New signaling pathway decoded in the decomposition of damaged lysosomes

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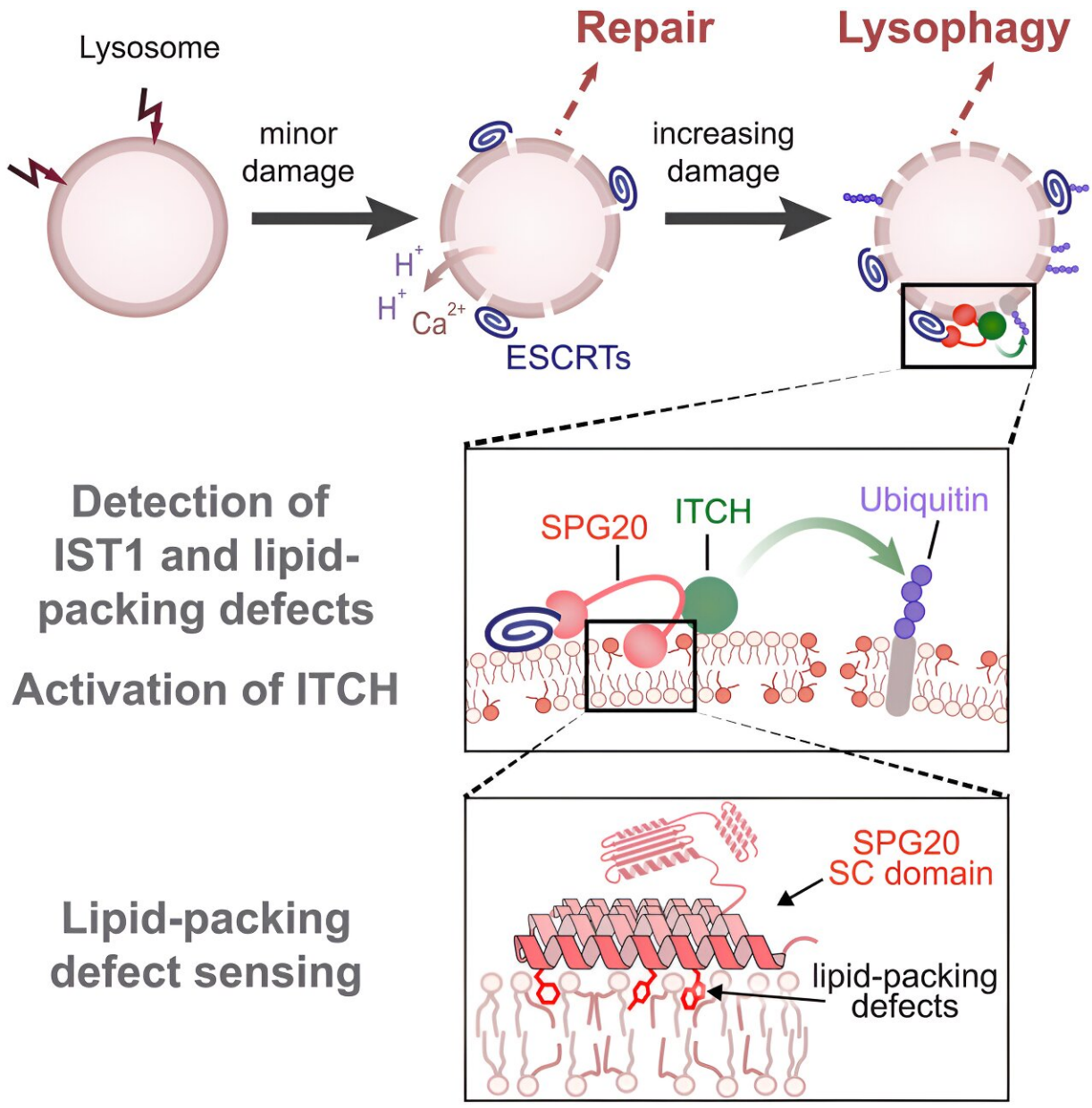

Credit: *Molecular Cell* (2024). DOI: 10.1016/j.molcel.2024.02.029

Lysosomes are surrounded by a lipid bilayer that separates the acidic environment and the digestive enzymes of the organelle from the cytoplasm. Damage to this layer—lysosomal membrane permeabilization, or LMP for short—can trigger inflammation and even lead to cell death.

In humans, LMP is particularly deleterious in nerve cells during aging, inflammation or trauma because nerve cells cannot easily regenerate; however, intentionally inducing LMP in cancer cells can also be a therapeutic option.

In the event of membrane damage to a lysosome, a cell has two options: attempt a repair or disintegrate the organelle under safe conditions. How this decision is made is not yet fully understood.

Scientists from Prof Dr. Hemmo Meyer's research group at the University of Duisburg-Essen (UDE), together with colleagues from Munich and Milan, have investigated the reaction of cells to damage in lysosomal membranes.

They were able to identify a previously unknown signaling pathway in human cells that is driven by the protein SPG20. It recognizes damage to the outer side of the lysosomal membrane, binds to the leaky organelle and triggers its breakdown before the membrane ruptures and the survival of the cell is endangered.

Their paper is published in the journal *Molecular Cell*.

"Our findings could help to better understand the cellular response to

lysosome damage and to develop new approaches for the treatment of neurodegenerative diseases associated with lysosome damage," says Pinki Gahlot, Ph.D. student in molecular biology and first author of the publication. "Conversely, certain cancer cells seem to be particularly vulnerable to LMP—so intentionally blocking the discovered factors could be a strategy in cancer therapy."

In further studies, the team wants to explore how the novel pathway is controlled by the cell to ensure cellular survival. For this purpose, they will use the new high-tech equipment in the university's microscopy facility.

More information: Pinki Gahlot et al, Lysosomal damage sensing and lysophagy initiation by SPG20-ITCH, *Molecular Cell* (2024). DOI: 10.1016/j.molcel.2024.02.029

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