CANCER

Two of a kind

Cytoskeletal proteins regulate cell adhesion and motility, and some have even been shown to mediate cell survival. In the June issue of *Cancer Cell*, Rakesh Kumar and colleagues report the surprising finding that two cytoskeletal proteins, p21-activated kinase 1 (PAK1) and the dynein light chain 1 (DLC1), interact to promote the survival and tumorigenic potential of breast cancer cells.

Kumar and colleagues began their studies by looking for new substrates of PAKs. PAKs phosphorylate Rho GTPases to control cytoskeletal organization, and also phosphorylate and inactivate the pro-apoptotic protein BAD to promote survival. In a yeast two-hybrid screen of a mammary-gland cDNA library, they found that PAK1 interacts directly with, and also phosphorylates, DLC1 — a component of the dynein motor complex. DLC1 not only regulates the microtubule-dependent motor function of dynein, but has also been shown to bind and inhibit activity of the pro-apoptotic protein BCL2-like-11 (BCL2L11, also known as BimL).

So what happens when these two pro-survival signalling proteins get together? Kumar and colleagues expressed normal and mutant forms of the proteins in a breast cancer cell line, and showed that the interaction between PAK1 and DLC1 is required for cell-cycle progression and survival. Cells that overexpressed either PAK1 or DLC1 were able to undergo anchorage-independent growth, indicating a malignant phenotype, and resulted in oestrogen-independent tumour growth when transplanted into nude mice, unlike control cells. A DLC mutant that lacked the PAK1 phosphorylation site did not show tumorigenic potential in mice. Therefore, PAK1 phosphorylation of DLC1 seems to be required for cell survival and tumour formation. Furthermore, DLC1 levels were increased in 90% of the human breast tumour samples that the authors analysed.

How does PAK1 activation of DLC1 inhibit apoptosis and promote tumorigenesis? The authors propose a model whereby DLC1 sequesters BCL2L11 to the microtubules. Following pro-apoptotic signals, DLC1–BCL2L11 dimers are released and are free to inhibit BCL2, leading to cell death. When cells are exposed to growth factors or other survival signals, PAK1 becomes activated, leading to phosphorylation of DLC1 and of BCL2L11. This prevents the ability of the DLC1–BCL2L11 dimer to interact with and inhibit BCL2, leading to cell survival. So, increased levels of either PAK1 or DLC1 could promote cell survival and tumorigenesis. Further experiments are required to support this model and to investigate the role of these proteins in other tumour types.

Kristine Novak,
Senior Editor,
Nature Reviews Cancer

References and links

ORIGINAL RESEARCH PAPER

Vadlamudi, R. K. *et al.* Dynein light chain 1, a p21-activated kinase 1-interacting substrate, promotes tumorigenesis. *Cancer Cell* **5**, 575–585 (2004)

WEB SITE

Rakesh Kumar's laboratory:
http://gsbs.gs.uth.tmc.edu/tutorial/kumar.html

IN BRIEF

CYTOSKELETON

Chemical inhibition of N-WASP by stabilization of a native autoinhibited conformation.

Peterson, J. R. *et al. Nature Struct. Mol. Biol.* 4 July 2004 (doi:10.1038/nsmb796)

Using a forward chemical-genetic screen to identify inhibitors of the pathway that mediates the nucleation of actin filaments, the authors identified the small molecule wiskostatin. It binds within a pocket in the GTPase-binding domain (GBD) of neural Wiskott–Aldrich syndrome protein (N-WASP), thereby inducing the GBD to fold into its natural autoinhibited conformation. This interaction is thought to inhibit N-WASP by stabilizing the interaction between the GBD and another domain (the VCA).

CYTOSKELETON

Relating microstructure to rheology of a bundled and cross-linked F-actin network *in vitro.*

Shin, J. H. *et al. Proc. Natl Acad. Sci. USA* **101**, 9636–9641 (2004)

Actin-binding proteins (ABPs), which bundle and crosslink actin filaments, are important in regulating the elasticity of the actin cytoskeleton, but techniques to study their effect are lacking. Shin *et al.* used biochemical techniques, electron microscopy, confocal microscopy and multiparticle tracking to assess the effects of varying the concentration of the ABP scruin. They found that the linear elasticity of the actin–scruin composite network correlated with the properties of individual bundles and their structural organization.

RNA

Dynamics of single mRNPs in nuclei of living cells.

Shav-Tal, Y. *et al. Science* **304**, 1797–1800 (2004)

The authors resolved a long-standing controversy, by showing that nuclear mRNA–protein particles (mRNPs) move by free diffusion rather than by an energy-dependent process. By monitoring real-time mRNA expression in single living cells, Shav-Tal *et al.* studied the movement of thousands of mRNPs in the nucleus. The mobility was not directed, and no accumulation of mRNPs in subnuclear domains was detected.

MECHANISM OF DISEASE

Cellular toxicity of polyglutamine expansion proteins: mechanism of transcription factor deactivation.

Schaffar, G. *et al. Mol. Cell* **15**, 95–105 (2004)

This study provides new insights into neurodegenerative disorders, such as Huntington's disease, that are caused by expanded polyglutamine (polyQ) mutant proteins. A polyQ-expanded, soluble form of huntingtin bound to certain transcription factors that contain normal polyQ repeats, thereby inhibiting their function and causing cellular toxicity, independent of insoluble aggregates. The presence of chaperone proteins interfered with the conformational change that rendered the mutant huntingtin protein toxic, and prevented the inactivation of transcription factors.