Interestingly, the ACA-containing vesicles themselves, not just their contents, are deposited behind the *Dictyostelium* cells like a breadcrumb trail as the cells crawl along. As cAMP is a small and diffusible molecule, perhaps the vesicles serve to package the chemoattractant so that it doesn’t immediately diffuse away, says author Carole Parent.

Kriebel, P.W., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200808105.

**Cofilin activity is a total coincidence**

Frantz et al. demonstrate how events coincide at the cell’s leading edge to regulate the activity of actin-severing cofilin.

Cofilin promotes the formation of actin filaments at the front of motile cells by binding to existing filaments and cutting them, creating barbed ends for new filament nucleation. Cofilin activation requires Ser3 dephosphorylation; however, this alone is not sufficient. Additional mechanisms—including deprotonation of His133 (by increasing cellular pH), and release from membrane phospholipid, PI(4,5)P2—might also be necessary. Cofilin presumably acts as a “coincidence detector” for these signals, explains author Diane Barber.

The question was, how do these individual regulatory events combine. Increased pH by H+ efflux had been suggested for the His133 deprotonation, and the authors now confirm that, in response to migratory cues, H+ efflux by the mammalian Na-H exchanger (NHE1) was required for increasing actin barbed end formation by cofilin. As for PI(4,5)P2 release, the authors found that His133 deprotonation in fact decreased cofilin binding to the phospholipid. Thus, these two regulatory steps are related.

The authors went on to determine how events combine at the structural level. Using computational modeling, NMR, and site-directed mutagenesis, they showed that dephosphorylation of Ser3 unblocked an amino-terminal actin-binding site on cofilin. Whereas at the other end of the protein, the decreased binding of PI(4,5)P2, after His133 deprotonation, freed up a second actin-binding site.

pH-dependent binding of membrane phospholipids is a growing phenomenon in protein biology, suggested to be a negative regulatory mechanism in some instances—as now shown for cofilin. It may be particularly relevant at the cell’s leading edge where actin regulators can be kept close at hand, but remain inactive until needed.

Frantz, C., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200804161.

**Dynein gives the “all clear”**

Whyte et al. now show how dynein gets to and from the kinetochore at mitosis. Their findings also suggest an unexpected role for dynein as a metaphase checkpoint regulator.

The molecular motor, dynein, is important for mitosis and is present at the spindle poles, cell cortex, and kinetochores. How it is targeted to these sites has been something of a mystery.

The authors looked for mitosis-specific post-translational modifications that might affect dynein’s targeting. They found a threonine residue in dynein’s intermediate chain (T89) that was phosphorylated from the onset of mitosis until metaphase. The authors made an antibody specific for the phospho-T89 form of dynein and showed that it located exclusively to kinetochores.

When the kinetochores were stretched as chromosomes aligned at the metaphase plate, T89 was dephosphorylated by the phosphatase PP1γ. As a result, dynein lost its association with the kinetochore and headed out along metaphase microtubules toward the spindle poles. Fluorescence colocalization studies showed that poleward-streaming dynein took with it metaphase checkpoint proteins like BubR1.

Kinetochoore dynein was thought to be involved in the poleward movement of chromosomes during anaphase. But, the stripping away of metaphase checkpoint proteins from the kinetochore might actually be the main role of kinetochore dynein in mitosis, says author Kevin Vaughan.

Whyte, J., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200804114.