RÉSUMÉ

Reverse polarity

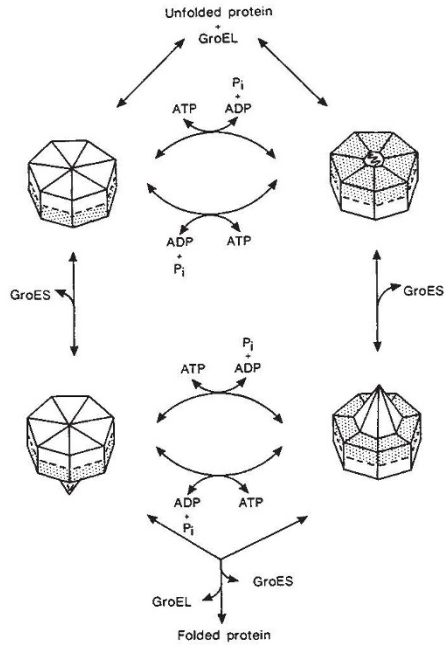
ONE of the characteristic features of autosomal dominant polycystic kidney disease, a common and fatal genetic disorder which maps to chromosome 16, is the accumulation of fluid in the renal tubules. Immunolocalization studies by P. D. Wilson *et al. (Am. J. Physiol.* **260,** F240–430; 1991) now show that the integral membrane protein Na^+, K^+-ATPase is confined to the apical (lumen-facing) membrane of the renal tubule epithelial cells of patients, whereas in normal cells it is found in the basolateral membrane. From analyses of cultured epithelial cells, it seems that Na^+ ions are consequently pumped into the lumen instead of out of it, which would explain the large amounts of fluid secreted into the renal tubules.

Faint hope

KNOWLEDGE of the ratio of deuterium to hydrogen created in the Big Bang would provide a strong pointer to the density of the early Universe. But the material seen in the stars nearest to us — even 'metal-poor' ones — is the product of billions of years of stellar processing and the original ratio may well have been distorted. The answer, according to J. K. Webb and colleagues (*Mon. Not. R. astr. Soc.* **250,** 657–665; 1991), may lie in the spectra of quasars. The light from these most distant of observable objects passes through clouds of relatively primitive gas, known as Lyman-α clouds after the hydrogen absorption lines seen in the spectra. Traces of deuterium in the clouds may also be just detectable and a reasonable measure of the ratio, confirming or excluding the locally reckoned values, should be possible.

Bloom with a view

THAT the biology of hummingbirds can be explained in terms of energetics runs counter to the general observation that animals trade time spent feeding against minimizing the risk of being eaten themselves; it is not that hummingbirds do not provide juicy bite-sized morsels, but that they are good at staying out of trouble. Experiments by S. L. Lima (*Evol. Ecol.* **5,** 220–230; 1991), using sugar-water feeders shaped like flowers with and without a corolla, suggest that female Anna's hummingbirds (*Calypte anna*) from Arizona are especially vigilant when feeding from large flowers, frequently withdrawing from blooms to survey the scene. They also prefer to feed high above the ground, in case they end up as fast food for roadrunners (*Geococcys californianus*). Evolution has thus forced them into the enviable position of enjoying both the sweetest cocktails and the best views.



Model for the action of GroE in refolding proteins suggested by the data of Martin *et al.*[2]. GroEL is depicted as a nonsymmetrical dimer of two rings of 7-mers. A single unfolded protein molecule can bind to any of seven sites in the central channel of only one of the rings (that stippled). The two possible isomers of the dimer are interconverted by a quaternary structure change[14]. This would require ATP hydrolysis when unfolded protein is bound, for the protein must be displaced from one 7-mer and transferred to the other. The unfolded protein would probably move through the channel between them, but it could also dissociate into the bulk solvent in the absence of GroES. The protein would tend to refold spontaneously while being transferred from one site to the other.

GroES is depicted as binding similarly to just one 7-mer of GroEL, not necessarily the same as that to which the protein is bound, and it must also be displaced from one to the other during the quaternary structure change. The function of GroES is postulated simply as preventing the bound protein from dissociating from GroEL until it has completed refolding, when it no longer binds to the sites on GroEL. Consequently, ATP hydrolysis ceases, GroES dissociates and the folded protein is released. This scheme does not include any steps for assembly of the refolding protein into higher order structures, which would have to occur in solution after release of the refolded monomers.

they have numerous interactions that occur simultaneously, not individually. A similar principle has been used to demonstrate that unfolded proteins can refold while bound reversibly to ion-exchange resins[11], which can be considered an artificial type of chaperone.

GroES is believed to exist as a ring of seven identical polypeptide chains[3,4], a structure that would be well-suited to bind to the open face of the GroEL disk, for both have seven-fold symmetry[12] (see figure). Two GroES 7-mers should bind to a symmetrical GroEL disk, yet Martin *et al.* show the functional stoichiometry to be one GroES 7-mer for each GroEL 14-mer. This suggests that GroEL is a nonsymmetric dimer of 7-mers. Moreover, GroES binds to GroEL only when ATP is being hydrolysed[4] (that is, when the unfolded protein is being released and re-bound by GroEL). There is a coupling on GroEL between binding of unfolded protein, hydrolysis of ATP and interaction with GroES.

So the situation is a highly dynamic one, and it is tempting to propose that there is "half-of-the-sites-reactivity"[13] that alternates between the two halves of GroEL as a result of a quaternary structure change. The binding of both GroES and the unfolded protein would occur first to one and then to the other half of the GroEL 14-mer. The quaternary structure change would need to be driven by ATP hydrolysis and would cause the unfolded protein to be transferred from the centre of one 7-mer ring to the other, during which time it might refold spontaneously or dissociate. GroES would also bind alternately to only one of the two asymmetric halves of GroEL and would keep the unfolded protein sequestered from the bulk solution. Once refolded, the protein would no longer bind to GroEL, ATP hydrolysis would stop, the GroES would dissociate, and the refolded protein could be released.

This scheme is speculative, but it has the appealing properties of being consistent with what is known about protein structure, function and folding *in vitro*, of not requiring an active role in folding of GroES, and of providing a plausible explanation for the unusual seven-fold symmetry of GroE. The model does not include a mechanism for assembling a multimeric protein, but this process could occur after release of the monomer into solution if the only function of GroE is to refold monomers by preventing them from precipitating when incompletely unfolded[12]. Given the amount of attention now being paid to chaperones, there should not be too long to wait for a verdict on this or any other model. □

T. E. Creighton is in the European Molecular Biology Laboratory, Postfach 10.2209, Meyerhofstrasse 1, 6900 Heidelberg, Germany.

1. Ellis, R. J. & Hemmingsen, S. M. *Trends biochem. Sci.* **14**, 339–342 (1989).
2. Martin, J. *et al. Nature* **352**, 36–42 (1991).
3. Hemmingsen, S. M. *et al. Nature* **333**, 330–334 (1988).
4. Georgopoulos, C. & Ang, D. *Seminars Cell Biol.* **1**, 19–25 (1990).
5. Hartl, F. -U. & Neupert, W. *Science* **247**, 930–938 (1990).
6. Viitanen, P. V. *et al. Biochemistry* **29**, 5665–5671 (1990).
7. Buchner, J. *et al. Biochemistry* **30**, 1586–1591 (1991).
8. Laminet, A. A. *et al. EMBO J.* **9**, 2315–2319 (1990).
9. Kuwajima, K. *Proteins struct. funct. Genet.* **6**, 87–103 (1989).
10. Ptitsyn, O. B. *et al. FEBS Lett.* **262**, 20–24 (1990).
11. Creighton, T. E. in *Protein Structure, Folding and Design* (ed. Oxender, D. L.) 249–257 (Liss, New York, 1986).
12. Gatenby, A. A., Viitanen, P. V. & Lorimer, G. H. *Trends Biotechnol.* **8**, 354–358 (1990).
13. Ward, W. H. J. & Fersht, A. R. *Biochemistry* **27**, 1041–1049 (1988).
14. Unwin, P. N. & Ennis, P. D. *Nature* **307**, 609–613 (1984).

© 1991 Nature Publishing Group