In This Issue

Tumor cells: a single signal to divide and conquer?

Metastatic tumor cells are dangerous because they not only proliferate but also migrate and invade other tissues. On page 817, Manes et al. reach the surprising conclusion that the cyclin-dependent kinase cdc2 regulates both of these activities. The work identifies a novel signaling pathway and points to a promising new strategy for targeting metastatic cells, but it may also force a reevaluation of some current drug development efforts.

Cdc2 is well known as a cell cycle regulator, but previous work had shown that it also phosphorylates multiple cytoskeletal proteins. In the new work, the authors found that αvβ3 integrin expression in a prostate cancer cell line increases cdc2 mRNA and protein levels and leads to an increase in cdc2 kinase activity. Using cyclin B2 as a cofactor, cdc2 acts in ruffles to phosphorylate the cytoskeleton-associated protein caldesmon. Others have recently shown that this phosphorylation relieve an inhibition of actin polymerization, and thus may be pro-migratory.

The results show that, besides regulating the cell cycle, cdc2 also acts as a downstream effector of αvβ3 to regulate cell migration. This result is surprising: cdc2 is the first cyclin-dependent kinase to be linked to both migration and the cell cycle, and cyclin-dependent kinases were not known to have their expression induced by integrin expression. Manes et al. have found that the unusual dual function of cdc2 in migration and proliferation appears to be a feature of normal cells as well as tumor cells.

Modulating AMPA receptors makes memories special

In current models of learning and memory, the brain stores information by remodeling synapses, specifically by changing the numbers of AMPA glutamate receptors at postsynaptic densities. Different brain regions lay down memories differently, though, and AMPA receptors are distributed throughout the brain, so there must be another component of the system providing specificity. On page 805, Tomita et al. address this long-standing problem by defining a family of four differentially expressed transmembrane proteins that regulate AMPA receptors in all types of neurons.

Previously, the authors showed that AMPA receptors in the cerebellum are regulated by a transmembrane protein called stargazin, which is mutated in a strain of epileptic mice, but it was unclear whether this was a general mechanism or restricted to the cerebellum. The new study shows that stargazin and three related proteins comprise a family of transmembrane AMPA receptor regulatory proteins (TARPs). TARPs promote the surface expression of functional AMPA receptors, and each TARP shows a specific pattern of expression in the brain. In areas that express multiple isoforms, TARP complexes are strictly segregated.

The expression patterns and properties of the four TARP isoforms could explain how AMPA receptors are differentially regulated in different parts of the brain. TARPs appear to stabilize AMPA receptors, either during biogenesis or at the cell surface, so the TARP isoforms expressed in a particular neuron could determine whether AMPA receptor concentrations are increased, decreased, or maintained at a synapse in response to a given stimulus.

All four isoforms contain a conserved cytoplasmic protein binding domain that appears to drive synaptic clustering, and phosphorylation of this domain might initiate synaptic remodeling. The authors are now studying the prototypic TARP, stargazin, to see whether calcium influxes can induce changes in the phosphorylation status and activity of the protein.
Coping with the stress of morphogenesis

As a multicellular organism develops, its tissues are often subjected to powerful internal and external mechanical stresses. On page 757, Bosher et al. describe a set of critical reinforcements that allow *C. elegans* embryos to weather these forces rather than be torn apart. Besides illuminating a critical aspect of morphogenesis, the work establishes a new model for analyzing the coupling of tissues during development.

Using a genetic screen, the authors found that mutations in a locus called *vab-10*, which corresponds to spectraplakin, cause defects in the elongation of worm embryos. *C. elegans* vab-10 encodes two protein isoforms. Mutations that affect VAB-10A isoforms disrupt fibrous organelles, which are molecular and functional homologues of vertebrate hemidesmosomes. These mutations cause epidermal cells to detach from the cuticle and muscles during elongation. When VAB-10B isoforms are disrupted, the epidermis instead becomes thicker.

The results suggest that VAB-10A proteins allow epidermal cells to resist external stresses, whereas VAB-10B proteins ensure that the basal and apical membranes of the cells are locked a fixed distance apart, even in the presence of powerful internal stresses. The *C. elegans* system should now provide a useful platform to study how spectraplakins modulate and direct these forces.