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A glue for microtubule cargos

Vaughan et al., reporting on page 305, have used live-cell imaging to characterize the dynamic interactions of dynactin with growing microtubule plus-ends. The results provide substantial new insights into the regulation of these interactions, and suggest a new model for organelle transport and anchoring.

Previous work identified the p150Glued subunit of dynactin as a specific binding partner for cytoplasmic dynein. To characterize this protein further, the authors tracked GFP-tagged p150Glued using time-lapse imaging. P150Glued associated with growing microtubule plus-ends to form “comet tails,” which reflect binding followed by delayed release. The delay suggests that p150Glued binding to the growing plus-ends may be followed by multiple molecular events at the microtubule tip, including the phosphorylation of p150Glued that mediates its release.

Contact of p150Glued comet tails with Golgi-derived membranes was correlated with the initiation of transport of these membranes. Vaughan et al. propose that growing microtubules probe the cytoplasm for organelles in need of transport. Dynactin on the organelles captures the microtubules, and also recruits motor proteins through its specific interaction with cytoplasmic dynein. A similar search-and-capture model has been proposed for kinetochore–microtubule interactions, potentially revealing a universal mechanism for microtubule-based transport.

Another name for autotaxin

A serendipitous discovery by Umezu-Goto et al., whose report appears on page 227, links two previously unrelated fields of study and suggests a new avenue of research for developing cancer therapies. The authors sought to study the production of lysophosphatidic acid (LPA), a lipid mediator with multiple biological functions that acts through G-protein–coupled receptors. LPA is produced in plasma from lysophosphatidylcholine (LPC) in a reaction catalyzed by the enzyme lysophospholipase D (lysoPLD), but the gene for lysoPLD had not been identified.

After biochemically purifying lysoPLD from fetal bovine serum, Umezu-Goto et al. discovered that the enzyme is identical to autotaxin, an enzyme associated with melanoma cells. Autotaxin was known to stimulate motility in tumor cells, but its mechanism of action was unclear. The new work shows that autotaxin/lysoPLD stimulates motility and proliferation in multiple cancer cell lines, apparently by producing LPA. In the microenvironment of a tumor, LPC secreted by tumor cells or available in the plasma could encounter autotaxin/lysoPLD released by the tumor cells, leading to the production of LPA and the stimulation of tumor growth and migration. Interfering with this signaling loop might be a promising strategy for cancer treatment.

New tricks for old neurons

Newborns seem to do much better than adults in healing injuries to their central nervous systems. At the cellular level, this is because inhibitory molecules in the adult central nervous system prevent neurons from extending their axons and dendrites, but the neurons in embryos and newborns are apparently insensitive to these inhibitors. Now, Tanaka et al., reporting on page 321, have uncovered the molecular mechanism underlying this change in sensitivity. The findings suggest a new approach for developing therapies for brain and spinal cord injuries.

Analyzing chick retinal neurons, the authors found that the differentiation of newborn neurons is associated with cytoplasmic expression of p21Cip1/WAF1, a protein best known as a nuclear-localized cell cycle inhibitor. Ectopic expression of p21Cip1/WAF1 lacking its nuclear localization sequence promotes neurite outgrowth, and the protein strongly inhibits Rho kinase in a dose-dependent manner.

As neurite outgrowth inhibitors like myelin-associated glycoprotein and tumor necrosis factor were previously shown to signal through Rho and Rho kinase, cytoplasmic p21Cip1/WAF1 appears to target the common pathway of these inhibitory signals. Inducing cytoplasmic p21Cip1/WAF1 expression in adult neurons might therefore make the neurons “younger,” permitting them to extend neurites to repair an injury.
**Signaling from strange places**

The tumor suppressor p53 can act as a transcription factor, but only a few p53-activated genes have been found, and the biochemical basis of p53-mediated apoptosis has been especially difficult to probe. Now, Bourdon et al. describe the discovery and characterization of a novel p53-inducible proapoptotic gene (page 235).

By comparing gene expression in normal and p53-knockout mice exposed to ionizing radiation, the authors identified *Scotin*, a novel gene that is directly trans-activated when p53 binds to a specific site in its promoter. Mouse *Scotin* and its human homologue appear to induce apoptosis in a caspase-dependent manner. *Scotin* has the structure of a type I transmembrane receptor, but is located in the endoplasmic reticulum and the nuclear membrane, not in the Golgi apparatus, mitochondria, or plasma membrane. The authors are now trying to determine whether this localization pattern is required for *Scotin* activity, and whether the protein can promote apoptosis in response to endoplasmic reticulum stress as well as DNA damage.

The chromosomal location of the human *Scotin* gene, 3p21.3, is also tantalizing, as this region is rearranged or deleted in a wide range of human tumor types. Bourdon et al. found a dominant-negative phenotype in *Scotin* mutants, indicating that a mutation in a single allele of the gene could be sufficient to block the apoptotic activity of the protein. In preliminary studies focusing on breast cancer, researchers have already found mutations in *Scotin* in tumors from several patients, suggesting that *Scotin* may be a clinically important new tumor suppressor gene.

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**Watching Ca\(^{2+}\) waves break**

Most models of intracellular Ca\(^{2+}\) signaling invoke calcium-induced calcium release (CICR), a positive feedback mechanism that amplifies small elevations in cytoplasmic Ca\(^{2+}\) to produce complex signals. But what determines the pattern of signaling, and how does a cell avoid triggering Ca\(^{2+}\) release in the wrong place? Ashby et al., reporting on page 283, addressed these questions with a powerful new technique and arrived at some surprising conclusions.

Using spatially restricted uncaging of caged Ca\(^{2+}\), the authors were able to boost cytosolic Ca\(^{2+}\) concentrations in specific regions within pancreatic acinar cells. These cells ordinarily produce polarized Ca\(^{2+}\) waves after stimulation with an agonist. When caged Ca\(^{2+}\) is uncaged in the apical region of the cells, a CICR wave spreads from the apical region toward the basal membrane. In contrast, uncaging Ca\(^{2+}\) in the basal region does not produce a CICR wave at all.

CICR is usually associated with ryanodine receptors, which are found in both the apical and basal regions of these cells. However, Ashby et al. found that inhibitors of either ryanodine receptors or IP3 receptors block the induced waves, indicating that CICR requires cooperation between both types of Ca\(^{2+}\) release channels. As IP3 receptors are restricted to the apical region, a CICR wave can only be induced there. Ca\(^{2+}\) uncaging did not stimulate IP3 production, so participation of the IP3 receptors in CICR wave generation does not require elevation of the IP3 concentration.

Although CICR waves could not be initiated in the basal region, waves that originate in the apical region can travel through the basal region. One possibility is that Ca\(^{2+}\) channels may be closely spaced along “gunpowder trails” in the basal region, allowing a signal that originated elsewhere to propagate along a route with a high density of Ca\(^{2+}\)-sensitive and Ca\(^{2+}\)-releasing sites. Such a system would help determine the pattern of Ca\(^{2+}\) signaling while preventing Ca\(^{2+}\) release in the wrong part of the cell.