Fences catch free-ranging lipids

Lipids diffuse in a cell membrane at least fivefold more slowly than they do in an artificial lipid bilayer, a discrepancy that has puzzled cell biologists for more than two decades. Now, on page 1071, Fujiwara et al. suggest an explanation: the cell surface is crisscrossed with picket fences made of immobile transmembrane proteins.

Until now, single-particle tracking (SPT) has been too slow to provide a high-resolution view of lipid diffusion. In an impressive technical achievement, the authors developed a SPT technique with 25-μs resolution, and then used it to follow the diffusion of a nonraft lipid in a cell membrane.

The lipid molecule was confined within a defined compartment for an average of 11 ms before hopping to an adjacent compartment on the cell membrane. Within the compartment, diffusion was about as fast as in artificial membranes, but movement from one compartment to another took much longer. The long-range diffusion rate of the lipid was determined primarily by the rate of hopping between compartments.

Surprisingly, compartmentalization of the membrane did not depend on the extracellular matrix, lipid rafts, or the extracellular domains of membrane proteins. Instead, the actin-based membrane cytoskeleton, located on the cytoplasmic face of the membrane, is responsible for confining diffusion on the extracellular face of the membrane. The authors propose that various transmembrane proteins interacting with the cytoskeleton act as rows of pickets, temporarily confining phospholipids to particular membrane domains.

Preliminary studies have now shown that raft lipids display hop diffusion rates similar to those of nonraft lipids, suggesting that rafts may continually form and disperse, rather than remaining intact as large structures. Because picket barriers would affect all membrane molecules, compartmentalization should also limit the movement of transmembrane and GPI-anchored proteins, possibly helping confine signaling complexes in compartments where extracellular signals are received.

Making straps from small movements

To enlarge a drawing, an artist might use a pantograph, a pivoting frame that mechanically amplifies small movements into larger ones. On page 1083, Sawhney and Howard propose that cells use a similar mechanical arrangement to amplify small-scale traction forces into large-scale reorganization of the surrounding matrix. Their model may describe a general mechanism underlying morphogenesis.

When explants of fibroblasts are placed in collagen gels, they exert mechanical forces that lead to the formation of ligament-like straps between explants. Though this system is considered a good model for tissue morphogenesis, it remained unclear how micrometer-scale cellular traction forces generate millimeter-scale structural changes in the matrix.

Using a novel computer algorithm to monitor the patterning of the matrix, the authors found that small cellular movements bring about nearly simultaneous reorganization in the collagen gel, suggesting that the collagen forms a mesh of interconnected fibers. The results can be explained by a geometric model in which a small movement along one axis of the collagen mesh (the axis running between explants) generates a large movement perpendicular to the axis, which draws collagen into the strap. Because biological meshes are widespread, this could be a general mechanism by which small, slow movements bring about the large, rapid changes required for tissue remodeling, development, and cell movement.
A Prion in yeast
Huntington’s disease

Merrin 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. Merrin 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.