Cellular stress can induce yeast to promote prion formation

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It's a chicken and egg question. Where do the infectious protein particles called prions come from? Essentially clumps of misfolded proteins, prions cause neurodegenerative disorders, such as mad cow/Creutzfeld-Jakob disease, in humans and animals. Prions trigger the misfolding and aggregation of their properly folded protein counterparts, but they usually need some kind of "seed" to get started.

Biochemists at Emory University School of Medicine have identified a yeast protein called Lsb2 that can promote spontaneous prion formation. This unstable, short-lived protein is strongly induced by cellular stresses such as heat. Lsb2's properties also illustrate how cells have developed ways to control and regulate prion formation. Research in yeast has shown that sometimes, prions can actually help cells adapt to different conditions.

The results are published in the July 22 issue of the journal *Molecular Cell*. The senior author is Keith Wilkinson, PhD, professor of biochemistry at Emory University School of Medicine The first author is senior associate Tatiana Chernova, PhD.

The aggregated form of proteins connected with several other neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's can, in some circumstances, act like prions. So the Emory team's finding provides insight into how the ways that cells deal with stress might lead to poisonous protein aggregation in human diseases.

"A direct human homolog of Lsb2 doesn't exist, but there may be a protein that performs the same function," Wilkinson says. "The mechanism may say more about other types of protein aggregates than about classical prions in humans, This mechanism of seeding and growth may be more important for aggregate formation in diseases such as Huntington's."

Lsb2 does not appear to form stable prions by itself. Rather, it seems to bind to and encourage the aggregation of another protein, Sup35, which does form prions.

"Our model is that stress induces high levels of Lsb2, which allows the accumulation of misfolded prion proteins," Wilkinson says. "Lsb2 protects enough of these newborn prion particles from the quality control machinery for a few of them to get out."

More information: T.A. Chernova et al. Prion Induction by the Short-lived Stress Induced Protein Lsb2 Is Regulated by Ubiquitination and Association with the Actin Cytoskeleton Mol. *Cell* (2011).

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