagen fibers are longitudinally aligned along the tendon axis that causes high mechanical strength and elasticity of the tendon (Spanoudes et al. 2014). Tenocytes and tenoblasts, two major cell types within the tendons, produce the complex tissue-specific extracellular environment. Tenocytes are fibroblast-like cells with an elongated morphology, which are located between the collagen fibers (Spanoudes et al. 2014). Tendons or surrounding tissue contribute to the healing process of an injured tendon by producing a new ECM. There are two healing mechanisms in tendons, intrinsic and extrinsic. Tenocytes and tenoblasts are actively involved in the intrinsic healing mechanism, whereas other cell types, such as BM-MSCs from surrounding tissues, are implicated in the extrinsic healing mechanism. Nevertheless, the healing mechanisms cannot effectively deal with rehabilitation of injured tissue because of the tendon's limited vascularity and low cellularity.

Among the available therapeutic strategies known to promote regeneration of injured tendons, cell-based TE appear to be the most promising. Studies have demonstrated that tenocytes cultured in vitro encounter numerous difficulties that include dedifferentiation, morphology deformation to spindle shape, and trans-differentiation (Yao et al. 2006). The phenotypic drift in tenocytes affects its function and makes it inappropriate for cell based therapy approaches. To overcome this issue, numerous studies have demonstrated the potential of transplanted MSCs for tendon repairs (Awad et al. 1999). Nevertheless, providing suitable mechanical and chemical cues for fully tenogenic differentiation of MSCs in vitro and in vivo is of significant importance. Due to the longitudinal alignment of collagen fibrils within the tendon units, it has been proven that aligned scaffolds promote tenogenic differentiation of MSCs as they imitate the tendon's architecture (Erisken et al. 2013). Despite promising preliminary outcomes, some reports indicated formation of ectopic bone after injection of MSCs in the defect site. In order to address this issue, pre-treatment of MSCs in vitro should be taken into consideration. Recent researches have shown that utilizing growth factors (GDF-5, BMP12) and mechanical stimulation upregulated collagen type I and other tendon specific markers in MSCs (Lee et al. 2011).

There are limited numbers of clinical trials in which the efficacy of MSCs for tendon repair is unclear. The lack of control groups and a defined protocol guideline make it difficult to show

successful tendon regeneration after MSCs transplantation (Veronesi et al. 2017). Despite the promising results from in vitro and in vivo studies, the optimal scaffold and cell population for tendon repair and regeneration has yet to be addressed to avoid ectopic bone formation after cell therapy.

5 MSCs in Non-skeletal Tissues

According to the official website of the NIH, most MSC-based clinical trials evaluated the biomedical potential of hMSCs to treat hematological, inflammatory, and graft versus host disease (GVHD) conditions. Bone and cartilage injuries, heart disease, diabetes, gastrointestinal conditions, diseases of the liver and kidneys, as well as neurological disorders are the targets of MSCs-based therapy (Table 1). Other diseases constitute 12% of total clinical studies (Squillaro et al. 2016). The least number of clinical trials of MSCs therapies belong to lung and related diseases (Liu et al. 2016). Use of MSCs for treatment of neurological disorders is relatively common, despite the scant evidence for their conversion to neural cells in vivo. Autologous MSCs isolated from BM and injected intrathecally into spinal cord cerebrospinal fluid, allowing access to the brain and spinal column, can be accomplished safely in patients with multiple sclerosis (MS) and ALS (Rushkevich et al. 2015). The combination of cell therapy and TE provide an efficient therapeutic approach in RM, particularly in complicated organs and limbs. Advances in tissue engineered materials are of crucial importance as they are the main tools in cell therapy used to rebuild damaged tissues. Material carriers designed to spatially and temporally mimic the tissue cell niche may be of particular importance for the complete regeneration of severely damaged organs. Hence, in complicated organs such as the limbs, a lack of tissue engineered proper composite and proper cell sources (Taghiyar et al. 2017) cause limitations in RM in this field. Here, we discuss MSC-based therapy in three organs.

5.1 Liver

The liver is the largest organ of the body. It displays a multicellular architecture. The liver performs a variety of functions that include detoxification, synthetic and metabolic processes. Liver diseases are caused by different factors such as viral infections, alcoholism, genetic syndromes, and autoimmune attacks. These diseases often lead to liver failure, which results in multiple organ dysfunctions and eventually death. The liver has a unique self-regenerative capacity to restore its function after massive injuries. However, in acute liver failure it is unable to repair the damage. Thus, the liver loses its function. In this cases, orthotropic liver transplantation is the only current treatment to save patients (Bhatia et al. 2014). Lack of a live human liver donor and the increasing demands for transplantation have urged scientists to find an alternative treatment to organ transplantation. TE and cell-based therapy have been recently offered as a promising method to treat end stage liver failures (Lee et al. 2015).

Hepatocytes constitute the main cell type in the liver and are responsible for hepatic regeneration. Transplantation of either hepatocytes or stem cells have been explored in a number of preclinical and clinical studies (Piscaglia et al. 2010). Although hepatocytes are the priority for cell based therapy approaches, they lose their function and proliferative capacity in vitro (Hu and Li 2015). Additionally, an insufficient supply of human hepatocytes is a challenge for therapeutic applications. In the quest for an alternative, since 2004, MSCs have been considered as appropriate cell sources that have the ability to give rise to functional hepatocytes (Ohkoshi et al. 2017). BM-MSCs, UCB-MSCs, and AD-MSCs have hepatogenic capabilities, but AD-MSCs are more likely to be an excellent source for liver regeneration (Alizadeh et al. 2016; Berardis et al. 2015). Interestingly, it has been proven that MSCs secrete anti-fibrotic, anti-inflammatory, and anti-apoptotic molecules, which enables them to treat acute and chronic liver injuries (Christ et al. 2015). Therefore, the idea of

utilizing MSC-CM culture seems to be as effective as using MSCs. Numerous in vivo studies have shown that MSC secretomes stimulate hepatic regeneration after transplantation (Fouraschen et al. 2012).

Since 2007, several clinical trials reported promising results of systemic injections of MSCs to treat liver disorders (Mohamadnejad et al. 2007). Nonetheless, the exact mechanism of MSCs in healing liver diseases has yet to be completely understood. In addition, some studies reported the formation of myofibroblasts upon MSCs transplantation, which must be addressed in future research.

5.2 Heart

Cardiovascular diseases account for the highest mortality worldwide and more than half are allocated to myocardial infarction (MI) (Go et al. 2014). The heart has a limited capacity to naturally regenerate; hence, cardiac diseases may lead to heart failure (HF) and death. Although there are various medical and surgical treatments, cardiac transplantation is the only current options for patients with end-stage myocardial failure. However, the limited numbers of donors preclude its extensive use. One of the leading treatments under investigation for HF is MSCs.

Numerous studies have been published about the therapeutic potential of autologous and allogeneic MSCs from various sources for treatment of cardiovascular diseases. In a pioneering study, Toma et al. injected hMSCs into murine hearts, which gave rise to a cardiac lineage (Toma et al. 2002). These researches showed that MSCs mediate the migration and differentiation of cardiac progenitor cells (CPCs) through paracrine signaling by secreting growth factors, cytokines, and angiogenic factors (Nakanishi et al. 2008; Zhao et al. 2016). Zhao et al. specifically showed that overexpression of HGF in UC derived MSCs reduced cardiomyocytes apoptosis, enhanced angiogenesis, and cardiomyocyte proliferation (Zhao et al. 2016). A recent work suggested that the chemotactic effect of MSCs on proliferation, migration, and differentiation of endogenous CSCs was regulated via the SDF1/CXCR4 and SDF1/CXCR4 signaling pathways (Hatzistergos et al. 2016).

A number of published or ongoing clinical trials have demonstrated beneficial effects of MSC-based therapy in cardiovascular settings. The findings of clinical trials on patients with MI treated with MSCs revealed the beneficial effects of MSCs on improving heart function (Jeong et al. 2018). IV infusion of allogeneic UC-MSC in patients with chronic heart failure considerably upregulated the expression of HGF involved in myogenesis, and improved left ventricular function (Bartolucci et al. 2017). In another clinical study, 53 patients with dilated cardiomyopathy (DCM) were randomized to IC infusion with either autologous MSCs, BM mononuclear cells (BMMC), or normal saline. Improved left ventricular ejection fraction, New York Heart Association (NYHA) classification, and myocardial perfusion were reported after 12 months of follow-up (Xiao et al. 2017). A recent work stated the importance of cell dose for achieving efficient clinical outcome. A total of 30 patients with ischemic cardiomyopathy randomly received 20 million (n=15) or 100 million (n=15) allogeneic MSCs. Only patients who received the high cell dose had an increased ejection fraction (Florea et al. 2017). A phase II clinical trial confirmed the safety and efficacy of ischemia-tolerant MSCs (itMSCs) in 22 patients with nonischemic cardiomyopathy (Butler et al. 2017). Despite the relative success of clinical trials, further studies are required to improve the efficacy of MSC therapy.

5.3 Kidneys

The kidney is a highly complicated organ that consists of millions of functional units, termed nephrons. Nephron production or nephrogenesis in mammals only occurs during gestation. Hence, no new nephrons are generated after birth. There are various specialized cell types in the kidneys –

podocytes, endothelial cells, and tubular epithelial cells. Depending on the type of disease, one or more cell types may be affected and lose their function (Humphreys et al. 2008).

The kidneys have limited regeneration capacity; therefore, an injury may more likely cause tubular necrosis, apoptosis and, eventually, acute kidney injury (AKI) (Liu and Brakeman 2008). AKI in turn, leads to chronic kidney disease (CKD) as a result of fibrosis, scarring, and organ failure (Moon et al. 2016). Dialysis and kidney transplantation are the current therapies for end stage kidney diseases. Nevertheless, long-term follow-up shows a high mortality rate in patients, which highlights the necessity of an alternative treatment. First attempts to administer MSCs in the kidneys has led to partial renal regeneration and opened up a new horizon towards treatment of renal diseases (Morigi et al. 2004). Recent studies have demonstrated the dedifferentiation of tubular epithelial cells and trans-differentiation of interstitial cells after injuries in the kidneys, which facilitated the regeneration process (Chawla and Kimmel 2012). According to these data, MSC-based therapy supposedly renders an efficient alternative to the current therapeutic approaches. In vitro studies have shown MSCs differentiation potential into the renal-specific lineage (Singaravelu and Padanilam 2009). However, the results of in vivo studies are not as promising in the regeneration of renal cells. Given the complexity of the kidney structure, TE might overcome numerous difficulties related to the regeneration of this organ. Combinations of various MSCs and scaffolds have been used to improve MSCs differentiation potential for renal lineages. BM-MSCs and AD-MSCs are two potential candidates for a cell-based therapy approach in kidney regeneration (Prodromidi et al. 2006). In terms of 3D structure for the cells, different scaffolds have been evaluated in which collagen and HA had some levels of similarity to the renal microenvironment (Rosines et al. 2007). However, the mechanical properties of hydrogels have been always an issue. More recently, decellularized kidney has been suggested as a unique microenvironment for seeded cells for kidney TE. In vivo experiments in a rat model showed promising results in a short term study (Song et al. 2013).

Preclinical studies showed some degrees of kidney regeneration which were attributed to the differentiation potential and paracrine properties of MSCs, yet more efforts are needed to develop a fully functional organ. Imitating this complex microenvironment is very challenging and necessitates increased basic knowledge regarding the kidney development and regeneration.

6 Future Trends and Concluding Remarks

Over the past decades, tremendous efforts have been made to disclose the unknown biological and functional characteristics of MSCs to pave the way for their perspective clinical applications. There are several major issues that remain controversial about the use of MSCs in RM. Completed and on-going clinical trials have shown that MSCs are a powerful therapeutics tool. However, these trials are inadequate to assure their safety. Subsequent to a recent report that intravitreal injection of AD-MSCs in patients with macular degeneration led to complete blindness, it increased the certainty to use the MSCs with caution (Kuriyan et al. 2017). Indeed, all beneficial characteristics of MSCs might cause adverse effects. Multilineage potential of MSCs might create unwanted tissue after transplantation. Intramyocardial calcification was observed as a consequence of BM cells injected into zones of acute myocardial ischemia (Yoon et al. 2004). Therefore, discovery of regulatory factors and signaling pathways in the MSC niche that determine the cell fate to a distinct lineage would be a breakthrough in RM. Risk of tumorigenicity is the major concern related to clinical administration of MSCs. Occurrence of increased immune-suppressive factors and prohibition of immune cells (B-cells and NK cells) as a result of the immunomodulatory properties of MSCs also increases the possibility of tumor progression. It has been indicated that MSCs preferentially migrate to a tumor site due to an inflammatory microenvironment and may contribute to growth

of cancer cells (Lee and Hong 2017). The potential for MSCs in new-blood vessel formation and angiogenesis could promote tumor growth and metastasis. These issues necessitate further effective clinical and preclinical studies to clearly address the safety of MSCs, particularly with long-term follow-up.

References

Adachi N, Ochi M, Deie M, Ito Y (2005) Transplant of mesenchymal stem cells and hydroxyapatite ceramics to treat severe osteochondral damage after septic arthritis of the knee. J Rheumatol 32(8):1615–1618

Agematsu K, Nakahori Y (1991) Recipient origin of bone marrow-derived fibroblastic stromal cells during all periods following bone marrow transplantation in humans. Br J Haematol 79(3):359–365

Alizadeh E, Eslaminejad MB, Akbarzadeh A, Sadeghi Z, Abasi M, Herizchi R, Zarghami N (2016) Upregulation of MiR-122 via trichostatin a treatments in hepatocyte-like cells derived from mesenchymal stem cells. Chem Biol Drug Des 87(2):296–305. https://doi.org/10.1111/cbdd.12664

Arinzeh TL, Peter SJ, Archambault MP, van den Bos C, Gordon S, Kraus K, Smith A, Kadiyala S (2003) Allogeneic mesenchymal stem cells regenerate bone in a critical-sized canine segmental defect. J Bone Joint Surg Am 85-A(10):1927–1935

Atiyeh BS, Costagliola M (2007) Cultured epithelial autograft (CEA) in burn treatment: three decades later. Burns 33(4):405–413. https://doi.org/10.1016/j.burns.2006.11.002

Awad HA, Butler DL, Boivin GP, Smith FN, Malaviya P, Huibregtse B, Caplan AI (1999) Autologous mesenchymal stem cell-mediated repair of tendon. Tissue Eng 5(3):267–277. https://doi.org/10.1089/ten.1999.5.267

Baek SJ, Kang SK, Ra JC (2011) In vitro migration capacity of human adipose tissue-derived mesenchymal stem cells reflects their expression of receptors for chemokines and growth factors. Exp Mol Med 43(10):596–603. https://doi.org/10.3858/emm.2011.43.10.069

Baghaban Eslaminejad M, Jahangir S, Aghdami N (2011) Mesenchymal stem cells from murine amniotic fluid as a model for preclinical investigation. Arch Iran Med 14(2):96–103. https://doi.org/10.11142/AIM.006

Bajada S, Harrison PE, Ashton BA, Cassar-Pullicino VN, Ashammakhi N, Richardson JB (2007) Successful treatment of refractory tibial nonunion using calcium sulphate and bone marrow stromal cell implantation. J Bone Joint Surg Br 89(10):1382–1386. https://doi.org/10.1302/0301-620X.89B10.19103

Ballini A, Scacco S, Coletti D, Pluchino S, Tatullo M (2017) Mesenchymal stem cells as promoters, enhancers, and playmakers of the translational regenerative medicine. Stem Cells Int 2017:3292810. https://doi.org/10.1155/2017/3292810

Barry F, Murphy M (2013) Mesenchymal stem cells in joint disease and repair. Nat Rev Rheumatol 9(10):584–594. https://doi.org/10.1038/nrrheum.2013.109

Bartholomew A, Sturgeon C, Siatskas M, Ferrer K, McIntosh K, Patil S, Hardy W, Devine S, Ucker D, Deans R, Moseley A, Hoffman R (2002) Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol 30(1):42–48

Bartolucci J, Verdugo FJ, Gonzalez PL, Larrea RE, Abarzua E, Goset C, Rojo P, Palma I, Lamich R, Pedreros PA, Valdivia G, Lopez VM, Nazzal C, Alcayaga-Miranda F, Cuenca J, Brobeck MJ, Patel AN, Figueroa FE, Khoury M (2017) Safety and efficacy of the intravenous infusion of umbilical cord mesenchymal stem cells in patients with heart failure: a phase 1/2 randomized controlled Trial (RIMECARD trial [Randomized clinical trial of intravenous infusion umbilical cord mesenchymal stem cells on cardiopathy]). Circ Res 121(10):1192–1204. https://doi.org/10.1161/CIRCRESAHA.117.310712

Berardis S, Dwisthi Sattwika P, Najimi M, Sokal EM (2015) Use of mesenchymal stem cells to treat liver fibrosis: current situation and future prospects. World J Gastroenterol 21(3):742–758. https://doi.org/10.3748/wjg.v21.i3.742

Bhang SH, Lee S, Shin JY, Lee TJ, Jang HK, Kim BS (2014) Efficacious and clinically relevant conditioned medium of human adipose-derived stem cells for therapeutic angiogenesis. Mol Ther 22(4):862–872. https://doi.org/10.1038/mt.2013.301

Bhanot Y, Rao S, Ghosh D, Balaraju S, Radhika CR, Satish Kumar KV (2011) Autologous mesenchymal stem cells in chronic spinal cord injury. Br J Neurosurg 25(4):516–522. https://doi.org/10.3109/02688697.2010.550658

Bhatia SN, Underhill GH, Zaret KS, Fox IJ (2014) Cell and tissue engineering for liver disease. Sci Transl Med 6(245):245sr2. https://doi.org/10.1126/scitranslmed.3005975

Blank A, Riesgo A, Gitelis S, Rapp T (2017) Bone grafts, substitutes, and augments in benign orthopaedic conditions current concepts. Bull Hosp Jt Dis (2013) 75(2):119–127

Boldrin L, Zammit PS, Morgan JE (2015) Satellite cells from dystrophic muscle retain regenerative capacity. Stem Cell Res 14(1):20–29. https://doi.org/10.1016/j.scr.2014.10.007

Bossolasco P, Corti S, Strazzer S, Borsotti C, Del Bo R, Fortunato F, Salani S, Quirici N, Bertolini F, Gobbi A, Deliliers GL, Pietro Comi G, Soligo D (2004) Skeletal muscle differentiation potential of human adult bone marrow cells. Exp Cell Res 295(1):66–78. https://doi.org/10.1016/j.yexcr.2003.12.015

Butler J, Epstein SE, Greene SJ, Quyyumi AA, Sikora S, Kim RJ, Anderson AS, Wilcox JE, Tankovich NI, Lipinski MJ, Ko YA, Margulies KB, Cole RT, Skopicki HA, Gheorghiade M (2017) Intravenous allogeneic mesenchymal stem cells for nonischemic cardiomyopathy: safety and efficacy results of a phase II-A randomized trial. Circ Res 120(2):332–340. https://doi.org/10.1161/CIRCRESAHA.116.309717

Camarero-Espinosa S, Rothen-Rutishauser B, Foster EJ, Weder C (2016) Articular cartilage: from formation to tissue engineering. Biomater Sci 4(5):734–767. https://doi.org/10.1039/c6bm00068a

Cantinieaux D, Quertainmont R, Blacher S, Rossi L, Wanet T, Noel A, Brook G, Schoenen J, Franzen R (2013) Conditioned medium from bone marrow-derived mesenchymal stem cells improves recovery after spinal cord injury in rats: an original strategy to avoid cell transplantation. PLoS One 8(8):e69515. https://doi.org/10.1371/journal.pone.0069515

Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M, Karli D (2008) Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. Pain Physician 11(3):343–353

Centeno CJ, Schultz JR, Cheever M, Freeman M, Robinson B, Faulkner SJ (2011) A case series of percutaneous treatment of non-union fractures with autologous, culture expanded, bone marrow derived, mesenchymal stem cells and platelet lysate. J Bioeng Biomed Sci 01:2–7

Chan J, O'Donoghue K, Gavina M, Torrente Y, Kennea N, Mehmet H, Stewart H, Watt DJ, Morgan JE, Fisk NM (2006) Galectin-1 induces skeletal muscle differentiation in human fetal mesenchymal stem cells and increases muscle regeneration. Stem Cells 24 (8):1879–1891. https://doi.org/10.1634/stemcells.2005-0564

Chawla LS, Kimmel PL (2012) Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int 82(5):516–524. https://doi.org/10.1038/ki.2012.208

Chen JL, Guo ZK, Xu C, Li YH, Hou CM, Mao N, Chen H (2002) Mesenchymal stem cells suppress allogeneic T cell responses by secretion of TGF-beta1. Zhongguo Shi Yan Xue Ye Xue Za Zhi 10(4):285–288

Chen CH, Budas GR, Churchill EN, Disatnik MH, Hurley TD, Mochly-Rosen D (2008) Activation of aldehyde dehydrogenase-2 reduces ischemic damage to the heart. Science 321(5895):1493–1495. https://doi.org/10.1126/science.1158554

Choi JS, Lee SJ, Christ GJ, Atala A, Yoo JJ (2008) The influence of electrospun aligned poly(epsilon-caprolactone)/collagen nanofiber meshes on the formation of self-aligned skeletal muscle myotubes. Biomaterials 29(19):2899–2906. https://doi.org/10.1016/j.biomaterials.2008.03.031

Christ B, Bruckner S, Winkler S (2015) The therapeutic promise of mesenchymal stem cells for liver restoration. Trends Mol Med 21(11):673–686. https://doi.org/10.1016/j.molmed.2015.09.004

Cohnheim JF (1867) Ueber entzündung und eiterung. Virch Arch Path Anat 40:1–79

Collins CA, Olsen I, Zammit PS, Heslop L, Petrie A, Partridge TA, Morgan JE (2005) Stem cell function, self-renewal, and behavioral heterogeneity of cells from the adult muscle satellite cell niche. Cell 122 (2):289–301. https://doi.org/10.1016/j.cell.2005.05.010

Connick P, Kolappan M, Crawley C, Webber DJ, Patani R, Michell AW, Du MQ, Luan SL, Altmann DR, Thompson AJ, Compston A, Scott MA, Miller DH, Chandran S (2012) Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. Lancet Neurol 11(2):150–156. https://doi.org/10.1016/S1474-4422(11)70305-2

Davatchi F, Abdollahi BS, Mohyeddin M, Shahram F, Nikbin B (2011) Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients. Int J Rheum Dis 14(2):211–215. https://doi.org/10.1111/j.1756-185X.2011.01599.x

Davatchi F, Sadeghi Abdollahi B, Mohyeddin M, Nikbin B (2016) Mesenchymal stem cell therapy for knee osteoarthritis: 5 years follow-up of three patients. Int J Rheum Dis 19(3):219–225. https://doi.org/10.1111/1756-185X.12670

De Bari C, Dell'Accio F, Vandenabeele F, Vermeesch JR, Raymackers JM, Luyten FP (2003) Skeletal muscle repair by adult human mesenchymal stem cells from synovial membrane. J Cell Biol 160(6):909–918. https://doi.org/10.1083/jcb.200212064

Dezawa M, Ishikawa H, Itokazu Y, Yoshihara T, Hoshino M, Takeda S, Ide C, Nabeshima Y (2005) Bone marrow stromal cells generate muscle cells and repair muscle degeneration. Science 309 (5732):314–317. https://doi.org/10.1126/science.1110364

Di Nicola M, Carlo-Stella C, Magni M, Milanesi M, Longoni PD, Matteucci P, Grisanti S, Gianni AM (2002) Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 99(10):3838–3843

Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop D, Horwitz E (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8(4):315–317. https://doi.org/10.1080/14653240600855905

Du Z, Wei C, Cheng K, Han B, Yan J, Zhang M, Peng C, Liu Y (2013) Mesenchymal stem cell-conditioned medium reduces liver injury and enhances regeneration in reduced-size rat liver transplantation. J Surg Res 183 (2):907–915. https://doi.org/10.1016/j.jss.2013.02.009

Duffield JS, Park KM, Hsiao LL, Kelley VR, Scadden DT, Ichimura T, Bonventre JV (2005) Restoration of tubular epithelial cells during repair of the postischemic

kidney occurs independently of bone marrow-derived stem cells. J Clin Invest 115(7):1743–1755. https://doi.org/10.1172/JCI22593

Emadedin M, Aghdami N, Taghiyar L, Fazeli R, Moghadasali R, Jahangir S, Farjad R, Baghaban Eslaminejad M (2012) Intra-articular injection of autologous mesenchymal stem cells in six patients with knee osteoarthritis. Arch Iran Med 15(7):422–428. https://doi.org/10.12157/AIM.0010

Emadedin M, Ghorbani Liastani M, Fazeli R, Mohseni F, Moghadasali R, Mardpour S, Hosseini SE, Niknejadi M, Moeininia F, Aghahossein Fanni A, Baghban Eslaminejhad R, Vosough Dizaji A, Labibzadeh N, Mirazimi Bafghi A, Baharvand H, Aghdami N (2015) Long-Term Follow-up of Intra-articular Injection of Autologous Mesenchymal Stem Cells in Patients with Knee, Ankle, or Hip Osteoarthritis. Arch Iran Med 18(6):336–344. https://doi.org/10.15186/AIM.003

Erisken C, Zhang X, Moffat KL, Levine WN, Lu HH (2013) Scaffold fiber diameter regulates human tendon fibroblast growth and differentiation. Tissue Eng Part A 19(3–4):519–528. https://doi.org/10.1089/ten.tea.2012.0072

Eslaminejad MB, Vahabi S, Shariati M, Nazarian H (2010) In vitro growth and characterization of stem cells from human dental pulp of deciduous versus permanent teeth. J Dent (Tehran) 7(4):185–195

Fang XQ, Zhang JF, Song HY, Chen ZL, Dong J, Chen X, Pan JJ, Liu B, Chen CX (2016) Effect of umbilical cord mesenchymal stem cell transplantation on immune function and prognosis of patients with decompensated hepatitis B cirrhosis. Zhonghua Gan Zang Bing Za Zhi 24(12):907–910. https://doi.org/10.3760/cma.j.issn.1007-3418.2016.12.006

Florea V, Rieger AC, DiFede DL, El-Khorazaty J, Natsumeda M, Banerjee MN, Tompkins BA, Khan A, Schulman IH, Landin AM, Mushtaq M, Golpanian S, Lowery MH, Byrnes JJ, Hendel RC, Cohen MG, Valasaki K, Pujol MV, Ghersin E, Miki R, Delgado C, Abuzeid F, Vidro-Casiano M, Saltzman RG, DaFonseca D, Caceres LV, Ramdas KN, Mendizabal A, Heldman AW, Mitrani RD, Hare JM (2017) Dose comparison study of allogeneic mesenchymal stem cells in patients with ischemic cardiomyopathy (The TRIDENT study). Circ Res 121(11):1279–1290. https://doi.org/10.1161/CIRCRESAHA.117.311827

Fouraschen SM, Pan Q, de Ruiter PE, Farid WR, Kazemier G, Kwekkeboom J, Ijzermans JN, Metselaar HJ, Tilanus HW, de Jonge J, van der Laan LJ (2012) Secreted factors of human liver-derived mesenchymal stem cells promote liver regeneration early after partial hepatectomy. Stem Cells Dev 21(13):2410–2419. https://doi.org/10.1089/scd.2011.0560

Friedenstein AJ, Chailakhjan RK, Lalykina KS (1970) The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet 3(4):393–403

Friedenstein AJ, Gorskaja JF, Kulagina NN (1976) Fibroblast precursors in normal and irradiated mouse hematopoietic organs. Exp Hematol 4(5):267–274

Fukada S, Miyagoe-Suzuki Y, Tsukihara H, Yuasa K, Higuchi S, Ono S, Tsujikawa K, Takeda S, Yamamoto H (2002) Muscle regeneration by reconstitution with bone marrow or fetal liver cells from green fluorescent protein-gene transgenic mice. J Cell Sci 115 (Pt 6):1285–1293

Galli D, Vitale M, Vaccarezza M (2014) Bone marrow-derived mesenchymal cell differentiation toward myogenic lineages: facts and perspectives. Biomed Res Int 2014:762695. https://doi.org/10.1155/2014/762695

Gang EJ, Darabi R, Bosnakovski D, Xu Z, Kamm KE, Kyba M, Perlingeiro RC (2009) Engraftment of mesenchymal stem cells into dystrophin-deficient mice is not accompanied by functional recovery. Exp Cell Res 315(15):2624–2636. https://doi.org/10.1016/j.yexcr.2009.05.009

Gangji V, Hauzeur JP, Matos C, De Maertelaer V, Toungouz M, Lambermont M (2004) Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells. A pilot study. J Bone Joint Surg Am 86-A(6):1153–1160

Gangji V, De Maertelaer V, Hauzeur JP (2011) Autologous bone marrow cell implantation in the treatment of non-traumatic osteonecrosis of the femoral head: five year follow-up of a prospective controlled study. Bone 49(5):1005–1009. https://doi.org/10.1016/j.bone.2011.07.032

Giangrande PLF (2000) The history of blood transfusion. British Journal of Haematology 110(4):758–767

Giannini S, Buda R, Cavallo M, Ruffilli A, Cenacchi A, Cavallo C, Vannini F (2010) Cartilage repair evolution in post-traumatic osteochondral lesions of the talus: from open field autologous chondrocyte to bone-marrow-derived cells transplantation. Injury 41 (11):1196–1203. https://doi.org/10.1016/j.injury.2010.09.028

Giuliani A, Manescu A, Langer M, Rustichelli F, Desiderio V, Paino F, De Rosa A, Laino L, d'Aquino R, Tirino V, Papaccio G (2013) Three years after transplants in human mandibles, histological and in-line holotomography revealed that stem cells regenerated a compact rather than a spongy bone: biological and clinical implications. Stem Cells Transl Med 2(4):316–324. https://doi.org/10.5966/sctm.2012-0136

Glassberg MK, Minkiewicz J, Toonkel RL, Simonet ES, Rubio GA, DiFede D, Shafazand S, Khan A, Pujol MV, LaRussa VF, Lancaster LH, Rosen GD, Fishman J, Mageto YN, Mendizabal A, Hare JM (2017) Allogeneic human mesenchymal stem cells in patients with idiopathic pulmonary fibrosis via intravenous delivery (AETHER): a phase i safety clinical trial. Chest 151(5):971–981. https://doi.org/10.1016/j.chest.2016.10.061

Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton

HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics, Committee, & Stroke Statistics, Subcommittee (2014) Heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation 129(3): e28–e292. https://doi.org/10.1161/01.cir.0000441139.02102.80

Goel A, Sangwan SS, Siwach RC, Ali AM (2005) Percutaneous bone marrow grafting for the treatment of tibial non-union. Injury 36(1):203–206. https://doi.org/10.1016/j.injury.2004.01.009

Goldberg A, Mitchell K, Soans J, Kim L, Zaidi R (2017) The use of mesenchymal stem cells for cartilage repair and regeneration: a systematic review. J Orthop Surg Res 12(1):39. https://doi.org/10.1186/s13018-017-0534-y

Goudenege S, Pisani DF, Wdziekonski B, Di Santo JP, Bagnis C, Dani C, Dechesne CA (2009) Enhancement of myogenic and muscle repair capacities of human adipose-derived stem cells with forced expression of MyoD. Mol Ther 17(6):1064–1072. https://doi.org/10.1038/mt.2009.67

Gussoni E, Blau HM, Kunkel LM (1997) The fate of individual myoblasts after transplantation into muscles of DMD patients. Nat Med 3(9):970–977

Hashemi SM, Hassan ZM, Pourfathollah AA, Soudi S, Shafiee A, Soleimani M (2013) Comparative immunomodulatory properties of adipose-derived mesenchymal stem cells conditioned media from BALB/c, C57BL/6, and DBA mouse strains. J Cell Biochem 114(4):955–965. https://doi.org/10.1002/jcb.24437

Hatzistergos KE, Saur D, Seidler B, Balkan W, Breton M, Valasaki K, Takeuchi LM, Landin AM, Khan A, Hare JM (2016) Stimulatory effects of mesenchymal stem cells on cKit+ cardiac stem cells are mediated by SDF1/CXCR4 and SCF/cKit signaling pathways. Circ Res 119(8):921–930. https://doi.org/10.1161/CIRCRESAHA.116.309281

Healey JH, Zimmerman PA, McDonnell JM, Lane JM (1990) Percutaneous bone marrow grafting of delayed union and nonunion in cancer patients. Clin Orthop Relat Res 256:280–285

Helbig L, Simank HG, Kroeber M, Schmidmaier G, Grutzner PA, Guehring T (2012) Core decompression combined with implantation of a demineralised bone matrix for non-traumatic osteonecrosis of the femoral head. Arch Orthop Trauma Surg 132(8):1095–1103. https://doi.org/10.1007/s00402-012-1526-3

Hernigou P, Bachir D, Galacteros F (2003) The natural history of symptomatic osteonecrosis in adults with sickle-cell disease. J Bone Joint Surg Am 85-A (3):500–504

Hernigou P, Poignard A, Beaujean F, Rouard H (2005) Percutaneous autologous bone-marrow grafting for nonunions. Influence of the number and concentration of progenitor cells. J Bone Joint Surg Am 87 (7):1430–1437. https://doi.org/10.2106/JBJS.D.02215

Horwitz EM, Prockop DJ, Fitzpatrick LA, Koo WW, Gordon PL, Neel M, Sussman M, Orchard P, Marx JC, Pyeritz RE, Brenner MK (1999) Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta. Nat Med 5(3):309–313. https://doi.org/10.1038/6529

Hosseini S, Baghaban Eslaminejad M (2017) Mesenchymal Stem Cells: An Optimistic Cell Source in Tissue Engineering for Bone Regeneration. In: Pham PV (ed) Bone and cartilage regeneration. Springer, Berlin

Hu C, Li L (2015) In vitro culture of isolated primary hepatocytes and stem cell-derived hepatocyte-like cells for liver regeneration. Protein Cell 6 (8):562–574. https://doi.org/10.1007/s13238-015-0180-2

Humphreys BD, Valerius MT, Kobayashi A, Mugford JW, Soeung S, Duffield JS, McMahon AP, Bonventre JV (2008) Intrinsic epithelial cells repair the kidney after injury. Cell Stem Cell 2(3):284–291. https://doi.org/10.1016/j.stem.2008.01.014

Hur JW, Cho TH, Park DH, Lee JB, Park JY, Chung YG (2016) Intrathecal transplantation of autologous adipose-derived mesenchymal stem cells for treating spinal cord injury: A human trial. J Spinal Cord Med 39(6):655–664. https://doi.org/10.1179/2045772315Y.0000000048

Introna M, Lucchini G, Dander E, Galimberti S, Rovelli A, Balduzzi A, Longoni D, Pavan F, Masciocchi F, Algarotti A, Mico C, Grassi A, Deola S, Cavattoni I, Gaipa G, Belotti D, Perseghin P, Parma M, Pogliani E, Golay J, Pedrini O, Capelli C, Cortelazzo S, D'Amico G, Biondi A, Rambaldi A, Biagi E (2014) Treatment of graft versus host disease with mesenchymal stromal cells: a phase I study on 40 adult and pediatric patients. Biol Blood Marrow Transplant 20 (3):375–381. https://doi.org/10.1016/j.bbmt.2013.11.033

Jeong H, Yim HW, Park HJ, Cho Y, Hong H, Kim NJ, Oh IH (2018) Mesenchymal stem cell therapy for ischemic heart disease: systematic review and meta-analysis. Int J Stem Cells. https://doi.org/10.15283/ijsc17061

Jiang PC, Xiong WP, Wang G, Ma C, Yao WQ, Kendell SF, Mehling BM, Yuan XH, Wu DC (2013) A clinical trial report of autologous bone marrow-derived mesenchymal stem cell transplantation in patients with spinal cord injury. Exp Ther Med 6(1):140–146. https://doi.org/10.3892/etm.2013.1083

Jo CH, Lee YG, Shin WH, Kim H, Chai JW, Jeong EC, Kim JE, Shim H, Shin JS, Shin IS, Ra JC, Oh S, Yoon KS (2014) Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. Stem Cells 32 (5):1254–1266. https://doi.org/10.1002/stem.1634

Jo CH, Chai JW, Jeong EC, Oh S, Shin JS, Shim H, Yoon KS (2017) Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a 2-year follow-up study. Am J Sports Med 45 (12):2774–2783. https://doi.org/10.1177/0363546517716641

Kanemura H, Go MJ, Shikamura M, Nishishita N, Sakai N, Kamao H, Mandai M, Morinaga C, Takahashi M, Kawamata S (2014) Tumorigenicity studies of induced pluripotent stem cell (iPSC)-derived retinal pigment epithelium (RPE) for the treatment of age-related macular degeneration. PLoS One 9(1): e85336. https://doi.org/10.1371/journal.pone.0085336

Karussis D, Karageorgiou C, Vaknin-Dembinsky A, Gowda-Kurkalli B, Gomori JM, Kassis I, Bulte JW, Petrou P, Ben-Hur T, Abramsky O, Slavin S (2010) Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. Arch Neurol 67 (10):1187–1194. https://doi.org/10.1001/archneurol.2010.248

Khojasteh A, Eslaminejad MB, Nazarian H, Morad G, Dashti SG, Behnia H, Stevens M (2013) Vertical bone augmentation with simultaneous implant placement using particulate mineralized bone and mesenchymal stem cells: a preliminary study in rabbit. J Oral Implantol 39(1):3–13. https://doi.org/10.1563/AAID-JOI-D-10-00206

Khojasteh A, Fahimipour F, Jafarian M, Sharifi D, Jahangir S, Khayyatan F, Baghaban Eslaminejad M (2017) Bone engineering in dog mandible: Coculturing mesenchymal stem cells with endothelial progenitor cells in a composite scaffold containing vascular endothelial growth factor. J Biomed Mater Res B Appl Biomater 105(7):1767–1777. https://doi.org/10.1002/jbm.b.33707

Kim YI, Ryu JS, Yeo JE, Choi YJ, Kim YS, Ko K, Koh YG (2014) Overexpression of TGF-beta1 enhances chondrogenic differentiation and proliferation of human synovium-derived stem cells. Biochem Biophys Res Commun 450(4):1593–1599. https://doi.org/10.1016/j.bbrc.2014.07.045

Knutsen G, Drogset JO, Engebretsen L, Grontvedt T, Isaksen V, Ludvigsen TC, Roberts S, Solheim E, Strand T, Johansen O (2007) A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. J Bone Joint Surg Am 89(10):2105–2112. https://doi.org/10.2106/JBJS.G.00003

Koh YG, Choi YJ, Kwon SK, Kim YS, Yeo JE (2015) Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 23 (5):1308–1316. https://doi.org/10.1007/s00167-013-2807-2

Kopen GC, Prockop DJ, Phinney DG (1999) Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. Proc Natl Acad Sci U S A 96(19):10711–10716

Krampera M, Glennie S, Dyson J, Scott D, Laylor R, Simpson E, Dazzi F (2003) Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. Blood 101(9):3722–3729. https://doi.org/10.1182/blood-2002-07-2104

Kuriyan AE, Albini TA, Townsend JH, Rodriguez M, Pandya HK, Leonard RE 2nd, Parrott MB, Rosenfeld PJ, Flynn HW Jr, Goldberg JL (2017) Vision loss after intravitreal injection of autologous "Stem Cells" for AMD. N Engl J Med 376(11):1047–1053. https://doi.org/10.1056/NEJMoa1609583

Labibzadeh N, Emadedin M, Fazeli R, Mohseni F, Hosseini SE, Moghadasali R, Mardpour S, Azimian V, Ghorbani Liastani M, Mirazimi Bafghi A, Baghaban Eslaminejad M, Aghdami N (2016) Mesenchymal stromal cells implantation in combination with platelet lysate product is safe for reconstruction of human long bone nonunion. Cell J 18(3):302–309

Le Blanc K, Gotherstrom C, Ringden O, Hassan M, McMahon R, Horwitz E, Anneren G, Axelsson O, Nunn J, Ewald U, Norden-Lindeberg S, Jansson M, Dalton A, Astrom E, Westgren M (2005) Fetal mesenchymal stem-cell engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. Transplantation 79(11):1607–1614

Lee HY, Hong IS (2017) Double-edged sword of mesenchymal stem cells: cancer-promoting versus therapeutic potential. Cancer Sci 108(10):1939–1946. https://doi.org/10.1111/cas.13334

Lee JY, Zhou Z, Taub PJ, Ramcharan M, Li Y, Akinbiyi T, Maharam ER, Leong DJ, Laudier DM, Ruike T, Torina PJ, Zaidi M, Majeska RJ, Schaffler MB, Flatow EL, Sun HB (2011) BMP-12 treatment of adult mesenchymal stem cells in vitro augments tendon-like tissue formation and defect repair in vivo. PLoS One 6(3):e17531. https://doi.org/10.1371/journal.pone.0017531

Lee HC, An SG, Lee HW, Park JS, Cha KS, Hong TJ, Park JH, Lee SY, Kim SP, Kim YD, Chung SW, Bae YC, Shin YB, Kim JI, Jung JS (2012) Safety and effect of adipose tissue-derived stem cell implantation in patients with critical limb ischemia: a pilot study. Circ J 76(7):1750–1760

Lee SY, Kim HJ, Choi D (2015) Cell sources, liver support systems and liver tissue engineering: alternatives to liver transplantation. Int J Stem Cells 8(1):36–47. https://doi.org/10.15283/ijsc.2015.8.1.36

Li Q, Tang J, Wang R, Bei C, Xin L, Zeng Y, Tang X (2011) Comparing the chondrogenic potential in vivo of autogeneic mesenchymal stem cells derived from different tissues. Artif Cells Blood Substit Immobil Biotechnol 39(1):31–38. https://doi.org/10.3109/10731191003776769

Liechty KW, MacKenzie TC, Shaaban AF, Radu A, Moseley AM, Deans R, Marshak DR, Flake AW

(2000) Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after in utero transplantation in sheep. Nat Med 6(11):1282–1286. https://doi.org/10.1038/81395

Linero I, Chaparro O (2014) Paracrine effect of mesenchymal stem cells derived from human adipose tissue in bone regeneration. PLoS One 9(9):e107001. https://doi.org/10.1371/journal.pone.0107001

Liu KD, Brakeman PR (2008) Renal repair and recovery. Crit Care Med 36(4 Suppl):S187–S192. https://doi.org/10.1097/CCM.0b013e318168ca4a

Liu Y, Yan X, Sun Z, Chen B, Han Q, Li J, Zhao RC (2007) Flk-1+ adipose-derived mesenchymal stem cells differentiate into skeletal muscle satellite cells and ameliorate muscular dystrophy in mdx mice. Stem Cells Dev 16(5):695–706. https://doi.org/10.1089/scd.2006.0118

Liu G, Zhang Y, Liu B, Sun J, Li W, Cui L (2013) Bone regeneration in a canine cranial model using allogeneic adipose derived stem cells and coral scaffold. Biomaterials 34(11):2655–2664. https://doi.org/10.1016/j.biomaterials.2013.01.004

Liu M, Zeng X, Wang J, Fu Z, Wang J, Liu M, Ren D, Yu B, Zheng L, Hu X, Shi W, Xu J (2016) Immunomodulation by mesenchymal stem cells in treating human autoimmune disease-associated lung fibrosis. Stem Cell Res Ther 7(1):63. https://doi.org/10.1186/s13287-016-0319-y

Lombard T, Neirinckx V, Rogister B, Gilon Y, Wislet S (2016) Medication-related osteonecrosis of the jaw: new insights into molecular mechanisms and cellular therapeutic approaches. Stem Cells Int 2016:8768162. https://doi.org/10.1155/2016/8768162

Ma K, Liao S, He L, Lu J, Ramakrishna S, Chan CK (2011) Effects of nanofiber/stem cell composite on wound healing in acute full-thickness skin wounds. Tissue Eng Part A 17(9-10):1413–1424. https://doi.org/10.1089/ten.TEA.2010.0373

Makhlough A, Shekarchian S, Moghadasali R, Einollahi B, Hosseini SE, Jaroughi N, Bolurieh T, Baharvand H, Aghdami N (2017) Safety and tolerability of autologous bone marrow mesenchymal stromal cells in ADPKD patients. Stem Cell Res Ther 8(1):116. https://doi.org/10.1186/s13287-017-0557-7

Makihara T, Yoshioka T, Sugaya H, Yamazaki M, Mishima H (2017) Autologous concentrated bone marrow grafting for the treatment of osteonecrosis of the humeral head: a report of five shoulders in four cases. Case Rep Orthop 2017:4898057. https://doi.org/10.1155/2017/4898057

Mao Q, Jin H, Liao F, Xiao L, Chen D, Tong P (2013) The efficacy of targeted intraarterial delivery of concentrated autologous bone marrow containing mononuclear cells in the treatment of osteonecrosis of the femoral head: a five year follow-up study. Bone 57(2):509–516. https://doi.org/10.1016/j.bone.2013.08.022

Mazzini L, Fagioli F, Boccaletti R, Mareschi K, Oliveri G, Olivieri C, Pastore I, Marasso R, Madon E (2003) Stem cell therapy in amyotrophic lateral sclerosis: a methodological approach in humans. Amyotroph Lateral Scler Other Motor Neuron Disord 4(3):158–161

Mendell JR, Kissel JT, Amato AA, King W, Signore L, Prior TW, Sahenk Z, Benson S, McAndrew PE, Rice R et al (1995) Myoblast transfer in the treatment of Duchenne's muscular dystrophy. N Engl J Med 333(13):832–838. https://doi.org/10.1056/NEJM199509283331303

Mendez JJ, Ghaedi M, Steinbacher D, Niklason LE (2014) Epithelial cell differentiation of human mesenchymal stromal cells in decellularized lung scaffolds. Tissue Eng Part A 20(11-12):1735–1746. https://doi.org/10.1089/ten.TEA.2013.0647

Moghadasali R, Mutsaers HA, Azarnia M, Aghdami N, Baharvand H, Torensma R, Wilmer MJ, Masereeuw R (2013) Mesenchymal stem cell-conditioned medium accelerates regeneration of human renal proximal tubule epithelial cells after gentamicin toxicity. Exp Toxicol Pathol 65(5):595–600. https://doi.org/10.1016/j.etp.2012.06.002

Mohamadnejad M, Namiri M, Bagheri M, Hashemi SM, Ghanaati H, Zare Mehrjardi N, Kazemi Ashtiani S, Malekzadeh R, Baharvand H (2007) Phase 1 human trial of autologous bone marrow-hematopoietic stem cell transplantation in patients with decompensated cirrhosis. World J Gastroenterol 13(24):3359–3363

Moon KH, Ko IK, Yoo JJ, Atala A (2016) Kidney diseases and tissue engineering. Methods 99:112–119. https://doi.org/10.1016/j.ymeth.2015.06.020

Morigi M, Imberti B, Zoja C, Corna D, Tomasoni S, Abbate M, Rottoli D, Angioletti S, Benigni A, Perico N, Alison M, Remuzzi G (2004) Mesenchymal stem cells are renotropic, helping to repair the kidney and improve function in acute renal failure. J Am Soc Nephrol 15(7):1794–1804

Nadri S, Kazemi B, Eslaminejad MB, Yazdani S, Soleimani M (2013a) High yield of cells committed to the photoreceptor-like cells from conjunctiva mesenchymal stem cells on nanofibrous scaffolds. Mol Biol Rep 40(6):3883–3890. https://doi.org/10.1007/s11033-012-2360-y

Nadri S, Yazdani S, Arefian E, Gohari Z, Eslaminejad MB, Kazemi B, Soleimani M (2013b) Mesenchymal stem cells from trabecular meshwork become photoreceptor-like cells on amniotic membrane. Neurosci Lett 541:43–48. https://doi.org/10.1016/j.neulet.2012.12.055

Nakanishi C, Yamagishi M, Yamahara K, Hagino I, Mori H, Sawa Y, Yagihara T, Kitamura S, Nagaya N (2008) Activation of cardiac progenitor cells through paracrine effects of mesenchymal stem cells. Biochem Biophys Res Commun 374(1):11–16. https://doi.org/10.1016/j.bbrc.2008.06.074

Negroni E, Riederer I, Chaouch S, Belicchi M, Razini P, Di Santo J, Torrente Y, Butler-Browne GS, Mouly V (2009) In vivo myogenic potential of human CD133+ muscle-derived stem cells: a quantitative study. Mol Ther 17(10):1771–1778. https://doi.org/10.1038/mt.2009.167

Ohkoshi S, Hara H, Hirono H, Watanabe K, Hasegawa K (2017) Regenerative medicine using dental pulp stem cells for liver diseases. World J Gastrointest Pharmacol Ther 8(1):1–6. https://doi.org/10.4292/wjgpt.v8.i1.1

Ortiz LA, Gambelli F, McBride C, Gaupp D, Baddoo M, Kaminski N, Phinney DG (2003) Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects. Proc Natl Acad Sci U S A 100(14):8407–8411. https://doi.org/10.1073/pnas.1432929100

Pak J (2012) Autologous adipose tissue-derived stem cells induce persistent bone-like tissue in osteonecrotic femoral heads. Pain Physician 15(1):75–85

Park CW, Kim KS, Bae S, Son HK, Myung PK, Hong HJ, Kim H (2009) Cytokine secretion profiling of human mesenchymal stem cells by antibody array. Int J Stem Cells 2(1):59–68

Pers YM, Rackwitz L, Ferreira R, Pullig O, Delfour C, Barry F, Sensebe L, Casteilla L, Fleury S, Bourin P, Noel D, Canovas F, Cyteval C, Lisignoli G, Schrauth J, Haddad D, Domergue S, Noeth U, Jorgensen C, Consortium, Adipoa (2016) Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee: a phase I dose-escalation trial. Stem Cells Transl Med 5 (7):847–856. https://doi.org/10.5966/sctm.2015-0245

Piscaglia AC, Campanale M, Gasbarrini A, Gasbarrini G (2010) Stem cell-based therapies for liver diseases: state of the art and new perspectives. Stem Cells Int 2010:259461. https://doi.org/10.4061/2010/259461

Ponte AL, Marais E, Gallay N, Langonne A, Delorme B, Herault O, Charbord P, Domenech J (2007) The in vitro migration capacity of human bone marrow mesenchymal stem cells: comparison of chemokine and growth factor chemotactic activities. Stem Cells 25(7):1737–1745. https://doi.org/10.1634/stemcells.2007-0054

Prodromidi EI, Poulsom R, Jeffery R, Roufosse CA, Pollard PJ, Pusey CD, Cook HT (2006) Bone marrow-derived cells contribute to podocyte regeneration and amelioration of renal disease in a mouse model of Alport syndrome. Stem Cells 24(11):2448–2455. https://doi.org/10.1634/stemcells.2006-0201

Quarto R, Mastrogiacomo M, Cancedda R, Kutepov SM, Mukhachev V, Lavroukov A, Kon E, Marcacci M (2001) Repair of large bone defects with the use of autologous bone marrow stromal cells. N Engl J Med 344(5):385–386. https://doi.org/10.1056/NEJM200102013440516

Richardson SM, Kalamegam G, Pushparaj PN, Matta C, Memic A, Khademhosseini A, Mobasheri R, Poletti FL, Hoyland JA, Mobasheri A (2016) Mesenchymal stem cells in regenerative medicine: focus on articular cartilage and intervertebral disc regeneration. Methods 99:69–80. https://doi.org/10.1016/j.ymeth.2015.09.015

Roberts TT, Rosenbaum AJ (2012) Bone grafts, bone substitutes and orthobiologics: the bridge between basic science and clinical advancements in fracture healing. Organogenesis 8(4):114–124. https://doi.org/10.4161/org.23306

Rosines E, Schmidt HJ, Nigam SK (2007) The effect of hyaluronic acid size and concentration on branching morphogenesis and tubule differentiation in developing kidney culture systems: potential applications to engineering of renal tissues. Biomaterials 28 (32):4806–4817. https://doi.org/10.1016/j.biomaterials.2007.07.034

Ruban P, Yeo SJ, Seow KH, Tan SK, Ng SC (2000) Deep vein thrombosis after total knee replacement. Ann Acad Med Singapore 29(4):428–433

Ruiz M, Cosenza S, Maumus M, Jorgensen C, Noel D (2016) Therapeutic application of mesenchymal stem cells in osteoarthritis. Expert Opin Biol Ther 16 (1):33–42. https://doi.org/10.1517/14712598.2016.1093108

Rushkevich YN, Kosmacheva SM, Zabrodets GV, Ignatenko SI, Goncharova NV, Severin IN, Likhachev SA, Potapnev MP (2015) The use of autologous mesenchymal stem cells for cell therapy of patients with amyotrophic lateral sclerosis in belarus. Bull Exp Biol Med 159(4):576–581. https://doi.org/10.1007/s10517-015-3017-3

Sackstein R (2011) The biology of CD44 and HCELL in hematopoiesis: the 'step 2-bypass pathway' and other emerging perspectives. Curr Opin Hematol 18 (4):239–248. https://doi.org/10.1097/MOH.0b013e3283476140

Sekiya I, Vuoristo JT, Larson BL, Prockop DJ (2002) In vitro cartilage formation by human adult stem cells from bone marrow stroma defines the sequence of cellular and molecular events during chondrogenesis. Proc Natl Acad Sci U S A 99(7):4397–4402. https://doi.org/10.1073/pnas.052716199

Sen RK, Tripathy SK, Aggarwal S, Marwaha N, Sharma RR, Khandelwal N (2012) Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis: a randomized control study. J Arthroplasty 27 (5):679–686. https://doi.org/10.1016/j.arth.2011.08.008

Shi M, Zhang Z, Xu R, Lin H, Fu J, Zou Z, Zhang A, Shi J, Chen L, Lv S, He W, Geng H, Jin L, Liu Z, Wang FS (2012) Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. Stem Cells Transl Med 1 (10):725–731. https://doi.org/10.5966/sctm.2012-0034

Singaravelu K, Padanilam BJ (2009) In vitro differentiation of MSC into cells with a renal tubular epithelial-like phenotype. Ren Fail 31(6):492–502

Song JJ, Guyette JP, Gilpin SE, Gonzalez G, Vacanti JP, Ott HC (2013) Regeneration and experimental orthotopic transplantation of a bioengineered kidney. Nat Med 19(5):646–651. https://doi.org/10.1038/nm.3154

Souied E, Pulido J, Staurenghi G (2017) Autologous induced stem-cell-derived retinal cells for macular degeneration. N Engl J Med 377(8):792. https://doi.org/10.1056/NEJMc1706274

Spanoudes K, Gaspar D, Pandit A, Zeugolis DI (2014) The biophysical, biochemical, and biological toolbox for tenogenic phenotype maintenance in vitro. Trends Biotechnol 32(9):474–482. https://doi.org/10.1016/j.tibtech.2014.06.009

Spasovski D, Spasovski V, Bascarevic Z, Stojiljkovic M, Vreca M, Andelkovic M, Pavlovic S (2018) Intra-articular injection of autologous adipose-derived mesenchymal stem cells in the treatment of knee osteoarthritis. J Gene Med 20(1). https://doi.org/10.1002/jgm.3002

Squillaro T, Peluso G, Galderisi U (2016) Clinical trials with mesenchymal stem cells: an update. Cell Transplant 25(5):829–848. https://doi.org/10.3727/096368915X689622

Stockmann P, Park J, von Wilmowsky C, Nkenke E, Felszeghy E, Dehner JF, Schmitt C, Tudor C, Schlegel KA (2012) Guided bone regeneration in pig calvarial bone defects using autologous mesenchymal stem/progenitor cells – a comparison of different tissue sources. J Craniomaxillofac Surg 40(4):310–320. https://doi.org/10.1016/j.jcms.2011.05.004

Stolk J, Broekman W, Mauad T, Zwaginga JJ, Roelofs H, Fibbe WE, Oostendorp J, Bajema I, Versteegh MI, Taube C, Hiemstra PS (2016) A phase I study for intravenous autologous mesenchymal stromal cell administration to patients with severe emphysema. QJM 109(5):331–336. https://doi.org/10.1093/qjmed/hcw001

Taghiyar L, Hesaraki M, Sayahpour FA, Satarian L, Hosseini S, Aghdami N, Baghaban Eslaminejad M (2017) Msh homeobox 1 (Msx1)- and Msx2-overexpressing bone marrow-derived mesenchymal stem cells resemble blastema cells and enhance regeneration in mice. J Biol Chem 292(25):10520–10533. https://doi.org/10.1074/jbc.M116.774265

Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126(4):663–676. https://doi.org/10.1016/j.cell.2006.07.024

Tawonsawatruk T, West CC, Murray IR, Soo C, Peault B, Simpson AH (2016) Adipose derived pericytes rescue fractures from a failure of healing–non-union. Sci Rep 6:22779. https://doi.org/10.1038/srep22779

Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic stem cell lines derived from human blastocysts. Science 282(5391):1145–1147

Timmers L, Lim SK, Hoefer IE, Arslan F, Lai RC, van Oorschot AA, Goumans MJ, Strijder C, Sze SK, Choo A, Piek JJ, Doevendans PA, Pasterkamp G, de Kleijn DP (2011) Human mesenchymal stem cell-conditioned medium improves cardiac function following myocardial infarction. Stem Cell Res 6(3):206–214. https://doi.org/10.1016/j.scr.2011.01.001

Toma C, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD (2002) Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. Circulation 105(1):93–98

Torrente Y, Belicchi M, Marchesi C, D'Antona G, Cogiamanian F, Pisati F, Gavina M, Giordano R, Tonlorenzi R, Fagiolari G, Lamperti C, Porretti L, Lopa R, Sampaolesi M, Vicentini L, Grimoldi N, Tiberio F, Songa V, Baratta P, Prelle A, Forzenigo L, Guglieri M, Pansarasa O, Rinaldi C, Mouly V, Butler-Browne GS, Comi GP, Biondetti P, Moggio M, Gaini SM, Stocchetti N, Priori A, D'Angelo MG, Turconi A, Bottinelli R, Cossu G, Rebulla P, Bresolin N (2007) Autologous transplantation of muscle-derived CD133 + stem cells in Duchenne muscle patients. Cell Transplant 16(6):563–577

Ulivi V, Tasso R, Cancedda R, Descalzi F (2014) Mesenchymal stem cell paracrine activity is modulated by platelet lysate: induction of an inflammatory response and secretion of factors maintaining macrophages in a proinflammatory phenotype. Stem Cells Dev 23(16):1858–1869. https://doi.org/10.1089/scd.2013.0567

van Gelder T, van Schaik RH, Hesselink DA (2014) Pharmacogenetics and immunosuppressive drugs in solid organ transplantation. Nat Rev Nephrol 10(12):725–731. https://doi.org/10.1038/nrneph.2014.172

Vandenburgh HH, Karlisch P, Farr L (1988) Maintenance of highly contractile tissue-cultured avian skeletal myotubes in collagen gel. Vitro Cell Dev Biol 24(3):166–174

Veronesi F, Salamanna F, Tschon M, Maglio M, Nicoli Aldini N, Fini M (2017) Mesenchymal stem cells for tendon healing: what is on the horizon? J Tissue Eng Regen Med 11(11):3202–3219. https://doi.org/10.1002/term.2209

Wakitani S, Mitsuoka T, Nakamura N, Toritsuka Y, Nakamura Y, Horibe S (2004) Autologous bone marrow stromal cell transplantation for repair of full-thickness articular cartilage defects in human patellae: two case reports. Cell Transplant 13(5):595–600

Wang C, Li Y, Yang M, Zou Y, Liu H, Liang Z, Yin Y, Niu G, Yan Z, Zhang B (2018) Efficient differentiation of bone marrow mesenchymal stem cells into endothelial cells in vitro. Eur J Vasc Endovasc Surg 55(2):257–265. https://doi.org/10.1016/j.ejvs.2017.10.012

Weng JY, Du X, Geng SX, Peng YW, Wang Z, Lu ZS, Wu SJ, Luo CW, Guo R, Ling W, Deng CX, Liao PJ, Xiang AP (2010) Mesenchymal stem cell as salvage treatment for refractory chronic GVHD. Bone Marrow Transplant 45(12):1732–1740. https://doi.org/10.1038/bmt.2010.195

Wiley LA, Burnight ER, Songstad AE, Drack AV, Mullins RF, Stone EM, Tucker BA (2015) Patient-specific induced pluripotent stem cells (iPSCs) for the study and treatment of retinal degenerative diseases. Prog Retin Eye Res 44:15–35. https://doi.org/10.1016/j.preteyeres.2014.10.002

Wilson JG, Liu KD, Zhuo H, Caballero L, McMillan M, Fang X, Cosgrove K, Vojnik R, Calfee CS, Lee JW, Rogers AJ, Levitt J, Wiener-Kronish J, Bajwa EK,

Leavitt A, McKenna D, Thompson BT, Matthay MA (2015) Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respir Med 3 (1):24–32. https://doi.org/10.1016/S2213-2600(14)70291-7

Witt R, Weigand A, Boos AM, Cai A, Dippold D, Boccaccini AR, Schubert DW, Hardt M, Lange C, Arkudas A, Horch RE, Beier JP (2017) Mesenchymal stem cells and myoblast differentiation under HGF and IGF-1 stimulation for 3D skeletal muscle tissue engineering. BMC Cell Biol 18(1):15. https://doi.org/10.1186/s12860-017-0131-2

Wong KL, Lee KB, Tai BC, Law P, Lee EH, Hui JH (2013) Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. Arthroscopy 29(12):2020–2028. https://doi.org/10.1016/j.arthro.2013.09.074

Wu Y, Chen L, Scott PG, Tredget EE (2007) Mesenchymal stem cells enhance wound healing through differentiation and angiogenesis. Stem Cells 25 (10):2648–2659. https://doi.org/10.1634/stemcells.2007-0226

Wynn RF, Hart CA, Corradi-Perini C, O'Neill L, Evans CA, Wraith JE, Fairbairn LJ, Bellantuono I (2004) A small proportion of mesenchymal stem cells strongly expresses functionally active CXCR4 receptor capable of promoting migration to bone marrow. Blood 104 (9):2643–2645. https://doi.org/10.1182/blood-2004-02-0526

Xiao W, Guo S, Gao C, Dai G, Gao Y, Li M, Wang X, Hu D (2017) A randomized comparative study on the efficacy of intracoronary infusion of autologous bone marrow mononuclear cells and mesenchymal stem cells in patients with dilated cardiomyopathy. Int Heart J 58(2):238–244. https://doi.org/10.1536/ihj.16-328

Xu G, Zhang L, Ren G, Yuan Z, Zhang Y, Zhao RC, Shi Y (2007) Immunosuppressive properties of cloned bone marrow mesenchymal stem cells. Cell Res 17 (3):240–248. https://doi.org/10.1038/cr.2007.4

Yan X, Liu Y, Han Q, Jia M, Liao L, Qi M, Zhao RC (2007) Injured microenvironment directly guides the differentiation of engrafted Flk-1(+) mesenchymal stem cell in lung. Exp Hematol 35(9):1466–1475. https://doi.org/10.1016/j.exphem.2007.05.012

Yao L, Bestwick CS, Bestwick LA, Maffulli N, Aspden RM (2006) Phenotypic drift in human tenocyte culture. Tissue Eng 12(7):1843–1849. https://doi.org/10.1089/ten.2006.12.1843

Yin H, Price F, Rudnicki MA (2013) Satellite cells and the muscle stem cell niche. Physiol Rev 93(1):23–67. https://doi.org/10.1152/physrev.00043.2011

Yoon YS, Park JS, Tkebuchava T, Luedeman C, Losordo DW (2004) Unexpected severe calcification after transplantation of bone marrow cells in acute myocardial infarction. Circulation 109(25):3154–3157. https://doi.org/10.1161/01.CIR.0000134696.08436.65

Yun SP, Ryu JM, Jang MW, Han HJ (2011) Interaction of profilin-1 and F-actin via a beta-arrestin-1/JNK signaling pathway involved in prostaglandin E(2)-induced human mesenchymal stem cells migration and proliferation. J Cell Physiol 226(2):559–571. https://doi.org/10.1002/jcp.22366

Zamiri B, Shahidi S, Eslaminejad MB, Khoshzaban A, Gholami M, Bahramnejad E, Moghadasali R, Mardpour S, Aghdami N (2013) Reconstruction of human mandibular continuity defects with allogenic scaffold and autologous marrow mesenchymal stem cells. J Craniofac Surg 24(4):1292–1297. https://doi.org/10.1097/SCS.0b013e318294288a

Zhao D, Cui D, Wang B, Tian F, Guo L, Yang L, Liu B, Yu X (2012) Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. Bone 50(1):325–330. https://doi.org/10.1016/j.bone.2011.11.002

Zhao L, Liu X, Zhang Y, Liang X, Ding Y, Xu Y, Fang Z, Zhang F (2016) Enhanced cell survival and paracrine effects of mesenchymal stem cells overexpressing hepatocyte growth factor promote cardioprotection in myocardial infarction. Exp Cell Res 344(1):30–39. https://doi.org/10.1016/j.yexcr.2016.03.024