

Peter Pan bone cells undermine skeleton

Protein that controls maturation of bone-building cells might be disease culprit.

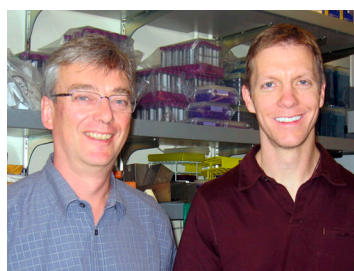
The skeleton's construction workers are cells known as osteoblasts. A little-known protein called Osteopotential helps these cells grow up and produce strong bones, Sohaskey et al. show (1).

Osteoblasts pump out type I collagen, the protein that accounts for almost all the non-mineral content of bone (2). "The main point of being an osteoblast is to make collagen," says lead author Mike Sohaskey, a postdoc in the lab of Richard Harland. As they are synthesized, type I collagen molecules feed into the rough endoplasmic reticulum (ER), where they are modified and folded into shape (3). The osteoblast then secretes the proteins for further processing and assembly into fibrils, the functional units of collagen.

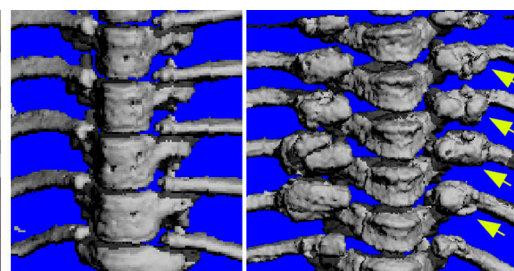
Bone construction surges before birth and during childhood. During this period, osteoblasts amass additional rough ER to cope with their increased collagen output. How the cells manage these changes isn't known, but the protein Osteopotential could be involved because its loss disrupts skeletal growth (4).

Sohaskey et al. studied mice with a disabled *osteopotential* gene. Bone building falters in osteogenesis imperfecta (OI), a rare disease characterized by a brittle, fracture-prone skeleton. The phenotype of mice lacking a working copy of the *osteopotential* gene resembled that of OI patients in several ways. They were smaller than normal, and their bones were thin and snapped easily.

The problem was a case of arrested development: without Osteopotential, many immature osteoblasts didn't grow up. Reflecting their immaturity, cultures of the cells fashioned up to 80% less type I collagen than normal. Some of the osteoblasts even morphed into osteocytes, a cell type that produces little bone.



FOCAL POINT



Richard Harland (left), Mike Sohaskey, and colleagues discovered that the protein Osteopotential reinforces the skeleton by prodding bone-making osteoblasts to mature. Mice lacking the protein have a weak skeleton and suffer frequent breaks. In this CT image of the rib cage of one of these mice (far right), the yellow arrows point to "fracture calluses" that formed at the junctions of the ribs and vertebrae. The middle image shows a normal mouse rib cage.

Osteoblasts partner with osteoclasts—cells that demolish bone—to fine-tune the strength of the skeleton (5). Overactive osteoclasts could explain the animals' fragile bones. But, to their surprise, Sohaskey et al. discovered that the rodents harbored sluggish osteoclasts. So although the animals create less bone than normal, they also dissolve less.

Where Osteopotential settled had been a mystery, but the team traced the protein to the rough ER—the right place to alter collagen synthesis. The protein enables the cell to expand the rough ER and meet the need for more collagen. In cells lacking Osteopotential, the organelle's membranes were small and fragmented.

The findings suggest that Osteopotential is a triple threat, controlling collagen

production, rough ER size, and osteoblast maturation. "This gives us a whole new perspective on a pathway responsible for bone formation," says Sohaskey. He speculates that in the mice lacking Osteopotential, problems start early in life, when collagen demand climbs. But osteoblasts manufacture little collagen.

That scarcity holds back the cells because they require surroundings that are rich in the protein to mature. The end result is a fragile skeleton.

How Osteopotential affects ER structure is one open question. Sohaskey et al. also want to determine whether faulty Osteopotential is the culprit in any human diseases. OI patients typically carry a mutation in one of the two collagen genes. But both genes are normal in some sufferers, suggesting that other genetic glitches can trigger the disease. In the team's preliminary study of OI patients, none had a defective *osteopotential* gene, but the researchers plan to check for mutations in a broader range of patients.

1. Sohaskey, M.L., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201003006.
2. Young, M.F. 2003. *Osteoporos. Int.* 14 (Suppl 3):S35–S42.
3. Lamande, S.R., and J.F. Bateman. 1999. *Semin. Cell Dev. Biol.* 10:455–464.
4. Mitchell, K.J., et al. 2001. *Nat. Genet.* 28:241–249.
5. Karsenty, G., and E.F. Wagner. 2002. *Dev. Cell.* 2:389–406.

"This gives us a whole new perspective on a pathway responsible for bone formation."