Steroids help reverse rapid bone loss tied to rib fractures

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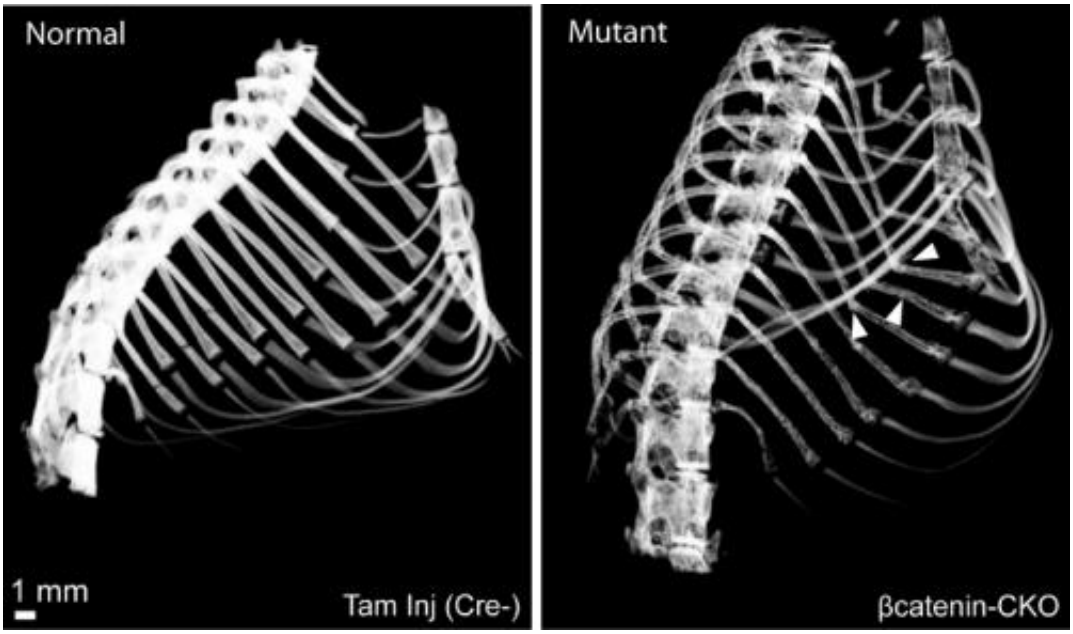

CT scan of normal rib cage (left) and rib cage (right) of mutated animal lacking beta catenin in stromal cells. Arrowheads point to fractures. Credit: Deb Lab, UNC School of Medicine.

New research in animals triggered by a combination of serendipity and counterintuitive thinking could point the way to treating fractures caused by rapid bone loss in people, including patients with metastatic cancers.

A series of studies at the University of North Carolina School of Medicine found that steroid drugs, known for inducing bone loss with

prolonged use, actually help suppress a molecule that's key to the rapid bone loss process. A report of the new findings appears online Feb. 5, 2013 in the journal PLOS ONE.

Osteoporosis or the loss of bone mass is a major public health problem in the Western world and commonly results in hip and spine fractures. "But rib fractures are the most common and yet most unreported osteoporotic fractures and also occur in many cancers such as breast cancer, malignant melanoma, and myelomas, that metastasize and spread to the ribs," says Arjun Deb, MD, assistant professor in the departments of Medicine and Cell Biology and Physiology at UNC.

"While little is known about the biology of rib fractures, we have identified a molecular mechanism that could have important implications for the treatment of fractures in cancers and other conditions often associated with rapid bone loss," adds Deb, who also is a member of UNC's McAllister Heart Institute and Lineberger Comprehensive Cancer Center.

The UNC researcher indicated that his lab arrived at the study "via serendipity." From stromal cells of adult mice, they had deleted a gene called beta catenin. These cells, also known as fibroblasts, form the connective tissue of almost all organs in the body. The Deb lab was working on the molecular regulation of these cells.

But something "amazing" occurred, he said. Following beta catenin deletion, the mice died within three weeks. The researchers looked at the functioning of every organ – heart, kidney, lung, spleen – wherever this gene could possibly be expressed. All appeared normal, except lung function. "With just a whiff of anesthesia, their blood oxygen saturation dropped precipitously. This was a first clue of a problem in the respiratory system of these animals." But the lungs looked absolutely fine under the microscope.

Deb then turned to UNC's physics & astronomy department, which had developed a novel contactless fiber-optic displacement sensor for monitoring respiration during mouse CT scans. In association with the department of radiology and the Biomedical Research Imaging Center at UNC, 3-D lung reconstruction revealed profound lung collapse on one or both sides. This was a puzzle. "How can an animal with normal lung tissue under a microscope have lung collapse and respiratory problems?" Deb wondered whether the chest wall could be the culprit.

CT scans of the chest wall in these animals revealed multiple spontaneous fractures affecting multiple ribs. The affected ribs had 60-70 percent less bone compared to normal ribs. Essentially the bony rib cage had disappeared within 3 weeks, said Deb, and he immediately realized that the animals were dying from respiratory failure because the frail chest wall was unable to support respiration.

Bone mass is usually maintained by a close functional coupling of osteoblasts (cells that form bone) and osteoclasts (cells that resorb bone). The study team found a huge infiltration of osteoclasts into the animals' ribs. Other bones, including the spine and femur, also showed some resorption but not as dramatic as in the ribs.

And when drugs such as bisphosphonates, commonly used to preserve bone mass in humans were given to the animals, their survival was prolonged only briefly. This led the study team to think that the osteoclast formation was so aggressive that the body was unable to form new bone to keep apace with the bone loss.

In conditions such as rheumatoid arthritis and other problems involving inflammation, many types of inflammatory cells promote bone resorption, which led the researchers to see if treatment with corticosteroids might be helpful in these animals. And it was: a 30-40 percent increase in bone mass, compared to animals that did not get

steroids. They also found 60-70 percent of the ribs were preserved.

"Notably, 75 percent of the animals survived," Deb said. "And after 80 days, we saw that the ribs showed evidence of repair, they were able to form new bone. And when we looked at new CT lung scans, the lungs were expanded and the ribs contained far less numbers of osteoclasts."

As to mechanism, Deb explains that a molecule in bone called rank ligand (RANKL) is important for osteoclast formation. "We found that steroids were suppressing RANKL to the extent that RANKL levels in these animals were the same as healthy animals."

"From that perspective, these studies are interesting and challenge the existing paradigm: that steroids are drugs that cause bone loss. They do, but in rapid bone loss from aggressive osteoclast overactivity, steroids may be helpful. That's the principle message of this story."

Provided by University of North Carolina Health Care