Date: Feb 12, 2024

Dear Editor:

On behalf of all the contributing authors, I would like to express our sincere appreciations of your letter and reviewers' constructive comments concerning our article entitled "Interplay between mesenchymal stem cells and macrophages: promoting bone tissue repair" (Manuscript No: 91531). These comments are all valuable and helpful for improving our article. According to the reviewers' comments, we have made extensive modifications to our manuscript to make the article more accurate and comprehensive. The reviewer comments are laid out below in italicized font and specific concerns have been numbered. In the revised version, changes to our manuscript were all highlighted within the document by using yellow colored.

We have given a serious response to the professional opinion of reviewers and hope the editorial office can consider this article.

Thank you for your attention.

Sincerely yours,

Jitian Li, MD, PhD

Email address: jitianlee@hotmail.com

Reviewer #1:

1. The authors should check the journal format to properly restructure this manuscript. See below, for example, the discussion section is not necessary. In fact, the discussion section should be replaced by a Future perspectives and challenges section.

Thank you for your advice. We have carefully revised the relevant content.

2. ***"and the immune response to tissue damage determines the speed and outcome of tissue healing[1]." In this phrase another reference is needed to support all the information in the phrase.***

Thank you for your advice. We have removed the reference here and changed it to a more appropriate reference.

3. ***"On these bases, the osteogenesis mediated by MSCs ……. bone homeostasis and bone remodeling together." The reference is missing here.***

Thank you for your advice. We have added the appropriate references here.

4. ***"They also promote bone tissue formation by secreting bone morphogenetic protein-2 (BMP-2) and other osteogenic marker proteins[9]." The reference 9 does not contain information related to BMP-2. Please add the appropriate reference.***

Thank you for your advice. We have re-edited the relevant sections and added appropriate citations.

5. ***"THE ROLES OF MSCs TO MACROPHAGES". This section should have its references, respectively.***

Thank you for your advice. We have added the appropriate references in this section.

6. ***"MSCs express various bioactive factors such as vascular endothelial growth factor-A (VEGF-A), PGE2, and NO through exosomes, which may promote macrophages recruitment by endocytosis[14]."The reference 14 does not contain information related to VEGF-A, PGE2, and***

NO. Please add the appropriate reference.
Thank you for your advice. We have removed the reference here and changed it to a more appropriate reference.

7. ***".....such as secreting hepatocyte growth factor (HGF) and IDO to inhibit T cell proliferation and induce T cell apoptosis[5,36]." The reference 5 belongs to an article original, but IDO acronym is only cited in this reference. Please add the appropriate reference.***
Thank you for your advice. We have re-edited the relevant sections and added appropriate citations.

8. ***"M2 macrophages secrete anti-inflammatory factors such as IL-4, IL-10, and TGF-β to prevent excessive activation of inflammatory responses[40]." The reference 40 does not contain information related to TGF-β. Please add another one.***
Thank you for your advice. We have added the appropriate references here.

9. ***"The phosphorylated STAT3 translocates to the nucleus, where it activates the expression of RANKL, ……. osteoclast differentiation through its action on TNF-α[68]." The reference 68 is not appropriate for the phrase. Please add the appropriate one.***
Thank you for your advice. We have removed the reference here and changed it to a more appropriate reference.

10. ***"L-4 inhibits the transcription factor NFATc1, weakening RANKL-induced OCs formation[33]." The reference 33 does not contain information related to NFATc1 and RANKL. Please add the appropriate one.***
Thank you for your advice. We have removed the reference here and changed it to a more appropriate reference.

11. ***"IL-3 can also reduce the expression of c-fos, inhibit OCs formation, and bone absorption[70]." The reference 70 does not contain information related to IL-3 and c-fos. Please add the appropriate one.***
Thank you for your advice. We have removed the reference here and changed it to a more appropriate reference.

12. ***".....activating signal molecules drosophila mothers against decapentaplegic homologue (SMAD) in OBs to promote the osteogenic function of MSCs[68]." Please add another SMAD-related reference because reference 68 does not contain SMAD-related information.***
Thank you for your advice. We have removed the reference here and changed it to a more appropriate reference.

13. ***"Denise Philipp et al discovered that the immunosuppressive effect of MSCs ……, thus significantly enhancing the immune regulatory capabilities of MSCs[40]." The reference 40 do not belong to Philipp.***
Thank you for your advice. We have removed the reference here and changed it to a more appropriate reference.

14. ***"The depletion of macrophages can lead to a decrease in MSCs, …….. M2***

macrophages can promote MSCs osteogenic differentiation and accelerate the bone repair." The reference is missing here.
Thank you for your advice. We have added the appropriate references here.

15. ***"Formation of the basic multicellular unit for bone tissue" This heading should have its references, respectively.***
Thank you for your advice. We have added the appropriate references in this section.

16. ***Please cite as Chang et al. found that……..instead of Chang MK et al found that…. Apply to all authors cited in this way.***
Thank you for your advice. We modified all the relevant reference sections in this way.

17. ***At the end of the following phrase: "Macrophages can secrete different active factors to regulate the immune microenvironment and affect the biological functions of MSCs through the polarization of their own phenotypes (Figure 1)." Please add the references which were considered to design the figure 1. In addition, the authors should change the words Polarization and Viability with downward orientation.***
Thank you for your advice. We have added the relevant references for figure 1 and made adjustments to the content of this figure.

18. ***In the next phrase: "Chemokines were considered to be chemotactic agents for immune cells,....." Please change the verb were to verb are.***
Thank you for your advice. We have corrected the incorrect writing.

19. ***The following heading is a little confusing: "Mediate the phenotypic transformation of macrophages." Who mediate? The same situation for the next headings: "Mediate the immunomodulatory activity of MSCs.", "Regulate the differentiation of MSCs.", "THE ROLE OF BOTH IN THE PROCESS OF BONE TISSUE REPAIR".***
Thank you for your advice. We have changed all the relevant titles.

20. ***Please define the acronym EVs in the next: "MSC-EVs can transfer miR-223-3p,....."***
Thank you for your advice. We have defined the acronym EVs.

21. ***Please write matrix metalloproteinase 1 (MMP1) instead of matrix metallo proteinase 1 (MMP1).***
Thank you for your advice. We have corrected the incorrect writing.

22. ***At the end of the following phrase: "Due to the roles of macrophages in bone, cartilage, and fat formation, they are considered potential targets for the treatment of various related diseases such as bone defects, osteoarthritis, and vascular diseases (Figure 2)." Please add the references which were considered to design the figure 2. In addition, it is not clear which type of cells (red) secrete OPG, RUNX2, ALPL, etc (Name should be added).***
Thank you for your advice. We have added the relevant references for figure 2 and made adjustments to the content of this figure.

23. ***The authors should review if it was correct to use the word absorption instead of the word resorption. For example: "Bone repair and remodeling are processes of "activation-absorption-formation".....", ".....and participating in metabolism related to bone absorption and bone formation." The reference is also missing here. "RANKL serves as a bridge between the inflammatory response and bone absorption." Wherever necessary.***

Thank you for your advice. We have substituted the word "resorption" for "absorption" in all corresponding places in the text.

24. ***I suggest designing a figure related to the header "Mesenchymal stem cells and macrophages in the process of bone tissue repair". According to the information considered in the manuscript.***

Thank you for your advice. We designed the figure 3 in relation to MSCs and macrophages during bone tissue repair.

Name of Journal: *World Journal of Stem Cell*
Manuscript Type: REVIEW

Interplay between mesenchymal stem cells and macrophages: promoting bone tissue repair.

Feifan Z *et al*. Bone repair: MSCs- macrophages synergy

Feifan Zhang, Yang Hao, Kuaixiang Zhang, Jiangjia Yang, Zhiqiang Zhao, Hongjian Liu, Jitian Li

Feifan Zhang, Jiangjia Yang, Jitian Li, Hunan University of Chinese Medicine, Changsha 410208, Hunan Province, China

Yang Hao, Kuaixiang Zhang, Jitian Li, Henan University of Chinese Medicine, Zhengzhou 450046, Henan Province, China

Hongjian Liu, Department of Orthopedics, the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Feifan Zhang, Yang Hao, Kuaixiang Zhang, Jiangjia Yang, Zhiqiang Zhao, Jitian Li, Henan Luoyang Orthopedic Hospital (Henan Provincial Orthopedic Hospital), Zhengzhou 450000, Henan Province, China

Author contributions: Feifan Z wrote the paper; Yang H, Kuaixiang Z, Jiangjia Y and Zhiqiang Z perfomed the collected the data; Manli L, Hongjian L and Jitian L responsible for review and revision, all authors read and approved the final manuscript.

Supported by the National Key Research and Development Program of China (Grant No. 2023YFC2508806), Key Research and Development Project in Henan Province (Grant No. 231111310500), Young Elite Scientists Sponsorship Program by CAST (Grant No. 2021-

QNRC2-A06), Scientific Research Project of Henan Zhongyuan Medical Science and Technology Innovation and Development Foundation (Grant No. ZYYC2023ZD), Youth Science Award Project of the Provincial-level Joint Fund for Science and Technology Research and Development Project in Henan Province (Grant No. 225200810084), Special Project on Training Top Talents in Traditional Chinese Medicine in Henan Province (Grant No. 2022ZYBJ24), and 2023 Hunan University of Chinese Medicine Postgraduate Innovation Project (Grant No. 2023CX64).

Corresponding author: Jitian Li, PhD, Chief Physician, Doctor, Henan Luoyang Orthopedic Hospital (Henan Provincial Orthopedic Hospital), No. 100 Yongping Road, Zhengzhou 450000, Henan Province, China. jitianlee@hotmail.com

Jitian Li, PhD, Chief Physician, Doctor, Hunan University of Chinese Medicine, No. 100 Xueshi Road, Changsha 410208, Hunan Province, China. jitianlee@hotmail.com

Jitian Li, PhD, Chief Physician, Doctor, Henan University of Chinese Medicine, No. 156 Jinshui East Road, Zhengzhou 450046, Henan Province, China. jitianlee@hotmail.com

Abstract

The repair of bone tissue damage is a complex and well-orchestrated process in time and space, which has always been a focus and difficulty in orthopedic treatment. In recent years, the success of mesenchymal stem cells (MSCs)-mediated bone repair in clinical trials of large-area bone defects and bone necrosis has made it a candidate in bone tissue repair engineering and regenerative medicine. Studies have shown that MSCs were closely related to macrophages. On one hand, MSCs regulate the immune regulatory function by influencing macrophages proliferation, infiltration, and polarization of phenotypes, as well as affecting the osteoclast differentiation of macrophages. On the other hand, macrophages activate MSCs and mediate the multilineage differentiation of MSCs by regulating the immune microenvironment. The cross-talk between MSCs and macrophages plays a crucial role in regulating the immune system and promoting tissue regeneration. Making full use

of the relationship between MSCs and macrophages will enhance the efficacy of MSCs therapy in bone tissue repair, as well as provide a reference for the further application of MSCs in other diseases.

Key words: Mesenchymal stem cells; macrophages; Inflammation; Bone tissue damage; Tissue regeneration

Core tip: Bone regeneration has always been a challenge and priority in the treatment of orthopedic diseases. The interaction between MSCs and macrophages mediating the multilineage differentiation potential and immunomodulatory capabilities plays a crucial role in bone tissue repair and remodeling. Therefore, we reviewed the interactions between MSCs and macrophages, summarized the roles and potential of MSCs and macrophages in bone tissue regeneration, and looked forward to how to better utilize their relationship to enhance the efficacy of MSCs therapy in orthopedic diseases such as bone defects and osteoarthritis.

INTRODUCTION

The destruction of bone tissue caused by violent injuries and chronic inflammation is an important pathological lesion in various orthopedic diseases such as bone defects, osteoarthritis, and osteoporosis. The repair of bone tissue damage is a complex and well-designed spatiotemporal process, which has always been the focus and difficulty of orthopedic treatment. Inflammation, tissue repair, and tissue remodeling are three important stages of tissue regeneration, involving the participation of various types of cells and strict regulation. Immune system plays a core role in tissue repair and regeneration, and the immune response to tissue damage determines the speed and outcome of tissue healing[1][~~1~~]. Mesenchymal stem cells (MSCs) and macrophages are the sources of bone tissue, in addition to the observation that MSCs and macrophages play important collaborative roles in immune regulation and bone tissue regeneration as "regulators" and "effectors" of the inflammatory response[2]. MSCs mediate the polarization of macrophages phenotypes involved in immune regulation of the body, and the pro-inflammatory and anti-inflammatory factors secreted by polarized macrophages mediate the biological functions of MSCs such as adhesion, migration, immune activity, and osteogenic activity. On these bases, the osteogenesis mediated by MSCs and the ~~bone absorption~~bone resorption mediated by macrophages-derived osteoclasts (OCs) maintain bone homeostasis and bone remodeling together[3].

MSCs, versatile and plastic effector cells, play multiple roles in bone tissue repair and regeneration. On one hand, as a pluripotent stem cell, MSCs have the abilities to self-renew and differentiate into multiple lineages. Under the influence of injury signals and chemokines, MSCs migrate to the site of injury, differentiate directionally, and secrete various growth factors such as transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), stromal cell-derived factor-1 (SDF-1), fibroblast growth factor (FGF), etc., to promote cell homing, stimulate tissue regeneration[4,5][~~2,3~~]. Factors in the injured environment, such as interferon gamma (IFN-γ) and tumor necrosis factor-α (TNF-α), stimulate the multilineage differentiation potential of MSCs, including osteogenic, adipogenic, and angiogenic differentiation, forming the various cells required for tissue repair[5][~~3~~]. On the other hand, as the first line of defense of the innate immune system, MSCs maintain the stability of the tissue

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microenvironment through the control of the inflammatory cascade [6]. MSCs can be activated by biomarkers in the inflammatory environment and respond to these signals through homing or paracrine effects, secreting soluble factors such as prostaglandin E2 (PGE2), TGF-β1, indoleamine 2,3-dioxygenase (IDO), IL-6, and IL-10, as well as proteins and RNAs that control macrophages differentiation and promote the anti-inflammatory phenotype transformation of macrophages to inhibit uncontrolled immune responses[4,5,7-11][~~2-8~~].

~~Macrophages show two phenotypes: pro-inflammatory M1 and anti-inflammatory M2. The plasticity of macrophages leads to a change in the balance between pro-inflammatory factors and anti-inflammatory factors. Various external stimuli, such as TNF-α, significantly alter the gene expression of resident macrophages and activate them. The conversion between the two phenotypes of macrophages plays an essential role in the progression and resolution of inflammation. They also promote bone tissue formation by secreting bone morphogenetic protein 2 (BMP-2) and other osteogenic marker protein*[9]. Chang MK *et al* found that osteal tissue macrophages can regulate osteoblasts (OBs) function *in vitro* and *in vivo*, which may be closely related to the formation of osteocalcin and the calcification of OBs.[10]~~ Macrophages, as important innate immune cells, are closely related to cells involved in bone tissue repair and regeneration [12]. In addition to being responsible for clearing cells and cell fragments after tissue damage, as well as invading organisms, macrophages also have a functional plasticity [13,14]. Macrophages play different roles at various stages of tissue repair, regulating inflammation by secreting pro-inflammatory and anti-inflammatory factors, and simultaneously secreting various biologically active factors such as chemokines, matrix metalloproteinases, growth factors, and osteogenesis-related proteins, which affect the recruitment, migration, proliferation, and differentiation of various tissue repair-related cells, including MSCs [15-19]. Studies have shown that the reduction of macrophages can lead to the disruption of the tissue microenvironment and the extension of tissue healing time [20]. Due to the critical role of macrophages in tissue repair, they have grown up to be a potential target for therapeutic tissue regeneration strategies.

In this article, based on the importance of the immune response in the repair of bone tissue damage, we explored the dual role of MSCs and macrophages in mutual regulation to

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maintain different functional phenotypes in immune regulation and bone regeneration, then discussed the prospects of this role in bone tissue repair.

BIDIRECTIONAL INTERACTION BETWEEN MSCs AND MACROPHAGES

MSCS can interact with macrophages to mutually regulate the host microenvironment. MSCs can promote the basic functions of macrophages and mediate the polarization of macrophages phenotypes. Macrophages can secrete different active factors to regulate the immune microenvironment and affect the biological functions of MSCs through the polarization of their own phenotypes (Figure 1)[4,21-43].

THE ROLES OF MSCs TO MACROPHAGES

Macrophages are an important part of the human immune system, whose polarization states and biological function changes of macrophages are closely related to the occurrence and development of various diseases[12]. Proteins, RNA, chemokines and other regulatory factors produced by MSCs enter macrophages through endocytosis, regulating macrophages genes expression, functional phenotype, and also physiological and pathological states[44,45]. By mediating macrophages phenotype and function, MSCs participate in regulating inflammation, tissue healing, immune diseases, tumor growth, and other biological processes, playing an important role in the treatment of orthopedic diseases, respiratory diseases, urological diseases, etc[17].

MSCs ~~Promote~~ promote the recruitment of macrophages

MSCs promote macrophages recruitment by interacting with macrophages. Chemokines ~~were~~are considered to be chemotactic agents for immune cells, and macrophages play a key role in inflammatory responses by migrating along an increased chemokine gradient signal. C-C motif chemokine ligand 2 (CCL2) is an inflammatory chemokine that can regulate the recruitment of immune cells during inflammation[46]~~[11]~~. The release of CCL2 by MSCs and its binding to C-C motif chemokine receptor 2 (CCR2) may increase intracellular calcium ion influx through the JAK/STAT1/STAT3 signaling pathway, activate important inflammatory signaling cascades, and promote the recruitment and infiltration of macrophages[47,48]~~[12,13]~~. MSCs express various bioactive factors such as vascular endothelial

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growth factor ~~-A~~ (VEGF ~~-A~~), PGE2, and NO through exosomes, which may regulate~~promote~~ macrophages recruitment by endocytosis [22,23][14]. Additionally, studies have shown that apoptosis of MSCs can inhibit macrophages recruitment. Research conducted by Zheng C and colleagues revealed that apoptotic MSCs release apoptotic vesicles (apoV), which are engulfed by macrophages and induce macrophages reprogramming at the transcriptional level, inhibiting the production of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8, thus inhibit the accumulation of macrophages. This mechanism involves the autocrine or paracrine action of MSCs' TGF-β[49][15].

MSCs ~~Enhance~~ enhance the phagocytic ability of macrophages

MSCs can secrete a variety of active ingredients to regulate the phagocytic ability of macrophages. TGF-β secreted by MSCs can stimulate the polarization of macrophages to M2 type and enhance their phagocytic ability through AKT/forkhead box transcription factor O1 (FoxO1) signaling pathway [24]. miR-466 secreted by MSCs increases the phagocytic ability of macrophages by downregulating the TIRAP-MyD88-NF-κB signaling pathway[25][16]. Scavenger receptor (SR) is a receptor related to phagocytic function on macrophages with extensive ligand binding ability. After interacting with macrophages, MSCs can upregulate the expression of scavenger receptors in macrophages, enhance their phagocytic ability against microbes, and reduce further stimulation of immune cells by invading microbes [26][17]. In addition, mitochondria of MSCs also play an important role in regulating macrophages function. Studies have found that MSCs can transfer mitochondria to macrophages through tunneling nanotube (TNT)-like structures, which not only promotes the oxidative phosphorylation of macrophages but also enhances their phagocytic ability[50][18].

MSCs ~~Mediate~~ mediate the phenotypic transformation of macrophages

Studies have shown that MSCs primarily regulate macrophages through paracrine effects, direct cell contact, mitochondrial transfer, and cell burial. The mechanism mediated by paracrine factors such as cytokines and hormones are the main pathway for MSCs to participate in tissue damage repair. Macrophages, derived from monocytes, are involved in innate immunity and cell-mediated immunity in the body and can be activated into M1 and

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M2 subtypes. Increasing evidence suggests that extracellular vesicles secreted by MSCs play a key role in regulating the balance of M1/M2, but the exact mechanism is not yet clear[51][19]. Pleiotropic hormones (PTN) are critical regulators of macrophages differentiation, and MSCs maintain the M2-like phenotype by secreting PTN to regulate the syndecan-3 (Sdc3) receptor-mediated cell adhesion molecule pathway[30][20]. Liu *et al* found that thrombospondin-1 (THBS-1) secreted by MSCs could induce the activation of TGF-β and stimulate the polarization of macrophages to the M2 phenotype[31][21]. In addition, other microRNAs through extracellular vesicles, affect the levels of transcriptional, post-transcriptional, and metabolic macrophages, regulating their function and phenotype, and participating in the physiological and pathological processes of diseases. Mesenchymal stem cell-derived small extracellular vesicles (MSC-EVs)~~MSC-Evs~~ can transfer miR-223-3p, miRNA-~~299~~124-3p, miRNA-~~148a~~125a~~, miR-216a-5p~~, etc., to macrophages, change gene expression and biological activity, and promote the polarization of macrophages from M1 to M2 anti-inflammatory phenotype[28,52,53]. Abe~~Y~~ *et al* found that MSCs could release paracrine factors through cell-cell contact, further inducing the polarization of macrophages from M1 to M2, and significantly reducing the expression of pro-inflammatory factors such as IL-6 and TNF-α[29,54][22,23]. Lu~~D~~ *et al* found that extracellular vesicles derived from MSCs (MSCs-EVs) could promote the polarization of macrophages M2 after transferring mitochondria to macrophages[55][24]. Ghahremani~~-Piraghaj M~~ *et al* found that the apoptotic vesicles of MSCs were engulfed by macrophages, promoting the polarization of macrophages M2, and reducing the production of TNF-α and NO, and increasing the level of IL-10[56][25].

THE EFFECTS OF MACROPHAGES ON MSCs

The functional phenotype and secretory profile of MSCs, as well as their availability, are regulated by the microenvironment, which determines their tissue repair capabilities. Multiple studies have shown that while MSCs regulate macrophages, the change in the polarization phenotype of macrophages also affects the biological activity and function of MSCs.

Macrophages ~~Affect~~ affect the migration and viability of MSCs

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Homing is one of the three major mechanisms of MSCs. In the damaged microenvironment, various chemokines, adhesion factors, and growth factors bind to receptors on the surface of MSCs, driving MSCs to migrate directionally to inflammatory or damaged areas and participate in tissue repair. There is an indispensable relationship between multiple chemokines and MSCs homing. There are various chemokine receptors on MSCs, such as CCR4, CCR7, CCR9, CXCR6, and stromal cell-derived factor-1α (SDF1a)[57-59][~~14,26,27~~]. The most studied is the SDF-1/CXCR4 axis, whose main functions include regulating the transplantation, chemotaxis, and homing of precursor cells to damaged sites, and it is a key signal mediating the migration and distribution of MSCs[60][~~28~~]. Numerous studies have shown that IL-1β has an important impact on the migration activity of MSCs. IL-1β can enhance the expression of CXCR4 and matrix metallo–proteinase 1 (MMP1) on MSCs, thereby promoting the endogenous recruitment of MSCs[33,61][~~29,30~~]. TNF-α was considered as a promoter of MSCs, and the anti-inflammatory IL-10 secreted by macrophages can enhance the promoting effect of TNF-α. Leucine-rich alpha-2-glycoprotein 1 (LRG1) is a proangiogenic protein that can promote the adhesion and migration of MSCs. TNF-α secreted by pro-inflammatory M1 macrophages can induce the secretion of LRG1, recruit MSCs, and promote angiogenesis and new bone formation[62][~~31~~]. Studies have shown that under hypoxic conditions, exosomes produced by macrophages M1 phenotype polarization can significantly reduce the viability and migration of MSCs, and induce MSC apoptosis by transporting miR-222 into MSCs[63][~~32~~]. High mobility group box 1 (HMGB1), NF-κB, and other inflammatory factors secreted by macrophages in the inflammatory microenvironment of bone injury have been confirmed to enhance the ability of MSCs attachment and migration via Rap1 activation[64-66][~~33-35~~]. In addition, macrophages also have a certain regulatory role on the proliferation ability of MSCs. IL-1β, IL-6, TNF-α, and IFN-γ secreted by M1 macrophages can inhibit the proliferation of MSCs, while IL-10, TGF-β1, TGF-β3, and VEGF secreted by M2 can promote the proliferation of MSCs[4,5][~~2,3~~].

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Macrophages ~~Mediate~~ mediate the immunomodulatory activity of MSCs

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During the organizational repair process, the interaction between MSCs and immune cells is necessary for activating the immune regulatory activity of MSCs. On the one hand, the immunomodulatory ability of MSCs is triggered by the inflammatory environment. The

changes in macrophages functional phenotype play an essential regulatory role in the inflammatory environment. Inflammatory factors released by M1 macrophages, such as ~~IFN-γIL-1 and IL-6~~, can activate the immune regulatory properties of MSCs, promoting the regulatory activity of MSCs on immune cells, such as secreting ~~hepatocyte growth factor (HGF) and~~ IDO to inhibit T cell proliferation and induce T cell apoptosis[35][~~5,36~~]. Anti-inflammatory factors produced by M2 macrophages, such as IL-10, can enhance the promoter activity of TNF-α, a pro-inflammatory cytokine, in MSCs, reducing the expression of inflammatory factors such as IL-6 and IFN-γ[27][~~37~~]. On the other hand, MSCs have poor survival ability in inflammatory areas, mainly through paracrine chemokines, growth factors, and cytokines, or direct contact to regulate macrophages polarization, resulting in anti-inflammatory or immunosuppressive effects, and playing an immune regulatory role. Exosomes derived from MSCs can significantly enrich miR-216a-5p in macrophages by transferring it, activate the HMGB1/ Toll-like receptor 4 (TLR4)/NF-κB signaling pathway, and promote the conversion of macrophages to M2 macrophages[67,68][~~38,39~~]. M2 macrophages secrete anti-inflammatory factors such as IL-4, IL-10, and TGF-β to prevent excessive activation of inflammatory responses[34,36][~~40~~].

Macrophages ~~Regulate~~ regulate the differentiation of MSCs

In 1999, scientists including Pittenger successfully induced the differentiation of MSCs into OBs, chondrocytes, and adipocytes *in vitro*[38][~~41~~]. Subsequently, scientists discovered the potential of MSCs to differentiate into muscle, ligament, endotheliocyte and hepatocytes among other cell types[38,51,69-71][~~19,41-44~~]. Multiple studies have shown that macrophages play a crucial role in the differentiation process of MSCs. Firstly, macrophages provide a certain protective effect on the multilineage differentiation potential of MSCs. Mitochondrial metabolic damage in MSCs can lead to differentiation disorders. Teissier ~~V~~ *et al* found that co-culture of M0 macrophages with mitochondrially impaired MSCs could correct the redox imbalance in MSCs, restore their metabolic homeostasis, and promote their differentiation[72][~~45~~]. Additionally, macrophages have an inducing effect on MSC differentiation. Current research mainly focuses on the impact of macrophages on the osteogenic, chondrogenic, and adipogenic differentiation of MSCs. Macrophages secrete certain anti-inflammatory factors, pro-inflammatory factors, and osteogenic factors such as

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BMP-2 and oncostatin-M (OSM), which can mediate the osteogenic differentiation of MSCs[39,73][46,47]. Recent studies have also shown that oxidative stress plays a key role in the regulation of MSCs by macrophages. Macrophages can reduce the level of reactive oxygen species in MSCs in a similar manner to the antioxidant N-acetyl cysteine (NAC) to regulate their osteogenic differentiation[74][48]. Cao D *et al* discovered that co-culture of macrophages with MSCs could inhibit the expression of C-X-C motif chemokine ligand 1 (CXCL1) and its receptor C-X-C chemokine receptor type 2 (CXCR2), reduce the phosphorylation of p38/ERK-Elk1 during the early stage of adipogenesis, and regulate the adipogenic differentiation of MSCs[40][49]. Some studies have found that physical stimuli and changes in chemical composition can enhance the chondrogenic differentiation of MSCs *in vitro* and *in vivo* by controlling macrophages activation. Wang L *et al* found that mechanical stimulation could promote the polarization of macrophages to the M2 phenotype and secreted TGF-β1 to promote MSCs chondrogenesis[41][50]. Hu T *et al* found that magnesium deficiency can increase the secretion of inflammatory factors such as IL-1β and IL-6 by M1 macrophages, inhibiting MSCs chondrogenesis[42][51]. Due to the roles of macrophages in bone, cartilage, and fat formation, they are considered potential targets for the treatment of various related diseases such as bone defects, osteoarthritis, and vascular diseases (Figure 2).

THE ROLE OF BOTH IN THE PROCESS THE INTERACTION BETWEEN MSCs AND MACROPHAGE IS AN IMPORTANT PART OF BONE TISSUE REPAIR

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The process of bone tissue damage includes an inflammatory response, which creates the basis for subsequent bone formation, mineralization, resorptionabsorption, and bone replacement. In the process of damage repair, the synergistic effect of MSCs and macrophages mainly involves intervention in the occurrence and regression of inflammation after damage and regulation of bone formation and remodeling. The polarization of macrophages M1/M2 phenotype is the basis of the inflammatory response, and MSCs can regulate the balance of M1/M2 macrophages to participate in the regulation of inflammation progression and regression[75][52]. In the stages of bone formation and remodeling, the mutual regulation between MSCs and macrophages plays an important role in balancing OBs and OCs and maintaining bone homeostasis. At the same time, the dynamic balance between MSCs osteogenic differentiation-mediated bone regeneration and

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OCs-mediated ~~bone absorption~~bone resorption also participates in the bone repair and remodeling process. The interaction between MSCs and macrophages creates a negative feedback loop, which plays an important role in bone tissue repair.

Maintain tissue microenvironment homeostasis

Inflammation occurrence is a necessary link in the repair of bone tissue damage. Innate and adaptive immune activation is beneficial for the body to make a sufficient response to bone tissue damage[76,77][~~53,54~~]. The temporary inflammatory response after damage helps the body to mobilize the immune system and activate the damage repair mechanism, which is conducive to wound healing. After tissue damage, cells autonomously conduct inflammatory signal transduction. Macrophages are large secretory cells that act as inflammation effectors and can shape the post-damage tissue environment by secreting a variety of bioactive factors. They play pro-anabolic roles throughout the entire stage of bone tissue damage repair and are key cells in the repair of bone tissue damage[78][~~55~~]. MSCs are key regulators of inflammation. Under the action of damage-associated molecular patterns (DAMPs), MSCs exhibit a pro-inflammatory phenotype [79]. After receiving stimulation signals through pattern recognition receptors, MSCs activate transcriptional effectors such as NF-κB and TLR4 for immune regulation[80][~~56~~]. For example, NF-κB can bind to the receptor activator of nuclear factor-κ B ligand (RANKL) receptor, stimulate the activation of the classical activation phenotype M1 of macrophages, and release a variety of inflammatory factors, while recruiting a variety of immune cells to enhance the immune response[81,82][~~57,58~~].

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Prolonged inflammatory responses are not conducive to the repair of injuries, as they can damage the osteogenic ability of MSCs and lead to secondary osteopathies such as osteoporosis, bone necrosis, and hyperostosis[83][~~59~~]. Therefore, improving the inflammatory state of the organizational microenvironment is the predecessor and basis for the recovery of tissue structure and function. Inflammatory signal transduction stimulation can cause changes in the biological activities and epigenetics of various cells, which is a key adaptation of cells to tissue damage. Once inflammatory factors in the microenvironment reach a certain level, MSCs are activated to inhibit the secretion of pro-inflammatory factors by M1 macrophages in various ways, promote the secretion of multiple anti-inflammatory

factors by M2 macrophages, effectively prevent excessive activation of inflammation, and ensure the smooth progress of tissue repair and remodeling. On the one hand, MSCs and macrophages interact with each other through direct receptor binding. Li~~Y~~ *et al* found that pro-inflammatory M1 macrophages can directly interact with MSCs, promoting the production of TNF-α-stimulated gene 6 protein (TSG-6) and CD200 expression in MSCs. Simultaneously, CD200 on MSCs can interact with CD200R on macrophages, promoting the polarization of M2 macrophages and enhancing the inhibitory effect on inflammation[27][37]. On the other hand, MSCs and macrophages also regulate each other through paracrine effects. The anti-inflammatory protein TGS-6 is a multifunctional protein associated with inflammation that has anti-inflammatory and tissue-protective properties and plays a critical role in inflammatory cell migration, cell proliferation, and development. Choi~~H~~ *et al* found that M1 macrophages secrete various pro-inflammatory cytokines, including TNF-α and IL-1β, at inflammation sites, which can activate MSCs to induce TSG-6 expression. TSG-6 can bind to CD44 receptors on macrophages and decrease zymosan/TLR2-mediated nuclear translocation of the NF-κB, inhibiting the activity of M1 macrophages, inducing M2 anti-inflammatory polarization, and promoting inflammation resolution[32][60]. IL-6 is a signaling molecule dependent on M1 macrophages polarization to M2 macrophages during inflammation. Denise~~Philipp~~ *et al* found that MSCs-derived IL-6 triggers macrophages M2 phenotype polarization[29][23]. IL-12 is an effective inducer of cell-mediated immune responses, mainly derived from monocytes and macrophages. Chahal~~J~~ *et al* found that the expression of pro-inflammatory M1 macrophages and IL-12 in synovial fluid significantly decreased after injecting MSCs into the joints of mice with osteoarthritis[84][61]. The heterodimer formed by the chemokines CCL2 and CXCL12 secreted by MSCs can upregulate IL-10 expression in CCR2(+) macrophages[85][62], promoting the polarization of M2 macrophages and driving an anti-inflammatory response. MSCs-secreted miR-466 promotes the polarization of macrophages to the M2 type by downregulating the TIRAP-MyD88-NF-κB signaling pathway[25][16].

Formation of the basic multicellular unit (BMUS) for bone tissue

Bone repair and remodeling are processes of "activation-resorption ~~absorption~~-formation" of BMUS~~basic multicellular units (BMUS)~~[86]. OBs derived from mesenchymal stem cells

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(MSCs) and OCs derived from macrophages are two major cell types present in bone tissue repair, playing essential roles in maintaining bone homeostasis[87]. OBs are the key cells for bone formation. MSCs and skeletal stem cells (SSCs) differentiate into osteoblast precursor cells (pre-OBs), while macrophages and endosteal OBs participate in bone mineralization side by side. Mature OBs embed in the gaps of the mineralized matrix and become bone cells. OCs are the key cells for ~~bone absorption~~bone resorption. Inflammatory factors and chemokines can attract circulating macrophages to migrate to the inflammatory site and become resident macrophages in bone (also known as bone macrophages)[88]. OBs-derived macrophages colony-stimulating factor (M-CSF) binds to colony-stimulating factor 1 receptor (CSF1R, also known as c-FMS)~~the receptor c-FMS~~ on the macrophages surface, activating the induction signal for osteoclast differentiation, RANKL/RANK[89]. Key factors such as M-CSF and RANKL can activate the expression of the primary switch regulatory factor for OCs generation, the transcription factor nuclear factor of activated T cells (NFATc1), promoting the migration of monocytes/macrophages, these osteoclast precursor cells (pre-OCs), to the bone surface for activation and differentiation into mature OCs[90-92].

Regulate a balance between bone resorption and bone formation ~~***Mediating the dialogue between the immune environment and bone tissue***~~

MSCs and macrophages not only serve as the sources of OBs and OCs for tissue repair but also interact closely with each other through common cellular precursors and molecular mediators of the immune system and bone tissue, shaping the various bioactive factors required for the bone tissue repair microenvironment, including osteogenic-related factors, tumor necrosis factor (TNF) family, interleukin (IL) family, interferon (IFN) family, chemokines, etc., and participating in metabolism related to ~~bone absorption~~bone resorption and bone formation (Figure2) [73,93-107].

In the acute phase of inflammation, the interaction between MSCs and M1 macrophages polarization releases various pro-inflammatory factors and chemokines, mainly involved in the differentiation and maturation of pre-OCs. RANKL serves as a bridge between the inflammatory response and ~~bone absorption~~bone resorption [93]. In the presence of RANKL, multiple pro-inflammatory cytokines synergistically coordinate to enhance the genesis of OCs. MSCs-secreted NF-κB binds to the OCs differentiation-inducing RANKL to control

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the expression of key factors in pre-OCs differentiation. Inflammatory factors such as TNF-α, IL-1, IL-1β, IL-6, IL-7, IL-8, IL-11, IL-17, IL-18, IL-23, etc., secreted by M1, can directly or indirectly affect OBs to promote RANKL expression, participating in OBs differentiation of MSCs and OCs differentiation of bone macrophages[93-99][~~57,63,66~~]. Among them, TNF-α and IL-6 are key regulatory factors. TNF-α acts on signaling pathways such as RANKL/RANK, downstream NF-κB, JNK, p38, AKT, etc., to reduce the expression of OCs-specific genes and proteins, promoting the activation of bone macrophages and the differentiation of OCs[81][~~57~~]. After binding to IL-6R and gp130, IL-6 activates the phosphorylation of JAK/STAT[108][~~67~~]. The phosphorylated STAT3 translocates to the nucleus, where it activates the expression of RANKL, directly participating in the osteoclast differentiation of bone macrophages, or indirectly influencing osteoclast differentiation through its action on TNF-α[109,110][~~68~~]. At the same time, these factors also provide key aspects of the feedback regulation mechanism of RANKL induction in bone macrophages. IL-4 inhibits the transcription factor NFATc1, weakening RANKL-induced OCs formation[104][~~33~~]. Interferons such as IFN-α and IFN-β, IFN-γ induce rapid degradation of RANK-associated protein tumor necrosis factor receptor-associated factor 6 (TRAF6) or mediate Fas/FasL signaling, strongly inhibiting the activation of RANKL-induced transcription factors NF-κB and *c-fos*, thus inhibiting excessive OCs formation[101][~~64~~]. TNF-α activates RANKL-related CD40/CD40L signaling to promote the production of OCs genesis inhibitory factor osteoprotegerin (OPG) and reduce the ~~bone absorption~~bone resorption[100][~~69~~]. IL-3 can also down-regulates TNF-α-induced c-fos nuclear translocation to ~~reduce the expression of *c-fos*,~~ inhibit OCs formation, and ~~bone absorption~~bone resorption[94][~~70~~].

In addition, researches have shown that the pro-inflammatory factors secreted by M1 macrophages are also related to the early and mid-stage osteogenic effects of MSCs. The absence of TNF-α and IL-6 has been proven to delay the differentiation of MSCs. TNF-α can selectively mediate the osteogenic differentiation of OBs. Low concentrations of TNF-α stimulate the differentiation of Pre-OBs into OBs, while high concentrations of TNF-α regulate the degradation of runt-related transcription factor 2 (Runx2) protein by smad ubiquitination regulatory factor 1 (Smurf1) and smad ubiquitination regulatory factor 2 (Smurf2) to block the expression of RUNX2, and simultaneously inhibit the expression of insulin-like growth factor-1 (IGF-1) and osterix (Osx) and osteocalcin (OCN), inhibiting OBs

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differentiation[106][71]. The effect of IL-6 on bone marrow-derived OCs stimulates the release of "bone messengers", which act through the cortical bone cell network to stimulate the formation of OBs on the bone membrane. Cyclooxygenase-2 (COX-2) and Prostaglandin E2 (PEG2) regulate the production of the IL-6 family cytokine OSM in classically activated inflammatory M1 macrophages[73]. OSM binds to oncostatin-M receptor (OSMR) on MSCs, then activates the STAT3-CCAAT-enhancer-binding protein delta-C/core binding factor alpha 1 (Cbfa1) differentiation pathway, mediates the recruitment and proliferation of MSCs, stimulates the maturation of o OBs in MSCs, and drives the mineralization of OBs. TGF-β and osteopontin (OPN) enhance the activity of alkaline phosphatase (ALP) in MSCs, promoting the maturation and mineralization of the matrix[107][72].

However, recent studies have shown that the microenvironment formed during the resolution stage of inflammation has a more important impact on bone formation and remodeling, which can significantly increase the ratio of OBs/OCs and promote the bone formation. On the one hand, MSCs promote M2 macrophages polarization, and release inflammatory factors, chemokine and other active factors to regulate bone homeostasis indirectly. Anti-inflammatory factors secreted by M2 macrophages, such as IL-4, IL-10, TGF-β, and IL-12, can promote the expression of OBs and inhibit the activity of OCs by regulating the expression of osteogenic markers such as RUNX2 , Alkaline phosphatase (ALPL) and COL1A1, and adjusting the OPG/RANKL signaling pathway[103,106][71]. Chemokines such as CXCL3, CXCL6, and CXCL14 are important mediators for promoting MSCs osteogenic differentiation and bone integration, these chemokines trigger the regulation of the downstream of actin cytoskeletal pathway in MSCs and promote the expression of distal-less homeobox 5 (Dlx5) and Runx2 by activating ~~C-X-C motif chemokine receptor 2 (~~CXCR2~~)~~ and C-C motif chemokine receptor 1 (CCR1)[30][20]. On the other hand, macrophages induce MSCs to release osteogenic factors such as BMP-2, activating signal molecules drosophila mothers against decapentaplegic homologue (SMAD) in OBs to promote the osteogenic function of MSCs[111][68]. These studies suggest that MSCs and macrophages play an important role in bone tissue repair (Figure 3)[30,31,43,81,88,93,100]

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~~DISCUSSION~~ FUTURE THERAPIES FOR BONE REGENERATION BASED THE CROSSTALK BETWEEN MSCs AND MACROPHAGES

~~A comprehensive understanding of the roles of MSCs and macrophages in immune regulation and bone regeneration is beneficial for the optimal application of cell therapy in bone tissue repair and regeneration.~~ The multilineage differentiation potential of MSCs and their susceptibility to microenvironmental regulation make their roles in bone tissue less clear and modulating immune cells to enhance the osteogenic effects of MSCs is becoming a new method to address current challenges. Co-transplantation of macrophages and MSCs may be a potential effective treatment~~.~~ Current research attempts to exploit the characteristics of mutual regulation and microenvironment sensitivity between MSCs and macrophages, exploring their potential applications in acute or chronic bone tissue injuries such as fractures and osteoarthritis. Co-culture of MSCs with macrophages can enhance the immunomodulatory and osteogenic ability of MSCs. Some studies have found that preconditioning can further enhance the regulatory ability of MSCs on macrophages.~~This includes studying the co-culture of the two to enhance the immune regulatory and osteogenic abilities of MSCs, or pre-treating to alter the *in vitro* culture environment of MSCs, enhancing their regulatory capacity over macrophages *in vivo*.~~

~~The paracrine function of MSCs is susceptible to changes in the microenvironment, which confers a strong plasticity on the immune regulatory abilities of MSCs. Enhancing the sensitivity of MSCs through pretreatment is a promising strategy in MSCs therapy, effectively altering the phenotypic function of MSCs, strengthening their dialogue with the injured environment, and enhancing their repair capabilities. Some studies have found that MSCs pretreated with bioactive factors significantly enhanced their regulatory activity on macrophages.~~ Denise ~~Philipp~~ *et al* discovered that the immunosuppressive effect of MSCs mediated by IFN-γ and IL-1β pretreatment mainly involved the active component IL-6, which stimulated the polarization of the M2 macrophages phenotype, promoting the expression of ~~CD1~~CD86, iNOS protein, and ~~TNF-α~~IL-10 secretion by macrophages, thus significantly enhancing the immune regulatory capabilities of MSCs [29]~~[40]~~. ~~Nakao Y *et al* found that TNF-α pretreatment of MSCs significantly increased the expression of CD73 in MSCs-Exos, further promoting the polarization of M2 macrophages, significantly inhibiting osteoclast activity, and effectively alleviating inflammatory bone loss. In addition to these~~

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~~factors, changes in the physiological environment also affect the biological functions of MSCs[57]~~. Furthermore, conditions such as hypoxia, lipopolysaccharide treatment, and heat shock pretreatment can enhance the impacts of macrophages on the immune regulatory capacity and osteogenic activity of MSCs, although these treatments may have some inhibitory effects on the survival of MSCs[112][~~73~~]. The depletion of macrophages can lead to a decrease in MSCs, and the use of IL-13 and IL-4 to induce an increase in the number of M2 macrophages can promote MSCs osteogenic differentiation and accelerate the bone repair [115,116].

~~The use of single MSCs transplantation for tissue repair has many limitations. The multilineage differentiation potential of MSCs and their susceptibility to microenvironmental regulation make their roles in bone tissue less clear and modulating immune cells to enhance the osteogenic effects of MSCs is becoming a new method to address current challenges. Co-transplantation of macrophages and MSCs may be a potential effective treatment, but there is currently no relevant clinical research. The positive interaction between MSCs and innate immune cells, macrophages, indicates that macrophages can enhance the immune regulatory activity and tissue repair function of MSCs to some extent, which may contribute to the application of MSCs in bone injury repair and immune bone diseases such as osteoarthritis. Many *in vitro* two-dimensional (2D) and three-dimensional (3D) co-culture experiments of MSCs and macrophages have shown that macrophages can directly or indirectly promote the migration, proliferation, and osteogenic differentiation abilities of MSCs[65,66,74]. Some studies have found that under different pretreatment stimuli, macrophages differentiate into different subtypes, producing different effects on MSCs. In the co-culture process of M2 macrophages and MSCs, the mineralization effect of MSCs is significantly enhanced. Using lipopolysaccharides (LPS) to induce the polarization of M1 macrophages, the treated macrophages culture medium can promote the upregulation of Runx2 and ALP genes in MSCs, promote MSCs osteogenic differentiation and mineralization, and inhibit the activity of OCs. In addition, research has shown that the number of macrophages also has a certain impact on the osteogenic function of MSCs. The depletion of macrophages can lead to a decrease in MSCs, and the use of IL-13 and IL-4 to induce an increase in the number of M2 macrophages can promote MSCs osteogenic differentiation and accelerate the bone repair.~~

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~~Furthermore, m~~Methods of effectively regulating the crosstalk between MSCs and macrophages through biomaterial scaffolds to promote bone healing are becoming a new research focus. The implantation of living cells wrapped in 3D bioprinted scaffolds can effectively improve the inflammatory microenvironment within the body, further accelerating bone repair. Yu ~~K~~ *et al* discovered that implanting a dual-channel bioprinting scaffold, formed by wrapping macrophages with 8% methacrylamidated gelatin (GelMA)/1% methacrylamidated hyaluronic acid (HAMA) and wrapping MSCs with 3% Alginate/0.5 mg/mL graphene oxide (GO), into the model of rat calvarial defects, can effectively promote the polarization of M2 macrophages in the early bone defect environment, avoid excessive inflammatory responses, and further promote bone repair. The results indicate that this method is more effective than using single-cell MSCs scaffolds[117][~~75~~]. Furthermore, some studies have chosen to use special coatings to modify the coatings of implanted scaffolds or hydrogels, etc., in order to regulate the biomaterial scaffolds to activate macrophages in the body and promote the differentiation of osteogenic phenotypes. For example, Majrashi ~~M~~ *et al* implanted dexamethasone, which has both anti-inflammatory and osteogenic differentiation promotional effects, into 3D scaffolds. According to the principle that early inflammation benefits MSCs' osteogenesis and excessive inflammatory responses harm it, they designed the use of the excipient-sucrose acetate isobutyrate (SAIB) to achieve sustained release of dexamethasone, regulate the activation of macrophages phenotype, and control the inflammatory microenvironment within the tissue to promote tissue regeneration. In the early stage of bone tissue injury repair, M1 macrophages can secrete IL-6 to promote osteogenesis. As inflammation progresses, dexamethasone can promote the polarization of M2 macrophages and enhance the osteogenic effect of MSCs by jointly secreting BMP-2 with M2 macrophages[118][~~68~~]. Niu ~~Y~~ *et al* wrapped hydrogels containing MSCs with a unique macrophages-affinitive glucomannan polysaccharide and found that after implantation into mice, it effectively promoted the adherence and activation of macrophages, and induced the release of osteogenic genes in MSCs, thereby effectively promoting bone tissue regeneration[119][~~76~~]. In addition, numerous studies are currently innovating in the composition of biomaterials for bone tissue engineering, all of which will provide a foundation for enhancing the application of MSCs and macrophages in bone tissue repair and remodeling[120-123][~~77-80~~].

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CONCLUSION

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~~A comprehensive understanding of the roles of MSCs and macrophages in immune regulation and bone regeneration is beneficial for the optimal application of cell therapy in bone tissue repair and regeneration.~~ ~~Currently, having a thorough understanding of the interactions between MSCs and macrophages, in conjunction with basic research on co-transplantation using novel biomaterial carriers such as hydrogels and 3D scaffolds, is beneficial for the future development of a modifiable treatment model that promotes MSCs osteogenic differentiation or endogenous tissue regeneration through the co-transplantation of MSCs and macrophages under specific conditions. This will provide new methods and strategies for regenerative treatment of clinical bone defects or other tissue injuries.~~ A comprehensive understanding of the roles of MSCs and macrophages in immunomodulation and bone regeneration is beneficial for the optimal application of cellular therapy in tissue repair and regeneration. This article discusses the important roles of both MSCs and macrophages in the immune microenvironment of bone injury and bone tissue regeneration by summarizing their mutual regulatory interactions. However, the regulatory mechanisms between MSCs and macrophages are very complex, and the repair and regeneration of bone tissue is a complicated dynamic process. Our research and discussion are not comprehensive, and with further study, new breakthroughs in their interactive mechanisms may emerge. Furthermore, through further exploration of potential therapeutic models based on the crosstalk between MSCs and macrophages, we have found that special pretreatment of MSCs and macrophages, or the combined use of new biological material carriers (such as hydrogels and 3D scaffolds) for the co-transplantation treatment model of MSCs and macrophages, may be effective therapies to promote the immunomodulatory capacity of MSCs or endogenous tissue regeneration. This could provide new methods and strategies for the repair and regeneration of clinical bone defects or other soft tissue injuries. However, most of the current research is still at the basic research stage, and its efficacy and safety still need to be further confirmed.

ACKNOWLEDGEMENTS

I would like to thank all people who helped me in the process of writing this article.

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Footnotes

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

ILLUSTRATIONS

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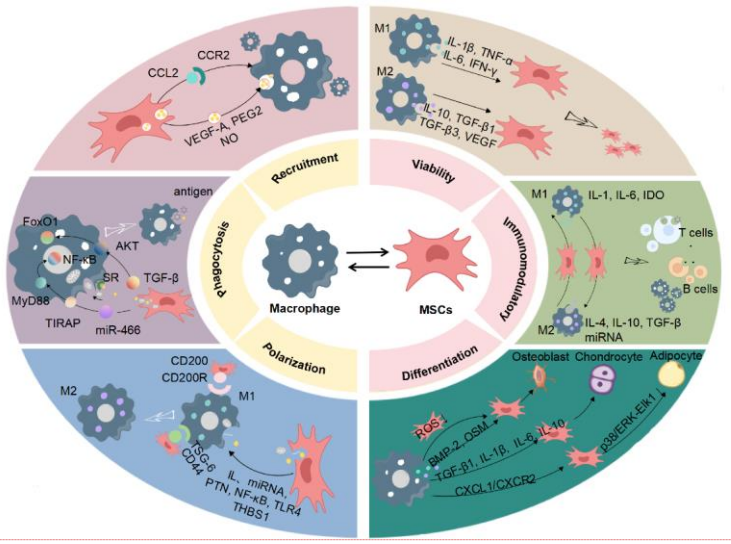

Figure 1 Bidirectional interaction between MSCs and macrophages. MSCs can facilitate the proliferation and infiltration of macrophages, enhance their phagocytic capabilities, and promote the polarization of macrophages phenotypes. Macrophages are capable of activating MSCs, boosting their proliferation and migration abilities, influencing the immune regulatory microenvironment of MSCs, and promoting the multilineage differentiation of MSCs through the secretion of inflammatory-related factors, chemokines, and osteogenic-related factors. CCL2: C-C motif chemokine ligand 2; CCR2: C-C motif chemokine receptor 2; VEGF-A: vascular endothelial growth factor-A; PEG2: Prostaglandin E2; FoxO1: forkhead box transcription factor O1; NF-κB: Nuclear factor kappa-B; MyD88: myeloid differentiation primary response gene 88; TIRAP: the Toll-interleukin-1 Receptor (TIR) domain-containing adaptor protein; SR: scavenger receptor; AKT: protein kinase B; TGF-β: transforming growth factor beta; PTN: pleiotropic hormones; TLR4: Toll-like receptor 4; THBS-1: thrombospondin-1; BMP-2: bone morphogenetic protein-2; OSM: oncostatin-M; IDO: indoleamine 2,3-dioxygenase; HGF: hepatocyte growth factor.

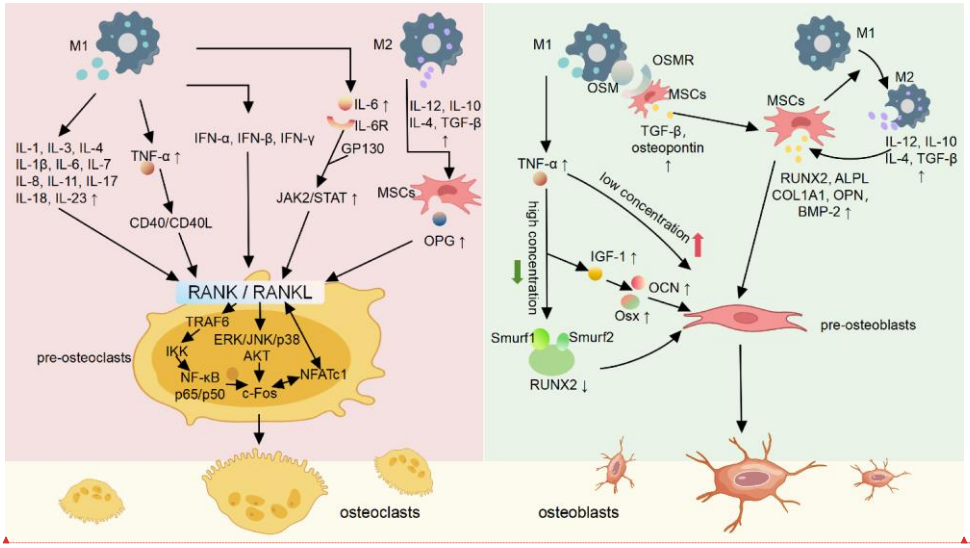

Figure 2 The dialogue between MSCs and macrophages in mediating the immune environment and bone tissue~~healing~~. Multiple inflammatory factors secreted by M1 macrophages can promote the differentiation of osteoclast precursors into OCs. When the inflammatory factors accumulate to a certain extent, the differentiation of osteoclasts is inhibited by the action of osteogenic factors secreted by M2 macrophages and MSCs. Macrophages can promote the secretion of various osteogenic induction factors by MSCs through direct contact or by secreting various bioactive factors indirectly, inducing further differentiation of osteogenic precursor cells into OBs. RANK: nuclear factor-κ B ligand; TRAF6: tumor necrosis factor receptor-associated factor 6; NFATc1: the transcription factor nuclear factor of activated T cells; OPG: osteoprotegerin; OSM: oncostatin-M; OSMR: oncostatin-M receptor; RUNX2: runt-related transcription factor 2; OCN: osteocalcin; Osx: osterix; OPN: osteopontin; ALPL: alkaline phosphatase; BMP-2: bone morphogenetic protein-2.

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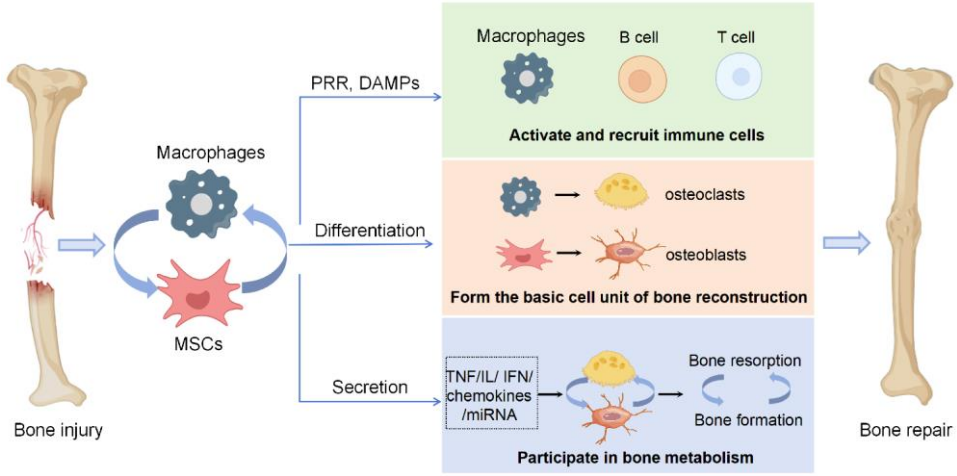

Figure 3 MSCs and macrophages promote bone tissue repair. The inflammatory microenvironment after injury promotes the activation of MSCs and macrophages. Through immune response patterns such as PRRs and DAMPs, the interaction between MSCs and macrophages further activates immune cells such as B cells and T cells, enhancing the immune response in the damaged microenvironment. MSCs and macrophages are precursor cells for OBs and OCs, respectively, and play an important role in bone tissue reconstruction. At the same time, MSCs and macrophages also affect the formation of OBs and OCs by secreting chemokines, TNF, IFN, IL and other bioactive factors, regulating the balance between bone resorption and bone formation, and promoting the repair of bone tissue. PRR: pattern recognition receptor; DAMPs: damage associated molecular patterns; TNF: tumor necrosis factor; IL: interleukin; IFN: interferon; miRNA: microRNA.

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