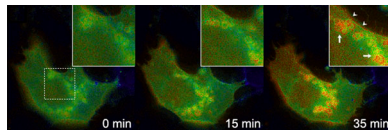


## KRas takes a different route



**Active KRas (red) accumulates on endosomes after stimulation with EGF.**

**T**he small GTPase KRas moves between different membranes within the cell by diffusion, but [Lu et al.](#) find it can use an alternative mode of transport to travel to another destination.

Ras proteins control many cellular functions including proliferation, differentiation, and apoptosis. Their location within the cell affects the downstream signals they send; KRas has been identified at the plasma membrane and on intracellular membranes. Previous reports suggested that KRas associates with negatively charged membranes via its positively charged C-terminus and moves between compartments by diffusing through the cytosol along an electrostatic gradient.

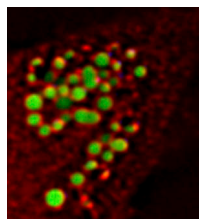
But when [Lu et al.](#) tracked GFP-labeled KRas, they discovered

that the protein moves to early endosomes by internalizing from the plasma membrane in clathrin-coated vesicles. Unlike other Ras family members, KRas then gets sorted into late endosomes (LEs) before traveling to the lysosomes for degradation. Fluorescent probes revealed that KRas was active on LEs, where it colocalized with a scaffolding complex called p14-MP1 and initiated a MAP kinase signaling cascade.

KRas' journey to the lysosomes is stimulated by EGF and its receptor, which share the ride all the way to the end, suggesting that lysosomal-degradation may be important for switching off the EGF/KRas signal. Indeed, when lysosomal degradation was blocked, the MAP kinase cascade remained active for longer on the LEs. The researchers now want to look at how LE KRas signaling is propagated and determine how it differs from KRas signaling at the plasma membrane.

[Lu, A., et al. 2009. \*J. Cell Biol.\* doi:10.1083/jcb.200807186.](#)

## Lipid droplets lead a Spartan existence



**Spartina (red) localizes on the surface of lipid droplets (green).**

**S**partin, a protein linked to the neuronal disease Troyer syndrome, was thought to function in endocytosis. Here, [Eastman et al.](#) identify an unexpected role for Spartina in regulating the cell's lipid storage depots.

Cells transport excess fats into lipid droplets (LDs), where they are kept until needed as sources of energy, but little is known about LD formation and regulation.

Spartin hadn't been connected to LDs. But

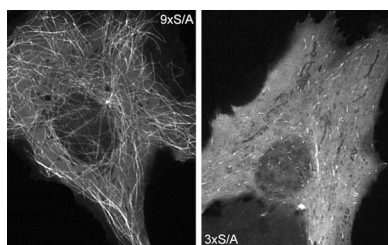
[Eastman et al.](#) found that Spartina localizes to LDs and binds to a known LD protein called TIP47.

Spartin seems to regulate LD turnover: overexpressing or knocking down the protein caused an increase in both the organelle's size and number. In turn, Spartina is regulated by ubiquitination by the ubiquitin ligase WWP1. Overexpressed WWP1 removed Spartina from LDs and promoted its degradation.

A truncated form of Spartina found in a rare neuronal disease called Troyer syndrome didn't localize to LDs or bind to TIP47. It remains to be seen whether defects in LD function are the root cause of the defects seen in Troyer patients, but author Paul Bieniasz points to precedents of defects in lipid turnover triggering neuronal disorders, such as mutations in the phospholipase NTE causing motor neuron disease.

[Eastman, S.W., et al. 2009. \*J. Cell Biol.\* doi:10.1083/jcb.200808041.](#)

## GSK3 $\beta$ loosens the CLASP on microtubules



**GSK3 $\beta$  phosphorylates CLASP, changing its localization from all along microtubules (left) to exclusive binding at growing microtubule plus ends (right).**

**M**icrotubules at the leading edge of migrating epithelial cells are stable and decorated along their length by a protein called CLASP. Back in the cell body, microtubules are much more dynamic, and CLASP only binds to their growing ends. [Kumar et al.](#) reveal how a gradient of phosphorylation by

GSK3 $\beta$  could cause this switch in CLASP's behavior.

The kinase activity of GSK3 $\beta$  changes from the front to back of migrating cells: low activity at the leading edge but higher in the cell body. Since expressing a highly active form of GSK3 $\beta$  completely removes CLASP from microtubules, [Kumar et al.](#) were interested to see whether phosphorylation could have more subtle effects on CLASP's localization.

The team identified nine sites in CLASP that could be phosphorylated by GSK3 $\beta$  all within a domain called MT#1 that recognizes growing microtubule ends. Although other domains are required for CLASP's binding along microtubules, phosphorylation of MT#1 was sufficient to regulate CLASP's localization: unphosphorylated CLASP bound along the length of microtubules while partial phosphorylation promoted its switch to microtubule ends. Author Torsten Wittmann thinks that increased CLASP binding at the cell front may help stabilize the microtubules by anchoring them to the cell cortex. CLASP probably links microtubules to the cortex through interactions with other proteins, like LL5b or ACF7, that bind to its C terminus; deleting CLASP's C terminus prevented stable cortical attachments from forming.

Many CLASP-stabilized microtubules cluster near focal adhesions, where the cell binds to the extracellular matrix. Wittmann now plans to investigate what these microtubules actually do: they could be involved in adhesion site turnover, or in the transport of cargo required for matrix degradation during cell migration.

[Kumar, P., et al. 2009. \*J. Cell Biol.\* doi:10.1083/jcb.200901042.](#)