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Protective effect of p38 MAPK inhibitor on wear debris-induced inflammatory osteolysis through downregulating RANK/RANKL in a mouse model

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ABSTRACT. Aseptic loosening associated with wear particle-induced inflammation is a major cause of joint implant failure. Recent studies have demonstrated the therapeutic effects of p38 mitogen-activated protein kinase (MAPK)-based therapies on chronic inflammatory diseases. The purpose of this study was to investigate whether SB203580, a p38 MAPK inhibitor, inhibits wear debris-induced inflammatory osteolysis in mice through downregulation of receptor activator of nuclear factor kβ (RANK)/RANK ligand (RANKL). We used a murine osteolysis model to study the effect of SB203580 on RANKL/RANK signaling and titanium particle-induced osteolysis *in vivo*. Pouch membranes

with intact bone implants were analyzed using histological analysis and transmission electron microscopy, and the levels of RANK and RANKL protein and mRNA were evaluated by immunohistological staining and real-time reverse transcriptase-polymerase chain reaction. SB203580 had less of an effect on RANK and RANKL expression under wear debris-induced conditions. The number of TRAP-positive cells was remarkably reduced in Ti-particle-induced pouch tissues. These effects were confirmed through the transmission electron microscopy results. These results suggest that p38 MAPK-based therapies are beneficial in preventing aseptic loosening associated with total joint replacement by modulating RANK-RANKL signaling.

Key words: Titanium particles; p38 mitogen-activated protein kinase; Inflammatory; Osteolysis; Receptor activators of nuclear factor-kβ

