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Mesenchymal Stem/Stromal Cells and Hydrogel Scaffolds for Tissue Engineering

Leisheng Zhang and Zhihai Han

Abstract

Hydrogels are splendid biomaterials and play a critical role in multiple applications for disease management via offering a microenvironment for drug metabolism and exerting the bonding effect attribute to the preferable physical and chemical properties. State-of-the-art renewal has indicated the combination of hydrogels with mesenchymal stem/stromal cells (MSCs), which are heterogeneous populations with unique hematopoietic-supporting and immunoregulatory properties. For decades, we and other investigators have demonstrated the promising prospects of MSCs in regenerative medicine, and in particular, for the administration of recurrent and refractory disease. Very recently, we took advantage of the hydrogel/MSC composite for the applications in osteoarthritis, burn wounds, and refractory wounds associated with diabetic foot as well. Strikingly, the composite showed superiority in continuous improvement of the biological functions of the injured areas over hydrogels or MSCs, respectively. Collectively, hydrogel-based biomaterials are of importance for disease treatment and the accompanied regenerative medicine. Therefore, in this chapter, we will summarize the latest updates of hydrogel/MSCs composite in tissue engineering and put forward the direction of hotspot issues in the future including hydrogel/MSC and hydrogel/MSC-exosome in preclinical and clinical studies.

Keywords: mesenchymal stem/stromal cells, exosomes, hydrogel scaffolds, tissue engineering, regenerative medicine

1. Introduction

Mesenchymal stem/stromal cells (MSCs) have been acknowledged as medicinal signaling cells as well as the most important niche cells in the microenvironment, and possess advantaged properties such as immunomodulatory capacity, hematopoietic-supporting effect and multi-lineage differentiation potential towards adipocytes, osteoblasts and chondrocytes, which thus hold promising prospects for tissue engineering and regenerative medicine [1–3]. MSCs were first isolated from bone marrow in the 1960s, and followed by various stromal fractions of adult tissues [4, 5], perinatal tissues [6–8], and even derived from stem cells [9–11]. For decades, due to the limitation of unique biomarkers and the wide range of cell sources, MSCs

are recognized as heterogeneous populations with great heterogeneity in cellular phenotypes and transcriptome characteristics [12–14]. Generally, MSCs with diverse origins mainly function via direct- or trans-differentiation, paracrine or autocrine, homing, dual immunomodulation, neovascularization, and constitutive microenvironment [4, 15, 16]. To date, more than 1340 MSC-based clinical trials have been registered for various disease treatment according to the ClinicalTrials.gov website. For instance, we and other investigators have indicated the therapeutic effects of MSCs upon multiple refractory and recurrent disorders including acute graft-versus-host diseases (aGVHD) [17], aplastic anemia [18, 19], osteoarthritis [11, 20], critical limb ischemia (CLI) [9], acute-on-chronic liver failure (ACLF) [21], Parkinson's syndrome [22], acute myocardial infarction (AMI) [23], rheumatoid arthritis (RA) [24], and coronavirus disease 2019 (COVID-19) [15, 25]. It's noteworthy that the variation of the therapeutic efficacy of MSCs upon acute liver failure and aGVHD has also been respectively observed by Zhang et al. and us, which further indicated the necessity and urgency of developing tissue engineering including biomaterials, three-dimensional (3D) printing, and MSC-based gene therapy [26, 27].

Simultaneously, state-of-the-art updates have further suggested the preferable application of biomaterial/MSC composite as well [11, 28, 29]. Of the current natural extracellular matrices (ECMs), hydrogels have been regarded as the most promising alternative biomaterials attribute to their excellent swelling property and the resemblance to soft tissues [11, 30]. In particular, synthetic biomimetic hydrogels with appropriate mechanical behavior and predictable biodegradation property can be easily synthesized and modulated for facilitating the biological phenotypes and bio-applications of the encapsulated MSCs such as adhesion, migration, differentiation, proliferation, and apoptosis [30]. For instance, Gwon et al. and Huang et al. reported the influence of heparin-hyaluronic acid (HA) hydrogel upon cellular activity and hydrogel scaffolds for the differentiation of adipose-derived stem cells, respectively [30, 31]. Very recently, we took advantage of the HA hydrogel/MSC composite and demonstrated the reinforced cell vitality of human pluripotent stem cell-derived MSCs (hPSC-MSCs) over monolayer-cultured MSCs for chondrogenesis and the management of osteoarthritis rabbits [11].

Herein, we summarize the current progress in MSCs or MSC-derived exosomes and hydrogel scaffold for tissue engineering, and in particular, the potentially reinforcing or attenuating effects of hydrogel scaffold with unique biochemical and biophysical properties upon the MSC-based cytototherapy for regenerative medicine.

2. The cell sources of MSCs for tissue engineering

Not until 2006, the International Society for Cellular Therapy (ISCT) defined the preliminary criteria of defining multipotent MSCs including adherent property, multi-lineage differentiation capacities *in vitro* towards adipocytes, osteoblasts, and chondrocytes, together with high-levels of mesenchymal biomarker expression (CD73, CD90, and CD105) whereas minimal expression of hematopoietic or endothelial markers (CD31, CD34, and CD45) [32]. After that, numerous studies aiming at dissecting the similarities and differences in biological phenotypes and biofunctions as well as transcriptome characteristics of MSCs derived from adult tissue, perinatal tissue, and PSCs have been extensively conducted (**Table 1**).

Classification	Type of scaffold	Disease	Applications	Reference
Adult tissue-derived MSCs	PF-127 hydrogel/AD-MSC	Diabetic wound healing	Preclinical study	Kaisang et al. [33]
	AdhHG hydrogel/G-MSCs	Craniofacial bone tissue regeneration	Preclinical study	Hasani-Sadrabadi et al. [34]
	HPCH-PCL-nHA hydrogel/BM-MSC	Massive bone defects	Preclinical study	Ji et al. [35]
Perinatal tissue-derived MSCs	PF-127 hydrogel/UC-MSC-exo	Chronic diabetic wound healing	Preclinical study	Yang et al. [36]
	Chitosan hydrogel/P-MSC-exo	Hindlimb ischemia	Preclinical study	Zhang et al. [37]
	Collagen/UC-MSCs	POF	Clinical study	Ding et al. [38]
Pluripotent stem cell-derived MSCs	HA hydrogel/PSC-MSCs	Osteoarthritis	Preclinical study	Zhang et al. [11]
	Hydrogel/iPSC-MSCs	Endometrial injury	Preclinical study	Ji et al. [39]

Table 1.
Representative applications of HA/MSC-based scaffold in tissue engineering.

2.1 Adult tissue-derived MSCs

As mentioned above, adult tissue-derived MSCs hold vast prospect in tissue repairing and organ reconstruction [3]. To date, massive literatures have reported the isolation and identification of MSCs from various adult tissues such as adipose tissue, bone marrow, synovium, dental pulp, peripheral blood, muscle tendon, and menstrual blood [40, 41]. According to the ClinicalTrials.gov website, a total of 1096 trials have been registered worldwide against disorders such as acute respiratory distress syndrome (ARDS), CLI, AMI, anoxic or hypoxic brain injury, moderate-to-severe Crohn’s disease, idiopathic pulmonary fibrosis (IPF), and COVID-19. For example, a phase I interventional trial was led by Dr. Jesus JV Vaquero Crespo in Puerta de Hierro University Hospital was aiming to evaluate the security of local administration of autologous bone marrow-derived MSCs (BM-MSCs) in traumatic injuries of the spinal cord (NCT01909154), which was consistent with another study by Geffner and their colleagues [42]. In details, 12 participants received 1×10^8 BM-MSCs by intrathecal injection (subarachnoid and intramedullary), and another 3×10^7 BM-MSCs by subarachnoid administration after 3 months depending on centromedullary post-traumatic injury. The safety outcomes of the patients were evaluated according to vital signs (ECG, blood pressure, and heart rate) and possibility of adverse reaction (headache, meningeal irritation, and infectious complications). The secondary outcomes were quantized from the view of sensitivity recovery (e.g., surface sensitivity and pain sensitivity), level of chronic pain, neurophysiological parameters, maximum cystometric capacity, and the decrease in volume and hyperintensity of intramedullary lesions. Very recently, Oraee-Yazdani et al. further verified that BM-MSCs in combination with autologous Schwann cell co-transplantation was safe and effective for treating 11 patients of spinal cord injury (SCI), and in particular for spinal cord regeneration during subacute period [43].

Notably, cutting-edge advances have also put forward the variations and limitations of adult tissue-derived MSCs in both preclinical and clinical studies [1, 14, 44].

For example, among the indicated adult tissue-derived MSCs, BM-MSCs are recognized as the widest application in clinical practices whereas with inherent disadvantages such as ethical risk, pathogenic risk, invasive pain, replicative senescence and individual diversity for cell source, and in particular, the limitation in healthy donors and declined long-term *ex vivo* amplification further restrict the large-scale application in future [11, 44]. Interestingly, despite the variations in signatures and functions, we recently verified the potential conservative properties in adipose tissue-derived stem cells (AD-MSCs) from type 2 diabetics and healthy donors [4]. However, multifaceted diversity among BM-MSCs, AD-MSCs, dental pulp stem cells (DPSCs), and supernumerary teeth-derived apical papillary stem cells (SCAP-Ss) were observed by investigators in the field [16, 45–47].

2.2 Perinatal tissue-derived MSCs

Perinatal tissues are abundant sources of MSCs and extracellular matrix with a wide range of therapeutic purposes in tissue engineering, which thus act as particularly interesting candidates for regenerative medicine [48, 49]. To date, a variety of perinatal tissue-derived MSCs have been identified such as placental-derived MSCs (P-MSCs), umbilical cord-derived MSCs (UC-MSCs), cord blood-derived MSCs (CB-MSCs) [49, 50], amniotic-derived MSCs (A-MSCs) [51], amniotic fluid-derived MSCs (AF-MSCs) [52], decidua-derived MSCs (D-MSCs) [53], and chorionic villi-derived MSCs (CV-MSCs) [54]. Of the aforementioned perinatal tissue-derived MSCs, UC-MSCs are promising sources with preferable properties in long-term proliferation *in vitro* and immunoregulation, and most of all, without ethical risks and limitation in supply, and thus hold great prospect for large-scale clinical investigation and investigational new drug (IND) purposes [18, 44]. Up to November 11th of 2021, a total of 317 interventional clinical trials have been registered for the administration of numerous refractory diseases by UC-MSC infusion such as diabetic nephropathy, heart failure, perianal fistulas with Crohn's disease, lumbar discogenic pain, chronic obstructive pulmonary disease (COPD), Duchenne muscular dystrophy (DMD), and cerebral hemorrhage sequela (CHS) according to ClinicalTrials.gov website.

Similarly, other types of MSC sources are of equal importance in offering “seeds” for tissue engineering and regenerative medicine (e.g., umbilical cord, placenta, amniotic membrane, and amniotic fluid). For instance, Liu and the colleagues took advantage of A-MSCs and conducted intragastric administration and intraperitoneal injection for the management of hydrogen peroxide-induced premature ovarian failure (POF) model. As expected, POF mice with A-MSC transfusion in bilateral ovaries revealed increased estrogen levels, decreased follicle-stimulating hormone level, and evaluated ovarian index and fertility rate, which collectively suggested the ameliorative effects of MSCs in improving the follicular microenvironment and recovering ovarian function in POF [55].

2.3 Pluripotent stem cell-derived MSCs

Pluripotent stem cells (PSCs), including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), possess self-renewal and multi-lineage differentiation potential, which thus provide advantaged “seeds” for disease modeling and drug validation as well as unprecedented opportunities for cytotherapy against intractable diseases [56–58]. Since the year of 2005, a number of literatures have reported the generation of MSCs from ESCs and iPSCs [59, 60]. Strikingly, the PSC-derived MSCs

(PSC-MSCs) revealed multifaceted superiority over those derived from adult tissues such as unlimited source, homogeneity, large-scale generation without pathogenic or ethical risks, and in particular, PSC-MSCs could be used for exploring the early development and molecular mechanism of MSCs [10, 53, 61, 62]. Notably, current studies have suggested the considerable efficacy of MSCs or MSC-derived exosomes in preclinical application including experimental inflammatory bowel disease (IBD) [63, 64], allergic tracheal inflammation (e.g., asthma and anaphylactic rhinitis) [65], experimental autoimmune encephalitis (EAE) of multiple sclerosis [66], lupus nephritis [67], acute colitis [68], kidney fibrosis [69], and hematopoietic reconstitution [70].

Generally, there are three strategies for PSC-MSC generation including monolayer induction, PSCs and stromal cell coculture and the embryoid body (EB) models. However, most of the existing strategies with drawbacks such as laborious manipulations (e.g., handpicking and scraping), time-consuming (3–8 weeks), low efficacy (approximately 5–20%), cell sorting (e.g., CD73⁺ and CD105⁺), and serial passages [10, 71, 72]. For instance, Wei et al., Deng et al., Vainieri et al., Wang et al., and Tran et al. reported the elevated generation of PSC-MSCs by modulating intracellular JAK-STAT [9], IKK/NF- κ B [73], PDGF-BB [74], bone morphogenetic protein 4 (BMP) [68], and ABB (activin A, 6-bromoindirubin-3'-oxime, and BMP4) [75] signaling pathways in feeder or serum-free model, respectively. Notably, we recently took advantage of the Msh homeobox 2 (MSX2) and small molecule library-based cell programming strategies for high-efficient induction of PSC-MSCs within 2 weeks, respectively [9–11]. Even though the convenience in practice as well as the promising prospects in tissue engineering and regenerative medicine [76, 77], the potential risks of PSCs attribute to genome editing and their inherent characteristics such as tumorigenicity, heterogeneity, and immunogenicity should cause enough attention [56, 78, 79].

3. Hydrogels/MSCs scaffolds for tissue engineering

The therapeutic effects of MSC transplantation largely attributed to the paracrine including soluble factors and extracellular vehicles (e.g., exosome and secretome), which could be rapidly sequestered and cleared [80]. Hydrogels are ideally suited for MSCs cultivation and are adequate to offer splendid delivery platforms, enhance vehicles retention rates and thus enhance immunomodulation and tissue regeneration after *in vivo* transplantation (**Figure 1**, **Table 1**) [80–82].

3.1 Hydrogels/MSCs scaffolds for wound healing

Wound healings are regulated by series of events with overlapping phases, which represent an intractable issue in clinical practice [83, 84]. State-of-the-art renewal has indicated the prospective applications of hydrogel in combination with MSCs or MSC-derived exosomes in skin wound healing, and in particular, the recurrent and refractory cutaneous types (**Table 1**) [83, 85]. Of them, chronic refractory wounds are disorders attribute to multifactorial comorbidity with characteristics of inflammation and impaired vascular networks, which eventually result in unfavorable prognosis due to the lack of effective treatments [36, 86]. Recently, Yang and the colleagues topically applied UC-MSC-derived exosomes encapsulated into the thermosensitive PF-127 hydrogel (hydrogel/MSC-exo) and demonstrated that hydrogel/MSC-exo scaffold significantly upregulated expression of multiple cytokines (e.g., VEGF and TGF β -1), enhanced regeneration of granulation tissue and accelerated wound closure

Figure 1.
Illustration of hydrogel/MSC-based cytotherapy for tissue engineering.

rate in a streptozotocin-induced diabetic rat model, which was further verified by another study in a streptozotocin-induced diabetic model with hydrogel/AD-MSC composite [33, 36]. Marusina et al. and Xin et al. reported the influence of tunable bio-inert poly (ethylene glycol)-based hydrogels and microporous annealed particle hydrogels on MSCs and the optimization of cell-degradable hydrogels/MSCs delivery for wound re-epithelialization [81, 87]. Zhang et al. took advantage of the bioluminescence imaging (BLI) technology and further demonstrated the therapeutic effects of prostaglandin E2 (PGE2) and chitosan (CS) hydrogel (PGE2 + CS hydrogel) in a murine wound healing model via modulating the M1 and M2 paradigms of macrophage activation [88]. Meanwhile, a full sheet consisting of A-MSCs on thermoresponsive polymers have been considered as advantaged skin substitute for the management of burn wounds [89]. Collectively, these studies suggested that hydrogel-based MSC/MSC-exo therapy represent a novel therapeutic approach for refractory cutaneous regeneration of chronic wounds.

3.2 Hydrogels/MSCs scaffolds for osteoarticular diseases

Despite the dramatic progress in bone reconstruction, the osteoarticular diseases and bone regeneration in clinical practices are still challenging [82]. Hydrogels have been extensively investigated in numerous osteoarticular diseases (e.g., osteoarthritis) and bone regeneration (e.g., craniofacial bone tissue) largely attribute to the high cell compatibility [34]. For example, Ji et al. recently combined MSCs with a newly synthesized hybrid scaffold consisting of thermosensitive hydroxypropyl chitin hydrogel (HPCH) and 3D-printed nano-hydroxyapatite (nHA)/poly

(ϵ -caprolactone) (PCL) for bone regeneration. Strikingly, they found the vascularization and osteogenesis and immunomodulation of encapsulated MSCs as well as cytokine secretion of macrophages were collectively orchestrated in bone defect mice model [35].

Osteoarthritis (OA) is recognized as the most prevalent chronic joint disease, which increases in prevalence with age and resultant in functional loss or decline in quality of life, and in particular, act as a major socioeconomic cost worldwide and a leading musculoskeletal cause of impaired mobility in individuals over 65-year-old [90, 91]. Despite joint replacement is an effective strategy for symptomatic end-stage disease, yet most of the functional outcomes are poor and the lifespans of prostheses are largely limited [91, 92]. Current studies have shown that MSC-based cytototherapy are promising for osteoarticular disease administration. For example, Portron et al. and Merceron et al. found that the *in vivo* chondrogenic potential of AD-MSCs encapsulated in a cellulose-based self-setting hydrogel (Si-HPMC) preconditioned by hypoxia (5% oxygen) was significantly enhanced compare to that in the control (20% oxygen) group, which was confirmed by subcutaneous transplantation of AD-MSCs with an injectable hydrogel in rabbits [93, 94]. Very recently, our group also found that the application of hyaluronic acid (HA) hydrogel/PSC-MSCs and HA hydrogel/hydroxyapatite/UC-MSC (HA/HAP/UC-MSC) composite with reinforced efficacy upon OA rabbits and mice, respectively (**Table 1**) [11]. It's noteworthy that Chung and their colleagues have systematically explored and detailed dissected the efficacy of articular cartilage repair *in vivo* by combining UC-MSCs with various hydrogels such as alginate, pluronic, HA, and chitosan. They finally concluded that HA hydrogel/UC-MSC composites resulted in preferable cartilage repair and collagen organization pattern, which were similar to adjacent uninjured articular cartilage [95]. Additionally, the gingival MSC-laden photocrosslinkable hydrogels were also confirmed with preferable biocompatibility, biodegradability, and osteoconductivity for craniofacial bone tissue engineering in rat peri-implantitis model as well [34]. Taken together, the biodegradable and biocompatible hydrogels can serve as advantaged scaffolds and supply structural integrity for cellular organization and morphogenic guidance of hydrogel scaffold-laden MSCs [88].

3.3 Hydrogels/MSCs scaffolds for reproductive diseases

Premature ovarian failure (POF) is a refractory disorder with declined fertility in females [96, 97]. In 2019, Yang and their colleagues took advantage of collagen scaffold loaded with UC-MSCs (collagen/UC-MSCs) and verified the efficacy in POF mice via increasing estrogen (E2) and ovarian volume, and promoting granulosa cell proliferation and ovarian angiogenesis [96]. Similarly, Ding et al. reported the rescue of E2 concentrations and activation of follicles in the dormant ovaries of premature ovarian failure (POF) patients with long history of infertility after transplantation of collagen/UC-MSC scaffold (**Table 1**) [38].

As to premature ovarian insufficiency (POI), an intractable endocrine disease that severely restricts the reproductive and physiological function of females and resultant in menopausal symptoms, a series of literatures have suggested the ameliorative effect of hydrogel/MSC composite or hydrogel/MSC-derived microvesicles/secretomes via facilitating angiogenesis, enhancing granulosa cell generation and steroidogenesis, and accelerating follicular regeneration [98–101]. Notably, Li et al. have summarized the current renewal of the therapeutic effects and molecular mechanisms of MSC-based cytototherapy in both preclinical research and clinical trials [102].

3.4 Hydrogels/MSCs scaffolds for vascular diseases

Peripheral arterial diseases (PAD) are severe medical conditions, which are characterized by blood vascular blockage and low limb Doppler signals and commonly associated with hind-limb ischemia or critical limb ischemia (CLI) [103]. For decades, we and other investigators have primarily suggested the therapeutic of MSCs or MSC-derived exosomes in hind limb ischemia models by alleviating the severity, promoting angiogenesis, and enhancing immunomodulation [9, 104, 105]. In recently years, a certain number of outstanding researchers turned to injectable hydrogels such as self-assembled Nap-GFFYK-Thiol hydrogel, nitric oxide-releasing hydrogels, and the novel hydrogel composed of pooled platelet lysate (PL) to enhance the efficacy of MSCs or derivations upon peripheral artery diseases (PADs) [37, 106–108]. For example, Lee et al. found that fucoidan was adequate to improve the bioactivity and vasculogenic potential of MSCs in hind limb ischemia murine with chronic kidney disease (CKD) whereas Nammian et al. further compared the variations of efficacy between BM-MSCs and AD-MSCs for CLI [109, 110]. Notably, Ding and their colleagues systematically dissected an injectable nanocomposite hydrogel consisting of chitosan, gelatin, β -glycerophosphate and Arg-Gly-Asp (RGD) peptide for potential applications of facilitating vascularization and tissue engineering [111]. Collectively, the aforementioned studies suggest that hydrogel/MSC-based composites occupy a greater angiogenic potential over single hydrogel- or MSC-based treatment for PADs.

3.5 Hydrogels/MSCs scaffolds for digestive diseases

Gastroparesis is characterized by pyloric dysfunction, vomiting, severe nausea, delayed gastric emptying and impaired fundamental structures, which is related with consume of enteric neurons and interstitial cells of Cajal [112]. Meanwhile, stem cell therapy has also been extensively explored in inflammatory bowel diseases (IBDs) including ulcerative colitis (UC) and Crohn's disease (CD) in both preclinical studies and clinical trials [113–115]. State-of-the-art updates have indicated the mitigatory effects of MSCs in gastrointestinal diseases such as acute ulcerative colitis and perianal CD [8, 10, 68, 116]. For example, we recently reported the spatio-temporal metabolokinetics and efficacy of placenta-derived MSCs (P-MSCs) on intractable CD with enterocutaneous fistula in mice via simultaneously accelerating neovascularization and downregulating reactive oxygen species (ROS) [8]. Interestingly, Joddar et al. conducted delivery of the MSC-alginate/gelatin/poly-l-lysine hydrogel atop stomach grafts facing the luminal side, and confirmed the significant advance towards the entire tissue-engineered “microgels” or “gastric patch” [112]. Of note, the therapeutic effects of MSCs via systemic administration are still contradictory largely due to the localization in the lungs, which is confirmed by the outcomes of two clinical trials with BM-MSC transplantation [117, 118]. Therefore, the local administration of hydrogel/MSC or hydrogel/MSC-exosomes are promising alternatives for resolving refractory digestive diseases.

4. Conclusions

Tissue engineering is an inveterate and promising area in the field of regenerative medicine, which also has long-lasting limitations in engineering and regenerating tissues. MSCs of different origins are splendid “seeds” for the efficient administration of various refractory and recurrent diseases. As mentioned above, MSCs as well as the

released extracellular vesicles (EVs) reveal substantial therapeutic effect in numerous pathophysiological conditions and potentially reconstructing an extensive range of diseased or damaged tissues and organs in tissue regeneration engineering, which have been predominantly demonstrated from pre-clinical or clinical *in vitro* and *in vivo* studies. MSC-encapsulated hydrogel scaffolds demonstrate enhanced cell vitality and committed differentiation, prolonged fundamental and operational consistency, which thus hold promising prospects for tissue engineering and the resultant regenerative medicine. Meanwhile, the exosomes and other nano-scale secretions released from the multivesicular MSCs encapsulated into appropriative hydrogel formulations (e.g., HA, nHAP, PLGA, pDA, and FHE) have manifested higher therapeutic potential in both fundamental research and clinical application. Overall, the current progress of regenerative medicine will extensively benefit from the “advantaged” artificial hydrogel/MSC-based cytototherapy in the near future.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

Not applicable.

Appendices and nomenclature

MSCs	mesenchymal stem/stromal cells
aGVHD	acute graft-versus-host diseases

CLI	critical limb ischemia
ACLF	acute-on-chronic liver failure
AMI	acute myocardial infarction
RA	rheumatoid arthritis
COVID-19	coronavirus disease 2019
ECMs	extracellular matrices
HA	hyaluronic acid
PSC-MSCs	pluripotent stem cell-derived MSCs
BM-MSCs	bone marrow-derived MSCs
ARDS	acute respiratory distress syndrome
IPF	idiopathic pulmonary fibrosis
DPSCs	dental pulp stem cells
UC-MSCs	umbilical cord-derived MSCs
P-MSCs	placental-derived MSCs
AF-MSCs	amniotic fluid-derived MSCs
A-MSCs	amniotic-derived MSCs
D-MSCs	decidua-derived MSCs
CV-MSCs	chorionic villi-derive MSCs
COPD	chronic obstructive pulmonary disease
CHS	cerebral hemorrhage sequela
DMD	Duchenne muscular dystrophy
POF	premature ovarian failure
EAE	experimental autoimmune encephalitis
IBD	inflammatory bowel disease
ESCs	embryonic stem cells
iPSCs	induced pluripotent stem cells
nHA	nano-hydroxyapatite
CKD	chronic kidney disease
PADs	peripheral artery diseases
CD	Crohn's disease
UC	ulcerative colitis
IUA	intrauterine adhesions
PGE2	prostaglandin E2
ROS	reactive oxygen species

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