【Ⅳ】研究成果の刊行に関する一覧表

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【Ⅴ】研究成果の刊行物・別刷

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Human Mesenchymal Stem Cells Inhibit Osteoclastogenesis Through Osteoprotegerin Production

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Objective. **Mesenchymal stem cells (MSCs) have been proposed to be a useful tool for treatment of rheumatoid arthritis (RA), not only because of their multipotency but also because of their immunosuppressive effect on lymphocytes, dendritic cells, and other proinflammatory cells. Since bone destruction caused by activated osteoclasts occurs in RA, we undertook the present study to investigate the effect of MSCs on osteoclast function and differentiation in order to evaluate their potential use in RA therapy.**

Methods. **Human MSCs and peripheral blood mononuclear cells were cultured under cell–cell contact–free conditions with osteoclast induction medium. Differentiation into osteoclast-like cells was determined by tartrate-resistant acid phosphatase staining and expression of osteoclast differentiation markers.**

Results. **The number of osteoclast-like cells was decreased and expression of cathepsin K and nuclear factor of activated T cells c1 (NF-ATc1) was downregulated by the addition of either MSCs or a conditioned medium obtained from MSCs. Osteoprotegerin (OPG) was constitutively produced by MSCs and inhibited osteoclastogenesis. However, osteoclast differentiation was not fully recovered upon treatment with either anti-OPG antibody or OPG small interfering RNA, suggesting that OPG had only a partial role in the inhibitory effect of MSCs. Moreover, bone-resorbing activity of osteoclast-like cells was partially recovered by addition of anti-OPG antibody into the conditioned medium.**

Conclusion. **The present results indicate that human MSCs constitutively produce OPG, resulting in inhibition of osteoclastogenesis and expression of NF-ATc1 and cathepsin K in the absence of cell–cell contact. Therefore, we conclude that human MSCs exert a suppressive effect on osteoclastogenesis, which may be beneficial in inhibition of joint damage in RA.**

Rheumatoid arthritis (RA) is a prototypical autoimmune inflammatory disease characterized by chronic inflammation. The major inflamed milieu is the synovium, where the presence of proinflammatory cells and cytokines leads to damage to cartilage and bone, resulting in deformity of the joints and decreased quality of life. Progression of bone destruction in RA involves abnormal activation of osteoclasts by interaction with synovial fibroblasts and T helper cells expressing RANKL (1,2). In addition, osteoblast function is known to be compromised at sites of focal bone erosion (3). Treatment of RA with biologic agents targeting tumor necrosis factor (TNF) and interleukin-6 (IL-6) improves

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disease activity and inflammation, leading to remission (4,5), and also has been associated with repair of bone erosions (6), presumably due to suppression of inflammatory cytokine–dependent activation of osteoclasts. However, only a small proportion of patients exhibit repair.

Human mesenchymal stem cells (MSCs) are multipotent cells that are able to differentiate to osteoblasts, chondrocytes, and adipocytes and can be isolated from bone marrow, adipose tissue, and other mesodermal tissues (7). This multipotency, especially the ability to differentiate to osteoblasts and chondrocytes, is attractive for tissue engineering of bone and cartilage in various disorders, including RA, osteoarthritis, and osteoporosis. Intriguingly, MSCs have also been shown to exert immunosuppressive effects. Although elucidation of the immunosuppressive mechanism has been limited, several in vitro and in vivo studies indicate that MSCs strongly suppress effector T cell responses and activation of dendritic cells and natural killer (NK) cells (8–13), suggesting the potential use of human MSCs as a novel cell therapy for autoimmune diseases, especially RA. Moreover, MSCs are known to secrete a variety of cytokines and growth factors that exert paracrine activities on various cells, i.e., inhibition of tissue fibrosis and cell apoptosis, enhancement of angiogenesis, and modulation of cell differentiation (referred to as trophic effects of MSCs) (14,15).

The above-described reports prompted us to postulate that MSCs may inhibit osteoclastogenesis from osteoclast precursors, namely peripheral blood mononuclear cells (PBMCs). In particular, we were interested in elucidating how MSCs act on osteoclasts, which play an important role in bone resorption and destruction in RA. We assessed the effects of human MSCs on osteoclastogenesis and found that MSCs constitutively produce osteoprotegerin (OPG), a decoy receptor for RANKL, leading to suppression of osteoclastogenesis.

MATERIALS AND METHODS

Cells. Human MSCs were purchased from Lonza Walkersville. The source of the human MSCs was bone marrow obtained from the posterior iliac crest of the pelvic bone of healthy volunteers. MSCs were cultured as recommended by the manufacturer. Briefly, cells were cultured in MSC growth medium including 10% fetal bovine serum (FBS; Lonza Walkersville) at 37°C in a 5% CO_2 atmosphere and were subcultured every 6–7 days. MSCs from passages 2–10 were used in this study.

Human PBMCs were isolated from peripheral blood obtained from healthy volunteers, using LSM lymphocyte separation medium (MP Biomedicals). PBMCs (1×10^6) were seeded into wells of 24-well plates (Corning) and cultured in minimum essential medium α (MEMα; Invitrogen) with 10% FBS (Tissue Culture Biologicals) and penicillin/streptomycin (Invitrogen) supplemented with osteoclast induction medium (OCIM) (50 ng/ml human macrophage colony-stimulating factor [M-CSF; GenScript], 50 ng/ml human soluble RANKL [sRANKL; PeproTech], and 100 nmoles/liter 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$; Sigma]) at 37°C in a 5% CO_2 atmosphere.

Coculture assay and MSC-conditioned medium assay. A coculture assay with PBMCs and MSCs was performed to evaluate the effects of MSCs on osteoclast differentiation. PBMCs (1×10^6) in OCIM were seeded in the lower wells and human MSCs in the upper wells of 24-well Transwell plates (Corning) with 0.4-μm–diameter pore. To determine cell viability, PBMCs were stained with fluorescein isothiocyanate–labeled annexin V antibody (BD Biosciences) and positive cells were detected as dead cells by flow cytometry. MSC-conditioned medium was obtained by collecting supernatants of MSCs cultured in MEMα for 3 days at the confluent phase and subsequently adding 50 ng/ml M-CSF and 50 ng/ml sRANKL. PBMCs (1×10^6) or peripheral blood CD14+ cells (5×10^5) were plated into 24-well plates and cultured in MSC-conditioned medium or OCIM. Anti-human OPG neutralizing monoclonal antibody or isotype control IgG1 (both from R&D Systems) was added as indicated.

Tartrate-resistant acid phosphatase (TRAP) staining. To confirm osteoclastogenesis from PBMCs or peripheral blood CD14+ cells, cultured cells were stained using a leukocyte acid phosphatase kit according to the instructions of the manufacturer (Sigma). TRAP-positive and multinuclear cells were counted under brightfield microscopy. TRAP-positive cells with ≥3 nuclei were regarded as osteoclast-like cells.

Measurement of cathepsin K, nuclear factor of activated T cells c1 (NF-ATc1), and OPG expression. PBMCs from healthy donors and OCIM-treated PBMCs were collected and lysed. Total messenger RNA (mRNA) was purified with an RNeasy Mini Kit (Qiagen), and complementary DNA was obtained by reverse transcription. Real-time polymerase chain reaction was performed using cathepsin K– and NF-ATc1–specific primers and TaqMan probes (Hs01080388_m1 and Hs00542678_m1, respectively; Applied Biosystems) with a Step One Plus instrument (Applied Biosystems). Cathepsin K and NF-ATc1 mRNA expression levels were normalized to levels of GAPDH (TaqMan probe Hs99999905_m1; Applied Biosystems) as an endogenous control, and relative quantity compared to a healthy control PBMC sample as a reference was calculated using the $\Delta\Delta C_t$ method. OPG mRNA expression was similarly determined by real-time polymerase chain reaction using TaqMan probes targeting OPG (Hs00900360_m1) and β-actin (Hs99999903_m1) (both from Applied Biosystems) as an endogenous control. Relative quantity compared to a reference sample of normal human MSCs was calculated by the $\Delta\Delta C_t$ method.

MSC culture supernatants were collected at the con-

fluent phase after MSC growth medium was exchanged for MEMα with 10% FBS for 3 days to exclude the effect of growth factors in MSC growth medium. Coculture supernatants were collected at intervals of 3 or 4 days. OPG concentration was measured with a DuoSet enzyme-linked immunosorbent assay development system for human OPG/TNF superfamily 11B (R&D Systems).

Transfection of small interfering RNA. Small interfering RNA (siRNA) targeting OPG mRNA (OPG siRNA; sequence 5′-UGAUCUUCUUGACUAUAUCUUGGUC-3′) was purchased from Invitrogen. Stealth RNAi Low GC Duplex (Invitrogen) was used as negative control siRNA. MSCs (1×10^3) were seeded into upper wells of Transwell plates in MSC growth medium supplemented with 10% FBS without antibiotics. After 24 hours, siRNA was transfected into MSCs using Lipofectamine RNAiMAX in Opti-MEM I according to the protocol recommended by the manufacturer (Invitrogen).

Pit formation assay. To evaluate bone-resorbing activity in osteoclast-like cells, CD14+ cells (1×10^5) isolated from PBMCs were plated onto dentin slices in 96-well plates and cultured in OCIM or MSC-conditioned medium for 14 days. Recombinant human OPG, anti-OPG antibody, or isotype control IgG1 was added to the culture medium. After culturing, dentin slices were stained with Mayer's hematoxylin (Wako) and analyzed by microscopy (Biorevo BZ-9000; Keyence).

Statistical analysis. Mean ± SEM or mean ± SD values from triplicate samples from 1 of at least 3 independent experiments were calculated. Statistical significance was ascertained by Student's *t*-test or one-way analysis of variance. *P* values less than 0.05 were considered significant.

RESULTS

Inhibition of osteoclast differentiation by human MSCs. Although human and murine MSCs have immunosuppressive potency, their effects on osteoclast differentiation and activation have not been well elucidated. Therefore, we first investigated the effect of human MSCs on osteoclastogenesis. PBMCs isolated from healthy donors were cultured with human MSCs under cell–cell contact–free conditions. Medium was supplemented with M-CSF, sRANKL, and $1\alpha,25(OH)_2D_3$ (OCIM) to induce osteoclast differentiation. After 16 days, ~300 osteoclast-like cells per square centimeter were observed when PBMCs were cultured alone (Figures 1A and B). However, the number of osteoclast-like cells was significantly decreased after coculture with human MSCs. The suppressive effect was dependent on the number of human MSCs and did not depend on apoptosis, as assessed by the presence of annexin V–positive cells (Figure 1C). Accordingly, viable cells

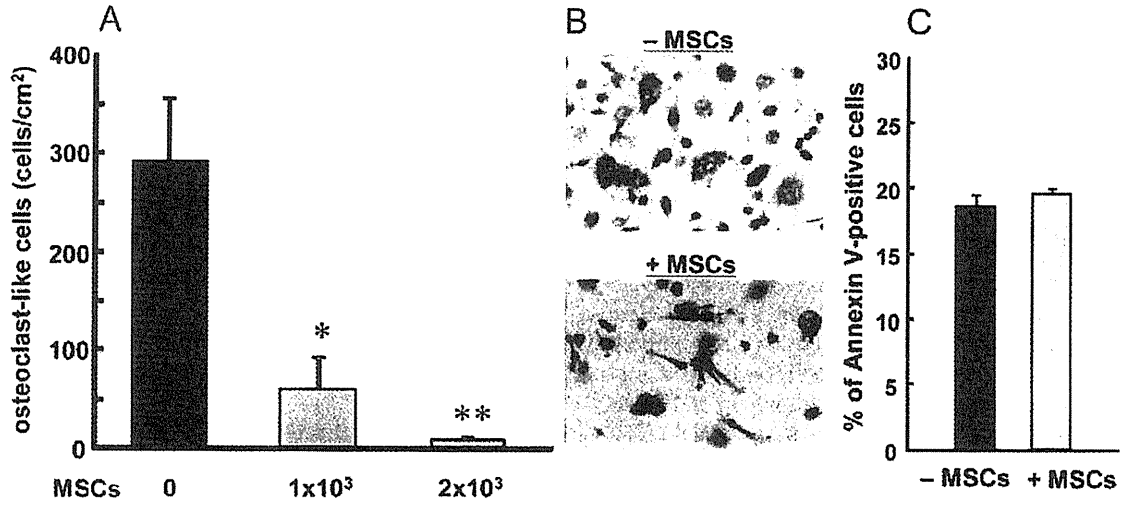

Figure 1. Human mesenchymal stem cells (MSCs) inhibit osteoclastogenesis in a cell–cell contact–free system. Peripheral blood mononuclear cells (PBMCs; 1×10^6/well) and human MSCs (2×10^3/well) were cocultured in osteoclast induction medium (OCIM), using Transwells. **A,** Number of osteoclast-like cells, counted by microscopy after tartrate-resistant acid phosphatase (TRAP) staining. **B,** TRAP-positive osteoclast-like cells observed on day 16 in PBMCs cultured with or without human MSCs. Original magnification × 100. **C,** Proportion of apoptotic and dead PBMCs (annexin V positive), determined by fluorescence-activated cell sorting, in PBMCs cultured for 3 days in OCIM with or without MSCs. Values in **A** and **C** are the mean ± SEM of triplicate samples from 1 of 3 independent experiments. * = $P < 0.05$; ** = $P < 0.01$ versus wells without MSCs, by Tukey's test. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131.