Are stressed-out brain cells the root cause of neurodegenerative disease?

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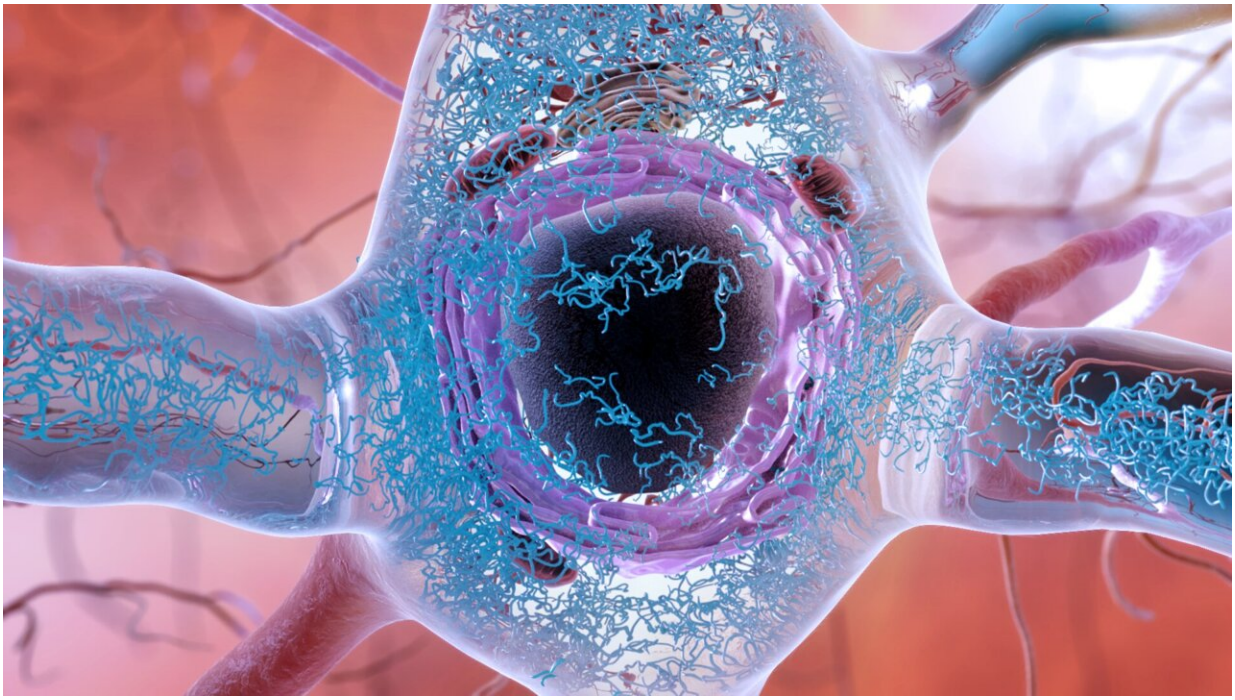

An illustration of a brain cell in a person with Alzheimer's disease, showing the accumulation and clumping of tau proteins (blue squiggles) in the cytoplasm of a brain cell. Protein clumps, also known as aggregates, are thought to lead to cell death and dementia. New research suggests that such clumps may not cause brain cell death directly, but rather throw the cell's response to stress off balance so that it never gets switched off. Credit: National Institute on Aging, National Institutes of Health

Many neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, are characterized by the accumulation of protein clumps, or aggregates, in the brain, which has led scientists to assume that the protein tangles kill brain cells. The search for treatments that break up and remove these tangled proteins has had little success, however.

However, a new discovery by the University of California, Berkeley, researchers suggest that the accumulation of aggregated proteins isn't what kills brain cells. Rather, it's the body's failure to turn off these cells' stress response.

In a study published online Jan. 31 in the journal *Nature*, the researchers reported that delivering a drug that forces the stress response to shut down saves cells that mimic a type of neurodegenerative disease known as early-onset dementia.

According to lead researcher Michael Rapé, the finding could offer clinicians another option for treatment for some neurodegenerative diseases, at least for those caused by mutations in the protein that switches off the cellular stress response. These include inherited diseases that lead to ataxia, or loss of muscle control, and early-onset dementia.

In addition, Rapé noted that other neurodegenerative diseases, including Mohr-Tranebjærg syndrome, childhood ataxia, and Leigh syndrome, are also characterized by stress responses in overdrive and have symptoms similar to those of the early onset dementia mimicked in the new study.

"We always thought that protein clumps directly kill neurons, for example, by puncturing membrane structures within these cells. Yet, we now found that aggregates prevent the silencing of a stress response that cells originally mount to cope with bad proteins. The stress response is always on, and that's what kills the cells," said Rapé, head of the new division of molecular therapeutics in UC Berkeley's Department of

Molecular and Cell Biology and a Howard Hughes Medical Institute investigator.

"We think that the same mechanisms may underlie more common pathologies that also show widespread aggregation, such as Alzheimer's disease or frontotemporal dementia, but more work is needed to investigate the role of stress signaling in these diseases."

Key to the discoveries by Rapé's lab was the researchers' finding that stress responses need to be turned off once a brain cell has successfully addressed a difficult situation. Rapé explained this finding to his son in simple terms: You not only need to clean up your room, but also turn out the light before going to bed. If you don't turn off the light, you can't fall asleep, but if you turn it off before you clean up your room, you will stumble if you have to get up in the dark.

Similarly, a cell has to clean up protein aggregates before turning off the stress response. If it doesn't turn off the stress response, the cell will ultimately die.

"Aggregates don't kill cells directly. They kill cells because they keep the light on," he said. "But that means that you can treat these diseases, or at least the dozen or so neurodegenerative diseases that we found have kept their stress responses on. You treat them with an inhibitor that turns off the light. You don't have to worry about completely getting rid of large aggregates, which changes how we think about treating neurodegenerative diseases. And most importantly, it makes this really doable."

In their paper, Rapé and his colleagues describe a very large protein complex they discovered called SIFI (SIlencing Factor of the Integrated stress response). This machine serves two purposes: It cleans up aggregates and, afterward, turns off the stress response triggered by the

aggregated proteins.

The stress response controlled by SIFI is switched on to deal with specific intracellular problems—the abnormal accumulation of proteins that end up at the wrong location in the cell. If components of SIFI are mutated, the cell will accumulate protein clumps and experience an active stress response. But it is the stress response signaling that kills the cells.

"The SIFI complex would normally clear out the aggregating proteins. When there are aggregates around, SIFI is diverted from the stress response, and the signaling continues. When aggregates have been cleared—the room has been cleaned up before bedtime—then the SIFI is not diverted away anymore, and it can turn off the stress response," he said. "Aggregates kind of hijack that natural stress response-silencing mechanism, interfere with it, stall it. And so that's why silencing never happens when you have aggregates, and that's why cells die."

A future treatment, Rapé said, would likely involve the administration of a drug to turn off the stress response and a drug to keep SIFI turned on to clean up the aggregate mess.

Ubiquitin

Rapé, who is also the Dr. K. Peter Hirth Chair of Cancer Biology, studies the role of ubiquitin—a ubiquitous protein in the body that targets proteins for degradation—in regulating normal and disease processes in humans. In 2017, he discovered that a protein called UBR4 assembles a specific ubiquitin signal that was required for the elimination of proteins that tend to aggregate inside cells.

Only later did other researchers find that mutations in UBR4 are found in some inherited types of neurodegeneration. This discovery led Rapé to

team up with colleagues at Stanford University to find out how UBR4 causes these diseases.

"This was a unique opportunity: We had an enzyme that makes an anti-aggregation signal, and when it's mutated, it causes aggregation disease," he said. "You put these two things together, and you can say, 'If you figure out how this UBR4 allows sustained cell survival, that probably tells you how aggregates kill cells.'"

They found that UBR4 is actually part of a much larger protein complex, which Rapé dubbed SIFI, and they found that this SIFI machinery was needed when a cell couldn't sort proteins into its mitochondria. Such proteins that end up at the wrong location in cells tend to clump and, in turn, cause neurodegeneration.

"Surprisingly, though, we found that the core substrates of the SIFI complex were two proteins, one of which senses when proteins don't make it into mitochondria. That protein detects that something is wrong, and it then activates a kinase that shuts down most of the new protein synthesis as part of a stress response, giving the cell time to correct its problem with bringing proteins to the right location," he said.

This kinase is also degraded through SIFI. A kinase is an enzyme that adds a phosphate group to another molecule, in this case, a protein, to regulate important activities in the cell. By helping degrade these two proteins, the SIFI complex turns off the stress response that is caused by clumpy proteins accumulating at the wrong location.

"That's the very first time that we've seen a stress response turned off in an active manner by an enzyme—SIFI—that happens to be mutated in neurodegeneration," Rapé said.

While investigating how SIFI can turn off the stress response at the right

time—only after the room had been cleaned up—the researchers found that SIFI recognizes a short protein segment that acts as a kind of ZIP code that allows proteins or protein precursors to get into the mitochondria, where they are processed. When they are prevented from getting in, they accumulate in the cytoplasm, but SIFI homes in on that ZIP code to eliminate them. The ZIP code looks just like the light switch.

"When you have aggregates accumulating in the cytoplasm, now the ZIP code is still in the cytoplasm, and there's a lot of it there," he said.

"And it's the same signal as you would have in the proteins that you want to turn off. So it basically diverts the SIFI complex from the light switch back to the mess. SIFI tries to clean up the mess first, and it cannot turn off the light. And so when you have an aggregate in the cell, the light is always on. And if the light is always on, if stress signaling is always on, the cell will die. And that's a problem."

Rapé suspects that many intracellular protein aggregates characteristic of neurodegenerative diseases have similar consequences and may prevent the cell from switching off the stress response. If so, the fact that a drug can turn off the response and rescue brain cells bodes well for the development of treatments for potentially many neurodegenerative diseases.

Already, another stress response inhibitor, a drug called ISRIB discovered at UCSF in 2013, has been shown to improve memory in mice and reduce age-related cognitive decline.

"That means there is the prospect that by manipulating stress silencing, by turning off the light with chemicals, you might target other neurodegenerative diseases, as well," he said. "At the very least, it's another way we could help patients with these diseases. In the best

possible way, I think it will change how we treat neurodegenerative diseases. That's why this is a really important story, why I think it's very exciting."

Rapé, already a co-founder of two startups, Nurix Therapeutics Inc., and Lyterian Therapeutics, is now looking to develop therapies to silence the stress response while maintaining the cell's cleanup of protein aggregates.

More information: Diane L. Haakonsen et al, Stress response silencing by an E3 ligase mutated in neurodegeneration, *Nature* (2024). DOI: 10.1038/s41586-023-06985-7

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