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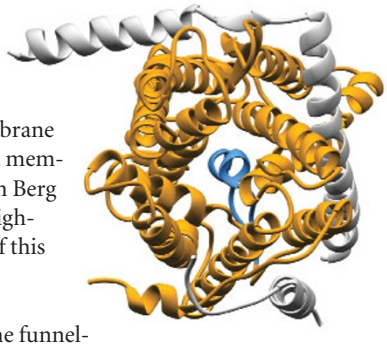

During protein synthesis, some polypeptides go through a channel known as the translocon to cross the endoplasmic reticulum membrane in eukaryotes and the plasma membrane in prokaryotes. van den Berg *et al.* report a long-awaited high-resolution crystal structure of this channel, a complex of three membrane proteins, from *Methanococcus jannaschii*. The funnel-shaped channel has a wide entrance at the cytoplasmic side and tapers to a narrow pore formed by the α subunit (gold). In what the authors suggest to be a 'closed' form of the channel, this pore is blocked by a short helical plug (blue). Without the plug, the channel would form an 'hourglass' structure with a ring of hydrophobic residues at its narrowest point. This pore ring, 5–8 Å wide, could specifically surround a polypeptide crossing the membrane while blocking the passage of other molecules. The structure of the closed channel provides a foundation for future studies into how the pore opens for translocation. (*Nature*, published online 3 December 2003, doi:10.1038/nature022180) *DL*

Exportin' pre-miRNAs

The biogenesis of eukaryotic microRNA requires processing events that transform a nuclear precursor to an export-competent pre-miRNA. After transport to the cytoplasm, the precursor miRNA is further processed to a duplex of 20–22 nucleotides, in which one strand becomes the mature miRNA that functions to control gene expression. Hence, nuclear export serves as a critical but uncharacterized quality control step in miRNA biogenesis. Two groups recently identified Exportin-5 (Exp5) as the required export receptor. Lund *et al.* showed directly that Exp5 transports pre-miRNAs across the nuclear membrane in a RanGTP-dependent manner. Yi *et al.* used reporter assays, which monitor miRNA function, to show that Exp5 is required for biogenesis of miRNAs and small interfering RNAs generated from artificial short hairpin RNAs. Both groups show that Exp5/RanGTP binds to pre-miRNA directly and specifically, preferring RNAs with a high degree of double-strand character and 3′ nucleotide overhangs. Furthermore, both groups demonstrate that Exp5 depletion reduces the levels of miRNAs in the cell. These data suggest that Exp5 may monitor the integrity of the pre-miRNAs prior to export and coordinate processing of these RNAs in the nucleus and cytoplasm. (*Science*, published online 20 November 2003, doi:10.1126/science.1090599; *Genes Dev.* 17, 3011–3016, 2003) ***EJ***

A TRiC for VHL folding

When protein folding goes awry, it can have a number of consequences for a cell. For example, correct folding of von Hippel-Lindau (VHL) is required for its assembly into the elongin BC complex. Incorporation of VHL into this complex allows the protein to function as tumor suppressor, acting against tumor formation in cells of the kidney, adrenal glands and central nervous system. The multi-subunit TRiC chaperonin complex is required for the folding of VHL, but exactly how the chaperonin selects VHL from the vast pool of nascent proteins is unknown. Feldman *et al.* show that two distinct hydrophobic regions, both within a β-sheet domain in VHL are required for stable association with TRiC. These hydrophobic regions are exposed in the unfolded protein but become buried when the protein is folded into its native conformation. Notably, a number of disease-causing mutations are shown to disrupt the interactions between VHL and TRiC, which eventually inhibits the folding pathway of VHL *in vivo*. Taken together, these observations indicate that TRiC not only enhances the proper folding of VHL but may also actively discourage mis-folding by keeping the aggregation-prone β-sheet rich regions occupied in a native-like configuration. (*Mol. Cell* **12**, 1213–1224, 2003) *MB*

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A new role for caspase-1

The caspase family of proteases has been segregated into two groups: those involved in inflammation and those involved in cell death. Caspase-1, which is known to play a key role in inflammatory pathways, is now shown also to have a role in apoptosis. Zhang, *et al.* show that after hypoxia mouse neuronal cells activate caspase-1, together with the apoptotic caspases-3, -8 and -9. They also detect the proapototic proteolytic fragment tBID and the release of several mitochondrial apoptogenic factors. Rip2, which is known to activate caspase-1 in inflammatory conditions, is also upregulated in neuronal cells in response to hypoxia and ischemia, suggesting that it plays a similar activation role in caspase-1 mediated cell death. The mechanistic details of the Rip2/caspase-1 pathway in hypoxia/ischemia-induced neuronal cell death remain to be investigated. (*Proc. Natl. Acad. Sci. USA* **100**, 16012–16017, 2003) *EG*

One protein, two functions

Sequence similarity among proteins is often used to infer functional homology. Experimental verification, however, can reveal an unexpectedly complex story. The study of Oeffinger and Tollervey is an example of this scenario. On the basis of sequence analysis alone, the essential yeast protein Nop15p seemed likely to be involved in nuclear RNA processing. Experimental data demonstrated that Nop15p directly binds RNA and is indeed required for proper processing of pre-ribosomal RNA (rRNA) species to generate mature 25S and 5.8S rRNA. However, the authors also observed that cells depleted of Nop15p displayed a sudden and complete growth arrest before ribosomal subunits were substantially turned over. A portion of these arrested cells are elongated with two separated nuclei and have a constriction corresponding to the bud neck but fail to undergo cytokinesis. Additional experimentation reveals that Nop15p is required for the formation of the contractile actin ring at the bud neck, a key step of cell separation. Thus, although the detailed mechanisms of Nop15p function remain to be defined, this study adds Nop15p to a growing list of proteins that have dual activities inside the cell. (*EMBO J.* 22, 6573–6583, 2003) ***HPF***