The effect of TNFα secreted from macrophages activated by titanium particles on osteogenic activity regulated by WNT/BMP signaling in osteoprogenitor cells

Sang-Soo Lee a,b,1, Ashish R. Sharma a,b,1, Byung-Soo Choi a,b, Jun-Sub Jung a, Jun-Dong Chang b, Seonghun Park b,c, Eduardo A. Salvati d, Edward P. Purdu e, Dong-Keun Song a, Ju-Suk Nam a,b,*

a Infectious Disease Medical Research Center & Department of Pharmacology, College of Medicine, Hallym University, Chucheon, Gangwon-do 200-702, Republic of Korea
b Institute for Skeletal Aging & Orthopaedic Surgery, Chunchon Sacred Heart Hospital, College of Medicine, Hallym University, Chucheon, Republic of Korea
c School of Mechanical Engineering, Pusan National University, Pusan, Republic of Korea
d Orthopedic Surgery & Osteolysis Research Laboratory, Hospital for Special Surgery, USA

ARTICLE INFO

Article history:
Received 1 February 2012
Accepted 3 March 2012
Available online 19 March 2012

Keywords:
Particle
TNFα
Osteolysis
WNT
BMP
SOST

ABSTRACT

Wear particles are the major cause of osteolysis associated with failure of implant following total joint replacement. During this pathologic process, activated macrophages mediate inflammatory responses to increase osteoclastogenesis, leading to enhanced bone resorption. In osteolysis caused by wear particles, osteoprogenitors present along with macrophages at the implant interface may play significant roles in bone regeneration and implant osteointegration. Although the direct effects of wear particles on osteoblasts have been addressed recently, the role of activated macrophages in regulation of osteogenic activity of osteoblasts has scarcely been studied. In the present study, we examined the molecular communication between macrophages and osteoprogenitor cells that may explain the effect of wear particles on impaired bone forming activity in inflammatory bone diseases. It has been demonstrated that conditioned medium of macrophages challenged with titanium particles (Ti CM) suppresses early and late differentiation markers of osteoprogenitors, including alkaline phosphatase (ALP) activity, collagen synthesis, matrix mineralization and expression of osteocalcin and Runx2. Moreover, bone forming signals such as WNT and BMP signaling pathways were inhibited by Ti CM. Interestingly, TNFα was identified as a predominant factor in Ti CM to suppress osteogenic activity as well as WNT and BMP signaling activity. Furthermore, Ti CM or TNFα induces the expression of sclerostin (SOST) which is able to inhibit WNT and BMP signaling pathways. It was determined that over-expression of SOST suppressed ALP activity, whereas the inhibition of SOST by siRNA partially restored the effect of Ti CM on ALP activity. This study highlights the role of activated macrophages in regulation of impaired osteogenic activity seen in inflammatory conditions and provides a potential mechanism for autocrine regulation of WNT and BMP signaling mediated by TNFα via induction of SOST in osteoprogenitor cells.

© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

Recent advances in biomaterials including titanium (Ti) have led to their frequent use as joint replacement and dental implants. Ti has been widely used due to its good osseointegration, excellent corrosion resistance and biocompatibility in biological fluids and high resistance/weight ratio. Unfortunately, wear debris, primarily generated from prosthetic joint articulations, modular interfaces, and non-articulating interfaces, remains the major factor limiting the survival of replaced implants by causing osteolysis around implant [1,2].

Particle phagocytosis by various cells is a critical component of biological response to implant debris [3]. Macrophages largely mediate inflammatory response in osteolytic conditions. On activation, macrophages releases matrix metalloproteinases, chemokines, and cytokines [4] including mediators of bone resorption such as TNFα and IL-1 [5]. These cellular mediators from macrophages may act in an autocrine and paracrine fashion to induce imbalance between bone formation and resorption either by enhancing the osteoclastic lineage or by acting on stromal or osteoblastic cells, leading to the loss of bone stock [6]. It has been well documented that monocyte-macrophage lineage cells exposed to diverse particles

---

1 Both authors contributed equally to this work.