New approach for growing bone

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The natural cycle of building bone to maintain skeletal strength and then breaking it down for the body's calcium needs is delicately balanced, but diseases like osteoporosis break down too much bone without adequate bone replacement, leading to bone fractures.

The results from a new study at Duke suggest a targeted approach by which drugs may be able to fight osteoporosis and other degenerative bone diseases. Diane Gesty-Palmer, M.D., a Duke Assistant Professor of Endocrinology and Metabolism, and her team have found a new mechanism of bone formation in mice that works without inducing the complementary bone breakdown. The work appears in the inaugural issue of *Science Translational Medicine*.

The science boils down to two biochemical pathways stemming from a cell surface receptor called G-protein coupled receptor (GPCR). This is the largest family of cell surface receptors and the target of numerous drugs for the treatment of many medical disorders. For many years, scientists thought the cellular actions of these receptors were solely controlled by activation of G-protein pathways.

But GPCR discoverer, Duke's Robert J. Lefkowitz, M.D., has also discovered that another molecule, beta-arrestin, works like a brake on G-protein activation. His lab has been learning about ways that beta-arrestin also can signal through different pathways and thus directly control certain cellular processes.

By combining their expertise in bone metabolism and GPCR signaling,

Drs. Gesty-Palmer and Lefkowitz have found that beta-arrestin can cause bone to form, even though it blocks receptor activation of the G proteins. They discovered this happens in the receptor for parathyroid hormone (PTH), which regulates the amount of calcium in the body, and is used to treat osteoporosis.

By turning off G-protein signaling with a PTH analogue called PTH-Beta-arr (for beta-arrestin), the researchers were able to separate the bone-forming actions of the PTH receptor from its damaging bone-resorbing actions. They found much less bone was resorbed, and overall the amount of bone grew.

"We didn't anticipate finding bone growth because we thought that once the G-protein coupled pathway was blocked, that bone formation would also be blocked," Gesty-Palmer said. "It is commonly believed that the bone-forming actions of the parathyroid hormone receptor are mediated exclusively through G-protein activation."

"I think we will find that the beta-arrestin pathways play very important roles in the body," Lefkowitz said. "It is scientific convention that the G-protein dependent signaling pathways are the best pharmaceutical targets, but as we are learning more, we see that beta-arrestin dependent pathways also have an impact on physiological processes. Getting others to accept this, however, has been like turning around a battleship - it happens very slowly."

"We keep refining the science," Lefkowitz said. "With this in vivo study, we have reached the next level of specificity. With what we have learned, we may begin to create the keys to unlock targeted groups of receptors with this higher level of specificity."

With this refinement, the researchers also may achieve the control needed to avoid certain drug side effects, Lefkowitz said. "We think the

next generation of drugs, in this instance for osteoporosis, will behave more as we would like them to."

Dr. Lefkowitz has taken to calling the GPCRs, which he discovered, the 7-transmembrane receptors. This name reflects the characteristic structure of the receptor proteins which weave across the cell membrane seven times, and accommodates the fact that beta-arrestin pathways may also be activated by these receptors.

Source: Duke University (news : web)