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Press Release

How do our cells react to starvation or stress?

Internal sensor coordinates the cellular stress response to alter the composition of extracellular proteins

Our cells communicate with their surroundings in a reciprocal manner. On the one hand, they constantly pick up signals from their environment via proteins on their surface and pass them on to the inside of the cell. On the other hand, they send signals to the outside by releasing secreted factors or through proteins that sit on their surface. Although it is well-known for decades that this bidirectional communication is crucial for cellular function, and that it is often disrupted in human disease, it was not clear until now how this actually works in cells. Researchers at the Max Planck Institute for Biology of Ageing and the University of Cologne have now discovered that a protein complex, called mTORC1, functions as a central coordinator of this process. In the future, these findings could be important for the development of treatments for conditions in which the activity of this protein complex is known to be dysregulated, such as in cancer, neurological or metabolic disorders, or when we age.

The cells that make up our bodies constantly send and receive signals to and from their environment. This allows them to sense whether they have enough nutrients, energy, oxygen, and everything else they need to grow and proliferate. When nutrients become limiting, or when cells are confronted with other stressful conditions, they need to respond and adapt accordingly, by changing how they move, how they take up nutrients, or how they interact with neighboring cells and surfaces. To achieve this, cells need to quantitatively and qualitatively reshape the set of surface and secreted proteins, which they do through the activation of complex cargo transportation mechanisms. “One route by which cells transport or secrete proteins is called Unconventional Protein Secretion, or UPS for short. This pathway is activated upon stress and was previously shown to transport proteins that play an important role in cancer, inflammation and bone formation”, explains Dr Julian Nüchel, currently a postdoctoral researcher at the Max Planck Institute for Biology of Ageing and first author of the study. “How UPS is activated in stressed or starved cells was not known. When we looked at the regulation of this secretory pathway in detail, we found that the cellular sensor mTORC1 controls this process.” The protein complex mTORC1 functions as the most important sensor of the cell and links signals such as energy and nutritional status to nearly all basic cellular activities.

Cellular stress alters the proteins on the cell surface and the extracellular space

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In their experiments, the Cologne scientists showed that various cellular stress factors, such as nutrient starvation, inactivate the protein complex mTORC1 and switch on the UPS transport pathway. "Under normal conditions, mTORC1 is active and adds a small chemical modification, called phosphorylation, to specific proteins, thus altering their activity or localization within the cell", explains research group leader Dr Constantinos Demetriades. In the case of the Cologne study, mTORC1 was shown to control the localization and function of a protein called GRASP55, which is normally located at the Golgi apparatus, the cell's protein cargo sorting center. "Under stress conditions, when mTORC1 is inactivated, GRASP55 is no longer retained at the Golgi and relocalizes to other compartments to promote UPS."

In addition to showing how UPS is regulated in cells, the researchers were also successful in revealing the identity of the proteins that depend on this pathway to reach the cell surface, and discovered factors with important roles in cell motility and communication, processes that often malfunction in human diseases. Dr Demetriades explains: "We find that, in cells in which mTORC1 activity is disturbed, the UPS transport pathway is also dysregulated. Therefore, in mTOR-related diseases, such as in Tuberous Sclerosis Complex, this secretory pathway may play a crucial role. Future studies in this direction will be necessary to explore the importance of UPS in human disease and ageing."

This study was a collaborative effort between the group of Dr Constantinos Demetriades at the MPI-AGE, and that of Dr Markus Plomann at the Center for Biochemistry of the University of Cologne, also supported by Dr Beate Eckes from the Translational Matrix Biology laboratory at the University of Cologne, and researchers from the CECAD Cluster of Excellence in Ageing research at the University of Cologne, and Colzyx AB from Sweden. The project has received funding from the European Research Council (ERC), the German Research Foundation (DFG), and the Max Planck Society (MPG).

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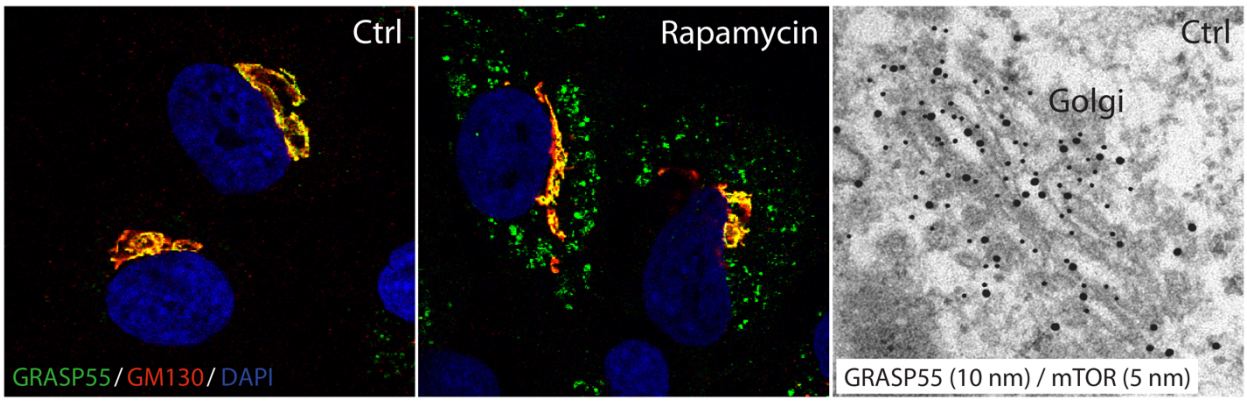

Immune fluorescence microscopy shows that the key UPS regulator, GRASP55, localizes primarily at the Golgi apparatus in non-stressed cells (left panel), whereas it readily relocalizes to secretory vesicles in response to stimuli that cause mTORC1 inhibition (middle panel). mTORC1 regulates GRASP55 directly at the Golgi, where both proteins colocalize in non-stressed cells (right panel, Image taken with the electron microscope). ©Nüchel/Max Planck Institute for Biology of Agein, 2021

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About the Max Planck Institute for Biology of Ageing

The Max Planck Institute for Biology of Ageing investigates the natural ageing process with the long-term goal to pave the way towards increasing health during ageing in humans. It is an institute within the Max Planck Society, which is one of Germany's most successful research organisation. Since its foundation in 2008 the institute is an integral part of a life science cluster in Cologne that pursue ageing research.

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