Shuttle service in cells: Scientists find new components for protein transport

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Research scientists at the Ruhr University Bochum discovered a new enzyme, which gives decisive insights into protein import into specific cellular organelles (peroxisomes). In the *Journal of Biological Chemistry*, the team of Prof. Erdmann (Medical Faculty, Department of Systemic Biochemistry) reports that the enzyme Ubp15p collaborates with two other proteins to convert the protein transport machinery back into its initial condition after work has been completed.

The enzyme detaches a specific signal sequence from a protein which is important for transportation and recycling of this protein. A new sequence of protein can then commence. "With Ubp15p we could unravel a further mystery concerning the transport of proteins into peroxisomes", explains Prof. Erdmann. "The comprehension of these organelles at a molecular level is a decisive prerequisite for the development of new diagnostic and therapeutic approaches for patients with peroxisomal disorders who only seldom survive the first year of their life."

Peroxisomes are multifunctional "tools." They are involved, for example, in the catabolism of fatty acids, and detoxify poisonous hydrogen peroxide. A malfunction of these organelles, as is the case in Zellweger Syndrome disorders, can have disastrous influences on the functioning of the liver, kidneys and brain. To be able to function correctly, peroxisomes need specific proteins, but they cannot produce these themselves. Thus, a shuttle system consisting of several receptors has to import them from the cytosol. The receptors recognize the proteins specified for the peroxisomes within the cytosol and escort them to their destination. Here they bond with the membrane of the peroxisome and form part of the "gate" through which the proteins are transported into the interior. An export signal (ubiquitin) is attached to the receptors, which ensures that they are released from the peroxisome membrane and available for transport yet again. What subsequently happens to the ubiquitin signal remains to be clarified.

In an earlier publication in *Nature Cell Biology*, Prof. Erdmann's team had already described two motor proteins that withdraw the ubiquitin-marked receptor Pex5p from the membrane and transport it back into the cytosol. In a further paper (*Nature Reviews Molecular Cell Biology*), they postulated that this export of the receptor is mechanistically linked to the import of the peroxisomal protein. To date, it has however not been possible to detect the ubiquitin together with Pex5p in the cytosol. "We thus assumed that the ubiquitin is removed from the receptor during or shortly after export", states Prof. Erdmann. His team, funded by the collaborative research center 642 of the German National Science Foundation (Sonderforschungsbereich 642 der Deutschen Forschungsgemeinschaft), has now established that the enzyme Ubp15p disconnects the export signal and collaborates with the two motor proteins to remove the receptor from the membrane of the peroxisome.

The scientists managed to locate Ubp15p in living yeast cells and to prove that the enzyme comes into direct contact with one of the motor proteins to reach the peroxisomes. When Prof. Erdmann's team deactivated the Ubp15p in the cells, the amount of ubiquitinated Pex5p increased. This result confirms the role of Ubp15p in cleaving the ubiquitin signal. The enzyme seems to have an important function in the import of proteins into the peroxisomes, particularly under stress conditions. "Ubp15p appears to play a vital role in the recycling of the receptor", points out Prof. Erdmann.

Provided by Ruhr-University Bochum