Microbial Cell Factories

Commentary

Keeping up with protein folding

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Protein folding and misfolding in the cellular environment has emerged as a major research theme over the past fifteen years. The implications are broad, ranging from the production of recombinant proteins in a soluble and bioactive form to the understanding of the etiology of neurodegenerative diseases. The basic principle enunciated by Afinsen – that all the information required for a polypeptide to reach a proper conformation is contained within its amino acid sequence [1] – remains unchallenged. However, it is now well established that many proteins require the assistance of folding modulators to adopt a native structure as they emerge from ribosomes, regain their original conformation following exposure to stress, or traffic to their ultimate destination [2].

One of the most extensively characterized group of folding modulators are molecular chaperones, a ubiquitous class of proteins that help other polypeptides reach a proper conformation or cellular location without affecting folding rates or becoming part of the final structure. Molecular chaperones function by transiently binding hydrophobic stretches of amino acids that should normally be buried within the core of their substrates but have become solvent-exposed due to improper de novo folding or imposition of cellular stress (e.g., temperature increase). As a result of the formation of chaperone-substrate complexes, interactive species are shielded from each other and from the solvent and "on-pathway" folding is facilitated.

Three functionally distinct sets of chaperones cooperate in the conformational quality control of the proteome. At the heart of chaperone networks are "folding chaperones" which use conformational changes fueled by ATP hydrolysis to promote the net refolding/unfolding of bound substrates. Archetypal folding chaperones are the DnaK-DnaJ-GrpE (Hsp70-Hsp40) and GroEL-GroES (Hsp60-Hsp10) systems of *E. coli*. "Holding chaperones" (e.g., small heat shock proteins) passively stabilize partially folded species until folding chaperones become available for their refolding. In doing so, they alleviate titration of folding chaperones by unfolding intermediates. Finally, "disaggregating chaperones" such as *E. coli* ClpB and *S. cerevisiae* Hsp104 employ ATP-driven conformational changes to solubilize protein aggregates and transfer partially folded species to folding chaperones for subsequent refolding.

Foldases embody the second group of folding modulators. These enzymes accelerate rate-limiting steps along the folding pathway and include peptidyl-prolyl *cis/trans* isomerases (PPIases), which catalyze the *trans* to *cis* isomerization of peptidyl-prolyl bonds, and thiol-disulfide oxidoreductases, which promote the formation and isomerization of disulfide bridges (e.g., the Dsb proteins of the *E. coli* periplasm). The final participants in the protein quality control machinery are proteases which degrade irreversibly damaged polypeptides that cannot be rescued by the above pathways.

Nevertheless, nature loves to frustrate reductionist efforts and it has recently become apparent that functional lines are often blurred. For instance, PPIases and oxidoreductases can combine chaperone and foldase functions, certain protease components remodel polypeptide substrates and can thus be viewed as chaperones, some proteases have the ability to switch from hydrolase to chaperone function, and there is evidence that certain proteins classified as chaperones may exhibit protease activity (see for instance [3-10]).

To keep readers abreast of the fast moving field of protein folding, *Microbial Cell Factories* has commissioned a series of reviews by experts in the topic. The first of these already appeared in January [11]. In "Unscrambling and egg: protein disaggregation by AAA+ proteins", Weibezahn, Bukau and Mogk discuss the discovery, functional characterization and mechanism of action of Hsp104/ClpB, two orthologous ATPases that have the unique ability to fragment protein aggregates. The remodeling activity of other AAA+ proteins (e.g., ClpA, ClpX and ClpC) which are best known more for their role in proteolysis is also examined. The authors close their thorough review by presenting enticing evidence for the roles of AAA+ proteins in the propagation of neurodegenerative diseases.

In the second paper of the series [12], Miot and Betton review the mechanisms of protein quality control in the periplasmic space of *E. coli*. After a brief discussion of the biogenesis of proteins destined for export from the bacterial cytoplasm, the authors describe the players involved in the periplasmic folding-degradation decision and how cells sense and respond to extracytoplasmic stress. The second half of the review provides a historical perspective on how the maltose binding protein has served as a useful model to understand the mechanisms of conformational quality control in the periplasm. With forthcoming reviews on disulfide bridge formation and in vitro refolding, it is a great time to turn to *Microbial Cell Factories* to keep up with protein folding.

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