A Prion in yeast
Huntington’s disease

Merin et al., reporting on page 997, have developed the first yeast model for studying Huntington’s disease. Yeast cannot undergo neurodegeneration, of course, but the simplicity and genetic manipulability of the system are already providing important mechanistic insights. The authors report that aggregation of a polypeptide with an expanded polyglutamine domain, mediated by a prion-like protein, is responsible for cell death in their system, suggesting revisions to earlier models of neurodegeneration.

In Huntington’s disease, expansion of the huntingtin polyglutamine domain leads to protein aggregation in inclusion bodies and neuronal cell death. In some systems, however, long polyglutamine peptides are toxic without aggregating, suggesting that aggregation of mutant huntingtin might not determine toxicity. Merin and colleagues found, however, that aggregation of long polyglutamine peptides in yeast correlated with toxicity. Mutations in certain chaperone genes, or curing the cells of the prion form of the Rnq1 protein, suppressed both aggregation and toxicity.

The results directly link polyglutamine peptide aggregation with cell death, and demonstrate that prion proteins are required for this process, at least in yeast. The evolutionary conservation of these mechanisms suggests that prion-like proteins might also be involved in mammalian polyglutamine expansion diseases.

A vitamin makes minerals

Growth plate chondrocytes help turn cartilage into bone by releasing specialized matrix vesicles, which contain the crystalline seeds for calcification. On page 1061, Wang and Kirsch show how retinoic acid (vitamin A) controls this process of mineralization.

Previous work showed that retinoic acid stimulates mineralization and induces the formation of matrix vesicles, but its molecular targets remained unknown. In the new study, the authors found that, in cultured growth plate chondrocytes, retinoic acid acts by increasing the transcription of three annexin family proteins and causing them to form calcium channels in the plasma membrane.

Retinoic acid is known to regulate transcription after binding to the retinoic acid receptor complex, but the new results imply that it can also control calcium homeostasis, perhaps through receptors yet to be discovered. After retinoic acid induces an initial calcium influx, the formation of induced annexins into channels in the plasma membrane further boosts cytosolic calcium, increasing annexin expression again and causing the release of matrix vesicles. These vesicles contain annexin channels that allow the entry of crystal-forming calcium.

Excess mineralization has been implicated in several disease processes, including osteoarthritis and the calcification of cardiovascular tissues. Recently, the authors have determined that annexin expression is induced in osteoarthritic chondrocytes. If annexins are as central to pathogenic mineralization as they appear to be in healthy tissue, they could be promising targets for a variety of therapies.

How fish oils work

For years, epidemiologists and nutritionists have known that a diet high in the ω-3 fatty acids found in fish oil correlates with a decreased risk of colon cancer. On page 915, Murray et al. explain why.

As colon carcinogenesis is accompanied by an increase in the expression of the lipid-dependent protein kinase CβII (PKCβII), the authors reasoned that ω-3 fatty acids might inhibit PKCβII signaling. Analysis of rat colonic epithelia and PKCβII transgenic mice demonstrated that ω-3 fatty acids block PKCβII activation and reduce the pro-carcinogenic effects of PKCβII in vitro and in vivo. PKCβII appears to repress the expression of transforming growth factor β receptor II (TGFβRII), desensitizing cells to the growth-inhibiting effects of TGFβ.

The results suggest that ω-3 fatty acids inhibit PKCβII, thus relieving the inhibition of TGFβRII expression. This renders colon epithelial cells sensitive to TGFβ, and prevents or reverses the hyperproliferative state that leads to colon cancer. Dietary ω-3 fatty acids are also associated with preventing prostate and breast cancer and some neurological conditions, suggesting that PKCβII may be a promising target for multiple chemoprevention strategies.

In This Issue 905