A new cellular garbage control pathway with relevance for human neurodegenerative diseases

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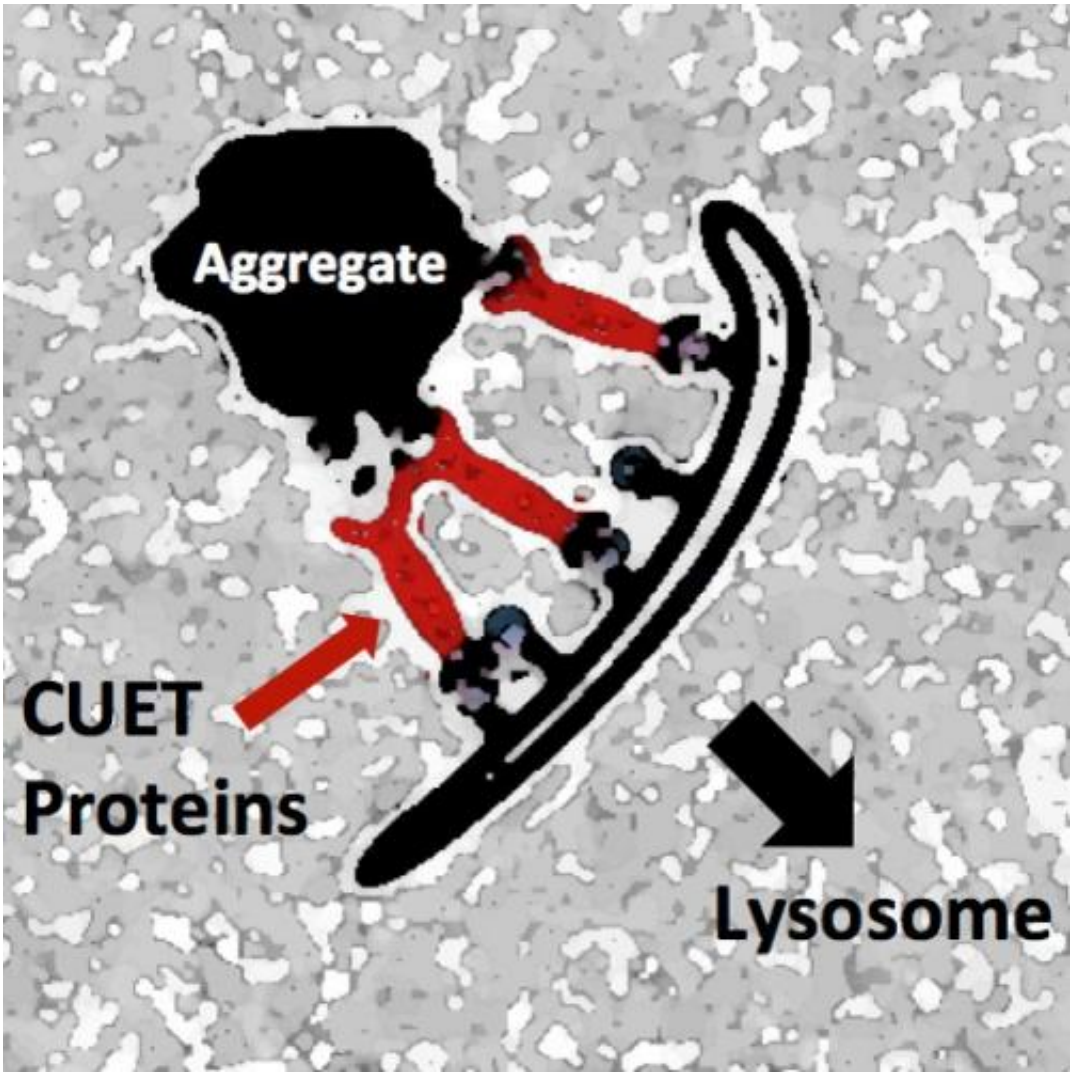

The newly identified proteins, termed CUET proteins (shown in red), recognize toxic protein aggregates and target the whole complex to the cellular waste

disposal and recycling station, the lysosome. Credit: Stefan Jentsch, MPI of Biochemistry

Proteins, the components of our body that execute, control and organize basically all functions in our cells, are made out of strings of amino acids, which – like an origami - are folded into specific and complex three-dimensional structures according to their desired functions. However, since folding and maintaining of such structures is highly sensitive to cellular or environmental stress, proteins can potentially misfold or form clumps (aggregates). Such undesired protein waste can be toxic for cells and may even lead to cell death. Because several human neurodegenerative diseases are known to be linked to an accumulation of abnormal protein aggregates, basic science aimed to understand how cells remove cellular garbage is elementary for designing strategies for a potential prevention or cure of such disorders.

Scientists in the laboratory of Stefan Jentsch at the MPIB now successfully used baker's yeast for screening for new cellular waste disposal pathways. Kefeng Lu, a postdoctoral researcher from China, discovered a new class of helper proteins (termed CUET proteins) present both in yeast and humans that recognize cellular garbage earmarked for disposal by an attached label in the form of the ubiquitously existing protein known as "ubiquitin". Importantly, these newly identified helper proteins channel the cellular garbage by a "self-eating" pathway (autophagy) to the lysosome, a compartment of cells dedicated for destruction and recycling. The Max Planck scientists could also show that a toxic protein related to the abnormal, aggregate-forming protein "huntingtin" of patients with the neurodegenerative Huntington's disease is efficiently destroyed by the newly identified pathway. Remarkably, this pathway seems specific for aggregated proteins like huntingtin and appears to be more potent than previously discovered

cellular garbage disposal mechanisms.

Because the identified cellular disposal mechanism operates in yeast as well, the researches will now take full advantage of its powerful experimental possibilities to investigate this pathway further. A detailed analysis of this mechanism will be crucial to understand how aggregate-forming proteins lead to human diseases and may help to develop concepts for possible disease preventions.

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