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Chapter

Mesenchymal Stem Cell-based Cytotherapy for Osteoarthritis Management: State of the Art

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Abstract

Osteoarthritis (OA), a principal and challenging disorder of articular cartilage, has been regarded as the most frequent and prevalent chronic disease of degenerative joints, which is caused by multiple factors including aging, trauma, overweight, joint deformity and congenital abnormality, together with the increase in life expectancy. In spite of considerable improvements that have been obtained by conducting multidisciplinary therapies such as surgical procedures and anti-inflammatory drugs, the pathogenesis and efficacy of OA with functional losses and degeneration are still elusively complicated for ascertainment. Mesenchymal stem/stromal cells (MSCs), also termed as multipotent mesenchymal progenitor/precursor cells, skeletal stem cells, or medicinal signaling cells, are heterogeneous cell populations with hematopoietic-supporting and immunomodulatory properties, together with multilineage differentiation property. For decades, investigators have illuminated the application of the advantaged and promising sources with/without remarkable biomaterials for the treatment of recurrent and refractory disorders including OA. In this chapter, we mainly concentrate on the current progress of MSC-based cytotherapy in both preclinical study and clinical practice as well as the promising prospective and critical challenges in the field, which will conformably benefit the administration of OA in future.

Keywords: osteoarthritis, mesenchymal stem cells, cytotherapy, biomaterials, tissue engineering

1. Introduction

Osteoarthritis (OA) is a whole organ disease characterized by the destruction or degeneration of articular cartilage, which is one of the most widespread and frequent chronic diseases and public health issues worldwide [1, 2]. During the course of OA, inflammatory response is a pivotal factor resulting in cartilage destruction or exacerbation of symptoms [2–4]. As satisfactory osteochondral repair, it's of great importance for the zonal restoration of adjacent cartilage and the subchondral bone [5]. For the past decades, despite the significant number of progress have been

achieved by multidisciplinary strategies such as surgeries (e.g., microfracture, mosaicplasty), autologous chondrocyte implantation (ACI), joint lubricants (e.g., hyaluronic acid), antiinflammatory drugs (e.g., NSAIDs) as well as cytotherapies (e.g., autologous chondrocyte implantation), the inherent limitations of regeneration and self-repair capacity in OA individuals still largely hinder the remission of the degeneration of articular cartilage [4, 6–8]. For example, even though joint replacement serves as an effective remedy for symptomatic end-stage disease including OA, most of the functional outcomes in patients are unsatisfactory and the lifespan of prosthesis is also largely limited [2, 9]. Distinguishing from the traditional remedies, cell-based strategies have emerged as an alternative with promising prospective in the treatment of OA and cartilage defects [10, 11].

State-of-the-art updates have turned to MSC-based cytotherapy for OA management both clinically and preclinically [5, 12]. The multifaceted superiorities of MSCs including multidirectional differentiation, high portability property, and low immunogenicity have made themselves ideal seed cells for OA treatment [3]. Meanwhile, MSCs or the derivatives are often encapsulated into natural or synthetic hydrogels, which can function by providing tunable biodegradability, and biocompatibility or enhancing cell vitality and functionality [10].

Herein, we mainly focus on the recent literatures relating to the application of MSCs for OA treatment based on the chondrogenic differentiation, and antiinflammatory and immunomodulatory effects of MSCs with or without biological scaffolds for cartilage regeneration. Meanwhile, we further discuss the promising prospective and formidable challenges of MSC-based cytotherapy in cartilage repair and regeneration as well.

2. MSCs and derivatives

MSCs are cell populations with unique immune-privileged and hematopoietic properties, which are capable of differentiating into a variety of functional cells such as adipocytes, osteoblasts and chondrocytes, which thus have garnered increased interest for clinical translation in the last few decades [13, 14]. Therewith, MSCs have been considered as the uppermost components in the bone marrow microenvironment as well as splendid sources for regenerative medicine [15, 16]. Not until the year of 2006, International Society for Cellular Therapy (ISCT) released the basic criteria for MSC definition including spindle-shaped morphology, high expression of mesenchymal-associated biomarkers (CD73, CD90, CD105) whereas minimal expression of hematopoietic-associated biomarkers (CD31, CD34, CD45), *in vitro* differentiation towards adipocytes, osteoblasts and chondrocytes [17].

Since the 1970s, MSCs have been isolated from various adult tissues including bone marrow, adipose tissues, synovial fluid, periosteum and dental tissues (e.g., dental pulp, periodontium) [18–20]. After that, perinatal or fetal tissues including umbilical cord, placenta, amniotic member and amniotic fluid have also been reported for MSC isolation [21]. Distinguish from those derived from adult tissues, MSCs isolated from the "discarded" perinatal tissues have been considered with preferable immunoregulatory properties and long-term *in vitro* proliferative capacity, and in particular, release from ethical risks, invasiveness and pathogenic contamination [14, 21–23]. Notably, current studies have also put forward the feasibility of generating large-scale MSCs from induced pluripotent stem cells

(iPSCs) or embryonic stem cells (ESCs) as well [24–26]. To date, MSCs with different origins have been involved in numerous refractory and relapse disease administration including acute-on-chronic liver failure (ACLF), acute myocardial infarction (AMI), aplastic anemia, premature ovarian failure (POF), fistulizing Crohn's disease, critical limb ischemia (CLI), cutaneous wounds, coronavirus disease 2019 (COVID-19)-induced acute lung injury and acute respiratory distress syndrome (ALI/ARDS) [26–32].

For decades, the derivatives generated from MSCs such as exosomes and relative microvesicles have been extensively investigated and regarded as the dominating factor during pathogenesis and disease treatment [20, 33]. Exosomes, also known as small extracellular vesicles (sEVs) or biological spherical lipid bilayer vesicles, are nano-sized extracellular vesicles secreted by various types of cells (e.g., MSCs, natural killer cells, T or B lymphocytes, epithelial cells, macrophages, dendritic cells, tumor cells) with partial sizes ranging from 20 to 200 nm according to the Minimal Information for Studies of Extracellular Vesicles 2018 (MISEV 2018) guidelines [34–36]. The plasma membrane-derived vesicles contain lipids, proteins (e.g., CD9, CD63, CD81, GTPases, HSP70, HSP90, Tsg101, Alix), nucleic acids (e.g., microRNAs, LncRNAs, mRNAs), and other bioactive substances, which thus play an important role in various physiological and pathological processes, and in particular, serving as intermediators for material exchange and intercellular communication via delivering a variety of the aforementioned bioactive substances [37, 38]. Numerous preclinical and clinical investigations including the International Society for Extracellular Vesicles (ISEV) have shown that MSC-derived extracellular vesicles (EVs) including exosomes and microvesicles (MV) are rich in growth factors, cytokines, mRNAs, signaling lipids and regulatory miRNAs, which are adequate to influence intercellular neighbors and tissue responses to infections, injuries, and diseases [39, 40]. However, the concomitant shortcomings of exosomes such as low purity, low yield, stability for storage and weak targeting collectively limit their preclinical investigation and clinical application. Therefore, there's still a long way to optimize the aforementioned problems and facilitate further exploration upon large-scale preparation (e.g., ultracentrifugation techniques, polymer precipitation, size-based isolation techniques, immunoaffinity chromatography, micro-vortex chips, commercial isolation kits) for translational purposes [41–43].

3. Biomaterials/MSC-based composites for osteoarthritis management

Biomaterials of different categories and characteristics have attracted great concerns of investigators in the field of MSC-based regenerative medicine, and thus allow the utilization of unique scaffolds to promote the expansion of MSCs and facilitate their differentiation into appropriate lineages [24, 44]. Biomaterials with highly biocompatible properties are adequate to act as splendid scaffolds for cell attachment and supply preferable microenvironment for the maintenance, differentiation, and biofunction of the encapsulated MSCs, which collectively benefit the *in situ* tissue engineering and translational medicine [45–47]. To date, a series of biomaterials with discrete advantages and disadvantages have been developed and combined with MSCs for regenerative purposes such as the highly biocompatible natural (e.g., collagen, chitosan) and synthetic (e.g., poly-ethyleneglycol, polycaprolactone) biomaterials [44, 46].

3.1 Hydrogel/MSC-based scaffolds for OA management

Hydrogels are splendid biomaterials with unique physical and chemical properties for both soft and hard tissue engineering and regenerative medicine, which largely attributes to the feasibility of orchestrating the critical properties (e.g., elasticity, water content, bioactivity, mechanical stiffness, degradation) rationally and conveniently [48–50]. For decades, hydrogels alone or in combination with appropriate biomaterials have been extensively investigated in various osteoarticular disorders such as OA and meniscus injury [51–53]. For example, our groups recently reported the reinforced efficacy upon OA rabbits by hyaluronic acid (HA) hydrogel and PSC-MSCs composite (HA/PSC-MSCs) compared to those with HA hydrogel or PSC-MSCs alone [24]. Instead, Chung and colleagues systematically compared the efficacy by implanting various hydrogels/UC-MSCs composites in rats such as alginate, chitosan, pluronic, hyaluronic acid (HA), and verified that HA/hUC-MSCs composites rather than relative hydrogels resulted in preferable cartilage repair and achieved collagen organization pattern and cellular arrangements much similar to the adjacent uninjured articular cartilage [54].

Recently, Yang and colleagues further reported the utilization of an injectable and biocompatible Diels-Alder crosslinked hyaluronic acid/PEG (DAHP) hydrogel for OA treatment, which was found with considerable improvement by controlling the release of MSC-derived small extracellular vesicles (MSC-sEVs) [55]. Similarly, Heirani-Tabasi et al. confirmed the enhanced chondrogenic differentiation capacity of adipose-derived MSCs (AD-MSCs) after incubation with an injectable chitosan-hyaluronic acid (CS-HA) hydrogel [56]. Additionally, Tang et al. demonstrated that sEVs derived from umbilical cord MSCs (UC-MSC-sEVs) revealed comparable therapeutic effects for OA but with upregulated proteins mostly involved in extracellular matrix (ECM) organization, immune effector process, PI3K-AKT and Rap1 signaling pathways [57]. Collectively, MSCs or derivatives (e.g., exosomes, sEVs) in combination with injectable hydrogels have attracted considerable attention in OA management for their advantaged chondrogenic differentiation capacity [51, 56, 58].

3.2 Hydroxyapatite (HAP)/MSCs scaffolds for OA management

State-of-the-art renewals have also highlighted the combination of HAP-based biomaterials with MSCs for OA administration and bone regeneration. For instance, Ji and colleagues recently took advantage of a novel hybrid scaffold composed of nano-hydroxyapatite (nHA)/poly ε-caprolactone (PCL) and thermosensitive hydroxypropyl chitin hydrogel (HPCH) for bone defect repair via a mechanism of enhancing vascularization and osteogenesis of encapsulated MSCs [59].

Instead, Shimomura et al. took advantage of a scaffold-free tissue-engineered construct (TEC) and a HAP artificial bone for the treatment of a rabbit osteochondral defect model, and found that osteochondral defects treated with the synovial MSC-derived TEC and HAP composite revealed more rapid and efficient subchondral bone repair coupled with cartilaginous tissues as well as good tissue integration to adjacent host cartilage. Moreover, the combined MSC-based implants significantly accelerated postoperative rehabilitation and sustained the longer-term durability of repaired osteochondral lesions in patients with OA [5]. Similarly, with the aid of bone marrow-derived MSCs (BM-MSCs) and an interconnected porous hydroxyapatite ceramic (IP-CHA), the large osteochondral defect of the knee in a 21-year-old man was effectively alleviated, and cartilage-like regeneration and bone formation were

observed as well [12]. Additionally, we recently also reported the preferable outcomes of OA by conducting multidimensional optimization of MSC-based formulation in combination with the advantageous HA/PG biomaterials, which showed evaluated therapeutic efficacy over HA alone in ameliorating osteoarthritis progression [60, 61].

4. Molecular mechanism of MSC-based cytotherapy for OA management

Generally, MSCs function mainly via orchestrating a series of mode of action including compositional microenvironment, immunoregulation, autocrine, paracrine, and direct- or trans-differentiation into functional cells [15, 62, 63]. In particular, the unique immunomodulatory property and paracrine manner have prompted the enthusiasm for allogenic transplantation of the "off-the-shelf" MSC products in both preclinical and clinical practices in the field of regenerative medicine.

4.1 Compositional microenvironment

In the bone marrow microenvironment, MSCs function as dominating component and stromal cells for the homeostasis and regeneration of hematopoietic stem cells (HSCs) and the concomitant derived cells [30, 64, 65]. In the context of physiological hematogenesis, MSCs are competent for the maintenance or replenishment of the stem cell pool in damaged tissues, and thus help reconstruct the microenvironment for the subsequent hematopoietic reconstitution [22, 30]. As to OA, by conducting MSC infusion into the articular cavity, the hyperactivated inflammatory response caused by inflammatory cytokines is supposed to be effectively suppressed by the released anti-inflammatory factors, extracellular organelles, and vesicles in the microenvironment [24, 66]. As to OA, the roles of MSCs are to orchestrate the spatiotemporal balance between the inflammation and cartilage tissue reconstruction via providing the damaged tissues including bone tissue and cartilage tissue with a relatively desirable environment for tissue repair [24, 67].

4.2 Immunomodulatory effect

To date, extensive literatures have demonstrated the therapeutic or ameliorative effects of MSCs on refractory and recurrent diseases via a bidirectional immunomodulatory approach [14, 25]. Notably, a variety of antiinflammatory factors and cytokines have been reported to play a pivotal role during inflammatory reactions such as interleukins (e.g., IL-6, IL-8, IL-10), transforming growth factor (TGF), stromal cell-derived factor 1 (SDF-1), and vascular endothelial growth factor (VEGF) [22, 68, 69]. The underlying molecular mechanism lies in the sensitive response of MSCs toward the concentration gradient of inflammatory cytokines and chemokines [70]. As to OA, low-grade inflammation has been demonstrated critically in the pathogenesis, which therefore hinders the deposition of cartilage matrix at the damaged sites, delays the proliferation of osteoblast and chondrocytes, and thus resulting in low efficiency of articular cartilage repair [71, 72]. Currently, various kinds of immune cells have been observed in the synovium of OA, including the classically activated and proinflammatory macrophages (M1Mφ), antiinflammatory macrophages (M2Mφ), and T cells. For example, as the major counterparts of immune cells in the joints, Mφ can be hyperactivated by proinflammatory factors in OA patients such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and even the pathogen-associated

molecular patterns [73]. Therefore, the efficient treatment of OA should also pay close attention to the regulation of the local inflammatory microenvironment. As mentioned above, MSC with multilineage differentiation potential and effective immunomodulatory properties have been supposed as an alternative remedy in the administration of cartilage degradation [74]. In detail, MSCs are purposefully recruited to the site of the damaged cartilage and initiate the therapeutic effects upon osteochondral defects, and thus accelerating the reconstruction of articular surface in OA patients [70]. MSCs have been demonstrated involved in the regulation of M1Mφ towards M2Mφ via releasing growth and angiogenic factors as well as down-regulating inflammation and accelerating the remodeling of damaged tissue in OA. Additionally, the immunoregulatory effect of MSCs or MSC-derived EVs upon T cell subsets has also been extensively and in-detail described during the Th1/Th2 cell transformation, Th17 cell and Treg cell generation, and the apoptosis of hyperactivated T cells [75–79]. Similarly, state-of-the-art renewal has also indicated the immunomodulatory effect of MSCs upon $CD24^{+}CD38^{+}$ B cells partially via soluble secreted factors. Interestingly, the role of MSC-derived EVs in mediating B-cell immunoregulation merit seems contradictory and still needs further investigation [67, 80].

4.3 Autocrine and paracrine

Autocrine and paracrine play a critical role in intercellular communications among MSCs and the adjacent osteochondral defects, which are at the cornerstone of regenerative medicine for MSC-based cytotherapy [81, 82]. The secreted substances such as cytokines and anti-inflammatory factors are responsible for the majority of the ascribed bioremediation via promoting the survival and proliferation of adjacent damaged cells and tissues. For example, mediators (e.g., VEGF, bFGF, IL-6, IL-8) in the conditioned media have been considered to play an important role in influencing the differentiation capacity of MSCs or cocultured cells through an autocrine loop [22, 23, 83]. Interestingly, Lee and colleagues have demonstrated that MSC-secreted PGE-2 plays a key role in the maintenance of self-renewal via EP2 receptor [84].

Of the indicated mode of action, the paracrine phenomenon has been widely recognized as the main benefit of MSC therapy based on the secreted factors acting on MSCs and the neighboring cells. Up to now, a variety of key factors have been isolated and verified including SDF-1, TGF, VEGF, prostaglandin E2 (PGE2), hepatocyte growth factor (HGF), and granulocyte-macrophage colony-stimulating factor (GM-CSF), and the diversity in the constitutive secretome has also been put forward by pioneering investigators in the field [23, 84–86]. As to OA, MSC-derived exosomes or sEVs are supposed to effectively avoid the inherent risks of MSCs and thus hold rosy prospects in clinical applications [87, 88]. However, the inherent disadvantages such as low efficacy in preparations, rapid degradation and clearance still need sustained efforts for further improvement [33, 80].

4.4 Direct- or trans-differentiation

For the past decades, the differentiation potential including direct-differentiation and tans-differentiation has been recognized as the key avenue for MSC-based repair [81]. Of note, the differentiation of MSCs into osteoblasts and chondrocytes has been extensively reported as achievable according to the ISCT guidelines [17]. However, current updates in the field indicate that it is likely that paracrine rather than the direct-differentiation or trans-differentiation play a core role in cartilage repair of OA

after MSC delivery because intrathecal injection has presented limited MSC retention and engraftment. For example, aw we previously reviewed, initial attempts upon the molecular mechanisms for disease treatment with MSC transplantation focused on seeking direct evidence for generating functional cells during the rehabilitation of damaged tissues, whereas it was found to be difficult by most investigators when considering the insufficiency of effective retention rate (<5%) [89]. Instead, based on the unique homing property, MSCs mainly migrate to the damaged tissues and perform the restorative function through an orchestration of modulation, which is further verified with the aid of fluorescence *in situ* hybridization [90].

5. Clinical trials of MSC-based cytotherapy for OA management

In recent years, MSC-based cytotherapy has also aroused the intense interest of clinicians in OA treatment. According to the Clinicaltrials.gov database, a total number of 128 clinical trials have been registered worldwide to explore the safety and effectiveness of MSC-based remedies for OA treatment, and in particular, for knee OA and hip OA (**Figure 1**). Of the aforementioned clinical trials, 22 were respectively registered in China and the United States (USA) and followed by 10 in Korea and 9 in Iran (**Table 1**). Meanwhile, we noticed that most of the registered clinical trials were in Phase 1 and/or Phase 2 stage(s), and a total number 13 trials were in the Phase 3 stage instead (**Table 1**). For instance, by conducting a two-year follow-up visit (NCT number: NCT01183728), Orozco and colleagues reported a significant improvement in cartilage quality in 11 of the 12 enrolled knee OA patients with autologous MSC intervention according to the Visual Analogue Scale (VAS) measurements and the pain relief–versus–initial pain score plot [91, 92]. Furthermore, the pain improvement was maintained without significant modifications during the 2-year follow-up, and no serious adverse effects were observed in the aforementioned patients as they previously reported [93].

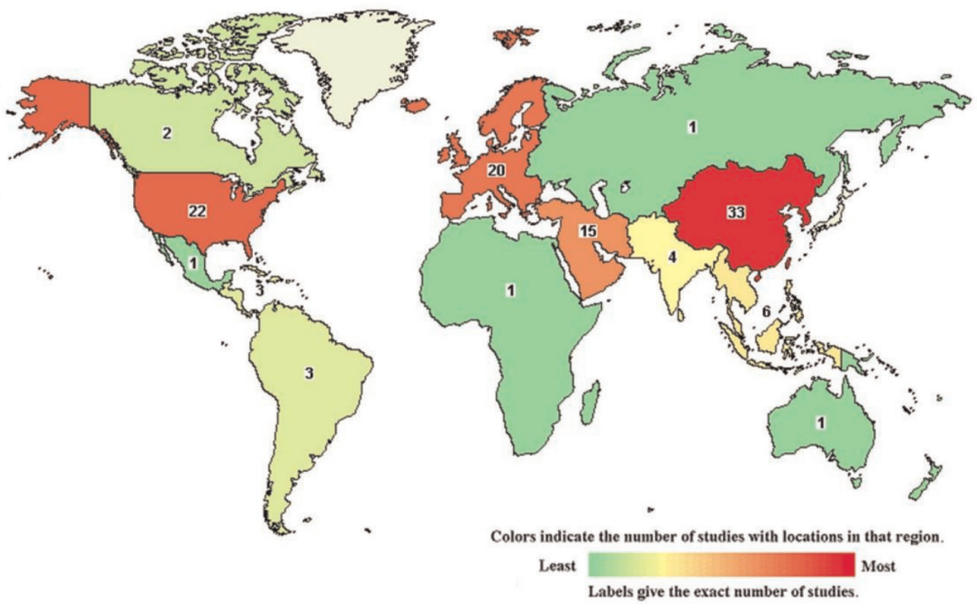

Figure 1.
Clinical trials upon MSC-based cytotherapy for OA administration.

Rank	NCT No.	Age	Phases	Enrollment	Location
1	NCT05160831	18–70	Not Applicable	50	
2	NCT03956719	15–65	Not Applicable	8	China
3	NCT01504464	18–65	Phase 2	40	Iran
4	NCT03383081	≤70	Phase 2	60	China
5	NCT04351932	18–70	Phase 3	54	Ecuador
6	NCT01459640	18–70	Phase 2	50	Malaysia
7	NCT03164083	25–65	Phase 2	0	Iran
8	NCT04130100	40–70	Early Phase 1	60	China
9	NCT03800810	30–80	Early Phase 1	9	Indonesia
10	NCT01809769	40–70	Phase 1, Phase 2	18	China
11	NCT01207661	18–65	Phase 1	6	Iran
12	NCT01499056	18–65	Phase 1	6	Iran
13	NCT02544802	50–70	Phase 1	4	China
14	NCT03357575	18–75	Not Applicable	14	
15	NCT02237846	18–80	Phase 1, Phase 2	0	Panama
16	NCT03166865	30–70	Phase 1, Phase 2	60	China
17	NCT04208646	40–75	Phase 2	108	China
18	NCT02963727	42–75	Phase 1	10	Jordan
19	NCT03869229	30–75	Phase 1, Phase 2	100	Poland
20	NCT02966951	42–75	Phase 1	10	Jordan
21	NCT01586312	18–75	Phase 1, Phase 2	30	Spain
22	NCT01985633	40–75	Phase 1, Phase 2	24	India
23	NCT02641860	18–70	Phase 1	22	China
24	NCT01183728	18–76	Phase 1, Phase 2	12	Spain
25	NCT03969680	40–70	Not Applicable	60	China
26	NCT04212728	40–70	Not Applicable	60	China
27	NCT04326985	18–65	Early Phase 1	20	China
28	NCT01453738	40–70	Phase 2	60	India
29	NCT02123368	50–80	Phase 1, Phase 2	30	Spain
30	NCT03602872	35–65	Phase 1	0	Mexico
31	NCT02365142	40–80	Phase 1, Phase 2	38	Spain
32	NCT03358654	18–75	Not Applicable	9	
33	NCT01448434	20–70	Phase 2	72	Malaysia
34	NCT01895413	25–65	Phase 1, Phase 2	10	Brazil
35	NCT01436058	18–65	Phase 1	6	Iran
36	NCT02162693	18–70	Phase 2	53	China
37	NCT03866330	30–75	Phase 1, Phase 2	100	Poland
38	NCT03477942	18–60	Phase 1	16	USA

Rank	NCT No.	Age	Phases	Enrollment	Location
39	NCT02003131	18–80	Phase 1, Phase 2	0	Panama
40	NCT04368806	≥18	Phase 2, Phase 3	140	USA
41	NCT04448106	≥18	Phase 2	300	USA
42	NCT02958267	40–70	Phase 2	32	USA
43	NCT05288725	18–80	Phase 1, Phase 2	120	USA
44	NCT04863183	30–75	Phase 1, Phase 2	30	
45	NCT05147675		Phase 1	20	Antigua and Barbuda
46	NCT04893174	40–90	Phase 1	6	China
47	NCT00850187	45–60	Phase 1	6	Iran
48	NCT04520945	30–70	Phase 2	100	Malaysia
49	NCT04314661	55–70	Phase 1, Phase 2	15	Indonesia
50	NCT01300598	18–75	Phase 1, Phase 2	18	Korea
51	NCT02776943	18–70	Phase 1, Phase 2	20	
52	NCT05016011	18–65	Phase 2	50	Malaysia
53	NCT03357770	18–75	Not Applicable	9	
54	NCT03589287	≥40	Phase 1, Phase 2	18	China
55	NCT05349565	41–70	Not Applicable	26	Pakistan
56	NCT01873625	10–65	Phase 2, Phase 3	60	Iran
57	NCT05086939	18–75	Phase 3	120	Spain
58	NCT04240873	20–80	Phase 1, Phase 2	24	Korea
59	NCT02291926	18–75	Phase 1	20	China
60	NCT03818737	40–70	Phase 3	480	USA
61	NCT05027581	40–80	Phase 2	70	China
62	NCT02118519	40–68	Phase 2	13	Jordan
63	NCT03955497	18–70	Phase 1, Phase 2	30	China
64	NCT01879046	≥18	Not Applicable	35	France
65	NCT03990805	20–100	Phase 3	260	Korea
66	NCT03000712	20–80	Not Applicable	26	Korea
67	NCT03509025	≥18	Phase 2	11	Korea
68	NCT03014037	18–70	Not Applicable	35	USA
69	NCT03337243	50–85	Not Applicable	60	USA
70	NCT02855073	18–70	Phase 2	28	China
71	NCT04037345	≥19	Phase 1	12	Korea
72	NCT05344157	40–75	Phase 1, Phase 2	54	Australia
73	NCT05182034	≥19	Phase 2	90	
74	NCT02674399	22–60	Phase 2	28	USA
75	NCT00891501	15–55	Phase 2, Phase 3	25	Egypt
76	NCT03028428	40–75	Phase 2	1	

Rank	NCT No.	Age	Phases	Enrollment	Location
77	NCT03943576	40–80	Phase 1, Phase 2	30	China
78	NCT04339504	≥19	Phase 1	12	Korea
79	NCT03648463		Not Applicable	20	
80	NCT01159899	30–75	Early Phase 1	50	France
81	NCT04427930	≥20	Phase 3	260	Korea
82	NCT04825730	≥20	Not Applicable	14	
83	NCT02468492	≥40	Early Phase 1	18	USA
84	NCT05280002	40–80	Phase 2	30	Bangladesh
85	NCT00557635	18–65	Phase 2	50	
86	NCT01931007	18–99	Phase 1	25	USA
87	NCT01041001	≥18	Phase 3	104	Korea
88	NCT03308006	45–65	Phase 2	18	Saudi Arabia
89	NCT02658344	≥18	Phase 2	24	Korea
90	NCT03379168	≥18	Not Applicable	100	USA
91	NCT02696876	16–55	Not Applicable	20	United Kingdom
92	NCT04230902	≥45	Phase 3	48	Lebanon
93	NCT05000593	30–75	Not Applicable	60	China
94	NCT04604288				USA
95	NCT02580695	18–70	Phase 1, Phase 2	30	Chile
96	NCT03790189	35–75	Not Applicable	25	Italy
97	NCT03067870	17–75	Phase 1	100	
98	NCT01626677	≥18	Phase 3	103	Korea
99	NCT04821102	≥20	Not Applicable	21	
100	NCT04716803	45–75	Not Applicable	10	USA
101	NCT01926327	18–65	Phase 3	150	Iran
102	NCT04234412	30–65	Not Applicable	10	
103	NCT03788265	≥18	Not Applicable	60	China
104	NCT02351011	40–65	Phase 1, Phase 2	12	Canada
105	NCT02582489	≥18	Not Applicable	100	USA
106	NCT01227694	18–65	Phase 1, Phase 2	15	Spain
107	NCT04990128	18–65	Phase 3	100	USA
108	NCT05276895	40–80	Phase 1, Phase 2	60	
109	NCT03048773	≥20	Not Applicable	40	China
110	NCT02964143	50–80	Not Applicable	306	
111	NCT04749758	≥18	Not Applicable	77	Andorra
112	NCT04310852	40–70		25	Italy
113	NCT05193877	55–85	Not Applicable	60	Iraq
114	NCT03410355	16–60	Not Applicable	6	Canada

Rank	NCT No.	Age	Phases	Enrollment	Location
115	NCT04453111	18–75	Phase 1, Phase 2	45	Ukraine
116	NCT04308213	35–75	Not Applicable	30	Italy
117	NCT05305833	18–65	Phase 1, Phase 2	20	Turkey
118	NCT04043819	18–80	Phase 1	125	USA
119	NCT05081921	40–70	Phase 1, Phase 2	200	Poland
120	NCT01739504	18–80	Not Applicable	10	USA
121	NCT01413061	18–80	Not Applicable	140	USA
122	NCT04222140	25–60	Not Applicable	40	USA
123	NCT04223622	≥18		24	Italy
124	NCT01585857	50–75	Phase 1	18	Germany
125	NCT03608579	18–65	Phase 1	24	USA
126	NCT02838069	45–75	Phase 2	153	France
127	NCT01038596	50–90		30	Germany
128	NCT01733186	≥18	Phase 1, Phase 2	12	USA

Table 1.
MSC-based clinical trials for OA management.

6. Conclusions

MSCs and concomitant derivatives have emerged as advantaged and alternative sources for OA administration and cartilage repair. MSC- or MSC-exo/sEVs- laden biomaterial systems have supplied overwhelming new tissue-engineering platforms to sequentially improve the osteochondral interface and alleviate the full-thickness articular cartilage defects, which collectively accelerates the reestablishment of osteochondral and cartilage tissues (**Table 2**). Of note, injecting MSCs into joints with

Cell type	Stage	Outcome	Ref.
UC-MSCs	Clinical trials	Safe and superior to active comparator in knee OA	Matas, et al. [94]
AD-MSC/BM-MSC/UC-MSC/AD-MSCs	Clinical trials	Subjective improvements in knee function and pain reduction	Buzaboon, et al. [95]
BM-MSCs/S-MSCs/AD-MSCs	Clinical trials	Pain relief and functional improvement	Cui, et al. [96]
HA hydrogel/ hPSC-MSCs	Preclinical study	Preferable restorative and ameliorative function on OA rabbits	Zhang, et al. [24]
HA hydrogel/UC-MSCs	Preclinical study	Significant gross and histological improvements in hyaline cartilage regeneration	Wu, et al. [97]
Hydrogel/MSCs	Preclinical study	The defects significantly better histologic scores with morphologic characteristics of hyaline cartilage	Zscharnack, et al. [98]
DAHP hydrogel/MSC-sEVs	Preclinical study	Enhanced efficacy for OA improvement	Yang, et al. [55]

Table 2.
Advances in MSC-based cytotherapy for OA.

an inflammatory environment may elevate the risk of ectopic calcification and osteoproliferation in patients with OA. Therefore, systematic and detailed investigations are urgently needed to ensure the maintenance of the intra-articular environment for cartilage repair before large-scale application in clinical practice. In spite of the tremendous progresses in the field of OA management and MSC-based regenerative medicine, it still remains challenging and there's a long way to go to efficiently and cost-effectively repair the full-thickness articular cartilage defects and osteochondral interface via achieving efficient osteogenesis and chondrogenesis.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

Not applicable.

Appendix A: appendices and nomenclature

Abbreviation	Nomenclature
MSCs	mesenchymal stem/stromal cells
OA	osteoarthritis
POF	premature ovarian failure
AMI	acute myocardial infarction

ACLF	acute-on-chronic liver failure
P-MSCs	placental-derived MSCs
DPSCs	dental pulp-derived stem cells
UC-MSCs	umbilical cord-derived MSCs
AD-MSCs	adipose-derived MSCs
sEVs	small extracellular vesicles
PSC-MSCs	pluripotent stem cell-derived MSCs
ESCs	embryonic stem cells
iPSCs	induced pluripotent stem cells
ECM	extracellular matrix
TEC	tissue-engineered construct
PCL	poly ε-caprolactone
HA	hyaluronic acid
nHA	nano-hydroxyapatite
HAP	hydroxyapatite
BM-MSCs	bone marrow-derived MSCs
HPCH	hydroxypropyl chitin hydrogel
MV	microvesicles
MISEV	Minimal Information for Studies of Extracellular Vesicles
COVID-19	corona virus disease 2019
CLI	critical limb ischemia
ALI/ARDS	acute lung injury and acute respiratory distress syndrome
ACI	autologous chondrocyte implantation
ISCT	International Society for Cellular Therapy
CS-HA	chitosan-hyaluronic acid
BM-MSCs	bone marrow-derived MSCs
IP-CHA	interconnected porous hydroxyapatite ceramic
SDF-1	stromal cell-derived factor 1
TGF	transforming growth factor
HSCs	hematopoietic stem cells
VEGF	vascular endothelial growth factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
Mφ	macrophages
PGE2	prostaglandin E2
HGF	hepatocyte growth factor

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