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# Novel mechanism for maintenance of bacterial proteostasis identified

Researchers at the Max Planck Institute of Biochemistry (MPIB) have identified a novel mechanism that ensures proteostasis maintenance in *E. coli* when chaperone availability is limited.

**Chaperones ensure the correct folding of proteins. But what happens if the chaperone network is defective? F.-Ulrich Hartl, Manajit Hayer-Hartl and their team have characterized the ribosome-associated chaperone network in *Escherichia coli*. For the first time, they discovered that a defect in this network results in a response at the ribosome. The release factor RF3 is recruited to the ribosome and then mediates the termination of misfolded nascent polypeptide chains. This leads to the clearance of misfolded proteins and thus ensures bacterial proteostasis. The results were published in *Molecular Cell*.**

## Investigating the chaperone network

Proteins - the building blocks of life - fulfil a large variety of functions in our body. They are synthesized in the cell at large complexes called ribosomes. During this process, information from the messenger RNA is translated into a sequence of amino acids, which are connected to form a polypeptide chain. For proteins to fulfil their function, these nascent polypeptide chains need to be folded into specific three-dimensional structures. How can cells ensure the correct folding of their proteins? This is where chaperones become relevant. The folding helpers ensure that proteins are folded correctly, repair misfolded proteins and initiate the degradation of faulty proteins at the proteasome.

Using quantitative proteomics, Liang Zhao (postdoctoral fellow in the groups of F.-Ulrich Hartl and Manajit Hayer-Hartl) and the team first established an overview of the chaperone network in the model organism *Escherichia coli (E. coli)*. They analyzed *E. coli* proteins via mass spectrometry and identified a large variety of chaperones important for protein folding at the co-translational level. They found Trigger factor (TF), DnaJ, and DnaK to be the most abundant chaperones. In case of functional loss of the central hub chaperone DnaK, the chaperones HtpG, GroEL and ClpB contribute increasingly to compensate the loss.

## Defects in the chaperone network lead to a response at the ribosome

But what happens at the ribosome when the chaperone network is defective? To investigate this question, the researchers collaborated with Pierre Genevaux and Marie-Pierre Castanié from the University of Toulouse and limited the number of chaperones available in the cell by using knock-out models. They thereby induced misfolding of nascent polypeptide chains. In response, release factor 3 (RF3) was recruited to the

ribosome. RF3 subsequently cooperated with another release factor, RF2, leading to the premature termination of protein synthesis and the ensuing release of incomplete misfolded nascent polypeptide chains from the ribosome. That way, the incomplete polypeptide chains could be degraded. Conversely, when this mechanism was inhibited through deletion of RF3, misfolded proteins accumulated in aggregates and impaired the synthesis of new peptide chains. The researchers thus identified, for the first time, a connection between a defect in or limitation of chaperones and an ensuing response involving RF3 at the ribosome. This mechanism is crucial to maintain proteostasis when chaperone availability is restricted as it facilitates clearance of misfolded proteins.

The next steps involve identifying similar mechanism in yeast or mammalian cells. If an analogous mechanism can be found, this might pave the way for future treatments in neurodegenerative diseases such as Alzheimer's.

**Original Publication:**

L. Zhao, M.-P. Castanié-Cornet, S. Kumar, P. Genevaux, M. Hayer-Hartl, and F. Ulrich Hartl: Bacterial RF3 Senses Chaperone Function in Co-translational Folding, *Molecular Cell*, June 2021
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**About F.-Ulrich Hartl**

F.-Ulrich Hartl was born in 1957. He studied Medicine at the University of Heidelberg, where he also obtained his doctoral degree. Hartl joined Walter Neupert's research group at LMU as a postdoc and then became a group leader in Neupert's department. A fellowship from the German Research Foundation (DFG) enabled him to undertake research at the University of California, Los Angeles. He did research as a Professor and Howard Hughes Medical Investigator at the Sloan Kettering Institute and Cornell University in New York, USA. In 1997, the Max Planck Society succeeded in enticing the renowned scientist back to Germany. Since then, he has been Director and head of the Department of Cellular Biochemistry at the Max Planck Institute of Biochemistry. Within the last years he was honored with multiple scientific prizes including 2002 the Gottfried Wilhelm Leibniz Prize, 2011 the Albert Lasker Award for Basic Medical Research, 2012 the Shaw Prize together with Horwich, and 2016 the Albany Medical Center-Prize together with Horwich and Susan Lee Lindquist. In 2018, Hartl was inducted into the Hall of Fame of German Research, in 2019 he received the Dr. Paul Janssen Award and the Paul Ehrlich- and Ludwig Darmstaedter-Prize, and in 2020 he was awarded the Breakthrough Prize.

**About Manajit Hayer-Hartl**

Manajit Hayer-Hartl received her Bachelor of Science degree at the University of Stirling, Scotland, UK, where she afterwards gained her PhD. Her interest in structural and cellular biology motivated her to several postdoctoral fellowships at renowned research institutions, among them the Louis Pasteur Institute in Strasbourg, France and the Sloan-Kettering Institute in New York, USA. Hayer-Hartl joined the Max Planck Institute of Biochemistry in 1997 as a group leader in the department "Cellular Biochemistry". Since 2006, she is head of the research group "Chaperonin-assisted Protein Folding". Her research focuses on chaperones and how these molecular machines assist in proper protein folding and assembly. Hayer-Hartl is an elected member of the European Molecular Biology Organization (EMBO) and of the German National Academy of Sciences (Leopoldina). For her research, she has previously received the Dorothy Crowfoot Hodgkin Award (Protein Society) and the Charles F. Kettering Award (American Society of Plant Biologists).

**About the Max Planck Institute of Biochemistry**

The Max Planck Institute of Biochemistry (MPIB) belongs to the Max Planck Society, an independent, non-profit research organization dedicated to top-level basic research. As one of the largest Institutes of the Max Planck Society, about 800 employees from 45 nations work here in the field of life sciences. In currently about 35 departments and research groups, the scientists contribute to the newest findings in the areas of biochemistry, cell biology, structural biology, biophysics and molecular science. The MPIB in Munich-Martinsried is part of the local life-science-campus in close proximity to the Max Planck Institute of Neurobiology, a Helmholtz Center, the Gene-Center, several bio-medical faculties of the Ludwig-Maximilians-Universität München and the Innovation and Founding Center Biotechnology (IZB).

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