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Introduction: the cellular protein folding machinery

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In the last decade, we have witnessed a dramatic change in our view of protein structure formation and function in the cellular environment. Previously, it was widely accepted that proteins emerge from the ribosome, fold into a stable structure, exert their biological functions and are finally degraded. This was in part due to Anfinsen's classic in vitro experiments in which he showed conclusively that protein folding is a spontaneous process (Anfinsen, 1973). Since this reaction did not require the input of external energy, information or regulation in the test tube, it was presumed to occur in an unassisted way also in vivo. The finding that a number of proteins underwent irreversible entanglement upon refolding in vitro (Jaenicke, 1987; Goldberg et al., 1991) was put aside as a consequence of the artifical test tube conditions. This view changed with the investigation of cellular response to stress and recombinant expression of proteins. In both cases, the formation of insoluble protein aggregates (inclusion bodies) was observed in living cells. Evidently, also in vivo, correct folding was found to depend on reaction conditions. Only under physiological conditions, folding seems to be an efficient reaction – assisted by a set of proteins which are increasingly expressed under stress conditions. In the following years, rapid progress was made in unravelling the cellular components involved in this process. An important contribution came from analyses of host factors responsible for virus replication in *Escherichia coli* which led to the identification of the GroE proteins (Georgopoulos, 1992). Soon, the trade name 'molecular chaperones' was established for this group of proteins involved in protein folding (Ellis and van der Vies, 1991). This picturesque term refers to initial observations that molecular chaperones, like their human counterparts, prevent illegitimate interactions between adolescent proteins. Interestingly, cells do not express only one chaperone protein to assist protein folding but rather a whole battery of chaperones which are unrelated in sequence but share functional principles. They have been found in all organisms studied so far and in all cellular compartments. Using purified chaperones and in vitro folding reactions employing 'model substrate proteins' their molecular mechanisms were dissected in considerable detail. In summary, their mode of action can be divided in three different steps (fig. 1 and Walter and Buchner, 2002):

- recognition and binding of nonnative proteins
- conformational processing, often assisted by ATP hydrolysis and cochaperones
- release of the processed polypeptide

These basic principles allow chaperones not only to assist protein folding after biosynthesis and stress-induced unfolding but also to regulate protein conformation in transport of proteins through membranes or during signal transduction, e. g. in the case of steroid hormone receptors.

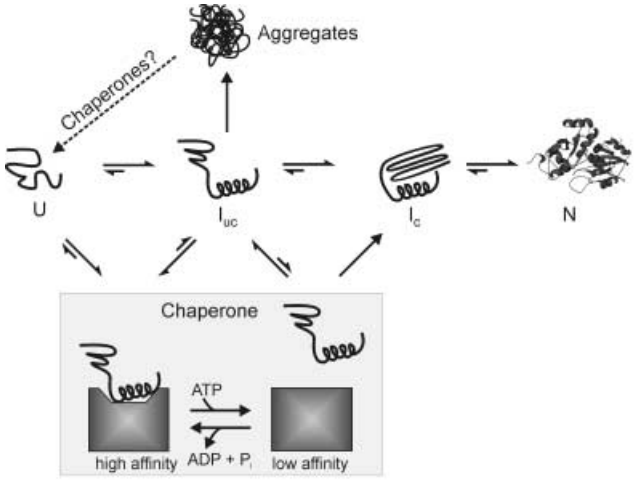

Figure 1. Principles of chaperone-assisted protein folding. Partially folded proteins occur after protein synthesis or as a result of unfolding due to unphysiological conditions. As a consequence, proteins often form large, irregular aggregates. Chaperones interfere with this process by selectively binding nonnative proteins in a reversible, often ATP-dependent manner.

The collection of nine reviews in this issue covers these and a number of additional aspects of chaperone function. The first review is devoted to the *E. coli* GroE system, which is the best understood chaperone in terms of structure and mechanism. In consequence, GroE serves as the role model for all other chaperones. The other major chaperone of prokaryotes is the Hsp70/DnaK system. The second review deals with the regulation of this chaperone system from a thermophilic bacterium and introduces the chaperone component of the Clp/Hsp100 proteolytic system, which is also stress induced and ATP regulated. The theme of protein folding versus degradation is continued in the following review, in which chaperone networks of *E. coli* are discussed in connection with the Clp system. To facilitate transport of proteins through the plasma membrane, bacteria use the Sec system, which contains its own cytosolic chaperone component, the SecB protein. This aspect of chaperone function is summarized in the forth review of this issue. The final review of the prokaryotic section covers a novel aspect, the rapid control of chaperone function by the redox conditions in the cell.

The remaining reviews deal with characteristic aspects of the eukaryotic cell, starting with chaperones associated with ribosomes and nascent polypeptide chains. The next review focuses on the Hsp90 system which, although present in prokarotes, seems to have gained functional importance in eukaryotes. Here, it is a central component for regulation of protein conformation in the cytosol. The idea of chaperones as part of a network is further discussed in the context of small Hsps, which are the most efficient chaperones in terms of binding nonnative proteins. The series of articles closes with a description of a specialized Hsp70 system of mitochondria which is of crucial importance for the integration of iron-sulfur centers in proteins.

Although this series of excellent reviews highlights a number of aspects important for understanding chaperone function, it should be noted that several others, such as chaperones of the endoplasmic reticulum and other organelles, substrate-specific chaperones, the eukaryotic Hsp100 family and periplasmic chaperones, are not included. Clearly, this field is about to enter a new stage in which the detailed analysis of the molecular mechanisms of chaperones will be complemented by the description of their contribution to functional networks in vivo. In this context, involvement of chaperones in a variety of diseases is an emerging theme. Stay tuned.

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