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REVIEW

Application of mesenchymal stem cells derived from human pluripotent stem cells in regenerative medicine

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Abstract

Mesenchymal stem cells (MSCs) represent the most clinically used stem cells in regenerative medicine. However, due to the disadvantages with primary MSCs, such as limited cell proliferative capacity and rarity in the tissues leading to limited MSCs, gradual loss of differentiation during *in vitro* expansion reducing the efficacy of MSC application, and variation among donors increasing the uncertainty of MSC efficacy, the clinical application of MSCs has been greatly hampered. MSCs derived from human pluripotent stem cells (hPSC-MSCs) can circumvent these problems associated with primary MSCs. Due to the infinite self-renewal of hPSCs and their differentiation potential towards MSCs, hPSC-MSCs are emerging as an attractive alternative for regenerative medicine. This review summarizes the progress on derivation of MSCs from human pluripotent stem cells, disease modelling and drug screening using hPSC-MSCs, and various applications of hPSC-MSCs in regenerative medicine. In the end, the challenges and concerns with hPSC-MSC applications are also discussed.

Key Words: Human pluripotent stem cells; Differentiation; Mesenchymal stem cells; Regenerative medicine; Disease modelling; Drug screening

Core Tip: Mesenchymal stem cells (MSCs) exhibit great potential in regenerative medicine. However, the clinical application of primary MSCs has been greatly hampered by the limitations of primary MSCs. MSCs derived from human pluripotent stem cells (hPSC-MSCs) are an attractive source of cells to overcome such problems with primary MSCs. This review summarizes the various derivation approaches and applications of hPSC-MSCs in regenerative medicine. Lastly, the challenges with the use of hPSC-MSCs are also discussed, which indicate that more efforts are needed for

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INTRODUCTION

Mesenchymal stem cells (MSCs) are adult stem cells with fibroblast-like morphology and plastic adherence. They express MSC surface antigens such as CD73, CD90, and CD105 but lack hematopoietic markers such as CD11b, CD19, CD34, and CD45[1]. More importantly, MSCs can give rise to multiple mesenchymal lineages, including bone, cartilage, and fat cells[1-3]. Friedenstain and colleagues first described an adherent subpopulation in bone marrow termed as marrow stromal cells[4-7]. The term of MSCs was later introduced in 1991 to refer to these cells[8]. MSCs reside in nearly all tissues, including bone marrow and adipose tissues, among others. Due to their expandability, multipotency, immunosuppression, and limited ethical concerns as compared to other types of stem cells, human MSCs have emerged as an attractive cell source for regenerative medicine. Moreover, MSCs exhibit low expression of major histocompatibility (MHC) antigens, thereby reducing the need for MHC match between different donors and recipients in allogeneic MSC transplant. Due to these characteristics that MSCs possess, MSC-based allogeneic transplantation is now the forefront of regenerative medicine. As a fast-growing field in regenerative medicine, MSCs represent the most clinically used stem cells with over 1000 registered clinical trials with an established safety record in patients that can efficaciously treat more than 30 diseases. However, there are several limitations of primary MSCs that greatly hamper their clinical application. They include limited cell proliferative capacity, gradual loss of differentiation potential during *in vitro* expansion, variation across donors, rarity in organs, invasive procedures required for harvesting, *etc.*

Human pluripotent stem cells (hPSCs), including human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs), represent a promising solution to overcome the issues associated with primary MSCs. Due to the pluripotency of hPSCs, they exhibit unlimited proliferation ability and are able to differentiate into various types of cells, including MSCs. Therefore, hPSCs can provide unlimited and uniform MSCs as an alternative cell source to primary MSCs. This review summarizes the derivation approaches and various applications of hPSC-MSCs, and ultimately the challenges associated with safety and efficacy of hPSC-MSCs are discussed.

DERIVATION OF HPSC-MSCS

Although primary MSCs have been widely used for clinical application, the previously mentioned limitations with the use of primary MSCs significantly hamper their clinical applications. To overcome the problems with primary MSCs, substantial advancements have been made to develop a number of approaches for derivation of MSCs from hPSCs, including hESCs and iPSCs. These approaches include spontaneous differentiation *via* coculture with OP9, fetal bovine serum (FBS)-containing media, and embryonic body (EB), or directed differentiation *via* delicate control of signalling pathways. The principle of these approaches is to deprive pluripotent signals of hPSCs, thereby driving differentiation into MSCs.

During embryonic development, MSCs develop from neural crest cells (NCCs), lateral plate mesoderm, or paraxial mesoderm, which further develop into craniofacial skeleton, appendicular skeleton, and axial skeleton, respectively. The neural crest is a transient structure formed through epithelial-mesenchymal transition (EMT) with potential to differentiate into a wide range of cell types, including MSCs. It was shown that neural crest cells were derived from hPSCs[9-13], which were able to develop or differentiate into MSCs[14-16]. Morikawa *et al*[15] showed that MSCs in the adult bone marrow had at least two developmental origins, one of which was the neural crest. By lineage tracing, Takashima *et al*[16] showed that Sox1+ neuroepithelium gave rise to

MSCs in part through a neural crest intermediate stage. The combination of the glycogen synthase kinase 3 beta inhibitor and transforming growth factor-beta (TGFβ) inhibitor very efficiently induced hPSCs towards hNCCs (70%-80%), which further differentiated into MSCs with chemically defined medium[14]. The mesoderm is a major source of MSCs, and we recently reported a stepwise, serum-free, chemically defined and highly efficient protocol to generate hPSC-MSCs *via* lateral plate mesoderm. The resultant iPSC-MSCs displayed similar MSC surface antigen profile, gene expression profile, and epigenetic profile. iPSC-MSCs had three lineage differentiation. Significantly, hPSC-MSCs were able to repair cartilage defects, similar to bone marrow-MSCs (BM-MSCs)[17]. Upon differentiation, mESCs gave rise to VEGFR-2$^+$ PDGFR$^+$ population followed by VEGFR-2$^-$PDGFR$^+$ population *via* paraxial mesoderm [18]. hESC-derived KDR$^-$PDGFRa$^+$ paraxial mesoderm-like cells showed robust chondrogenic activity and generated a hyaline-like translucent cartilage particle whereas STRO1$^+$ BM-MSCs showed relatively weaker chondrogenesis and formed more fibrotic cartilage particles *in vitro*[19].

MSCs in the placenta develop from trophoblasts in the extraembryonic tissue chorion[20]. MSCs can also be derived *via* trophoblasts. hESCs cultured in serum containing medium[21] and serum free medium[22] containing BMP4 and A83-01 were able to differentiate into trophoblasts and then into MSCs. Trophoblast-derived MSCs produced less interleukin 6 (IL-6), C-X-C motif chemokine ligand 10, and C–C motif chemokine ligand 2 but more programmed death-ligand 1 in response to IFN gamma (IFNγ) treatment as compared with MSCs[21]. Compared with MSCs from serum containing medium, serum free approach took longer than serum containing approach to derive MSCs, but serum-free derived MSCs grew faster and produced less IL-6 and interleukin 8[22].

Barberi *et al*[23] first reported that MSCs were derived from hESCs by coculturing hESCs with monolayer of murine OP9 stromal cells. However, the undefined condition in this approach inevitably led to spontaneous differentiation, giving rise to an undesired type of cells. Besides MSCs, non-MSCs such as CD34 (+) primitive hematopoietic cells, were also present[24]. Vodyanik *et al*[25] showed that MSCs were derived from a common precursor of mesenchymal and endothelial cells called mesenchymoangioblast by coculturing hESCs with OP9.

Culturing hPSCs in the undefined condition of FBS-containing MSC medium is another way to derive hPSC-MSCs by providing growth factors required for differentiation towards MSCs. When hESCs or iPSCs were cultured in FBS-containing MSC medium for 4 wk to derive hPSC-MSCs, hPSC-MSCs inhibited cell proliferation and cytolytic function of natural killer (NK) cells in the same fashion that BM-MSCs did. However, they were more resistant to preactivated NK cells as compared with adult BM-MSCs[26]. A high density of hESCs on a porcine gelatin-coated dish were cultured in a medium containing 10% FBS for 7 d to outgrow the cells and then enrich hESC-MSCs by 1-2 passages[27]. Functional iPSC-MSCs were also derived on coating with gelatin, and the resultant iPSC-MSCs pre-induced into osteogenesis for 4 d formed bone in the calvaria defects confirmed by human specific nuclear antigen and mitochondrial antibodies[28]. hESC/iPSCs were seeded onto collagen coating and cultured in FBS-containing medium for 10 d to generate hESC/iPSC-MSCs[29]. Spontaneously differentiated cells (raclures) from feeder-free hESCs were cultured in FBS-containing MSC medium for 4 wk, and hESC-MSCs were enriched by following passage[30]. Chen *et al*[31] reported the derivation of hPSC-MSCs by serum-free medium containing TGFβ inhibitor and EMT inducer (SB431542) for 10 d to induce the mesoderm followed by induction of MSCs in FBS-containing MSC medium. The resultant hPSC-MSCs had robust osteogenesis and chondrogenesis but weaker adipogenesis. This approach does not require EB and feeder cell coculture.

To mimic *in vivo* development, Brown *et al*[32] derived hESC-MSCs *via* EB in MSC medium and enriched them by sorting for CD73 and CD105. EBs from iPSCs were exposed to TGFβ1-containing medium, and two types of MSCs were generated. Although early (aiMSCs) and late (tiMSCs) outgrowing cells were similar in surface antigen profile and three lineage differentiation, aiMSCs were better in osteogenesis than tiMSCs and BM-MSCs. Compared with BM-MSCs, aiMSCs were more of stemness whereas tiMSCs were more osteogenic, and *in vivo* bone formation was confirmed *via* ectopic injection[33].

The use of undefined components (such as FBS and feeder) or animal-derived components affects clinical applications of hPSC-MSCs. To overcome the problems from undefined conditions, serum-free and chemically defined protocols are desired to generate clinically compliant hPSC-MSCs. Lian *et al*[34,35] reported a clinically compliant protocol to generate hESC-MSCs and iPSC-MSCs. After 1 wk of differentiation, MSCs were enriched by FACS for CD24- CD105+ cells. The transplanted iPSC-

MSCs were superior to BM-MSCs in attenuating severe hindlimb ischemia, which may result from better *in vivo* survival and trophic factors of iPSC-MSCs, and higher proliferation of iPSC-MSCs related to increased hEAG1 potasium channel expression[36]. The use of animal products, such as gelatin for coating, compromises the application of hPSC-MSCs. To generate xeno-free MSCs, FBS was replaced with human serum, and porcine gelatin was replaced with human gelatin. Transplanted hESC-MSCs into renal capsule formed cartilage[27]. Human platelet lysate is an alternative to FBS for the generation of hPSC-MSCs. Compared with the FBS-containing medium, the hPL-supplemented medium generated significantly more MSCs[37].

COMPARISON BETWEEN PRIMARY MSCS AND HPSC-MSCS

hPSC-MSCs are similar to primary MSCs in morphology, immunophenotype, differentiation potential, gene expression profile, and epigenetic modification[17,22,38-40]. However, there are some differences observed between primary MSCs and hPSC-MSCs. hPSC-MSCs are smaller in size and proliferate faster than BM-MSCs and adipose tissue-MSCs[22,36,39-41]. hPSC-MSCs express higher levels of cell proliferation-related genes whereas BM-MSCs express higher levels of immune-related genes, therefore hPSC-MSCs had a superior proliferative ability to BM-MSCs[39,42,43]. In addition, iPSC-MSCs express higher levels of pluripotent genes and lower levels of mesodermal genes compared with original MSCs, which harbor mtDNA mutations from original MSCs as well as iPSCs. Compared with primary MSCs, iPSC-MSCs express a lower level of VCAM1, leading to lower initiating cell frequency of HSCs after long-term culture with iPSC-MSCs as feeder[44]. Compared with dental tissue-derived MSCs, re-differentiated iPSC-MSCs expressed higher levels of pluripotent genes and lower levels of mesodermal genes, but displayed lower mitochondrial respiration[45]. iPSC-MSCs also express the lowest level of the HLA-II upon stimulation with IFNγ compared with BM-MSCs and fetal-MSCs. Compared with BM-MSCs, more iPSC-MSCs survived, and less inflammatory cell accumulations and better recovery of hind limb ischemia were also observed upon transplant. These suggest that iPSC-MSCs are not sensitive to IFNγ stimulation and have a stronger immune privilege after transplantation[46]. In differentiation potential, hPSC-MSCs differentiated less effectively along the adipogenic, osteogenic, or chondrogenic lineages compared with BM-MSCs[42], especially poorer adipogenesis[31,47,48]. Both hESCs and iPSCs inefficiently formed hyaline cartilage compared with BM-MSCs[43]. In immunosuppression, iPSC-MSCs were impaired in suppressing T cell proliferation compared with primary MSCs but were rejuvenated with regard to age-related DNA methylation, and this suggests that iPSC-MSCs reacquire incomplete immunomodulatory function, and MSC-specific DNA methylation pattern associates with tissue type and aging[38] (Table 1).

DISEASE MODELLING AND DRUG SCREENING

The understanding of the pathological mechanism is critical to developing the therapeutic drugs for the treatment of various genetic diseases. *In vitro* models to mimic *in vivo* development are very useful to investigate the pathology of human genetic diseases and further develop therapeutic drugs. However, due to inaccessible human tissues and the lack of animal models, research on human genetic diseases and drug screening remains very limited. With the breakthrough in iPSC technology, it makes it possible to model human diseases and develop their therapeutic drugs *in vitro*. The iPSC-MSC platform can recapitulate the embryonic bone and cartilage development, and therefore provide new insights into pathological progression of human genetic bone and cartilage diseases for disease modelling and further the development of therapeutic drugs.

Hutchinson-Gilford progeria syndrome (HGPS) is a rare but fatal genetic disorder caused by progerin, a truncated and farnesylated form of Lamin A, which causes systemic accelerated aging in children. Zhang *et al*[49] generated iPSC-MSCs from HGPS patients and showed that HGPS-iPSC-MSCs displayed abnormalities, including increased nuclear dysmorphology, DNA damage, and accumulation of calponin-staining inclusion bodies, leading to their compromised viability under stress, especially to hypoxia. Using HGPS iPSC-MSCs platform, seven compounds were screened from 2800 small molecules, including all-trans retinoic acid and 13-cis-retinoic acid, which decreased ALP activity and progerin expression[50].

Table 1 Comparison between primary mesenchymal stem cells and mesenchymal stem cells derived from human pluripotent stem cells

Comparison	Primary MSCs	hPSC-MSCs	Ref.
Cell number	Limited	Unlimited	[17,36]
Proliferation	Slower	Faster	[36,39,42,43,48,57]
Life span	Shorter	Longer	[17]
Variation	Higher	Lower	[119]
Differentiation potential	Higher	Lower, *esp*. adipogenesis	[31,43,47,48]
Immunosuppression	Higher	Lower	[38,46]
Pluripotent genes	Lower	Higher	[45]
Mesenchymal genes	Higher	Lower	[45]
VCAM1	Higher	Lower	[44]
HLA-II	Higher	Lower	[46]

MSCs: Mesenchymal stem cells; hPSC-MSCs: Human pluripotent stem cells derived MSCs; VCAM1: Vascular cell adhesion molecule 1; HLA-II: Human leukocyte antigen gene complex class II.

Fibrodysplasia ossificans progressiva (FOP) is an inherited disease characterized by heterotopic endochondral ossification in soft tissues after birth and caused by a point mutation in ACVR1. iPSC-MSCs from FOP patients were generated, and it was found that SMAD1/5/8 and SMAD2/3 were activated and chondrogenesis was enhanced *via* MMP1 and PAI1 in FOP-iMSCs[51-53]. Hino *et al*[54] screened 6809 small molecule compounds using high-throughput screening, and mTOR signaling was identified to be a critical pathway for aberrant chondrogenesis. Further mechanism study showed that ectonucleotide pyrophosphatase/phosphodiesterase 2 linked FOP-ACVR1 to mTOR signaling, causing FOP pathogenesis.

APPLICATIONS OF HPSC-MSCS IN REGENERATIVE MEDICINE

Due to the multipotency, immunosuppression, and unlimited cell sources, hPSC-MSCs have been used for various applications in regenerative medicine (Table 2).

Bone regeneration

Like BM-MSCs, iPSC-MSCs had osteogenic potential, and therefore they could form typically calcified structure in the scaffolds[55]. iPSC-MSCs had good viability and osteogenic differentiation on the CPC scaffold[56]. iPSC-MSCs were similar to BM-MSCs in preventing bone loss and promoting bone repair for the necrosis region of the femoral head[57]. Engineered non-native peptides increased the attachment of iPSC-MSCs to the scaffolds and enhanced bone and vasculature formation *in vivo*[58]. Biofunctional agents, such as Arg-Gly-Asp (RGD), improved the proliferation and bone mineralization of iPSC-MSCs[59]. When iPSC-MSCs were treated with metformin, a widely used drug for diabetes, they showed enhanced bone formation and increased osteogenic markers and mineralized nodule formation, suggesting that metformin might be used to improve bone and periodontal regeneration[60]. Recently increasing reports have shown that MSCs exerted their pleiotropic effects by the secretion of soluble paracrine factors rather than their differentiation potential[61]. MSC-derived exosomes contain cytokines, growth factors, mRNAs, and regulatory miRNAs[62]. iPSC-MSC exosomes increased the proliferation, migration, and osteogenesis of BM-MSCs[63], significantly prevented bone loss, and promoted local angiogenesis by activating the PI3K/Akt signalling pathway in endothelial cells in a steroid-induced rat osteonecrosis model[64] (Figure 1).

Genetic modification can improve the bone formation of iPSC-MSCs. Distal-less homeobox 3 (DLX3) overexpression enhanced bone formation of iPSC-MSCs as shown by increased osteogenic genes and mineralized nodules at the expense of decreased proliferation[65]. Bone morphogenetic protein 2 overexpression enhanced bone formation on RGD-grafted calcium phosphate cement (CPC) of iPSC-MSCs[66]. Neural EGFL like 1 (NELL1) overexpression greatly improved osteogenesis of iPSC-MSCs on

Table 2 Mesenchymal stem cells and mesenchymal stem cells derived from human pluripotent stem cells

hPSC-MSCs	Disease model or application	Animal model or human	Therapeutic effects	Ref.
iPSC-MSCs	CKD	Rat	Protect the kidney against CKD injury	[85]
iPSC-MSCs	Adriamycin nephropathy	Mouse	Prevent adriamycin nephropathy	[82]
iPSC-MSCs	Obesity-associated Kidney injury	Mouse	Ameliorate endoplasmic reticulum stress	[83]
hPSC-MSCs	UUO	Mouse	Protect against kidney fibrosis in vivo and *in vitro*	[84]
hESC-MSCs	LN	Mouse	Prevent the progression of LN	[81]
iPSC-MSCs	TNBC	Mouse	Significantly decrease the incidence and burdon of metastases	[117]
iPSC-MSCs	Breast cancer	Mouse	Decrease EMT, invasion, stemness, and growth of cancer cells	[119]
iPSC-MSCs	Skin wounds, pressure ulcers, and osteoarthritis	Mouse	Have therapeutic potential in skin wounds, pressure ulcers, and osteoarthritis	[127]
hESC-MSCs	Arthritis	Mouse	Ameliorate collagen-induced arthritis by inducing IDO1	[72]
iPSC-MSCs	Osteonecrosis of the femoral head	Rat	Prevent osteonecrosis of the femoral head	[64]
iPSC-MSCs	Vascularized composite allotransplantation	Rat	Induce T cell hyporesponsiveness to prolong hind limb survival	[106]
iPSC-MSCs	Limb ischemia	Mouse	Exosomes of iPSC-MSCs attenuate limb ischemia by promoting angiogenesis	[121]
iPSC-MSCs	Limb ischemia	Mouse	Insensitivity of iPSC-MSCs to interferon γ potentiates repair efficiency of hind limb ischemia	[46]
iPSC-MSCs	Limb ischemia	Mouse	Attenuate limb ischemia	[35]
iPSC-MSCs	Periodontal defects	Rat	Aid periodontal regeneration	[68]
iPSC-MSCs	Bone defects	Mouse	Regenerate non-union bone defects more efficiently than BM-MSCs upon BMP6 overexpression	[33]
iPSC-MSCs	Calvaria defects	Mouse	Repair calvaria defects	[28]
iPSC-MSCs	Osteochondral defects	Rat	iPSC-MSCs are able to repair cartilage defects	[17]
iPSC-MSCs	FOP		FOP-iPSC-MSCs enhance chondrogenesis *via* activin A enhanced mTOR signalling	[53,54]
hESC-MSCs	Lupus and uveitis	Mouse	Increase survival of lupus-prone mice and decrease symptoms of uveitis	[40]
hESC-MSCs	EAE model of multiple sclerosis	Mouse	Improve EAE symptoms	[101]
hESC-MSCs	EAE	Monkey	Attenuate disease progression in a primate EAE model	[41]
hESC-MSCs	EAU	Mouse	Slow down the development of EAU	[103]
iPSC-MSCs	Inflammatory bowel disease models	Mouse	Promote intestinal repair *via* TSG-6	[111]
hESC-MSCs	Experimental inflammatory bowel disease	Mouse	Protect against experimental inflammatory bowel disease	[107]
iPSC-MSCs	SS	Mouse	Prevent the progression of SS	[112]
iPSC-MSCs	Allergic rhinitis		Modulate T-cell phenotypes towards Th2 suppression through inducing Treg expansion	[108]
iPSC-MSCs	Asthma Inflammation	Mouse	Alleviate asthma inflammation by CX43-mediated mitochondrial transfer	[110]
iPSC-MSCs	Corneal injury	Mouse	Exert therapeutic effects in the cornea by reducing inflammation	[99]
iPSC-MSCs	Skin wound	Rat	iPSC-MSC-Exos improve cutaneous wound healing by promoting collagen synthesis and	[120]

			angiogenesis.	
iPSC-MSCs	SR-aGvHD	Human	iPSC-MSCs are safe and well tolerated	[114]

CKD: Chronic kidney disease; UUO: Unilateral ureteral obstruction; LN: Lupus nephritis; TNBC: Triple-negative breast cancer; EMT: Epithelial–mesenchymal transition; IDO1: Indoleamine 2, 3-dioxygenase 1; FOP: Fibrodysplasia ossificans progressive; mTOR: Mammalian target of rapamycin; EAE: Experimental autoimmune encephalomyelitis; EAU: Experimental autoimmune uveitis; TSG-6: TNFα-stimulated gene-6; SS: Sjogren's syndrome; CX43: Connexin 43; Exos: Exosomes; SR-aGvHD: Acute steroid-resistant graft versus host disease.

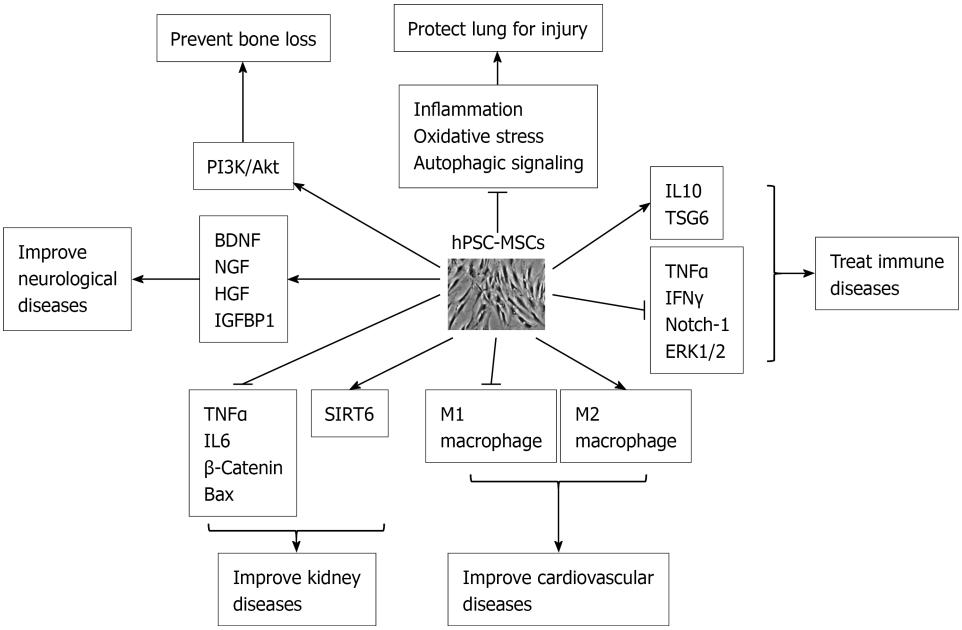

Figure 1 Signaling pathways of mesenchymal stem cells derived from human pluripotent stem cells in improving various diseases. Mesenchymal stem cells derived from human pluripotent stem cells (hPSC-MSCs) improve diseases or prevent against injury through immunosuppression or paracrine effects. hPSC-MSCs secrete a variety of soluble paracrine factors to exert their therapeutic effects on immunosuppression, proliferation, differentiation, anti-apoptosis, angiogenesis, *etc.* PI3K: Phosphoinositide 3-kinase; Akt: Protein kinase B; BDNF: Brain-derived neurotrophic factor; NGF: Nerve growth factor; HGF: Hepatocyte growth factor; IGFBP1: Insulin-like growth factor-binding protein 1; TNFα: Tumor necrosis factor; IL6: Interleukin 6; Bax: BCL2-associated X; SIRT6: Sirtuin 6; IL10: Interleukin 6; TSG6: TNFα-stimulated gene-6; IFNγ: Interferon γ; ERK1/2: Extracellular signal-regulated protein kinases 1 and 2.

RGD-CPC[67].

Due to osteogenic differentiation potential, iPSC-MSCs have the capacity for periodontal regeneration. When transplanted into periodontal defects, iPSC-MSCs formed new mineralized tissues and significantly improved regeneration, suggesting that iPSC-MSCs represent a promising stem cell source for clinical application in periodontitis[68].

Cartilage repair

Articular cartilage has limited intrinsic healing potential, leading to a loss of joint function. Like BM-MSCs, iPSC-MSCs can differentiate into chondrocytes *in vitro*[69]. In view that autologous chondrocytes and primary MSCs are limited in cell number, iPSC-MSCs are gaining attention as a new cell therapy for cartilage regeneration due to unlimited cells and chondrogenic differentiation potential. Our previous data showed that primary BM-MSCs were able to repair cartilage defects effectively[70]. Multiple injections of hESC-MSCs into knee joint of osteoarthritis (OA) rats induced by anterior cruciate ligament transection repaired cartilage better than the single dose and negative control groups in a rat OA model[71]. hESC-MSCs also ameliorated collagen-induced arthritis by inducing indoleamine 2,3-dioxygenase 1 (IDO1) in mice[72]. In addition, exosomes from hESC-MSCs prevented cartilage destruction by maintaining the chondrocyte function[73]. By our defined, step-wise and chemically defined protocol, we generated iPSC-MSCs *via* lateral plate mesoderm and have shown that iPSC-MSCs repaired osteochondral defects similar to BM-MSCs[17].

Lung repair

As an attractive candidate for cell-based therapy, MSCs are therapeutically beneficial

to improving lung disease or repairing lung damage. iPSC-MSCs protected lung cells against mitochondrial dysfunction and apoptosis induced by oxidative stress to reduce lung injury and inflammation in *in vivo* models of lung disease[74]. iPSC-MSCs reduced airway inflammation and hyperresponsiveness to protect against lung diseases induced by oxidative stress, such as chronic obstructive pulmonary disease [75]. iPSC-MSCs protected the lung against ischemia-reperfusion injury (IRI) by suppressing the inflammatory, oxidative stress, and autophagic signalling pathways [76]. Treatment with iPSC-MSCs also significantly prevented airway allergic inflammation, decreased Th2 cytokine levels, and changed long non-coding RNAs profiles [77]. iPSC-MSCs ameliorated cigarette smoke (CS)-induced apoptosis and proliferation imbalance of airway cells partly through the paracrine section of stem cell factor (SCF) [78]. Asthma is a chronic disease with inflamed airways. iPSC-MSCs were able to prevent chronic allergic airway inflammation[79]. Compared with BM-MSCs, iPSC-MSCs transferred mitochondria to bronchial epithelial cells more effectively *via* tunnelling nanotubes. Therefore, iPSC-MSCs were superior to BM-MSCs in attenuating CS-induced airspace enlargement[80].

Kidney disease

hPSC-MSCs improved both acute and chronic adriamycin nephropathy (AN) by preventing renal function loss. hESC-MSCs prevented the progression of fatal lupus nephritis in a mouse model by significantly decreasing two inflammatory cytokines associated with systemic lupus erythematosus, tumour necrosis factor α (TNFα) and IL-6[81]. iPSC-MSCs prevented the apoptosis of tubular cells by downregulating B-cell lymphoma 2 associated X (Bax) and Bax/B-cell lymphoma 2 and upregulating survivin in the short-term AN model whereas iPSC-MSCs inhibited fibrosis *via* hedgehog signalling in the long-term AN model[82]. iPSC-MSCs also ameliorated palmitic acid-induced lipotoxic kidney injury by alleviating endoplasmic reticulum (ER) stress, inflammation, and apoptosis to suppress ER stress and its downstream pro-inflammatory and pro-apoptotic effects *via* hepatocyte growth factor (HGF)/c-Met signalling[83]. Chronic kidney disease (CKD) is characterized by a gradual loss of kidney function over time due to renal fibrosis[84]. Intravenously administrated iPSC-MSCs effectively protected the kidney against CKD injury in CKD parenchyma[85]. iPSC-MSCs were also able to effectively protect kidney from acute ischemia-reperfusion injury[86]. hPSC-MSC-derived exosomes reduced the renal fibrosis, decreased inflammatory reactions, and improved renal function in unilateral ureteral obstruction mice by increasing SIRT6 and decreasing β-catenin[84] (Figure 1).

Cardiovascular diseases

MSCs have the potential to improve cardiovascular diseases. Coculture with hESC-MSCs promoted the maturation of hESC-derived cardiomyocyte microtissues[87]. iPSC-MSCs increased the level of M2 macrophages and deceased the level of M1 macrophages after cardiac arrest (Figure 1), suggesting that iPSC-MSCs play a crucial role in immunomodulation during cardiopulmonary resuscitation[88]. iPSC-MSCs improved CS-induced cardiac remodelling and dysfunction better than BM-MSCs as shown by an increase in percentage of left ventricular ejection fraction and fractional shortening. iPSC-MSCs attenuated cardiac pro-inflammatory cytokines and restored anti-inflammatory cytokines[89]. Conditioned medium from iPSC-MSCs alleviated heart failure and reduced cardiomyocyte apoptosis and fibrosis better than that from BM-MSCs, showing that iPSC-MSCs could provide cell-free therapeutic cardioprotection[90]. Extracellular vesicles (EVs) of iPSC-MSCs mitigated arterial ageing by attenuating ageing-associated vascular endothelial dysfunction, arterial stiffness, and hypertension[91]. In addition, overexpression of myocardin in iPSC-MSCs resulted in partial transdifferentiation into cardiomyocyte phenotype[92].

Neurological diseases

MSCs demonstrate significant neuroprotection and promote functional recoveries of the pathological nervous system. MSCs were shown to secret brain-derived neurotrophic factor and nerve growth factor, which supported neuronal cell survival and induced nerve regeneration (Figure 1). Conditional medium of hESC-MSCs could significantly ameliorate neurological deficits and infarct volume in middle cerebral artery occlusion (MCAO) rats[93]. hESC-MSCs differentiated into neural-like cells in standard neurogenic differentiation medium, and hESC-MSCs in sphere secreted more HGF and IGFBP1 than those in single-cell suspension[94] (Figure 1). hPSC-MSCs expressed higher levels of neural genes than BM-MSCs and rapidly differentiated into neural-like cells when differentiated into neural lineage[95]. Although ESC-MSCs

induced autophagy similar to BM-MSCs, ESC-MSCs survived better in amyloid-β (Aβ) -induced cellular models and reduced more intracellular Aβ levels compared with BM-MSCs. ESC-MSCs significantly decreased Aβ-induced cell death and promoted autophagolysosomal clearance of Aβ in a rat model of Alzheimer's disease, leading to higher memory performance. Intra-arterially transplanted ESC-MSCs were safe and free from cerebral ischemia[96]. iPSC-MSCs markedly decreased brain-infarct volume and improved neurological function mainly by inhibiting inflammation[97]. ESC-MSCs had a superior neuroprotective capacity over fetal MSCs in mouse hypoxic-ischemic brains[98].

In addition, hESC-MSC EVs also protected retinal ganglion cells and preserved retinal function in a mouse model of optic nerve injury by improving retinal ganglion cell (RGC) survival and preventing retinal nerve fiber layer degeneration. iPSC-MSCs significantly reduced corneal opacity by reducing inflammation similar to BM-MSCs [99]. Transplanted iPSC-MSCs significantly improved the survival of RGCs by effectively transferring functional mitochondria to RGCs[100].

Multiple sclerosis (MS) is a potentially disabling disease of the central nervous system caused by an attack of the protective sheath by the immune system, leading to communication problems between the brain and the rest of the body. As yet, there is no cure for MS, the most common demyelinating disease. Compared with BM-MSCs, hESC-MSCs improved efficacy in a mouse experimental autoimmune encephalitis (EAE) model of MS due to its lowered IL-6 expression. In addition, hESC-MSCs are less vulnerable than BM-MSCs in therapeutic capacity during *in vitro* culture[101]. After hESC-MSCs were intrathecally injected into the central nervous system of EAE-induced monkeys, hESC-MSCs greatly decreased the clinical symptoms, brain lesions, and neuronal demyelination in the EAE monkeys. hESC-MSCs could transdifferentiate into neural cells *in vivo* in the CNS of the treated monkeys as shown by elevated expression of genes for neuronal markers, neurotrophic factors, and neuronal myelination[41].

Immune disease

hPSC-MSCs have a strong immune regulatory effect during anti-inflammation. Microphages serve as a bridge between innate and specific immune responses. hPSC-MSCs altered macrophage polarization by suppressing the Notch-1 signalling pathway[102] (Figure 1). Due to the immunosuppression property of iPSC-MSCs, they have been used for the treatment of various immune diseases. hESC-MSCs slowed down the development of severe experimental autoimmune uveitis through systemic immune modulation[103], whereas iPSC-MSCs inhibited proliferation, shifted the secretome of peripheral blood mononuclear cells, and significantly suppressed CD8 T proliferation, activation, and differentiation[104]. iPSC-MSCs also suppressed T-cell effector cells of Th1/Th2 and increased regulatory T cell (Treg) response[105]. iPSC-MSCs prolonged hind limb survival by reducing mononuclear cell infiltration, lowering TNFα and IFNγ, increasing interleukin 10, and thus protecting against acute rejection in a rat vascularized composite allotransplantation model[106] (Figure 1). iPSC-MSCs disrupted NK cell cytolytic machinery to prevent allograft rejection by decreasing activation markers and ERK1/2 signalling, leading to impaired immunologic synapses and secreted cytotoxic granules. However, iPSC-MSCs were more resistant than BM-MSCs to pro-activate NK cells[26]. hESC-MSCs could protect against an experimental model of inflammatory bowel disease[107]. iPSC-MSCs modulated T-cell phenotypes towards Th2 suppression by inhibiting lymphocyte proliferation and promoting Treg response, suggesting that iPSC-MSCs can treat allergic airway diseases[108]. iPSC-MSCs regulate T cell responses by decreasing secreted soluble factors[109]. iPSC-MSCs also improved asthma inflammation by connexin 43-mediated mitochondrial transfer[110]. iPSC-MSCs accelerated intestinal epithelial cell proliferation to promote intestinal repair in murine colitis through tumor necrosis factor-stimulated gene-6 (TSG-6) *via* Akt-dependent interaction between the extracellular matrix HA and CD44+ cells[111]. iPSC-MSC EVs prevented the progression of Sjogren's syndrome (SS), a chronic autoimmune disease, by suppressing activation of immune cells and proinflammation factors essential for SS progression[112]. Due to intrinsic immunosuppression, MSCs significantly prolonged the survival of humanized mouse model of graft *vs* host disease (GvHD)[113]. The first iPSC-MSC clinical trial was reported in 2020. iPSC-MSCs were produced using an optimized and good manufacturing practice-compliant manufacturing process to treat steroid-resistant acute GvHD. Based on the complete response, overall response, and overall survival of participants, the higher dose level of iPSC-MSC showed better outcomes than the lower dose, and iPSC-MSCs were safe and well tolerated without serious adverse events reported[114].

Cancer treatment

Like primary MSCs, hPSC-MSCs also have therapeutic potentials in treating cancer or repairing tissue damages caused by cancers. hPSC-MSCs can overcome the limitation of drug delivery. iPSC-MSCs expressing cytosine deaminase limited tumor growth and decreased lung metastases in a mouse xenogeneic model of human breast cancer [115]. EVs from hPSC-MSCs also showed promising results to improve cancer treatment. hESC-MSC microvesicles decreased the proliferation of leukemia cells[116]. Treatment with iPSC-MSC nanovesicles showed no detectable immunogenicity and significantly decreased the incidence of metastases from triple-negative breast cancer in mouse models[117]. iPSC-MSC nanovesicles also significantly decreased tumor growth of metastatic prostate cancer[118]. These suggest that iPSC-MSC nanovesicle is a promising platform to improve the treatment of metastatic cancer. iPSC-MSCs can home to cancers with a similar efficiency as BM-MSCs. As compared with BM-MSCs, iPSC-MSCs expressed lower levels of interleukin-1 and TGFβ receptors, downstream pro-tumor factors, and hyaluronan and its cofactor TSG6, and therefore iPSC-MSCs have much less potential to promote tumours than BM-MSCs by promoting the EMT, invasion, stemness, and growth of cancer cells[119].

Other applications

hPSC-MSCs are also used for other applications. iPSC-MSC exosome improved cutaneous wound healing by promoting collagen synthesis and angiogenesis[120]. Furthermore, iPSC-MSC exosome *via* intramuscular injection could enhance microvessel density and blood perfusion by activating angiogenesis-related molecule expression and promoting HUVEC migration, proliferation, and tube formation[121]. iPSC-MSCs supported the proliferation of hematopoietic stem and progenitor cells (HPCs), and maintained a primitive immunophenotype and colony forming unit of CD34+ HPCs. Long-term culture initiating cell frequency was lower compared with primary MSCs, suggesting that iPSC-MSCs are less suitable than primary MSCs as feeder cells[44]. iPSC-MSCs also can be used as feeder cells to culture human iPSCs. Human iPSCs cultured on human iPSC-MSC feeder were slightly thinner and flatter than the other feeder system. However, iPSC-MSCs still maintain the proliferation and pluripotency of iPSCs[122]. hESC-MSCs restored the structure of the injured ovarian structure and function in premature ovarian failure *via* paracrine effect and ovarian cell survival to rescue fertility in mice[123,124]. hESC-MSC secreted trophic factors to support hepatocytes on an acute liver failure model[125]. hESC-MSC EVs ameliorated cirrhosis in thioacetamide-induced chronic liver injury[126].

DISCUSSION

Primary MSCs have drawbacks due to their limited scalability, interdonor variability, and inconsistent outcomes of clinical trials. iPSC-MSCs have the potential to overcome the fundamental limitations of conventional and donor-derived MSC production processes. The derivation of hPSC-MSCs has made substantial progress with an increasing number of reports on the use of hPSC-MSCs for regenerative medicine over the past years. However, the issues and challenges related to safety and efficacy of hPSC-MSCs remain to be understood and addressed. These include the effects of cell origins and derivation approaches on hPSC-MSCs, the understanding of difference between hPSC-MSCs and primary MSCs, MSC stemness/potency biomarkers, the differentiation potential of hPSC-MSCs, choice of autologous or allogeneic hPSC-MSC source, manufacturing of clinical grade hPSC-MSCs, *etc.*

Effects of cell origins and derivation approaches on the features of hPSC-MSCs

The use of MSCs is already in various phases of clinical applications. However, little is known about the difference in features of hPSC-MSCs from different origins, particularly in their differentiation potential, a critical feature to their clinical application. Although hPSC-MSCs derived from various approaches exhibit MSC morphology and express MSC surface antigens, their differentiation potential is not as efficient as BM-MSCs, especially in adipogenesis[31,47]. Due to epigenetic memory or incomplete reprogramming, iPSC variations exist, and iPSC-MSCs exhibit preferential differentiation into their original cell lineage. Eto *et al*[127] showed that iPSC-MSCs *via* the mesoderm and neuroepithelium had the capacity for self-renewal and multipotency as well as therapeutic potential in skin wounds, pressure ulcers, and OA in a mouse model. However, different therapeutic effects of iPSC-MSCs from different origins were also observed, suggesting that the therapeutic efficacy of hPSC-MSCs is

dependent on cell origins. In addition, hPSC-MSCs derived by differentiation approaches vary extensively in their quality and efficiency. The use of fibroblast growth factor in the differentiation medium[27,47,128] promotes MSC proliferation at the expense of its differentiation potential[129]. Therefore, the effects of cell origins and differentiation approaches on iPSC-MSCs need to be elucidated.

Mechanisms underlying difference between hPSC-MSCs and primary MSCs

Compared with primary MSCs, hPSC-MSCs have advantages of faster proliferation, longer life span, more reliable and homogeneous cell source, but somehow immature differentiation potential and impaired immunosuppression. What are intrinsic and extrinsic mechanisms underlying the difference between iPSC-MSCs and primary MSCs?

The lack of MSC stemness/potency biomarkers to identify good quality of MSCs

So far, little is known about regulators or biomarkers associated with MSC stemness/potency, and there is no critical quality attribute available for use to distinguish good MSCs from bad ones before cellular manufacturing. The mechanism underlying MSC stemness or potency remains poorly understood, which greatly hampers the clinical application of hPSC-MSCs. It was shown that kindlin-2 increased the survival, proliferation, stemness, and migration of iPSC-MSCs. Kindlin-2 knockdown increased apoptosis and differentiation response whereas kindlin-2 overexpression increased proliferation, decreased apoptosis, and slowed down trilineage differentiation. More significantly, kindlin-2 overexpression increased the migration of iPSC-MSCs in the wound-scratch assay[130]. In the future, substantial efforts are needed to explore MSC stemness/potency-related regulators or biomarkers for clinical application.

Differentiation potential of hPSC-MSCs

It is well accepted that MSCs have potential to differentiate into multiple mesenchymal lineages, such as osteoblasts, chondrocytes, and adipocytes. However, it is still controversial that MSCs can directly differentiate into other types of functional cells, such as cardiomyocytes-like cells[131], hepatocytes[132], neuron-like cells[133], and pancreatic β cells[134]. The underlying mechanism of iPSC-MSCs improving these conditions need to be elucidated.

Autologous vs allogeneic hPSC-MSCs

MSCs have anti-inflammatory and immune-modulatory properties. However, patient-derived autologous hPSC-MSCs still represent a better option for regenerative medicine as there are lesser concern regarding the immune response compared with allogeneic MSCs.

Clinical grade hPSC-MSCs

Although iPSCs are generated by integration-free methods and iPSC-MSCs are derived by a number of approaches, there are few approaches available to regenerate clinical-grade hPSC-MSCs for clinical application. Most protocols have used undefined components, such as FBS, feeder cells, and other animal-derived components, which compromise the clinical application of iPSC-MSCs. To generate clinical grade iPSC-MSCs, reliable, efficient, scalable, and clinically compliant approaches are required throughout the whole manufacturing process of iPSC-MSCs. These processes include generation and expansion of iPSCs, freezing and thawing of iPSCs, differentiation of iPSCs towards MSCs, expansion of iPSC-MSCs, freezing and thawing iPSC-MSCs, *etc.* In addition, comprehensive assays should be established to evaluate the safety, quality, or potency of hPSC-MSCs during cellular manufacturing for clinical application.

CONCLUSION

hPSC-MSCs have enormous potential for regenerative medicine, and can be used for disease modelling, drug screening, and treatment of various diseases in regenerative medicine. Although multiple approaches have been reported in deriving MSCs from hPSCs, the use of undefined and animal-derived components greatly compromises the clinical application of hPSC-MSCs. Much effort is needed to derive clinically relevant and sufficient hPSC-MSCs with good quality for clinical application, and criteria need be established to evaluate the safety and efficacy of hPSC-MSCs before clinical

application. In addition, many issues or challenges with hPSC-MSCs also need to be addressed.

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