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Scientists discover a key pathway that protects cells against death by stress

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When it comes to protecting cells from death brought on by the calamities of environmental stress, the human body is particularly ingenious. From cellular components that suck up misfolded proteins to a vigilant immune system, the ways we protect our cells (and ourselves) are many and mysterious.

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have now uncovered the workings of another cell-protection device, one that may play a major role in a number of age-related diseases, including diabetes and Parkinson's, Alzheimer's and Huntington's diseases.

The study, led by Srinivasa Subramaniam, a TSRI assistant professor, and Solomon H. Snyder, a neuroscience professor at Johns Hopkins University School of Medicine, was published February 5 in the journal *Cell Reports*.

More or Less Acceleration

The study focuses on a new pathway through which Rheb, a regulator that many believe is active in the brain's ability to change in response to learning, actually plays two roles, rather than one—stimulating and inhibiting protein synthesis.

The interplay between the two roles may be the key that enables cells to

alter protein synthesis and protect the cell in response to varying environmental stresses.

"We found Rheb acts like the gas pedal in a car," Subramaniam said. "It can either increase translation or decrease it. And because translation is a fundamental process that is affected in a lot of diseases, we now think that Rheb may act like a switch in some disease states—helping to turn them off and on."

Rheb is known to bind and activate mTOR, a developmentally important gene that integrates signals from multiple pathways and regulates critical cell functions such as protein synthesis. Besides its role as an activator of mTOR, which plays a major role in conditions from diabetes to neurodegenerative disease, the mTOR-independent role of Rheb is less known. The new study defines crucial mTOR-independent effects of Rheb. Results showed that, when stressed, Rheb instead inhibits protein synthesis by amplifying the phosphorylation (adding a phosphate group to a protein to alter its function) of another protein known eIF2α. As a result, cell resources can be conserved rather than squandered when the environment is challenging.

"We don't really understand the full role of the Rheb-mTOR pathway, but we have uncovered a new fundamental process of Rheb that is independent of mTOR and very intriguing," said Neelam Shahani, a member of Subramaniam's lab who was co-first author of the study with Richa Tyagi of Johns Hopkins University School of Medicine. "Rheb can inhibit protein synthesis, and we know that protein misfolding via environmental stress factors is present in a lot of diseases."

Subramaniam noted that, intriguingly, an earlier study had suggested the Rheb pathway had been implicated in Alzheimer's disease. "We also want to look at Rheb's role in other neurodegenerative diseases," he said.

Provided by The Scripps Research Institute