Orchestrator of waste removal rescues cells that can't manage their trash

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Just as we must take out the trash to keep our homes clean and safe, it is essential that our cells have mechanisms for dealing with wastes and worn-out proteins. When these processes are not working properly, unwanted debris builds up in the cell and creates a toxic environment. Now, a new study published by Cell Press on September 1st in the journal *Developmental Cell* describes a master regulator of the intracellular recycling and waste removal process and suggests an alternative strategy for treatment of metabolic disorders associated with the abnormal accumulation of waste in the cell.

Lysosomes are the cellular structures that are primarily involved in the degradation and recycling of waste. Lysosomes ingest trash and degrade it with powerful enzymes. Failure of this process causes lysosomal storage diseases (LSDs), which are characterized by the progressive accumulation of waste and are often associated with neurodegeneration. Lysosomes are also involved in "lysosomal exocytosis", where they are recruited to the inner surface of the cell and then fuse with the cell membrane to dump their contents outside the cell.

"While the main steps of lysosomal exocytosis had been elucidated, little was known about its regulation," says senior study author Dr. Andrea Ballabio. In the current study, scientists from the Telethon Institute of Genetics and Medicine in Italy, also affiliated with the Jan and Dan Duncan Neurological Research Institute and Baylor College of Medicine in Houston Texas, found a way to exploit this mechanism to get rid of toxic cellular waste. The researchers built on their earlier discovery that

production of lysosomes and the ability of lysosomes to degrade wastes are regulated by transcription factor EB (TFEB) and that activation of TFEB reduces accumulation of pathogenic protein in a cellular model of Huntington's disease. Here, they examined whether TFEB also regulates lysosomal exocytosis.

TFEB modulated lysosomal exocytosis by increasing the pool of lysosomes recruited to the cell membrane and by promoting their fusion with the membrane. Importantly, induction of lysosomal exocytosis by increased TFEB activity rescued pathogenic storage and rescued cells in multiple models of LSDs. "Our findings demonstrate that lysosomal exocytosis is regulated by TFEB," concludes Dr. Ballabio. "Although these strategies will have to be tested by long-term studies in animal models to verify their therapeutic potential, our data indicate that lysosomal exocytosis can be exploited to promote cellular clearance in lysosomal storage diseases, suggesting an alternative strategy to treat LSDs and common neurodegenerative disorders."

Provided by Cell Press