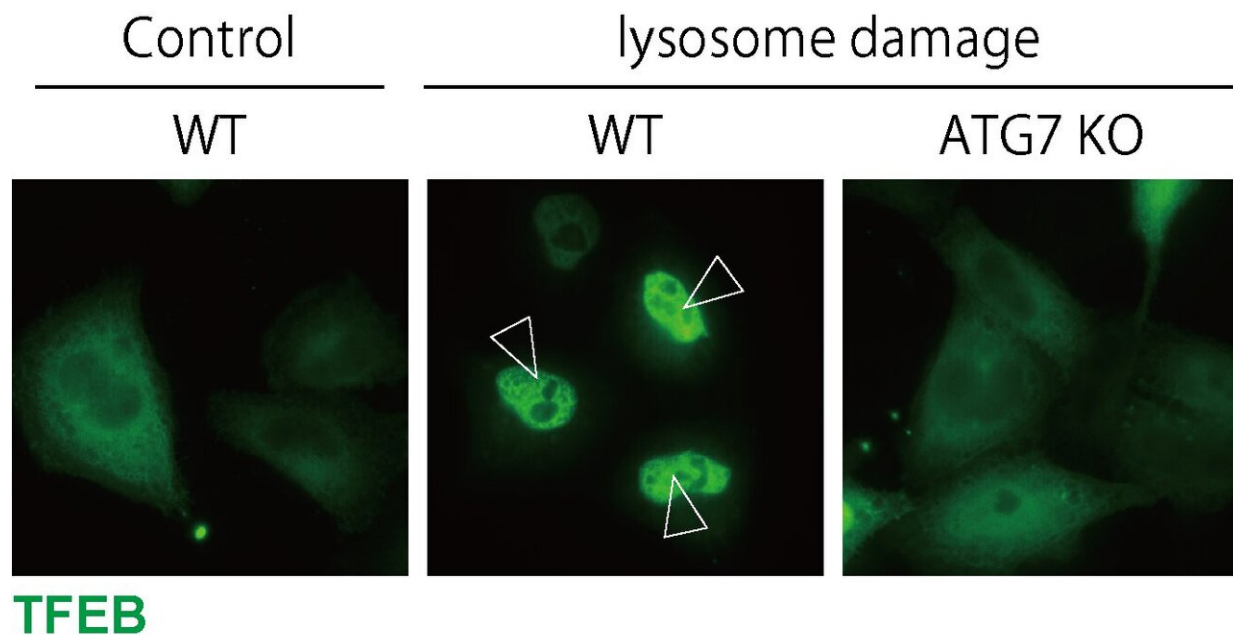


Lipids, lysosomes, and autophagy: The keys to preventing kidney injury

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TFEB is localized to the nucleus upon lysosomal damage in WT cells, while ATG7 KO cells, in which LC3 lipidation is defective, show impaired TFEB nuclear localization. Credit: Osaka University

Lysosomes are cellular waste disposal organelles containing potent enzymes. These enzymes can cause cellular damage if they leak out of ruptured lysosomes. In a recent study led by Osaka University, researchers found that several distinct pathways involved in the repair or elimination of damaged lysosomes work together in response to

lysosomal damage. The proper activation and function of these pathways was essential for preventing kidney injury in a mouse model of oxalate crystal-induced kidney damage.

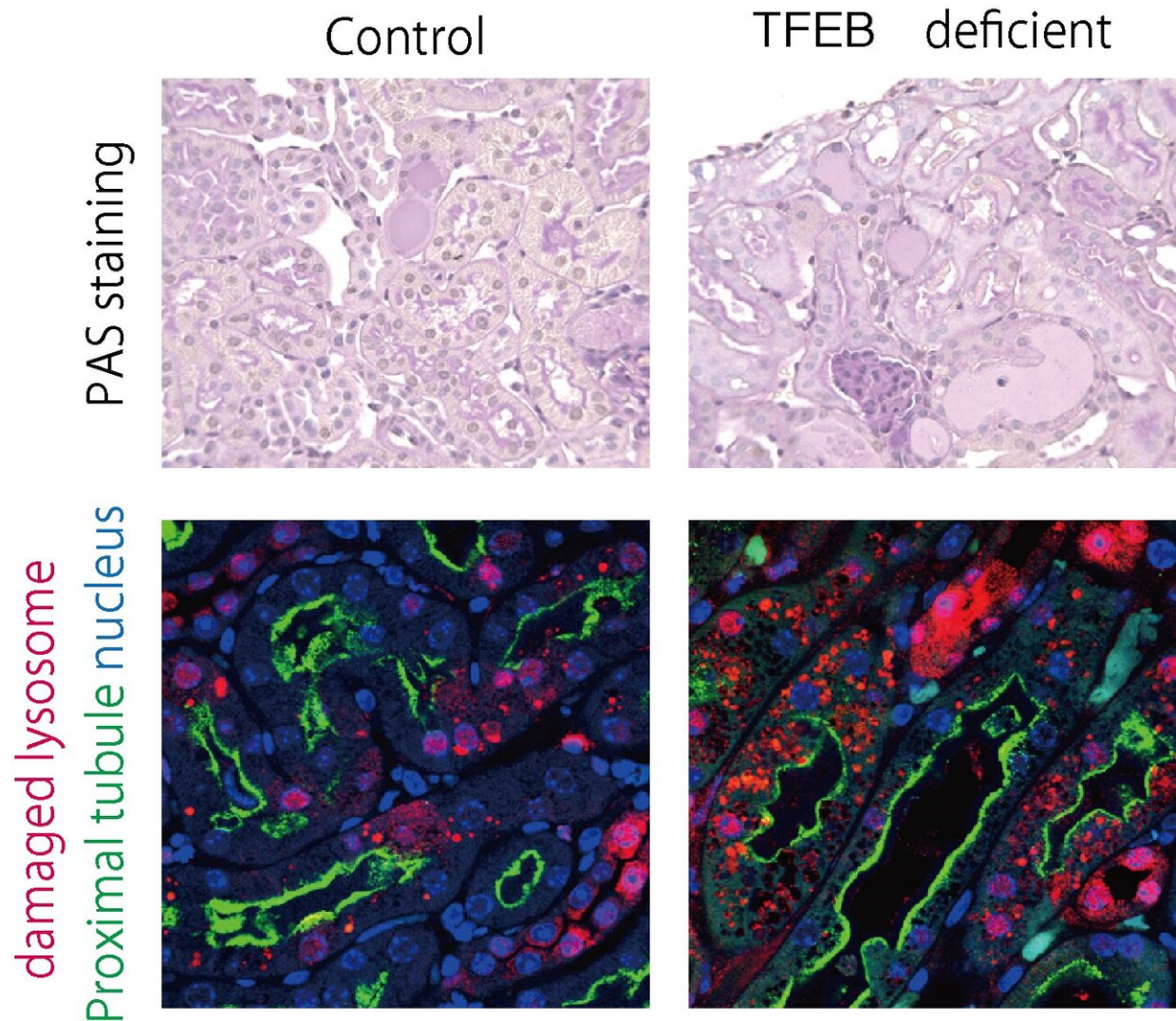
Human cells need to work like well-oiled machines to keep our bodies running as they should. Waste products such as misfolded proteins, damaged cellular components, and carbohydrates get in the way and must be quickly disposed of. Dealing with this cellular "trash" are spherical, membrane-bound organelles called lysosomes filled with a mixture of potent enzymes. In a process called autophagy, [waste products](#) are contained within a double-membraned vesicle, called an autophagosome, that fuses with a [lysosome](#). The lysosomal enzymes then get to work breaking down the waste into components that can be recycled.

The problem with lysosomes is that if they are ruptured, their contents can leak out and cause serious damage to the cell. Calcium oxalate crystal-induced [kidney injury](#), which is linked to the progression of chronic [kidney](#) disease, is actually the result of lysosomal damage caused by the crystals. It is not surprising then that cells have several pathways to repair or quickly eliminate damaged lysosomes. Yet the exact steps in these pathways and how they interact during the lysosomal damage response are not entirely clear.

In a study published in *Nature Cell Biology*, a team of researchers led by Osaka University have finally unraveled the interactions among the lysosomal damage response pathways and determined how they prevent oxalate-induced kidney injury.

"A protein called TFEB turns on genes necessary for autophagy and the production of new lysosomes in response to lysosomal damage," explains lead author Shuhei Nakamura. "By inhibiting TFEB function in HeLa cells and then inducing lysosome damage, we confirmed that TFEB is

activated upon lysosomal damage and is necessary for the removal of damaged lysosomes."



In the crystal nephropathy mouse model, TFEB-deficient mice showed increased severity of kidney injury and lysosomal damage compared with control mice.
Credit: Osaka University

Attachment of lipids to a protein called LC3 is an essential step in the

formation of the autophagosome. To their surprise, the researchers also found that lipidated LC3 was necessary for the activation of TFEB during the lysosomal damage response, but there was no clear link between the systems.

"Calcium is a known activator of TFEB," says senior author Tamotsu Yoshimori. "To identify how the TFEB and LC3 systems overlapped, we investigated lysosomal calcium channel TRPML1. We found that lipidated LC3 was recruited by lysosomes in response to damage, and that the lipidated protein interacted with TRPML1, causing increased calcium efflux from the lysosome, which activated TFEB."

The physiological importance of this interaction was then confirmed using a mouse model of oxalate crystal-induced [kidney damage](#). Mice lacking TFEB had more severe kidney damage compared with control animals. Understanding how these pathways interact is the first step in preventing lysosomal damage-associated diseases.

More information: LC3 lipidation is essential for TFEB activation during the lysosomal damage response to kidney injury, *Nature Cell Biology* (2020). [DOI: 10.1038/s41556-020-00583-9](https://doi.org/10.1038/s41556-020-00583-9) , www.nature.com/articles/s41556-020-00583-9

Provided by Osaka University

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