When more bone-making cells equal less bone

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Researchers at UConn Health have shown how a mutated gene causes excess bone resorption in a rare bone disease known as Lehman Syndrome. Their research is the cover article in the Sept. 7, 2018 edition of *Journal of Biological Chemistry*. Credit: Jungeun Yu/UConn Photo

A rare mutation in a gene causes weak bones in mice and people – but

not for the reasons you might expect. UConn researchers report in the Sept. 7 issue of the *Journal of Biological Chemistry* how this mutation creates more bone-making cells but results in less bone, and find intriguing hints as to how the gene might affect other conditions as diverse as breast cancer and dementia.

Our bodies are constantly making new bone and reabsorbing the old. Weak bones occur when that cycle gets out of balance, and too much bone is reabsorbed. This imbalance of bone production is most common in the elderly, but it sometimes happens in younger people. Studying what goes wrong in these special cases of younger people might give clues to what causes weakened bones in older people, too.

One such special case appeared in 1977, when a girl with thinning bones and meningocele – parts of her spinal cord membrane protruded through openings in her spinal cord vertebrae – went to see her doctor. Because her mother had the same features, the doctor suspected it was inherited and named it Lehman syndrome.

Only around 100 people with Lehman syndrome have ever been identified, and they all have the same mutation in their DNA. The mutation changes a gene called Notch3, part of a family of genes that control the fate of cells; the Notch genes make proteins that help the cells decide what they want to be when they grow up. The mutant Notch3 was obviously doing something to disrupt the delicate balance of bone cells.

The director of the Center for Skeletal Research at UConn Health, Ernesto Canalis, and his colleagues Jungeun Yu, Lauren Schilling, and Stefano Zannotti, wondered exactly what was going on. To find out, they bioengineered a mouse to have the same Notch3 mutation as people with Lehman syndrome.

The Lehman syndrome mice showed them exactly how the delicate balance of bone making and bone breaking-down cells had gone awry. What happened was this: the mutated Notch3 made a protein that was sturdier than the normal version. This protein's job is to tell cells to turn into bone-making cells, called osteoblasts. The sturdier protein stuck around longer, and encouraged more cells to grow up to be osteoblasts. Sounds like a good thing, right? But it's not. Because as the cells matured, these extra osteoblasts were buried in their bones. And once buried, the osteoblasts began to produce RANK ligand, a signal that tells the body to make cells that reabsorb bone. These bone recyclers are called osteoclasts. Because there were extra osteoblasts, more were getting buried and making RANK ligand than usual. And the extra RANK ligand led to more osteoclasts – the bone reabsorbers – which led to too much bone getting resorbed by the body.

"Nobody had studied Notch3 mutations in the skeleton before us. There was nothing," says Canalis. He believes the mouse model accurately replicates what's going on in humans with the mutation. "These are subtle increases in Notch3, and the changes in the mice are within the expectations of real life," he says.

Canalis and his colleagues are now treating the Lehman syndrome mice to see if they can reverse the effects of the mutant Notch3, and they are also creating mice that only have the mutation in specific cells, to make sure that it is indeed Notch3 that's responsible for the weak bones, and to identify the type of cell that is the true culprit.

Mutations in Notch3 have also been associated with the ability of breast cancers to invade bone, and are involved inCADASIL, an inherited stroke disease that causes early dementia. Canalis hopes that gaining a better understanding of how the gene influences the fate of cells will offer insights into both skeletal and other diseases.

More information: Ernesto Canalis et al. The lateral meningocele syndrome mutation causes marked osteopenia in mice, *Journal of Biological Chemistry* (2018). DOI: 10.1074/jbc.RA118.004242

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