P7C3 Ameliorates Bone Loss by Inhibiting Osteoclast Differentiation and Promoting Osteogenesis

Bo Tian, Jinyu Bai, Lei Sheng, Hao Chen, Wenju Chang, Yue Zhang, Chenlu Yao, Chenmeng Zhou, Xiaoyu Wang, Huajian Shan, Qirong Dong, Chao Wang, and Xiaozhong Zhou

1Department of Orthopedics, The Second Affiliated Hospital of Soochow University, Suzhou, China
2Laboratory for Biomaterial and ImmuNoEngineering, Institute of Functional Nano & SoftMaterials (FUNSOM), Soochow University, Suzhou, China

ABSTRACT
Bone homeostasis, the equilibrium between bone resorption and formation, is essential for maintaining healthy bone tissue in adult humans. Disruptions of this process can lead to pathological conditions such as osteoporosis. Dual-targeted agents, capable of inhibiting excessive bone resorption and stimulating bone formation, are being explored as a promising strategy for developing new treatments to address osteoporosis. In this study, we investigated the effects of P7C3 on bone remodeling and its potential therapeutic role in osteoporosis treatment in mice. Specifically, P7C3 can remarkably suppress receptor activator of nuclear factor-xB (NF-xB) ligand (RANKL)-induced osteoclast differentiation in bone marrow macrophages via the Akt-NF-kB-NFATc1 signaling pathway. Additionally, RNA sequencing (RNAseq) analysis revealed that P7C3 promoted osteoblast differentiation and function through the Wnt/β-catenin signaling pathway, thereby enhancing bone formation. Furthermore, μCT analysis and histological examination of bone tissues from P7C3-treated mice showed attenuation of both Ti-induced bone erosion and ovariectomy (OVX)-induced bone loss. These findings suggest that P7C3 may have a novel function in bone remodeling and may be a promising therapeutic agent for the treatment of osteoporosis. © 2023 The Authors. JBMRI Plus published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research.

KEY WORDS: BONE HOMEOSTASIS; OSTEOSTAR; OSTEOCLAST; OSTEOPOROSIS; P7C3

Introduction
The skeleton is a dynamic tissue that serves as the body scaffold to protect vital organs, facilitating body movement and supporting hematopoiesis. Throughout the lifespan of organisms, the bones undergo constant remodeling through coordinated activities of osteoclasts and osteoblasts, which mediate bone resorption and formation, respectively. Maintaining a balance between resorption and formation is critical for preserving skeletal mass. However, with aging or certain diseases, bone homeostasis becomes disrupted, leading to an imbalance of the resorption over formation. This imbalance further contributes to bone loss and increased susceptibility to fragility fracture, which affects hundreds of millions of people worldwide, especially postmenopausal women.

Osteoclasts originate from the fusion of mononuclear macrophages lineage of hematopoietic stem cells, while osteoblasts derive from mesenchymal stem cells of bone marrow (BMSCs). However, these two types of cells are intertwined with each other. During the remodeling process, bone resorption occurs first, followed by bone formation in the resorption cavity. Osteoclasts not only play a bone-resorbing role, but also secrete certain bone osteoblast-stimulating factors, thereby regulating osteoblast activity. These certain factors promote the activation of the essential transcription factors run-related transcription factor 2 (Runx2), osteonectin (Oxn), and β-catenin, which govern the expression of osteoblast-specific genes, including alkaline phosphatase (ALP), osteopontin (OPN), and osteocalcin (OCN), thus exhibiting osteogenic function. Meanwhile, macrophage-colony stimulating factor (M-CSF) and the receptor activator of nuclear factor-xB (NF-xB) ligand (RANKL), produced by osteoblast-lineage cells, play an essential role in osteoclast differentiation and function. Binding between RANKL and its cell-surface receptor RANK activates various downstream

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Address correspondence to: Xiaozhong Zhou and Qirong Dong, Department of Orthopedics, The Second Affiliated Hospital of Soochow University, 1055 San’xiang Road, Suzhou, Jiangsu 215004, China. E-mail: zhzhou@suda.edu.cn; dongqirong@suda.edu.cn
Chao Wang, Laboratory for Biomaterial and ImmuNoEngineering, Institute of Functional Nano & SoftMaterials (FUNSOM), Soochow University, 199 Ren’Ai Road, Suzhou, Jiangsu 215123, China. E-mail: cwang@suda.edu.cn
BT, JB, and LS contributed equally to this work.
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