The effect of metallic magnesium degradation products on osteoclast-induced osteolysis and attenuation of NF-κB and NFATc1 signaling

ZJ Zhai1*, XH Qu1*, HW Li1*, K Yang2, P Wan2, L Tan,2 ZX Ouyang1,3, XQ Liu1, KR Dai1#

1 Shanghai Key Laboratory of Orthopaedic Implants, Department of Orthopaedic Surgery, Shanghai Ninth People’s Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; 2 Institute of Metal Research, Chinese Academy of Sciences, Shenyang, China; 3 Department of Orthopaedics, Hunan Provincial Tumor Hospital and Tumor Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan 410013, The People's Republic of China

INTRODUCTION: Wear particle-induced aseptic prosthetic loosening is one of the most common reasons for total joint arthroplasty (TJA). Extensive bone destruction (osteolysis) by osteoclasts plays an important role in wear particle-induced peri-implant loosening. Thus, strategies for inhibiting osteoclast function may have therapeutic benefit for prosthetic loosening.

METHODS: In this study, we examined the effect of metallic magnesium degradation products (MDP) from magnesium (Mg), which has long been used in orthopedic implants with superior properties, in osteoclast formation and function and wear-particle-induced osteolysis. We mimicked the process of Mg degradation in vivo and obtained MDP by immersing pure Mg in culture medium. Firstly, in vitro we examined the MDP cytotoxicity via CCK8, flow cytometry, and colony assay. Then the effect of MDP on osteoclastogenesis, F-actin ring formation and bone resorption were examined via osteoclast-specific staining and SEM technique. Next a wear particle-induced osteolysis model was generated to examine the inhibitory effect of MDP in bone lesion in vivo via micro-CT and histological & histomorphometric analysis. Finally, molecular techniques were adopted to identify the potential mechanisms though which MDP inhibited osteoclast formation and function both in vitro and in vivo.

RESULTS: For the first time, we demonstrated that MDP suppresses osteoclast formation, polarization, and osteoclast bone resorption in vitro. An in vivo assay demonstrated that MDP attenuates wear particle-induced osteolysis. Furthermore, we found that MDP significantly inhibits nuclear factor-κB (NF-κB) activation by retarding inhibitor-κB degradation and subsequent NF-κB nuclear translocation. We also found that MDP attenuates the expression of NFATc1 at both the protein and mRNA levels. These results demonstrate that MDP has anti-osteoclast activity in vitro and prevents wear particle-induced osteolysis in vivo.

DISCUSSION & CONCLUSIONS: Collectively, our study suggests that metallic magnesium, one of the orthopedic implants with superior properties, has significant potential for the treatment of osteolysis-related diseases caused by excessive osteoclast formation and function.

*Contributed equally; #Co-corresponding authors.

ACKNOWLEDGEMENTS: Key National Basic Research Program of China (Grant No. 2012CB619101); Major Basic Research of Science and Technology Commission of Shanghai Municipality (Grant No. 11DJ1400303); Doctoral Innovation Foundation from Shanghai Jiaotong University School of Medicine (BXJ201330).