Medical Xpress

Protective prion keeps yeast cells from going it alone

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Most commonly associated with such maladies as "mad cow disease" and Creutzfeldt-Jakob disease, prions are increasingly recognized for their ability to induce potentially beneficial traits in a variety of organisms, yeast chief among them.

Now a team of scientists has added markedly to the job description of prions as agents of change, identifying a prion capable of triggering a transition in yeast from its conventional single-celled form to a cooperative, multicellular structure. This change, which appears to improve yeast's chances for survival in the face of hostile environmental conditions, is an epigenetic phenomenon—a heritable alteration brought about without any change to the organism's underlying genome.

This latest finding, reported in the March 28 issue of the journal *Cell*, has its origins in work begun several years ago in the lab of Whitehead Institute Member Susan Lindquist. In 2009, Randal Halfmann, then a graduate student in Lindquist's lab, identified dozens of proteins in yeast that have the ability to form prions. That research greatly expanded the known universe of prion elements in yeast, but it failed to answer a key question: What function, if any, do these prions actually have?

In search of an answer, Halfmann, now a fellow the University of Texas Southwestern Medical Center, and colleagues in the Lindquist lab attempted to exploit the fact that several of the prion-forming proteins they had identified acted to modify transcription of yeast genes. It stood to reason that if they could identify which genes were being regulated,

they might be able to determine the prions' function.

"We looked at the five transcriptional regulators that are known to be prions in yeast, and we found that in fact, only one gene in the entire yeast genome was regulated by all five transcription factors," says Halfmann.

That gene, as it turns out, was FLO11, a key player in multicellularity in yeast. Indeed changes in FLO11 expression have been shown to act as a toggle, switching yeast from spherical to filamentous form. Halfmann notes that FLO11, which has been shown to be regulated by epigenetic elements, is also highly responsive to environmental stress. Knowing that the prion form of a protein is essentially a misfolded form of that protein, and that stressful conditions increase the frequency of protein misfolding and prion formation, the scientists began to consider the possibility that the prions themselves might be among the epigenetic switches influencing the activity of FLO11.

The group focused on one transcription factor known as mot3, finding that yeast cells containing the prion form of this factor, [MOT3+], acquired a variety of multicellular growth forms known to require FLO11 expression. This was a clear indication that prion formation was causing the differentiation of the cells and their subsequent cooperation. But what about the stress aspect of the hypothesis?

By testing yeast cells against a variety of stressors, the scientists discovered that exposure to a concentration of ethanol akin to that occurring naturally during fermentation increased [MOT3+] formation by a factor of 10.They also found that as the cells exposed to ethanol shifted their metabolism to burn surrounding oxygen through respiration, the prions reverted to their non-prion conformation, [mot3-], and the yeast returned to the unicellular state. In essence, prion formation drove a shift to multicellularity, helping the yeast to ride out the ethanol storm.

"What we have in the end is two sequential environmental changes that are turning on a heritable epigenetic element and then turning it off," says Halfmann. "And between those two changes, the prion is causing the cells to acquire a multicellular growth form that we think is actually important for their survival."

Lindquist, who is also a Howard Hughes Medical Institute investigator, has long argued that prions have played a vital role in yeast evolution and has amassed a body of strong supporting evidence.

"We see them as part of a bet-hedging strategy that allows the yeast to alter their biological properties quickly when their environments turn unfavorable," Lindquist says. She also theorizes that prions may play such roles beyond yeast, and her lab intends to take similar approaches in the hunt for prions and prion-like mechanisms that are potentially beneficial in other organisms.

For Lindquist lab postdoctoral scientist Alex Lancaster, who is also an author of the new *Cell* paper, these latest findings hint at a potentially novel approach to understanding basic mechanisms underlying the complexities of human diseases, including cancer, whose hallmarks include protein misfolding, epigenetic alterations, metabolic aberrations, and myriad changes in cell state, type, and function. Lancaster likens the opportunity to that of opening a black box.

"It's exciting to think that this could become another tool in the toolbox in the study of multicellularity," Lancaster says. "We know that some tumors are a heterogeneous population of cells and we know that tumor cells can evolve within in their environments to help ensure their own survival. This system could help us further understand the role of epigenetic inheritance within tumors and how it might be influencing cell-cell interactions and even affecting the effectiveness of drug therapies."

More information: "Heritable Remodeling of Yeast Multicellularity by an Environmentally Responsive Prion" *Cell*, March 28, 2013

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