

APOPTOSIS

Deadly FLAME

Human transcription factor IIC (TFIIC) is a multi-subunit transcriptional complex that recognizes the promoters for transfer RNA and virus-associated RNA genes. According to a report in *Cell Death and Differentiation*, it also turns out to be an unexpected binding partner for a newly discovered death-effector domain (DED) protein — FLAME-3.

Emad Alnemri and colleagues identified FLAME-3 in a search for sequences homologous to DED-containing proteins, which are important in death-receptor signalling. FLAME-3 shows almost 50% identity to another DED-containing protein, DEDD, and both proteins are localized to the nucleus. Co-immunoprecipitation experiments showed that the two proteins can form homo- and heterodimers, and that they can both also bind to cellular FLIP (c-FLIP), a protein that antagonizes the death-receptor pathway.

The authors next did a yeast two-hybrid screen for other proteins that interact with DEDD, and pulled out the TFIIC102 subunit of TFIIC. Co-immunoprecipitation and GST-pull-down experiments confirmed that TFIIC102 interacts with both DEDD and FLAME-3 *in vitro*. Alnemri and colleagues then co-transfected cells with GFP-tagged TFIIC102 and DEDD or FLAME-3. In both cases, the TFIIC102 relocated from the cytoplasm to the nucleus, hinting that DEDD and FLAME-3 could act as chaperones to translocate TFIIC102 across the nuclear membrane.

Finally, the authors showed that overexpression of DEDD or FLAME-3 can inhibit the transcriptional machinery, perhaps by sequestering TFIIC102, consistent with a role for these proteins in regulating TFIIC.

Alison Mitchell

References and links
ORIGINAL RESEARCH PAPER Zhan, Y. *et al.* Death effector domain-containing proteins DEDD and FLAME-3 form nuclear complexes with the TFIIC102 subunit of human transcription factor IIC. *Cell Death Diff.* **9**, 439–447 (2002)



makers, who require fruit with high levels of pectin as, when boiled, this causes jam to set. This approach might also be applicable to other fruits, as a pectate lyase has already been found in ripening bananas.

Christopher Surridge,
Senior Editor, Nature

References and links

ORIGINAL RESEARCH PAPER Jiménez-Bermúdez, S. *et al.* Manipulation of strawberry fruit softening by antisense expression of a pectate lyase gene. *Plant Physiol.* **128**, 751–789 (2002)

turnover, and concluded that this amide nitrogen is likely to be detecting motional changes that are linked to transition-state rearrangements in the protein and/or substrate. By combining their results with structural data, the authors also predicted a reaction trajectory for CypA.

Kern and co-workers have described an elegant approach for identifying dynamic ‘hot spots’ during catalysis, and have found that the time scales of enzyme dynamics match those of substrate turnover. Ultimately, side-chain dynamics will be required to obtain a more detailed motion picture of catalysis, but NMR relaxation measurements during catalysis promise to be invaluable for understanding both enzyme dynamics and their connection with catalysis.

Rachel Smalridge

References and links

ORIGINAL RESEARCH PAPER Eisenmesser, E. Z. *et al.* Enzyme dynamics during catalysis. *Science* **295**, 1520–1523 (2002)

WEB SITES

Encyclopedia of Life Sciences: www.els.net
NMR spectroscopy for monitoring molecular dynamics in solution

Dorothee Kern's laboratory: <http://www.bio.brandeis.edu/faculty01/kern.html>

IN BRIEF

ADHESION

Integrins regulate GTP-Rac localized effector interactions through dissociation of Rho-GDI.

Del Pozo, M. A. *et al.* *Nature Cell Biol.* **4**, 232–239 (2002)

Integrin-mediated cell adhesion is required to translocate the small GTPase Rac to the plasma membrane, where it can interact with its effectors. In this study, the authors used fluorescence resonance energy transfer to show that Rac only interacts with its effectors at specific regions at the edges of cells. This was due to the ability of integrins to target Rac to these regions and to dissociate it from Rho-GDI, which binds to cytoplasmic Rac and blocks effector binding.

SUMOYLATION

Members of the PIAS family act as SUMO ligases for c-Jun and p53 and repress p53 activity.

Schmidt, D. & Müller, S. *Proc. Natl Acad. Sci. USA* **99**, 2871–2877 (2002)

Like ubiquitylation, sumoylation requires an E1-activating enzyme and an E2-type conjugating enzyme, Ubc9. Until now, Ubc9 was also thought to be sufficient for substrate recognition, which, in the case of ubiquitylation, is carried out by E3 ligases. Now, however, Schmidt and Müller report that protein inhibitor of activated STAT (PIAS) proteins can function as specific SUMO ligases, in a similar manner to E3 ubiquitin ligases, and can mediate the sumoylation of p53 and c-Jun. PIAS-mediated sumoylation of p53 markedly repressed p53's transcriptional activity, indicating a role for the PIAS-SUMO pathway in transcriptional regulation.

CELL SIGNALLING

Cbl–CIN85–endophilin complex mediates ligand-induced downregulation of EGF receptors.

Soubeyran, P. *et al.* *Nature* **416**, 183–187 (2002)

The endophilin–CIN85–Cbl complex mediates ligand-dependent downregulation of c-Met.

Petrelli, A. *et al.* *Nature* **416**, 187–190 (2002)

The adaptor protein Cbl is involved in downregulating receptor-tyrosine kinases in response to ligand-induced activation by binding, through its Src-homology-2 (SH2) domain, to phosphorylated tyrosine residues. It then targets the receptors for ubiquitylation and subsequent degradation in lysosomes. But two new studies in *Nature* now show that Cbl also has a regulatory role in receptor internalization that is functionally separable from its ubiquitylation activity. Both research groups found that Cbl interacts, through its carboxyl terminus, with a complex that consists of endophilins — components of clathrin-coated vesicles that mediate endocytosis — and Cbl-interacting protein of 85 kDa, CIN85. The model proposed is that endophilin can alter the shape of the plasma membrane, thereby promoting membrane invagination, and that CIN85, an adaptor protein, might regulate receptor transport.

