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Cellular power outage

A common feature of neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's disease are deposits of aggregated proteins in the patient's cells that cause damage to cellular functions. Scientists at the Max Planck Institute of Biochemistry and Ludwig-Maximilians-Universität (LMU) in Munich report that, even in normal cells, aberrant aggregation-prone proteins are continually produced due to partial failure of the respiratory system. Unless they are removed by degradation, aggregates accumulate preferentially in the mitochondria, the cellular power plants, ultimately blocking energy production. In order to get rid of these toxic aggregates, cells have developed an elaborate protein quality control system, which the researchers now describe in the journal *Cell*.

Misfolded proteins made from defective blueprints are often sticky and clump together. Accumulation of such faulty proteins is known to contribute to the progression of several diseases. Therefore, cells have internal quality control mechanisms that detect and rapidly destroy faulty proteins. Proteins are produced by ribosomes, and misfolding can occur if they stall while decoding a damaged template. If the necessary ribosome-associated quality control machinery (RQC) does not function properly, defective proteins accumulate and form toxic aggregates in the cytoplasm of the cells. A previous study reported that this aggregation mechanism is mediated by so-called CAT-tails – C-terminal alanine-threonine sequences that are added to the defective proteins. So far, studies have focused on how the RQC recognizes and clears blocked ribosomes in the cytosol. The collaborating groups at the MPIB and LMU have now investigated the clearance of ribosome-blocked proteins destined for the mitochondria.

Mitochondria are the cell's power plants, converting the energy from nutrients into ATP. ATP is the universal "energy carrier" and is essential for all processes in living cells. Damage to the mitochondria thus has fatal consequences for cells. Their dysfunction not only plays a role in the

development of metabolic diseases such as diabetes, but also in neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's disease. "This is why the mitochondria are also referred to as the 'Achilles' heel' of the cell," says Walter Neupert from the Department of Cell Biology at the LMU Biomedical Center. Neupert and his team have been studying mitochondria for a long time. They discovered that even normal, unstressed cells continually produce faulty proteins under respiratory conditions. Apparently, a side reaction in the respiratory system in the mitochondria causes them to steadily release reactive oxygen species that can damage DNA, RNA and proteins. To determine how aggregates can arise in mitochondria and cause damage to cells, they cooperated with the team led by F.-Ulrich Hartl at the Max Planck Institute of Biochemistry. Hartl has been investigating protein aggregates, a cellular cause of neurodegenerative diseases, for many years.

Faulty proteins inside mitochondria

“CAT-tailed proteins have a particularly toxic effect on mitochondrial function. Once CAT-tailed proteins are imported into the mitochondria, they form aggregates that may act as a seed, and ultimately bind proteins free of defects that have vital roles for the cell” explains Toshiaki Izawa, first author of the study, together with Sae-Hun Park. Among the latter are the mitochondrial chaperones and proteases, which – once clumped – can no longer efficiently perform their normal function of repairing the damaged proteins and eliminating faulty proteins. A vicious cycle begins, and eventually such aggregates can damage the molecular power plants and shut down ATP production.

The mitoRQC pathway

“The elimination by the degradation machinery in the cytoplasm of mitochondrial proteins that have been marked as faulty by the attachment of CAT-tails is tricky. The synthesis of these proteins in the cytosol is tightly coupled to their import into the mitochondria. Therefore, cells have developed another strategy to get rid of faulty mitochondrial proteins and maintain cellular homeostasis”, says Park. “We identified the cytosolic protein Vms1 as a key component of a novel pathway termed mitoRQC that protects mitochondria from the toxic effects of such aberrant proteins”, explain the authors of the study. Vms1 suppresses these toxic effects by reducing CAT-tailing of ribosome-stalled polypeptides, thereby preventing aggregation and directing aberrant polypeptides to intra-mitochondrial quality control systems. “Our results suggest a way in which mitochondrial toxicity may contribute to neurodegenerative diseases. These findings provide important novel insights into the mechanisms of cellular protein quality control as well as disease progression” Hartl concludes. [SiM]

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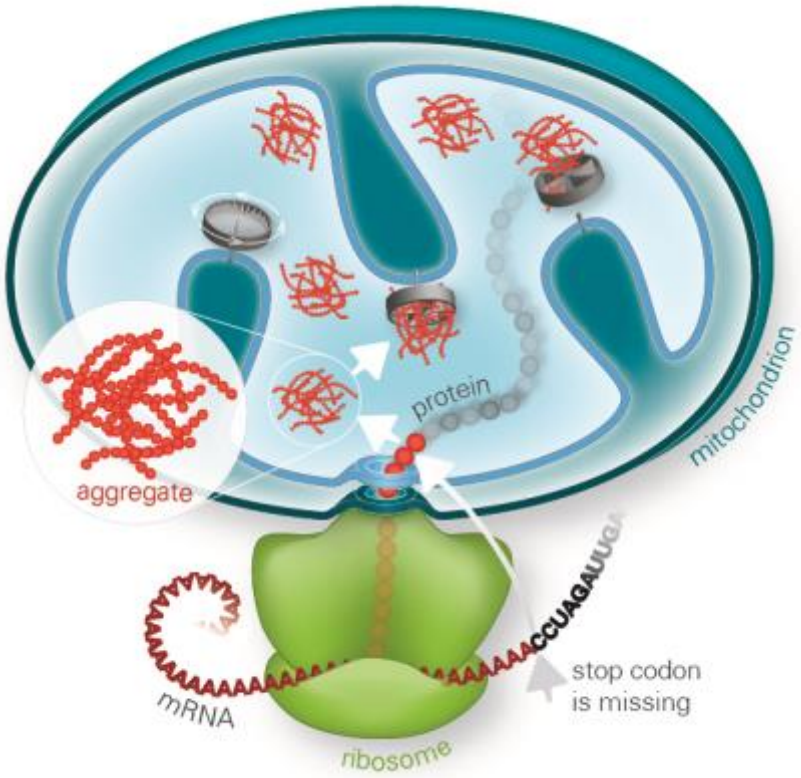

Caption
Failure of ribosome-associated quality control (RQC) for the clearance of ribosome-blocked proteins destined for the mitochondria leads to accumulation of toxic aggregates and mitochondrial toxicity. Monika Krause © Max Planck Institute of Biochemistry

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About F.-Ulrich Hartl
Ulrich Hartl was born in 1957. He studied Medicine at the University of Heidelberg, where he afterwards gained his PhD. Hartl joined Walter Neupert's research group at LMU as scientific assistant. A fellowship from the German Research Foundation (DFG) enabled him to undertake research at the University of California, Los Angeles. He did research as professor and Howard Hughes Medical Investigator at the Sloan Kettering Institute and at Cornell University in New York,

USA. In 1997, the Max Planck Society succeeded in enticing the renowned scientist back to Germany. Since then, he is director and head of the Department of Cellular Biochemistry at the Max Planck Institute of Biochemistry.

About Walter Neupert

Walter Neupert was born in Munich in 1939. He obtained doctoral degrees in Biochemistry and Medicine from LMU in 1968 and 1970, respectively. In 1977 he became a professor in the Institute of Biochemistry at Göttingen University. In 1983 he was appointed to the Chair of Physiological Chemistry in the Adolf Butenandt Institute at LMU, a position which he held until his retirement in 2010. Between 2008 and 2016 Neupert was a Senior Fellow of the Max Planck Society, working in the Max Planck Institute for Biochemistry in Martinsried. Since then, he has continued his research at LMU's Biomedical Center.

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 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://biochem.mpg.de)

About LMU Munich

As one of Europe's leading research universities, LMU Munich is committed to the highest international standards of excellence in research and teaching. Building on its 500-year-tradition of scholarship, LMU covers a broad spectrum of disciplines, ranging from the humanities and cultural studies through law, economics and social studies to medicine and the sciences. 16 percent of LMU's 50,000 students come from abroad, originating from 130 countries worldwide. The know-how and creativity of LMU's academics form the foundation of the University's outstanding research record. This is also reflected in LMU's designation of as a "university of excellence" in the context of the Excellence Initiative, a nationwide competition to promote top-level university research. www.en.lmu.de

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