Movements of a swift kinase keep up with quick calcium bursts, based on findings of Reither et al. (page 521).

Cellular Ca\textsuperscript{2+} signals come in many flavors—from long-lasting global increases to waves to brief local plumes. Each flavor is translated into a specific cellular response by Ca\textsuperscript{2+} sensors, including calmodulin and conventional PKCs (cPKCs).

Upon Ca\textsuperscript{2+} binding, PKC\textsuperscript{a}—a common cPKC—translocates to the plasma membrane, the location of most of its targets, including ion channels and transporters. The bulkiness of PKC\textsuperscript{a} might suggest that its diffusion constants should be too low for rapidly following the fast and brief Ca\textsuperscript{2+} signals. Many researchers thus suspected that tiny calmodulin must be the main translator of these signals.

But the new findings reveal that PKC\textsuperscript{a} is fleet-footed. The authors found that PKC\textsuperscript{a}’s membrane translocation mimics—in both space and time—the full range of the cellular Ca\textsuperscript{2+} signals.

Just fractions of a second after a Ca\textsuperscript{2+} burst, PKC\textsuperscript{a} was found at the membrane, where it lingered either for mere milliseconds or for longer stretches of several seconds. The short-lived membrane residence solely depended on cytosolic Ca\textsuperscript{2+}. The more intimate interactions required PKC\textsuperscript{a}’s binding to the membrane lipid diacylglycerol (DAG). Since this binding is required for full activation of the kinase, the authors suspect that the shorter interactions might not necessarily lead to downstream signaling events.

Copies of PKC\textsuperscript{a} that encounter Ca\textsuperscript{2+} in the center of the cell are unlikely ever to make it to the plasma membrane, as the Ca\textsuperscript{2+}-PKC\textsuperscript{a} complex is short lived. The authors thus suggest that PKC\textsuperscript{a} activation depends solely on sub–plasma membrane Ca\textsuperscript{2+} signals. Perinuclear signals probably trigger an entirely different set of downstream events—perhaps via calmodulin, which has many cytoplasmic substrates.

Integrins for mitosis

Integrins are widely known for their adhesive and migratory functions. On page 491, Reverte et al. reveal that integrins are also needed for the microtubule assembly that makes cell division possible.

For many cell types, division does not occur unless the cells are stuck to a matrix. The blockade to division was first linked to integrins when it was discovered that cells do not enter S phase in response to growth factors unless integrins are engaged.

In the new report, the authors identify an inactive integrin \( \beta \) mutant that nevertheless supports entry into S phase. Once in mitosis, however, cells adhering via this mutant are unable to build a proper microtubule array. Although some cells had no spindle, others were multipolar. Most never completed cytokinesis, probably due to a defective spindle midzone, which helps to establish the cytokinetic furrow.

The cytoskeletal problems were not restricted to mitosis; interphase microtubule arrays were also disorganized, failing to radiate normally from centrosomes. In the mutants, the centrosomes did not coordinate microtubule regrowth in response to depolymerization. The faulty interphase array probably creates problems in transport and organelle positioning, but the authors have not yet examined these issues.

Ligation of the mutant integrin \( \beta \) with an activating antibody restored microtubule polymerization and cell division. The authors suppose that active integrins turn on downstream signaling molecules—perhaps kinases or small GTPases—that might help to stabilize microtubule networks or localize centrosomal proteins. They are currently narrowing down the possibilities by screening for signaling pathway inhibitors that mimic the integrin mutant. The end result might be a better understanding of how some cell types, such as tumor cells, bypass the need for adhesion during mitosis.
Cohesin loops DNA

The glue that holds together sister chromatids also compacts meiotic chromosomes, according to Ding et al. on page 499. This cohesin subunit, called Rec8, seems to tie up chromosomes into loops.

The role of Rec8, a meiosis-specific cohesin subunit, in chromosome architecture was identified by the authors in a fission yeast screen for meiosis mutants. During meiotic prophase, the yeast nuclei oscillate via microtubule pulling forces that extend chromosomes along the direction of movement. The abnormal movements of chromosomes in rec8− cells suggested an unusual DNA architecture.

The DNA extension that accompanies oscillation offered the group the opportunity to compare chromosome compaction in wild-type and mutant strains. The authors’ measurements of the distance between the telomeres and a particular locus revealed long and loose chromosomes in the absences of Rec8. They found the opposite situation—hypercompaction—in a second strain that was mutated in a Rec8 binding partner called Pds5.

Given this contrast, the authors expected to see more Rec8 on chromosomes in the pds5− mutant. But instead they found fewer Rec8 binding sites, suggesting that Pds5 helps to load Rec8.

To explain the discrepancy, the authors suggest that the meiotic DNA is compacted as loops, with Rec8 sites serving as loop base attachment points along the chromosomal axis. In the absence of Rec8, loops do not form and chromosomes are extended. When Rec8 is present in low quantities, there are fewer attachment points along a shorter than normal axis, resulting in longer loops but more highly compacted chromosomes.

Meiotic compaction was not affected by the loss of condensins, which control mitotic condensation. Perhaps the specific Rec8-mediated arrangement exposes particular loci in a precise orientation that assists homologue pairing.

A cadherin that holds together vascular cells also keeps a growth factor receptor fixed in place, say Lampugnani et al., on page 593. The cadherin’s tug keeps the receptor on the surface, where it cannot induce the cell to proliferate.

Proliferation is fine when there is room to grow, but endothelial cells prevent overcrowding by becoming insensitive to growth factors such as VEGF. This insensitivity requires an association between the VEGF receptor type 2 (VEGFR-2) and a cell–cell junction adhesion molecule called VE-cadherin. In the new work, the authors discover that this connection prevents VEGFR-2 internalization.

In disperse cells, the authors found, VEGF-bound receptor was phosphorylated and internalized into early endosomes via clathrin-mediated endocytosis. Although internalization often ends a receptor’s signaling abilities (by leading to receptor recycling or degradation), several receptors have been recently shown to be most active from within early endosomes, where they are protected from degradation. Indeed, endosomal VEGFR-2 turned on proliferation-inducing MAPK pathways.

VEGFR-2 endocytosis was prevented, however, when the receptor was associated with VE-cadherin, which may be a mechanical obstacle to the clathrin machinery. Left on the surface, VEGFR-2 was vulnerable to dephosphorylation—and thus deactivation—by the DEP-1 phosphatase. Dephosphorylation might also further prevent internalization.

Before forming new blood vessels, endothelial cells dismantle their cell–cell junctions by down-regulating VE-cadherin, thus freeing VEGFR-2 from the grips of VE-cadherin and allowing its endocytosis in response to growth factors. Blocking this internalization step with drugs might be an alternative way to prevent new vessel formation, which is necessary for tumor growth.