WEB WATCH

Molecules in motion

The study of a protein's structure is a powerful way to learn more about its function. Often, however, such structural studies can provide only a single snapshot in space and time. Yet proteins and other macromolecules are dynamic, fluid structures, and the motions that occur within them are key to many of the processes in which they are involved.

To facilitate the study of such motions, Mark Gerstein and colleagues at Yale University have created the Database of Macromolecular Movements. Their aim, they say, is to "survey all the known instances of domain movements in proteins and other molecules for which there is experimental evidence for the movement".

The database is first divided into broad sections — motions in domains, for example, or in fragments smaller or larger than domains. Within each section, molecules are then classified according to the various low-energy conformational changes that are known to occur. The result is a logically organized, albeit rather list-like, collection of information.

But the site is much more than simply a database. The motions analysis includes a gallery of movies, where proteins come to life in two dimensions. Each can be viewed in various representations (ribbon, CA trace, ball-and-stick or hinge), with three-dimensional movies also available for some proteins. There is also a 'MorphServer', which allows users to produce two- and three-dimensional animations of the pathway between two protein subunit conformations.

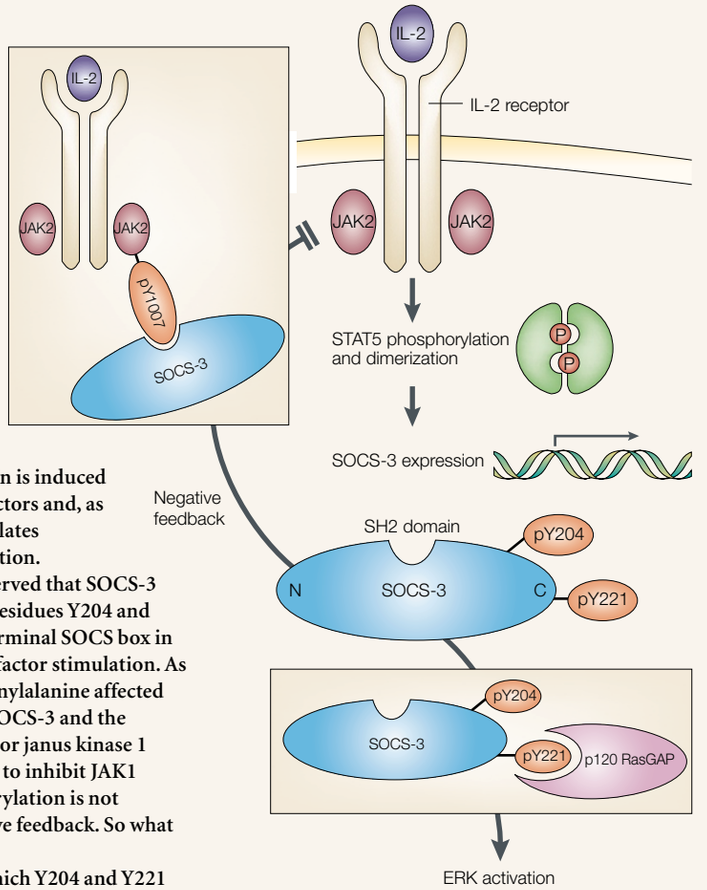
Other features include free software for studying macromolecular geometry, allowing volumes, surfaces, axes, angles and distances to be calculated, and a useful page of links related to protein motions.

Alison Mitchell

SIGNAL TRANSDUCTION

How to cope with negative feedback

Negative feedback is something we all find hard to deal with, but for cells it can mean the difference between life and death. In particular, balancing negative feedback with the need to survive can be tricky. Reporting in *Nature Cell Biology*, however, Nicholas Cacalano, David Sanden and James Johnston describe how the suppressors of cytokine signalling 3 (SOCS-3) protein can act as a selective molecular switch, allowing cells to survive despite being a critical factor in the negative feedback of cytokine-mediated signalling.



Expression of the SOCS-3 protein is induced by many cytokines and growth factors and, as its name suggests, negatively regulates cytokine-induced signal transduction. Johnston and colleagues also observed that SOCS-3 was tyrosine phosphorylated on residues Y204 and Y221 in the conserved carboxy-terminal SOCS box in response to cytokine and growth factor stimulation. As mutation of these residues to phenylalanine affected neither the interaction between SOCS-3 and the interleukin (IL)-2 cytokine receptor janus kinase 1 (JAK1), nor the ability of SOCS-3 to inhibit JAK1 kinase activity, tyrosine phosphorylation is not thought to be required for negative feedback. So what purpose does it serve?

When a peptide of SOCS-3 in which Y204 and Y221 were phosphorylated was mixed with lysates of IL-2-dependent cells, it co-precipitated with a protein corresponding to p120 RasGAP, a GTPase-activating protein that negatively regulates Ras. As the interaction requires the SH2-domain-containing amino terminus of RasGAP, and the sequence surrounding Y221 of SOCS-3 conforms to the consensus YXXP motif known to mediate the binding of RasGAP to other GAP-interacting proteins, it is likely that SOCS-3 and RasGAP associate in an SH2-dependent manner.

The consequences of the interaction between SOCS-3 and RasGAP were revealed using cells in which the expression of wild-type or mutant SOCS-3 (Y221F) could be controllably induced. In response to IL-2, expression of wild-type SOCS-3 attenuated the activation of signal transducer and activator of transcription 5 (STAT5), whereas IL-2-induced activation of extracellular-signal-related-kinase (ERK) — a downstream target of Ras in the Raf/MEK/ERK pathway — was unaffected. However, expression of mutant SOCS-3, while continuing to inhibit STAT5 activation, severely abrogated ERK activity. Further analysis revealed that Ras activity was also considerably impaired when the SOCS-3 mutant was expressed, implicating inhibition of RasGAP in the maintenance of ERK pathway signalling.

The consequence, then, of expressing the mutant SOCS-3 protein in cells is inhibition of proliferation in response to growth factors and cytokines. So, it seems that wild-type SOCS-3 can sustain ERK activation while repressing cytokine-mediated signalling. SOCS proteins are thought to inhibit cytokine signalling by binding in an SH2-domain-dependent manner to tyrosine-phosphorylated JAK proteins and blocking catalytic activity. But the mechanisms by which SOCS-3 inhibits RasGAP activity remains a mystery

Katrin Bussell

References and links

ORIGINAL RESEARCH PAPER Cacalano, N. A. *et al.* Tyrosine-phosphorylated SOCS-3 inhibits STAT activation but binds to p120 RasGAP and activates Ras. *Nature Cell Biol.* **3**, 460–465 (2001)

FURTHER READING Yasukawa, H. *et al.* Negative regulation of cytokine signaling pathways. *Annu. Rev. Immunol.* **18**, 143–164 (2000)

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