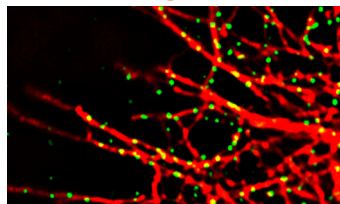


## $\gamma$ -TuRC gives microtubules pause for thought



$\gamma$ -TuRC (green) acts as a stabilizing factor along the length of microtubules (red).

A protein complex better known for its role in microtubule nucleation at the centrosome is also a stabilizing factor that controls cytoskeletal dynamics, say [Bouissou et al.](#)

$\gamma$ -Tubulin and its partners in the  $\gamma$ -tubulin ring complex ( $\gamma$ -TuRC) initiate the growth of new microtubules.

This is particularly important during mitosis—cells missing  $\gamma$ -TuRC subunits either fail to divide or go through the process slowly. Little is known about the complex's function in interphase, however.

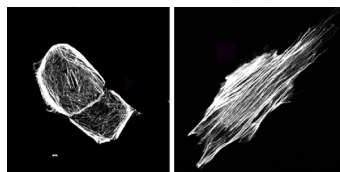
Bouissou et al. depleted several  $\gamma$ -TuRC components (including  $\gamma$ -tubulin itself) in *Drosophila* cells and found that microtubule organization was unaffected. But live microscopy

revealed that the microtubules in these cells were more dynamic and more likely to switch from growing to shrinking, whereas microtubules from control cells often remained paused. The researchers saw  $\gamma$ -TuRC dotting the length of microtubules, and determined that these spots corresponded to sites where dynamic microtubules would either pause or begin to regrow. Microtubules tended not to depolymerize past the points of  $\gamma$ -TuRC, suggesting that the complex acts as a stabilizing factor, perhaps by counteracting the binding of other microtubule-associated proteins that promote disassembly.

Because *Drosophila* cell microtubules are arranged somewhat differently to those in most animal cells, the group now wants to see whether  $\gamma$ -TuRC has a similar function in other cell types. Senior author Brigitte Raynaud-Messina also plans to investigate whether the complex regulates specialized subsets of microtubules that particularly need stabilizing.

Bouissou, A., et al. 2009. *J. Cell Biol.* doi:[10.1083/jcb.200905060](https://doi.org/10.1083/jcb.200905060).

## Raf-1 sheds then spreads its inhibitions



Cells lacking Raf-1 contract due to Rok- $\alpha$  overactivation (left). Raf-1's regulatory domain inhibits Rok- $\alpha$  and restores normal cell shape (right).

The regulatory domain of the kinase Raf-1 switches from inhibiting its own protein's activity to blocking a different kinase in a separate signaling pathway, say [Niault et al.](#), uncovering a novel type of signaling cross talk.

Raf-1 and Rok- $\alpha$  are two kinases, activated respectively by the small GTPases Ras and Rho. Before their activation, both kinases keep themselves quiet through intramolecular interactions between their inhibitory regions and catalytic domains. Activated Raf-1 also keeps Rok- $\alpha$  in check to promote cell migration, survival, and tumorigenesis—the inhibition of Rok- $\alpha$  by Raf-1 is essential for the development

and maintenance of Ras-induced epidermal tumors. But how this cross talk occurs is unclear.

Niault et al. found that when both kinases are activated by their GTPases, the regulatory domain of Raf-1 binds directly to the Rok- $\alpha$  kinase region to attenuate its activity. Cells lacking Raf-1 are abnormally shaped, migrate more slowly, and are more sensitive to cell death due to Rok- $\alpha$  overactivation, but the reintroduction of the Raf-1 regulatory domain alone reversed these phenotypes by blocking Rok- $\alpha$  function.

The inhibition of one kinase by another through direct binding is a new kind of regulation, says senior author Manuela Baccarini—cross talk between kinases and different signaling pathways is usually achieved through phosphorylation. Given the interaction's importance in cancer progression, Baccarini now wants to develop molecules that block the inhibitory association, and test these in animal tumor models.

Niault, T., et al. 2009. *J. Cell Biol.* doi:[10.1083/jcb.200906178](https://doi.org/10.1083/jcb.200906178).

## Chemosensitivity depends on the dependency

Two different anti-apoptotic proteins support cancer cell survival via an identical mechanism, yet differ in their sensitivity to chemotherapeutic drugs, report [Brunelle et al.](#)

Cancer cells often become dependent on one or more anti-apoptotic proteins to avoid death while continuing to proliferate. BCL-2, for example, is overexpressed in many cancers and mops up pro-apoptotic proteins to prevent them from permeabilizing mitochondria and initiating cell death. Other tumors are reliant on a related protein called MCL-1, but less is known about this member of the BCL-2 family. Brunelle et al. created leukemic mice overexpressing MCL-1 and compared them to similar mice that produced excess BCL-2.

The leukemias suffered by these two types of mice were identical, yet a technique called BH3 profiling was able to distinguish between cells derived from the different animals by demonstrating a dependency on one or other of the two anti-apoptotic proteins.

Immunoprecipitation experiments revealed that MCL-1 and BCL-2 both work by sequestering the same two pro-apoptotic targets. Surprisingly then, leukemia cells reliant on MCL-1 were much more sensitive to a range of chemotherapeutic drugs than their BCL-2-dependent counterparts were. Brunelle et al. found that the different cytotoxic drugs all caused a rapid decrease in MCL-1 protein levels via proteasome-mediated degradation, allowing cell death to proceed quickly. BCL-2 protein is more stable however, so additional time and more drug is needed to kill BCL-2-dependent cancer cells.

Thus, the block in apoptosis selected during oncogenesis is not necessarily complete, and can have a major influence on the cancer's chemosensitivity. Senior author Anthony Letai now plans to use BH3 profiling on human tumors, to determine which anti-apoptotic protein a patient's cancer is dependent on and to correlate this with the tumor's response to chemotherapy.

Brunelle, J.K., et al. 2009. *J. Cell Biol.* doi:[10.1083/jcb.200904049](https://doi.org/10.1083/jcb.200904049).