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REVIEW

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Induced pluripotent stem cell-derived mesenchymal stem cells: whether they can become new stars of cell therapy

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Abstract

Stem cell therapy constitutes a pivotal subject in contemporary discourse, with donor stem cells having been employed in research and clinical treatments for several decades. Primary cell transplantation encompasses diverse stem cell types, including ectomesenchymal stem cells, hematopoietic stem cells, and various stem cell derivatives such as vesicles and extracellular vesicles. Nevertheless, the emergence of cell engineering techniques has heralded a new epoch in stem cell therapy, markedly broadening their therapeutic potential. Induced pluripotent stem cells (iPSCs) epitomize a significant milestone in modern medical biology. This groundbreaking discovery offers significant potential in disciplines such as biology, pathophysiology, and cellular regenerative medicine. As a result, iPSCs derived differentiated cells have become a pioneering avenue for cell therapy research. Induced mesenchymal stem cells (iMSCs), derived from iPSCs, represent a novel frontier in MSCs related research. Empirical evidence suggests that iMSCs demonstrate enhanced proliferative capacities compared to natural MSCs, with diminished age-related variability and heterogeneity. Numerous clinical trials have highlighted the prospective superiority of iMSCs. This article synthesizes current basic research and clinical trials pertaining to iMSCs, aiming to provide a reference point for future research endeavors.

Introduction

MSCs, also referred to as mesenchymal stem cells, exhibit the potential to differentiate into a variety of mesodermal cell lineages, such as adipocytes, chondrocytes, osteocytes, and myocytes [1]. These cells are defined by the expression of specific surface markers, including CD73, CD90, and CD105, and the absence of markers such as CD45, CD34, CD14 or CD11b, CD79 or CD19, and HLA-DR [2]. As research advances, controversy surrounding the definition of MSCs has grown, largely due to the increasing acknowledgment of their heterogeneity across different tissue origins. Extensive investigations have been conducted on MSCs derived from various tissues, with the most frequently studied sources including umbilical cord, bone marrow, adipose tissue, synovium, and dental pulp, among others [3]. MSCs from different origins exhibit variations in surface markers and subtle differences in their differentiation potential into adipocytes, chondrocytes, and osteocytes [4]. Numerous studies and reviews have extensively explored these aspects, and this article avoids reiterating redundant explanations on this topic. Why is considering the heterogeneity of MSCs important? MSCs are currently a primary cell source for stem cell

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therapy, demonstrating promising therapeutic effects in numerous preclinical studies and clinical trials. However, variability in clinical trial outcomes and results has been observed, closely tied to the inherent heterogeneity of MSCs.

Numerous studies have documented the diversity of MSCs sourced from various individuals and tissue origins, leveraging advancements such as single-cell RNA sequencing (scRNA-seq) technology to explore these variances. This analytical approach has enabled detailed investigations into the disparities among MSCs derived from distinct tissue sources and individuals. Wang et al. identified seven tissue-specific subpopulations with distinct gene expression profiles from multiple tissue sources, as well as five conserved subtypes of MSCs. Umbilical cord MSCs (UC-MSCs) demonstrate advantages in terms of immunosuppressive properties [5]. Xie et al. employed scRNA-seq to identify clusters within bone marrow MSCs (BM-MSCs), which encompass the $CD26^{+}$ osteogenic subtype, the $CMKLR1^{+}$ functional subtype, and the proliferative subtype [6]. Zhang et al. investigated freshly isolated, uncultured UC-MSCs using scRNA-seq. They observed that after in vitro culture, MSCs differentiated into subtypes enriched in immune response regulation, as well as subtypes associated with osteogenic and chondrogenic differentiation, and growth-related subtypes related to bone and cartilage.

Induced pluripotent stem cells (iPSCs) are generated through the reprogramming of differentiated somatic cells, typically via the introduction of specific transcription factors. This reprogramming process reverts the differentiated cells to a pluripotent state, enabling them to form cell lines analogous to embryonic stem cells [7]. The technology for producing iPSCs has attained a high degree of sophistication, with substantial advancements achieved in optimizing both the induction and differentiation methodologies.Consequently, the development of iPSC technology has facilitated substantial progress in research focused on differentiating iPSCs into various cell types [8, 9]. Differentiation into MSCs has been achieved through various methodologies and techniques. iMSCs offer several advantages over tissue-derived MSCs. Notably, tissue-derived MSCs exhibit more pronounced replicative senescence, whereas iMSCs demonstrate reduced heterogeneity. Additionally, iMSCs can be generated from donor or patient cells, positioning them as a pivotal cell source for future personalized cell therapies. Furthermore, iMSCs acquire youthful genetic characteristics irrespective of donor age and cell origin [10]. The potential of iMSCs as a superior cell source for stem cell therapy represents a significant question in contemporary research [11]. This article provides a comprehensive review of the methodologies for obtaining iMSCs, a comparative analysis between iMSCs and MSCs, and an overview of current foundational research on iMSCs. The objective of this review is to offer insights and references for future research and translational applications of iMSCs.

Methods for induction of iMSCs

Over the past decade, methodologies for inducing differentiation of iPSCs into MSCs have undergone significant advancements. A variety of techniques are now available to facilitate the differentiation of iPSCs into MSCs, and the resultant iMSCs may exhibit variations depending on the method employed. These variations are critical for the clinical translation of iMSCs. Lian et al. successfully induced MSCs differentiation by replacing the culture medium of iPSCs with a specialized induction medium tailored for MSC differentiation. This induction medium comprised standard DMEM and FBS, augmented with 10 ng/mL of bFGF, 10 ng/mL PDGF-AB, and 10 ng/mL of EGF. These additives were intended to promote the proliferation and enrichment of iMSCs. iMSCs were successfully derived following a 10-day induction culture period [12]. Tran NT et al. induced iMSCs by supplementing the basal medium with 5 ng/mL Activin A, 2 μM BIO, and 20 ng/mL BMP for 3 days. Subsequently, they cultured the cells with 10 ng/mL bFGF and 10 ng/mL EGF for an additional 10 days to complete the induction process [13]. It has also been reported that only 6 ng/mL bFGF was added to the base medium [14], or direct use DMEM low glucose, supplemented with 10% FBS and 2 mM L-glutamine, basic medium culture for 14 days can be successfully induced[15]. The differentiation outcomes were consistent with the established criteria for MSCs identification. Furthermore, various induction methodologies have been documented, highlighting the essential function of bFGF throughout the induction process. bFGF, a peptide recognized for its ability to stimulate cell division in mesodermal and neuroectodermal tissues, is instrumental in facilitating mesodermal transformation and angiogenesis. Consequently, the inclusion of bFGF during induction processes significantly enhances the generation of iMSCs (Table 1). All iMSCs meet the identification criteria, but whether there are phenotypic differences needs to be further studied. In the process of induction, it is necessary to consider the balance of cost and differentiation efficiency, and a productized kit is also a good choice.

Comparison of iMSCs and MSCs

In the investigation of iMSCs induction, a recurrent question has emerged among researchers: what are the differences compared to MSCs derived directly from

Table 1 Methods for induction of iMSCs

Methods	Surface markers	Reference
8–10 ng/mL bFGF 2d 5 ng/mL Activin A,2 μM BIO and 20 ng/mL BMP 3d	positive markers: CD29, CD44, CD73, CD90, CD105, and HLA-ABC negative markers: CD34, CD45, CD31, and HLA-DR	[13]
10 ng/mL bFGF, 10 ng/mLPDGF AB 10 ng/mL EGF 7d-10d	positive markers: CD44,CD49e,CD73,CD90, CD105,CD166, negative markers: CD34,CD45,CD133	[12] [28]
10 ng TGFβ1 10 μM SB431542 35d	positive markers: CD73,CD90,CD105,CD44, CD166 negative markers: CD45,CD34,CD14,CD19, HLA-DR	[46]
100 nM dexamethasone 50 μM magnesium L—ascorbic acid phosphate 2d	positive markers: CD73,CD90, CD105, CD146 and CD166, negative markers: CD34 and CD45	[47]
8 ng/mL bFGF	positive markers: CD166,CD105,CD90and CD73 negative markers: CD31, CD34 and CD45	[14]
10% hPL for 7 days standard cultivation conditions containing 10% hPL 35d	positive markers: CD29, CD73, CD90, and CD105 negative markers: CD14, CD31, CD34, and CD45	[48]
DMEM, 10%FBS and 2 mm L—glutamine, 14d	positive markers: CD29, CD44, CD73, CD90, CD105 and CD146 negative markers: CD34, CD45, CD133 and HLA-DR	[15]

* BIO: 6-bromodierythroin-3 '-oxime; bFGF: basic fibroblast growth factor; PDGF AB: platelet-derived growth factor AB; EGF: epidermal growth factor; hPL: human platelet lysate; FBS:fetal bovine serum

organisms? Do iMSCs present specific advantages, and could these advantages potentially impact future research and applications? As a result, numerous studies have undertaken comparative analyses of iMSCs and MSCs obtained from various sources. Xu et al. conducted a comparative analysis of the phenotypes and biological functions of iMSCs and BM-MSCs. Their findings revealed no significant difference in the proliferation capacity between iMSCs and BM-MSCs. However, iMSCs exhibited elevated expression levels of KDR and MSX2, while BM-MSCs showed notably higher expression of PDGFRα. Furthermore, iMSCs demonstrated a superior capacity for adipogenic differentiation in comparison to BM-MSCs. Analysis of specific extracellular matrix (ECM) components revealed abundant synthesis of COL2, COL6, COMP, and proteoglycans in BM-MSC microspheres, whereas these components were less expressed in iMSCs microspheres. Notably, similarities were observed between iMSCs and smooth muscle cells [16]. Joana Frobel et al. conducted a comparative analysis of the global gene expression profiles of BM-MSCs and iMSCs, identifying an enrichment in pathways related to T cell activation and immune response. Subsequent validation experiments demonstrated that BM-MSCs exhibited a significantly greater capacity to inhibit T cell proliferation compared to iMSCs. Nonetheless, other examined aspects displayed comparable expression patterns between the two cell types. Wang et al. discussed the differences between iMSCs and UC-MSCs. They observed no significant differences in cell proliferation and growth assessed through growth curves, β-galactosidase (β-GAL) staining, and telomerase activity analysis. RNA-seq analysis indicated high expression of Hox family genes in iMSCs, suggesting potential similarities between iMSCs and MSCs in their original tissue microenvironment. Regarding immune-related functions, iMSCs demonstrated stronger immunosuppressive abilities. Pro-inflammatory factors such as IL6, CXCL8, and IL1β were highly expressed in UC-MSCs, whereas anti-inflammatory factors including NOS1, CD24, FOXP3, FOXP2, TGFBR1, and TGFB2 were highly expressed in iMSCs. Immunofluorescence staining confirmed significantly reduced IL6 in the iMSC population[17]. iMSCs exhibited higher homogeneity and better proliferation capacity compared to theoretically tissue-derived MSCs. In contrast to BM-MSCs, iMSCs

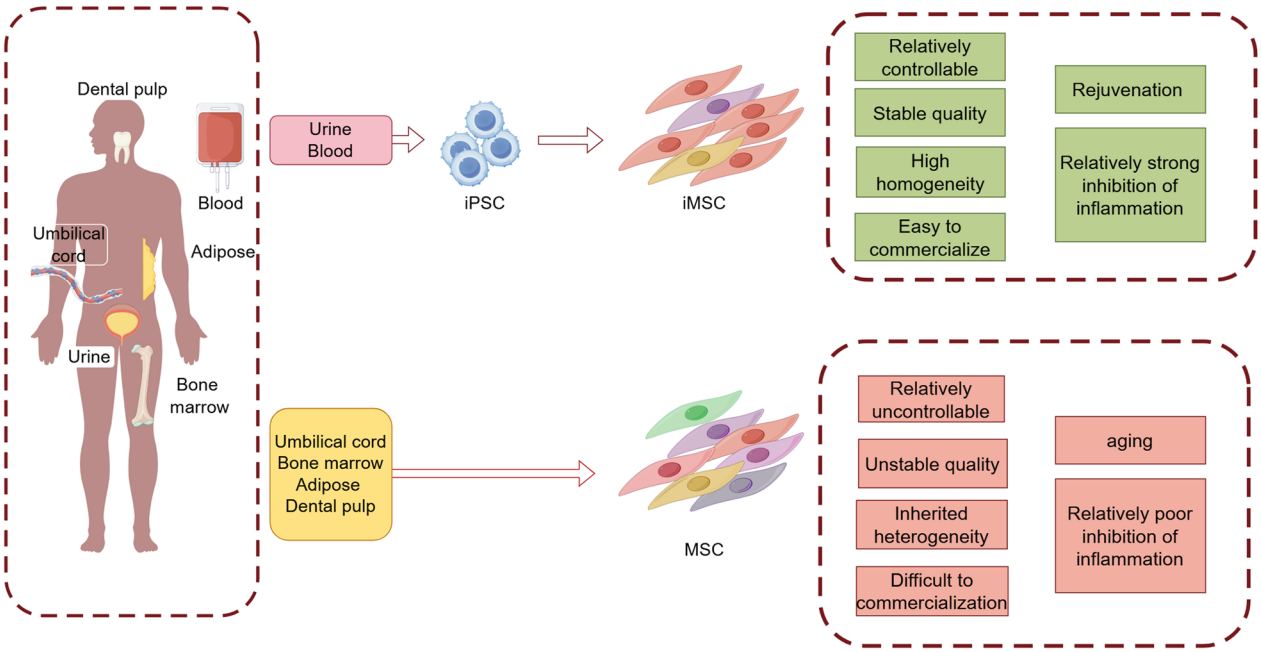

Fig. 1 Comparison of iMSCs with tissue-derived MSCs

demonstrated stronger proliferation abilities and could be expanded over 40 generations while maintaining a normal diploid karyotype, consistent gene expression, and surface antigen profile[12]. Hae-Ri Lee et al. compared iMSCs and MSCs from the original generation, it was observed that iMSCs exhibit higher proliferative activity. Additionally, the differentiation potential of these cells varies in a donor cell-dependent manner. The iMSC-specific pattern is characterized by a shift in cell fate towards a pericytoid state and an enhanced secretion of paracrine cytokines and growth factors[18]. Tackla Winston et al. studied the transcriptomic characteristics of early developmental cell types, two lineage-specific iMSCs, and six provence-specific pMSCs, and found that MSCs are rich in genes related to osteogenesis, immune regulation, and cell-ECM interactions. NC-iMSCs have higher MSC purity and stronger osteogenic differentiation potential than CT-iMSCs. CT-iMSCs have better EVs production and immunomodulatory functions than NC-iMSCs (Fig. 1).

iMSCs for cell therapy research

iMSCs have exhibited considerable potential in the treatment of a diverse array of diseases, particularly those characterized by ischemic and inflammatory processes. This includes conditions such as myocardial infarction, lower limb ischemia, inflammatory bowel disease (IBD), and acute lung injury, among others. In disease model studies, the principal function of iMSCs is to modulate immune responses and promote tissue repair, similar to the roles performed by tissue-derived MSCs. Nonetheless, the specific functions of iMSCs may vary depending on the particular disease context. Hynes et al. reported that iMSCs, in conjunction with newly formed mineralized tissue, facilitated periodontal regeneration in a rat model of periodontitis[19]. Similarly, Lian et al. found that iMSCs could mitigate limb ischemia in mice[12]. In a murine model of IBD, iMSCs were found to promote mucosal healing mechanisms via the production of TSG-6. When iMSCs were applied in accordance with clinical standards, an enhancement in colonic mucosa healing was observed in the mice. This improvement was characterized by increased proliferation of epithelial cells, as well as elevated numbers of $CD44^{+}$ $Lgr5^{+}$ cells[20]. The potential of mitochondrial donation from iMSCs to sustain retinal ganglion cell (RGC) survival and restore retinal function is currently under investigation. The observed improvements in retinal function are associated with a significant increase in RGC survival rates following iMSCs injection into the retina of Ndufs4 knockout mice. iMSCs transplanted into the vitreous efficiently transfer functional mitochondria to RGCs, thereby preventing mitochondrial damage-induced RGC loss[21]. The transplantation of iMSCs in mice experiencing asthma inflammation resulted in a significant reduction of T helper 2 cytokines and alleviated epithelial cell mitochondrial dysfunction. The iMSCs formed tunneling nanotubes (TNTs) with epithelial cells, aiding in the

transfer of mitochondria as observed both in vitro and in mice[22]. The studies suggest that iMSCs primarily restore functional cells through paracrine signaling or mitochondrial transfer for disease treatment, with a low likelihood of in vivo self-differentiation.

In terms of immune regulation, studies have found that iMSCs mainly play the function of immunosuppression. Hui Shi et al. administered iMSCs intravenously to ApoE knockout mice on a high-fat diet for 12 weeks, resulting in a substantial reduction in plaque size. The administration of iMSCs resulted in a decrease in serum inflammatory cytokines, specifically TNFα and IL6, thereby contributing to the mitigation of arterial sclerosis (AS) inflammation[23]. The transplantation of iMSCs resulted in the suppression of T cell proliferation, a decrease in Th1 and Th2 phenotypes and cytokines, and an upregulation of Th17 and Treg [24]. Additionally, iMSCs have been shown to significantly inhibit the proliferation, activation, and differentiation of cytotoxic CD8 T cells into Tc1 cells and CD8 T cells expressing IL17[25]. Comparative analyses between iMSCs and tissue-derived MSCs have been conducted across various disease models. In a study utilizing an IBD model, Kagia et al. evaluated the therapeutic efficacy of BM-MSCs, umbilical cord blood-derived MSCs (UCB-MSCs), embryonic stem cell-derived MSCs (ESC-MSCs), and iMSCs. Their findings indicated that both UCB-MSCs and BM-MSCs significantly mitigated inflammation, whereas ESC-MSCs and iMSCs demonstrated comparatively weaker anti-inflammatory effects [26]. Similarly, Soontararak et al. conducted a comparative study on the efficacy of iMSCs and AD-MSCs within a murine model of IBD. Their findings indicated that both iMSCs and AD-MSCs were equally effective in significantly ameliorating intestinal inflammation, enhancing the population of intestinal $Lgr5^{+}$ stem cells, and promoting intestinal vascularization [27]. In an animal model of COPD, iMSCs were more effective than BM-MSCs in reducing cigarette smoke-induced lung damage. iMSCs significantly lowered CS-induced COX2 and CINC1 levels and better mitigated macrophage and neutrophil infiltration, as well as the imbalance between apoptosis and proliferation in lung tissues [28]. Research comparing iMSCs and tissue-derived MSCs is limited, but shows similar therapeutic outcomes. Due to iMSCs' low heterogeneity and easy expansion, their secretome may offer greater clinical potential.

iMSC-EVs as cell therapy

Extracellular vesicles (EVs) are released by cells and encompass a wide range of cellular constituents, including DNA, RNA, lipids, metabolites, cytoplasmic proteins, and cell surface proteins. These vesicles play a crucial role in intercellular signaling and impact the behavior of recipient cells[29]. Owing to their molecular cargo and capacity to mitigate immune responses linked to direct cell transplantation, EVs have emerged as a prominent therapeutic modality in cell-based therapies[30]. Research on MSC-EVs is well-established in diverse disease contexts, with ongoing efforts to enhance their modification and optimization for various therapeutic interventions[31, 32]. Similarly, induced mesenchymal stem cells (iMSCs) exhibit the ability to secrete extracellular vesicles (EVs) externally. Given their enhanced proliferative capacities relative to conventional mesenchymal stem cells (MSCs) and their limited sources, iMSCs present a significant advantage in the context of external secretion for therapeutic applications. In the realm of bone and joint diseases, Zhu et al. conducted a comparative analysis of the EV secretion profiles between iMSCs and synovial membrane-derived MSCs (SM-MSCs) within the framework of osteoarthritis (OA). The study's results indicated no substantial differences in the characteristics of the extracellular vesicles, including particle size and surface markers. Both types of EVs were effective in alleviating symptoms in an OA mouse model. However, the iMSC-EVs demonstrated superior therapeutic effects compared to those from SM-MSCs, particularly in enhancing chondrocyte migration[33]. Cui et al. engineered exosomes (BT-Exo-siShn3) that were modified with a bone-targeting peptide to specifically deliver siRNA to osteoblasts. Knockdown of Shn3 in osteoblasts resulted in enhanced osteogenic differentiation and decreased autologous receptor activator of RANKL expression, thereby inhibiting osteoclast formation and potentially offering a therapeutic approach for osteoporosis[34]. A separate study illustrated that iMSC-EVs have the ability to decelerate the advancement of intervertebral disc degeneration (IVDD) in comparison to conventional EVs. iMSC-EVs demonstrated anti-aging properties by transporting miR-105-5p to senescent nucleus pulposus cells (NPC) and activating the Sirt6 pathway[35]. iMSC-EVs have been shown to effectively decrease infarct volume, promote angiogenesis, and mitigate long-term neurological impairments in rats following a stroke. Additionally, iMSC-EVs have been found to activate STAT3, leading to enhanced angiogenesis[36].

In the field of oncology research, iMSC-EVs have shown considerable potential in the treatment of triple-negative breast cancer (TNBC). Notably, iMSC-EVs have exhibited pronounced cytotoxic effects on adriamycin-resistant TNBC cells, outperforming both free and liposomal formulations of doxorubicin. Additionally, in a preclinical TNBC mouse model, iMSC-EVs were found to significantly reduce tumor burden and metastasis [37].

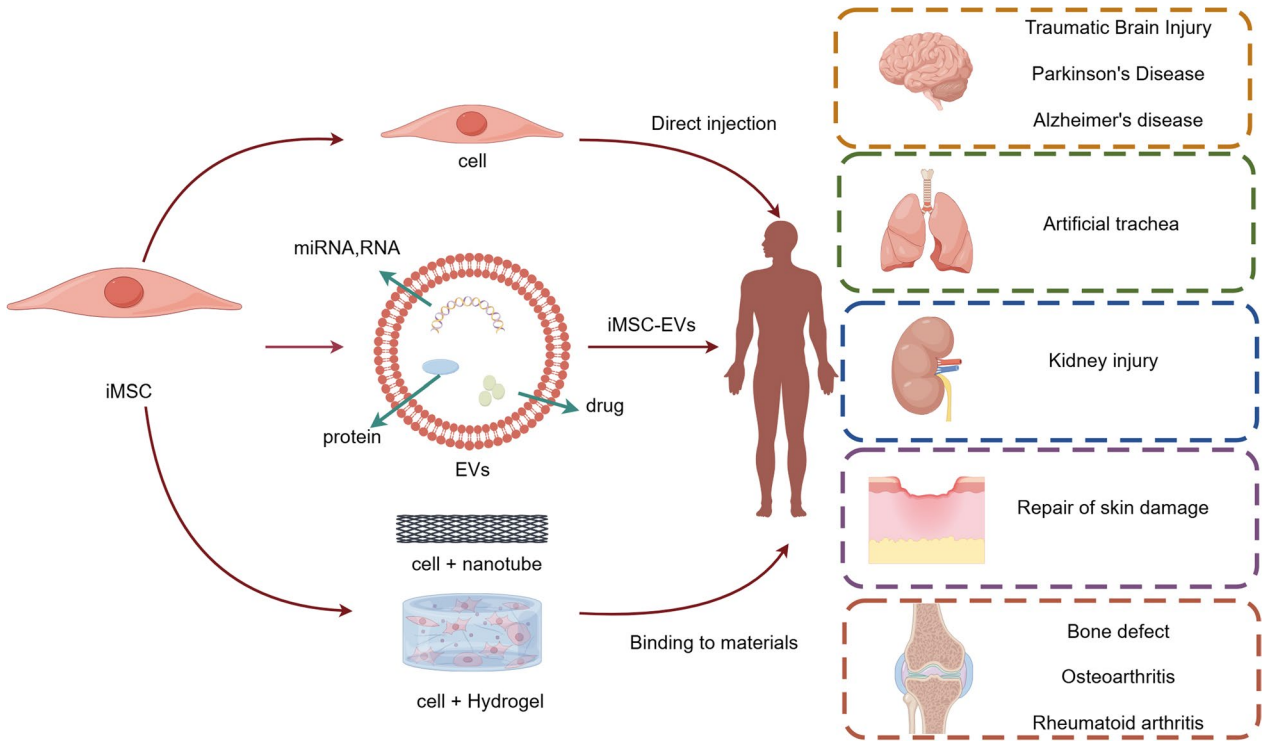

Fig. 2 Application of iMSCs in cell therapy research

iMSC-EVs are similar in size and formation mechanism to those produced by cancer cells. In addition, these iMSC-EVs containing activated STING induced IFNβ expression in receptor THP1 monocytes and anti-tumor immunity in mice. iMSC-EVs containing activated STING is a promising cell-free anti-tumor immune strategy[38]. The efficacy of EVs for therapeutic purposes is significantly influenced by their production status. EVs derived from early passage iMSC-EVs exhibited higher immunomodulatory efficacy when compared to those derived from late passage iMSCs, as evidenced in TLR4-stimulated splenocytes and in a mouse model of primary Sjogren's syndrome[39]. In conclusion, the therapeutic potential of tissue-derived MSC-EVs is hindered by their restricted expansion capabilities and donor variability. Human iMSCs present an opportunity for improved scalability, making them a promising candidate for tissue repair treatments.

iMSCs combined with material treatment strategy

The current study highlights the significant therapeutic potential of MSCs in tissue repair interventions, with ongoing research exploring their synergistic effects with various biomaterials. Investigations iMSCs have revealed that their integration with biomaterials can yield considerable therapeutic benefits. For instance, the coadministration of iMSC-EVs with hydrogels has been demonstrated to reduce scarring and expedite the wound healing process[40]. Using iMSCs with 3D-printed hydrogel scaffolds can improve their survival post-transplant by optimizing their microenvironment. This approach has proven effective in an endometrial injury model, fully restoring endometrial structure and function and partially recovering embryo implantation and pregnancy maintenance [38]. Upon integration with scaffold materials, a more biomimetic structure can be realized. Kim et al. employed a comparable approach in the development of an artificial trachea aimed at promoting the regeneration of tracheal mucosa and cartilage. This was achieved using a bilayer tubular scaffold combined with iMSCs. The artificial trachea framework consisted of electrospun polycaprolactone (PCL) nanofibers on the internal layer and 3D-printed PCL microfibers on the external layer. The lumen was populated with human bronchial epithelial cells (hBECs), iMSCs, and iPSC-derived chondrocytes, thereby facilitating optimal tracheal mucosa and cartilage regeneration in vivo. The implantation of a tissue-engineered artificial trachea into a rabbit model with a segmental tracheal defect led to the development of ciliated columnar epithelium integrated with iMSCs, thereby enhancing new cartilage formation at the site of the defect[41]. The combination of materials can prolong the presence

of iMSCs in the organism and aid in the generation of biomimetic organs for tissue transplantation, among other possible uses (Fig. 2).

Challenges of iMSCs to overcome

iMSCs offer advantages such as a wide availability, ample quantity, effective treatment, high homogeneity, and resolution of immune rejection and ethical issues. As a derivative of iPSCs, iMSC-EVs may exhibit similar or even superior efficacy compared to MSC-EVs. However, in the process of clinical transformation, there are still some key problems to be solved. Firstly, concerns exist regarding the characteristics of reprogrammed iPSCs. While it is currently believed that the stemness of iPSCs is similar to that of embryonic stem cells, specific differences still require further investigation. Secondly, the tumorigenic risks associated with iPSC reprogramming technology must also be considered. However, with advancements in iPSC small molecule reprogramming technology [42], new possibilities have emerged for iPSC quality control and potential MSC sources. In theory, iPSCs offer multi-lineage differentiation and self-renewal capabilities, making iMSCs suitable for large-scale culture and addressing tissue and age-related heterogeneity [43]. The phenotypes of iMSCs under stress conditions such as inflammation and hypoxia need to be verified experimentally and further explored.

Challenges of iMSC-EVs to overcome

As an alternative to iMSCs, iMSC-EVs exhibit significant potential for clinical application. Nevertheless, there are persisting challenges related to standardization, scalability, and the mitigation of heterogeneity that must be addressed. Tertel et al. demonstrated that the extraction of iMSCs from GMP grade iPSCs can yield immunomodulatory active EVs. However, iMSC-EVs also exhibit functional variability across different batches. Although iMSCs present extensive growth advantages, they have not yet resolved the persistent issue of functional inconsistency in the resultant MSC-EV products[44]. Therefore, establishing a standardized system and protocol for the extraction, purification, and storage of MSC-EVs is of paramount importance and represents a critical research direction. Initially, it is imperative to develop efficient separation and purification technologies to facilitate large-scale production. Additionally, the standardized cultivation of iMSCs is necessary to ensure the uniformity of the EVs. Prior to the clinical application of iMSC-EVs, the quantitative and qualitative analysis of their contents constitutes the most crucial area of investigation. Numerous researchers have proposed various hypotheses for the homogenization of EVs. These include preconditioning iMSCs to ensure uniform secretion profiles and the direct modification of EVs to enhance their carrier functions. Furthermore, extensive large-scale studies are required to thoroughly investigate the biosafety of MSC-EVs, the stability of their contents within the human physiological environment, the optimal injection dosage, and their distribution patterns throughout the body.

Summary and prospect

The field of cell therapy has experienced notable growth, with stem cell therapy demonstrating advanced development. Extensive research has been conducted on MSC-based cell therapy, ranging from initial treatments utilizing direct cell application to subsequent advancements in cell manipulation and related products. These advancements highlight the crucial role of MSCs in research opportunities and their significant transformative potential. This article provides an overview of various diseases and their treatment using MSC-based strategies. Nevertheless, the issue of treatment disparities continues to pose a significant obstacle. It is imperative to comprehend the intricacies of cell preparation, cultivation, and amplification alterations in the context of cloning to improve clinical interventions. Harnessing the potential of iMSCs has the potential to advance stem cell therapies significantly. Ongoing clinical trials are currently assessing the safety and initial effectiveness of iMSCs in individuals with steroid-refractory acute graft-versus-host disease (SR-aGVHD). The establishment of a standardized safety framework for human pluripotent stem cell (hPSC)-derived cells remains a persistent challenge[45]. In contrast to iPSCs, iMSCs generally do not elicit tumor formation in teratoma assays. iMSCs exhibit a slower replicative senescence and can sustain a more youthful phenotype during expansion in culture compared to tissue-derived MSCs. These unique attributes confer iMSCs and their derivatives with notable advantages for clinical utilization, suggesting their potential as a promising frontier in the realm of cell therapy.

Abbreviations

bFGF	Basic Fibroblast growth factor
AD-MSCs	Adipose-derived MSCs
BM-MSCs	Bone marrow MSCs
CINC-1	Cytokine-induced neutrophil chemoattractant-1
COL2	Type II Collagen
COL6	Type VI Collagen
COMP	Cartilage oligomeric matrix protein
COX2	Cyclooxygenase-2
DMEM	Dulbecco's Modified Eagle Medium
ECM	Extracellular matrix
EGF	Epidermal growth factor
EVs	Extracellular vesicles
iMSCs	iPSCs-derived MSCs
iPSCs	Induced pluripotent stem cells

MSCs	Mesenchymal stem cells
PDGF-AB	Platelet-derived growth factor AB
RANKL	Nuclear factor kappa-**B** ligand
scRNA-seq	single-cell RNA sequencing
SM-MSCs	Synovial membrane-derived MSCs
TSG-6	TNF-alpha-stimulated gene 6
UC-MSCs	Umbilical cord MSCs

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Author contributions
WZW and SYZ: Wrote the paper. LJX, LXL, LLX, and LY: Implemented methods. ZL: Analyzed the data. ZLY: Paper editing and proofreading. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
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