Learning how the brain takes out its trash may help decode neurological diseases

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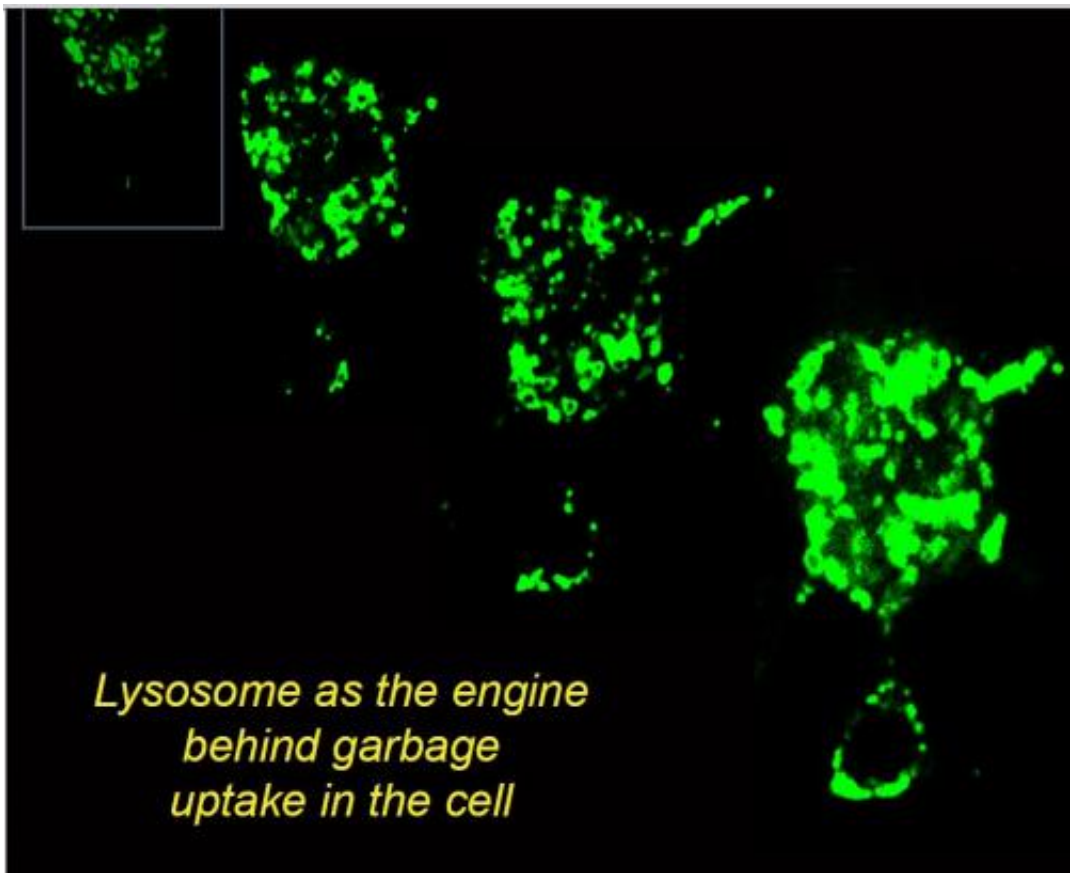

Credit: University of Michigan

Imagine that garbage haulers don't exist. Slowly, the trash accumulates in our offices, our homes, it clogs the streets and damages our cars, causes illness and renders normal life impossible.

Garbage in the brain, in the form of dead cells, must also be removed before it accumulates, because it can cause both rare and common neurological diseases, such as Parkinson's. Now, University of Michigan researchers are a leap closer to decoding the critical process of how the brain clears dead cells, said Haoxing Xu, associate professor in the U-M Department of Molecular, Cellular and Developmental Biology.

A new U-M study identified two critical components of this cell clearing process: an essential calcium channel protein, TRPML1, that helps the so-called garbage collecting cells, called microphages or microglia, to clear out the dead cells; and alipid molecule, which helps activate TRPML1 and the process that allows the microphages to remove these dead cells.

Moreover, the Xu lab identified a synthetic chemical compound that can activate TRPML1. Because this chemical compound ultimately helps activate this cell-clearing process, it provides a drug target that could help combat these neurological diseases.

"This is clearly a drug target," Xu said. "What this paper picks out is exactly what is going wrong in this process."

Scientists began by looking at a very rare neurodegenerative disease called Type IV Mucolipidosis, a childhood neurodegenerative disease characterized by multiple disabilities.

Xu's group found that lack of TRPML1 function, which is the channel through which calcium is released from the lysosome—the cell's recycling center—into the microphage cells, contributes to these neurodegenerative conditions. If this calcium channel doesn't work, calcium cannot be released, and dead cells aren't removed, Xu said. The synthetic chemical compound stimulates the TRPML1 calcium channel to release the calcium into the cell.

Further, dead cells "are bad for live cells," Xu said. An excess of dead cells leads the macrophage cells to also kill healthy neurons necessary for neurological function, which in turn can lead to these neurodegenerative diseases.

There are many neurodegenerative diseases, some very rare and some more common, such as Parkinson's and ALS. The common thread among them is the dearth of live and functioning neurons, which prevents the neurological system from carrying out normal functions, Xu said.

Thus, identifying a lipid molecule and also chemical compounds that stimulates proper function of the TRMPL1 function could revolutionize the treatment of these neurodegenerative diseases.

The next step in Xu's research is to test how these general observations are helpful to the neurological diseases and whether the compound is effective in animal models of neurological diseases.

The paper, "A TRP channel in the lysosome regulates large particle phagocytosis via focal exocytosis," appears Aug. 29 online in *Developmental Cell*.

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