Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Mesenchymal Stromal/Stem Cell (MSC)-Based Vector Biomaterials for Clinical Tissue Engineering and Inflammation Research: A Narrative Mini Review

Junshuai Xue[1], Yang Liu[2]

[1]Department of General Surgery, Qilu Hospital of Shandong University, Jinan, People's Republic of China; [2]Department of General Surgery, Vascular Surgery, Qilu Hospital of Shandong University, Jinan City, People's Republic of China

Correspondence: Yang Liu, Department of General surgery, Vascular Surgery, Qilu Hospital of Shandong University, Jinan, Shandong, 250012, People's Republic of China, Tel +86 18560088317, Email liuyang_sdu@126.com

Abstract: Mesenchymal stromal/stem cells (MSCs) have the ability of self-renewal, the potential of multipotent differentiation, and a strong paracrine capacity, which are mainly used in the field of clinical medicine including dentistry and orthopedics. Therefore, tissue engineering research using MSCs as seed cells is a current trending directions. However, the healing effect of direct cell transplantation is unstable, and the paracrine/autocrine effects of MSCs cannot be effectively elicited. Tumorigenicity and heterogeneity are also concerns. The combination of MSCs as seed cells and appropriate vector materials can form a stable cell growth environment, maximize the secretory features of stem cells, and improve the biocompatibility and mechanical properties of vector materials that facilitate the delivery of drugs and various secretory factors. There are numerous studies on tissue engineering and inflammation of various biomaterials, mainly involving bioceramics, alginate, chitosan, hydrogels, cell sheets, nanoparticles, and three-dimensional printing. The combination of bioceramics, hydrogels and cell sheets with stem cells has demonstrated good therapeutic effects in clinical applications. The application of alginate, chitosan, and nanoparticles in animal models has also shown good prospects for clinical applications. Three-dimensional printing technology can circumvent the shortage of biomaterials, greatly improve the properties of vector materials, and facilitate the transplantation of MSCs. The purpose of this narrative review is to briefly discuss the current use of MSC-based carrier biomaterials to provide a useful resource for future tissue engineering and inflammation research using stem cells as seed cells.

Keywords: mesenchymal stromal/stem cells, vector biomaterial, tissue engineering, inflammation, cell transplantation

Background

Mesenchymal stromal/stem cells (MSCs) have the ability of self-renewal, the potential of multidirectional differentiation, and a strong paracrine capacity. The term mesenchymal is derived from the word mesenchyme, which is used to describe loosely organized tissue that is extensively associated with connective and bone marrow tissues during embryonic development. Stem cells are cell populations with demonstratable progenitor cell functionality of self-renewal and differentiation. Stromal cells are a bulk cell population with notable secretory, immunomodulatory, and homing properties.[1,2] Compared with heterologous stem cells, MSCs exhibit both a self-renewal capacity and multipotent differentiation potential, and have greater advantages in terms of the quantity of cells obtained. Compared with embryonic stem cells, MSCs avoid medical ethical issues and can be easily extracted from autologous tissues.[3] MSCs are widely distributed in various tissues of the human body, including trabecular bone, salivary glands, the synovial membrane, dermis, periodontal ligament, and dental pulp.[4–6] There are various MSC types depending on the tissue source, mainly including bone marrow (BM), umbilical cord, and adipose MSCs.[7] BM-MSCs were mainly used until 2008, but BM-, perinatal tissue (PT)-, and adipose tissue (AT)-derived MSC products have been more commonly applied in recent years and their concomitant safety and hemocompatibility profiles are used via systemic infusion.[8,9] In general, AT- and PT-derived MSC products express much higher levels of highly procoagulant tissue factor (CD142) and thus

Received: 3 November 2022
Accepted: 18 January 2023
Published: 21 January 2023

trigger a strong instant blood-mediated inflammatory reaction (IBMIR) with concomitant thromboembolic events unless carefully antagonized with anticoagulants. Biomaterial-based MSC delivery might be a good alternative to avoid IBMIR-mediated cell destruction and thromboembolic risks upon systemic MSC infusion.[10]

The study of MSCs as seed cells is a current hot topic, which are mainly used in the field of clinical medicine including dentistry and orthopedics. In addition to their multipotent differentiation potential, the strong paracrine capacity is considered to be a major mechanism that promotes tissue repair.[11–14] Stimuli from the extracellular environment affect the proliferation and differentiation properties of MSCs. Therefore, the repair of defective tissues is usually implemented by either directly transplanting MSCs into the target tissue or stimulating their differentiation into mature tissue.[15] However, the use of various factors secreted by MSCs, which is called the secretomes, may provide a more efficient alternative, including direct secretion of proteins and two major subpopulations of biologically active extracellular vesicles, namely exosomes and microvesicles (Figure 1).[16–19] Although MSCs exert profound immunomodulatory effects on both adaptive and innate immune systems by producing numerous immunomodulatory and immunosuppressive factors to inhibit alloantigen and mitogen-activated mixed lymphocyte culture, rapid cell destruction upon cell infusion occurs through an IBMIR.[20–22] MSCs combined with biomaterials can effectively prolong cell survival when implanted outside of the bloodstream, which is necessary to suppress and prevent graft-versus-host disease.[23] Additionally, MSCs secrete various cytokines, chemokines, angiogenic factors, and growth factors that act autocrine/paracrine manners to regulate several physiological processes, including directing endogenous progenitor cells to the injury site, and mediating apoptosis, scar formation, and tissue remodeling.[21,24] For example, when MSCs and hydrogels are assembled into spheroids, they accelerate the secretion of endogenous trophic factors and extracellular matrix, increase the levels of cytokines and immunomodulatory paracrine factors and suppress the LPS-induced inflammatory response.[25] Additionally, MSCs have homing properties and can migrate to an injury site to exert a healing effect that can be enhanced by cytokines, chemical modifications, and bioparticle coating technique.[26,27] Moreover, MSCs applied with

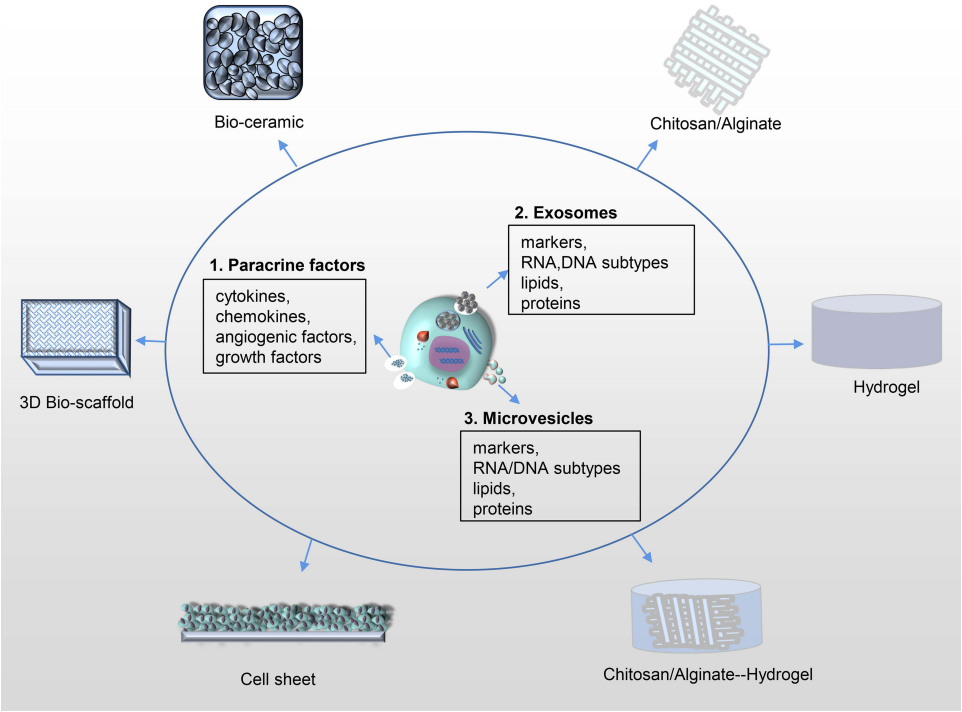

Figure 1 Current vector materials for MSCs used in tissue engineering and inflammation research include bioceramics, chitosan, alginate, hydrogels, interbinding materials, cell sheets and 3D bio-scaffolds. Vector materials promote the paracrine activity of MSCs, including the secretion of paracrine factors to the extracellular through the fusion of secretory granules with the plasma membrane, such as cytokines, chemokines, angiogenic factors, and growth factors. This promotes the release of exosomes to the extracellular environment through the fusion of multivesicular bodies with the plasma membrane, thereby promoting the shedding of microvesicles directly from the plasma membrane through outgrowth. Additionally, exosomes and microvesicles contain biomarkers, RNA/DNA isoforms, lipids, and proteins.

biomaterials might survive better than cryopreserved/freeze-thawed cells.[28,29] These properties of MSCs have made them an optimal candidates to repair damaged tissues and organs.

The concept of tissue engineering was first introduced by Lange and Vacanti in 1993 to apply biological and engineering principles to the development of functional replacements for damaged tissues, providing solutions for tissue generation and repair.[30–32] Subsequently, the combination of biological scaffolds and cell transplantation has gradually become an important aspect of applied research in regenerative medicine, in which a scaffold structure, scaffold materials, and cell inoculation techniques are crucial.[28,29] The combination of MSCs as seed cells and vectors forms a three-dimensional cell growth environment for spatial organization of cells, promoting cell-cell and cell-matrix interactions for certain physiological functions generated by tissue-specific cells within organs.[35,36] Therefore, the vector material needs to be capable of promoting the growth, secretory function, and differentiation of stem cells, which in turn need to be able to promote modifications of the mechanical properties and environmental remodeling of the vector material. These interactions drive multicellular responses to form a multicellular system that is consistent with the growth patterns of the internal environment of the human body, resulting in a multicellular structure with enhanced robustness and physiological relevance.[34–37] Additionally, vector materials can be used to deliver drugs and various secreted factors.[38,39] Therefore, the biocompatibility of these materials is also essential and their combination with stem cells can effectively improve the tissue response of these vector materials.[40,41] There are numerous studies on tissue engineering of various biomaterials, mainly regarding bioceramics, alginate, chitosan, hydrogels, cell sheets, nanoparticles and 3D printing (Figure 1). The purpose of this narrative review is to briefly discuss the current use of mesenchymal stromal/stem cell (MSC)-based carrier biomaterials to provide a useful resource for future tissue engineering and inflammation research using stem cells as seed cells. The detailed search strategy is presented as Supplementary Material.

Bioceramics

Bioceramics have distinct advantages to construct efficient and safe materials for bone defect repair as bone graft substitutes.[42,43] Although ceramics are highly brittle, the application of techniques, such as plasma spraying and electrophoretic deposition, have facilitated the development of ceramic composites. Titanium-ceramic composites composed of titanium and bioactive ceramics, such as hydroxyapatite, calcium phosphate, and wollastonite provide, have both in vitro bioactivity and enhanced mechanical properties.[44,45] Calcium phosphate bone cement was developed in 1986 and consists of tetracalcium phosphate and anhydrous dicalcium phosphate, which has good biocompatibility, osteoconductivity and resorbability. Its combination with mesenchymal stem cells can greatly promotes the regeneration of bone tissue and accelerates the repair of bone defects.[33,46–49] Porous bioceramics constructed from calcium phosphate exhibited better biocompatibility when cotransplanted with stem cells that repair experimentally induced bone defects in animal models.[50–53] Powder injection molding of titanium-hydroxyapatite composites generates complex shapes and geometries, forms more complex porous structures, improves the distribution density of mesenchymal stem cells and interior compatibility with the scaffold, which effectively promotes the differentiation of stem cells and the growth of bone tissue.[54,55] However, because of high brittleness and biomechanical strength, these materials are generally only used in bone tissue repair. In clinical practice, Gómez-Barrena et al treated long bone nonunion using mesenchymal stem cells in combination with bioceramics, and found effective bone consolidation by clinical and radiological evaluation and bone biopsy confirming bone formation around bioceramic particles.[56,57]

Alginate

Alginate is a class of polycationic copolymers derived from brown algae, which has diverse ratios of 1,4-linked B-D-mannuronic acid (M) and α-L-glutamine (G) residues, mild ionic gelation, good biocompatibility, biodegradability, injectability, and hydrophilicity, low immunogenicity, and cost-effectiveness, and provides excellent support for cell transplantation.[58] Alginate forms gels under mild physiological conditions and can be crosslinked by ions to form microspheres that deliver cells, drugs, and growth factors, but also have a pliable consistency that allows them to fully adapt to defective tissues. Alginate microbeads are usually produced by dripping a cell-alginate solution into a calcium chloride solution, which controls the inflammatory response and promotes angiogenesis by creating an appropriate interface between the transport signal and receptor environment.[59] However, the main drawback of alginate is the lack of

mechanical stability, and its biocompatibility is very dependent on the molecular weight, composition, purity, and solution viscosity of the alginate.[60,61] The combination of alginate with other biomaterials, such as bone morphogenetic protein-2, RGD, and vascular endothelial growth factor, increases its mechanical strength and can be applied to cell transplantation to promote the regeneration of tissues and organs such as bone, cartilage, and heart.[62–64] The combination of alginate with stem cells also improves mechanical strength and tissue regeneration, which is mainly reflected by an expanded secretion profile of proangiogenic, neuroprotective, and immunomodulatory paracrine factors in bio-instructive hydrogel-encapsulated MSCs with a predicted augmented proangiogenic potential.[65] Sahu et al co-cultured alginate-encapsulated MSCs with patient-derived OA cartilage.[66] Cytokines, including IL-10, HGF, and sFAS, were significantly increased in the experimental group compared with the control group, followed by an increase in the total thioglycosaminoglycan content and tissue inhibitor of matrix metalloproteinase inhibitor 1 levels, and a decrease in the percentage of apoptotic cells.[66] Therefore, alginate-encapsulated MSCs created a synthetic, proliferative, and anti-apoptotic microenvironment for the OA cartilage response and induced endogenous regeneration in OA cartilage.

Chitosan

Chitosan (CHS) is a bioactive polymer with a wide range of clinical applications because it is antibacterial, non-toxic, easily modified, and biodegradable, and has a low cost and is suitability for mass production.[67,68] Additionally, chitosan is functional in various forms such as membranes, sponges, gels, scaffolds, microparticles, nanoparticles and nanofibers.[63,64,66] Thus, chitosan has played a great role in drug delivery, gene therapy, tissue engineering, and wound healing.[69] Macroporous scaffolds composed of alginate-chitosan polyelectrolyte complexes co-cultured with MSCs allow better retention of MSCs (> 90%) for long-term survival and secretion of FGF2 to promote tissue repair and regeneration in acute and chronic injuries, which is an attractive tool to optimize the therapeutic effect of MSCs.[70] In vitro experiments have shown that cultured with chitosan show both good compatibility and high osteogenic properties.[71] Moreover, in vivo experiments have shown that CHS scaffolds implanted into femoral defects in rats induce a higher grade of bone healing compared with the control.[72] Some studies have found that pore size and porosity have a great influence on the mechanical stability of the scaffolds. For example, an increase in porosity is associated with a concomitant decrease in mechanical stability.[73] Additionally, chitosan hydrogel-loaded MSC-derived extracellular vesicles obtaining by extracellular vesicles mixed with an equal volume of a 2% CS solution showed good performance in skin injury repair models.[74] They increase the proliferation, migration, and expression of anti-aging-related genes in naturally senescent fibroblasts and promote extracellular matrix regeneration of senescent fibroblasts by decreasing MMPS levels and increasing TIMPs levels.[74]

Hydrogels

Hydrogels are widely used for various tissue engineering applications because of their low cost, simple synthesis, low immunoreactivity, relative stability, good hydrophilicity, and tight conformational control, which can be categorized as injectable hydrogels or mucoadhesive hydrogels.[75–77] The injectability of hydrogels is achieved by enzyme-mediated crosslinking, Schiff base crosslinking, photocrosslinking, and in situ polymerization of thermosensitive polymers.[78–82] The adhesion of the hydrogel is then facilitated by electrostatic interactions, covalent bonding, and/or physical interactions with the cell-attached integrin recognition site.[83] Additionally, hydrophilicity is conferred by the presence of hydrophilic groups in polymers forming hydrogel structures, such as -OH, -CONH-, -$CONH_2$-, and -SO_3H. These structures form hydrogels with similar physical properties to living tissues because of the high water content, soft and rubbery consistency, and low interfacial tension with water or biological fluids.[84] Hydrogels combined with MSCs facilitate good tissue repair in animal models and clinical studies.[75] Genovese et al aggregated MSCs into spheres combined with hydrogels in vitro, encapsulated them in hydrogels containing fibrinogen, and injected them into muscle tissue to treat volumetric muscle loss injury in mice, which enhanced the protein expression of myogenic markers (MyoD and myogenin) proteins, improved muscle mass, increased the presence of central nuclei in myofibers and small fibers, and modulated pro- and anti-inflammatory macrophage markers expression.[85] Fibrin gels used with stem cell transplantation can also be applied to repair injured peripheral nerves. The combination of a fibrin gel-based drug delivery system with MSCs allows for sustained local release of tacrolimus in vitro. Tacrolimus in PLGA microspheres and suspended in

fibrin gel is released by sustained diffusion through surface erosion of the PLGA microspheres and then through the gel. Additionally, a hydrogel scaffold that combines local tacrolimus and MSC delivery overcomes the systemic side effects of immunosuppressants, while inducing a local immunotolerant environment, extending the survivability of stem cells, which may promote peripheral nerve regeneration.[86] A study of 50 patients with chronic ischemic heart disease found that, after 12 months of treatment, the infarct size had increased by 5.19% (−1.85–12.22%) in patients treated by myocardial injection of a human umbilical cord mesenchymal stem cell-loaded collagen hydrogel compared with 8.59% in the control group (−3.06–20.25%). This study demonstrated that collagen hydrogels used for cellular transport are safe and feasible to repair myocardial infarction lesions.[87]

Cell Sheets

Cell sheets are based on ordered accumulation and adhesion of cell monolayers in two-dimensional cell culture. There is no complicated enzymatic step before cell sheet implantation, which effectively preserves intercellular connections and some cell surface proteins.[88,89] Intercellular junctions also provide protective and mechanically supportive effects to the microenvironment and exert a positive influence on cell proliferation, differentiation, and migration.[90] The shortcoming is that multilayer cell sheets can undergo necrosis and have decreased survival due to hypoxia or nutrient deficiencies caused by the high cell density.[91] However, cell sheets as extracellular matrix-rich structures can be implanted directly into living tissues without artificial scaffolds or structural intermediates, and they act as support structures in combination with scaffolds as vectors.[92] Cell sheets have been widely used in the clinical treatment of diseases and provided positive therapeutic results.[93–97] For example, Long et al wrapped allogeneic structures of regenerated allograft bone in thin sheets of MSCs as tissue-engineered bone membranes.[93] In vitro experiments showed that MSCs maintained good morphology on the membrane, and transplantation into mouse femoral defects revealed prolonged cartilage formation at the graft-host junction, enhanced bone crust formation, and enhanced graft-host osseointegration. Additionally, biomechanical tests showed significant improvements in the structural and functional properties of thin sections of MSC-transplanted femurs. This study demonstrated the feasibility of this tissue engineering strategy for large-scale allograft bone repair.[93] Another clinical study confirmed the safety and efficacy of autologous PDL-derived cell sheets in patients with periodontitis, during which a temperature-responsive culture dish was used to construct three-layer PDL-derived cell sheets and transplanted them in an autologous fashion after standard flap surgery. The study included 10 patients and found improvements the in periodontal probing depth (mean SD of 3.2±1.9 mm), an increase in clinical attachment (2.5 ±2.6 mm), and an increase in bone height (2.3±1.8 mm). These treatment effects persisted for an average follow-up period of 55±19 months without serious adverse events. This cellular membrane engineering-based cell therapy may provide an innovative treatment for severe periodontal defects.[96] Additionally, stem cells from human exfoliated deciduous in dental regeneration have been assessed. Xuan et al found that aggregates of stem cells from human exfoliated deciduous teeth increase the root length and decrease the apical foramina width of recipient immature permanent teeth and regenerate complete pulp tissues in patients with pulp necrosis, which are equipped with blood vessels and nerves.[97] Some studies of animal models and clinical trials have also demonstrated that MSCs have an enormous potential in regenerative medicine for bone and teeth.[98–100]

Nanoparticles

Nanoparticles have been used as a carrier system for targeted delivery of bioactive molecules to ensure long-term maintenance of MSCs in vitro and enhance their regenerative potential. Nanostructured materials have also been developed to recapitulate the stem cell niche in tissues and to direct MSCs to create a regeneration-permitting environment.[101–103] Compared with gelatin and chitosan, nanofiber scaffolds formed by polyelectrolyte composites have a high energy storage modulus and excellent mechanical properties.[104] Sahu et al incorporated Prussian blue nanoparticles as biocompatible reactive oxygen species-scavenging nanoparticles into MSCs without affecting their stemness or differentiation potential of MSCs and significantly improved MSCs survival under high oxidative stress conditions and enhanced their paracrine effects and anti-inflammatory properties. The study demonstrated profound in vivo therapeutic effects in an animal model of hepatic ischemia-reperfusion injury.[105] Fan et al used kartogenin (KGN)-coupled polyurethane nanoparticles in combination with hydrogel-loaded TGF-β3, which exhibited good

biological properties.[106] The addition of TGF-β3 significantly increased the levels of phosphorylated Smad3 compared with the control. Furthermore, the addition of KGN did not change the levels of phosphorylated Smad3. These results indicated that TGF-β3 promotes the chondrogenesis of MSCs by activating Smad2/3, and the effect of KGN on MSC chondrogenesis was not mediated by directly phosphorylating Smad3. Moreover, the nanoparticles promoted MSC migration and cartilage regeneration by attracting endogenous MSCs and inducing recruitment of cells to form cartilage, providing a promising strategy for cartilage repair.[106]

3D Printing

3D printing is compatible with biomaterials using its unique advantages to complement materials such as the spatial structure and mechanical strength.[107,108] 3D printing reduces the time and cost of producing physical models and implants, creates personalized implants, and reduces the time and space constraints of conventional methods.[43,109] Lian et al found that multilayer porous bionic sponges prepared by LDM printing were shown to promote cell-material interactions and modulate MSC paracrine functions, enhance MSC adhesion, retention, survival, and growth, and significantly promote immunomodulation, angiogenesis, and osteogenic factor secretion.[110] In a rat distal femoral defect model, prior to the animal experiment, MSCs were separately seeded on the LDM- and FDM-printed scaffolds and incubated for 24 h which significantly promoted the regeneration of vascularized bone.[110] In an animal study on endometrial repair, Ji et al used 3D printing to construct porous lattice-type human induced multipotent stem cell-derived mesenchymal stem cell-loaded hydrogel scaffolds to repair the damaged endometrium.[111] They promoted restoration of endometrial tissue morphology (endometrial tissue and gland regeneration) and regeneration of endometrial cells (stromal and epithelial cells) and endothelial cells, improved endometrial receptive function indices, including pinopode formation and leukemia inhibitory factor and integrin αvβ3 expression, and partially restored embryo implantation and pregnancy maintenance functions of the damaged endometrium.[111]

Limitations

MSCs transplantation is a safe and effective cell regeneration therapy, but the repair effect of direct cell transplantation is unstable. Vector materials have their own advantages and shortcomings when combined with MSCs, but have shown good performance in in vivo and in vitro experiments and effectively promote the paracrine/autocrine effect of stem cells and enhance their healing effect. However, there are still several limitations.

The inherent defects of carrier materials limit their wide application.Bioceramics are often used for bone tissue engineering because of their good mechanical properties, brittleness, and poor toughness.[112] Conversely, hydrogels offer the advantages of good biocompatibility, high water content, and degradability. Alginate is susceptible to pH effects because of its polyanionic properties.[113] Chitosan has good antibacterial, hemostatic, and anti-inflammatory effects. However, because of the poor mechanical properties, solubility, and controlled release and loading of drugs, they are more often used in skin and soft tissue injury repair. Additionally, cell sheets are formed mainly on culture substrates constructed from sensitive materials and have a great potential to repair tissue organ defects. However, it should be noted that they lack functional blood vessels and are susceptible to ischemia and hypoxia, which limits the thickness of the cell sheet. Without the involvement of a scaffold, the strength may be insufficient and it is susceptible to the influence of the culture substrate material.[114] Nanomaterials improve the precision of material applications from a microscopic viewpoint and indirectly compensate for the shortcomings of other materials. 3D printing provides individualized treatments and will be well applied in tissue engineering in the future. However, because of its advanced nature, it needs strong and robust technical support.

MSCs are currently available from a wide range of sources, but are limited in terms of the quantities of cells obtained, potential for expansion, and ability to be modified and integrated. MSCs from various sources also have different properties in response to different tissue injuries.[115] The selection of MSC donors should be strictly controlled and kept aseptic. Factors that adversely affect MSCs should be excluded, such as immunodeficiency viruses and human T-lymphotropic viruses. Additionally, MSCs become large when cultured in vitro and do not easily pass through small vessels after implantation. Under the influence of blood flow and cell–cell interactions, MSCs tend to form clumps that block blood vessels and affect blood flow, leading to serious risks such as thrombosis and embolism.[116] Long-term

in vitro expansion can lead to epigenetic variation, morphological and biological changes, immune rejection, and even neoplasia, which may reduce implantability and affect survival rates to a certain extent.[117–120] After long-term treatment, there is a lack of clarity about the survival or regression of MSCs in vivo.

Although the multipotent differentiation potential and paracrine function of MSCs have been verified in vitro, the mechanism by which they function in vivo is not fully clarified. Furthermore, the compatibility between cells and biomaterials and the mechanisms by which they function are unclear and require further research. In terms of clinical translation, because of efficacy and ethical limitations, most current research is limited to basic research and there is insufficient research on clinical treatments.

Conclusions

The combination of bioceramics, hydrogels, and cell sheets with stem cells has demonstrated good therapeutic effects in clinical applications. The application of alginate, chitosan, and nanoparticles in animal models has also shown good prospects for clinical applications. 3D printing can circumvent the shortage of biomaterials, greatly improve the properties of vector materials, and facilitate the transplantation of MSCs, which will be a critical fields for future research in tissue engineering and regenerative medicine.

Acknowledgments

We thank Mitchell Arico from Liwen Bianji (Edanz) (https://www.liwenbianji.cn) for editing the language of a draft of this manuscript.

Funding

This report is supported by the National Natural Science Foundation of China (Grant No.82000451).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Viswanathan S, Shi Y, Galipeau J, et al. Mesenchymal stem versus stromal cells: International Society for Cell & Gene Therapy (ISCT®) Mesenchymal Stromal Cell committee position statement on nomenclature. *Cytotherapy*. 2019;21(10):1019–1024. doi:10.1016/j.jcyt.2019.08.002
2. Bianco P, Cao X, Frenette PS, et al. The meaning, the sense and the significance: translating the science of mesenchymal stem cells into medicine. *Nat Med*. 2013;19(1):35–42. doi:10.1038/nm.3028
3. Lo B, Parham L. Ethical issues in stem cell research. *Endocr Rev*. 2009;30(3):204–213. doi:10.1210/er.2008-0031
4. Ayoub S, Berbéri A, Fayyad-Kazan M. An update on human periapical cyst-mesenchymal stem cells and their potential applications in regenerative medicine. *Mol Biol Rep*. 2020;47(3):2381–2389. doi:10.1007/s11033-020-05298-6
5. Zhu Y, Wang Y, Zhao B, et al. Comparison of exosomes secreted by induced pluripotent stem cell-derived mesenchymal stem cells and synovial membrane-derived mesenchymal stem cells for the treatment of osteoarthritis. *Stem Cell Res Ther*. 2017;8(1):64. doi:10.1186/s13287-017-0510-9
6. Xu X, Liang Y, Li X, et al. Exosome-mediated delivery of kartogenin for chondrogenesis of synovial fluid-derived mesenchymal stem cells and cartilage regeneration. *Biomaterials*. 2021;269:120539. doi:10.1016/j.biomaterials.2020.120539
7. Maqsood M, Kang M, Wu X, et al. Adult mesenchymal stem cells and their exosomes: sources, characteristics, and application in regenerative medicine. *Life Sci*. 2020;256:118002. doi:10.1016/j.lfs.2020.118002
8. Moll G, Ankrum JA, Kamhieh-Milz J, et al. Intravascular mesenchymal stromal/stem cell therapy product diversification: time for new clinical guidelines. *Trends Mol Med*. 2019;25(2):149–163. doi:10.1016/j.molmed.2018.12.006
9. Moll G, Ankrum JA, Olson SD, et al. Improved MSC minimal criteria to maximize patient safety: a call to embrace tissue factor and hemocompatibility assessment of MSC products. *Stem Cells Transl Med*. 2022;11(1):2–13. doi:10.1093/stcltm/szab005
10. Moll G, Rasmusson-Duprez I, von Bahr L, et al. Are therapeutic human mesenchymal stromal cells compatible with human blood? *Stem Cells*. 2012;30(7):1565–1574. doi:10.1002/stem.1111
11. Cagliani J, Grande D, Molmenti EP, et al. Immunomodulation by mesenchymal stromal cells and their clinical applications. *J Stem Cell Regen Biol*. 2017;3(2). doi:10.15436/2471-0598.17.022
12. English K, French A, Wood KJ. Mesenchymal stromal cells: facilitators of successful transplantation? *Cell Stem Cell*. 2010;7(4):431–442. doi:10.1016/j.stem.2010.09.009
13. Fu Y, Karbaat L, Wu L, et al. Trophic effects of mesenchymal stem cells in tissue regeneration. *Tissue Eng Part B Rev*. 2017;23(6):515–528. doi:10.1089/ten.teb.2016.0365

14. El Agha E, Kramann R, Schneider RK, et al. Mesenchymal stem cells in fibrotic disease. *Cell Stem Cell*. 2017;21(2):166–177. doi:10.1016/j.stem.2017.07.011
15. Berebichez-Fridman R, Montero-Olvera PR. Sources and clinical applications of mesenchymal stem cells: state-of-the-art review. *Sultan Qaboos Univ Med J*. 2018;18(3):e264–e77. doi:10.18295/squmj.2018.18.03.002
16. Tsiapalis D, ODriscoll L. Mesenchymal stem cell derived extracellular vesicles for tissue engineering and regenerative medicine applications. *Cells*. 2020;9(4):991. doi:10.3390/cells9040991
17. Hade MD, Suire CN, Suo Z. Mesenchymal stem cell-derived exosomes: applications in regenerative medicine. *Cells*. 2021;10(8):1959. doi:10.3390/cells10081959
18. Kusuma GD, Carthew J, Lim R, et al. Effect of the microenvironment on mesenchymal stem cell paracrine signaling: opportunities to engineer the therapeutic effect. *Stem Cells Dev*. 2017;26(9):617–631. doi:10.1089/scd.2016.0349
19. Zhou Y, Yamamoto Y, Xiao Z, et al. The immunomodulatory functions of mesenchymal stromal/stem cells mediated via paracrine activity. *J Clin Med*. 2019;8(7):1025. doi:10.3390/jcm8071025
20. Le Blanc K, Tammik L, Sundberg B, et al. Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. *Scand J Immunol*. 2003;57(1):11–20. doi:10.1046/j.1365-3083.2003.01176.x
21. Doorn J, Moll G, Le Blanc K, et al. Therapeutic applications of mesenchymal stromal cells: paracrine effects and potential improvements. *Tissue Eng Part B Rev*. 2012;18(2):101–115. doi:10.1089/ten.teb.2011.0488
22. Erkers T, Nava S, Yosef J, et al. Decidual stromal cells promote regulatory T cells and suppress alloreactivity in a cell contact-dependent manner. *Stem Cells Dev*. 2013;22(19):2596–2605. doi:10.1089/scd.2013.0079
23. Ringdén O, Moll G, Gustafsson B, et al. Mesenchymal stromal cells for enhancing hematopoietic engraftment and treatment of graft-versus-host disease, hemorrhages and acute respiratory distress syndrome. *Front Immunol*. 2022;13:839844. doi:10.3389/fimmu.2022.839844
24. Tran C, Damaser MS. Stem cells as drug delivery methods: application of stem cell secretome for regeneration. *Adv Drug Deliv Rev*. 2015;82–83:1–11. doi:10.1016/j.addr.2014.10.007
25. He J, Zhang N, Zhu Y, et al. MSC spheroids-loaded collagen hydrogels simultaneously promote neuronal differentiation and suppress inflammatory reaction through PI3K-Akt signaling pathway. *Biomaterials*. 2021;265:120448. doi:10.1016/j.biomaterials.2020.120448
26. Kuang S, He F, Liu G, et al. CCR2-engineered mesenchymal stromal cells accelerate diabetic wound healing by restoring immunological homeostasis. *Biomaterials*. 2021;275:120963. doi:10.1016/j.biomaterials.2021.120963
27. Kavanagh DP, Robinson J, Kalia N. Mesenchymal stem cell priming: fine-tuning adhesion and function. *Stem Cell Rev Rep*. 2014;10(4):587–599. doi:10.1007/s12015-014-9510-7
28. Moll G, Alm JJ, Davies LC, et al. Do cryopreserved mesenchymal stromal cells display impaired immunomodulatory and therapeutic properties? *Stem Cells*. 2014;32(9):2430–2442. doi:10.1002/stem.1729
29. Moll G, Geißler S, Catar R, et al. Cryopreserved or fresh mesenchymal stromal cells: only a matter of taste or key to unleash the full clinical potential of MSC therapy? *Adv Exp Med Biol*. 2016;951:77–98.
30. Afflerbach AK, Kiri MD, Detinis T, et al. Mesenchymal stem cells as a promising cell source for integration in novel in vitro models. *Biomolecules*. 2020;10(9):1306. doi:10.3390/biom10091306
31. Halim A, Ariyanti AD, Luo Q, et al. Recent progress in engineering mesenchymal stem cell differentiation. *Stem Cell Rev Rep*. 2020;16(4):661–674. doi:10.1007/s12015-020-09979-4
32. Langer R, Vacanti JP. Tissue engineering. *Science*. 1993;260(5110):920–926. doi:10.1126/science.8493529
33. Wang P, Zhao L, Chen W, et al. Stem cells and calcium phosphate cement scaffolds for bone regeneration. *J Dent Res*. 2014;93(7):618–625. doi:10.1177/0022034514534689
34. Brassard JA, Lutolf MP. Engineering stem cell self-organization to build better organoids. *Cell Stem Cell*. 2019;24(6):860–876. doi:10.1016/j.stem.2019.05.005
35. Wechsler ME, Rao VV, Borelli AN, et al. Engineering the MSC secretome: a hydrogel focused approach. *Adv Healthc Mater*. 2021;10(7):e2001948. doi:10.1002/adhm.202001948
36. Yin X, Mead BE, Safaee H, et al. Engineering Stem Cell Organoids. *Cell Stem Cell*. 2016;18(1):25–38. doi:10.1016/j.stem.2015.12.005
37. Swanson WB, Omi M, Zhang Z, et al. Macropore design of tissue engineering scaffolds regulates mesenchymal stem cell differentiation fate. *Biomaterials*. 2021;272:120769. doi:10.1016/j.biomaterials.2021.120769
38. Hiew SH, Wang JK, Koh K, et al. Bioinspired short peptide hydrogel for versatile encapsulation and controlled release of growth factor therapeutics. *Acta Biomater*. 2021;136:111–123. doi:10.1016/j.actbio.2021.09.023
39. Muslimov AR, Timin AS, Bichaykina VR, et al. Biomimetic drug delivery platforms based on mesenchymal stem cells impregnated with light-responsive submicron sized carriers. *Biomater Sci*. 2020;8(4):1137–1147. doi:10.1039/C9BM00926D
40. Mangir N, Roman S, MacNeil S. Improving the biocompatibility of biomaterial constructs and constructs delivering cells for the pelvic floor. *Curr Opin Urol*. 2019;29(4):419–425. doi:10.1097/MOU.0000000000000621
41. Giri TK, Alexander A, Agrawal M, et al. Current Status of stem cell therapies in tissue repair and regeneration. *Curr Stem Cell Res Ther*. 2019;14(2):117–126. doi:10.2174/1574888X13666180502103831
42. Ohnishi H, Oda Y, Ohgushi H. Stem cell technology using bioceramics: hard tissue regeneration towards clinical application. *Sci Technol Adv Mater*. 2010;11(1):014110. doi:10.1088/1468-6996/11/1/014110
43. Wen Y, Xun S, Haoye M, et al. 3D printed porous ceramic scaffolds for bone tissue engineering: a review. *Biomater Sci*. 2017;5(9):1690–1698. doi:10.1039/C7BM00315C
44. Sharma S, Soni VP, Bellare JR. Chitosan reinforced apatite-wollastonite coating by electrophoretic deposition on titanium implants. *J Mater Sci Mater Med*. 2009;20(7):1427–1436. doi:10.1007/s10856-009-3712-6
45. Liu X, Ding C. Plasma sprayed wollastonite/TiO2 composite coatings on titanium alloys. *Biomaterials*. 2002;23(20):4065–4077. doi:10.1016/S0142-9612(02)00143-6
46. Hurle K, Weichhold J, Brueckner M, et al. Hydration mechanism of a calcium phosphate cement modified with phytic acid. *Acta Biomater*. 2018;80:378–389. doi:10.1016/j.actbio.2018.09.002
47. Xia Y, Guo Y, Yang Z, et al. Iron oxide nanoparticle-calcium phosphate cement enhanced the osteogenic activities of stem cells through WNT/β-catenin signaling. *Mater Sci Eng C Mater Biol Appl*. 2019;104:109955. doi:10.1016/j.msec.2019.109955

48. Prati C, Gandolfi MG. Calcium silicate bioactive cements: biological perspectives and clinical applications. *Dent Mater*. 2015;31(4):351–370. doi:10.1016/j.dental.2015.01.004
49. Omar O, Engstrand T, Kihlström Burenstam Linder L, et al. In situ bone regeneration of large cranial defects using synthetic ceramic implants with a tailored composition and design. *Proc Natl Acad Sci U S A*. 2020;117(43):26660–26671. doi:10.1073/pnas.2007635117
50. Cancedda R, Bianchi G, Derubeis A, et al. Cell therapy for bone disease: a review of current status. *Stem Cells*. 2003;21(5):610–619. doi:10.1634/stemcells.21-5-610
51. Ohgushi H, Goldberg VM, Caplan AI. Repair of bone defects with marrow cells and porous ceramic. Experiments in Rats. *Acta Orthop Scand*. 1989;60(3):334–339. doi:10.3109/17453678909149289
52. Krebsbach PH, Mankani MH, Satomura K, et al. Repair of craniotomy defects using bone marrow stromal cells. *Transplantation*. 1998;66 (10):1272–1278. doi:10.1097/00007890-199811270-00002
53. Quarto R, Mastrogiacomo M, Cancedda R, et al. Repair of large bone defects with the use of autologous bone marrow stromal cells. *N Engl J Med*. 2001;344(5):385–386. doi:10.1056/NEJM200102013440516
54. Zakaria MY, Sulong AB, Muhamad N, et al. Incorporation of wollastonite bioactive ceramic with titanium for medical applications: an overview. *Mater Sci Eng C Mater Biol Appl*. 2019;97:884–895. doi:10.1016/j.msec.2018.12.056
55. Raza MR, Sulong AB, Muhamad N, et al. Effects of binder system and processing parameters on formability of porous Ti/HA composite through powder injection molding. *Mater Des*. 2015;87:386–392. doi:10.1016/j.matdes.2015.08.031
56. Gómez-Barrena E, Padilla-Eguiluz N, Rosset P, et al. Early efficacy evaluation of mesenchymal stromal cells (MSC) combined to biomaterials to treat long bone non-unions. *Injury*. 2020;51(Suppl 1):S63–S73. doi:10.1016/j.injury.2020.02.070
57. Gómez-Barrena E, Padilla-Eguiluz NG, García-Rey E, et al. Validation of a long bone fracture non-union healing score after treatment with mesenchymal stromal cells combined to biomaterials. *Injury*. 2020;51(Suppl 1):S55–S62. doi:10.1016/j.injury.2020.02.030
58. Shapiro L, Cohen S. Novel alginate sponges for cell culture and transplantation. *Biomaterials*. 1997;18(8):583–590. doi:10.1016/S0142-9612(96)00181-0
59. Saltz A, Kandalam U. Mesenchymal stem cells and alginate microcarriers for craniofacial bone tissue engineering: a review. *J Biomed Mater Res A*. 2016;104(5):1276–1284. doi:10.1002/jbm.a.35647
60. Orive G, Carcaboso AM, Hernández RM, et al. Biocompatibility evaluation of different alginates and alginate-based microcapsules. *Biomacromolecules*. 2005;6(2):927–931. doi:10.1021/bm049380x
61. Orive G, Tam SK, Pedraz JL, et al. Biocompatibility of alginate-poly-L-lysine microcapsules for cell therapy. *Biomaterials*. 2006;27 (20):3691–3700. doi:10.1016/j.biomaterials.2006.02.048
62. Xu L, Urita A, Onodera T, et al. Ultrapurified alginate gel containing bone marrow aspirate concentrate enhances cartilage and bone regeneration on osteochondral defects in a rabbit model. *Am J Sports Med*. 2021;49(8):2199–2210. doi:10.1177/03635465211014186
63. Choe G, Kim SW, Park J, et al. Anti-oxidant activity reinforced reduced graphene oxide/alginate microgels: mesenchymal stem cell encapsulation and regeneration of infarcted hearts. *Biomaterials*. 2019;225:119513. doi:10.1016/j.biomaterials.2019.119513
64. Lv K, Li Q, Zhang L, et al. Incorporation of small extracellular vesicles in sodium alginate hydrogel as a novel therapeutic strategy for myocardial infarction. *Theranostics*. 2019;9(24):7403–7416. doi:10.7150/thno.32637
65. Drzeniek NM, Mazzocchi A, Schlickeiser S, et al. Bio-instructive hydrogel expands the paracrine potency of mesenchymal stem cells. *Biofabrication*. 2021;13:4. doi:10.1088/1758-5090/ac0a32
66. Sahu N, Agarwal P, Grandi F, et al. Encapsulated mesenchymal stromal cell microbeads promote endogenous regeneration of osteoarthritic cartilage ex vivo. *Adv Healthc Mater*. 2021;10(8):e2002118. doi:10.1002/adhm.202002118
67. Muxika A, Etxabide A, Uranga J, et al. Chitosan as a bioactive polymer: processing, properties and applications. *Int J Biol Macromol*. 2017;105 (Pt 2):1358–1368. doi:10.1016/j.ijbiomac.2017.07.087
68. Younes I, Rinaudo M. Chitin and chitosan preparation from marine sources. Structure, properties and applications. *Mar Drugs*. 2015;13 (3):1133–1174. doi:10.3390/md13031133
69. Anitha A, Sowmya S, Kumar PT, et al. Chitin and chitosan in selected biomedical applications. *Prog Polym Sci*. 2014;39(9):1644–1667.
70. Bushkalova R, Farno M, Tenailleau C, et al. Alginate-chitosan PEC scaffolds: a useful tool for soft tissues cell therapy. *Int J Pharm*. 2019;571:118692. doi:10.1016/j.ijpharm.2019.118692
71. Sheehy EJ, Mesallati T, Vinardell T, et al. Engineering cartilage or endochondral bone: a comparison of different naturally derived hydrogels. *Acta Biomater*. 2015;13:245–253. doi:10.1016/j.actbio.2014.11.031
72. Bhat A, Dreifke MB, Kandimalla Y, et al. Evaluation of cross-linked chitosan microparticles for bone regeneration. *J Tissue Eng Regen Med*. 2010;4(7):532–542. doi:10.1002/term.270
73. Zwingenberger B, Vater C, Bell RL, et al. Treatment of critical-size femoral bone defects with chitosan scaffolds produced by a novel process from textile engineering. *Biomedicines*. 2021;9(8):1015. doi:10.3390/biomedicines9081015
74. Zhao X, Liu Y, Jia P, et al. Chitosan hydrogel-loaded MSC-derived extracellular vesicles promote skin rejuvenation by ameliorating the senescence of dermal fibroblasts. *Stem Cell Res Ther*. 2021;12(1):196. doi:10.1186/s13287-021-02262-4
75. Yin S, Cao Y. Hydrogels for large-scale expansion of stem cells. *Acta Biomater*. 2021;128:1–20. doi:10.1016/j.actbio.2021.03.026
76. Hasani-Sadrabadi MM, Sarrion P, Pouraghaei S, et al. An engineered cell-laden adhesive hydrogel promotes craniofacial bone tissue regeneration in rats. *Sci Transl Med*. 2020;12(534):eaay6853. doi:10.1126/scitranslmed.aay6853
77. Koh RH, Jin Y, Kim J, et al. Inflammation-modulating hydrogels for osteoarthritis cartilage tissue engineering. *Cells*. 2020;9(2):419. doi:10.3390/cells9020419
78. Jin R, Teixeira LS, Dijkstra PJ, et al. Enzymatically-crosslinked injectable hydrogels based on biomimetic dextran-hyaluronic acid conjugates for cartilage tissue engineering. *Biomaterials*. 2010;31(11):3103–3113. doi:10.1016/j.biomaterials.2010.01.013
79. Yan S, Wang T, Feng L, et al. Injectable in situ self-cross-linking hydrogels based on poly(L-glutamic acid) and alginate for cartilage tissue engineering. *Biomacromolecules*. 2014;15(12):4495–4508. doi:10.1021/bm501313t
80. Kim HD, Heo J, Hwang Y, et al. Extracellular-matrix-based and Arg-Gly-Asp-modified photopolymerizing hydrogels for cartilage tissue engineering. *Tissue Eng Part A*. 2015;21(3–4):757–766. doi:10.1089/ten.tea.2014.0233
81. Park H, Choi B, Hu J, et al. Injectable chitosan hyaluronic acid hydrogels for cartilage tissue engineering. *Acta Biomater*. 2013;9(1):4779–4786. doi:10.1016/j.actbio.2012.08.033

82. Jung HH, Park K, Han DK. Preparation of TGF-β1-conjugated biodegradable pluronic F127 hydrogel and its application with adipose-derived stem cells. *J Control Release*. 2010;147(1):84–91. doi:10.1016/j.jconrel.2010.06.020
83. Balakrishnan B, Joshi N, Jayakrishnan A, et al. Self-crosslinked oxidized alginate/gelatin hydrogel as injectable, adhesive biomimetic scaffolds for cartilage regeneration. *Acta Biomater*. 2014;10(8):3650–3663. doi:10.1016/j.actbio.2014.04.031
84. Hamidi M, Azadi A, Rafiei P. Hydrogel nanoparticles in drug delivery. *Adv Drug Deliv Rev*. 2008;60(15):1638–1649. doi:10.1016/j.addr.2008.08.002
85. Genovese P, Patel A, Ziemkiewicz N, et al. Co-delivery of fibrin-laminin hydrogel with mesenchymal stem cell spheroids supports skeletal muscle regeneration following trauma. *J Tissue Eng Regen Med*. 2021;15(12):1131–1143. doi:10.1002/term.3243
86. Saffari TM, Chan K, Saffari S, et al. Combined local delivery of tacrolimus and stem cells in hydrogel for enhancing peripheral nerve regeneration. *Biotechnol Bioeng*. 2021;118(7):2804–2814. doi:10.1002/bit.27799
87. He X, Wang Q, Zhao Y, et al. Effect of intramyocardial grafting collagen scaffold with mesenchymal stromal cells in patients with chronic ischemic heart disease: a randomized clinical trial. *JAMA Netw Open*. 2020;3(9):e2016236. doi:10.1001/jamanetworkopen.2020.16236
88. Kim K, Bou-Ghannam S, Kameishi S, et al. Allogeneic mesenchymal stem cell sheet therapy: a new frontier in drug delivery systems. *J Control Release*. 2021;330:696–704. doi:10.1016/j.jconrel.2020.12.028
89. Yamato M, Okano T. Cell sheet engineering. *Mater Today*. 2004;7(5):42–47. doi:10.1016/S1369-7021(04)00234-2
90. Zurina IM, Presniakova VS, Butnaru DV, et al. Tissue engineering using a combined cell sheet technology and scaffolding approach. *Acta Biomater*. 2020;113:63–83. doi:10.1016/j.actbio.2020.06.016
91. Shimizu T, Sekine H, Yang J, et al. Polysurgery of cell sheet grafts overcomes diffusion limits to produce thick, vascularized myocardial tissues. *FASEB J*. 2006;20(6):708–710. doi:10.1096/fj.05-4715fje
92. Baksh N, Gallant ND, Toomey RG. Cell sheet engineering for integrating functional tissue in vivo: successes and challenges. *MRS Bulletin*. 2017;5(42):350–355. doi:10.1557/mrs.2017.91
93. Long T, Zhu Z, Awad HA, et al. The effect of mesenchymal stem cell sheets on structural allograft healing of critical sized femoral defects in mice. *Biomaterials*. 2014;35(9):2752–2759. doi:10.1016/j.biomaterials.2013.12.039
94. Oka M, Sekiya S, Sakiyama R, et al. Hepatocyte growth factor-secreting mesothelial cell sheets suppress progressive fibrosis in a rat model of CKD. *J Am Soc Nephrol*. 2019;30(2):261–276. doi:10.1681/ASN.2018050556
95. Imafuku A, Oka M, Miyabe Y, et al. Rat mesenchymal stromal cell sheets suppress renal fibrosis via microvascular protection. *Stem Cells Transl Med*. 2019;8(12):1330–1341. doi:10.1002/sctm.19-0113
96. Iwata T, Yamato M, Washio K, et al. Periodontal regeneration with autologous periodontal ligament-derived cell sheets - A safety and efficacy study in ten patients. *Regen Ther*. 2018;9:38–44. doi:10.1016/j.reth.2018.07.002
97. Xuan K, Li B, Guo H, et al. Deciduous autologous tooth stem cells regenerate dental pulp after implantation into injured teeth. *Sci Transl Med*. 2018;10(455):eaaf3227. doi:10.1126/scitranslmed.aaf3227
98. Trounson A, McDonald C. Stem cell therapies in clinical trials: progress and challenges. *Cell Stem Cell*. 2015;17(1):11–22. doi:10.1016/j.stem.2015.06.007
99. Volponi AA, Pang Y, Sharpe PT. Stem cell-based biological tooth repair and regeneration. *Trends Cell Biol*. 2010;20(12):715–722. doi:10.1016/j.tcb.2010.09.012
100. Grayson WL, Bunnell BA, Martin E, et al. Stromal cells and stem cells in clinical bone regeneration. *Nat Rev Endocrinol*. 2015;11(3):140–150. doi:10.1038/nrendo.2014.234
101. Yamamoto K, Yamato M, Morino T, et al. Middle ear mucosal regeneration by tissue-engineered cell sheet transplantation. *NPJ Regen Med*. 2017;2:6. doi:10.1038/s41536-017-0010-7
102. Raghav PK, Mann Z, Ahlawat S, et al. Mesenchymal stem cell-based nanoparticles and scaffolds in regenerative medicine. *Eur J Pharmacol*. 2022;918:174657. doi:10.1016/j.ejphar.2021.174657
103. Corradetti B, Ferrari M. Nanotechnology for mesenchymal stem cell therapies. *J Control Release*. 2016;240:242–250. doi:10.1016/j.jconrel.2015.12.042
104. Xu J, Cai N, Xu W, et al. Mechanical enhancement of nanofibrous scaffolds through polyelectrolyte complexation. *Nanotechnology*. 2013;24(2):025701. doi:10.1088/0957-4484/24/2/025701
105. Sahu A, Jeon J, Lee MS, et al. Nanozyme impregnated mesenchymal stem cells for hepatic ischemia-reperfusion injury alleviation. *ACS Appl Mater Interfaces*. 2021;13(22):25649–25662. doi:10.1021/acsami.1c03027
106. Fan W, Yuan L, Li J, et al. Injectable double-crosslinked hydrogels with kartogenin-conjugated polyurethane nano-particles and transforming growth factor β3 for in-situ cartilage regeneration. *Mater Sci Eng C Mater Biol Appl*. 2020;110:110705. doi:10.1016/j.msec.2020.110705
107. Critchley S, Sheehy EJ, Cunniffe G, et al. 3D printing of fibre-reinforced cartilaginous templates for the regeneration of osteochondral defects. *Acta Biomater*. 2020;113:130–143. doi:10.1016/j.actbio.2020.05.040
108. Cantore S, Crincoli V, Boccaccio A, et al. Recent advances in endocrine, metabolic and immune disorders: Mesenchymal Stem Cells (MSCs) and engineered scaffolds. *Endocr Metab Immune Disord Drug Targets*. 2018;18(5):466–469. doi:10.2174/1871530318666180423102905
109. Trombetta R, Inzana JA, Schwarz EM, et al. 3D printing of calcium phosphate ceramics for bone tissue engineering and drug delivery. *Ann Biomed Eng*. 2017;45(1):23–44. doi:10.1007/s10439-016-1678-3
110. Lian M, Sun B, Han Y, et al. A low-temperature-printed hierarchical porous sponge-like scaffold that promotes cell-material interaction and modulates paracrine activity of MSCs for vascularized bone regeneration. *Biomaterials*. 2021;274:120841. doi:10.1016/j.biomaterials.2021.120841
111. Ji W, Hou B, Lin W, et al. 3D Bioprinting a human iPSC-derived MSC-loaded scaffold for repair of the uterine endometrium. *Acta Biomater*. 2020;116:268–284. doi:10.1016/j.actbio.2020.09.012
112. Li H, Xue K, Kong N, et al. Silicate bioceramics enhanced vascularization and osteogenesis through stimulating interactions between endothelia cells and bone marrow stromal cells. *Biomaterials*. 2014;35(12):3803–3818. doi:10.1016/j.biomaterials.2014.01.039
113. Shariatinia Z. Pharmaceutical applications of chitosan. *Adv Colloid Interface Sci*. 2019;263:131–194. doi:10.1016/j.cis.2018.11.008
114. Owaki T, Shimizu T, Yamato M, et al. Cell sheet engineering for regenerative medicine: current challenges and strategies. *Biotechnol J*. 2014;9(7):904–914. doi:10.1002/biot.201300432

115. Si YL, Zhao YL, Hao HJ, et al. MSCs: biological characteristics, clinical applications and their outstanding concerns. *Ageing Res Rev*. 2011;10(1):93–103. doi:10.1016/j.arr.2010.08.005
116. Jung JW, Kwon M, Choi JC, et al. Familial occurrence of pulmonary embolism after intravenous, adipose tissue-derived stem cell therapy. *Yonsei Med J*. 2013;54(5):1293–1296. doi:10.3349/ymj.2013.54.5.1293
117. Wagner W, Horn P, Castoldi M, et al. Replicative senescence of mesenchymal stem cells: a continuous and organized process. *PLoS One*. 2008;3(5):e2213. doi:10.1371/journal.pone.0002213
118. Tang Q, Chen Q, Lai X, et al. Malignant transformation potentials of human umbilical cord mesenchymal stem cells both spontaneously and via 3-methycholanthrene induction. *PLoS One*. 2013;8(12):e81844. doi:10.1371/journal.pone.0081844
119. Teng IW, Hou PC, Lee KD, et al. Targeted methylation of two tumor suppressor genes is sufficient to transform mesenchymal stem cells into cancer stem/initiating cells. *Cancer Res*. 2011;71(13):4653–4663. doi:10.1158/0008-5472.CAN-10-3418
120. Zhu Y, Song X, Wang J, et al. Placental mesenchymal stem cells of fetal origin deposit epigenetic alterations during long-term culture under serum-free condition. *Expert Opin Biol Ther*. 2015;15(2):163–180. doi:10.1517/14712598.2015.960837