

Researchers identify a fundamental process in lysosomal function and protein degradation

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The degradation of proteins and other macromolecules in cells is vital to survival. Disruption of this process can result in serious disease. The research group of Professor Thomas Jentsch (Leibniz Institute for Molecular Pharmacology, Germany) has now succeeded in identifying an essential cellular process necessary for the transport and degradation of macromolecules in endosomes and lysosomes, respectively. In two studies published in the same issue of the journal *Science*, they showed that - contrary to scientific consensus - the function of these tiny cell organelles not only depends on the pH, but also on chloride ion accumulation in their interior.

Proteins are the building blocks and machines of life. Tens of thousands of them are present in each cell, where they perform essential tasks for the organism. Once they have fulfilled their function, they must be degraded to avoid causing damage. One way in which proteins can be degraded is via the digestion processes inside tiny cellular organelles, the lysosomes. The transport of the proteins destined for degradation to these cellular "trash bins" is partly carried out by endosomes, which deliver proteins from the cell surface to the cell interior.

The functionality of both endosomes and lysosomes depends on the ion concentration within their membrane-enclosed interior. In particular, an important role is ascribed to a high concentration of hydrogen ions, i.e. an acidic pH, inside those organelles.

The two studies by Dr. Stefanie Weinert, Dr. Gaia Novarino and Professor Thomas Jentsch focus on two ion transport proteins, the chloride transporters ClC-5 and ClC-7. These are located in the membrane of endosomes and/or lysosomes and exchange negatively charged [chloride ions](#) for positively charged [hydrogen ions](#) (protons).

ClC-5 is located in the membrane of endosomes in renal cells. If ClC-5 is defective or lacking altogether, proteins can hardly be absorbed from the urine any longer. In a cascade of indirect mechanisms, this leads to the development of kidney stones in Dent's disease.

ClC-7 is located in the membrane of lysosomes in all cells of the body. The research group by Thomas Jentsch showed already a few years ago that mutations of ClC-7 in mice and humans lead to severe disease symptoms. Impaired lysosomal function in the brain results in severe degenerative changes that leads to massive neuronal death. A dysfunction of bone-degrading osteoclasts causes an excessive calcification of bones (osteopetrosis).

The chloride-proton exchangers ClC-5 and ClC-7 function parallel to proton pumps, which ensures an acidic environment within endosomes and lysosomes. ClC-5 and ClC-7 transport chloride ions into these organelles, thereby electrically balancing the inward transport of positively charged protons through the "pump". Hitherto researchers had assumed that maintaining the charge balance was the sole task of ClC-5 and ClC-7, without which both the transport of endosomes and lysosomal [protein](#) degradation are impaired.

However, Professor Jentsch and his team showed several years ago that the pH in lysosomes devoid of ClC-7 is normal and that nevertheless lysosomal storage disease and osteopetrosis ensue. This means that charge balancing in lysosomes may involve a different, previously unknown mechanism, and that the main task of ClC-7 may rather be the

regulation of lysosomal chloride concentration. The Berlin research group proposed that the exchange of chloride for protons, which are more highly concentrated in the acidic environment of lysosomes than in the rest of the cell, accumulates chloride ions in lysosomes. A high lysosomal chloride concentration may be functionally important.

"In an elegant experimental approach" as Professor Jentsch explains the test of this hypothesis, "Dr. Novarino and Dr. Weinert converted the ClC-5 and ClC-7 chloride-proton exchangers in the mouse into pure chloride conductors (channels). They exchanged a single amino acid out of a total of around 800 present in the ion transporters". These mutated transport proteins are optimally suited to compensate the charge transfer by the proton pump and therefore should, according to the hypothesis of the research group, support the acidification of the organelles very well.

On the other hand, the uncoupling of chloride transport from proton transport should significantly lower the accumulation of chloride into these organelles. Indeed, this prediction was confirmed experimentally in their mouse model. "Surprisingly," Professor Jentsch said, "the corresponding mice showed almost the same disease symptoms as with a total lack of the respective proteins."

With this experiment, the MDC and FMP researchers were able to show for the first time that not only the lack of endosomal/lysosomal acidification, but also a reduced accumulation of chloride ions in these organelles plays a crucial role in generating the severe symptoms of these hereditary diseases, that is a form of kidney stone disease as well as neurodegeneration. A dysregulation of organellar chloride concentration may also play a role in other human diseases.

More information: *Science* 11 June 2010, Vol. 328. no. 5984, pp. 1398-1401, [DOI: 10.1126/science.1188070](https://doi.org/10.1126/science.1188070); pp. 1401-1403, [DOI: 10.1126/science.1188072](https://doi.org/10.1126/science.1188072); originally published in *Science Express* on 29

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