Notch controls bone formation and strength

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Notch, a protein known to govern the determination of cell differentiation into different kinds of tissues in embryos, plays a critical role in bone formation and strength later in life, said researchers from Baylor College of Medicine in Houston in a report that appears online today in the journal *Nature Medicine*. Their findings may provide a basis for understanding osteoporosis and in diseases in which there is too much bone.

“We knew that Notch is important in patterning the skeleton,” said Dr. Brendan Lee, professor of molecular and human genetics and pediatrics at BCM and a Howard Hughes Medical Institute investigator. “After this initial patterning of the skeleton, we saw a dimorphic or two-pronged function for Notch. If there was an increase of Notch activity in bone cells, we get a lot more bone. Notch stimulates early proliferation of osteoblastic cells (cells responsible for bone formation). However, when they ‘knocked out’ the Notch function in such cells in the laboratory, they found osteoporosis or the loss of bone, similar to age-related osteoporosis in humans.”

“Mice had an acceptable amount of bone at birth, but as they got older, they lost more and more bone,” said Lee, senior author of the report. “Loss of Notch signaling might relate to what happens when we get older.”

They found that the osteoblasts, which promote bone formation, worked fine when they abolished Notch function in bone forming cells. However, the animals lacked the ability to regulate activity of

osteoclasts, whose primary function is to resorb or remove bone. Many women who have osteoporosis actually have a similar problem, an imbalance of bone formation vs. bone resorption. They make enough bone but they resorb bone cells at an abnormally high rate.

In the laboratory, Lee and his colleagues found that when animals were bred to lack Notch, they lost also the ability to suppress bone resorption. That balance between bone formation and resorption allows organisms to maintain a healthy skeleton.

Future studies may look at the possiblity that loss of Notch interferes with the natural signal between osteoblasts and osteoclasts (bone resorbing cells) and prevents the homeostasis or natural balance between the two.

That means the protein Notch and the cellular pathways that express and control it might be targets for drugs to treat bone disorders, said Lee, also a researcher in the Dan L. Duncan Cancer Center at BCM.

The work demonstrates the importance of going from patients to the laboratory and back again, he said. This study began with patients who suffer from a problem called spondylocostal dysplasia. These children and adults have problems with the pattern of their spine. They have fusions of parts of the spine or ribs. Several years ago, other scientists showed that a mutation of the pathway for Notch causes some of these problems. “Our care of these patients suggested to us that Notch may have important function even after the establishment of this initial pattern of the skeleton.”

Notch also plays a role in other disorders, including those of the blood and cancer.

“Notch is important in the blood system,” said Lee. “It regulates whether

a stem cell becomes a ‘T’ or a ‘B’ cell. When Notch is mutated in the blood system, it causes cancer.”

That knowledge led him and his colleagues to look at the protein in bone.

“This is a complex system and it is why personalized medicine is important,” said Lee. “By identifying all of the major (cellular) pathways that contribute to a specific trait or feature like bone mass in each person, we could one day develop therapies specific for that person.”

Source: Baylor College of Medicine