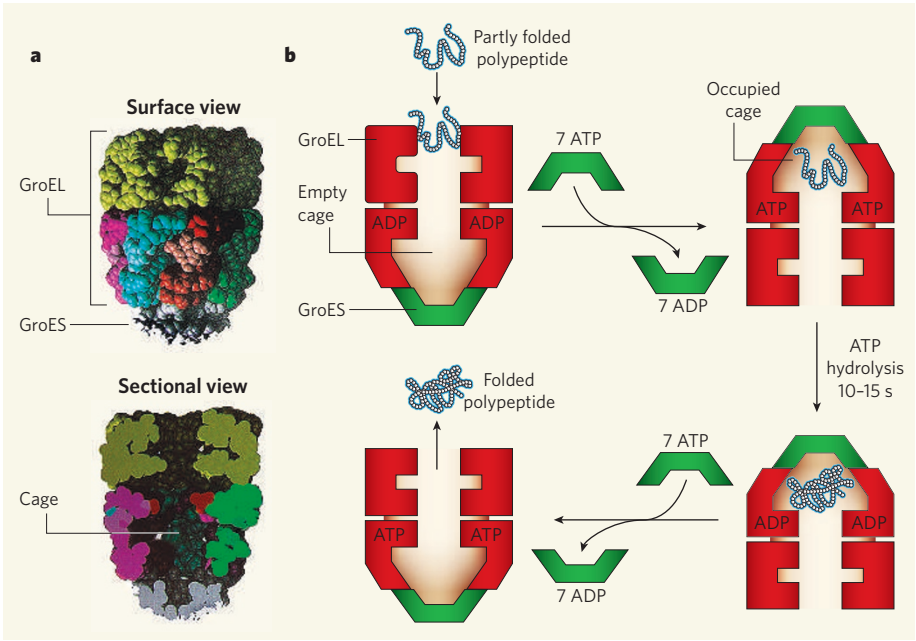

Figure 1 | The GroEL–GroES nanocage in action. **a**, Space-filling model of the GroEL–GroES complex. GroEL consists of two rings, each made of seven ATPase subunits arranged back to back, whereas GroES consists of a single dome-shaped ring of seven smaller subunits. The nucleotide-binding abilities of the two GroEL rings are mutually exclusive (that is, only one ring at a time can bind either ATP or ADP). In the presence of ATP or ADP, GroES binds to the same ring that binds the nucleotide, creating a cage at that end. (Reprinted from ref. 10.) **b**, A single, partly folded polypeptide chain released from the ribosome binds to hydrophobic residues exposed at the end of GroEL uncapped by GroES. Binding of GroES and ATP to that end triggers release of the chain into the newly created cage because GroES competes for binding sites with the partly folded chain. The chain has 10–15 seconds to fold inside this cage, because this is the time it takes for the ATP to be hydrolysed to ADP by the ring that contains the folding protein. The ADP then unbinds, allowing ATP to bind to the opposite ring. This binding triggers the release of GroES and of the folded polypeptide from the ring containing the cage. If the released chain has not internalized all its hydrophobic residues, it is likely to be rebound by the same ring. (Revised from ref. 1.)

volume of the cage in increments from +4% to −13%, and measured the effects of these changes on the rate of folding of four different proteins in the size range 33–50 kDa.

The folding rate of the smaller proteins rhodanese (33 kDa) and MetF (33 kDa) increased by up to two times when the volume of the cage was reduced by 4.4%, but reduction by 8.7% returned the rate to that found in the normal, wild-type chaperonin. Further reduction to 13% decreased the rate fivefold for both proteins. In the case of rhodanese, the spontaneous rate of folding outside the cage, under conditions where aggregation was minimal, was the same as inside the wild-type cage — a clear difference from Rubisco. For the larger substrates, maltose-binding protein (41 kDa) and bacterial Rubisco (50 kDa), either reducing or increasing the cage volume slowed the folding. The same results were observed when the experiment was repeated with a single-ring mutant of GroEL that cannot release GroES, indicating that the rate changes reflect effects of encapsulation rather than protein release into solution. The conclusion is that the cage has an optimal volume for folding rate, depending on the size of the encapsulated protein. So size matters. What about other factors?

The interior wall of the cage contains 189 negatively charged amino-acid residues but only 147 positively charged residues. Tang *et al.*[5] altered the overall net negative charge of 42 residues in steps down to zero by replacing some of them with neutral or positively charged residues. There were several effects on protein-folding rate. For example, reducing the net charge to zero abolished the folding of Rubisco but enhanced the folding rate of rhodanese by about 50%. The original idea[6] that GroEL–GroES is an inert protective container is clearly incorrect — it is an active protective container, at least *in vitro*.

But does this activity have any biological relevance? By co-expressing the modified GroEL–GroES complexes with the same substrate proteins in intact cells of *E. coli*, Tang *et al.*[5] show that reducing the ability to accelerate folding also reduces the amount of some proteins that fold correctly inside the cell. The size and surface properties of the cage represent an evolutionary compromise that helps the bacterial cell to produce functional proteins fast enough to survive in a competitive microbial world.

The effects of cage volume on folding rate are consistent with the predictions of a branch of macromolecular crowding theory called confinement[8]. Crowding describes the fact that the total concentration of macromolecules inside cells is so high that the thermodynamic

50 YEARS AGO

"Energy requirements of Europe" — The report on Europe's future needs of energy recently issued by the Organization for European Economic Co-operation contains a most interesting examination of the position... No doubt in time the competitive position of the coal industry may be affected, for after 1975 nuclear energy is expected to free the coal burnt in thermal power stations to an increasing extent... The share of oil in supplying the energy needs of Western Europe must also rise rapidly... The world's reserves of oil will be adequate for this requirement, but large investments must be made by the oil companies in Western Europe as well as abroad... A potent factor in reducing the menacing gap between indigenous production and the overall requirements of energy resides in the still existing possibilities of saving energy at every stage, from its winning and conversion...to its final utilization in industry and in the home.
From *Nature* 28 July 1956.

100 YEARS AGO

"With wires and without" — Of the numerous achievements of which the electrical engineer can boast, telegraphy is the one of which he has greatest reason to be proud. If we combine with telegraphy the sister subject of telephony, there can be little doubt but that by the application of these two sciences he has effected a greater revolution in human affairs than by all successes in the way of heavy engineering. He may "electrify" our railways, especially the suburban lines, to the great advantage of both the travelling public and the shareholder, but he is still only doing for us in another way what the mechanical engineer has already accomplished. He may harness great waterfalls and transmit their power over hundreds of miles to localities at which it may be more easily utilised, but he is only saving Mahomet the trouble of going to the mountain... But with telegraphy he has given us something entirely new—an art which, while actually annihilating distance, virtually annihilates time.
From *Nature* 26 July 1906.

50 & 100 YEARS AGO