Missing protein helps mice to bone up

The vertebrate skeleton plays host to a constant tug-of-war. Bone-forming cells called osteoblasts counter the efforts of their bone-destroying counterparts, the osteoclasts.

Through most of life, this tussle allows vertebrates to remodel and strengthen their skeletons as they grow. Yet if osteoclasts gain a competitive edge over osteoblasts, as can happen in elderly people, bones weaken and diseases such as osteoporosis result.

Working with genetically engineered mice, investigators have now found one of the generals issuing orders to osteoblasts. Osteocalcin, a protein that osteoblasts themselves secrete, appears to inhibit the bone-creating action of the cells, Gerard Karsenty of the University of Texas M.D. Anderson Cancer Center in Houston and his colleagues report in the Aug. 1 NATURE.

The study has surprised bone researchers, because earlier studies had indicated that high concentrations of osteocalcin in the blood paralleled increased activity of osteoblasts.

“These findings are interesting in that they suggest entirely different things than we had suspected before. . . . Osteocalcin might be a negative regulator of bone formation,” says Stavros C. Manolagas of the Center for Osteoporosis and Metabolic Bone Diseases at the University of Arkansas for Medical Sciences in Little Rock.

Bone is living tissue formed of cells, including osteoblasts and osteoclasts, enmeshed in an extracellular matrix. A fibrous protein called collagen makes up most of this matrix. Minerals deposited around the collagen give bone its hardness and strength.

Osteocalcin is the most abundant of several noncollagen proteins in the extracellular matrix of bone. In mice, two genes independently encode the protein. To study osteocalcin’s function, the researchers made so-called knockout mice. “We deleted the two genes and generated a mouse strain that had no osteocalcin,” explains Karsenty.

At birth and at age 3 months, these knockout mice were indistinguishable from normal mice. When checked at 6 months, however, the knockouts displayed a difference: Their bones were denser than those of normal mice. Moreover, their bones proved superior to those of normal mice on a biomechanical stress test. “The bone is of better quality,” says Karsenty. “It’s the opposite of osteoporosis in many respects.”

Since osteoblasts secrete osteocalcin, the researchers originally thought the slow improvement in bone formation stemmed from an inhibition of osteoclast activity by the protein; however, the osteoclasts behaved normally.

Further tests showed that the osteoblasts in the knockout mice were simply more effective. They constructed more mineralized bone than did the osteoblasts in mice that had osteocalcin. “Each osteoblast is laying down more matrix. That’s the only abnormality of this mouse,” says Karsenty.

To explain the results, Karsenty’s group suggests that osteocalcin binds to molecules on the surface of osteoblasts, slowing their bone-forming activity. If so, compounds that thwart osteocalcin might prove useful in treating osteoporosis and other bone diseases, the researchers observe.

That aid may be some time in coming, however. “I don’t think we have the cure or explanation for osteoporosis. We just have the function of one protein,” cautions Karsenty.

In addition to probing how osteocalcin dampens osteoblast activity, the investigators plan to create more knockout mice to understand the roles of the other noncollagen bone proteins.

— J. Travis