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Starvation and other Stresses: Internal Sensor in Cells Coordinates Cellular Stress Response

Scientists in Cologne have discovered an important role for the protein complex mTORC1 that centrally regulates cell communication. The findings may lead to the development of new treatment methods in the future.

Researchers at the University of Cologne and the Max Planck Institute for the Biology of Ageing have discovered that the protein complex mTORC1 acts as a central sensor of environmental signals, including information about the availability of nutrients, energy or oxygen, to regulate the transport of proteins to the cell surface and to the extracellular environment, thus influencing multiple cellular functions. Although it has been known for decades that communication is essential for proper cell function and is disturbed in many diseases and in old age, the exact mechanism was previously unknown. The article, "An mTORC1-GRASP55 signaling axis controls unconventional secretion to reshape the extracellular proteome upon stress," appears in the journal Molecular Cell.

"One pathway that cells use to transport and secrete proteins is the unconventional protein secretion, short UPS. This pathway is activated upon stress, and it has previously been shown that UPS transports proteins that play important roles in cancer, inflammation and bone formation," explains Dr. Julian Nüchel, first author of the study. "We have now discovered in our detailed investigation that the cell sensor mTORC1 controls UPS."

With their experiments, the Cologne scientists were able to show that various cell stress factors such as starvation switch off the protein complex mTORC1 and thus activate UPS transport pathways. Under normal conditions, mTORC1 is active and adds a small chemical modification, called phosphorylation, to certain proteins to change their activity or intracellular localization. In the Cologne study, mTORC1 controls the localization and function of the protein GRASP55, which normally resides at the Golgi apparatus, the cargo sorting center of the cell. Under stress

conditions, when mTORC1 is inactive, GRASP55 is no longer held at the Golgi, but instead attaches to other cellular components to enable UPS.

In addition to clarifying how UPS is regulated in cells, the researchers identified numerous proteins whose transport to the cell surface depends on this pathway, including factors with important roles in cell movement and communication, two processes that are often impaired in human disease. In cells with impaired mTORC1 activity, the UPS transport pathway is also dysregulated. "Therefore, it stands to reason that in mTOR-dependent diseases such as tuberous sclerosis, this secretion pathway may play a critical role. The importance of unconventional protein secretion in human diseases and in aging needs to be clarified by future studies," said Markus Plomann, Ph.D., co-leader of the study.

This study was a collaboration between the research group of Dr. Markus Plomann at the Center for Biochemistry of the University of Cologne and that of Dr. Constantinos Demetriades at the Max Planck Institute for Biology of Ageing. It was supported by Dr. Beate Eckes from the Translational Matrix Biology Group, headed by Prof. Thomas Krieg at the University of Cologne, scientists from the CECAD Cluster of Excellence for Aging Research at the University of Cologne, and Colzyx AB from Lund, Sweden. The project was funded by the European Research Council (ERC), the German Research Foundation (DFG) and the Max Planck Society (MPG).

The press release was produced in collaboration with the Max Planck Institute for Biology of Ageing.

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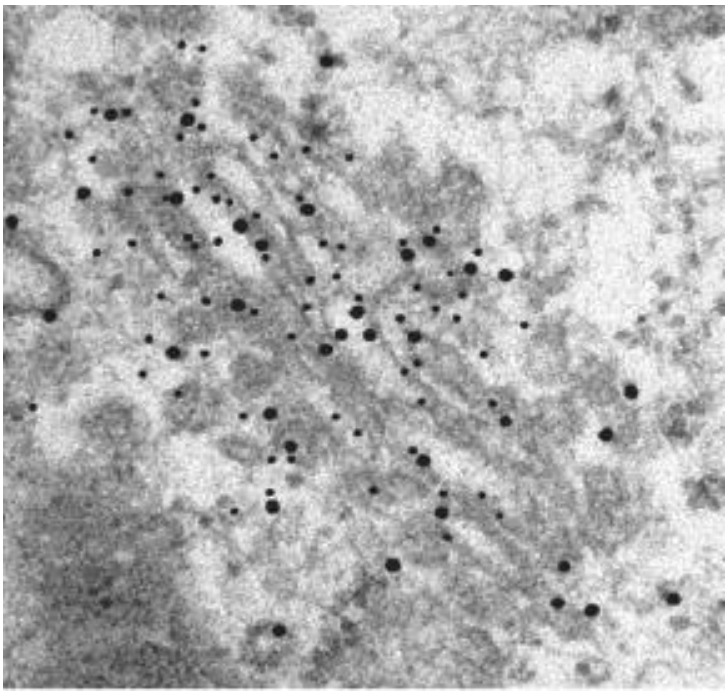
Picture:



In non-stressed cells, mTORC1 regulates GRASP55 directly at the Golgi, where both proteins colocalize (black dots). Image taken with the electron microscope. Picture credit: Nüchel/Max Planck Institute for Biology of Ageing