Journal club

THE FIRST CHAPERONIN

Today, it is textbook knowledge that cells contain molecular chaperones to mediate protein folding, preventing the formation of useless or even dangerous aggregates. But readers new to the field may be surprised to learn that some of the early observations that gave rise to the chaperone concept stem from research on plant chloroplasts. Here, we tell the story of a paper that has influenced us for many years. This study was published in 1980, at a time when protein folding was believed to occur spontaneously.

During the 1970s and 1980s, John Ellis at the University of Warwick studied the proteins that are encoded and synthesized inside chloroplasts. The most prominent of these is the large subunit of RuBisCo (ribulose-1,5-bisphosphate carboxylase–oxygenase), which is the enzyme responsible for the fixation of atmospheric CO_2 into organic matter during photosynthesis. The biogenesis of RuBisCo is complicated: eight large subunits (RbcL) must assemble with eight small subunits (RbcS) into a complex of ~550 kDa. Unlike RbcL, RbcS subunits are encoded in the nucleus, synthesized in the cytosol and imported into the chloroplast. Barraclough and Ellis made the unexpected discovery that newly synthesized RbcL is bound to another protein prior to its correct association with RbcS to form the RuBisCo holoenzyme. The RbcL-binding protein subsequently became known as the chloroplast chaperonin, a complex of ~800 kDa. This chaperonin was thought to keep non-assembled RbcL from aggregating, which happens when the denatured holoenzyme is diluted into refolding buffer. This was the first chaperonin–polypeptide interaction documented in the literature.

We learned later from studies by Ostermann *et al.* in mitochondria that chaperonins mediate ATP-dependent protein folding rather than subunit assembly. Curiously, it took 30 years after the Barraclough and Ellis paper was published for the discovery of the first assembly factor of RuBisCo. This protein, called RbcX, accepts folded RbcL subunits from chaperonin and transiently clamps them together to facilitate complex formation. Using chaperonin and RbcX it has now been possible to fold and assemble the RuBisCo from cyanobacteria *in vitro*, as shown by Liu *et al.* in 2010. However, the enzyme from plants studied by Barraclough and Ellis still stubbornly resists *in vitro* reconstitution, which led Feiz *et al.* to suggest that assembly of the RuBisCo complex in plants might involve additional factors.

F. Ulrich Hartl and Manajit Hayer-Hartl
Department of Cellular Biochemistry,
Max Planck Institute of Biochemistry, Martinsried, Germany.
e-mails: uhartl@biochem.mpg.de; mhartl@biochem.mpg.de

The authors declare no competing financial interests.

ORIGINAL RESEARCH PAPERS Barraclough, R. & Ellis, R. J. Protein synthesis in chloroplasts. IX. Assembly of newly-synthesized subunits into ribulose bisphosphate carboxylase in isolated intact pea chloroplasts. *Biochim. Biophys. Acta* **608**, 19–31 (1980) | Ostermann. J. *et al.* Protein folding in mitochondria requires complex formation with Hsp60 and ATP hydrolysis. *Nature* **341**, 125–130 (1989) | Liu, C. *et al.* Coupled chaperone action in folding and assembly of hexadecameric Rubisco. *Nature* **463**, 197–202 (2010) | Feiz, L. *et al.* Ribulose-1,5-bis-phosphate carboxylase/oxygenase accumulation factor 1 is required for holoenzyme assembly in maize. *Plant Cell* **24**, 3435–3448 (2012)
FURTHER READING Saibil, S. Chaperone machines for protein folding, unfolding and disaggregation. *Nature Rev. Mol. Cell Biol.* **14**, 630–642 (2013)