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Original Article

Parathyroid hormone enhances the therapeutic effect of mesenchymal stem cells on temporomandibular joint osteoarthritis in rats

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Abstract: Objectives: Temporomandibular joint osteoarthritis (TMJOA) is a degenerative disease affecting the joint, which is characterized by injury to the articular cartilage, as well as changes in the synovial and subchondral bone. TMJOA has a high incidence rate, without any effective treatment. Despite the therapeutic potential of mesenchymal stem cells (MSCs) in various diseases, their efficacy in treating TMJOA is constrained by the local hypoxic conditions and elevated reactive oxygen species (ROS) environment within the damaged temporomandibular joint. In recent years, many studies have reported that parathyroid hormone (PTH) can effectively treat TMJOA, and has an important impact on MSC differentiation. Therefore, we hypothesized that PTH may influence the potential of MSCs, thereby improving their therapeutic effect on TMJOA. Methods: First, we isolated and cultured rat bone marrow MSCs, and evaluated their proliferation and differentiation after adding PTH. Next, the *in vitro* environment of hypoxia and high ROS was established by hypoxia condition and H_2O_2 treatment, and the resistance of PTH-treated MSCs to hypoxia and ROS was subsequently investigated. Finally, PTH-treated MSCs were used to treat TMJOA in a rat model to evaluate the efficacy of PTH. Results: PTH enhanced the proliferation ability of MSCs, promoted the osteogenic differentiation of MSCs, and improved the tolerance of MSCs to hypoxia and ROS. Finally, the therapeutic effect of PTH-treated MSCs on TMJOA was significantly improved. Conclusion: PTH enhances the therapeutic effect of MSCs on TMJOA in rats.

Keywords: Temporomandibuar joint osteoarthritis, parathyroid hormone, mesenchymal stem cells, homing, repair, proliferation and differentiation ability

Introduction

Temporomandibular joint osteoarthritis (TMJOA) is distinguished by articular cartilage injury, along with synovial and subchondral bone alterations. The prevalence of TMJOA is 18.27-42.9% in China, and it can lead to maxillofacial pain and movement impairments, thereby imposing a significant psychological and physiological burden on affected individuals [1]. The etiology and progression of TMJOA involve complex mechanisms such as tissue damage and inflammation, which makes the treatment more challenging. Currently, clinical management of TMJOA primarily focuses on disease progression control, pain reduction, drug therapy, physical therapy, and inflammation control. However, there is a lack of pharmacological interventions and methodologies that can effectively manage the progression of TMJOA [2].

In recent years, the study of stem cells, particularly mesenchymal stem cells (MSCs), has presented new hope for the treatment of many diseases. Compared to traditional treatment methods, it offers several distinct advantages. First, MSCs have the ability to home in on the site of injury and subsequently differentiate into specific tissue cells, facilitating repair of the injured area. Second, MSCs can secrete cytokines that promote damage repair and regulate the local inflammatory response, thereby reduc-

ing the "inflammatory pressure" and preserving homeostasis in the microenvironment [3, 4]. Given the therapeutic effects of MSCs on other diseases, some researchers investigated its potential application in treating osteoarthrosis (OA) but with limited success [5]. The reason for this is that the temporomandibular joint is relatively small compared to larger joints, resulting in inadequate blood and oxygen supply. When inflammatory injuries occur, oxygen supply becomes even more challenging, leading to the inhibition of proliferation and differentiation of transplanted MSCs in the damaged temporomandibular joint cavity [6]. Therefore, how to improve the proliferation and differentiation ability of MSCs in the temporomandibular joint cavity has become a research hotspot.

Parathyroid hormone (PTH) is an alkaline single-chain polypeptide hormone secreted by parathyroid cells. Its primary function is to regulate the metabolism of calcium and phosphorus in vertebrates, promoting an increase in blood calcium levels and a decrease in blood phosphorus levels. Hence, it plays a vital role in bone development and formation. PTH (1-34) is currently the only anabolic drug approved by the US Food and Drug Administration (FDA) for the treatment of osteoporosis [7]. Jun Zhang et al. proved that PTH can effectively treat TMJOA, especially degenerative temporomandibular arthritis [8]. Studies have shown that PTH can regulate the differentiation of MSCs *in vitro*, as well as expand the number of MSCs, indicating that PTH can promote the proliferation and osteogenic differentiation of MSCs [9]. Based on the above role of PTH in bone development and MSC regulation, we hypothesized that PTH may enhance the therapeutic effect of MSCs on TMJOA. In this study, we explored the effect of PTH-treated MSCs on TMJOA, and the results showed that PTH significantly enhanced the proliferation of MSCs and increased their tolerance to ROS and hypoxia, ultimately enhancing the therapeutic effect of MSCs on TMJOA.

Methods

Experimental animals

Ninety 8-week-old female Wistar rats weighing approximately 200 g were purchased from the SPF rat feeding center at Zunyi Medical University's Experimental Animal Center. The rats underwent adaptive feeding for one week at the Laboratory of Experimental Animal Center at Zunyi Medical University, and were provided with free access to food and drinking water. The rats remained in good health throughout the study, with no instances of death. All subsequent experimental procedures were conducted in accordance with the ethical standards for animal research. To minimize the discomfort to rats, all operations were performed under anesthesia.

Experimental reagents

Sodium iodoacetate (MIA) was purchased from MERCK (No. 57858, Merck KGaA, Darmstadt, Germany). Parathyroid hormone (1-34) (rat) acetate [PTH (1-34)] was purchased from MCE (No. HY-P2279A, New Jersey, USA). The CCK-8 assay kit was purchased from Dongren Chemical Technology (Shanghai) Co., Ltd. (No. CK04, Shanghai, China). The EdU assay kit was purchased from Beyotime Biotechnology (No. C0071S, Shanghai, China). The Annexin V-FITC/PI cell apoptosis detection kit was purchased from TransGen Biotech (Beijing) Co., Ltd. (No. FA101-01, Beijing, China).

Experimental grouping and processing

The rats were randomly allocated into five groups: normal control group (0.9% normal saline was injected into the upper cavity of the temporomandibular joint), model group (sodium iodoacetate (MIA) was injected into the upper cavity of the temporomandibular joint), MSC treatment group (upper cavity of the temporomandibular joint was injected with MSCs after MIA induction), PTH treatment group (PTH was injected alone) and PTH combined with MSC treatment group (PTH-treated MSCs were injected). In this experiment, the model group was induced by 1 mg/kg MIA. After the injury was determined, BMSCs (1×10^6) or PTH-treated (50 ng/ml) BMSCs were injected. After five days, the rats were sacrificed by cervical dislocation, and topotemporal mandibular tissue was collected. Hematoxylin and Eosin staining was used to detect the damage, and Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining was used to determine the apoptosis of tissue cells, so as to comprehensively evaluate the condition of temporomandibular arthritis in rats and the

therapeutic effect of PTH combined with BMSCs.

Establishment of TMJOA animal model

After weighing, the rats were anesthetized using 10% chloral hydrate (0.3 ml/100 g). For establishing the rat model of TMJOA, the skin in the area was disinfected with iodophor, and then 1 mg/kg sodium iodoacetate (MIA) was injected into the upper cavity of the temporomandibular joint on one side using a 50 μL micro syringe. Rats in the control group were operated using the same method, but instead of MIA, the same amount of normal saline was injected into the superior cavity of the temporomandibular joint. After three weeks, the TMJOA model was completed.

Hematoxylin and Eosin staining

The temporomandibular condylar tissue of the rats was extracted, fixed, made transparent, dehydrated, waxed, and embedded to obtain routine pathological sections with a thickness of 5 μm. From each group, four sections were taken and then routinely dewaxed using xylene and dehydrated with gradient ethanol until properly hydrated. The sections were stained with hematoxylin to indicate the nuclei and were subsequently rinsed with tap water to regain their blue color. To highlight the cytoplasm, the sections were stained with eosin, routinely dehydrated, and made transparent. Finally, the sections were mounted using neutral balsam. An optical microscope was used to observe the structural lesions of the temporomandibular condyle.

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining

Paraffin sections with a thickness of 5 μm were taken for TUNEL fluorescence staining. The nuclear changes and apoptosis of temporomandibular condylar tissue were observed under a microscope. The nucleus was stained brown as a positive expression, and the apoptosis rate of temporomandibular condylar tissue was calculated.

BMSC culture

Mesenchymal stem cells from rat bone marrow were isolated as previously described. Briefly, we collected bone marrow from 12-week-old rats and removed the attached soft tissues, followed by digestion with 3 mg/mL collagenase type I (Worthington Biochem) and 4 mg/mL dispase II (Roche Diagnostic) for 60 minutes at 37°C. The cells were cultured in α-MEM (Gibco) supplemented with 10% fetal calf serum (Gibco) and 1% penicillin-streptomycin (HyClone) at 37°C, 5% (v/v) CO_2.

5-Ethynyl-2'-deoxyuridine (EdU) cell proliferation assay

EdU is an analogue of thymine nucleoside that can replace thymine during DNA synthesis. It contains its own fluorescent group, which indirectly indicates the cell proliferation ability. The fluorescence signal strength corresponds to the extent of proliferation, with stronger signals indicating higher proliferation, and vice versa. The cells were cultured with EdU for 8 hours prior to treatment. After washing, the nuclei were stained with DAPI and then observed under a fluorescence microscope or quantitatively analyzed using flow cytometry.

Detection of BMSC surface markers by flow cytometry

The cells were digested with trypsin, centrifuged at 1000 rpm for 5 minutes, and resuspended in PBS to a concentration of approximately 1×10^6 cells/ml. Then, 100 μL of the cell suspension was transferred to another EP tube, and 2 μL of the appropriate antibody was added, followed by incubation at room temperature for 30 minutes in the dark. Finally, 500 μL of stain buffer was added to each tube. After thorough pipetting, flow cytometry was used for detection.

Alizarin red S (ARS) staining

To assess osteogenic differentiation of MSCs, the cell supernatant was discarded, and MSCs were washed twice with PBS containing Ca/Mg, then fixed with neutral buffered formalin (10%) for 30 minutes and re-washed with PBS. ARS (40 mM in deionized water, pH 4.2) was added to the cells and incubated for 45 minutes in the dark. MSCs were washed four times, followed by addition of PBS. For quantification, the absorbance of the extracted supernatant was measured at 562 nm by a microplate reader.

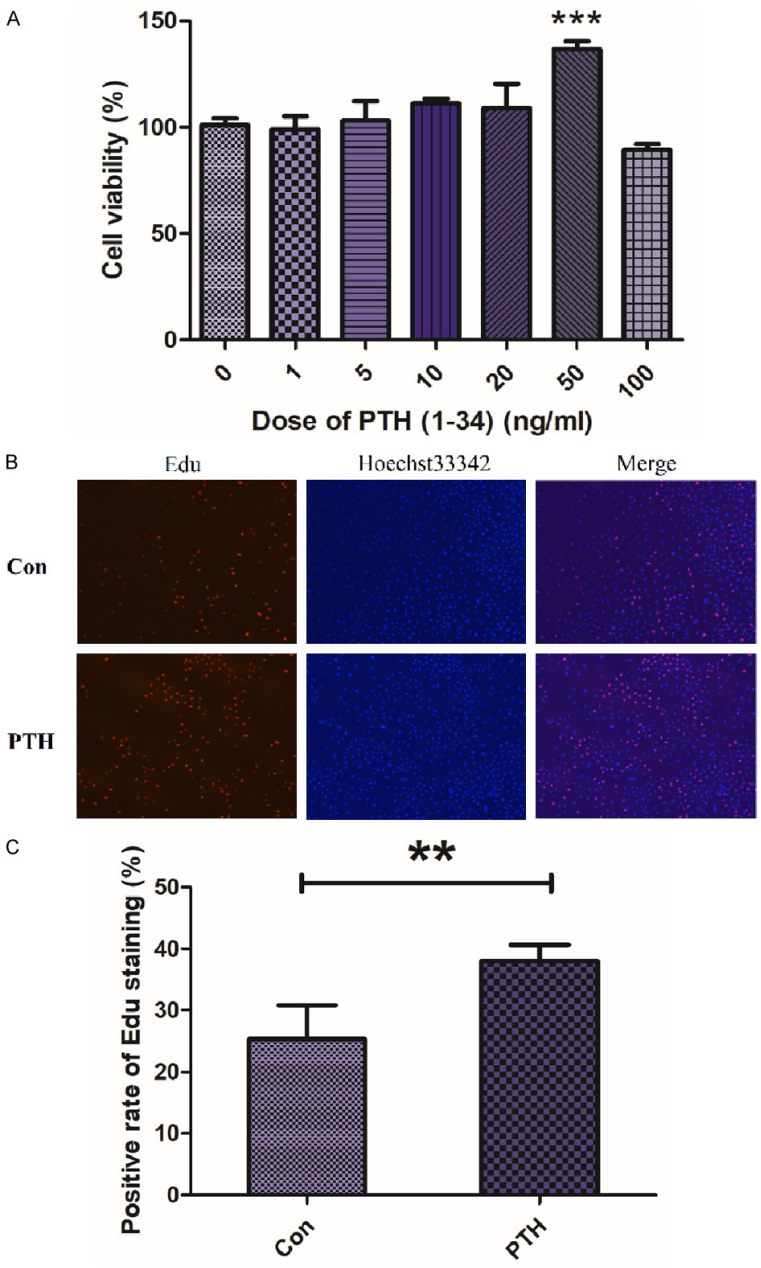

Figure 1. PTH promotes the proliferation of MSCs. MSCs that underwent stable passaging to the third generation were treated with varying doses of PTH (1-34) for 24 hours. Cell viability was subsequently measured to assess the toxicity of PTH (1-34) (A). Additionally, the proliferation of MSCs was evaluated using the Edu assay (B, C). Significant differences between groups are denoted as **P < 0.01, and ***P < 0.001 indicates the significant differences compared with dose of PTH (1-34) at 0 μM.

Statistical methods

The data are expressed as x±s. For the evaluation of the significance between groups, two-way analysis of variance (ANOVA) was used as appropriate, followed by the Bonferroni test as a post hoc test. SPSS 17.0 software was used for statistical analysis, and $P < 0.05$ was considered as statistically significant.

Results

PTH promotes MSC proliferation

First, we examined the toxicity of MSCs treated with different concentrations of PTH (1-34). After 24 hours, the cell viability was detected. While PTH (1-34) exhibited significant toxicity on MSCs at a concentration of 100 ng/ml, it promoted cell viability at lower doses, with the most significant effect observed at 50 ng/ml (**Figure 1A**). To further investigate the effect of PTH on the proliferation of BMSCs, we performed an EdU cell proliferation assay. The results indicated that PTH increased the EdU-positive rate of BMSCs, suggesting an enhancement in the proliferation ability of MSCs (**Figure 1B**, **1C**).

PTH affects MSC differentiation

Next, we evaluated the effect of PTH on MSC differentiation. First, we examined the expression of MSC markers, including CD45, CD34, CD105, and CD90. The results showed that the positive rates of CD45, CD34, CD105, and CD90 in the control group were 3.75±2.38%, 2.25±0.90%, 72.59±8.55%, and 51.73±3.59%, respectively. In contrast, the positive rates in the PTH induction group were 4.68±1.29%, 11.54±5.43%, 63.59±7.38%, and 26.83±5.77% (**Figure 2A**, **2B**). Among them, the expression of CD34 and CD90 in the two groups of MSCs was significantly different ($P < 0.05$). Furthermore, we

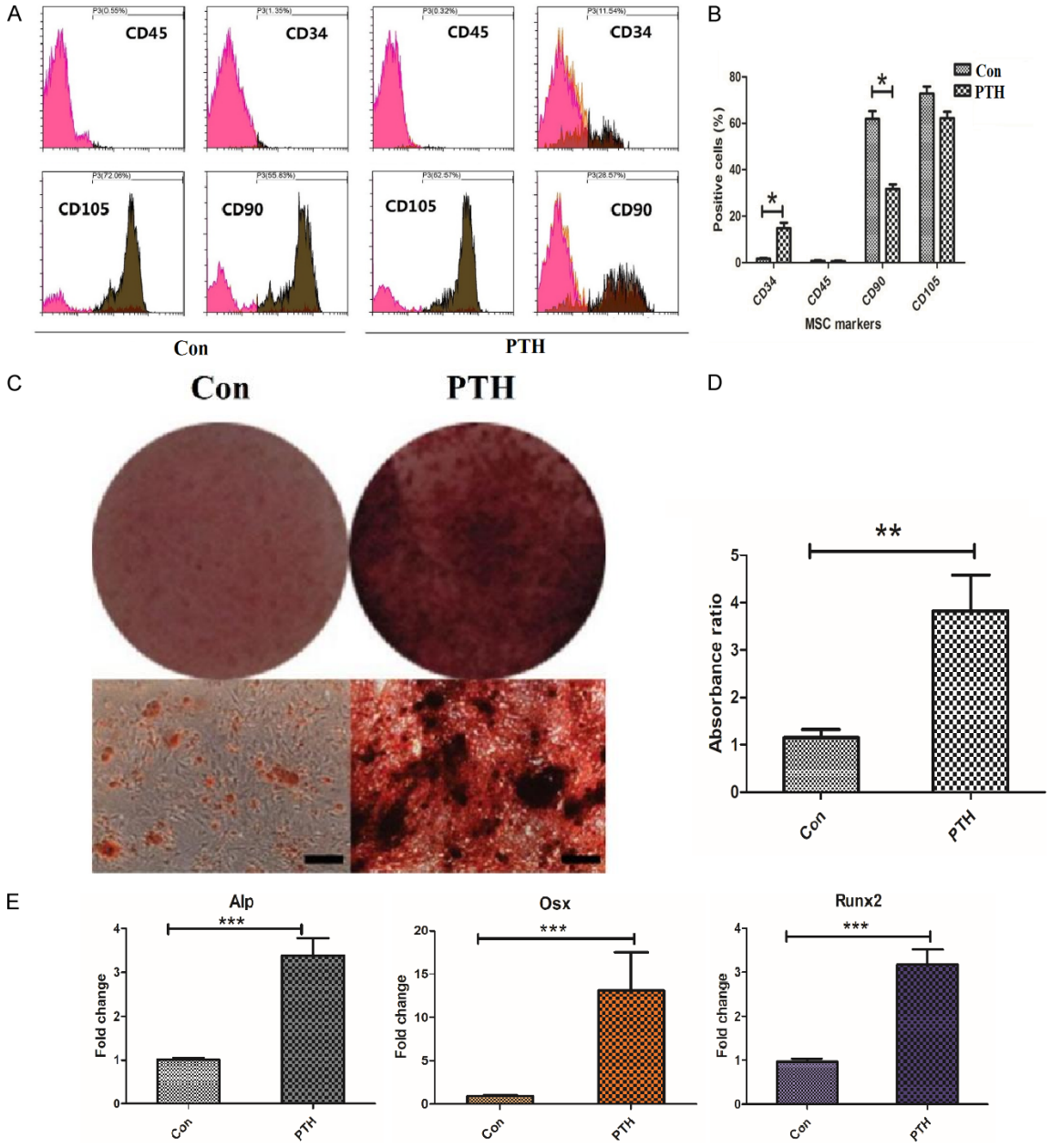

Figure 2. PTH affects MSC differentiation. MSCs were labeled with CD45, CD34, CD105, and CD90, and then flow cytometry (A) was used to analyze them (B). The potential for osteogenic differentiation was determined through ARS staining (C) and quantified (D). After treating MSCs with PTH (1-34) at a dose of 50 ng/ml for 12 hours, RNA was extracted to evaluate the expression of Alp, Osx, and Runx2 through PCR (E). Significant differences between groups are denoted as *P < 0.05, **P < 0.01, and ***P < 0.001.

examined the osteogenic capacities of MSCs, and found that PTH mainly promoted the osteogenic differentiation of MSCs (**Figure 2C**, **2D**). Consistent with the differentiation result, the expression of osteogenesis-related genes, including *Alp*, *Osx*, and *Runx2*, was up-regulated (**Figure 2E**). These results indicated that PTH does not significantly affect BMSC-specific markers, but can promote the osteogenic differentiation of MSCs.

PTH enhances hypoxia tolerance and reactive oxygen species resistance of MSCs

The limitations of MSC treatment for TMJOA are due to hypoxia and a high ROS environment.

Therefore, we conducted further experiments to confirm the tolerance of MSCs to hypoxia and their resistance to ROS. Initially, we treated MSCs with various oxygen concentrations (21%, 5%, 1%) and assessed cell viability at different time points. The findings revealed that 1% O_2 greatly hindered the proliferation and viability of MSCs, with viability decreasing by 85% after 24 hours (**Figure 3A**). Therefore, we used 1% O_2 as the hypoxic condition for subsequent tests. Next, we conducted an EdU assay to analyze the effect of PTH on MSC proliferation under hypoxia (1% O_2). The results indicated that 1% O_2 significantly inhibited MSC proliferation, but PTH increased the EdU-positive rate (**Figure 3B**, **3C**), suggesting that PTH enhanced the hypoxia tolerance of MSCs.

Next, we simulated the ROS environment by adding H_2O_2, and detected the apoptosis of MSCs using flow cytometry. The results revealed that H_2O_2 (100 μM) significantly induced apoptosis. However, PTH reduced the apoptosis rate, indicating that PTH could enhance the resistance of MSCs to ROS (**Figure 3D**, **3E**).

PTH can improve the therapeutic effect of MSCs on TMJOA

We investigated whether PTH-induced MSCs could improve the therapeutic effect on TMJOA. To construct a TMJOA model, we injected MIA into the temporomandibular joint of rats. Subsequently, we treated the rats with MSCs and PTH-induced MSCs separately. After 2 weeks, we performed H&E staining and TUNEL staining on the temporomandibular joints of the rats. The results revealed that MIA induced the occurrence of TMJOA, which was characterized by a disordered arrangement of the condylar cartilage layer, inconsistent thickness, osteophyte formation, and thinning of the cartilage layer. While the MSC treatment group did not show significant improvement compared to the model group, the PTH-induced MSC treatment group showed a significant reduction in condylar tissue damage, with the pathological manifestations of flat articular cartilage, lower wear and degeneration, increased bone mass in joint plane, and remission of inflammation (**Figure 4A**). Furthermore, TUNEL staining demonstrated that PTH-induced MSCs significantly reduced apoptosis in the temporomandibular joint tissue (**Figure 4B**, **4C**). These findings suggested that PTH can enhance the therapeutic effect of MSCs on TMJOA.

Discussion

Temporomandibular arthritis is a highly prevalent oral disease among adolescents, with reported rates of 17-87% [1], and its overall prognosis is generally poor. Various diagnostic methods have been used to evaluate temporomandibular arthritis. There are numerous treatment options for temporomandibular arthritis, including physical therapy, social psychological support therapy, drug therapy, and surgery. While all these approaches have proven effective, each has its own limitations. For example, surgical treatment is mostly used for temporomandibular arthritis caused by trauma, especially for temporomandibular arthritis with no obvious drug treatment. Moreover, with the continuous development of technology, the application of minimally invasive surgery in temporomandibular arthritis is increasing. However, surgical treatment may also lead to failure or deformity due to improper operation and other reasons [10, 11]. At present, drugs are commonly used for temporomandibular arthritis, including diclofenac sodium and glucosamine. Diclofenac sodium can inhibit inflammation by inhibiting cyclooxygenase, prostaglandin synthesis and arachidonic acid metabolism, and has analgesic and anti-inflammatory effects [12]. Glucosamine can relieve pain and promote functional recovery by promoting the formation of chondrocytes [13, 14]. These drugs have obvious effects on relieving acute symptoms, but they have little effect on long-term injury repair and anti-inflammation of temporomandibular joint. In recent years, MSCs have shown a more significant therapeutic effect in various diseases, including arthritis [15, 16] and osteoporosis [17]. However, their treatment for temporomandibular arthritis is limited by local ischemia, hypoxia, and a high ROS environment. It is urgent to find an effective method to enhance the survival of MSCs in the damaged temporomandibular joint cavity and improve their efficiency.

The therapeutic effects of PTH on arthritis have been extensively reported. Several studies have confirmed that PTH regulates differen-

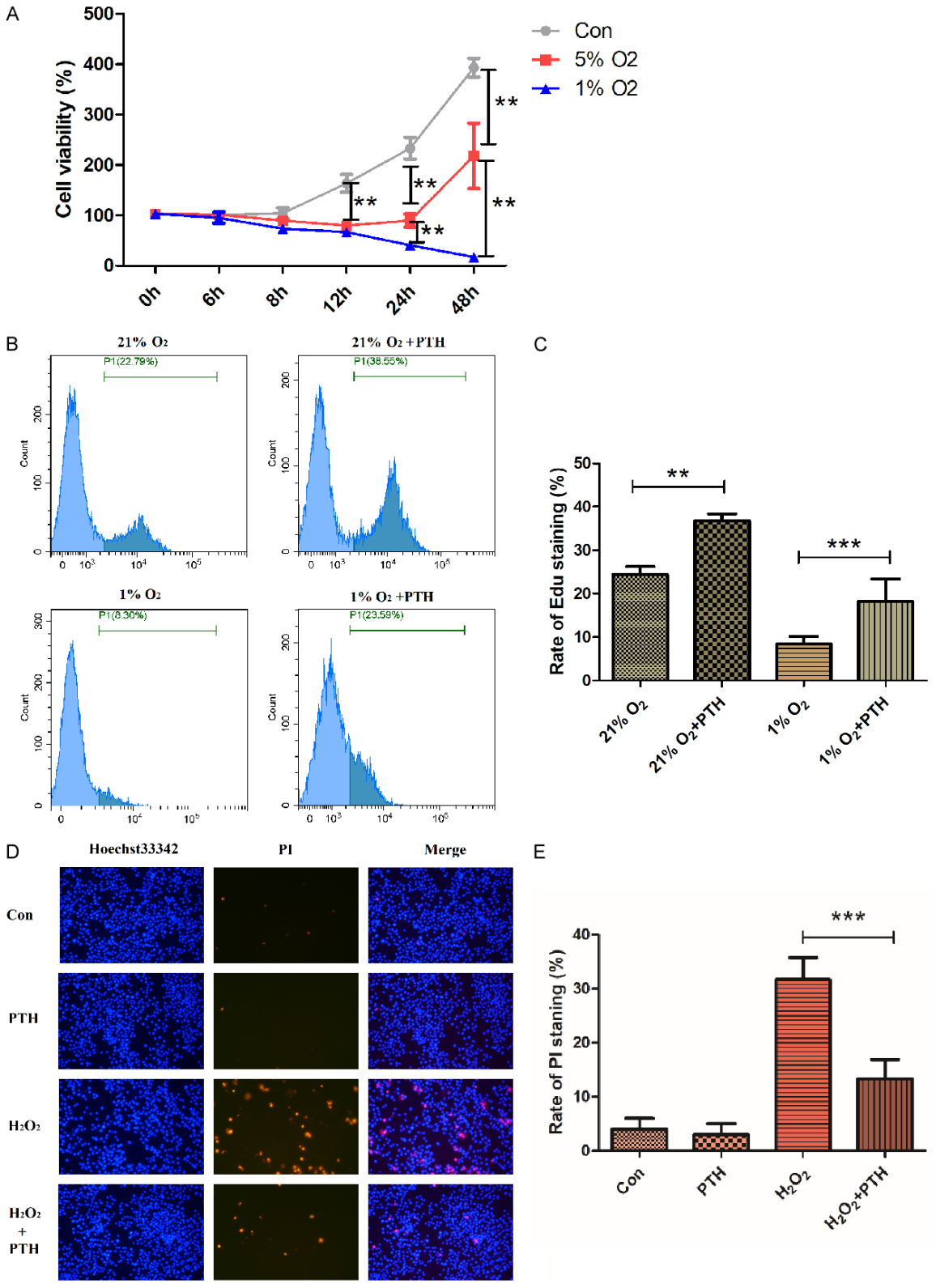

Figure 3. PTH enhances the hypoxia tolerance and reactive oxygen species resistance of MSC. MSCs were cultured under different oxygen concentrations (21%, 5%, 1%) for 24 hours. Subsequently, the cell viability was assessed using the CCK-8 assay (A). The proliferation of MSCs was evaluated using the Edu assay with or without PHT (1-34) treatment under 21% and 1% O_2 conditions (B, C). The apoptosis of MSCs was examined using Hoechst33342/PI staining after a 12-hour treatment with H_2O_2 (100 μM). In this staining, blue represents Hoechst33342 and red indicates PI (D, E). Significant differences between the groups are denoted as **P < 0.01 and ***P < 0.001.

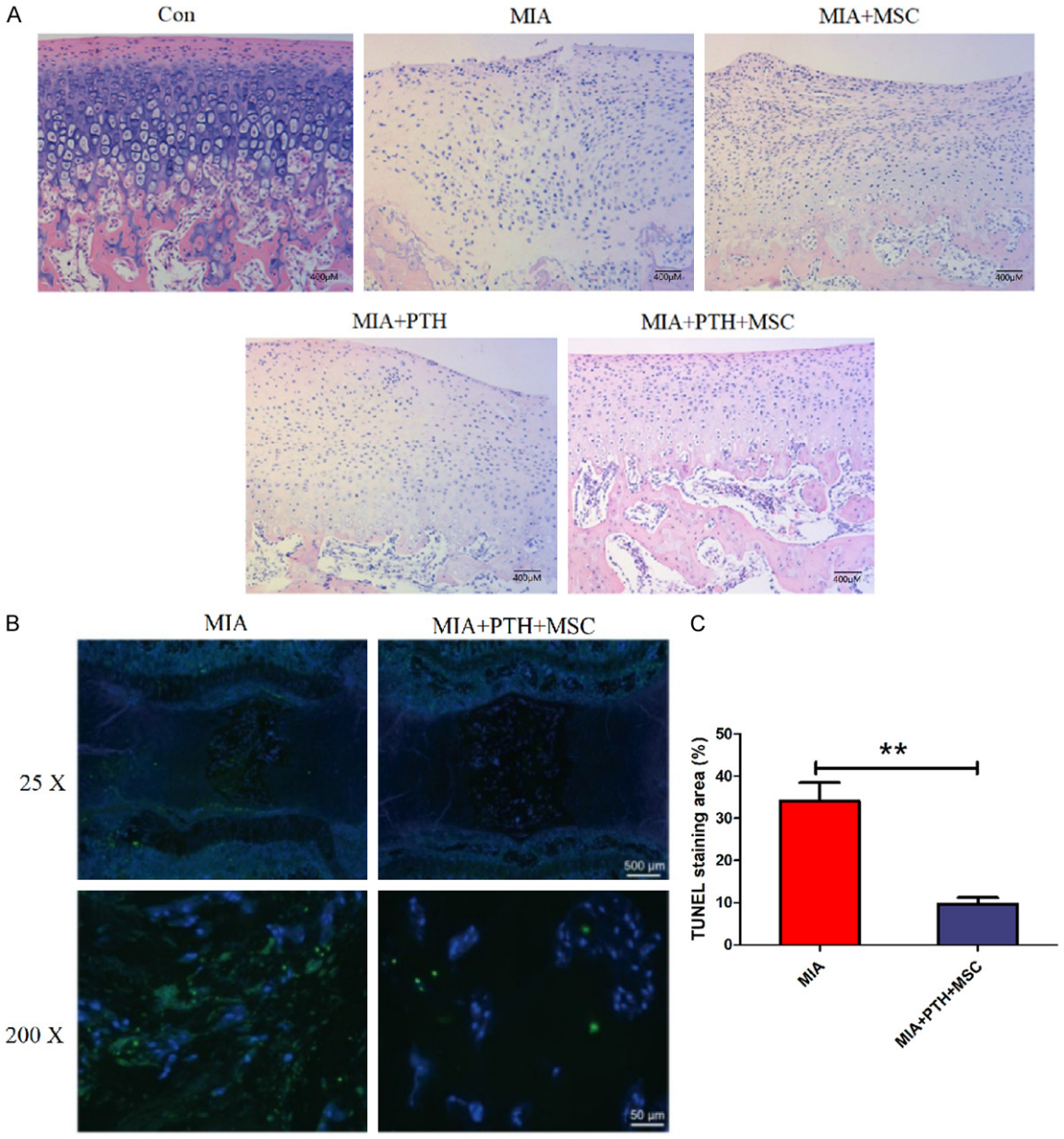

Figure 4. PTH can enhance the therapeutic effects of MSC on TMJOA. The TMJOA model in rats was induced by injecting MIA (1 mg/kg) into the temporomandibular joint cavity. After establishing the TMJOA model, MSC and PTH-treated MSC were injected into the joint cavity. Two weeks later, the temporomandibular joints were examined using H&E staining (A) and TUNEL staining (B, C). Green indicates TUNEL staining and blue indicates DAPI staining. The representative image, with a sample size of N=6, is displayed. Significant differences between groups are denoted by **P < 0.01.

tiation and promotes proliferation of MSCs. It is suggested that PTH may play a crucial role in enhancing the efficiency of MSCs. Therefore, this study aimed to investigate the therapeutic effect of PTH-induced MSCs on temporomandibular arthritis in rats.

The results showed that PTH can effectively enhance the proliferation ability of MSCs, as well as change the differentiation tendency of MSCs. Previous studies have reported that PTH can enhance the function of MSCs and promote their proliferation [18]. However, the effect of PTH on MSC differentiation has not been reported. Our results showed the effect of PTH on MSC differentiation. The expression of CD34 increased and CD90 decreased, suggesting that the characteristics of stromal cells

decreased. Furthermore, PTH significantly up-regulated the expression of osteogenic differentiation-related genes in MSCs, indicating that PTH can regulate the differentiation of MSCs and promote its osteogenic tendency. The potential reasons may be that PTH may directly affect the differentiation pathway of MSCs, and also affect the differentiation of MSCs by regulating calcium and phosphorus. Furthermore, we constructed an *in vitro* hypoxic and hyperactive oxygen environment to simulate the conditions present inside the damaged temporomandibular joint cavity. The results showed that PTH not only promotes the proliferation of MSCs but also enhances their tolerance to hypoxic and high ROS environments. Ultimately, this improves the therapeutic effect of MSCs on temporomandibular arthritis in rats.

Based on the above findings, the role of PTH in promoting the efficacy of MSCs has been clarified, providing new ideas for the future treatment of temporomandibular arthritis using MSCs. Although previous studies have demonstrated the therapeutic effect of PTH on temporomandibular arthritis [8], and PTH has been shown to promote osteogenic differentiation of MSCs in temporomandibular arthritis [19], the significance of our study lies in systematically investigating whether PTH can effectively improve MSC function, which distinguishes it from previous studies. The results of our study on the effects of PTH and MSCs were generally consistent with previous reports [20-22], showing the promotion of osteogenic differentiation and proliferation. Additionally, we examined the effect of PTH on the anti-oxidation and anti-hypoxia capabilities of MSCs, thereby enhancing the understanding of the impact of PTH on MSCs.

In this study, the main limitation was the difficulty of establishing a TMJOA model, due to which we primarily observed the therapeutic effect of PTH-induced MSCs on TMJOA, without studying the specific mechanisms. However, the *in vitro* experiments showed that PTH predominantly up-regulates the expression of *Alp*, *Osx*, and *Runx2*, which are known to primarily promote osteogenic differentiation. We speculated that the primary reason PTH enhances the effects of MSCs in treating TMJOA is that the MSCs are pre-treated with osteogenic stimulation before being injected into the temporomandibular joint cavity of rats. This pre-treatment accelerates their differentiation into osteoblasts, thereby reducing bone damage. Additionally, MSCs have the ability to reduce inflammation. Therefore, PTH further enhances the proliferative capacity of MSCs and in turn, strengthens its regulatory function in the joint cavity in terms of anti-inflammation. The other limitation of this study was the lack of *in vivo* observation to check whether the transplanted MSCs enter the temporomandibular joint. The temporomandibular joint cavity is relatively narrow, so it is very difficult to observe the cells inside. Therefore, it is important to dynamically observe the trajectory of transplanted MSCs in the temporomandibular joint, and clarify the specific anti-inflammatory and injury repair mechanisms in the future.

In summary, PTH was found to effectively enhance the efficacy of MSCs. Moreover, this was the first study to confirm that the therapeutic effect of induced MSCs on TMJOA was significantly improved, which provides new ideas for the future treatment of TMJOA.

Acknowledgements

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Disclosure of conflict of interest

None.

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References

[1] Valesan LF, Da-Cas CD, Réus JC, Denardin ACS, Garanhani RR, Bonotto D, Januzzi E and de Souza BDM. Prevalence of temporomandibular joint disorders: a systematic review and meta-analysis. Clin Oral Investig 2021; 25: 441-453.

[2] Delpachitra SN and Dimitroulis G. Osteoarthritis of the temporomandibular joint: a review of aetiology and pathogenesis. Br J Oral Maxillofac Surg 2022; 60: 387-396.
[3] Soontararak S, Chow L, Johnson V, Coy J, Wheat W, Regan D and Dow S. Mesenchymal Stem Cells (MSC) derived from Induced Pluripotent Stem Cells (iPSC) equivalent to adipose-derived MSC in promoting intestinal healing and microbiome normalization in mouse inflammatory bowel disease model. Stem Cells Transl Med 2018; 7: 456-467.
[4] Mathew B, Ravindran S, Liu X, Torres L, Chennakesavalu M, Huang CC, Feng L, Zelka R, Lopez J, Sharma M and Roth S. Mesenchymal stem cell-derived extracellular vesicles and retinal ischemia-reperfusion. Biomaterials 2019; 197: 146-160.
[5] Xiang XN, Zhu SY, He HC, Yu X, Xu Y and He CQ. Mesenchymal stromal cell-based therapy for cartilage regeneration in knee osteoarthritis. Stem Cell Res Ther 2022; 13: 14.
[6] Zhao Y and Xie L. An update on mesenchymal stem cell-centered therapies in temporomandibular joint osteoarthritis. Stem Cells Int 2021; 2021: 6619527.
[7] Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O and Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001; 344: 1434-41.
[8] Zhang J, Pi C, Cui C, Zhou Y, Liu B, Liu J, Xu X, Zhou X and Zheng L. PTHrP promotes subchondral bone formation in TMJ-OA. Int J Oral Sci 2022; 14: 37.
[9] Ohishi M and Schipani E. PTH and stem cells. J Endocrinol Invest 2011; 34: 552-6.
[10] Schmidt C, Ertel T, Arbogast M, Hügle B, Kalle TV and Neff A; Collaborators. The diagnosis and treatment of rheumatoid and juvenile idiopathic arthritis of the temporomandibular joint. Dtsch Arztebl Int 2022; 119: 47-54.
[11] Bouloux G, Koslin MG, Ness G and Shafer D. Temporomandibular joint surgery. J Oral Maxillofac Surg 2017; 75: e195-e223.
[12] Cen X, Pan X, Zhang B, Liu C, Huang X and Zhao Z. Hyaluronan injection versus oral glucosamine and diclofenac in the treatment of temporomandibular joint osteoarthritis. Clin Oral Investig 2022; 26: 2703-2710.
[13] Cömert Kılıç S. Does glucosamine, chondroitin sulfate, and methylsulfonylmethane supplementation improve the outcome of temporomandibular joint osteoarthritis management with arthrocentesis plus intraarticular hyaluronic acid injection. A randomized clinical trial. J Craniomaxillofac Surg 2021; 49: 711-718.
[14] Cen X, Liu Y, Wang S, Yang X, Shi Z and Liang X. Glucosamine oral administration as an adjunct to hyaluronic acid injection in treating temporomandibular joint osteoarthritis. Oral Dis 2018; 24: 404-411.
[15] Matas J, Orrego M, Amenabar D, Infante C, Tapia-Limonchi R, Cadiz MI, Alcayaga-Miranda F, González PL, Muse E, Khoury M, Figueroa FE and Espinoza F. Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial. Stem Cells Transl Med 2019; 8: 215-224.
[16] Wang L, Huang S, Li S, Li M, Shi J, Bai W, Wang Q, Zheng L and Liu Y. Efficacy and safety of umbilical cord mesenchymal stem cell therapy for rheumatoid arthritis patients: a prospective phase I/II study. Drug Des Devel Ther 2019; 13: 4331-4340.
[17] Liu D, Kou X, Chen C, Liu S, Liu Y, Yu W, Yu T, Yang R, Wang R, Zhou Y and Shi S. Circulating apoptotic bodies maintain mesenchymal stem cell homeostasis and ameliorate osteopenia via transferring multiple cellular factors. Cell Res 2018; 28: 918-933.
[18] Zhang LX, Balani YM, Trinh S, Kronenberg HM and Mu Y. Differential effects on bone and mesenchymal stem cells caused by intermittent and continuous PTH administration. Zhonghua Yi Xue Za Zhi 2018; 98: 781-787.
[19] Cui C, Zheng L, Fan Y, Zhang J, Xu R, Xie J and Zhou X. Parathyroid hormone ameliorates temporomandibular joint osteoarthritic-like changes related to age. Cell Prolif 2020; 53: e12755.
[20] Sheyn D, Shapiro G, Tawackoli W, Jun DS, Koh Y, Kang KB, Su S, Da X, Ben-David S, Bez M, Yalon E, Antebi B, Avalos P, Stern T, Zelzer E, Schwarz EM, Gazit Z, Pelled G, Bae HM and Gazit D. PTH induces systemically administered mesenchymal stem cells to migrate to and regenerate spine injuries. Mol Ther 2016; 24: 318-330.
[21] Yang C, Frei H, Burt HM and Rossi F. Effects of continuous and pulsatile PTH treatments on rat bone marrow stromal cells. Biochem Biophys Res Commun 2009; 380: 791-6.
[22] Bhandi S, Alkahtani A, Reda R, Mashyakhy M, Boreak N, Maganur PC, Vishwanathaiah S, Mehta D, Vyas N, Patil V, Raj AT, Testarelli L and Patil S. Parathyroid hormone secretion and receptor expression determine the age-related degree of osteogenic differentiation in dental pulp stem cells. J Pers Med 2021; 11: 349.