How ERK5 prompts proliferation

Overactive ERK5 drives cell proliferation and transformation and is associated with highly aggressive forms of breast and prostate cancer. Now, Cude et al. (page 253) reveal that this MAP kinase pushes the cell cycle forward by promoting entry into M phase.

ERK5 is activated by various growth factors. Its known targets include cyclin D and NFκB, both of which help cells enter S phase. It had been suggested, therefore, that growth factor–induced ERK5 might promote cell proliferation by kick-starting S phase. No one had yet looked, however, at how ERK5 activity normally changes during the cell cycle.

Cude et al. have now done just that. They found that ERK5 activity peaked at G2/M phase, not S phase. Suppressing this activation reduced the number of cells entering mitosis, while overactivating ERK5 drove more cells into mitosis. The ERK5-driven entry into M phase was dependent on the activity of the transcription factor NFκB, which the team found up-regulated a number of mitosis-promoting genes.

It’s unclear yet whether high levels of ERK5 activity are a direct cause of cancer. But if high ERK5 is enough to overcome G2/M phase DNA damage checkpoints, as the team now plans to investigate, then mutations might accumulate over subsequent cell divisions. Given that ERK5 might also promote S phase entry, and that high ERK5 activity suppresses apoptosis, it’s plausible that mutations causing ERK5 overactivity might be enough to drive aggressive tumor development. JCB

PIP₂ in endocytosis

Sites of endocytosis are enriched in PIP₂, but its removal is required for endocytosis to be completed, report Sun et al. (page 355).

The membrane minor phospholipid PIP₂ has long been implicated in endocytosis. Many endocytotic proteins contain binding sites for it, and, without this binding, endocytosis is impaired. Evidence for the enrichment of PIP₂ at sites of endocytosis, however, has been lacking. The team used a PIP₂-binding domain, tagged with a fluorescent protein, to follow the dynamics of PIP₂ during endocytosis in live cells.

They show that PIP₂ is present in patches on the membrane and that these patches move into the cell over time and disappear. To confirm this inward movement was indeed endocytosis, the team used a second fluorescently labeled endocytosis coat protein to follow the dynamics of PIP₂ during endocytosis in live cells.

The disappearance of PIP₂ coincided with the recruitment of phosphoinositide phosphatase, which is known to break down PIP₂. In cells in which PIP₂ breakdown was impaired, the team saw abnormal membrane invaginations that are thought to be the sites of multiple attempts and failures at endocytosis.

Indeed, without PIP₂ turnover, the endocytotic machinery still arrived at the membrane patches but hung around for longer without completing their job. It thus appears that the breakdown of PIP₂ is required for the scission of endocytotic vesicles. JCB

The critical chaperone balance

Chaperones protect proteins during their vulnerable folding stages. But too much chaperoning is counterproductive, as it keeps proteins in this vulnerable stage for too long, suggest Landsverk et al. (page 205).

The UNC-45 chaperone protects immature myosin from degradation while it folds into a form compatible with assembly into myofilaments. Without UNC-45, worms have fewer myofilaments in their muscle cells and are, as a result, severely paralyzed. The team now shows, however, that too much UNC-45 also results in myosin degradation, reduced myofilament numbers, and decreased mobility.

Myosin degradation caused by the loss of UNC-45 occurs via ubiquitination-mediated targeting to the proteasome. This same pathway was also the fate of myosin in the presence of too much UNC-45. Inhibiting the proteasome restored myosin levels and worm mobility.

The authors propose that, when there’s too much UNC-45, it holds more myosin proteins in their immature, nonmyofilament form. Because most chaperone–substrate interactions are highly dynamic, UNC-45 and myosin are probably constantly binding and releasing. During these moments of release, all this immature myosin would be available for ubiquitination.

Other chaperones have been similarly reported to have optimal concentration ranges. Ensuring that this optimal range is not exceeded might, itself, be achieved by the ubiquitination–proteasome pathway. Indeed, the team has previously shown UNC-45 to be degraded by this route. JCB