Researchers identify new mechanism to aid cells under stress

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A team of biologists from NYU and Harvard has identified new details in a cellular mechanism that serves as a defense against stress. The findings potentially offer insights into tumor progression and neurodegenerative diseases, such as Parkinson's and Alzheimer's—the cell's inability to respond to stress is a major cause of these diseases.

"Our findings point to a previously unknown role for a widely known protein modification in the defense of a cell," explains Christine Vogel, an assistant professor in NYU's Department of Biology and the study's senior author. "Such modifications can change the protein structure or convey signals in the cell. Here, we found that an unusual type of this modification can help spur protein synthesis, an essential cellular process, in response to an attack. Keeping protein synthesis up and running is vital for the cell to survive."

The research, which appears in the journal *Nature Structural & Molecular Biology*, focuses on a particular type of attack on cells—oxidative stress, which occurs when we are exposed to harmful conditions, such as industrial pollution, cigarette smoke, solar radiation, or radiotherapy. Such incidents damage important components in our cells and hence trigger a highly complex defense response in our cells.

In combatting oxidative stress, damaged proteins that do not function as they once had are removed from our cells using the degradation machinery - and the removal is signaled by a protein modification called ubiquitination, which occurs in virtually all of an organism's cells.

However, while the degradation of proteins upon ubiquitination is well understood, the other roles of this modification are much less clear.

In the newly published study, the researchers found an entirely novel function for ubiquitination, which is completely independent of its role in signaling degradation: it appears to modify and stabilize the function of ribosomes, which are the engines behind protein synthesis.

In their study, the researchers focused on the work of a particular type of ubiquitin chain, called K63, whose role is much less known than that of other ubiquitin chains involved in degradation. The researchers used yeast to study this K63 modification—an extremely useful model organism to work with. But, perhaps more significantly, they also discovered that the new mechanism is also present in mouse neurons, which demonstrates its functionality in mammals and therefore relevance to human health.

To help verify their findings, the scientists prevented yeast to build K63 ubiquitin chains and found that without K63, protein production is hugely diminished, rendering cells highly sensitive to stress.

The researchers observe that the findings offer a pathway for better understanding of the nature of neurodegenerative diseases, and - in the far future - even means of treatment. The researchers can draw this conclusion because oxidative stress and an inability to keep producing new proteins significantly diminish the proper functioning of the body's neurons. Subsequent studies in this area, they note, may now be guided by more detailed knowledge of how a cell responds to stress and, as a result, can better isolate the causes of neuronal malfunctioning.

More information: K63 polyubiquitination is a new modulator of the oxidative stress response, DOI: 10.1038/nsmb.2955

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