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The nucleolus – a known organelle with new tasks

The nucleolus is a well-known cellular structure that is easily visible under a light microscope. This nuclear structure is known as the site of ribosome production. In a recent study, researchers at the Max Planck Institute of Biochemistry in Martinsried, Germany, have shown that the nucleolus is also a site of quality control for proteins. When cells are stressed, proteins tend to misfold and to aggregate. To prevent proteins from clumping, some are temporarily stored in the nucleolus. The special biophysical conditions found in this organelle prevent harmful protein aggregation. The results of this study have now been published in the journal *Science*.

One would like to believe that the basic cellular processes have already been deciphered and that research can now focus on the details. But even today, new fundamental principles are being discovered through the combination of modern methods. The nucleolus is a nuclear structure that was first described in the 1830s. In the 1960s it was recognized that ribosomes, the protein factories, are produced in this organelle. Researchers have known for some time that protein folding helpers, so-called chaperones, move into the nucleolus under certain circumstances. It has been suggested that this relocation is related to protein production. Now researchers from the Max Planck Institute (MPI) of Biochemistry have shown that the chaperones that move into the nucleolus are bound to stress-sensitive proteins.

As pioneer of chaperone research, F.-Ulrich Hartl and his team have discovered that chaperones are crucial for the correct folding of proteins and play a central role in the quality control of proteins. If protein folding does not work correctly, misfolded proteins can accumulate and clump together. The resulting protein aggregates can often be observed in neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's disease.

Mark Hipp, corresponding author of the study and member of F.-Ulrich Hartl's department, comments: “We have been using luciferase as a model protein for many years in order to investigate

the mechanisms of protein folding". Bound to a fluorescent protein, the scientists can see under the microscope whether the protein is correctly folded or if it is misfolded and aggregates. "We were able to show that stressing cells by heating them to 43°C, results in the transport of the misfolded luciferase protein together with the chaperones into the nucleolus."

The researchers cooperated with the groups of Ralf Jungmann, developer of high-resolution fluorescence methods, and Jürgen Cox, developer of bioinformatic analysis methods, both also located at the MPI of Biochemistry, in order to elucidate the mechanistic details of this process. Together they were able to show that the misfolded luciferase protein behaved differently within the nucleolus than in the rest of the cell. "In the nucleolus, misfolded proteins were kept in a liquid-like state instead of aggregating," explains Frédéric Frottin, first author of the study. This is possible due to the specific biophysical conditions of this organelle. "Proteins that usually tend to aggregate are stored in a less dangerous form during the stress which protects cells from damage. Once the cell had time to recover, the proteins can be refolded and released from the nucleolus," continues Frottin. Now, the cells have the capacity to activate further mechanisms that enable the protein to be repaired or degraded. The researchers could also show that this protective mechanism fails if the cell stress lasts too long. "This is a new mechanism that maintains the integrity of the cell," says Mark Hipp. Maintaining this integrity is ultimately essential to prevent aging and the development of disease.

Original publication:

F. Frottin, F. Schueder, S. Tiwary, R. Gupta, R. Körner, T. Schlichthaerle, J. Cox, R. Jungmann, F.U. Hartl, M.S. Hipp: The nucleolus functions as a phase-separated protein quality control compartment. *Science*. July 2019
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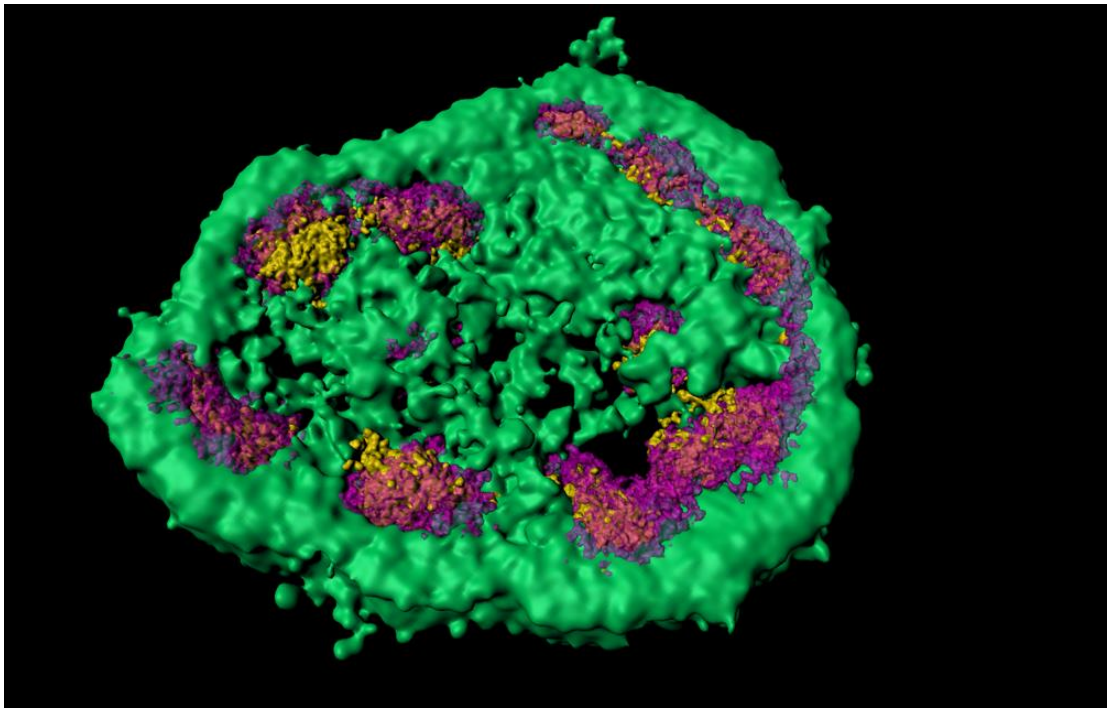

Caption:

Super-resolution light microscopy shows that the nucleolus is not separated from the rest of the cell by a membrane and that it consists of different zones (here marked green, magenta, and yellow), which are distinct from each other and membrane-less as well. The work in this study has shown that misfolded proteins can be temporarily stored in the green area.

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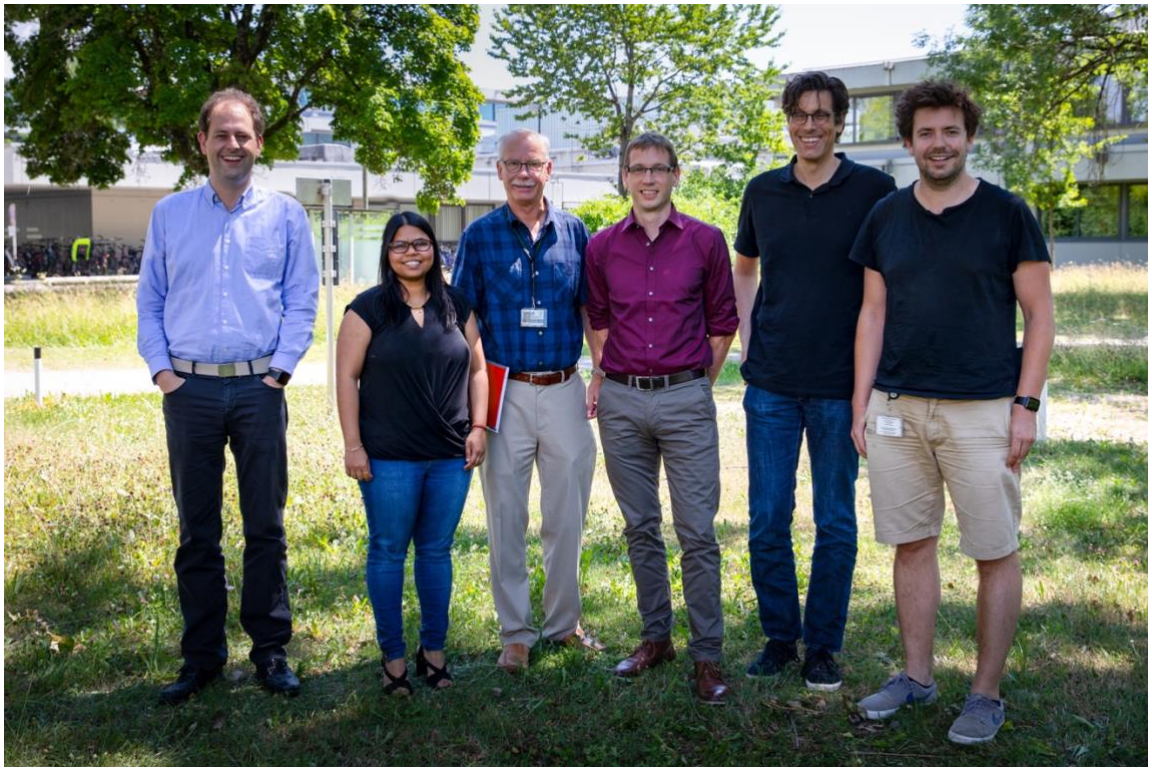

Caption:
Some of the authors from the MPI of Biochemistry who were involved in the study (left to right): Ralf Jungmann, Shivani Tiwary, F.-Ulrich Hartl, Frédéric Frottin, Mark Hipp, Florian Schüder
Photo: Susanne Vondenbusch-Teetz © MPI of Biochemistry

About Mark Hipp
Mark Hipp studied Biochemistry in Tübingen and had research stays in St. Gallen, Constance and Stanford. Since 2010, he has been a group leader in the department of F.-Ulrich Hartl at the Max Planck Institute of Biochemistry in Martinsried. There, he is working on the mechanisms of protein aggregation as part of the EU-funded project ToPAG.

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

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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 Arthur L. Horwich and 2016 the Albany Medical Center-Prize together with Arthur L. Horwich and Susan Lee Lindquist. In 2018, Hartl was inducted into the Hall of Fame of German Research.

Further information on research by F.-Ulrich Hartl
Movie: Chaperones - Folding helper in the cell (English): https://youtu.be/XKiwOZ3oVJw

About Ralf Jungmann
Ralf Jungmann studied physics at Saarland University in Saarbrucken from 2001 to 2006. After graduating from the University of California Santa Barbara, USA, he earned a doctorate from the Technical University of Munich in 2010. This was followed by a postdoctoral fellowship at the Wyss Institute for Biologically Inspired Engineering at Harvard University. Since 2014, he has been head of the independent Research Group "Molecular Imaging and Bionanotechnology" at the Max Planck Institute of Biochemistry in Martinsried and Ludwig Maximillian University (LMU) in Munich. He has held a professorship in experimental physics at LMU since 2016. In 2016, Jungmann was awarded an ERC Starting Grant of the European Research Council. Since 2017, he is a Paul Allen Distinguished Investigator and was awarded an HFPS Young Investigator Award in 2018.

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, 850 employees coming from 45 nations work here in the field of life sciences. In currently eight departments and about 25 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 where two Max Planck Institutes, a Helmholtz Center, the Gene-Center, several bio-medical faculties of two Munich universities and several biotech-companies are located in close proximity. http://www.biochem.mpg.de

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