MEDS Basic Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/medbm.2023.010215
ISSN 2616-2091 Vol. 1 Num. 2

Recent Advances in Mesenchymal Stem Cell-mediated Bone Regeneration

Yundong Fan[1,2,a], Guiquan Chen[1,2,b,*]

[1]School of Integrated Traditional Chinese and Western Medicine, Southwest Medical University, Luzhou, Sichuan, 646608, China
[2]Department of Acupuncture and Moxibustion, Rehabilitation Massage, The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University, Luzhou, Sichuan, 646000, China
[a]1305553701@qq.com, [b]chenguiquan1973@126.com
[*]Corresponding author

Keywords: Bone regeneration; mesenchymal stem cells (MSCs); osteogenic differentiation; microenvironment; angiogenesis

Abstract: Bone plays an important role in the normal physiological activities of the human body, such as mechanical support, organ protection and maintenance of mineral homeostasis. Different degrees of bone defects can lead to functional limitation and cosmetic deformity of patients and promoting bone regeneration ability is a current research focus. Among them, mesenchymal stem cells (MSCs) are a major research hotspot in the field of regenerative medicine in recent years and have been widely used in clinical studies of various bone tissue regeneration. Many studies have shown that the bone regeneration effect of MSCs can directly or indirectly improve the aging, migration, proliferation and differentiation of MSCs to promote bone regeneration and accelerate the process of bone repair by changing the microenvironment, reducing inflammatory infiltration, regulating the balance between bone and immune system, and increasing angiogenesis and regulating dysbacteriosis. This review summarizes the function and mechanism of MSCs in bone regeneration and repair. Understanding the mechanism behind will help understand the process of MSC-mediated bone remodeling and optimization of MSC-based therapy will guide the treatment of bone regeneration and provide new and customizable cell-based treatment strategies to promote bone regeneration in vivo.

1. Introduction

The bone is a unique organ with self-repair and regeneration ability. Bone regeneration is an extremely complex and well-coordinated process. Loss of bone repair ability can be caused by diseases such as trauma, cancer, infection, and arthritis. Delayed or stopped ability to fully heal may lead to permanent bone defects, which in turn lose the ability of related sites [1]. At present, treatment strategies for bone defects include non-surgical treatment and surgical treatment, which have shown different degrees of efficacy. They also have many unavoidable side effects, which may further cause cancer, stroke, and heart attack.

Mesenchymal stem cells (MSCs) have been confirmed to be involved in the entire

physiopathological process of bone regeneration and serve as a key candidate for cell therapy and regenerative medicine. They have several unique advantages compared with other cell therapies: They have a wide range of cell sources and exist in multiple tissues such as bone marrow, fat, muscle, tendon, umbilical cord, amniotic fluid, urine, and peripheral blood [2]; They have immune privilege potential and can be used to control immune-mediated inflammation and tissue rejection and there are few ethical problems in therapeutic [3]; The pluripotency of MSCs allows them to differentiate into the desired type of cells to achieve the purpose of cell replacement [4]. Previous studies have shown that MSCs are not only the cellular basis of osteogenesis, but also activators and fusions that release various factors or structural frameworks, making them the most promising cell source for promoting bone regeneration. MSCs promote bone regeneration at the damaged site [5]. Meanwhile, it has also been found that MSCs directly or indirectly improve the aging, migration, proliferation, and differentiation of MSCs to promote bone regeneration and accelerate the process of bone repair by changing the microenvironment, reducing inflammatory infiltration [6], regulating the balance between bone and immune system, increasing angiogenesis, and regulating dysbacteriosis [7]. Currently, it has been shown that transplanted MSCs are beneficial in the treatment of delayed union or nonunion of fractures.

According to data from www. ClinicalTrials. gov, MSCs are safe and effective in the treatment of a variety of diseases in completed clinical trials, including tissue regeneration and transplantation safety studies, bone and cartilage injury repair, neurological, vascular and cognitive dysfunction diseases, inflammatory enteritis, optic neuropathy, myocardial injury repair, gynecology-related diseases, and autoimmune diseases. MSCs are also characterized by convenience in sampling, rapid expansion, multilineage differentiation potential, low immunogenicity, and stable genetic background [8]. This review summarizes the relevant mechanisms of action in how MSCs promote bone regeneration and recent studies on interventions and diagnostic criteria to improve bone regeneration. Finally, we emphasize some questions that remain unanswered.

2. MSCs aging and bone regeneration

There is increasing recognition of the association between stem cell aging and bone regeneration and the underlying molecular mechanisms. It has been found that cellular senescence leads to pathophysiological aging of MSCs, which in turn leads to bone tissue dysfunction. Processes known to occur in normal aging, including genomic instability, mitochondrial dysfunction, telomere attrition, protein misfolding, dystrophy, and cellular senescence, are also implicated in the pathogenesis of bone regeneration [9]. Under sustained oxidative stress, the age-related genes p21 and p16 are upregulated and cell cycle arrest, proliferation restriction and telomere length shortening are observed. Besides, MSC pluripotency is compromised, such as relative imbalance in force balance, osteogenic and adipogenic differentiation [10]. Normal mitochondria can enhance the proliferation, migration and osteogenic differentiation of MSCs and promote the healing of bone defects [11]. With aging, the metabolic phenotype of aging-induced mitochondrial oxidative phosphorylation and decreased glycolysis may reduce the activity and differentiation potential of MSCs, while inhibition of mitochondrial oxidative phosphorylation enhances the status of stem cells in anaerobic or hypoxic environments [12]. In addition, it has been shown that inhibiting the expression of mitochondrial function blocks and NFATc1 expression induced by the key RankL signaling pathway that regulates osteoclasts can also enhance the regenerative capacity of MSCs [13]. Study has also demonstrated that active mitochondria promote osteogenic differentiation by promoting the differentiation and activity of β-catenin [14]. The above findings suggest that multiple mechanisms are involved in cellular aging of MCSs which may compromise bone regeneration.

3. MSCs and inflammation

Inflammation, as a protective response of tissues to noxious stimuli, not only eliminates noxious stimuli, but also initiates the healing process. Persistent chronic inflammation is one of the main causes of bone regeneration. Defect in intercellular exchange and inhibition of the natural process of resolution, or chronic inflammation due to persistent adverse stimuli can lead to impaired fracture healing. MSCs have been found to be involved in critical intercellular communication or crosstalk to regulate bone healing. Thus, the initial and optimal instantaneous stages of inflammation are one of the key factors for successful, robust bone healing [15]. It has been investigated that MSCs are activated and polarized in the inflammatory milieu of acute respiratory distress syndrome (ARDS) patients, shifting them toward a proinflammatory phenotype [16]. During bone regeneration or bone repair, the increase of pro-inflammatory cytokines such as IL-1, IL-4, IL-3, IL-6, IL-17a, IL-10, IL-22 and TNF-α leads to instability of the bone microenvironment, which affects the migration, repair, proliferation, and differentiation of MSCs [2,17]. Research evidence have shown that the adhesion and efficacy of MSCs in inflammatory arthritis can be regulated intraarticularly in mouse models, and inflammatory cells have anabolic effects on bone repair by recruiting MSCs and directing their migration and differentiation [18]. Evidence from clinical and in vivo studies suggests that increases in these cytokines lead to decoupling of bone remodeling through multiple mechanisms, including receptor activators that enhance NF-κB ligand expression, promoting osteoclast differentiation, activation, and survival; and inhibiting osteoblast survival and mineralization [19]. At the same time, impairment of anti-inflammatory capacity may lead to loss of therapeutic efficacy in bone regeneration.

4. Balance between osteogenic differentiation of MSCs and the immune system

MSCs are capable of self-renewal and have the ability to differentiate into multiple cell types, including chondrocytes, osteocytes, myocytes, and adipocytes. They have also received increasing attention as potential treatments for bone damage by secreting bioactive factors such as growth factors, chemokines, and cytokines to modulate immune responses and enhance tissue regeneration, thereby exhibiting immunomodulatory properties and tissue repair capacity [20]. Research findings reveal that coordinated cross-talk between immune cells and osteoblasts is considered a prerequisite for successful bone regeneration [21]. Because of the role of immune cells in bone dynamics, they have aroused increasing attention in bone tissue regeneration and repair. Among them, macrophages, as the main immunoregulatory cells, promote MSC migration to the fracture site by secreting a variety of cytokines, chemokines, and growth factors, and promote osteogenic differentiation of MSCs, which will remodel bone balance, and actively participate in bone formation and homeostasis [22]. At the same time, the interaction between MSCs and macrophages is complex. It has been found in MSC and macrophage co-culture experiments that communication between them may form a feedback loop through paracrine or/and paracrine soluble mediators, which not only affects the function of macrophages, but also affects the differentiation potential of MSCs [23]. It has also been confirmed that T cells are necessary in promoting bone resorption. The anti-proliferative effect mediated by MSCs is attenuated in T lymphocyte co-culture, and MSCs can exert immunomodulatory ability by increasing MCP-1 secretion and attracting chemotactic T lymphocytes and monocytes to migrate to the site of inflammation [24]. Studies have shown that the interaction between immune cells and bone morphogenetic cells may be regulated by the three-dimensional structure of the tissue, and continuous construction of new biomaterials activates or reproduces this spatial "crosstalk" between immune cells and bone morphogenetic cells during natural bone formation [25]. Recent studies have shown that enhancing the paracrine effect of MSCs can significantly improve the immune system, angiogenesis and osteogenic resorption, which may be one of the prerequisites for

successful fracture healing and bone regeneration. Others have shown that ex vivo expanded MSCs can promote the repair and regeneration of damaged tissues through their immunomodulatory effects [26], which confers the therapeutic efficacy of MSCs in various degenerative and inflammatory diseases. The immune system can be used as a therapeutic target for bone repair, and MSCs are considered to have broad prospects in the treatment of immune-related diseases. Currently it is necessary to gain more insight into the relationship between MSCs and the bone-immune system.

5. MSCs and angiogenesis

Co-cultures of MSCs and endothelial progenitor cells (ePCs) revealed that osteogenesis and angiogenesis are closely linked. Angiogenesis is a limiting factor in bone defect regeneration [27], and bone regeneration requires a lot of energy to support angiogenesis in addition to various cells, growth factors, chemokines, and stimuli. Besides, some researchers believe that the ability of MSCs to act as regenerative agents, which is independent of their ability to directly form new tissues, may due to interaction with endothelial cells and thus promote regeneration in bone [28]. However, MSCs from different sources differ significantly in angiogenic transcripts, highlighting the importance of reciprocal interference between local MSCs and endothelial cells in functional vascular networks in regenerating tissues. In co-culture, it was found that the expression of pluripotency factors OCT4, SOX2, Nanog and Klf4 (core regulators of cell stem cells) was up-regulated, further indicating that endothelial progenitor cells have a dynamic role in maintaining MSCs and regulating their differentiation potential, and have a positive effect on the osteogenic proliferation ability of MSCs [29]. It has also been shown that functional perfusion mediates osteoprogenitor cells and plays an important role in tissue regeneration and remodeling after promoting angiogenesis by recruiting hematopoietic stem cells (HSCs) and immune cells [30]. Among them, tissue repair and regeneration are directly regulated by VEGF, HGF, FGF and IL-10, which are of specific significance in vascularization, fibrosis remission, cell regeneration and inflammation mediation, respectively [31]. MSCs promote angiogenesis through different mechanisms of interaction. In addition, various studies have highlighted the importance of maintaining the microenvironment through the release of extracellular vesicles (EV) and are important for regenerative medicine [1], where MSCs are closely associated with driving angiogenesis.

6. MSCs and dysbacteriosis

According to studies, under infectious conditions, E. coli, Gram-negative bacteria, Gram-positive bacteria and other flora do not necessarily reduce MSCs controlled regeneration. LPS and peptidoglycan have been found to induce the canonical NFκB transcription factor p65 to activate TAZ expression, and TAZ interacts with RUNX2 to increase its transcriptional activity and inhibit PPARγ transcriptional activity. This may induce proliferation and osteogenic differentiation of MSCs to some extent and reduce adipogenic differentiation. LPS also inactivates the NLRP3 inflammasome and dose-dependently inhibits the function of MSCs, thereby accelerating the dysfunction of MSCs and delaying wound healing. Further studies have found that maintaining oral microbiota balance can enhance migration, osteogenic differentiation and cell proliferation of MSCs, regulate the physiological function of MSCs, and promote wound healing. Meanwhile, microbiota, LPS or IFN-γ promoted SCFA receptor expression in monocytes/macrophages (osteoclast-derived). SCFAs indirectly regulate bone remodeling by regulating circulating IGF-1 which, as a major fermentation product of the gut microbiota, can directly affect host cell function (e.g., T-cell differentiation) and is also thought to regulate many host endocrine molecules, including peptide YY (PYY), leptin, and serotonin, and directly or indirectly regulate the bone remodeling process [32]. In general, dysregulation of intestinal flora or invasion by other pathogenic microorganisms is the main cause of

intestinal inflammatory infiltration, and it has been suggested that there are differences in osteogenic potential when MSC is exposed to different flora conditions, which may be related to its mediated anti-inflammatory immune response [33]. When treated by LPS or Gram-negative Escherichia coli, MSCs have increased osteogenesis and reduced adipogenesis, while stimulation with Gram-positive Staphylococcus aureus reduces osteogenesis and adipogenesis, in which the production of pro-inflammatory cytokines, osteogenic differentiation-related protein/mRNA expression, and mineralized nodules are inhibited. In summary, these studies suggest that different microbiota and their virulence factors directly or indirectly affect MSC migration, proliferation, osteogenic differentiation [34], thereby affecting the balance of bone remodeling.

7. MSCs and the bone microenvironment

MSCs can modulate the microenvironment of host tissues, thereby promoting regenerative processes. According to a variety of studies, MSC treatment effects are due to their support of regenerative microenvironment and paracrine effects rather than their differentiation capacity [35]. MSC paracrine function is arguably one of their most clinically beneficial features, mediated by the secretion of countless pro-regenerative cytokines and subsequent paracrine activity in host tissues. Exosomes, as an important mediator for cell-cell signaling communication, are the most important paracrine form of stem cells and play a very important role in signal transmission between MSCs and affecting differentiation trends [36]. It has been found that in addition to inhibiting inflammatory responses and promoting angiogenesis, exosomes can promote bone formation by repairing the function of damaged MSCs and improving the activity of osteoblasts, indicating that exosomes are prospective therapeutic agent for osteoporosis [37]. Studies have shown that MSC-derived exosomes effectively ameliorate osteoporosis symptoms and promote MCS proliferation, osteogenic differentiation, and bone regeneration and immunoregulatory function [38]. With the deepening investigation of MSC-derived exosomes, many small RNAs have been found to be involved in the functional regulation of different stages of MSCs. Simulated miRNA-19b-3p transfection can promote the proliferation and osteogenic differentiation of MSCs, and knockdown of miR-128-3p gene can reverse adipogenic differentiation and migration of age-related MSCs and improve bone loss in aged mice [39]. In addition, miR-29a-loaded MSCs could serve as potential therapeutic targets for osteoporosis. MSCs-29a-derived MSCs directly regulate VASH1 to affect angiogenesis and osteogenesis [40]. Several studies have shown that MSCs can interact with the damaged microenvironment and shift the balance from toxic to protective regenerative events by releasing bioactive factors. These particular capabilities make them potentially effective treatments for bone regeneration. However, maintaining exosome retention and stability and resisting variation after in vivo transplantation of the microenvironment over time is one of the main directions for important clinical applications to enhance the therapeutic efficacy of MSC-derived secretions.

8. Conclusions and future perspectives

Currently, MSC-based therapy is considered as a state-of-the-art method for bone tissue regeneration. MSCs, as key candidates for regenerative medicine, especially bone regeneration, are the most common cell populations with strong proliferative and differentiation potential, anti-inflammatory, and immune privilege potential. They are stimulated to some extent by different stimuli (inflammatory factors, cytokines, growth factors, cell flora, especially exosomes), which can further affect the progression of bone remodeling (Figure 1). With the progress of research, it has been found that when transplanted into new living organisms, MSCs have limited proliferative potential, and the differentiation trend is affected by many factors. At the same time, it has been reported that when given systematically, MSCs can be entrapped around the microvascular system of the lung through

the pulmonary first-pass effect, which limit their access to the target apparatus, and provide low protective potential. Even before reaching the damaged site, with the increasing proportion of senescent cells and undesired inflammation, unpredictable consequences occur, further hindering bone regeneration. These factors may limit the widespread clinical use of MSCs. Further investigations of the mechanisms behind them will help understand the pathophysiology of MSCs and identify optimal cell-based therapies for the treatment of bone regeneration. Bone regeneration is a complex phenomenon involving cellular sources, scaffolds, tissue inducers (signaling factors), and mechanical stimuli. Basic and clinical studies together suggest that MSCs have added value in bone regeneration. However, the large differences in the source, dose, method, and outcome measures of MSCs make direct comparative studies difficult and future standardized studies are needed.

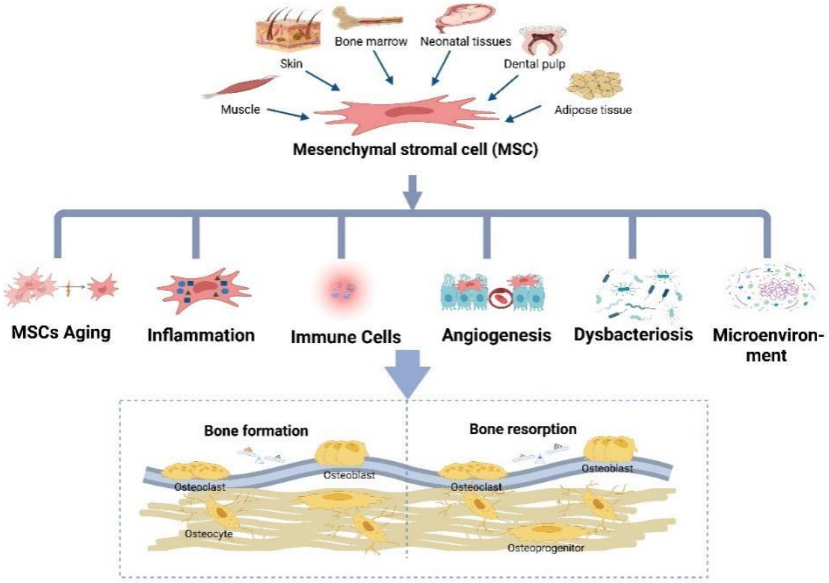

Figure 1: Proposed mechanism of salubrinal's action of MSC in bone remodeling. Salubrinal Different sources of MSC alter the senescence, proliferation, differentiation and migration properties of MSC by modulating cellular ageing, anti-inflammation, immune mechanisms, vascular renewal, flora regulation and altering the bone microenvironment to mediate bone remodeling homeostasis and promote bone regeneration, thereby reducing bone loss

Acknowledgements

This work was supported by Sichuan Science and Technology Project (2020YFS0382), and University level scientific research project of Southwest Medical University, China (ZYGD18014).

References

[1] Bouland Cyril, Philippart Pierre, Dequanter Didier, et al. Cross-Talk between Mesenchymal Stromal Cells (MSCs) and Endothelial Progenitor Cells (EPCs) in Bone Regeneration [J]. Frontiers in Cell and Developmental Biology, 2021, 9:674084-674084.

[2] Ortiz Adriana de Cássia, Fideles Simone Ortiz Moura, Pomini Karina Torres, et al. Effects of Therapy with Fibrin Glue combined with Mesenchymal Stem Cells (MSCs) on Bone Regeneration: A Systematic Review [J]. Cells, 2021, 10(9):2323-2323.

[3] Shan Zhifu, et al. Therapeutic effect of autologous compact bone-derived mesenchymal stem cell transplantation on prion disease [J]. The Journal of general virology, 2017, 98(10):2615-2627.

[4] Wang Jiechen, Guo Fengyuan, Chen Guangjin, et al. Spatial-Temporal Patterns and Inflammatory Factors of Bone Matrix Remodeling [J]. Stem Cells International, 2021, 2021:4307961-4307961.

[5] Liesveld Jane L, Sharma Naman, Aljitawi Omar S, et al. Stem cell homing: From physiology to therapeutics [J]. Stem

cells (Dayton, Ohio), 2020, 38(10):1241-1253.
[6] Li Hui, He Zihao, Li Wenjing, et al. Self-assembled microtissues loaded with osteogenic MSCs for in vivo bone regeneration [J]. Frontiers in Bioengineering and Biotechnology, 2022, 10:1069804.
[7] Pittenger Mark F, Discher Dennis E, Péault Bruno M, et al. Mesenchymal stem cell perspective: cell biology to clinical progress [J]. NPJ Regenerative medicine, 2019, 4(11):22.
[8] Arjmand Babak, Sarvari Masoumeh, Alavi-Moghadam Sepideh, et al. Prospect of Stem Cell Therapy and Regenerative Medicine in Osteoporosis [J]. Frontiers in endocrinology, 2020, 11:430.
[9] Juliana Redondo, Pamela Sarkar, Kevin Kemp, et al. Reduced cellularity of bone marrow in multiple sclerosis with decreased MSC expansion potential and premature ageing in vitro [J]. Multiple Sclerosis Journal, 2018, 24(7):919-931.
[10] Hu Meilin, Xing Liangyu, Zhang Li, et al. NAP1L2 drives mesenchymal stem cell senescence and suppresses osteogenic differentiation [J]. Aging cell, 2022, 21(2):e13551-e13551.
[11] Guo Yusi, Chi Xiaopei, Wang Yifan, et al. Mitochondria transfer enhances proliferation, migration, and osteogenic differentiation of bone marrow mesenchymal stem cell and promotes bone defect healing [J]. Stem cell research & therapy, 2020, 11(1):245.
[12] Li Xiaoyu, Wang Xue, Zhang Chunmei, et al. Dysfunction of metabolic activity of bone marrow mesenchymal stem cells in aged mice [J]. Cell proliferation, 2022, 55(3):e13191-e13191.
[13] Liu Fei, Yuan Yujia, Bai Lin, et al. LRRc17 controls BMSC senescence via mitophagy and inhibits the therapeutic effect of BMSCs on ovariectomy-induced bone loss [J]. Redox Biology, 2021, 43:101963-101963.
[14] Shares Brianna H, Busch Melanie, White Noelle, et al. Active mitochondria support osteogenic differentiation by stimulating β-catenin acetylation [J]. The Journal of biological chemistry, 2018, 293(41):16019-16027.
[15] Ma Maoxiao, Cui Guofeng, Liu Youwen, et al. Mesenchymal stem cell-derived extracellular vesicles, osteoimmunology and orthopedic diseases [J]. PeerJ, 2023, 11:e14677-e14677.
[16] Enes S. Rolandsson, McKenna D., dos Santos C., et al. Inflammatory microenvironment in ARDS patients polarize clinically utilized MSCs towards a pro-inflammatory MSC phenotype [J]. Cytotherapy, 2020, 22(5):S99-S99.
[17] Shen Huaishuang, Kushioka Junichi, Toya Masakazu, et al. Sex differences in the therapeutic effect of unaltered versus NFκB sensing IL-4 over-expressing mesenchymal stromal cells in a murine model of chronic inflammatory bone loss [J]. Frontiers in Bioengineering and Biotechnology, 2022, 10:962114-962114.
[18] Jones Fiona K., Stefan Andrei, Kay Alasdair G., et al. Syndecan-3 regulates MSC adhesion, ERK and AKT signalling in vitro and its deletion enhances MSC efficacy in a model of inflammatory arthritis in vivo [J]. Scientific Reports, 2020, 10(1):20487-20487.
[19] Qiao Wei, Wong Karen H M, Shen Jie, et al. TRPM7 kinase-mediated immunomodulation in macrophage plays a central role in magnesium ion-induced bone regeneration [J]. Nature communications, 2021, 12(1):2885-2885.
[20] Miclau Katherine, Hambright William S, Huard Johnny, et al. Cellular expansion of MSCs: Shifting the regenerative potential [J]. Aging cell, 2022, 22(1):e13759-e13759.
[21] Dietrich Jana, Ott Lolita, Roth Mathias, et al. MSC Transplantation Improves Lacrimal Gland Regeneration after Surgically Induced Dry Eye Disease in Mice [J]. Scientific reports, 2019, 9(1):18299.
[22] Shin Rita Lih Ying, Lee Chien Wei, Shen Oscar Yuan Jie, et al. The Crosstalk between Mesenchymal Stem Cells and Macrophages in Bone Regeneration: A Systematic Review [J]. Stem Cells International, 2021, 2021:8835156-8835156.
[23] Zhang Bingjun, Zhang Meng, Sun Yuhua, et al. Haversian bone-mimicking bioceramic scaffolds enhancing MSC-macrophage osteo-imunomodulation [J]. Progress in Natural Science: Materials International, 2021, 31:883-890.
[24] He Yifan, Qu Yan, Meng Bowen, et al. Mesenchymal stem cells empower T cells in the lymph nodes via MCP-1/PD-L1 axis [J]. Cell Death & Disease, 2022, 13(4):365-365.
[25] Lv Bin, Zhang Xing, Yuan Jishan, et al. Biomaterial-supported MSC transplantation enhances cell–cell communication for spinal cord injury [J]. Stem Cell Research & Therapy, 2021, 12(1):36-36.
[26] Mukherjee Shayanti, Darzi Saeedeh, Paul Kallyanashis, et al. Mesenchymal stem cell-based bioengineered constructs: foreign body response, cross-talk with macrophages and impact of biomaterial design strategies for pelvic floor disorders [J]. Interface focus, 2019, 9(4):20180089.
[27] Chen Wenchuan, Liu Xian, Chen Qianmin, et al. Angiogenic and osteogenic regeneration in rats via calcium phosphate scaffold and endothelial cell coculture with hBMSCs, hUCMSCs, hiPSC-MSCs and hESC-MSCs [J]. Journal of tissue engineering and regenerative medicine, 2018, 12(1):191-203.
[28] Shao F, Liu R, Tan X, et al. MSC Transplantation Attenuates Inflammation, Prevents Endothelial Damage and Enhances the Angiogenic Potency of Endogenous MSCs in a Model of Pulmonary Arterial Hypertension [J]. Journal of Inflammation Research, 2022, 15:2087-2101.
[29] Samaneh Keshavarz, Seyed Mahdi Nassiri, Vahid Siavashi, et al. Regulation of plasticity and biological features of endothelial progenitor cells by MSC-derived SDF-1 [J]. BBA - Molecular Cell Research, 2018, 1866(2):296-304.
[30] Schwarz Constanze S, Bucher Christian H, Schlundt Claudia, et al. Spatio-Temporal Bone Remodeling after Hematopoietic Stem Cell Transplantation [J]. International journal of molecular sciences, 2020, 22(1):267.
[31] Bou Ghannam Sophia, Kim Kyungsook, Grainger David W., et al. 3D cell sheet structure augments mesenchymal

stem cell cytokine production [J]. Scientific Reports, 2021, 11(1):8170-8170.
[32] Ren Yi, Su Shenping, Liu Xingyu, et al. Microbiota-derived short-chain fatty acids promote BMP signaling by inhibiting histone deacetylation and contribute to dentinogenic differentiation in murine incisor regeneration [J]. Stem cells and development, 2020, 29(18):1201-1214.
[33] Yu Jingjun, Chen Shuangshuang, Lei Shuang, et al. The effects of Porphyromonas gingivalis on the inflammatory and immune responses and osteogenesis of mesenchymal stem cells [J]. Stem cells and development, 2021, 30(24):1191-1201.
[34] Mohamad Fauzi Nuradilla, Shaw Claire, Foutouhi Soraya H., et al. Salmonella enhances osteogenic differentiation in adipose-derived mesenchymal stem cells [J]. Frontiers in Cell and Developmental Biology, 2023, 11:1077350-1077350.
[35] Chen Xiao, Liang Huaibin, Xi Zhiyu, et al. BM-MSC Transplantation Alleviates Intracerebral Hemorrhage-Induced Brain Injury, Promotes Astrocytes Vimentin Expression, and Enhances Astrocytes Antioxidation via the Cx43/Nrf2/HO-1 Axis [J]. Frontiers in cell and developmental biology, 2020, 8:302.
[36] Fu Xiaorong, Liu Ge, Alexander Halim, et al. Mesenchymal Stem Cell Migration and Tissue Repair[J]. Cells, 2019, 8(8):784-784.
[37] Jiang Yuhe, Zhang Ping, Zhang Xiao, et al. Advances in mesenchymal stem cell transplantation for the treatment of osteoporosis [J]. Cell proliferation, 2020, 54(1):e12956-e12956.
[38] Lu Guodong, Cheng Peng, Liu Ting, et al. BMSC-Derived Exosomal miR-29a Promotes Angiogenesis and Osteogenesis [J]. Frontiers in Cell and Developmental Biology, 2020, 8:608521-608521.
[39] Xu Tao, Luo Yongjun, Wang Jiaxing, et al. Exosomal miRNA-128-3p from mesenchymal stem cells of aged rats regulates osteogenesis and bone fracture healing by targeting Smad5 [J]. Journal of nanobiotechnology, 2020, 18(1):47.
[40] Lian Wei-Shiung, Wu Ren-Wen, Lee Mel S, et al. Subchondral mesenchymal stem cells from osteoarthritic knees display high osteogenic differentiation capacity through microRNA-29a regulation of HDAC4 [J]. Journal of molecular medicine (Berlin, Germany), 2017, 95(12):1327-1340.