Tidying up: A new way to direct trash to autophagy

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Credit: AI-generated image (disclaimer)

Marie Kondo herself couldn't do it any better.

Usually cells are good at recognizing what doesn't spark joy. They're constantly cleaning house—picking through their own stuff to clear out what no longer works.

Damaged or superfluous organelles. Proteins that don't fold just so.

But what happens when the cell fails to recognize trash? Accumulation of defective cellular material has been implicated in disorders such as Huntington's disease, Alzheimer's, Parkinson's disease and Lou Gehrig's Disease/ALS, where this trash blocks neurons from transmitting signals.

Now, researchers at Washington University in St. Louis have uncovered a previously unknown structural feature of living cells that is critical to tidying up.

The research, led by Richard S. Marshall, research scientist, and Richard Vierstra, the George and Charmaine Mallinckrodt Professor of Biology in Arts & Sciences, is published in the April 4 issue of the journal *Cell*.

New receptors for taking out the trash

One major way that cells clean up their trash is through autophagy. In this process, cells engulf unwanted material in vesicles that are then deposited in a trash bin called the vacuole or lysosome. There, the trash is degraded and its building blocks reused.

Key to this recycling process are the receptors that recognize the trash and tether it to a protein called ATG8 that lines the engulfing vesicle. Previously, all of these receptors were thought to be related and bound to ATG8 via the same mechanism.

"There is the binding site on ATG8 that everyone knew about before, and how it interacts with autophagy receptors," Marshall said. "But we found that if you completely rotate the molecule 180 degrees, there is the new site on the opposite side that recognizes a long list of additional cargo receptors.

"A whole slew of proteins in plants, yeast and humans are using this new binding site and its suite of cognate receptors to interact with ATG8," he added.

To latch to this particular docking platform, the newly discovered cargo receptors use a binding site known as a ubiquitin-interacting motif, or UIM, previously not linked to autophagy.

"This is a completely different mechanism of interaction," Marshall said. "Its discovery represents an explosion in the number of potential ATG8-interacting proteins that could be controlling autophagy, all of which are using this new site."

Human health implications

Understanding how these new cargo receptors work could shed light on new preventive or therapeutic targets relevant to human disease.

Marshall and Vierstra also described a particular receptor in this new collection that helps trash a key protein called CDC48 or p97.

Proteotoxic stress occurs when faulty proteins build up, and cells can't get rid of them. CDC48 is part of this process, but even it can go bad. The faulty proteins and CDC48 tend to start forming tangled aggregates like those recognized in Alzheimer's and Parkinson's disease.

"CDC48 is an unfoldase, which means it grabs proteins, unfolds them and delivers them to proteases that will degrade them," Vierstra said. "Keeping your protein complement happy and functional requires CDC48. If it doesn't work, you have all kinds of problems, including clogged neurons."

Vierstra notes that CDC48 exists as a hexamer—a molecular complex

with six repeating units—and even one bad copy within the complex will send the whole thing to autophagic turnover.

"As they say, one bad apple seems to spoil the whole barrel," Vierstra said. "But in several neurological disorders, you only need one faulty CDC48 to go awry to have bad consequences—if you can't clean up its mess."

More information: Richard S. Marshall et al, ATG8-Binding UIM Proteins Define a New Class of Autophagy Adaptors and Receptors, *Cell* (2019). DOI: 10.1016/j.cell.2019.02.009

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