Public release date: 4-Nov-2010

Contact: Cathleen Genova

cgenova@cell.com

617-397-2802

Cell Press

Timing is everything in combination therapy for osteoporosis

The adult human skeleton undergoes constant remodeling, with new bone forming at sites that have been broken down by a precise process called resorption. During remodeling, skeletal stem cells are recruited to resorption sites and directed to differentiate into bone-forming cells. Osteoporosis, a condition characterized by weak and fragile bones, develops when there is an imbalance in the remodeling process and more bone is lost than replaced. Now, new research published by Cell Press in the November issue of the journal *Cell Stem Cell* uncovers a mechanism that may guide development of better strategies for treatment osteoporosis.

Osteoporosis is often treated with drugs that inhibit bone resorption, such as alendronate, or drugs that stimulate bone formation, such as parathyroid hormone (PTH). Surprisingly, previous attempts to combine these approaches were not effective. "In clinical trials where PTH and alendronate were administered concurrently, the bone building effects of PTH were impaired," explains senior study author Dr. Xu Cao from The Johns Hopkins School of Medicine in Baltimore, MD. "This suggests that bone resorption is necessary for PTH-induced bone formation, but the underlying mechanisms are obscure. An improved understanding of the role that bone resorption plays in PTH-induced bone formation would provide a key mechanistic rationale for the development of strategies that maximize use of both PTH and antiresorptive drugs in the treatment of osteoporosis."

Dr. Cao's group had previously shown that transforming growth factor (TGF)-?1 plays a key role in bone formation after bone resorption. In the current study, the researchers identified a subset of skeletal stem cells that were recruited to bone remodeling sites in response to bone resorption. Importantly, the authors demonstrated the TGF-?1 is essential for recruitment of skeletal stem cells during PTH-stimulated bone remodeling. Further, alendronate inhibited release of TGF-?1 during bone resorption.

"Our research shows that inhibition of TGF-?1 activation by alendronate leads to insufficient recruitment of skeletal stem cells to resorptive sites for the new bone formation during PTH-stimulated bone

remodeling," says Dr. Cao. "Given this mechanism, it is possible that the use of PTH before treatment by an antiresorptive drug like alendronate could be an effective therapy." Taken together, the findings help to explain why the order and timing of combination drug therapy may be critical for successful treatment of osteoporosis and may help to direct the design of future clinical trials.

###

The researchers include Xiangwei Wu, The Johns Hopkins University School of Medicine, Baltimore, MD, Tongji Hospital, Tongji Medical School, Huazhong University of Science and Technology, Wuhan, China; Shihezi University, Shihezi, Xinjiang, China; Lijuan Pang, The Johns Hopkins University School of Medicine, Baltimore, MD, Tongji Hospital, Tongji Medical School, Huazhong University of Science and Technology, Wuhan, China, Shihezi University, Shihezi, Xinjiang, China; Weiqi Lei, The Johns Hopkins University School of Medicine, Baltimore, MD William Lu, The University of Hong Kong, Hong Kong, China; Jun Li, The Johns Hopkins University School of Medicine, Baltimore, MD, Tongji Hospital, Tongji Medical School, Huazhong University of Science and Technology, Wuhan, China; Shihezi University, Shihezi, Xinjiang, China; Zhaoyang Li, The University of Hong Kong, Hong Kong, China; Frank J. Frassica, The Johns Hopkins University School of Medicine, Baltimore, MD; Xueling Chen, The Johns Hopkins University School of Medicine, Baltimore, MD; Shihezi University, Shihezi, Xinjiang, China; Mei Wan, The Johns Hopkins University School of Medicine, Baltimore, MD and Xu Cao, The Johns Hopkins University School of Medicine, Baltimore, MD.
