Mechanism underlying cell stress response discovered

November 13 2015, by Krishna Ramanujan

When cells are under stress, proteins misfold. And when not properly handled, misfolded proteins can build-up in the cell, leading to cell death and disease.

Until now, no one has fully understood how cells regulate an appropriate response to the build-up of misfolded proteins. For optimal function, cells must maintain the right balance of fixing and clearing out misfolded proteins, but without taxing the system by responding when the number of damaged proteins is low.

New Cornell research published online Nov. 9 in *Nature Cell Biology* describes a system that controls levels of a cell's sensors, called IRE1α, which are responsible for sensing the accumulation of misfolded proteins.

IRE1α is ubiquitous in almost every cell type and is known to trigger the action of a complex named the endoplasmic reticulum-associated degradation (ERAD), to fix or degrade misfolded proteins before they accumulate.

In the study, the researchers discovered that the ERAD complex actually controls the level of the IRE1α sensor so it doesn't trigger a major response during normal or low levels of cell stress and protein misfolding.

"We showed that the ERAD complex can recognize the sensor and put it

in the trash when there is low level of activation or under basal conditions," said Ling Qi, associate professor of nutritional sciences and the paper's senior author.

Shengyi (Iris) Sun and Guojun Shi, both postdoctoral associates in the Qi lab, are co-lead authors of the paper.

"Cells can't have too much of an IRE1α response, because that actually can lead to cell death, so they need just the right response," Shi added.

The researchers discovered that in the event of high levels of cellular stress, when misfolded proteins are accumulating, an intermediary protein called BiP uncouples the IRE1α sensor from ERAD's control. Then, the IRE1α sensor can accumulate and generate a response to call the ERAD complex to clear out misfolded proteins, like a fire truck rushing to put out a big fire.

When the researchers disabled the ERAD complex in gut lining cells in mice, those mice developed colitis with an overt activation of the sensor IRE1α, a result that opens the door for more research and better treatment.

"If the sensor protein level is too high, it triggers an unwanted alarm, like a tiny fire getting a big response. This check-and-balance mechanism seems to be essential in gut lining in the development of colitis," Sun said.

Future research will look at how ERAD recognizes and trashes the IRE1α sensor and other proteins; how the mechanism relates to colitis, and how this discovery might lead to possible treatments; and how problems with ERAD defects may lead to other diseases in other types of cells.

More information: IRE1α is an endogenous substrate of endoplasmic-reticulum-associated degradation, DOI: 10.1038/ncb3266

Provided by Cornell University