Volume 93 Issue 37 | p. 7 | News of The Week
Issue Date: September 21, 2015

Study Paints New Portrait Of Cell's Response To Stress

Cell Biology: Protein aggregates formed during heat shock aren't necessarily a death sentence

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Department: Science & Technology
News Channels: Biological SCENE
Keywords: protein aggregation, heat shock, stress response

The textbook picture of what happens to proteins in cells stressed by heat might need to be redrawn, according to a new study (*Cell* 2015, DOI: 10.1016/j.cell.2015.08.041).

The conventional understanding is that misfolded and otherwise damaged proteins aggregate in response to heat shock. Those aggregated proteins need to be fixed or, if they can't be fixed, degraded and disposed of.

But D. Allan Drummond of the University of Chicago and coworkers found that the aggregates are reversible and certain proteins maintain their activity while aggregated. "When we looked at recovery from severe heat shock, we found essentially all aggregates are disassembled back into their components without degradation," Drummond says. "No matter how severely they've clumped up, proteins emerge intact during recovery."

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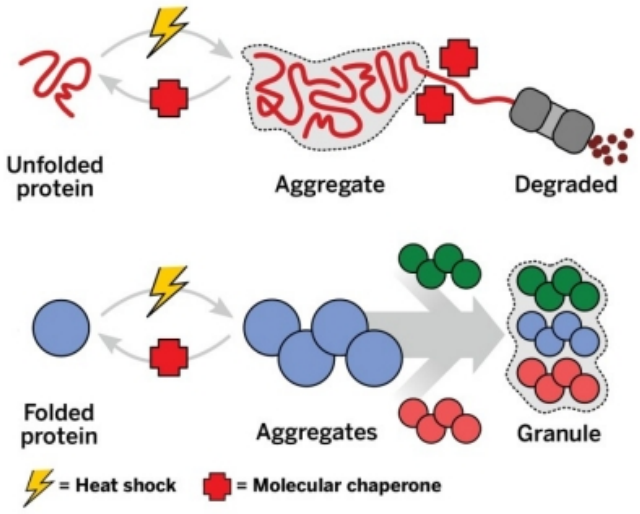

FATE FROM FOLDING
Newly synthesized, unfolded proteins (top row) and mature, folded proteins (bottom row) respond differently to heat shock. Unfolded proteins form aggregates that can be reversed by molecular chaperones but are often degraded. Folded proteins form reversible aggregates that collect into granules. During recovery, chaperones help the aggregate disassemble into functioning proteins.
Credit: Allan Drummond

The traditional heat-shock picture comes from work that focused on the molecular chaperones that guide the repair of aggregating proteins. Drummond and colleagues instead studied the aggregating proteins themselves to arrive at this new picture.

The researchers studied the heat-shock response in yeast cells. Their isotope labeling strategy enabled them to distinguish between proteins that were mature and ones that had been newly synthesized at the time of heat shock. They separated aggregating proteins from soluble proteins by ultracentrifugation and identified them using high-resolution mass spectrometry.

They were able to detect nearly 1,000 proteins, about 180 of which formed aggregates.

The researchers also used fluorescence microscopy to visualize the heat-triggered formation of protein-containing granules in cells, which are the result of protein aggregation.

Drummond thinks that the conventional heat-shock model will still hold true for some proteins. Newly synthesized proteins "are very threatened by heat because their folding process is truly disrupted," he says.

The work "has major implications for how we think about protein homeostasis and quality control," says Kevin A. Morano, a microbiologist at the University of Texas Medical School, in Houston, who studies stress responses in yeast. "We can no longer assume that all aggregates detected via proteomics or fluorescence or electron microscopy are indicators of protein damage." Instead, he says, these aggregates could be a way the cell protects proteins from damage.

Justin L. P. Benesch, a biophysical chemist at the University of Oxford who studies heat-shock proteins, says: “This work makes clear that the dogma of cellular aggregates being potentially dangerous protein scrap-heaps is far too simplistic. We have much to learn about the cell’s response to stress.”

Chemical & Engineering News
ISSN 0009-2347

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