Mechanisms of Chaperones and Proteases

Introduction

The ensemble of molecular chaperones and proteases constitutes an essential cellular system that assists the folding and assembly of newly synthesized proteins, the translocation of unfolded proteins across membranes, as well as the refolding and degradation of misfolded and aggregated proteins. Chaperones furthermore control signal transduction pathways through the transient association with kinases and transcription factors, thereby leading to their regulated inactivation or degradation. Our research aims at understanding the molecular basis of the intricate functional network of chaperones and proteases that controls protein folding in the cytosol. As model systems we are using bacteria, yeast and mammalian cells, and as experimental approaches we combine genetics and cell biology with biochemistry and biophysics. The three subgroups of the lab focus on (i) the mechanisms of chaperone-assisted folding of newly synthesized proteins, (ii) the functional network of Hsp70 machines, and (iii) the role of AAA-chaperones in protein disaggregation and degradation.

Mechanisms of chaperone-assisted folding of newly synthesized proteins

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Each newly synthesized protein must be folded into its correct tertiary structure. How this is achieved is one of the most basic, and complicated, questions of molecular biology. During protein biosynthesis, nascent polypeptide chains that emerge from the ribosomal exit tunnel encounter ribosome-associated chaperones, such as the bacterial Trigger Factor (TF), which assist the initial steps of their folding to the native state. Downstream acting chaperones such as the bacterial DnaK and GroEL systems provide further folding assistance until the newly synthesized polypeptides have reached their native states. We currently focus on the initial steps of co-translational protein folding.
Although TF is not essential in *E. coli*, the combined absence of TF and the DnaK chaperone was found to cause cell death above 30°C accompanied by aggregation of more than 340 different newly synthesized proteins. We determined that TF binds to nascent chains and associates with

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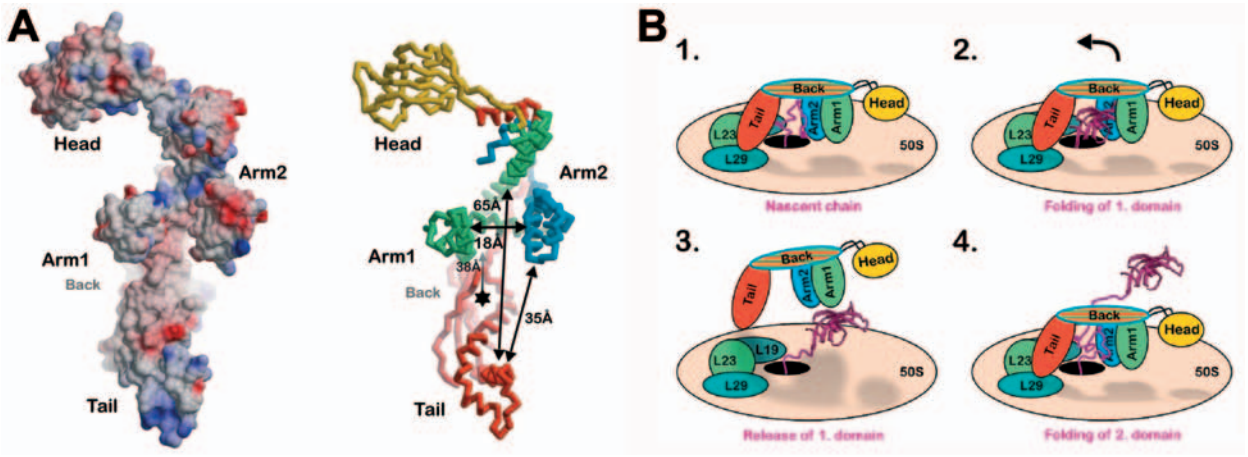

Fig. 1: Trigger Factor assists co-translational folding of proteins.
A. Crystal structure of Trigger Factor (charged residues are coloured) and size of the putative substrate folding cage.
B. Model of the mechanism of Trigger Factor´s activity in co-translational folding of proteins.

ribosomes in a 1:1 stoichiometry via interaction of its N-terminal domain with the ribosomal protein L23 located next to the peptide tunnel exit. This association is crucial for its interaction with nascent polypeptides and its *in vivo* function.
In close collaboration with N. Ban (ETH Zürich) the atomic structure of TF was solved at 2.7 Å resolution, together with the structure of its ribosome-binding domain in complex with the *Haloarcula marismortui* large ribosomal subunit. TF adopts a unique conformation resembling a crouching dragon with separated domains forming the N-terminal ribosome-binding "tail", the peptidyl-prolyl isomerase (PPIase) "head", the C-terminal "arms", and connecting regions building up the "back" (Fig. 1A). From its attachment point on the ribosome, TF projects the extended domains over the exit of the ribosomal tunnel. TF, together with the ribosome, forms a protective cage of sufficient size to accommodate a folded protein domain at the peptide tunnel exit site. Our current hypothesis is that TF promotes the co-translational folding of domains by providing a shielded environment in which the folding is initially postponed through hydrophobic contacts, but then allowed to proceed, perhaps in a self-promoted fashion, when sufficient sequence information is available for the generation of a folded core (Fig. 1B). The chaperone would then dissociate from the ribosome and rebind once a significant new portion of the unfolded polypeptide becomes exposed at the tunnel exit. The structural information which we have obtained now directs further experiments addressing the mechanism of co-translational protein folding.

Functional network of Hsp70 machines

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Hsp70 chaperones, with their co-chaperones, comprise a set of abundant cellular machines that assist a large variety of protein folding processes in almost all cellular compartments. We are interested in the molecular mechanism of Hsp70 proteins and their dynamic interactions with co-chaperones, and the still enigmatic role of the Hsp110 subfamily of Hsp70 chaperones.
Central to the Hsp70 mechanism is the control of substrate interaction by ATP. ATP binding to the ATPase domain opens up the substrate binding cavity in the adjacent substrate binding domain; ATP hydrolysis closes the cavity and traps bound substrates. To elucidate this coupling mechanism we performed a structure-function analysis of the DnaK homologue. Analysis of mutants in the ATPase domain and the linker connecting this domain with the substrate binding domain, revealed a complex hydrogen bonding network which coordinates the nucleotide in the catalytic center, and transmits the nucleotide binding status via a proline switch to a surface exposed arginine residue (Fig. 2). Nucleotide-dependent conformational changes of this residue are proposed to reposition the linker thereby generating conformational changes in the substrate binding domain that lead to an opening/ closing movement of the substrate binding cavity.
What exactly the binding of Hsp70 is triggering within substrate proteins is unclear. We hypothesize that Hsp70 binding may induce conforma-

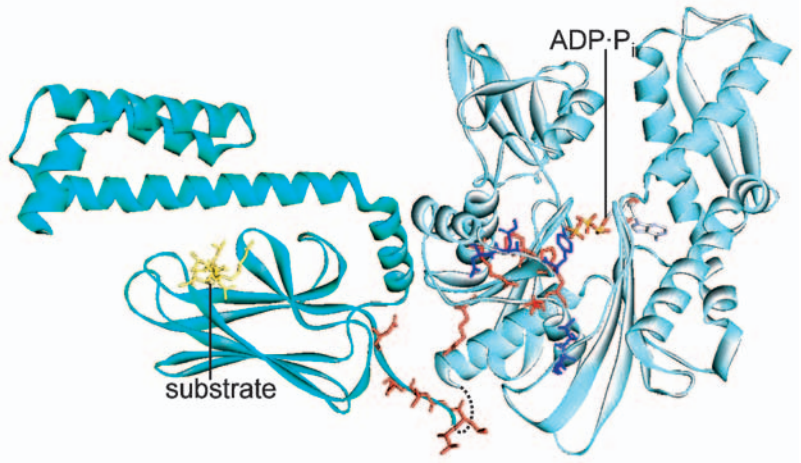

Fig. 2: Hsp70 proteins: residues involved in interdomain coupling
Structure of the substrate binding domain (left) of DnaK in complex with a substrate peptide (yellow) and of the ATPase domain (right) in complex with ADP and inorganic phosphate. In red are shown residues involved in the ATP control of substrate binding.

tional changes which remodel the protein structure such that refolding or disassembly or even degradation is facilitated. To test this possibility we are identifying binding sites and potential conformational changes in protein substrates of DnaK, such as the heat shock transcription factor sigma 32 and the DNA replication protein RepE. The DnaK binding site in sigma 32 is located in an unfolded segment of the protein. DnaK binding induces unfolding of a helical segment of sigma 32 which is distant to this binding site. These allosteric conformational changes are likely to explain the role of DnaK in the stress-dependent regulation of both, the activity and the half life of sigma 32.

How co-chaperones regulate the chaperone activity of Hsp70 proteins is another topic of our research. We established that DnaJ co-chaperones bind to sites within protein substrates that are distinct from DnaK binding sites. Through additional interaction with the ATPase domain of DnaK, within the “J-channel” which overlaps with the region involved in interdomain coupling, DnaJ triggers ATP hydrolysis and concomitant substrate binding by DnaK.

The Hsp70-interacting E3-ubiquitin ligase CHIP is a co-chaperone specific for eukaryotic Hsp70 homologs. CHIP has been implicated in the decision as to whether a target protein enters the refolding or the degradation pathway. We found that in contrast to other E3 ligases, CHIP forms homodimers through interaction via a central coiled coil region. Dimerization is a prerequisite for the activity of CHIP in ubiquitination and thus may provide a mechanism for regulation of CHIP activity. We also found that CHIP becomes phosphorylated *in vivo* which may regulate CHIP activity as well.

Our interest in understanding the functional network of Hsp70 chaperones has also led us to focus on the functions of the Hsp110 subclass of Hsp70 proteins. The Hsp110 proteins of the yeast cytosol, Sse1 and Sse2, were found to physically interact with other Hsp70 proteins of this compartment, raising the possibility of a functional and physical link between Hsp110 proteins and the classical Hsp70 proteins.

Role of AAA-chaperones in protein disaggregation and degradation

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Chaperones constitute a powerful network to repair misfolded proteins. Alternatively, misfolded proteins are degraded by ATP-dependent proteolytic systems. In similarity to the proteasome of eukaryotes, the protease systems of the bacterial cytosol are composed of ring-shaped oligomeric assemblies of 6-7 subunits of a regulatory AAA chaperone with ATPase activity (e.g. ClpA, ClpX) and an associated peptidase (e.g. ClpP). Under conditions of massive protein misfolding e.g. after severe heat stress, the capacity of this quality control network may not suffice and proteins aggregate, which is linked to cell death. Cell survival under severe thermal stress requires the activity of ClpB (Hsp104) (Fig. 3). This AAA chaperone does not associate with a peptidase, but instead solubilizes and reactivates aggregated proteins in concert with the DnaK system. How protein disaggregation is achieved, and whether survival is dependent on ClpB-mediated elimination of aggregates or through reactivation of aggregated proteins is unclear and has been investigated by us.

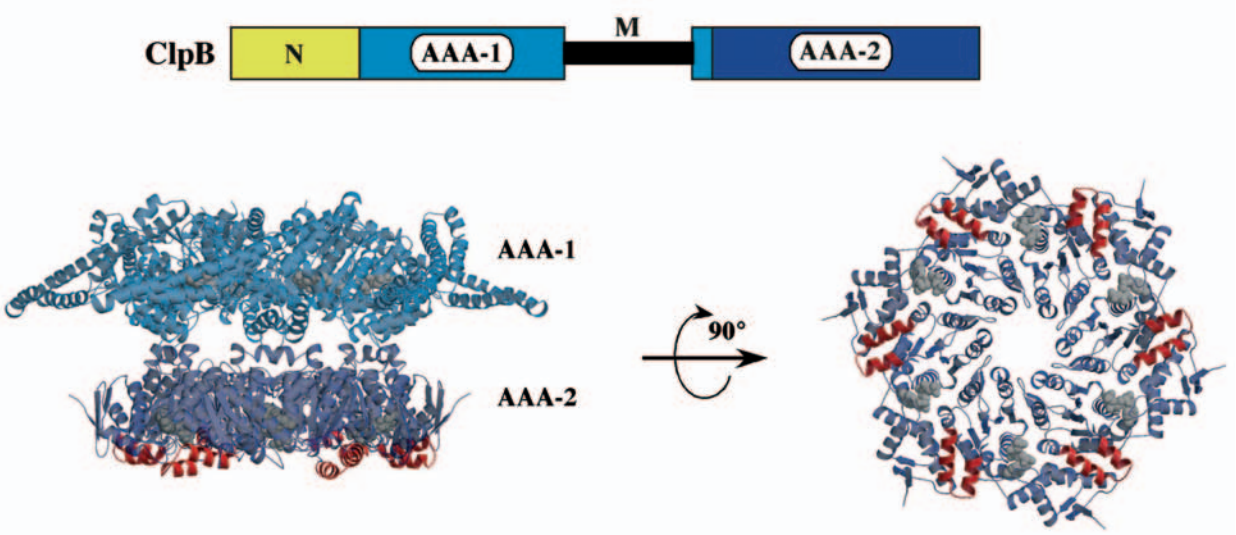

Fig. 3: Domain structure and hexameric model of ClpB.
ClpB has two ATPases (AAA domain), a linker insertion (M-domain) forming a coiled coil structure and an N-domain. The ClpP-interacting loop that has been engineered into the ClpB variant, BAP, is shown in red.

ClpB was found to recognize substrates through binding to hydrophobic peptide stretches enriched with aromatic and basic residues which normally are hidden in the interior of native proteins. We identified a substrate binding site at the central pore of the oligomeric ring in the first (N-terminal) of two ATPase domains. The conserved Tyr251 residues that are lining the central pore contribute to substrate binding. Since the positioning of an aromatic residue at the central pore is conserved in many AAA proteins, a central substrate binding site involving this residue may be a common feature of this protein family. Furthermore, the pore entrance to the second ATPase domain, which is entirely buried inside the central cavity of the ClpB ring, also contains a Tyr residue which is crucial for chaperone activity of ClpB and directly involved in substrate interaction (Fig. 4).

In a following-up study, we engineered a ClpP binding loop into ClpB, generating a variant termed BAP, which associates with the ClpP peptidase and thereby is converted into a disaggregating protease (Fig. 3). BAP translocates substrates through its central pore directly into the catalytic chamber of ClpP for degradation. Protein disaggregation and translocation by BAP are directly coupled and affected by mutational alteration of ClpB pore residues, demonstrating that ClpB-dependent translocation is an integral part of the disaggregation mechanism (Fig. 4). The activity switch of BAP to a protease also occurs *in vivo*, and leads to complete abolishment of thermotolerance development, demonstrating that reactivation of aggregated proteins is essential for cell survival during severe thermal stress. Using similarly engineered variants we are currently investigating the role of Hsp104 in protein disaggregation and cell survival in yeast.

To understand the relationship between proteases and chaperones, we are investigating the

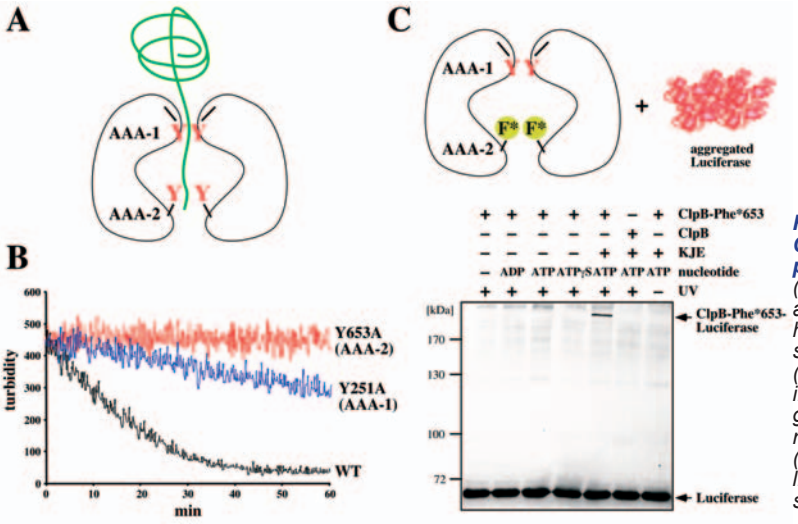

Fig. 4: Pore-located tyrosine residues of ClpB mediate substrate translocation and protein disaggregation.
(A) Aromatic residues (Y251, Y653) located at the central pore of both AAA domains are hypothesized to act as molecular levers for substrate threading.
(B) Exchange of pore-located Tyr to Ala impaires the activity of ClpB in protein disaggregation (measured as decrease in turbidity of malate dehydrogenase aggregates).
(C) Aggregated luciferase molecules are cross-linked to Y653 (Phe) in presence of the DnaK system and ATP.*

mechanisms by which AAA chaperones that associate with peptidases, recognize substrates and target them for degradation. We identified a novel adaptor protein for the ClpAP proteolytic machine, ClpS, which directly influences the substrate specificity of ClpAP via interaction with the N-terminal domain of ClpA. *In vitro* ClpS inhibits the degradation of some ClpAP substrates (e.g. SsrA-tagged proteins) while it stimulates the degradation of aggregated proteins. ClpS acts as a molecular switch for ClpA substrate recognition. In collaboration with C. Zeth (MPI Martinsried) we solved the atomic structure of ClpS in complex with the N-domain of ClpA. We are currently investigating the *in vivo* role of ClpS and the mode of ClpS interaction with substrates and ClpA.

In the Gram-positive bacterium *Bacillus subtilis* the general stress protein ClpC, is a AAA+ chaperone which associates with the peptidase ClpP to form a proteolytic machine. ClpC is not only involved in the removal of unwanted misfolded and aggregated proteins but also controls, through regulated proteolysis, key steps of several developmental processes. We demonstrated that ClpC requires the adaptor protein MecA for the assembly of an active oligomeric ring consisting of ClpC and the adaptor protein. Using hybrid proteins of ClpA and ClpC, we identified the N-terminal and the linker domain of the first AAA+ domain of ClpC as the essential MecA interaction sites. This new adaptor-mediated mechanism adds another layer of control to the regulation of the biological activity of AAA+ proteins.

Collaborations

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Master Thesis

Rauch, Thomas (2004): The interaction of *E. coli* Trigger Factor and SRP with hybrid ribosomes.

Dissertation

Kluck, Christoph (2003): Alternative Hsp70-Systeme in *Escherichia coli*

Patzelt, Holger (2003): Structural and functional characterization of Trigger Factor, a ribosome-associated chaperone in *Escherichia coli*

Rist, Wolfgang (2004): Mass spectrometric analysis of chaperone-substrate interactions

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Habilitations

Mayer, Matthias (2002): Untersuchungen zum Mechanismus der Hsp70-vermittelten Proteinfaltung

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