IN THE NEWS

Tricking the ribosome

Nerve cells can take over the normal cellular protein synthesis machinery in the same way that viruses do when they infect a cell, according to a report published in *Nature Neuroscience*. When a virus infects a cell, it 'kidnaps' the host cell's ribosomes to boost the production of virus particles. The virus achieves this by using an internal ribosome entry site (IRES), which shuts down and bypasses the normal mechanisms that regulate binding of messenger RNAs to ribosomes.

In a study of egg laying in the sea slug *Aplysia*, researchers from McGill University observed that the protein production of the egg-laying hormone (ELH) in neurons increased markedly. They found that the 5′ untranslated region of *ELH* mRNA contained an IRES — which are common in viral mRNAs but not in normal cellular mRNAs.

Wayne Sossin and colleagues also noticed that the stimulus for egg laying caused dephosphorylation of the initiation factor eIF4E. And this single event was sufficient for the cells to switch to IRES-mediated translation. "Egg laying is an important investment for an animal, thus when stimulated to do so, it wants to get it right," explains Sossin (*ScienceDaily*, 20th February 2003).

"The discovery … reveals an unexpected regulatory role of the IRES in nerve cells" according to Nahum Sonenberg, who first discovered the IRES in poliovirus in 1988 (*ScienceDaily*, 20th February 2003). IRES-regulated protein production might be important in other physiological events, and Sossin predicts that "…IRES regulation may be particularly important at synapses where there are limiting numbers of ribosomes" (*Nature Neuroscience*).

Arianne Heinrichs

SIGNALLING

New Polo player

Phosphopeptide-binding domains and phosphorylated serine, threonine or tyrosine residues fit together like molecular lego to mediate protein–protein complexes. The number of domains that specifically recognize phosphorylated motifs is growing, and in their study, published in *Science*, Elia, Cantley and Yaffe used a proteomic approach to identify the 'polo-box domain', a new phosphoserine (pSer)/phosphothreonine (pThr)-binding domain, which they found to be present in the mitotic kinase Polo-like kinase 1 (Plk1).

Because protein kinases and phosphopeptide-binding domains recognize overlapping amino-acid motifs, the authors took the approach of biasing a partially degenerate phosphopeptide library towards the phosphorylation motif of a kinase and then immobilizing this library and using it as bait in a screen for interacting proteins. In this case, they used a pThr-proline library biased towards the motif that is generated by cyclin-dependent kinases (CDKs) and mitogen-activated protein kinases, which is also recognized by the antibody MPM-2, a mitotic phosphoprotein-specific monoclonal antibody. Using a collection of peptides, rather than a single peptide, increases the chances of an interaction. Conversely, to control for phospho-independent binding, an identical unphosphorylated peptide library was used.

One of the clones isolated encoded the carboxy-terminal part of Plk1. It was missing some of its kinase domain, though, implying that phosphopeptide binding occurred independently of catalytic activity. Polo kinase family members have two 'polo boxes' in their carboxy-terminal domain, and a series of deletion constructs showed that both polo boxes and the linker between the kinase domain and polo box 1 constituted what the authors called the 'polo-box domain' (PBD).

By screening several pSer- and pThr-containing orientated peptide libraries and using isothermal titration calorimetry, the authors determined the optimal binding motif for the PBD — a strong preference for serine in the (pThr or pSer) −1 position and proline at (pThr or pSer) +1, leading them to propose a core consensus binding motif of Ser-(pThr/pSer)-(Pro/X).

The conserved (pSer/pThr)-Pro epitope that is recognized by the MPM-2 antibody occurs on ~50 mitotic phosphoproteins. Many of these were specifically bound by the Plk1 PBD, and the interaction was blocked by incubation with its optimal phosphopeptide ligand. One mitotic phosphoprotein, the phosphatase Cdc25C, has a consensus Plk1 PBD-binding motif in its amino terminus. Transfection of Cdc25C point mutants that are expected to have a disrupted PBD-binding motif abrogated their interaction with the Plk1 PBD and interfered with their subsequent mitotic phosphorylation.

In addition, Yaffe and colleagues found the PBD of Plk1 to be responsible for localizing Plk1 to centrosomes during prophase. As the PBD also binds to the kinase domain of Plk1, there seem to be parallels between PBD and phosphotyrosine-binding Src-homology-2 (SH2) domains, in that both domains target their kinases towards phosphorylated substrates on activation, but inhibit phosphotransferase activity in the basal state. Also similar to SH2 domains, PBDs might provide particularly attractive targets for small-molecule mimetics as potential therapeutics.

Katrin Bussell

References and links

ORIGINAL RESEARCH PAPER Elia, A. E. H., Cantley, L. C. & Yaffe, M. B. Proteomic screen finds pSer/pThr-binding domain localizing Plk1 to mitotic substrates. *Science* **299**, 1228–1231 (2003)

FURTHER READING Yaffe, M. B. & Elia, A. E. Phosphoserine/threonine-binding domains. *Curr. Opin. Cell Biol.* **13**, 131–138 (2001)

WEB SITE

Michael Yaffe's laboratory:
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