Researchers discover how rheumatoid arthritis causes bone loss

August 20 2008

Researchers have discovered key details of how rheumatoid arthritis (RA) destroys bone, according to a study published in the Aug. 22 edition of the *Journal of Biological Chemistry*. The findings are already guiding attempts to design new drugs to reverse RA-related bone loss and may also address more common forms of osteoporosis with a few adjustments.

Two million Americans suffer from rheumatoid arthritis (RA), which causes swelling, pain and deformity in joints and also lead to the thinning of bone. In autoimmune diseases like RA, the body's disease-fighting immune cells mistakenly identify parts of a person's body as foreign invaders, akin to bacteria, and produce chemicals to destroy them. Among the immune chemicals known to play a central in autoimmune disease is tumor necrosis factor alpha (TNF alpha), which ramps up the production of immune cells and chemicals as part of the body's response to disease. When overproduced in RA patients, TNF alpha signals for the destruction of cartilage and bone.

Beyond its control over immune cells, TNF alpha also influences bone mass. Human bone is continually regenerated to maintain strength. Under the control of signaling molecules which include TNF alpha, two cell types, balanced against each other, make bone recycling possible. Osteoclasts break down aging bone to make way for new bone, while osteoblasts build new bone at the sites where osteoclasts have removed it. Going into the study, the field understood that TNF alpha decreases the number of bone-building osteoblasts, but not how. The current study

provides the first direct proof that the TNF alpha affects osteoblasts through an enzyme called Smad Ubiquitin Regulatory Factor 1 (Smurf1), which in turn shuts down two proteins that would otherwise drive bone-building.

While traditional RA drugs like NSAIDs and steroids treat symptoms, a newer class of best-selling drugs (e.g. Humira, Remicade and Enbrel) reverses the disease process by shutting down TNF alpha activity. While the new drugs are effective for many patients, others experience infections and even lymphoma in a few cases. The new drugs are based on bioengineered versions of proteins made by human immune cells called antibodies, and are very expensive to make. Thus, the field has been searching for smaller, simpler chemicals that would be effective, but with lower costs and fewer side effects.

"The significance of our study is that it identifies SMURF1 as the signaling partner through which TNF does damage in RA-related bone loss," said Lianping Xing, Ph.D., assistant professor of Pathology and Laboratory Medicine at the University of Rochester Medical Center. "That has enabled researchers to begin designing small molecule drugs to shut down the action of Smurf 1 and its relatives. Furthermore, since mice engineered to have less Smurf1 expression develop thicker bones, future drugs that shut down Smurf1 may be also useful against more common forms of osteoporosis simply by changing the dose. Of course, this is early-stage work with many obstacles ahead, but it is exciting nonetheless."

Study Details

In the late 1990s, Gerald H. Thomsen, Ph.D., at Stony Brook University in New York discovered that Smurf1 helps to attach a protein tag called ubiquitin to aging proteins in need of disposal. The tag then attracts the attention of cellular machines called proteosomes that degrade proteins.

Xing's team generated two lines of mice – one with high TNF alpha levels and with Smurf1 present, and a second group with high TNF alpha production but no Smurf1. Bone volume and strength of both groups of mice were then examined using a combination of imaging technologies and were compared. Experiments showed that increased TNF alpha levels dramatically decreased the levels of two key factors, Smad1 and Runx2. Both Smad1 and Runx2 signaled to increase the number of bone-building osteoblasts, but only if Smurf1 was present to pass on the signal from TNF alpha.

Genetically engineered mice with the Smurf1 gene removed no longer responded to TNF alpha because Smurf1 was not present to label Smad1 and Runx2 with the ubiquitin destruction tag. As expected, mice with increased TNF alpha had lesser bone mass than their counterparts, a result partially reversed in mice where Smurf1 had been removed.

Bolstering the importance of the current paper is the fact that TNF alpha promotes the destruction of some types of cancer cells. While toxic when administered systemically, it has found a niche in preventing the spread of skin cancer, where it can be injected directly into a tumor. Other drugs then became available that shut down the TNF signal by directly inhibiting the protein-eating proteosomes that receive the signal. There is an existing anti-myeloma drug on the market, bortezomib, which shuts down the proteosomes that Smurf1 partners with to destroy Smad 1 and Runx2.

Thus, Xing's team will be looking at the effect of bortezomib over the next year to see if shutting down proteosomes in bone cells does indeed increase bone mass in mice engineered to have high levels of TNF alpha. Bortezomib, is a general proteosome inhibitor, however, and does not specifically target Smurf 1, and future efforts will seek to identify Smurf1-specific drug candidates. In the meantime, the team is also seeking other groups of ligases that, like Smurf1, contribute to bone loss

because experiments revealed that Smurf1 is not responsible for 100 percent of the bone loss under inflammatory conditions.

Along with Xing, the study was led by Ruolin Guo, Motozo Yamashita, Qian Zhang, Quan Zhou, Di Chen, David G. Reynolds, Hani Awad, Laura Yanoso, Lan Zhao, Edward Schwarz, Ying Zhang and Brendan Boyce within the Department of Pathology at University of Rochester. The article published today in hard copy was first published online on June 19, 2008.

"Our over-all hypothesis is that in inflammatory diseases like RA, the function of a group of enzymes like Smurf1 gets turned on to cause proteasome degradation of key regulator proteins leading to bone loss," Xing said. "The real, future solution will involve a treatment that specifically addresses each of these."

Source: University of Rochester