**AMPK amplifies Huntington’s disease**

Ju et al. describe how hyperactivation of AMPK-activated protein kinase (AMPK) promotes neurodegeneration in Huntington’s disease (HD).

The aggregation of mutant Huntingtin protein in HD disrupts many cellular processes, including metabolism.

AMPK—a protein that maintains energy homeostasis—is abnormally active in the brains of mice with HD, but whether the kinase protects neurons from the metabolic imbalances associated with HD or whether AMPK contributes to neuronal death is unknown.

Ju et al. determined that the α1 isofrom of AMPK was specifically activated and translocated into the nuclei of neurons in a mouse model of HD, whereas AMPK-α2 was unaffected. An inhibitor of Ca2+/calmodulin-dependent protein kinase II reduced AMPK activity, suggesting that AMPK-α1 is activated by this kinase, probably because Ca2+ signaling is disrupted in HD neurons. Further stimulation of AMPK by injection of the AMPK-activating drug AICAR increased neuronal death and decreased the lifespan of HD mice. AICAR also promoted the death of neuronal cell lines, an effect reversed by an AMPK inhibitor. Active, nuclear AMPK-α1 promoted neuronal apoptosis by reducing expression of the survival factor Bcl2. Bcl2 levels and cell survival were restored by CGS21680, a drug that alleviates the symptoms of HD mice.

AMPK was also hyperactivated in the brains of human HD patients, suggesting that the kinase could be a therapeutic target. Senior author Yijuang Chen now wants to investigate how AMPK-α1 and –α2 isoforms are differentially regulated in neuronal tissue. Ju, T.-C., et al. 2011. J. Cell Biol. doi:10.1083/jcb.201105010.

**HJURP puts the centromere in place**

The histone chaperone HJURP directs the formation of functional centromeres by assembling the histone variant CENP-A into chromatin. Barnhart et al. reveal.

CENP-A is a specialized version of histone H3 that marks the position of centromeres. A protein called HJURP helps deliver CENP-A to centromeric chromatin, but whether HJURP simply protects CENP-A until the histone is incorporated or whether the protein actively assembles CENP-A into nucleosomes is unclear.

Barnhart et al. targeted HJURP to noncentromeric chromatin by tagging it with the Lac repressor protein LacI and expressing this fusion protein in cells carrying an array of LacI-binding DNA sequences on one of their chromosomes, LacI-HJURP.

**Sphingomyelinase helps bones get their minerals**

Khavandgar et al. demonstrate that bone-forming osteoblasts require the enzyme neutral sphingomyelinase 2 (nSMase2) to mineralize the extracellular matrix during skeletal development.

nSMase2 cleaves sphingomyelin to generate ceramide and other bioactive lipids. Mice lacking nSMase2 have severe skeletal abnormalities such as shortened and bent limb bones. The precise nature of these skeletal defects has remained unclear, however, as has the site of nSMase2’s action. Some studies have suggested that nSMase2 acts in the brain to regulate endocrine signals controlling bone development.

Khavandgar et al. analyzed mice lacking nSMase2 activity due to a chemically induced mutation called *fragilitas ossium* (*fro*) and found that although their osteoblasts differentiated and secreted collagen matrix as normal, they failed to mineralize this matrix with calcium and inorganic phosphate. Mutant osteoblasts also failed to mineralize in culture. In addition, the long bones of *fro/fro* embryos contained increased numbers of hypertrophic chondrocyte-like cells that normally die during long bone growth. Restoring wild-type nSMase2 expression to the osteoblasts of *fro/fro* mice rescued the bone mineralization and skeletal defects of these animals. Osteoblast-specific nSMase2 expression failed to boost hypertrophic chondrocyte apoptosis, however, indicating that nSMase2 has tissue-specific functions during skeletal development.

The results may explain why some osteogenesis imperfecta patients have bone mineralization defects despite having intact collagen genes and normal levels of mineral ions in their serum. Senior author Monzur Mursheed now wants to investigate how nSMase2 promotes mineralization. The enzyme may regulate the release of specialized matrix vesicles from osteoblasts that initiate the mineralization process. Khavandgar, Z., et al. 2011. J. Cell Biol. doi:10.1083/jcb.201102051.