

Researchers identify potential new drug for neurodegenerative disease

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Scientists have discovered a small molecule that helps human cells get rid of the misfolded, disfigured proteins implicated in Alzheimer's disease and other neurodegenerative ailments. This potential drug could have applications for other conditions as well.

Cells create and discard proteins continuously, a process that relies on a balance between the speed with which new proteins are created and damaged ones destroyed. Protein destruction occurs through a sophisticated system that marks proteins for disposal by tagging them with a small molecule called ubiquitin. Ubiquitin latches onto these proteins, often forming long chains. The cell's protein waste-disposal system, the proteasome, recognizes these ubiquitinated proteins and breaks them down.

If that finely tuned system malfunctions, damaged or misfolded proteins begin to accumulate in the cell and may become toxic. A number of ailments, including Parkinson¹s, Creutzfeldt Jakob and Alzheimer's have been linked to this build up of misfolded proteins.

To better understand just what causes this malfunction, a research team led by Harvard Medical School researchers Daniel Finley, professor of cell biology, and Randall King, associate professor of cell biology, zeroed in on an enzyme called Usp14. They found that, when activated, Usp14 disassembles the ubiquitin chain, slowing down the proteasome's ability to rid the cell of bad proteins. As a result, the cell makes new proteins faster than it rids itself of the old ones, leading to a build-up of



misfolded proteins.

The researchers wanted to see if they could find a molecule that inhibited Usp14, thus allowing the proteosome to work effectively. To identify such a selective inhibitor, Byung-Hoon Lee, a postdoctoral researcher, developed a special screening assay with assistance from the Institute of Chemistry and Cell Biology-Longwood Screening Facility at HMS. Lee screened 63,000 compounds, looking for molecules that inhibited only Usp14 and could easily infiltrate the cell. The strongest candidate was a small molecule they named IU1.

Experimenting in both human and mouse cell cultures, Min Jae Lee, also a postdoctoral researcher, and his coworkers found that IU1 inhibited Usp14 and allowed the proteasome to dispose of proteins more quickly. In other words, adding IU1 to cells boosted proteasome activity.

Though scientists are still investigating just how IU1 works, it appears that the molecule suppresses Usp14's ability to trim the ubiquitin chain.

In addition to discovering IU1, this research has also shed light on an aspect of proteasome function that was not previously understood, King says. Scientists had thought that the proteasome was not involved in regulating the speed of protein degradation, but that other proteins work with ubiquitin to modulate the process. "Our work suggests that there is another level of control where the rate at which the proteasome can degrade these ubiquinated proteins is also controlled," King says. "It looks like there are multiple control steps along the way in this pathway."

As scientists learn more about the link between misfolded proteins and human disease, interest in the proteasome has increased. While much of that focus has been on ways to inhibit proteasome function, there may be an advantage to developing a drug that boosts proteasome activity rather than hinders it, Finley speculates.



"If you take a typical cell growing in culture and kill its Usp14 activity, the cell will continue to thrive," he says. "If you kill its proteasome activity, it would immediately die."

This research could have far-reaching implications for the development of drugs to treat not only neurodegenerative diseases, but also other illnesses that have been linked to an accumulation of misfolded proteins, King says.

For example, when a cell suffers oxidative damage<say from a stroke or heart attack<proteins may fold improperly and be marked for degradation by the ubiquitin system. If the proteasome becomes overwhelmed, misfolded proteins could accumulate in the cell, triggering a cascade of problems. In this latest study, researchers induced protein oxidation in cells and then treated them with IU1, which resulted in rapid elimination of the oxidized proteins. At the same time, the ability of cells to survive oxidative insult was enhanced.

More information: Enhancement of Proteasome Activity by a Small-Molecule Inhibitor of Usp14, *Nature*, Volume 467, issue 7312, pp 179-184

Provided by Harvard Medical School

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