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Quality control in the nucleus

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Researchers have discovered the first protein quality control system in the yeast nucleus. They report in *Cell* this week that the system involves a ubiquitin-protein ligase that specifically targets four distinct mutant nuclear proteins for destruction by the proteosome.

Protein quality control systems, which fix or rid the cell of unfolded, misfolded, or improperly modified proteins, have long been known to exist both in prokaryotes and eukaryotes. But they have been found only in compartments where protein synthesis occurs: the cytoplasm, the endoplasmic reticulum, and the mitochondria, senior author Dan Gottschling, of Seattle's Fred Hutchinson Cancer Research Center, told *The Scientist*.

"It largely has been thought that as proteins are being made, they're being sampled and destroyed right during the process of folding and assembly," said Gottschling. "We wanted to find a place where proteins that become old could be recognized and degraded, and the nucleus is the only compartment in which that could potentially happen, because there's no protein synthesis there."

The team conducted what they called a "virtual genetic screen." It means that we didn't do anything except read the literature," joked Gottschling.

Their approach was a rather smart one, according to Christian Hirsch of the Max-Delbrück Center for Molecular Medicine, who coauthored a related preview in the same issue of *Cell*. "They looked at screens that had found suppressors of temperature-sensitive mutant proteins that are functional in the cell, but that are degraded because they are recognized by a quality control system," Hirsch told *The Scientist*. Those results pointed to a gene that was an excellent candidate for a component of a degradation system of misfolded proteins.

"First we looked for nuclear proteins in yeast that were temperature sensitive," said Gottschling. "Then we looked at the subset in which there had been a suppressor screened, and we looked for a common gene that was a suppressor of all these different temperature-sensitive mutations. We found one gene, and that was SAN1, which turned out to be a ubiquitin-ligase." The team later discovered that San1 only targets aberrant proteins - not wildtype ones - and that it only functions in the nucleus.

"The mechanisms by which the cell recognizes misfolded proteins and destroys them are poorly understood because there are not a lot of actual molecules yet attributed to them," said Randy Hampton of the University of California, San Diego, who did not participate in the research. "What's incredibly interesting and useful about this work is that it provides another concrete example of a molecular device that the cell somehow uses to recognize misfolded proteins. You need to know the components before understanding the mechanisms. That's why this is a breakthrough."

The team has not yet figured out how San1 specifically recognizes aberrant proteins - or what exactly aberrant proteins are - but came up with a few interesting results. "When San1 is not functional, the yeast shows a stress response," Gottschling said. "This means that San1 was dealing with proteins that become aberrant in the normal life cycle of the cell so, when San1 is not doing its job, those proteins build up and tell the cell that something is wrong in the nucleus. We think that there's a sensor specific for the nucleus that sends out a signal. No one has seen this before."

"It would be interesting to know if a similar system exists in mammalian cells," Hirsch said. "If that is the case, it could be extremely important." The importance lies in the fact that many aging-related diseasessuch as Alzheimer, Huntington, and Parkinson, in which proteins start to aggregate in the nucleus, are linked to defects in protein quality control.

"We are wondering if analogous pathways exist in mammals," said Gottschling. "We are starting to look for that."

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