Small protein may have big role in making more bone and less fat

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A small protein may have a big role in helping you make more bone and less fat, researchers say. "The pathways are parallel, and the idea is if you can somehow disrupt the fat production pathway, you will get more bone," says Dr. Xingming Shi, bone biologist at the Medical College of Georgia Institute of Molecular Medicine and Genetics.

He's found the short-acting protein GILZ appears to make this desirable shift and wants to better understand how it does it with the long-term goal of targeted therapies for osteoporosis, obesity and maybe more.

"Osteoporosis and obesity are two major public health problems, but people have no idea whether they have a connection," says Dr. Shi. Bone and fat do have a common source: both are derived from mesynchymal stem cells. Bone loss and fat gain also tend to happen with age and with use of the powerful, anti-inflammatory steroid hormones glucocorticoids. "When you age, your bone marrow microenvironment changes; the balance between the bone and fat pathway is broken," says Dr. Shi, a faculty member in the MCG Schools of Medicine and Graduate Studies. "You have more fat cells accumulate."

"The bones of elderly people or those who take glucocorticoids are yellow inside instead of red," he says. And it gets worse: in a classic vicious cycle, the more fat, the more cytokines that stimulate production of bone-destroying osteoclasts and inhibit bone-forming osteoblasts. He recently showed that even the stem cells change with age: their numbers and their ability to differentiate decrease.

Weight gain and bone loss are established side effects of glucocorticoids, whose wide-ranging uses include treatment for arthritis, asthma, infections and organ transplants. Ironically, glucocorticoids also induce a short burst of GILZ. GILZ, in turn, inhibits the transcription factor PPARã2, called the master regulator of adipogenesis, or fat production, as well as CCAAT/enhancer-binding proteins that turn on this fat-producing gene. One way GILZ does this is by binding to the regulatory region of PPARã2, Dr. Shi has shown.

To restore a healthier balance of bone and fat production, sustained GILZ action is needed. "When you permanently express GILZ, cells cannot differentiate into fat cells. Instead, you increase bone formation. People like this idea," says Dr. Shi, who has watched the mesynchymal stem cell production shift.

One point of controversy is that, at least in the lab, glucocorticoids seem to enhance bone formation. But Dr. Shi believes it's the short burst of GILZ at work there. He wants to know exactly how it works to see if it could offer a targeted therapy for osteoporosis and obesity and maybe a safer option for many who need glucocorticoids.

A recent $1.5 million, five-year grant from the National Institute of Diabetes and Digestive and Kidney Diseases is enabling Dr. Shi to further test his hypothesis about how GILZ represses PPARã2 and to see if GILZ over-expression in mice reduces PPARã2 expression and consequently increases bone and decreases fat. A long-term goal is to understand exactly how PPARã2 controls fat and bone production.

GILZ also is a powerful immune and inflammation suppressor. It inhibits two key inflammatory molecules, NF-kB and AP-1, which turn on inflammatory genes in response to cytokines, such as TNF-á and IL-1â, involved in rheumatoid arthritis and other inflammatory diseases, Dr. Shi showed in research published on the cover of the April 15 issue

of *Journal of Cellular Biochemistry*. That study notes GILZ's potential as a novel anti-inflammatory therapy.

In fact, Dr. Shi believes GILZ is a key factor mediating the anti-inflammatory effects of glucocorticoids. A long-acting version of GILZ or a similar substance would be needed to produce, for example, a powerful new arthritis treatment minus the undesirable effects. About 50 percent of arthritis patients who take glucocorticoids develop osteoporosis, he notes, worsening an already difficulty condition worse.

People can't take GILZ now, but another long-term goal is to develop a GILZ-like pill that would dramatically reduce fat production. Dr. Shi already has developed a cell line that continuously expresses GILZ.

Source: Medical College of Georgia

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