Journal Website: https://www.icjn.net/cl ISSN: 3106-5058 | EISSN: 3106-5066

ICJN Press

Cytotherapy and Longevity (CL)

Volume. 01 | Issue. 01 | Aug. 2026 DOI: 10.66729/cl202604201



REVIEW

Decoding Mesenchymal Stem Cell Heterogeneity by Single-Cell Transcriptomics: From Molecular Insights to Harnessing Heterogeneity for Precision Therapy of Musculoskeletal Degenerative Diseases

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Abstract

Mesenchymal stem/stromal cells (MSCs) hold great promise for treating musculoskeletal degenerative diseases such as osteoarthritis, sarcopenia, and osteoporosis, yet their clinical translation is severely hindered by cellular heterogeneity. This review systematically examines the multidimensional origins of MSCs heterogeneity, including donor background, tissue source, *in vitro* culture conditions, and intra-population functional diversity and highlights how single-cell RNA sequencing (scRNA-seq) has revolutionized our ability to decode this complexity. We summarize recent advances in constructing single-cell transcriptomic maps of MSCs from bone marrow, adipose tissue, umbilical cord, placenta, and discuss how different culture systems (serum-free vs. serum-containing, normoxia vs. hypoxia, 2D vs. 3D, and serial passaging) dynamically shape MSCs heterogeneity. Importantly, we present the homogeneity advantage of induced pluripotent stem cells (iPSCs)-derived MSCs (iMSCs), which exhibit higher transcriptomic consistency and rejuvenation features, making them attractive for standardized "off-the-shelf" cell therapies. Despite challenges such as epigenetic memory, tumorigenicity risk, and long-term genetic stability, iMSCs have entered Phase I/II clinical trials for multiple system atrophy and spinal cord injury. This review provides a complete perspective from "decoding heterogeneity" to "harnessing heterogeneity", offering theoretical and practical guidance for developing safer, more effective, and more predictable MSCs-based therapies for musculoskeletal degeneration.

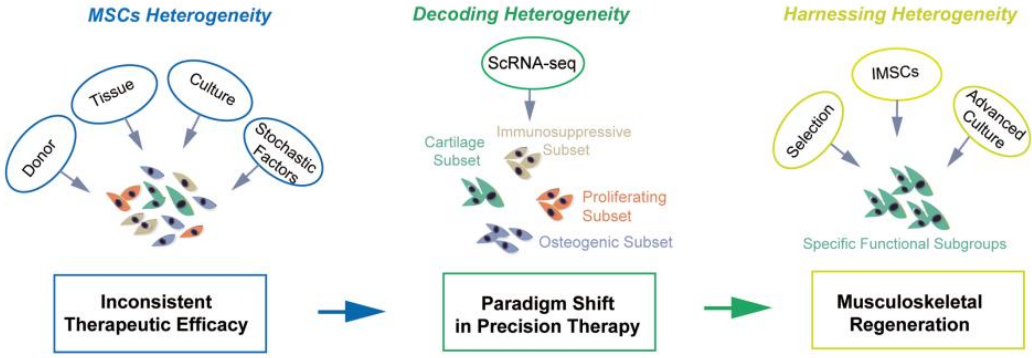
Keywords

Mesenchymal stem/stromal cells; Single-cell RNA sequencing; Heterogeneity; Aging; Musculoskeletal degenerative; Osteoarthritis; Precision cell therapy

Citation: Wenbo Gao, Min Wu, Yuwen Liang, *et al*. Decoding Mesenchymal Stem Cell Heterogeneity by Single-Cell Transcriptomics: From Molecular Insights to Harnessing Heterogeneity for Precision Therapy of Musculoskeletal Degenerative Diseases. *Cytotherapy and Longevity*. 2026, 01 (1): 1-14. doi: 10.66729/cl202604201.

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Received 23 April 2026; Revised 15 May 2026; Accepted 12 June 2026; Available online 20 August 2026.

Graphical Abstract



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Highlights

- MSCs heterogeneity arising from donor, tissue, culture, and stochastic factors etc, potentially hindering therapeutic efficacy.
- ScRNA-seq reveals functional subsets, such as cartilage-repair and immunosuppressive types, which show promise for musculoskeletal degenerative diseases.
- IMSCs appear to show lower heterogeneity and rejuvenation features, while 3D culture may synchronize phenotypes.
- Subset selection, engineering, and multi-omics might enable a paradigm shift in precision therapy.

1. Introduction

Global population aging is one of the most significant demographic and social changes of the 21st century[1]. According to estimates from the U.S. Census Bureau, the number of adults aged 60 – 79 will increase from 760 million in 2015 to 1.646 billion in 2050, or from 10.40% to 17% of the world's population. China is one of the countries with the fastest aging population and the largest elderly population in the world. In 2022, the proportion of people aged 65 and above reached 14.90%, and it is expected to rise to 26.10% by 2050[2]. The significant shift in the aging demographic structure has made musculoskeletal degenerative diseases such as osteoarthritis, sarcopenia, and osteoporosis, a major challenge in the field of public health in the 21st century[3].

Musculoskeletal degenerative diseases with high prevalence, such as osteoarthritis and sarcopenia, are important factors leading to falls, frailty, and disability in the elderly[4,5]. They not only severely impair patients' quality of life but also place a heavy burden on healthcare systems. Current treatment options for osteoarthritis primarily focus on symptomatic relief with medications and functional compensation, which fail to halt disease progression[6]. Although surgical interventions such as joint replacement are effective, they are associated with significant trauma, high costs, and risks of complications[7,8]. These limitations highlight the urgent need to develop novel therapies capable of genuinely repairing damaged tissues and restoring organ function.

Mesenchymal stem cells, also referred to as mesenchymal stromal cells (MSCs) are a class of adult stem cells with self-renewal capacity and multilineage differentiation potential, which are widely distributed in various tissues, including bone marrow, adipose tissue, umbilical cord, and placenta, etc[9]. High self-renewal and multilineage differentiation biological characteristics have made MSCs a focus of attention in the treatment of musculoskeletal degenerative diseases[10]. In recent years, remarkable progress has been made in preclinical studies and clinical trials of MSCs for musculoskeletal degenerative diseases. For example, in the field of osteoarthritis, multiple clinical trials have confirmed that intra-articular injection of autologous or allogeneic MSCs can significantly improve patients' pain scores and joint function[11,12]. In the field of sarcopenia, MSCs have demonstrated therapeutic potential by modulating chronic inflammation and promoting muscle regeneration[13,14].

Despite the encouraging clinical prospects of MSCs, their practical application faces a fundamental challenge, which is named cellular heterogeneity (**Figure. 1**). This cellular heterogeneity leads to inconsistent therapeutic outcomes and hinders the development of MSCs as therapeutic agents for musculoskeletal degenerative diseases[15,16]. The heterogeneity of MSCs is associated with multiple factors, including donor genetic differences[17-19], tissue source variations[20-22], differences in *in vitro* culture systems[23], and functional heterogeneity within cell populations[24,25]. For example, MSCs derived from elderly donors often exhibit aging-related characteristics such as reduced proliferative capacity, limited differentiation potential, and altered secretome profiles[26-28], whereas MSCs from patients with chronic diseases may carry functional imprints of the pathological state[29,30]. The *in vitro* culture process itself induces dynamic changes in the transcriptome and epigenome of MSCs[31,32]. As passage number increases, MSCs gradually lose their “stemness” characteristics and undergo replicative senescence, manifested by telomere shortening, proliferative arrest, reduced differentiation capacity, and altered paracrine function[33]. Moreover, even among MSCs derived from the same donor, the same tissue, and the same culture batch, significant transcriptomic heterogeneity is observed at the single-cell level, with different subpopulations exhibiting differences in proliferative capacity, differentiation potential, immunomodulatory activity, and secretory function[34]. The MSCs heterogeneity arising from the above multidimensional factors makes it difficult for the traditional “bulk MSCs therapy” strategy to ensure consistency and predictability of therapeutic outcomes.

Different cell batches, different patients, or even the same batch of cells at different time points may exhibit distinct functional characteristics, which directly affect the reliability of clinical trial results and the standardization of treatment protocols. Therefore, systematic analysis of MSCs heterogeneity, identification of functionally superior subpopulations, and establishment of precision cell therapy strategies based on molecular subtyping have become core scientific issues in the field of MSCs research.

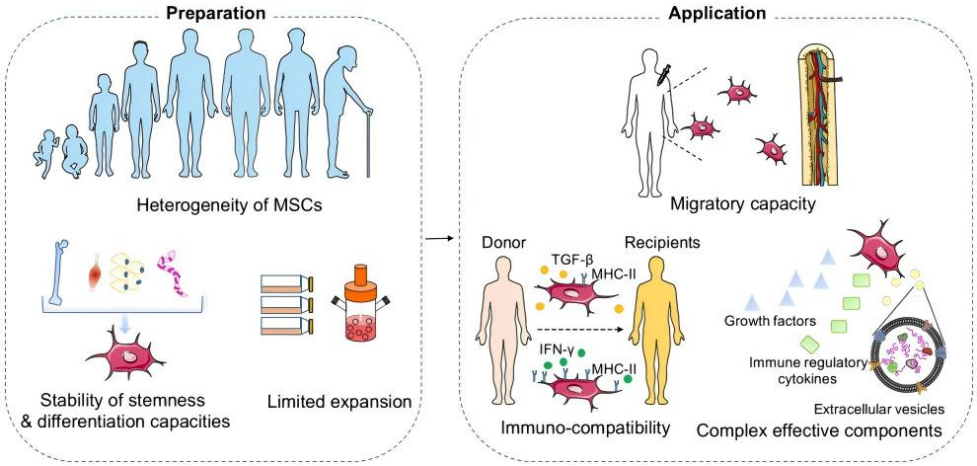


Figure. 1 The main challenges in clinical applications of MSCs[15]. The main clinical challenges for MSCs include donor-related heterogeneity (health, genetics, gender, age), source-dependent variations in stemness and differentiation, and culture-induced differences (confluence, surface, oxygen, passage, modifications). During application, MSC heterogeneity influences homing capacity, immune compatibility (via MHC-II alteration by inflammatory molecules), and paracrine effects (shaped by host microenvironment), thereby affecting the safety and efficacy of MSC therapies. **NOTE:** MSCs: mesenchymal stem/stromal cells; IFN-γ: interferon-gamma; MHC-II: major histocompatibility complex class II; TGF-β: transforming growth factor-beta. Copyright© 2021 Tian Zhou, Zenan Yuan, Jianyu Weng, Duanqing Pei, Xin Du, Chang He and Peilong Lai. (https://pubmed.ncbi.nlm.nih.gov/33579329/)

With rapid technological advances, single-cell RNA sequencing (scRNA-seq) enables the measurement of genome-wide gene expression profiles at the single-cell level[35]. Through unsupervised clustering analysis, it identifies cell subpopulations with distinct transcriptional characteristics and infers their potential functions, screens molecular markers of specific functional subpopulations, and employs pseudotime analysis to investigate the dynamic changes of different subpopulations during MSCs aging at single-cell resolution, thereby revealing the molecular features of senescence-sensitive and senescence-resistant subpopulations. In recent years, scRNA-seq has achieved a series of important breakthroughs in the study of MSCs heterogeneity[36,37]. Researchers have successively constructed single-cell transcriptomic maps of MSCs derived from different tissues, identified several MSC subpopulations with specific functional advantages, and begun translating these findings into clinical application strategies[38].

In summary, MSCs heterogeneity is both a "roadblock" limiting the clinical application of cell therapy and an "opportunity window" for advancing precision cell therapy[39]. We have searched the primary literature in PubMed, Embase, and SciELO from inception to April 2026 using the terms "Mesenchymal stem cells ," "scRNA-seq," "Heterogeneity," "Aging," "Musculoskeletal degenerative diseases," "Osteoarthritis," "Sarcopenia", as well as their combinations. This review is a narrative synthesis of the literature, aiming to provide a comprehensive overview of MSCs heterogeneity decoded by scRNA-seq and its implications for precision therapy of musculoskeletal degenerative diseases. We focus on the multidimensional origins of MSCs heterogeneity, key findings from scRNA-seq technologies in revealing functional subpopulations of MSCs, breakthroughs in leveraging functional MSC subpopulations for osteoarthritis and sarcopenia precision medicine, and future perspectives and challenges. Through this systematic review, we aim to provide a complete perspective from "decoding heterogeneity" to "harnessing heterogeneity" for translational research in the MSCs field, offering theoretical references and practical guidance for the development of safer, more effective, and more predictable MSCs-based cell therapy products.

2. Single-Cell Transcriptomics Reveals MSCs Heterogeneity

2.1 The Principle and Technical Workflow of ScRNA-seq

scRNA-seq captures transcriptome information at the single-cell level, revealing cellular heterogeneity. Its core workflow includes: first, dissociating tissues into individual cells and isolating them using microfluidics or microwell technology; then, lysing the cells and reverse-transcribing mRNA into cDNA; next, amplifying the cDNA via *in vitro* transcription or PCR to obtain sufficient library material; after constructing the sequencing library, high-throughput sequencing is performed; finally, bioinformatics analyses (such as quality control, clustering, differential expression, and pseudotime analysis) are applied to resolve cell subpopulations and their functions. This technology provides a powerful tool for deciphering cellular states and dynamic changes within complex tissues.

There are three commonly used scRNA-seq platforms: the droplet-based 10x Genomics, the domestically developed Chinese DNBC4 (C4 platform), and the plate-based Smart-seq2. Among these, 10x Genomics is the most widely adopted commercial platform. It utilizes a water-in-oil droplet system to encapsulate individual cells with gel beads, achieving a capture efficiency of 65%–75% and a doublet rate below 5%. It is suitable for large-scale cell atlas mapping, rare cell identification (e.g., circulating tumor cells), and cell subpopulation analysis[40]. DNBC4 is a droplet-based microfluidics platform independently developed by MGI. When

paired with the DNBSEQ sequencing system, it offers high data fidelity and includes proprietary bioinformatics tools. It is well-suited for immune microenvironment analysis, tumor heterogeneity studies, and developmental biology lineage tracing, particularly in research scenarios that require cost-effectiveness and locally developed solutions[41]. Smart-seq2 is a representative plate-based method that uses FACS or manual sorting to allocate single cells into 96- or 384- well plates for independent library preparation. Its core advantage lies in obtaining full-length mRNA transcripts, enabling the detection of alternative splicing events and rare mutations, and it typically identifies more genes per cell than droplet-based methods. It is ideal for in-depth analysis of small numbers of cells, such as early embryonic development cells and stem cell differentiation trajectory inference[42]. Due to their high throughput, standardized analysis workflows, and relatively low cost, 10x Genomics and BGI DNBC4 (C4 platform) are commonly used technical platforms in MSCs research. Despite its power, scRNA-seq has inherent limitations, including batch effects, dissociation-induced transcriptional artifacts, dropout events (especially for low-abundance transcripts), and the inability to capture spatial context. Functional validation and orthogonal methods (e.g., spatial transcriptomics, proteomics) are needed to confirm findings from single-cell transcriptomic analyses.

2.2 Comparison of Single-Cell Transcriptome Maps of MSCs from Different Tissue Origins

With the rapid development of scRNA-seq technology, single-cell transcriptome maps of MSCs from various tissue origins have been successively constructed[24,43]. For the bone marrow mesenchymal stem cells (BM-MSCs), in 2015, Freeman *et al.,* first performed scRNA-seq on BM-MSCs and uncovered significant intercellular variability in differentiation and immunomodulation-related gene expression, indicating lineage priming[44]. In 2019, Liu *et al.,* identified an FGFR2-high subpopulation in early passages that may contain skeletal stem cells[45]. In 2021, Wang *et al.,* profiled freshly isolated human $CD271^+$ BM-MSCs, defined $LEPR^{high}CD45^{low}$ BM-MSCs, and mapped osteogenic, chondrogenic, and adipogenic trajectories along with quiescent subsets[46]. Also in 2021, Lu *et al.,* found that IFN-γ/TNF-α licensing reduced osteogenic potential but enhanced chondrogenesis and immunomodulation without affecting cell cycle or stemness[47]. Kanazawa *et al.,* classified mouse $Sca\text{-}1^+PDGFR\text{-}\alpha^+$ BM-MSCs into seven subpopulations and integrated ATAC-seq to reveal epigenetic features[48]. In 2022, Zhu *et al.,* divided elderly BM-MSCs into three subsets with self-renewal, multilineage differentiation, or cytokine secretion functions[49]. In 2023, Wan *et al.,* showed that inflammatory cytokines upregulated immunoregulatory, stemness, and anti-apoptotic genes while downregulating differentiation and senescence signatures, suggesting that cytokine priming enhances therapeutic efficacy regardless of heterogeneity[50]. In 2024, Zhao *et al.,* identified Lamc1 and three other genes promoting BM-MSC osteogenesis[51]. Wei *et al.,* discovered that $LEPR^+$ BM-MSCs play a key role in osteoporosis and that specnuezhenide activates METTL3 to promote their osteogenesis and angiogenesis[52]. In 2025, Wang *et al.,* reported that GPx3 is specifically upregulated during adipogenic differentiation, marking adipocyte lineage commitment[53]. Overall, scRNA-seq has revealed BM-MSC heterogeneity, including lineage priming, skeletal stem-like subsets, and distinct differentiation trajectories; inflammatory licensing shifts differentiation bias, while cytokine priming boosts efficacy; regulators like Lamc1 and GPx3, and $LEPR^+$ subsets, offer therapeutic targets.

For the adipose-derived mesenchymal stem cells (AD-MSCs), in 2019, Liu *et al.,* provided the first scRNA-seq dataset of 24,358 human AD-MSCs from three donors, enabling analysis of heterogeneity and lineage priming[54]. In 2020, Doshida *et al.,* profiled uncultured AD-MSCs from young and old mice, identified three candidate subsets and novel genes (e.g., ADAMTS7), and found aging-related dysregulation of differentiation genes[55]. In 2021, Qu *et al.,* studied osteogenic differentiation, revealing cellular heterogeneity and stress-related gene expression[56]. In 2023, Grigorieva *et al.,* found that NTM and CHD3 are upregulated under profibrotic conditions while RDH10 is expressed under adipogenic conditions, providing profibrotic markers relevant to sarcopenia[57]. In 2024, Chun *et al.,* identified four heterogeneous subsets during chondrogenic induction and revealed proliferation-differentiation balance mechanisms[58]. Kostecka *et al.,* reviewed clinical trials and single-cell studies, noting that AD-MSCs are approved for Crohn's perianal fistulas and subcutaneous defects but require standardized quality control[59]. In 2025, Parsons *et al.,* identified two subpopulations: Scissor-positive cells act via IL6/SEMA4, and Scissor-negative cells via FN1/THY1/MIF, enabling functional sorting from primary SVF[60]. In 2026, Maruiwa *et al.,* demonstrated that AD-MSC-derived extracellular vesicles (EVs) alleviate synovial inflammation, induce M2 polarization, and upregulate PRG4/FGF-18, improving rat osteoarthritis[61]. Thus, scRNA-seq of AD-MSCs informs osteoarthritis (via EVs) and sarcopenia (via profibrotic markers NTM, CHD3).

For the umbilical cord-derived mesenchymal stem cells (UC-MSCs). In 2019, Huang *et al.,* performed scRNA-seq on 361 UC-MSCs and found limited heterogeneity, primarily driven by cell cycle status[62]. In 2020, Sun *et al.,* identified highly variable genes enriched in development and inflammation, and showed that *CD142* distinguishes proliferation and healing capacity[63]. In 2021, Zhang *et al.,* identified two functional subsets from uncultured UC-MSCs, suggesting subset-specific expansion for different diseases[64]. Wang *et al.,* constructed a single-cell transcriptome map of umbilical cord tissue and culture-expanded MSCs, showing relatively high homogeneity yet multiple subsets[65]. In 2022, Leng *et al.,* reported high heterogeneity with only 12.60% of cells being genuine stem cells, and a potential lack of immune privilege[66]. In 2023, Bai *et al.,* found PD-L1 expression correlated with immunosuppressive capacity, and high PD-L1 UC-MSCs showed superior efficacy in autoimmune hepatitis[67]. In 2024, Chen *et al.,* showed that UC-MSCs secrete COL6A2 to activate FAK/PI3K/AKT, improving microvascular function and repairing steroid-induced osteonecrosis[68]. Cyr-Depauw *et al.,* identified progenitor-like vs. fibroblast-like subsets; only the progenitor-like subset alleviated hyperoxia-induced lung injury, while high MHC-I reduced efficacy[69]. In 2025, Shen *et al.,* found CTGF as an optimal tenogenic factor, and *Hes1* overexpression promoted differentiation and rotator cuff repair[70]. Huang *et al.,* revealed heterogeneity under different culture systems and identified an $IL1R1^+PDGFRA^+$ subset with high osteo/chondrogenic potential regulated by Wnt5 signaling[71]. Notably, Zhou *et al.,* compared AD-MSCs and BM-MSCs and found that AD-MSCs have lower heterogeneity and stronger immunosuppression, and a meta-analysis suggested AD-MSCs are more suitable for osteoarthritis[72]. Barrett *et al.,* compared UC-MSCs and BM-MSCs, highlighting UC-MSCs' immunomodulatory advantages[73]. Collectively, UC-MSCs exhibit limited but functionally relevant heterogeneity; high PD-L1 predicts immunosuppressive efficacy; progenitor-like subsets enhance lung repair; CTGF/*Hes1* drives tendon differentiation – all supporting applications in osteoarthritis and sarcopenia.

For the placenta-derived mesenchymal stem cells (PMSCs) and other tissues sources of MSCs. In 2022, Li *et al.,* generated the first transcriptomic and epigenomic map of human PMSCs, revealing unique immunomodulatory traits[74]. Ren *et al.,* performed scRNA-seq on human dental pulp cells, identified odontoblasts and early SEPTIN-expressing MSCs with strong proliferation/differentiation potential, aiding dental pulp regenerations[75]. Kan *et al.,* used scRNA-seq, spatial transcriptomics, and lineage tracing to reveal MSCs transition from quiescence to proliferation and chondro/osteogenic differentiation within an inflammatory microenvironment, regulated by STAT and PI3K/AKT pathways, offering insights for heterotopic ossification[76]. These findings inform osteoarthritis and sarcopenia strategies (e.g., Wnt5-driven IL1R1^{+}PDGFRA^{+} UC-MSCs for cartilage repair, and SEPTIN^{+} dental pulp MSCs for muscle regeneration)(**Table 1**).

Table 1. Summary of scRNA-seq studies on MSCs from different tissue sources

MSC Origin	ScRNA-seq Platform	Key Subgroups	Marker Genes	Functional Significance	References	Year
BM-MSCs	Smart-seq2	Lineage-primed subsets	*Cd200* for osteogenic differentiation and *IL6* for immunomodulation	First evidence of lineage priming in BM-MSCs	Freeman *et al*[44].	2015
	Fluidigm C1 system	Skeletal stem cell-like subsets	*FGFR2*	Early passage subpopulation with skeletal stem cell potential	Liu *et al*[45].	2019
	10x Genomics	Osteogenic differentiation subsets	*LEPR, CD167b, CD91, CD130, CD118*	Bone homeostasis	Wang *et al*[46].	2021
	10x Genomics	IFN-γ/TNF-α licensed immunomodulate subsets	IFN-γ / TNF-α	Immunomodulate licensing alters differentiation bias without affecting stemness	Lu & Qiao[47]	2021
	10x Genomics	MSCs Functional subsets	*CD24*, *Sca-1*, *Ly6C1 et al* for bone / cartilage differentiation	Transcriptional and epigenetic multi-level analysis of MSCs subpopulation characteristics	Kanazawa *et al*[48].	2021
	10x Genomics	Self-renewal, multilineage differentiation, cytokine secretion	*CDCA5*, *FAM64A* for Self-renewal; *TGM2*, *NEAT1* for multi-directional differentiation; *CYBA*, *TIMP1* for cytokine secretion	Heterogeneity in elderly BM-MSCs	Zhu *et al*[49].	2022
	10x Genomics	Cytokine-primed subsets	Cytokine genes sets	Cytokine priming enhances therapeutic efficacy irrespective of heterogeneity	Wan *et al*[50].	2023
	10x Genomics	Osteogenic-promoting subsets	*Lamc1, Tln2*, *Hexb*	Promote osteogenic differentiation of BM-MSCs	Zhao *et al*[51].	2024
	10x Genomics	Osteogenic differentiation subsets	*LEPR*	Osteoporosis treatment via specnuezhenide activating METTL3	Wei *et al*[52].	2024
	10x Genomics	Adipocyte lineage-committed subsets	*GPx3*	Marker of adipocyte lineage commitment	Wang *et al*[53].	2025
AD-MSCs	10x Genomics	Heterogeneous subsets	Lineage priming patterns genes sets	High-quality dataset	Liu *et al*[54].	2019
	Microwell slide based Nx1-seq	Aging-related three subsets	ADAMTS7, *Egfr*, I*gfbp4*, *Gsn*, *Lpl*	Aging-related dysregulation of differentiation genes	Doshida *et al*[55].	2020
	10x Genomics	Stress-responsive subsets	Stress-related genes sets	Transcriptional dynamics during osteogenesis	Qu *et al*[56].	2021
	10x Genomics	Profibrotic subsets	*NTM*, *CHD3*	Targets for sarcopenia intervention	Grigorieva *et al*[57].	2023
	Drop-seq	Chondrogenic differentiation heterogeneous subpopulations	Proliferation/differentiation balance genes sets	Regulation of chondrogenic differentiation	Chun *et al*[58].	2024
	10x Genomics	Scissor-positive AD-MSCs	*ICAM1*, GPC3, *CD44*	Screening functional AD-MSCs	Parsons *et al*[60].	2025
	10x Genomics	Chondrocyte progenitor cells subpopulations	*PRG4*, *FGF-18*	Alleviate osteoarthritis via synovial inflammation reduction	Maruiwa *et al*[61].	2026

Table 1. Summary of scRNA-seq studies on MSCs from different tissue sources (continued)

MSC Origin	ScRNA-seq Platform	Key Subgroups	Marker Genes	Functional Significance	References	Year
UC-MSCs	Fluidigm C1 system	Cell cycle-dominant subsets	*CD168*	Limited heterogeneity, primarily cell cycle status	Huang *et al*[62].	2019
	10x Genomics	Multiple functional subsets	*CD142*	The specific subpopulation has a stronger ability to promote wound healing	Sun *et al*[63].	2020
	10x Genomics	Two functional subsets	*COL1A1*, *COL1A2*, *COL3A1*	Functions related to ECM synthesis, osteoblast differentiation	Zhang *et al*[64].	2021
	10x Genomics	Three functional subsets	*SSRP1*	The dynamic microenvironment of proliferating and differentiating subpopulations	Wang *et al*[65].	2021
	10x Genomics Smart- seq2	Three functional subsets	*HMGN2*, *RPL31*, *CRIM1*	Proliferating and differentiating subpopulations	Leng *et al*[66].	2022
	10x Genomics	Four functional subsets	*PD-L1*	Highly efficient immunomodulatory MSC subpopulations for autoimmune hepatitis	Bai *et al*[67].	2023
	10x Genomics	*COL6A2*-secreting subsets	*COL6A2*	Repair of steroid-induced osteonecrosis	Chen *et al*[68].	2024
	10x Genomics	Two functional subsets	*MHC-I*	Progenitor-like subset improves lung injury	Cyr-Depauw *et al*[69].	2024
	10x Genomics	Three functional subsets	*Hes1*	Tendon differentiation and rotator cuff repair	Shen *et al*[70].	2025
	10x Genomics	Inducible functional subsets	*IL1R1*, *PDGFRA*	High osteogenic/chondrogenic potential for osteoarthritis	Huang *et al*[71].	2025
PMSCs	10x Genomics	Immunomodulatory subsets	*PRDM1*	Dynamic MSC subsets microenvironment	Li *et al*[74].	2022

NOTE: BM-MSCs: bone marrow mesenchymal stem cells; AD-MSCs: adipose-derived mesenchymal stem cells; UC-MSCs: umbilical cord-derived mesenchymal stem cells; PMSCs: placenta-derived mesenchymal stem cells; *Cd200*: *CD200* molecule; *IL6*: Interleukin 6; *FGFR2*: Fibroblast growth factor receptor 2; *LEPR*: Leptin receptor; *CD91*: *CD91* molecule (also known as LRP1, low density lipoprotein receptor-related protein 1); *CD130*: *CD130* molecule (also known as IL6ST, interleukin 6 signal transducer); *CD118*: *CD118* molecule (also known as LIF receptor subunit alpha); IFN-γ: Interferon gamma; TNF-α: Tumor necrosis factor alpha; *CD24*: *CD24* molecule; *Sca-1*: Stem cell antigen-1 (also known as Ly6A, lymphocyte antigen 6 family member A); *Ly6C1*: Lymphocyte antigen 6 family member C1; *CDCA5*: Cell division cycle associated 5; *FAM64A*: Family with sequence similarity 64 member A; *TGM2*: Transglutaminase 2; *NEAT1*: Nuclear paraspeckle assembly transcript 1 (non-coding RNA); *CYBA*: Cytochrome b-245 alpha chain; *TIMP1*: TIMP metallopeptidase inhibitor 1; *Lamc1*: Laminin subunit gamma 1; *Tln2*: Talin 2; *Hexb*: Hexosaminidase subunit beta; *GPx3*: Glutathione peroxidase 3 (also known as *GPX3*); ADAMTS7: ADAM metallopeptidase with thrombospondin type 1 motif 7; *Egfr*: Epidermal growth factor receptor; *Igfbp4*: Insulin like growth factor binding protein 4; *Gsn*: Gelsolin; *Lpl*: Lipoprotein lipase; *NTM*: Neurotrimin; *CHD3*: Chromodomain helicase DNA binding protein 3; *ICAM1*: Intercellular adhesion molecule 1; GPC3: Glypican 3; *CD44*: *CD44* molecule; *PRG4*: Proteoglycan 4 (also known as lubricin); *FGF-18*: Fibroblast growth factor 18; *CD168*: *CD168* molecule (also known as HMMR, hyaluronan mediated motility receptor); *CD142*: *CD142* molecule (also known as F3, coagulation factor III, tissue factor); *COL1A1*: Collagen type I alpha 1 chain; *COL1A2*: Collagen type I alpha 2 chain; *COL3A1*: Collagen type III alpha 1 chain; *SSRP1*: Structure specific recognition protein 1; HMGN2: High mobility group nucleosomal binding domain 2; RPL31: Ribosomal protein L31; CRIM1: Cysteine rich transmembrane BMP regulator 1; *PD-L1*: Programmed death-ligand 1 (also known as *CD274*); *COL6A2*: Collagen type VI alpha 2 chain; *MHC-I*: Major histocompatibility complex class I; *Hes1*: Hes family bHLH transcription factor 1; *IL1R1*: Interleukin 1 receptor type 1; *PDGFRA*: Platelet derived growth factor receptor alpha; *PRDM1*: PR/SET domain 1.

2.3 Comparative Analysis of MSCs Across Multiple Tissue Sources

In 2021, Wang *et al.,* performed massively parallel scRNA-seq on > 130,000 BM-MSCs, AD-MSCs, and UC-MSCs, constructing a human MSC atlas; they identified seven tissue-specific and five conserved subsets, with ECM as a major source of heterogeneity, and an umbilical-cord-specific subset showing immunosuppressive advantages[77]. In 2022, Cai *et al.,* compared foreskin and umbilical cord MSCs, found the highest proportion of immune-modulating subsets in foreskin, and demonstrated stronger immunomodulatory capacity of foreskin MSCs[78]. In 2024, Danev *et al.,* performed donor-matched bovine AD-MSCs and BM-MSCs scRNA-seq, comparing across species; bovine BM-MSCs were transcriptomically closer to human BM-MSCs than to mouse MSCs, suggesting cattle as a translational model[79]. In 2023, Yang *et al.,* integrated microarray, bulk and single-cell data to construct a "TF-miRNA-Target" network, revealing replicative senescence mechanisms and quality control indicators[80]. Wu *et al.,* reviewed scRNA-seq in skeletal research, showing skeletal stem/progenitor cells differentiate into chondrocytes, osteoblasts, osteocytes, and marrow adipocytes; with aging, BM-MSCs shift toward adipogenesis, driving senile osteoporosis[81]. Chen

et al., performed single-cell multi-omics on MSCs from four donors, finding that donor-specific chromatin accessibility differences determine osteogenic potential, with osteoporosis-associated variants enriched in high-osteogenic donors[82]. In 2025, Cyr-Depauw *et al.,* found that most term and preterm UC-MSCs alleviated hyperoxia-induced lung injury, but MSCs from preeclamptic donors had aberrant transcriptomes and no benefit, demonstrating scRNA-seq can guide MSC selection[83]. In addition, Zhao *et al.,* profiled UC-MSCs and synovial fluid-derived MSCs (SF-MSCs), identifying several subsets respectively, with many differentially expressed genes related to differentiation, immunomodulation, and joint repair[84]. Medrano-Trochez *et al.,* compared thawed BM-MSCs and UC-MSCs, showing that tissue-of-origin differences outweighed donor differences, and cell cycle status affected immunomodulatory potential[85]. In summary, single-cell comparisons reveal tissue-specific traits: UC-MSCs excel in immunomodulation; AD-MSCs show lower heterogeneity and stronger immunosuppression for osteoarthritis; foreskin MSCs offer potent immune effects; replicative senescence and donor-specific epigenetics impact differentiation (**Figure. 2**). These insights guide MSC selection for osteoarthritis and sarcopenia therapies.

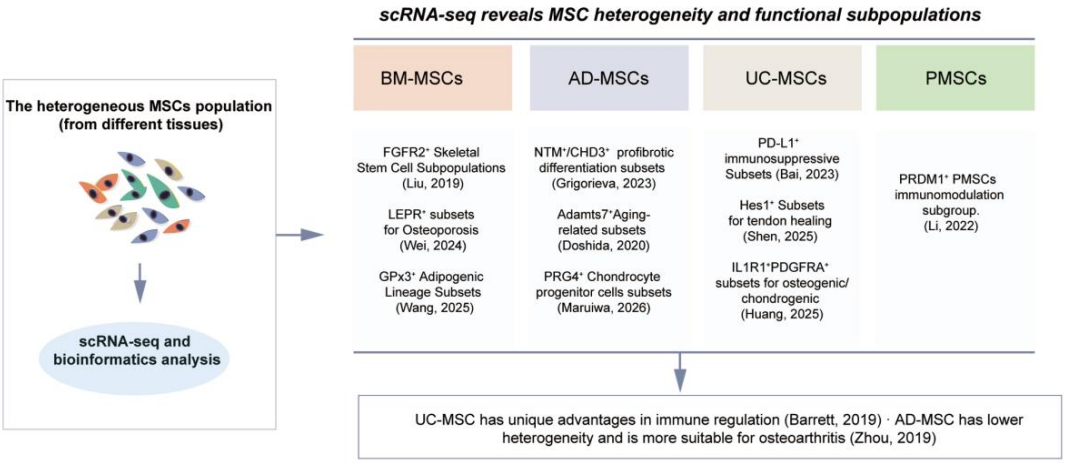


Figure. 2 ScRNA-seq reveals the heterogeneity of MSCs derived from different tissue origins. This figure summarizes scRNA-seq-identified functional subpopulations within MSCs from four tissue sources[45,52,53,57,61,67,70-74]. In BM-MSCs, FGFR2$^+$ skeletal stem cells, LEPR$^+$ osteoporosis-related subsets, and GPx3$^+$ adipogenic lineages have been characterized. In AD-MSCs, profibrotic (NTM$^+$/CHD3$^+$), aging-related (Adarms7$^+$), and chondroprogenitor (PRG4$^+$) subsets are noted. UC-MSCs contain PD-L1$^+$ immunosuppressive, *Hes1*$^+$ tendon-healing, and IL1R1$^+$PDGFRA$^+$ osteo/chondrogenic subsets. PMSCs feature a PRDM1$^+$ immunomodulatory subgroup. Notably, UC-MSCs exhibit unique advantages in immune regulation, while AD-MSCs show lower heterogeneity and greater suitability for osteoarthritis treatment. These findings provide a theoretical basis for precision targeting of age-related musculoskeletal degenerative diseases. **NOTE:** BM-MSCs: bone marrow mesenchymal stem cells; AD-MSCs: adipose-derived mesenchymal stem cells; UC-MSCs: umbilical cord-derived mesenchymal stem cells; PMSCs: placenta-derived mesenchymal stem cells. Created using the Adobe Illustrator 2018 version.

2.4 ScRNA-seq Reveals Dynamic Heterogeneity of MSCs under Different Culture Conditions

In vitro culture parameters are major sources of induced MSC heterogeneity. ScRNA-seq has provided high-resolution insights into these condition-dependent variations. The relevant findings can be categorized into four aspects: culture medium composition, oxygen concentration, spatial configuration, and passage number. For the effects of culture medium composition, in 2024, Xiao *et al.,* showed that serum-free cultured UC-MSCs had comparable therapeutic efficacy to serum-cultured cells in a knee osteoarthritis mouse model, avoiding xenogeneic concerns[86]. Also, in the same year, Shi *et al.,* found that different medium batches increase heterogeneity, and the CD317$^+$ subset correlates with immunosuppressive activity; purifying CD317$^+$ MSCs reduces heterogeneity[87]. Then, for the effects of oxygen concentration. Studies indicated physiological hypoxia (1%–5% O_2) differs from normoxic (21% O_2) culture. In 2024, Yi *et al.,* observed that hypoxia alters the distribution of functional subsets from different tissues, linked to vascular and reproductive regeneration[88]. For the effects of spatial configuration (2D vs. 3D culture), in 2022, Gallo *et al.,* found that 3D culture of amniotic-derived MSCs induced broad gene expression changes regulating proliferation, differentiation, immunomodulation, and angiogenesis[89]. Then, in 2024, Lu *et al.,* reported that after 5–6 passages in 2D, 3D spheroid culture synchronizes heterogeneous MSCs into a uniform population with reduced cell volume and elevated immunosuppressive genes and growth factors. Also, Lu *et al.,* showed that 3D spheroids synchronize heterogeneous PMSCs into a uniform immunosuppressive phenotype composed of only two subsets, enhancing anti-inflammatory effects[90]. Moreover, passaging induces replicative senescence. For instance, in 2021, Wang *et al.,* showed that with increasing passage, MSCs transition from "naive" to "culture-adapted" to "replicative senescence" at different rates and trajectories across cells, generating heterogeneous senescent phenotypes[65]. Similarly, in 2024, Taherian Fard *et al.,* performed scRNA-seq on serially passaged human embryonic stem cell-derived MSCs, identifying pre-senescent states and three distinct senescent states, with progressively decreasing regulatory network connectivity; this map offers a basis for senotherapeutic strategies[91]. In summary, scRNA-seq reveals how medium, oxygen, spatial configuration, and passage number shape MSC transcriptomic heterogeneity, guiding optimization of expansion protocols for more consistent and predictable cell therapies.

2.5 Homogeneity Advantage of IPSC-derived MSCs

The generation of induced pluripotent stem cell-derived MSCs (iPSC-MSCs, also termed iMSCs) has emerged as a promising strategy to overcome the fundamental limitations of tissue-derived MSCs, including restricted *in vitro* expansion capacity, donor-to-donor variability, and cellular heterogeneity. Currently, iMSCs can be obtained through a relatively simple and stable technical approach that mimics the development of cell lineages *in vivo* using

a cocktail of cytokines (**Figure. 3**). Multiple studies have demonstrated that iMSCs exhibit superior characteristics compared to tissue-derived MSCs in several key aspects. Research suggests that iMSCs show enhanced proliferation ability, improved immune modulation capacity, and greater biological efficiency[92]. In 2023, A comparative study by Wang *et al.,* directly compared iMSCs with donor-matched umbilical cord MSCs (UMSCs) and found that iMSCs exhibited high expression of MSCs positive markers (CD73, CD90, CD105) and successfully differentiated into osteocytes, chondrocytes and adipocytes. Moreover, iMSCs demonstrated enhanced immunosuppression capacity through downregulation of pro-inflammatory factors (including IL6, IL1B) and upregulation of anti-inflammatory signals (NOS1, TGFB). The iMSCs also exhibited similar proliferative state and rejuvenation status compared to their parental UMSCs, as assessed by CCK-8 assay, β-Galactosidase staining, and telomerase activity analysis[93]. In 2024, Yuan *et al.,* using single-cell sequencing, found that iMSCs overexpressing CCR5 enhanced homing, reduced T cells and activated microglia, inhibited the Nlrp3 inflammasome, thereby intervening in autoimmune diseases[94].

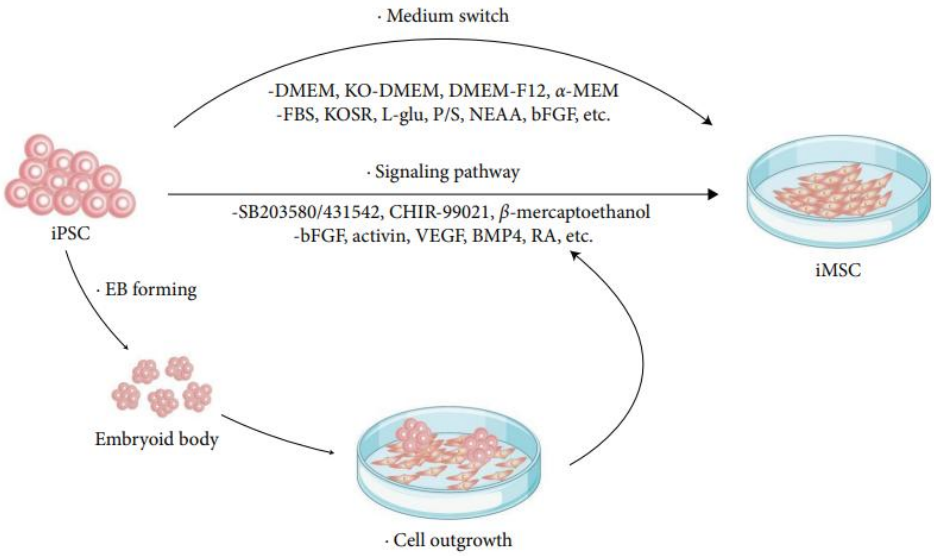


Figure. 3 Flowchart of the differentiation process from iPSCs to iMSCs[92]. This schematic illustrates three predominant strategies for directing iPSCs toward iMSCs: (1) Medium switch-replacing pluripotent medium with mesenchymal-promoting media (e.g., DMEM/F-12, α-MEM) supplemented with FBS, KOSR, and bFGF. (2) Signaling pathway modulation - applying small molecules (e.g., SB431542, CHIR-99021) and growth factors (e.g., activin, BMP4, RA) to direct differentiation. (3) Embryoid body (EB) formation-generating 3D EB aggregates followed by cell outgrowth. These strategies are often combined to efficiently generate iMSCs. **NOTE**: iPSCs: induced pluripotent stem cell; EB: embryoid body; iMSCs: iPSCs-derived MSCs; RA: retinoic acid; FBS: Fetal Bovine Serum; KOSR: KnockOut™ Serum Replacement; bFGF: basic Fibroblast Growth Factor; NEAA: Non-Essential Amino Acids; DMEM: Dulbecco's Modified Eagle Medium; KO-DMEM: KnockOut ™ Dulbecco's Modified Eagle Medium; VEGF: Vascular Endothelial Growth Factor; BMP4:Bone Morphogenetic Protein 4. Copyright© 2023 Xiaoyu Shi, Kun Zhang, Fengshi Yu, Qi Qi, Xiaoyu Cai and Yu Zhang. (https://pubmed.ncbi.nlm.nih.gov/39377039/)

One of the most significant advantages of iMSCs is their lower heterogeneity compared to tissue-derived MSCs. The features of iMSCs include their single-cell clone origins, as well as defined and controllable culture conditions for their derivation and proliferation[95]. iMSCs exhibit higher transcriptomic consistency at the single-cell level, providing a novel strategy to overcome the intrinsic heterogeneity of primary MSCs. Transcriptome and microRNA profile analysis revealed that iMSCs derived from iPSCs favor the expression of genes conferring high proliferation, differentiation, and migration properties, all of which contribute to a rejuvenated state of iMSCs compared to primary MSCs[96]. This relatively lower heterogeneity may render iMSCs a promising cell source for standardized cellular therapy and precision medicine applications, though further validation is needed.

Despite their promising advantages, iMSCs face several challenges that must be addressed before widespread clinical adoption, including epigenetic memory, tumorigenicity risk and long-term culture and genetic stability. Despite these challenges, iMSCs hold great promise as "off-the-shelf" cell products. Notably, clinical-grade, allogeneic, universal, off-the-shelf iPSC-derived cell therapeutic products have entered Phase I/II registrational clinical trials for various conditions, including multiple system atrophy and spinal cord injury[97]. The above development suggest that iMSCs are increasingly becoming a clinically viable option for regenerative medicine applications. In the future, in-depth single-cell studies and integrated single-cell multi-omics technologies (such as simultaneous analysis of the transcriptome and epigenome) will help to more comprehensively understand the functional subpopulations of iMSCs and their precise applications in regenerative medicine.

3. Harnessing MSCs Heterogeneity for Precision Therapy of Musculoskeletal Degenerative Diseases

The recognition of MSCs heterogeneity, far from being an obstacle, provides a unique opportunity to develop precision cell therapies for musculoskeletal degenerative diseases. By leveraging single-cell transcriptomic maps, researchers can now identify, isolate, and expand functionally superior subpopulations or engineer MSCs with tailored therapeutic properties. This "harnessing" approach has shown particular promise in two common and debilitating age-related musculoskeletal degenerative diseases, such

as osteoarthritis and sarcopenia.

3.1 Precision Targeting of Osteoarthritis: from Subpopulation Selection to Engineered MSCs

Osteoarthritis is characterized by progressive cartilage degradation, synovial inflammation, and subchondral bone remodeling. The therapeutic potential of MSCs in osteoarthritis has been widely recognized, yet clinical outcomes remain variable due to cell heterogeneity. ScRNA-seq studies have identified several functional subpopulations with enhanced chondroprotective and anti-inflammatory capacities. For instance, the IL1R1^{+}PDGFRA^{+} subpopulation derived from UC-MSCs, discovered by Huang *et al.,* exhibits high osteogenic and chondrogenic potential, with the Wnt5 signaling pathway regulating its phenotypic conversion[71]. These MSC subsets could be selectively expanded for intra-articular injection to promote cartilage repair. Similarly, single-cell analysis of AD-MSCs has revealed that Scissor-positive (ICAM1^{+}, GPC3^{+}, *CD44*$^{+}$) subsets exert greater immunomodulation through IL6/SEMA4 pathways[60]. These molecular signatures enable the prospective enrichment of AD-MSCs with superior immunomodulatory activity for osteoarthritis treatment.

Beyond subpopulation selection, extracellular vesicles (EVs) derived from specific MSC subpopulations have shown disease-modifying effects. Recently, Maruiwa *et al.,* demonstrated that AD-MSC-derived EVs alleviate synovial inflammation, induce M2 macrophage polarization, and upregulate PRG4/FGF-18, thereby improving pain and cartilage degeneration in a rat osteoarthritis model[61]. ScRNA-seq confirmed that these EVs reshape the synovial microenvironment, suggesting that EV-based therapies may circumvent the complexities of live cell heterogeneity while preserving therapeutic efficacy. Furthermore, 3D spheroid culture has been shown to synchronize heterogeneous MSCs into a more uniform immunosuppressive phenotype. Lu *et al.,* reported that 3D-cultured PMSCs consist of only two subpopulations with high expression of immunosuppressive factors, enhancing their anti-inflammatory effects[89]. Applying this approach to osteoarthritis treatment could improve consistency and reduce batch-to-batch variability.

Clinical evidence supporting MSC-based therapy for osteoarthritis has rapidly accumulated. In a phase II triple-blinded randomized controlled trial, Sadri *et al.,* reported that intra-articular injection of allogeneic AD-MSCs promoted cartilage regeneration and significantly reduced serum inflammatory markers ($P < 0.001$) in patients with knee osteoarthritis[98]. A separate double-blind RCT demonstrated that allogeneic BM-MSCs provided sustained pain relief and delayed cartilage degeneration as assessed by MRI T2 mapping[99]. More recently, Tong *et al.,* confirmed the safety and efficacy of UC-MSCs for moderate-to-severe knee osteoarthritis with synovitis[100]. A comprehensive meta-analysis published in the Journal of Orthopaedic Translation further confirmed that MSC therapy yields superior pain relief compared to viscosupplementation (VAS MD -1.91, 95% CI -3.23 to -0.59; $P < 0.00001$), with comparable safety profiles[101]. These clinical trials collectively underscore the translational promise of harnessing MSCs heterogeneity for osteoarthritis precision therapy.

3.2 Precision Strategies for Sarcopenia: Modulating Chronic Inflammation and Promoting Muscle Regeneration

Sarcopenia is characterized by age-related loss of muscle mass and function, driven by chronic low-grade inflammation, mitochondrial dysfunction, and impaired regenerative capacity of satellite cells. MSCs counteract sarcopenia through paracrine mechanisms, including the secretion of anti-inflammatory cytokines (e.g., IL10, TGF-β) and growth factors (e.g., HGF, IGF-1). ScRNA-seq has identified subpopulations with enhanced anti-fibrotic and pro-regenerative properties. For example, in AD-MSCs under profibrotic conditions, NTM and CHD3 are upregulated, while RDH10 is expressed under adipogenic conditions[57]. Targeting NTM/CHD3-positive subpopulations could mitigate muscle fibrosis, a key pathological feature of sarcopenia. Additionally, dental pulp MSCs expressing the SEPTIN gene exhibit stronger proliferation and differentiation potential[75], making them a candidate for systemic administration to promote muscle regeneration. Moreover, iMSCs offer particular advantages for sarcopenia therapy due to their lower heterogeneity and rejuvenated features. IMSCs have been shown to downregulate pro-inflammatory factors (IL6, IL1B) and upregulate anti-inflammatory signals (NOS1, TGFB) compared to primary MSCs[93]. Their enhanced immunosuppressive capacity and transcriptomic consistency make them suitable for "off-the-shelf" products targeting the chronic inflammatory milieu of sarcopenia.

3.3 Clinical Translation and Regulatory Considerations

Translating these precision strategies into clinical practice requires several steps. First, validated surface markers (e.g., PD-L1 for immunosuppressive UC-MSCs, *CD142* for proliferation and healing capacity, and GPx3 for adipocyte lineage commitment) should be used to sort functional subpopulations via flow cytometry or magnetic-activated cell sorting. Second, quality control protocols must incorporate single-cell transcriptomic assessment to ensure batch-to-batch consistency. Third, phase I/II trials should compare unselected MSCs versus purified subpopulations or engineered iMSCs in OA and sarcopenia patients, with endpoints including pain scores, joint function, muscle mass, and grip strength.

Regulatory challenges include the need for standardized potency assays linked to specific subpopulation markers, the high cost of single-cell quality control, and the potential for epigenetic drift during expansion. Nevertheless, ongoing clinical trials with iMSCs for multiple system atrophy and spinal cord injury provide a precedent for regulatory pathways[97].

3.4 Integrating Multi-omics and Spatial Transcriptomics

To fully harness MSCs heterogeneity, future research should integrate single-cell transcriptomics with epigenomics (scATAC-seq), proteomics, and spatial transcriptomics. This multi-omics approach will reveal how chromatin accessibility and spatial niche signals shape functional subpopulation behavior. Additionally, CRISPR screens combined with single-cell readouts can identify key regulatory genes that control beneficial phenotypes, enabling the engineering of "super MSCs" with enhanced therapeutic potency for musculoskeletal degenerative diseases. In summary, moving from "decoding heterogeneity" to "harnessing heterogeneity" represents a paradigm shift in MSC-based therapy. By leveraging scRNA-seq-defined subpopulations and iMSCs with lower heterogeneity, precision cell therapy for osteoarthritis, sarcopenia, and other degenerative diseases is becoming an achievable goal.

4. Future Perspective

MSCs heterogeneity arises from donor-specific factors (age, sex, disease background, genetics), tissue origin (BM-MSCs, AD-MSCs, UC-MSCs, PMSCs, etc.), *in vitro* manipulation (culture

media, oxygen tension, 2D/3D configuration, passaging), and intrinsic stochastic variation at the single-cell level. scRNA-seq has enabled the identification of functionally superior subpopulations (e.g., IL1R1^{high}PDGFRA^{high} UC-MSCs with enhanced osteochondrogenic potential) and revealed that 3D spheroid culture synchronizes heterogeneous MSCs into a more uniform immunosuppressive phenotype. Notably, iMSCs exhibit lower heterogeneity, higher proliferation, and rejuvenation features, representing a promising direction for precision cell therapy.

To translate these insights into clinical practice, several key priorities and challenges must be addressed in the future. Standardization of culture protocols, including chemically defined, xeno-free, and hypoxia-mimicking conditions, should be optimized to minimize batch-to-batch variation and preserve therapeutic potency. Serum-free media and 3D bioreactor systems can reduce heterogeneity induced by undefined supplements. Potency assay development-Regulatory-acceptable potency assays must be established based on a matrix of complementary methods (quantitative RNA analysis, flow cytometry of functionally relevant surface markers, protein-based secretome assays). Candidate markers from scRNA-seq findings, such as PD-L1 for immunomodulation, CD317 for immunosuppressive activity, or IL1R1/PDGFRA for osteochondrogenic potential, could serve as release criteria. Batch consistency and large-scale production. Strategies such as pooling selected functional subpopulations or using clonal iMSCs can improve uniformity. Bioreactor expansion must overcome replicative senescence, genetic instability, and loss of stemness; advanced bioreactor designs, cryopreservation protocols, and quality-by-design approaches are essential. Regulatory requirements, such as Agencies like the FDA and EMA require robust characterization of MSC heterogeneity[102]. The use of scRNA-seq as a quality control tool to monitor subpopulation composition and detect unwanted senescent or malignant cells is increasingly recognized. The updated ISCT in 2025 identification criteria have shifted from the 2006 standards toward mechanism-aligned potency characterization[103]. Future technological integration, for instance, multi-omics (scRNA-seq combined with scATAC-seq, spatial transcriptomics, proteomics) will provide a multidimensional understanding of MSC functional subpopulations and their niche interactions. Artificial intelligence-driven analysis of large-scale scRNA-seq datasets may predict MSC functional outcomes based on donor and culture parameters, enabling personalized cell therapy matching. Advanced gene-editing tools (e.g., CRISPR-Cas9) could eliminate residual undifferentiated iPSCs and engineer "super MSCs" with enhanced therapeutic potency.

By systematically addressing these translational hurdles, the field can move from "decoding heterogeneity" to "harnessing heterogeneity," accelerating the development of reliable, off-the-shelf MSC products for musculoskeletal degenerative diseases and ultimately improving the quality of life for the aging population.

5. Conclusion

MSCs heterogeneity is a double-edged sword: it underlies the functional versatility of MSCs but also compromises therapeutic consistency and predictability. ScRNA-seq has revolutionized our ability to decode this complexity, revealing the multidimensional origins of heterogeneity-donor background, tissue source, culture conditions, and intrinsic stochastic variation-and enabling the identification of functionally superior subpopulations (e.g., IL1R1^{high}PDGFRA^{high} UC-MSCs for cartilage repair, CD317^{+} MSCs for immunosuppression). Importantly, induced pluripotent stem cell-derived MSCs (iMSCs) exhibit lower transcriptomic heterogeneity, higher proliferative capacity, and rejuvenation features, offering a promising path toward standardized "off-the-shelf" cell therapies. Despite remaining challenges-epigenetic memory, tumorigenicity risk, long-term genetic stability, and regulatory hurdles-ongoing clinical trials and emerging technologies (multi-omics, artificial intelligence, CRISPR-based engineering) are poised to address these limitations. By systematically moving from "decoding heterogeneity" to "harnessing heterogeneity", the field can develop safer, more effective, and more predictable MSC-based precision therapies for age-related musculoskeletal degenerative diseases such as osteoarthritis and sarcopenia, ultimately fulfilling the regenerative medicine promise for the aging population.

Author Contributions

Wenbo Gao, Min Wu drafted and reviewed the manuscript and performed revision of the manuscript, and they contributed equally to this work as co-first authors. Denghui You, Yuwen Liang, Gang Wu, Xiyin Ye, Shun Ruan independently performed literature searches and reviewed the information of the selected literature and performed the analyses. Penggang Luo help drafted and guided the professional discussion the manuscript. Yuanzan Zhu, Sangui Wang supervision, conceptualization, data curation and funding acquisition. Quanlei Wang writing, review, and editing, project administration. All authors contributed to manuscript revision and read and approved the submitted version.

Ethics Approval

Not applicable. This review article does not involve human or animal subjects. Ethical approval is not required for review articles.

Artificial Intelligence (AI) Statements

The author(s) declared that generative AI was not used in the creation of this manuscript.

Data Availability

No original data were generated or analyzed in this study. Data sharing is not applicable.

Informed Consent Statement

No participants were involved in this study.

Conflicts of Interest

The authors have no relevant financial or non-financial interests to disclose.

Funding

We thank all the colleagues in the Orthopedics Department of Dongguan Nancheng Hospital for their support of this research. This study was supported by the Project of Traditional Chinese Medicine Bureau of Guangdong Province (No. 20251430) and

supported by Guangdong Province's "10,000 Young and Mid-Career Scientific and Technological Talents Going Global Program-Yueyi (Guangdong Medical) Going Global Program" [Yue Yi Xue (2026) No. 8].

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