A direct path for understanding and treating brittle bones

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A study by researchers at Children's Hospital Boston and collaborators at other institutions has provided new insights into the means by which bone cells produce new bone in response to mechanical stresses, such as exercise. Their findings lay a path for developing new strategies for treating diseases characterized by low bone density, such as osteoporosis in adults and osteogenesis imperfecta in children.

The research team, led by Matthew Warman, MD, of the Orthopedic Research Laboratories (ORL) in the Department of Orthopedic Surgery at Children's Hospital Boston, published their findings on May 22 in the advanced online edition in Nature Medicine.

Warman, director of the ORL, and his colleagues developed mouse models to better understand the role of a gene called Lrp5 in bone growth. While the gene's exact functions remain unclear, Lrp5 is believed to help mature bone cells called osteocytes respond to changes in mechanical load and call for the production of more bone when needed. Mutations that turn Lrp5 off lead to brittle bones, while others that turn Lrp5 on too much, called high bone mass (HBM) mutations, cause bones to become extra strong.

Using a system that allowed the investigators to selectively express HBM mutations of Lrp5 in osteocytes, the team accurately recreated in the mice the increased bone strength seen in human patients with the same mutations, showing that Lrp5 functions locally in bone to regulate bone mass.

"These HBM mutations seem to fool the osteocytes, the most mature bone cells, into thinking they hadn't made enough bone tissue," said Warman, who is also a Howard Hughes Medical Institute investigator and a professor of genetics at Harvard Medical School. "This knowledge should bolster efforts to develop pharmacologic agents that function similarly to the HBM mutations, in order to trick bone cells into making more bone. In fact, several companies are pursuing these strategies, and our data provides strong support for their continuing this line of investigation."

The researchers also found that Lrp5's effects are quite localized. By turning HBM-Lrp5 on only in the bone cells of the limbs, and not of the spine, they found that bone density increased only in the limbs and not in the spine.

"These results tell us that Lrp5 is really working in mature bone cells," Warman said. "They also tell us that targeting mature bone cells might be enough to increase bone mass and treat diseases like osteoporosis and other skeletal fragility disorders."

In addition, the team found no connection between Lrp5, bone mass, and serotonin, a compound better known for its role as a neurotransmitter in the brain but which is also produced in the intestines. This disagrees with studies that had suggested that Lrp5 affects bone density indirectly through intestinal serotonin production, rather than directly within bone tissue itself.

"We wanted to independently confirm the previous publications which suggested that Lrp5 exerts its effect on bone via intestinal serotonin, but our data do not support this hypothesis," Warman noted. "While the notion that gut serotonin affects bone mass is intriguing, we hope that our results encourage other investigators to focus on examining the local role of Lrp5 in bone."

The findings also raise a number of new questions meriting further study. "We need to understand when we can influence Lrp5 in order to induce bone cells to build more bone. In our mice, the Lrp5 mutations causing increased bone mass were present at birth, whereas if we want to design therapies that could improve bone strength in adults with osteoporosis, who are in their 60's or 70's, we would need to study the effect of inducing the HBM mutations in aged mice, instead of newborn mice," Warman noted.

Warman continued, "We also need to better understand which genes and proteins function upstream and downstream in the Lrp5 signaling pathway. And we want to see whether strategies that target Lrp5 can help increase bone mass and improve bone strength in persons with inherited skeletal fragility conditions like osteogenesis imperfecta (OI). Even though using Lrp5 to increase bone formation will not fix the underlying genetic cause of a child's osteogenesis imperfecta, it may still be helpful in reducing the high rates of fracture that patients with OI commonly experience."

Warman went on to give high praise to the multi-institutional team from across academia and industry that worked on the study. "This was one of the best collaborative efforts that I've been privileged to be part of."

Provided by Children's Hospital Boston