Original Article

Chemerin/ChemR23 signaling mediates the effects of ultra-high molecular weight polyethylene wear particles on the balance between osteoblast and osteoclast differentiation

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Background: Ultra-high molecular weight polyethylene (UHMWPE) is one of the favored materials for total joint replacement, but its wear particles cause osteolysis. This study aims to elucidate the signaling that mediates the effects of UHMWPE particles on bone cells.

Methods: RAW264.7 and MC3T3-E1 cells were treated with UHMWPE particles. Chemerin/ChemR23 signaling was manipulated by either overexpressing *Rarres2* and *Cmklr1* or silencing *Cmklr1*. The osteoblast and osteoclast differentiation was evaluated by Alizarin red and TRAP staining, respectively. The expression of osteogenic and osteoclastogenic markers was assessed with quantitative real time PCR and western blot.

Results: UHMWPE particles upregulated the expression of *Rarres2* and *Cmklr1* in both osteoblast and osteoclast precursor cells. UHMWPE particles induced osteoclast differentiation while inhibited osteoblast differentiation, and this effect was abrogated by silencing *Cmklr1* but augmented by the overexpression of *Rarres2* and *Cmklr1*. Similarly, the expression of osteogenic marker genes was inhibited while that of osteoclastogenic marker genes was activated by UHMWPE particles, and this effect was abolished by silencing *Cmklr1* and enhanced by *Rarres2* and *Cmklr1* overexpression.

Conclusions: These results demonstrated that chemerin/ChemR23 signaling plays a central role in the effects of UHMWPE particles on the balance of osteogenic and osteoclastogenic differentiation, which changes the course of bone remodeling and eventually results in osteolysis.

Keywords: Ultra-high molecular weight polyethylene wear particle (UHMWPE wear particle); chemerin; ChemR23; osteoblast differentiation; osteoclast differentiation

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Introduction

Ultra-high molecular weight polyethylene (UHMWPE) has long been the material of choice for the load bearing in total joint replacements (e.g., the tibial plateau in total knee replacements and the acetabular cup in total hip prostheses) due to its excellent energetic toughness and inherent biocompatibility (1). Even with numerous improvements, oxidative damage and wear remain the main and interconnected material-related causes of UHMWPE failure, as oxidative degradation leads to decreased wear resistance (1,2). UHMWPE wear particles cause the two closely connected processes of inflammation and

osteolysis (3-5). Wear particles elicit the production of pro-inflammatory cytokines and chemokines (5,6) that recruit and polarize macrophages and osteoclast precursor cells in periprosthetic tissues, increase local osteoclastogenesis, and inhibit osteoblast differentiation and function (7-9), which in turn leads to prosthesis loosening. However, it is not yet evident which signaling pathway functions as the master mediator of UHMWPE particles in disrupting the balance between osteogenesis and osteoclastogenesis.

Chemerin is widely considered an adipokine as it is highly expressed in adipocytes and plays autocrine and paracrine roles in adipose development. It also plays an endocrine role by modulating immunity and metabolism (10). Chemerin binds the G-protein-coupled receptors *Cmklr1* (known as ChemR23) and GPR1 to activate a variety of downstream signaling pathways (11,12). ChemR23 is widely expressed in immune cells and allows quick recruitment and activation of these immune cells upon chemerin signaling (11). Chemerin/ChemR23 signaling promotes joint inflammation (13) and plays a role in molar tooth development (14). Silencing either chemerin or ChemR23 in bone marrow stem cells inhibits adipocyte differentiation but enhances osteoblast differentiation and mineralization (15). On the other hand, neutralization of chemerin blocks the osteoclast differentiation of hematopoietic stem cells, and the reintroduction of exogenous chemerin can reverse this effect (16). The aim of this study is to examine the role of chemerin/ChemR23 signaling in UHMWPE particle-induced osteolysis. We present the following article in accordance with the MDAR reporting checklist (available at https://dx.doi.org/10.21037/atm-21-2945).

Methods

Cell culture and transfection

MC3T3-E1 and RAW264.7 cells were purchased from the cell bank of the Chinese Academy of Sciences (Shanghai, China). MC3T3-E1 was maintained in α-MEM and RAW264.7 in DMEM (high glucose), respectively, supplemented with 10% FBS, 100 U/mL penicillin, and 100 mg/mL streptomycin (all from Gibco, Shanghai, China) at 37 ℃ in a humidified atmosphere with 5% CO_2.

Runx2, chemerin, and ChemR23 overexpression and *NfatC1*, chemerin, and ChemR23 shRNA knockdown plasmids were synthesized and cloned by GenScript (Nanjing, China). Transfection was achieved with lipofectamine 3000 (ThermoFisher, Shanghai, China) according to the manufacturer's protocols.

Osteoblast differentiation

After reaching 80% confluency, MC3T3-E1 cells were changed to an osteoblast differentiation medium (a complete α-MEM culture medium containing 10 mmol/L β-glycerol phosphate (G9422, Sigma-Aldrich, Shanghai, China), 50 mg/L L-Ascorbic acid (A4544, Sigma-Aldrich), and 10 mmol/L dexamethasone (D4902, Sigma-Aldrich) for 3 weeks. The differentiation medium was changed every 3 days.

Induction of osteoclast differentiation with UHMWPE particles

We seeded 2×10^4 RAW264.7 cells into a 96-well plate and cultured them to 80% confluency. Then, 10^8 UHMWPE particles (17) were added into each well. The culture medium was changed every 48 h. The induction lasted for 7 days.

Alizarin red staining

The medium was removed. The cells were washed once with PBS and fixed in 70% ethanol at room temperature for 30 min. The cells were washed three times with PBS and incubated with Alizarin red S staining solution (Solarbio, Beijing, China) at 37 ℃ for 30 min. The cells were washed twice with ddH_2O before being examined and photographed using XDS-1A microscopy (Wuzhou New Found Instrument, Wuzhou, China).

TRAP staining

The cells were spun at 500 g for 5 min, washed twice with PBS, fixed with 70% ethanol at room temperature for 30 min, and stained with a Leukocyte Acid Phosphatase Kit (387A, Sigma, St. Louis, MO, USA). TRAP-positive cells with three or more nuclei were counted as mature osteoclasts.

Quantitative real-time PCR

Total RNA was extracted from the cells using an RNA purification kit (DP412, Tiangen Bio, Beijing, China) and reverse transcribed using a TIANScript RT Kit (KR107, Tiangen Bio). Quantitative real-time PCR was performed with an AB 7500 system (Applied Biosystems, Forest City, CA, USA) using a Talent fluorescence quantitative detection kit (SYBR Green) (FP209, Tiangen Bio). The primers used in this study are listed in *Table 1*. Relative gene expression was calculated with the $2^{-\Delta\Delta Ct}$ method with GAPDH as the internal control.

Table 1 Sequences of primers used in this study

Gene	Sequence	
	Forward primer	Reverse primer
ChemR23	ACCACTGGGTGTTCGGGAAGG	ACGGAGATGCAGCGGTCAAA
Rarres2	CCCTGAGAACCAAATAAGCCCT	AGCCTGGAGTTGAAAGTCTCTG
NfatC1	TGGTTGAGATACCACCTTTCCG	AGAGTTACCATTGGCAGGAAGG
Acp5	GAAAGTCAAGGGAGTGGCAGGG	ACCTCAGGGCCTTTGTCCTCA
Ctsk	GTTGTATGTATAACGCCACGGC	CTCTCTTCAGGGCTTTCTCGTT
Itgb3	ACATCACACATGCTAGGCAAGA	GGTCAACATTCCAGCCTCCTTA
Runx2	ACCCATTGGTATCTGCCATTGT	AGGAAGCCACACTTAGGGATTG
Alp	ATATCGACGTGATCATGGGTGG	GATGAGATCCAGGCCATCTAGC
Osx	TCCCCTAGGTTATCTCCTTGCA	TAGGAACTAGGCACTGGCAAAG
GAPDH	GGTGAAGGTCGGTGTGAACG	CTCGCTCCTGGAAGATGGTG

Western blot

The cells were lysed on ice for 10 min with RIPA lysis buffer (P0013C, Beyotime, Shanghai, China) containing 1× Protease Phosphatase Inhibitor Cocktail (P1050, Beyotime) before being centrifuged at 13,000 g for 10 min at 4 ℃. Total protein samples (40 μg) were resolved on 8% SDS-PAGE gel and transferred onto PVDF membranes. The membranes were blocked with 5% nonfat milk in PBST (0.05% Tween 100 in PBS), incubated with specified primary antibodies overnight at 4 ℃, washed and incubated with a horseradish peroxidase-conjugated secondary antibody (Jackson ImmunoResearch, West Grove, PA, USA), and then washed and detected with an enhanced chemiluminescence substrate (Roche, Indianapolis, IN, USA).

Statistical analysis

All experiments were independently performed three times with triplicates. Data are shown as mean ± standard deviation of the mean. All statistical analyses were performed using Prism 5 (Graphpad, San Diego, CA, USA). The differences between groups were analyzed by one-way analysis of variance followed by the Bonferonni test. A P value <0.05 was considered statistically significant.

Results

UHMWPE wear particles upregulated chemerin and ChemR23 expression

As the chemerin/ChemR23 system is known to play an important role in both osteoblastogenesis and osteoclastogenesis (15,16), we first investigated whether UHMWPE wear particles regulated the expression of chemerin (*Rarres2*) and ChemR23 in bone cells. The UHMWPE particles gradually upregulated *Rarres2* (*Figure 1A*) and *ChemR23* (*Figure 1B*) during both osteoclast (*Figure 1A,B*) and osteoblast (*Figure 1C,D*) differentiation.

Chemerin/ChemR23 mediated UHMWPE wear particle-induced osteoclastogenesis

As UHMWPE particles were previously shown to induce osteoclast differentiation (17) and osteoclastogenesis was blocked by chemerin neutralization (16), we examined the role of chemerin/ChemR23 in UHMWPE particle-induced osteoclast differentiation. We found that UHMWPE particles induced RAW264.7 macrophages to differentiate into osteoclasts (*Figure 2A*). Silencing ChemR23 expression alone did not change the behavior of the RAW264.7 cells but greatly inhibited UHMWPE particle-induced osteoclast differentiation. Overexpression of chemerin and ChemR23 caused the RAW264.7 cells to spontaneously differentiate into osteoclasts and enhanced the osteoclastogenic effect of the UHMWPE particles (*Figure 2A*).

The mRNA (*Figure 2B*) and protein (*Figure 2C*) levels of the osteoclastogenic gene *NfatC1* and the osteoclast markers *Itgb3*, *Acp5*, and *CtsK* were increased by about 2- to 4-fold by the UHMWPE particles, and this effect was almost completely abrogated by ChemR23 silencing. Overexpressing chemerin and *ChemR23* upregulated the *NfatC1*, *Itgb3*, *Acp5*, and *CtsK* expression and further augmented the effects of the

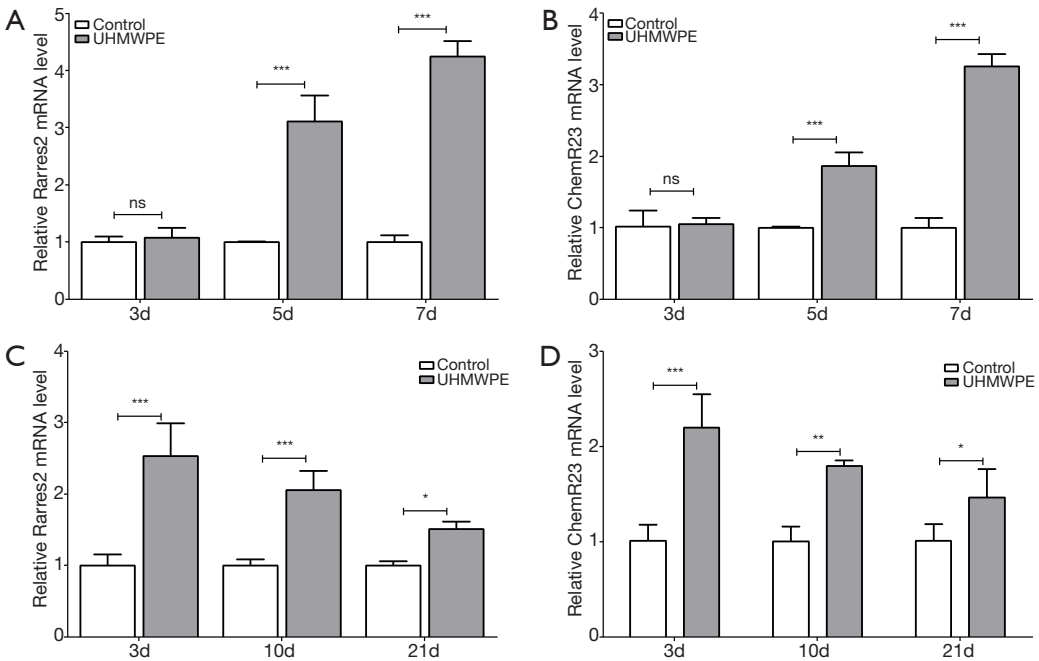

Figure 1 UHMWPE particles upregulate *Rarres2* and *ChemR23* expression during osteoblast and osteoclast differentiation. RAW264.7 cells are treated with UHMWPE particles for 3, 5, and 7 days (A,B). MC3T3-E1 cells are cultured in an osteogenic medium with or without UHMWPE particles for 3, 10, and 21 days (C,D), and the *Rarres2* (A,C) and *ChemR23* (B,D) mRNA levels are analyzed by quantitative real-time PCR. *, P<0.05; **, P<0.01; ***, P<0.001. UHMWPE, ultra-high molecular weight polyethylene.

UHMWPE particles (*Figure 2B,C*).

AP1 and NF-κB were activated by UHMWPE particles in RAW264.7 cells

We then looked into the activation of *AP-1* and *NF-κB* in RAW264.7 cells upon exposure to UHMWPE particles with or without intervening chemerin signaling. Neither *c-fos* nor *NF-κB p65* was phosphorylated 15 seconds after UHMWPE particle treatment (*Figure 3A*). However, the levels of phosphorylated *c-fos* and *NF-κB p65* were significantly increased after UHMWPE particle treatment for 45 (*Figure 3B*) and 120 (*Figure 3C*) seconds, and this effect was inhibited by shRNA silencing of ChemR23 and enhanced by chemerin and ChemR23 overexpression (*Figure 3B,C*).

NfatC1 was required for chemerin/ChemR23-mediated induction of osteoclast differentiation by UHMWPE particles

We next examined if *NfatC1* was essential for the UHMWPE particle induction of osteoclast differentiation as it is the master regulator of osteoclastogenesis (18). UHMWPE particles induced the overexpression of chemerin and ChemR23, upregulated osteoclastogenic genes *NfatC1*, *ACP5*, *Ctsk*, and *Itgb3* (*Figure 4A*), and strongly induced the osteoclast differentiation of RAW264.7 cells (*Figure 4B*). Silencing *NfatC1* expression did not impact the UHMWPE particle-induced overexpression of chemerin and ChemR23 (*Figure 4A*) but inhibited the UHMWPE particle-induced expression of osteoclastogenic transcription factor *NfatC1*, the osteoclast specific markers *Acp5*, *Ctsk*, *Itgb3* (*Figure 4A*), and osteoclast differentiation (*Figure 4B*).

Silencing ChemR23 abrogated the inhibition of osteogenesis by UHMWPE particles

UHMWPE particles inhibited osteoblast differentiation of MC3T3-E1 cells in a dose-dependent manner (Figure S1), and the expression of chemerin and ChemR23 was upregulated by UHMWPE particles (*Figure 1C,D*). We investigated the role of chemerin/ChemR23 signaling in the inhibition of osteoblast differentiation by UHMWPE particles. The UHMWPE particles significantly inhibited

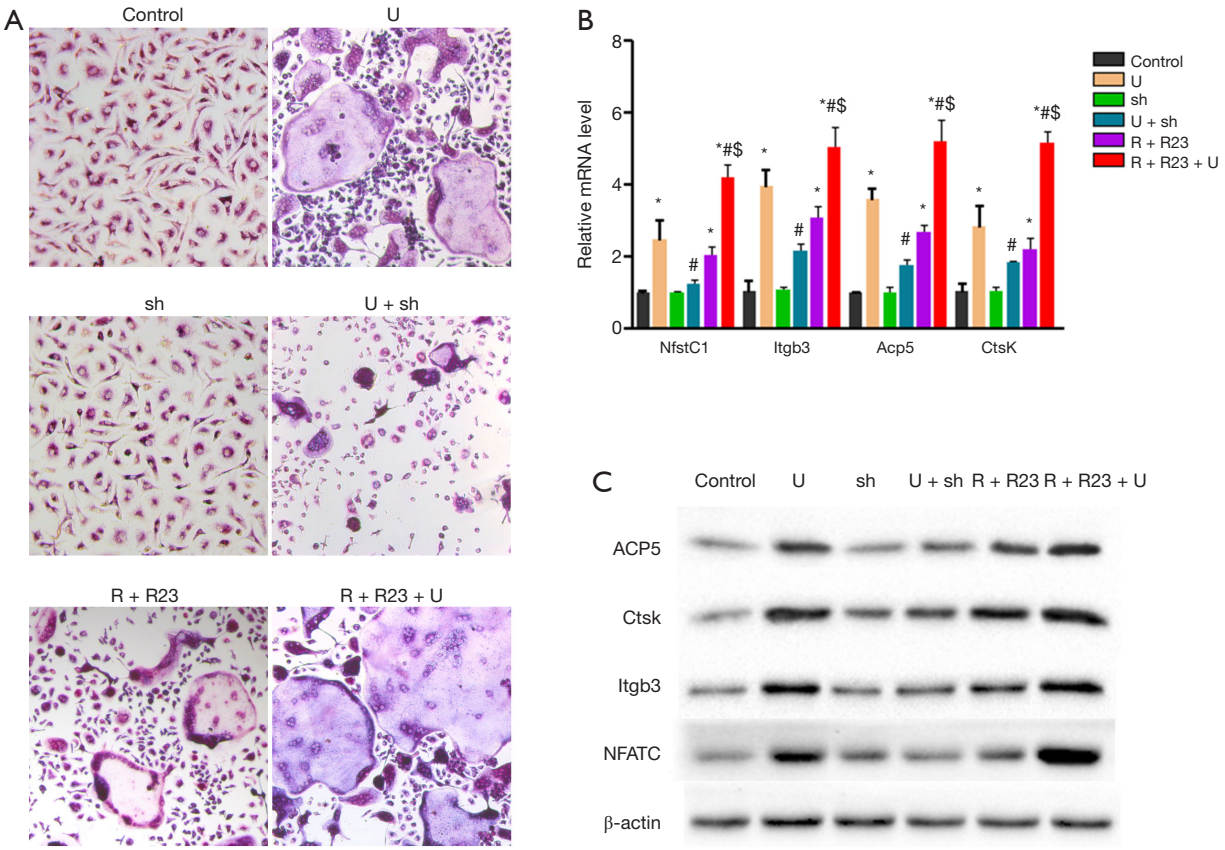

Figure 2 Chemerin/ChemR23 signaling mediates UHMWPE particle-induced osteoclast differentiation. (A) RAW264.7 cells are cultured in a complete medium with or without UHMWPE particles for 7 days and subjected to TRAP staining. (B) mRNA levels of osteoclastogenic markers *NfatC1*, *Itgb3*, *Acp5*, and *Ctsk* are examined by quantitative real-time PCR. (C) The protein levels of osteoclastogenic markers *NfatC1*, *Itgb3*, *Acp5*, and *Ctsk* are assessed by western blot. Bar =100 μm. *, P<0.05 compared to C; #, P<0.05 compared to U; $, P<0.05 compared to R + R23. UHMWPE, ultra-high molecular weight polyethylene; U, UHMWPE particles; sh, shRNA silencing Cmklr1 (ChemR23); R, Rarres2 (chemerin) overexpression; R23, Cmklr1 (ChemR23) overexpression.

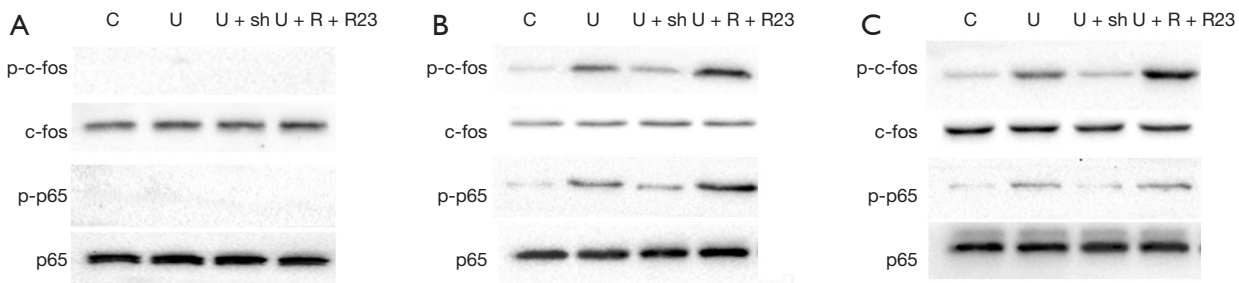

Figure 3 UHMWPE particles activate AP-1 and NF-κB signaling through Chemerin/ChemR23 system. RAW264.7 cells are transfected with shRNA targeting *Cmklr1* or *Rarres2* and *Cmklr1* overexpressing vectors (or their corresponding control vector). Forty-eight hours later, cells are exposed to UHMWPE particles for 15 (A), 45 (B), and 120 (C) seconds. The phosphorylation of c-fos and NF-κB p65 is evaluated by western blot. UHMWPE, ultra-high molecular weight polyethylene; C, control; U, UHMWPE particles; sh, shRNA silencing Cmklr1 (ChemR23); R, Rarres2 (chemerin) overexpression; R23, Cmklr1 (ChemR23) overexpression.

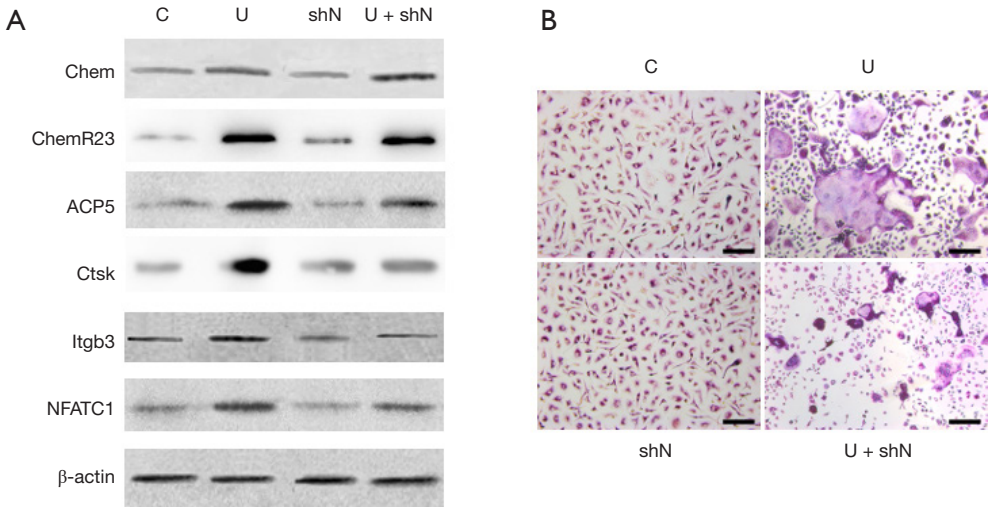

Figure 4 Chemerin/ChemR23 transduces the osteoclastogenic signal of UHMWPE particles through *NfatC1*. (A) The protein levels of chemerin, ChemR23, and the osteoclastogenic markers *NfatC1*, *Itgb3*, *Acp5*, and *Ctsk* are assessed by western blot. (B) RAW264.7 cells with or without *NfatC1* silencing are cultured in complete medium with or without UHMWPE particles for 7 days and subjected to TRAP staining. Bar =100 μm. UHMWPE, ultra-high molecular weight polyethylene; C, control; U, UHMWPE particles; shN, shRNA silencing NfatC1.

osteoblast differentiation (reduction of mineralized nodules). Silencing ChemR23 did not obviously impact the osteogenesis of the MC3T3-E1 cells. However, ChemR23 knockdown abolished the inhibition of the UHMWPE particles on osteoblast differentiation (*Figure 5A*).

Consistently, UHMWPE particles inhibited the mRNA (*Figure 5B*) and protein (*Figure 5C*) levels of the osteogenic genes *Runx2*, *ALP*, and *Osx*. Silencing ChemR23 relieved the inhibition of *Runx2*, *ALP*, and *Osx* expression by the UHMWPE particles (*Figure 5B,C*).

RUNX1 transduced chemerin/ChemR23 signaling in mediating the inhibition of osteoblast differentiation by UHMWPE particles

Overexpressing *Runx2* did not change the levels of chemerin and ChemR23 in the MC3T3-E1 cells with or without UHMWPE particles (*Figure 6A*). However, ectopic *Runx2* not only enhanced osteoblast differentiation of the MC3T3-E1 cells but also relieved the inhibition of osteoblast differentiation by the UHMWPE particles (*Figure 6A,B*).

Discussion

Bone health is maintained by the balance between osteoclasts and osteoblasts. Any disruption of this balance can lead to various diseases, including osteolysis, osteoporosis, and rheumatoid arthritis. For total joint replacement, periprosthetic osteolysis is the most significant long-term complication (19). Implant failure results from excessive bone resorption caused by prosthetic wear particles activating innate immune responses (20,21). Activation of *NF-κB* plays a central role in osteoclastogenesis. UHMWPE particles induce the activation of *NF-κB* and promote the production of *TNF-α* and *TCP-1*, which leads to osteoclast differentiation (17). The current study showed that UHMWPE particles stimulated the phosphorylation of both *NF-κB p65* and *c-fos*. Transcription factor *AP-1* (*c-fos* and *c-jun*) and *NfatC1* independently or cooperatively promoted the osteoclast cell marker gene cathepsin K (*Ctsk*) transcription (22). Inhibition of *NF-κB* and *AP-1* activation suppressed the RANKL-induced osteoclast differentiation of RAW264.7 cells (23). These results are consistent with current data showing that UHMWPE particles activate *NF-κB* and *c-fos* (*AP-1*), upregulate osteoclastogenic genes, and induce osteoclast differentiation. Moreover, UHMWPE particles may induce the secretion of pro-osteoclastogenic factors by osteoblasts (24), which promotes bone resorption and eventually leads to osteolysis.

The differentiation, turnover, and function of osteoblasts is the other half of the equation in periprosthetic

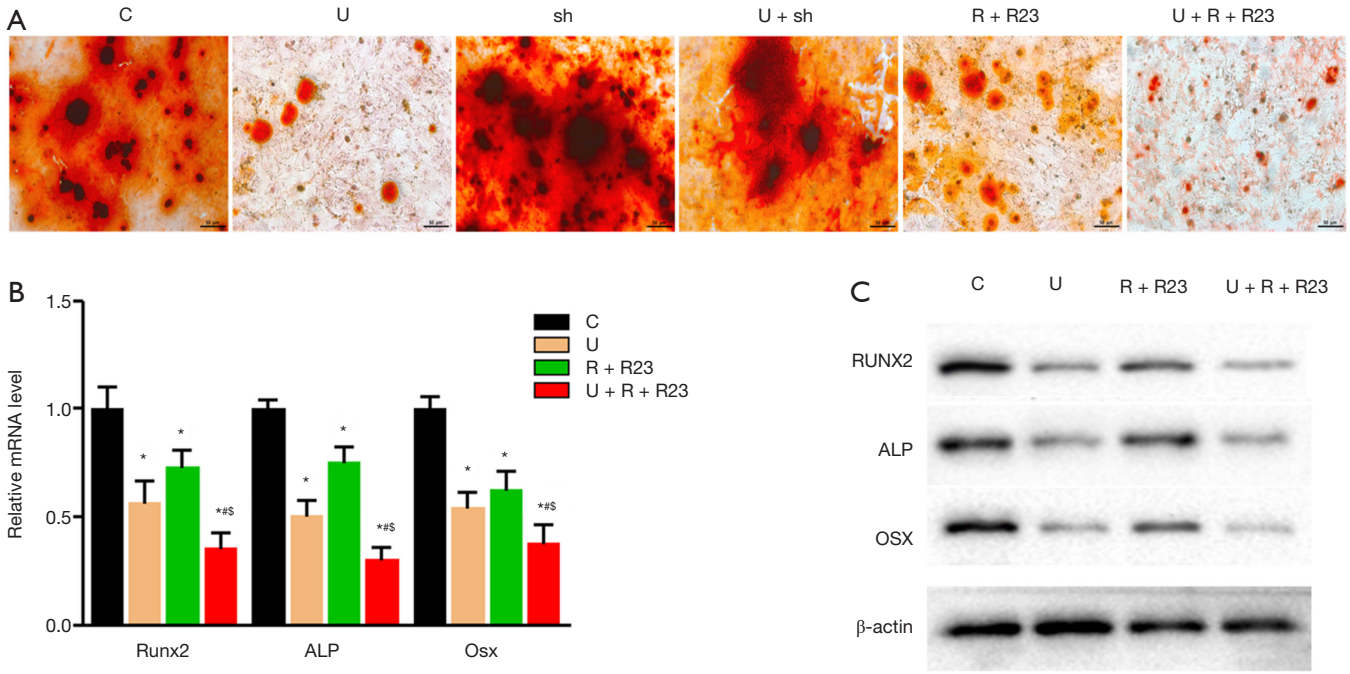

Figure 5 Chemerin/ChemR23 signaling is required for the inhibition of osteoblast differentiation by UHMWPE particles. MC3T3-E1 cells are transfected with shRNA targeting *Cmklr1* or *Rarres2* and *Cmklr1* overexpressing vectors (or their corresponding control vector). Forty-eight hours later, cells are cultured in an osteoblast differentiation medium with or without 4×10^6/mL UHMWPE particles for 21 days. (A) Mineral deposition is assessed with Alizarin red staining. (B) The mRNA levels of osteoblastogenic markers *Runx2*, *Alp*, and *Osx* are analyzed using quantitative real-time PCR. (C) The protein levels of osteogenic genes *Runx2*, *Alp*, and *Osx* are assayed by western blot. Bar =50 μm. *, P<0.05 compared to C; #, P<0.05 compared to U; $, P<0.05 compared to R + R23. UHMWPE, ultra-high molecular weight polyethylene; C, control; U, UHMWPE particles; sh, shRNA silencing Cmklr1 (ChemR23); R, Rarres2 (chemerin) overexpression; R23, Cmklr1 (ChemR23) overexpression.

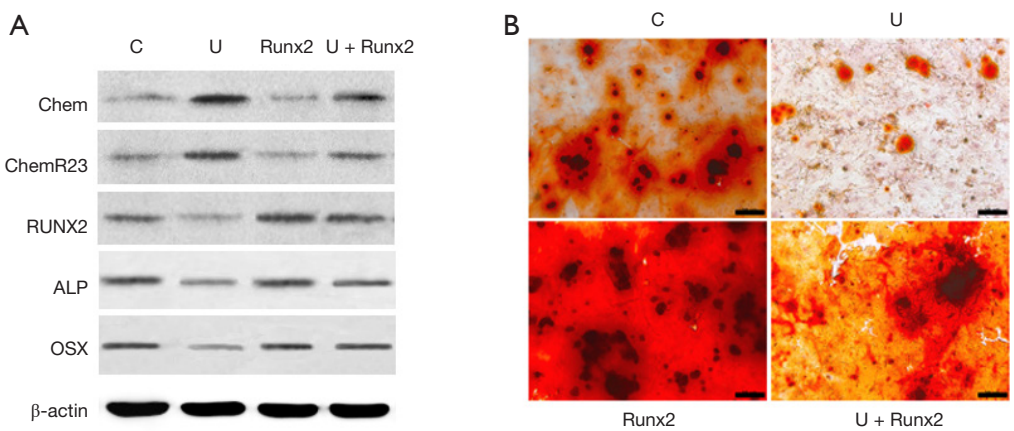

Figure 6 Chemerin/ChemR23 signaling through *Runx2* transduces the anti-osteogenic effect of UHMWPE particles. (A) The protein levels of chemerin, ChemR23, and the osteogenic markers *Runx2*, *Alp*, and *Osx* are assessed by western blot. (B) MC3T3-E1 cells are transfected with *Runx2* overexpressing vectors (or their corresponding control vector). Forty-eight hours later, cells are cultured in an osteoblast induction medium with or without 4×10^6/mL UHMWPE particles for 21 days and subjected to Alizarin red staining. Bar =100 μm. UHMWPE, ultra-high molecular weight polyethylene; C, control; U, UHMWPE particles; Runx2, Runx2 expression vector.

osteolysis. Most studies have focused on osteoclasts, but prosthetic wear particles may impact osteoblasts and contribute to periprosthetic osteolysis by inhibiting osteoblast differentiation, proliferation, and activities, as well as stimulating osteoblasts to produce inflammatory cytokines (25). A previous study reported that CoCrMo metal particles induced apoptosis in MC3T3-E1 cells *in vitro* and caused particle-induced osteolysis by autophagy in the osteoblasts of mouse calvaria (26). The TSIX/miR-30a-5p axis was also shown to mediate CoCrMo metal particle-induced osteoblast apoptosis (27). Additionally, LncRNA DANCR inhibited osteoblast differentiation by downregulating the expressions of *FOXO1*, *Runx2*, Osterix (*Ostx*), and osteocalcin (*OCN*) in the osteolysis process after total hip arthroplasty (28). The current study demonstrated that UHMWPE particles dose-dependently inhibit osteoblast differentiation of MC3T3-E1 cells. Moreover, UHMWPE particles upregulate chemerin and ChemR23 expression in both osteoblast and osteoclast precursor cells.

Furthermore, we showed that chemerin/ChemR23 signaling plays different roles in mediating the UHMWPE particle effects on osteoblast and osteoclast differentiation. Inhibition of chemerin/ChemR23 signaling canceled out the inhibition of osteoblastogenesis by UHMWPE particles, which is consistent with the notion that chemerin/ChemR23 is an anti-osteogenic signal (15,16). Moreover, overexpression of *Runx2* abrogated the inhibitory effects of UHMWPE particles/chemerin/ChemR23 on osteoblast differentiation. Meanwhile, silencing ChemR23 expression abolished the osteoclastogenic effect of UHMWPE particles. Chemerin/ChemR23 has been reported to prompt *NF-κB* activation and inflammatory factors secretion (29). A further study reported that hematopoietic ChemR23 sustained the activated M1 macrophage population and promoted the homing of plasmacytoid dendritic cells to lymphatic organs and recruitment to atherosclerotic lesions (30). As chemerin can act as an autocrine, paracrine, and endocrine mediator, it may recruit monocytes/macrophages to periprosthetic tissue, activate macrophages, and promote osteoclast differentiation upon exposure to UHMWPE wear particles.

Conclusions

Chemerin and ChemR23 were upregulated by UHMWPE wear particles in the precursor cells of both osteoblasts and osteoclasts. Silencing ChemR23 abolished the inhibitory effect on osteoblastogenesis and the inductive effect on osteoclastogenesis of the UHMWPE wear particles by regulating the master regulators *Runx2* in pre-osteoblasts and *NfatC1* in pre-osteoclasts. These results indicate that chemerin/ChemR23 signaling may be a novel target for preventing periprosthetic osteolysis.

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Footnote

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Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-2945

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-2945). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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