What does this tell us about the mechanisms that drive transport through the pore? The authors find that different import receptors are differentially affected by deletion of particular FG domains, which suggests there might be at least two distinct routes through the pore. Furthermore, we learn that one type of FG domain — the GLFG domain — is more critical than others: mutant strains containing only GLFG domains can mediate transport in the absence of the other types of FG domain, whereas its deletion seems to have dire consequences for cell viability.

Existing transport models — including the 'affinity gradient' model, which proposes that transport receptors move through the pore by sequential interactions with FG domains of increasing affinity — will now need to be re-evaluated. In fact, it might turn out that parts of several current models are at work. Of course, there are important questions to address, such as what contribution non-FG domains make to transport through these minimal pores, but nevertheless these results provide an essential basis on which to build an understanding of nuclear transport.

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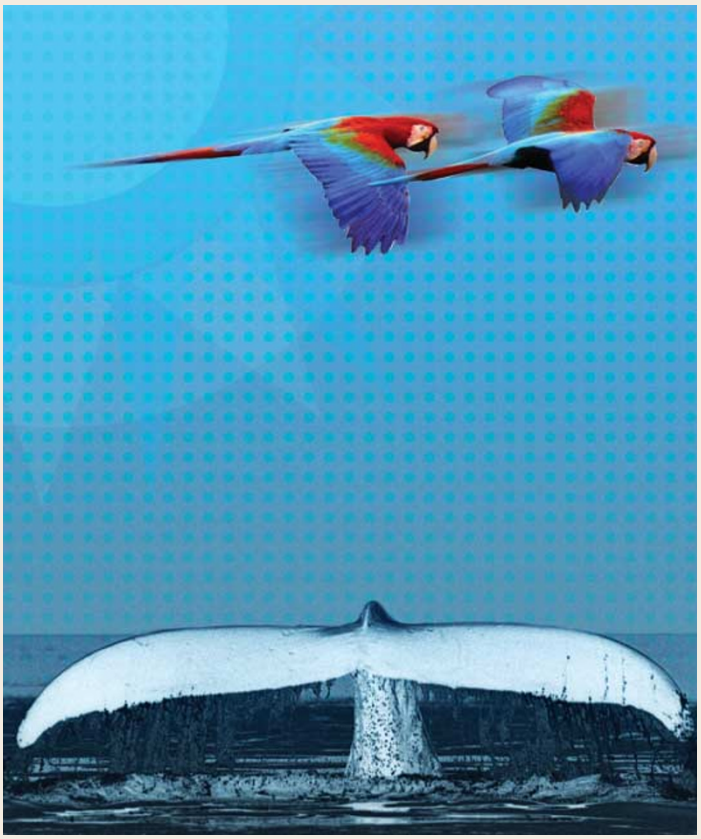
References and links

ORIGINAL RESEARCH PAPER
Strawn, L. A. *et al.* Minimal nuclear pore complexes define FG repeat domains essential for transport. *Nature Cell Biol.* **6**, 197–206 (2004)

FURTHER READING
Timney, B. L. & Rout, M. P. *et al.* Robbing the pore. *Nature Cell Biol.* **6**, 177–179 (2004)



STRUCTURE WATCH

A shared site

The eukaryotic signal-recognition particle 54 (SRP54; Ffh in prokaryotes) and its receptor SRα (FtsY in prokaryotes) are GTPases that directly interact during the co-translational targeting of proteins to the endoplasmic-reticulum membrane (or plasma membrane in prokaryotes). On complex formation, these proteins stimulate each other's GTPase activity to induce GTP hydrolysis, which ensures the unidirectional targeting of the nascent protein through a pore in the membrane. But how does this reciprocal activation occur? Papers in *Nature* and *Science* — by Stroud and colleagues and Freymann and co-workers, respectively — now provide insights into this process by reporting crystal structures of a complex of Ffh, FtsY and a non-hydrolysable GTP analogue (GMPPCP).

The structures highlight a symmetrical heterodimer that has an extensive interaction interface, and show that complex formation produces a composite active site that contains two GMPPCP molecules. Remarkably, the GMPPCP molecules interact directly; such a nucleotide–nucleotide interaction was not expected. By contrast with most other GTPases, there are only small differences between the free GTP- and GDP-bound states of Ffh and FtsY, whereas significant conformational changes occur in these proteins when they interact with each other. The extensive protein interface and the direct nucleotide–nucleotide interaction seen in this complex explain the coordinate activation of these GTPases, and clarify why complex formation is GTP-dependent and GTP hydrolysis leads to complex dissociation.

REFERENCES Egea, P. F. *et al.* Substrate twinning activates the signal recognition particle and its receptor. *Nature* **427**, 215–221 (2004) | Focia, P. J. *et al.* Heterodimeric GTPase core of the SRP targeting complex. *Science* **303**, 373–377 (2004)

Keeping control

There has been much speculation about how the juxtamembrane domain of type III receptor tyrosine kinases (RTKs) regulates their activity, but the need for conjecture is now over. Saxena and colleagues, reporting in *Molecular Cell*, describe the crystal structure of the kinase and juxtamembrane domains of an autoinhibited, unphosphorylated form of FLT3 — a type III RTK that is important in haematopoiesis and is mutated in numerous patients with acute myelogenous leukemia (AML).

The structure contains a bilobed (N- and C-lobe) kinase domain and an activation loop, and it conforms to the prototypical conformation of other inactive kinases in that the 'closed' activation loop is folded between the N- and C-lobes. However, the FLT3 structure also includes the juxtamembrane domain, which contacts all of the key features of FLT3 and has three topological regions. The authors suggest that the dephosphorylation of tyrosine residues in the 'switch' region of the juxtamembrane domain allow it to move close to the C-lobe, which allows the 'binding' region to insert into its autoinhibitory binding site. A further 'zipper' region functions to keep the switch region in register. They believe that this autoinhibition mechanism is used by other type III RTKs. Furthermore, this structure has provided a framework for understanding mutations that cause AML, and might allow the design of new treatments for this disease.

REFERENCE Griffith, J. *et al.* The structural basis for autoinhibition of FLT3 by the juxtamembrane domain. *Mol. Cell* **13**, 169–178 (2004)