How meals become bones

Amylin, a hormone produced along with insulin after food intake, is vital for strengthening bones, according to Dacquin et al. (page 509). A lack of amylin production in type I (autoimmune) diabetics may explain the prominent bone loss in these individuals—a problem that amylin replacement therapy may alleviate.

When food is short, strengthening bone may not be the body’s top priority. But when the food arrives it is time to build up bone mass. After food enters the digestive tract, amylin is cosecreted with insulin from pancreatic islet cells, but there is no known function for amylin in glucose metabolism. In the new work, the authors found that mice lacking either one or both copies of the amylin gene have normal appetites, but exhibit low bone mass and an increased number of bone-chewing osteoclasts. Ex vivo analysis of bone marrow macrophages from the mutant mice shows that amylin specifically regulates osteoclast differentiation.

Previous work had shown that amylin can bind to the calcitonin receptor in vitro, but the new study shows that heterozygous calcitonin receptor deletion increases bone mass, exactly opposite to the amylin knockout phenotype. Mice with heterozygous deletions in both calcitonin receptor and amylin genes show both increased osteoclast numbers and increased bone formation, with bone formation enjoying a slight edge.

Based on the results, Dacquin et al. propose that amylin, using a receptor other than the calcitonin receptor, regulates bone resorption by inhibiting the differentiation of osteoclasts. In patients with Type 1 diabetes, the absence of pancreatic islet cells should severely reduce the secretion of amylin, which would explain the bone loss associated with that disease. The authors are now trying to identify the real amylin receptor, and hope to use the new mouse model to search for therapies for diabetes-associated osteoporosis.

A primordial mover for sphingolipids

In people with Niemann Pick Type C disease (NP-C), a fatal neurodegenerative disorder, both sphingolipids and cholesterol accumulate in lysosomes, but controversy swirls around which of these metabolites causes the disease. On page 547, Malathi et al. present evidence that NPC1, the protein that is defective in most NP-C patients, may have evolved primarily to transport sphingolipids, as it can be replaced by a yeast version with only the sphingolipid functionality. The data favor the idea that sphingolipids are the offending metabolite in NP-C, and suggest that a redundant pathway for sphingolipid transport could be an attractive target for novel NP-C therapies.

Chinese hamster ovary cells lacking NPC1 exhibit aberrant sphingolipid and cholesterol accumulation. In the new work, the authors found that expressing NCR1, the yeast orthologue of NPC1, repairs all of the lipid transport defects in these mammalian cells. Functional conservation across a billion years of evolution is especially surprising in this case, since yeast do not engage in receptor-mediated transport of exogenous cholesterol.

Extraordinary conservation implies a critical function, but deleting NCR1 in yeast cells has no detectable effect on sterol metabolism. A dominant-negative mutation in the conserved putative sterol-sensing domain of NCR1, however, causes pronounced sphingolipid trafficking defects in yeast without affecting sterol trafficking. NCR1 and its homologues appear to share a primordial function in sphingolipid transport, and it is possible that defects in cholesterol transport in NP-C are simply a byproduct of the close association of cholesterol with sphingolipids in membrane rafts.

The lack of a phenotype in NCR1-null yeast cells also indicates that some other sphingolipid transport pathway must be able to compensate for the loss of NCR1. The authors are now trying to identify NCR1 binding proteins and to elucidate the alternate pathway, efforts that could uncover novel therapeutic targets for the treatment of NP-C.