# Experimental Approach May Reverse Rheumatoid Arthritis and Osteoporosis

September 21 2009

(PhysOrg.com) -- Researchers have identified a mechanism that may keep a well known signaling molecule from eroding bone and inflaming joints, according to an early study published online today in the *Journal of Clinical Investigation*.

Bone is continually recycled to maintain its strength through the competing action of osteoclasts, cells that break down aging bone, and osteoblasts, which build new bone. Osteoclasts also play a central role in common diseases that erode bone, where two signaling molecules, TNFα and RANKL, cause too much bone breakdown. Both are known to turn on the nuclear factor kappa B complex (NF-κB), which turns on genes that cause the stem cell precursors of osteoclasts to mature and start eating bone. While both TNFα and RANKL encourage bone loss, the current study argues that TNFα and RANKL have different effects on levels of a key inhibitory protein within the NF-κB pathway called NF-κB p100, with important consequences for drug design.

The NF-κB pathway as a whole signals for more active osteoclasts, but NF-κB p100 (p100) interferes with the ability of that same pathway to pass on the bone loss signal. While both TNFα and RANKL activate NF-κB signaling, RANKL efficiently converts p100 into a form that no longer blocks NF-κB pathway signaling and that leads to bone loss. In contrast, the current study is the first to show that TNFα lets p100 build up. Thus, TNFα both causes bone loss through NF-κB signaling and limits it via p100 accumulation.

Experiments found further that mice genetically engineered to lack NF-κB2 p100 suffered more severe joint erosion and inflammation than their normal littermates in the face of TNFα. TNFα, but not RANKL, also increased levels of a protein in osteoclast precursors called TNF receptor-associated factor 3 (TRAF 3), which may help NF-κB p100 block osteoclast formation and inflammation.

“While further studies will be required to confirm and detail this mechanism, our results argue strongly that increasing levels of either TRAF3 or NF-κB p100 could represent a powerful new way to limit bone destruction and inflammation-induced bone loss seen in osteoporosis and rheumatoid arthritis,” said Brendan Boyce, M.D., professor within the Department of Pathology and Laboratory Medicine at the University of Rochester Medical Center, and the study’s corresponding author. “NF-κB p100 levels may vary with each person’s genes, making some more susceptible to TNFα-driven disease. Future solutions may be local delivery of p100 into diseased joints via gene therapy, or to target with a drug the enzyme, NIK, which otherwise limits the p100 supply.”

At the Center of Bone Loss and Inflammation

Drugs that block the function of TNFα are blockbusters (e.g. Enbrel, Humira and Remicade) because they effectively prevent bone loss and inflammation in most patients with rheumatoid arthritis. They have also been shown to reduce bone loss in women early after menopause.

Other studies, however, have suggested that TNFα cannot cause precursor cells to become osteoclasts unless RANKL first “primes” them. The debate has been spirited because it goes to which molecule should be targeted in near-future attempts to design more precise drugs.

The current results show that TNFα can signal for bone loss without

RANKL, providing NF-κB p100 is also absent. By engineering mice with neither RANKL nor NF-κB p100, Boyce and colleagues found that TNFα had greatly increased ability to signal for osteoclast maturation and bone loss in this scenario.

Another unexpected result was measured in changes in gene expression, the process by which information encoded in DNA chains is used to build proteins that make up the body's structures and carry it messages. The team found that mice engineered to over-express TNFα, but also to lack NF-κB p100, had significantly increased inflammation in their joints when compared to mice with high TNFα levels, but also with p100 present to counter it.

Along with Boyce, the study was led by Zhenqiang Yao and Lianping Xing in the Department of Pathology and Laboratory Medicine at the University of Rochester Medical Center. The study was funded in part by the National Institutes of Health.

"We believe NF-κB p100 limits not only osteoclast maturation, but also the number of inflammatory cells attracted to the joints in response to TNFα," Boyce said. "If confirmed, it would mean that p100 has more than one role in more than one major bone disease, and thus would create new opportunities to reverse disease by manipulating p100 levels."

Provided by University of Rochester Medical Center (news : web)