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Traffic jam in the cell

A German-Polish team with scientists from Freiburg revealed how cells survive mistargeting of mitochondrial proteins

A team of scientists led by Prof. Dr. **Bettina Warscheid** from the University of Freiburg and Prof. Dr. **Agnieszka Chacinska** from the International Institute of Molecular and Cell Biology in Warsaw/Poland discovered a mechanism called "Unfolded Protein Response activated by mistargeting of proteins", UPRam for short. This mechanism protects cells against the accumulation of mitochondrial precursor proteins that missed their target – the mitochondrion – due to a defect in the protein import system. The study shows how cells react to and survive stress that is triggered by the accumulation of mitochondrial precursor proteins. The data may help to better understand mechanisms of age-related and neurodegenerative diseases in the future. These are often accompanied by mitochondrial dysfunctions and impairment of the protein homeostasis, the maintenance of the steady state of a cell. The study was published in the journal *Nature*.

Mitochondria, commonly known as powerhouses of the cell, need more than a thousand proteins to fulfill their multitude of functions. The majority of mitochondrial proteins are synthesized in the cytosol, the intracellular fluid, and need to be transported into the mitochondria. Defects in the protein import machinery lead to mitochondrial dysfunctions and the accumulation of mitochondrial precursor proteins in the cytosol.

How the cell reacts to the resulting stress has been unknown so far. To address this question, Dr. **Silke Oeljeklaus** and Dr. **Sebastian Wiese** from

the Warscheid group investigated, with the help of high resolution mass spectrometry, how the proteome of cells with a defect in the mitochondrial protein import is altered. The proteome of a cell comprises all proteins that are present in the cell at a given point of time. Based on these data, the research team discovered that UPRam consists of two main pathways that are used by the cell to protect itself against a defective mitochondrial protein import. First, the cell inhibits translation, that is the generation of proteins in the cytosol, to counteract further accumulation of mitochondrial precursor proteins. Second, the cell activates the proteasome, a protein degradation machinery, which removes the already existing traffic jam on the mitochondrial import pathway.

In order to provide proof for UPRam, the scientists decoupled the activation of the proteasome from translational inhibition by the use of artificially mistargeted mitochondrial proteins. They showed that the cell maintains its inner balance as it adjusts the mechanisms for the regulation of the cellular protein homeostasis to the state of its mitochondria. The cell activates the proteasome by a more efficient assembly and, thus, reacts directly to the amount of proteins that fail to be imported into the mitochondria.

Bettina Warscheid is head of the department of Biochemistry - Functional Proteomics, Institute of Biology II, and member of the Cluster of Excellence BIOSS Centre for Biological Signalling Studies at the University of Freiburg. Silke Oeljeklaus is senior scientist in the department of Biochemistry - Functional Proteomics. Sebastian Wiese was postdoctoral fellow in the group of Bettina Warscheid and now leads the core unit "Mass Spectrometry and Proteomics" at the Medical Faculty of the University of Ulm.

Original publication:

Lidia Wrobel*, Ulrike Topf*, Piotr Bragoszewski, Sebastian Wiese, Malgorzata E. Sztolsztener, Silke Oeljeklaus, Aksana Varabyova, Maciej Lirski, Piotr Chroscicki, Seweryn Mroczek, Elzbieta Januszewicz, Andrzej Dziembowski, Marta Koblowska, Bettina Warscheid[#] & Agnieszka Chacinska[#]. Mistargeted mitochondrial proteins activate a proteostatic response in the cytosol. (2015). Nature. doi:10.1038/nature14951. (*[#]These authors contributed equally.)

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Traffic jam on the mitochondrial protein import pathway in the cell. Source: Lena Reimann, Working Group Warscheid

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