

Claudin 11 tight junctions (arrow-heads) in a radial cross section of an axon.

Claudin 11 stops the leaks

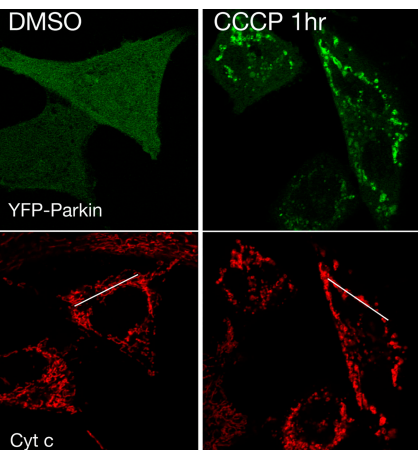
Devaux and Gow demonstrate how a tight junction protein called claudin 11 makes the neuronal myelin sheath a snug fit.

Like the rubber coating on a copper wire, the myelin sheath—a membrane extension of glial cells that spirals around the axons of neurons—creates an insulation layer that prevents current leakage from axons and aids electrical conduction along the length of the axon.

Claudin 11 forms tight junctions between successive spiral layers of the myelin sheath, but it was unknown whether it was required for myelin to act as a good insulator. To examine this question, Devaux and Gow compared electrical recordings from the optic nerve of wild-type and claudin 11 knockout mice. They found that although claudin 11 deficiency caused no gross defects in the appearance of the myelin sheath, it slowed electrical signals—at least in neurons with small-diameter axons.

Using a computer model that incorporates the resistive and capacitive properties of axons (and their myelin sheaths), the authors showed that claudin 11 adds to the electrical resistance of myelin by preventing leakage of charged ions (and electrical current) through the spiral space between myelin layers. The reduced resistance in the absence of claudin 11 affects small-diameter axons most severely because such axons have thinner myelin sheaths and thus less insulation to begin with. Because neurons with small-diameter axons are mostly found in the CNS, the authors speculate that defects in claudin 11 could be associated with deficits in cognition and perception, like those found in schizophrenia or neurodegenerative diseases.

Devaux, J., and A. Gow. 2008. *J. Cell Biol.* doi:10.1083/jcb.200808034.



Parkin (green) goes to mitochondria (Cyt c labeling, red) when these organelles are depolarized by the drug CCCP.

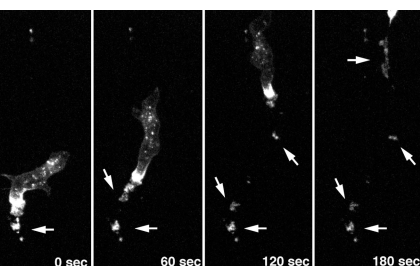
Parkin cleans house

A study by **Narendra et al.** suggests that Parkin, the product of the Parkinson's disease-related gene Park2, prompts neuronal survival by clearing the cell of its damaged mitochondria.

Loss-of-function mutations in the gene Park2, which encodes an E3 ubiquitin ligase (Parkin), are implicated in half the cases of recessive familial early-onset Parkinson's disease. Several lines of evidence suggest that Parkin loss is associated with mitochondrial dysfunction, but exactly how was unknown. To learn more about Parkin's role in cells, Narendra et al. examined the protein's subcellular location. They found that Parkin was present in the cytoplasm of most cells, but translocated to mitochondria in cells that had undergone mitochondrial damage such as membrane depolarization.

Damaged mitochondria can trigger cell death pathways; indeed, dysregulation of mitochondrial health was already thought to be a possible cause of the neuronal cell death associated with Parkinson's disease. The relocation of Parkin to damaged mitochondria, the team showed, sends these defunct organelles to autophagosomes for degradation. Parkin may thus prevent the damaged mitochondria from triggering cell death. Because neurons are not readily replicable, disposing of damaged mitochondria may be especially important in the adult brain.

Narendra, D., et al. 2008. *J. Cell Biol.* doi:10.1083/jcb.200809125.



***Dictyostelium* leave ACA-containing vesicles (arrows) behind them as they crawl.**

Dictyostelium cells lay a breadcrumb trail

When starved of their food source and then presented with a chemoattractant signal like cAMP, individual *Dictyostelium* cells acquire a polarized morphology and aggregate to form a migrating stream. This is the first step in a developmental program that culminates in the formation of a multicellular organism. **Kriebel et al.** show how this streaming response is coordinated at a single-cell level.

Besides acquiring a polarized morphology and beginning to chemotax, *Dictyostelium* cells respond to cAMP signals by making their own cAMP, thereby recruiting yet more cells to join the parade. The team previously discovered that ACA—the enzyme that makes cAMP—is highly enriched at the back of migrating cells. They thus proposed that the attractant is released mainly from the rear of cells, which prompts fellow cells to align and generate head-to-tail streaming structures. Kriebel et al. now show that ACA is packaged into intracellular vesicles that cluster at the rear of cells in a process that is dependent on actin and microtubule networks. They also show that de novo protein synthesis is required to maintain the asymmetrical distribution of the ACA vesicles.

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](https://doi.org/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](https://doi.org/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.

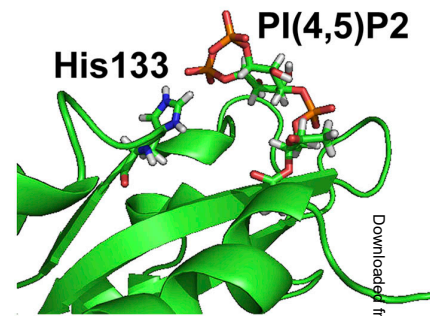
The molecular motor, dynein, is important for mitosis and is present at the spindle poles, cell cortex, and kinetochores. How it is targeted to these sites has been something of a mystery.

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.

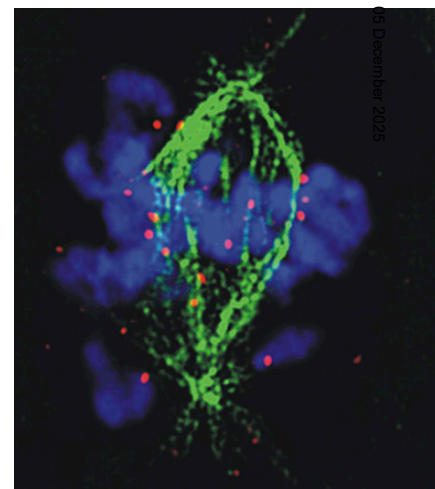
When the kinetochores were stretched as chromosomes aligned at the metaphase plate, T89 was dephosphorylated by the phosphatase PP1 γ . As a result, dynein lost its association with the kinetochore and headed out along metaphase microtubules toward the spindle poles. Fluorescence colocalization studies showed that poleward-streaming dynein took with it metaphase checkpoint proteins like BubR1.

Kinetochore 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](https://doi.org/10.1083/jcb.200804114).



Deprotonation at His133 releases PI(4,5)P2 from cofilin.



Phosphorylated kinetochore dynein (red) at late prometaphase.