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In This Issue

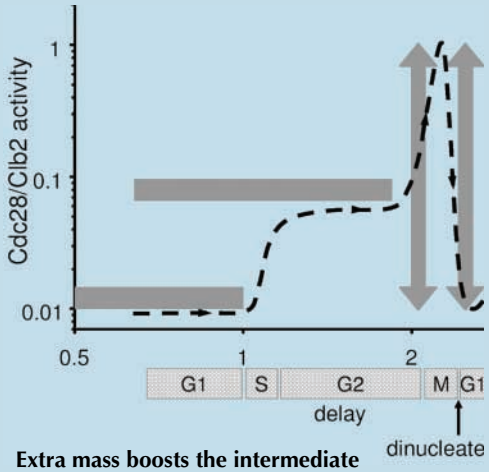
Math models morphogenesis and mitosis

When a budding yeast cell is unable to form a new bud, cell division pauses in G2 phase, either until a bud can grow or until the cell "adapts" to the situation by becoming dinucleate. Ciliberto et al. collected the available experimental data on this morphogenesis checkpoint, and on page 1243 they present a mathematical model that explains previous results and makes some surprising predictions.

The morphogenesis checkpoint relies on antagonism between the Swe1 kinase, which inhibits entry into mitosis, and the active form of the Cdc28–Clb2 cyclin complex, which promotes it. In the model, a set of differential equations accounts for the phenotypes of a dozen morphogenesis checkpoint mutants by incorporating a few initial assumptions. Although previous work showed that Hsl1 kinase flags Swe1 for degradation, the mathematical model demonstrates that Hsl1 must also indirectly inhibit Swe1 activity.

The model also illuminates adaptation. Numerical simulation shows that small cells keep Cdc28–Clb2 activity at a low steady-state level, but at a critical cell size, Cdc28–Clb2 activity abandons the steady-state and enters an oscillatory regime. Normally, a single oscillation ends in mitosis, producing two smaller cells that are reset to the low steady-state leve. But when bud formation is impaired, the morphogenesis checkpoint enforces an intermediate steady-state level of Cdc28 kinase activity. At this level, DNA synthesis proceeds, but cells pause in G2. Once these arrested cells reach a second critical size threshold, they bypass the morphogenesis checkpoint and enter the Cdc28–Clb2 oscillatory state, dividing their nuclei.

The morphogenesis checkpoint seems to raise the size threshold for progression of the cell cycle. The model predicts that once that threshold is passed in the absence of bud formation, the mitotic cycle should continue unchecked, and the next cycle should be faster. Testing these predictions should further refine the model. ■



Extra mass boosts the intermediate level of Cdc2 activity to induce mitosis.

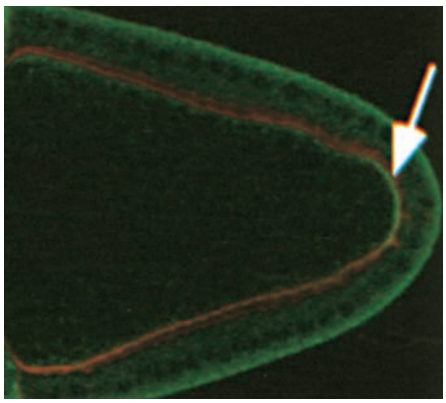
Cup puts a lid and a handle on mRNA

Using a biochemical approach to a longstanding problem in *Drosophila* genetics, Wilhelm et al. (page 1197) have identified a novel protein that links translational repression to mRNA localization and also uncovered a surprisingly specific localization pattern for a ubiquitous translation factor.

Polarized cells often rely on mRNA localization to restrict protein distribution. During fly oocyte development, for example, *oskar* mRNA moves from the posterior end of the oocyte to an anterior position, then back to the posterior end before being translated. As Oskar expression determines posterior patterning and germline establishment, the mRNA must be repressed until it reaches its final position. Something must coordinate the localization and translational repression of the message, but genetic studies have only found mutants that affected localization or repression, not both.

Wilhelm et al. now identify the product of the *Cup* gene as the missing link. Cup is part of a multiprotein complex that copurifies with *oskar* mRNA. Interfering with Cup disrupts both the localization and translational repression of *oskar*. Surprisingly, the ubiquitous translation factor eIF4E, which is generally assumed to be homogeneously distributed in cells, specifically binds to Cup and substantially localizes to the posterior end of fly oocytes.

The authors propose a model in which Cup binds to *oskar* mRNA as a repressor and also recruits the transport components of the protein complex. Once the mRNA reaches its destination, a posterior signal could then disrupt the Cup–eIF4E interaction and permit translation. Since the need to coordinate repression with mRNA localization is common to many polarized cells, recruiting transport components could be a feature of many translational repressors. The authors are now examining *Drosophila* mutants with phenotypes similar to *Cup* in an effort to identify additional mRNA regulators. ■



Cup (green) keeps *oskar* translation repressed during transport to the posterior (right).

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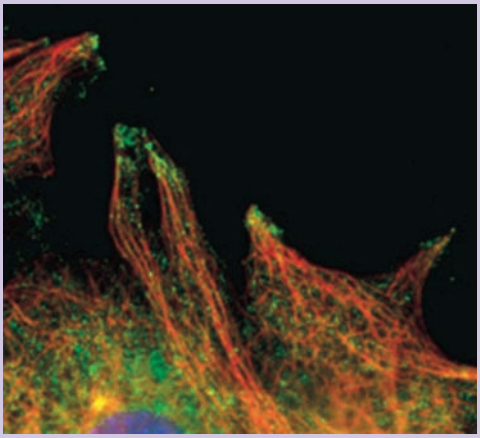


Dynein (green) at the front of the cell helps the cell move.

Cells need backward motor to move forward

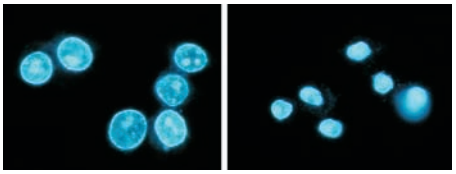
Cytoplasmic dynein associates with a variety of intracellular cargos and pulls them toward the minus ends of microubules. But this retrograde motor protein is also essential for forward cell migration, as Dujardin et al. demonstrate on page 1205.

After observing dynein and its associated regulatory proteins at the leading edges of migrating cells in a monolayer model of wound healing, the authors inhibited dynein activity at various times to identify its functions. Early in cell migration, dynein helps reorganize the microtubule cytoskeleton, placing the centrosome on the leading edge side of the nucleus. Once this rearrangement is completed, inhibiting dynein does not change the location of the centrosome.

The motor protein is still required for cell migration even after cytoskeletal rearrangement. During migration, dynein appears in a diffuse area along the leading edge of the cell, where it seems to capture the plus ends of microtubules that enter the region. It is unclear whether dynein at the leading edge is activating lamellipodial protrusion or serving a strictly mechanical function, but the mechanism might have parallels with the action of dynein at the kinetochore, where it both pulls on microtubules and participates in mitotic checkpoint signaling. ■

Death and the shrinking nucleus

During heart disease and stroke, cells deprived of oxygen often die in a way that is distinct from caspase-dependent apoptosis. On page 1219, Shinzawa and Tsujimoto provide a first look at the molecular basis of this poorly understood process, showing that a phospholipase A_2 (PLA_2) enzyme causes the characteristic nuclear shrinkage that accompanies hypoxic cell death.



PLA_2 (right) shrinks nuclei during hypoxic death.

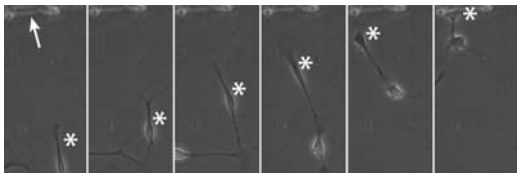
Using a novel permeabilized cell assay, the authors purified a protein that can cause nuclear shrinkage and identified it as PLA_2. Inhibitor studies confirmed that PLA_2 is essential for nuclear shrinkage in caspase-independent hypoxic cell death. In hypoxic cells, PLA_2 activity increases and the calcium-independent form of the enzyme accumulates in the nucleus. Blocking calcium-independent PLA_2 activity prevents both nuclear shrinkage and hypoxic cell death.

An increase in PLA_2 activity leads to the cleavage of nuclear lamins, which could explain how it causes nuclear shrinkage. Since PLA_2 cleaves phospholipids, it could also contribute to cell death by disrupting mitochondrial and plasma membranes, processes the authors now hope to study biochemically. The identification of PLA_2 as an important mediator of caspase-independent death should also help uncover additional components of the pathway, such as the regulators of PLA_2 activity and translocation. ■

Neural progenitors find VEGF attractive

Blood vessels and neural stem cells can be led to their targets by the same factor, say Zhang et al. on page 1375. The factor, vascular endothelial growth factor A (VEGF), is known as a major inducer of angiogenesis. Zhang et al. show that it is also a powerful attractant for immature neural progenitor cells. In the developing mammalian brain, it may be used when both neural stem cell migration and blood vessel growth must head for the same brain region.

The authors purified neural progenitors from the subventricular zones of newborn rats, and cultured them in the presence of fibroblast growth factor 2 (FGF-2) to prevent them from differentiating. The progenitor cells migrate up gradients of VEGF, in a chemotactic response specifically mediated by VEGF receptor 2. In cocultures in three-dimensional collagen matrices, the progenitors migrate toward VEGF-secreting cells. Progenitor cells that are allowed to differentiate into neuron- or glia-restricted lineages become insensitive to VEGF.



Neural progenitors migrate toward VEGF.

The data suggest that VEGF links angiogenesis to neurogenesis to establish neurogenic niches within the developing brain. Once the niches are established by immature progenitors, they could act as launching points for migrations by more differentiated cells. VEGF and FGF-2 might be useful in treating brain injuries by directing transplanted progenitor cells to migrate into damaged areas. ■