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Control Switch That Modulates Cell Stress Response May Be Key to Multiple Diseases

Researchers at the University of California, San Diego School of Medicine have discovered a control switch for the unfolded protein response (UPR), a cellular stress relief mechanism drawing major scientific interest because of its role in cancer, diabetes, inflammatory disorders and several neural degenerative disorders, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), otherwise known as Lou Gehrig's disease.

The normal function of the UPR pathway is to protect cells from stress but it can also trigger their death if the stress is not resolved. The researchers' discovery of a control switch that acts on the UPR pathway, published March 25 in the online edition of *EMBO Reports*, opens new drug development avenues for treating a wide variety of diseases by modulating the UPR pathway to prevent excessive cell death.

"Our paper reports that two highly conserved pathways – the UPR and the nonsense-mediated RNA decay pathway – intersect with each other at a pivotal point in cell stress," said Miles Wilkinson, PhD, senior author and professor in the Department of Reproductive Medicine and a member of the UC San Diego Institute for Genomic Medicine. "In essence, we've shown that the nonsense-mediated RNA decay pathway, typically referred to as 'NMD,' keeps the UPR in check to avoid the potentially dangerous consequences if the UPR pathway were allowed to mount an inadvertent response to innocuous stress."

In cells, like people, too much stress can cause bad things to happen. In the case of cells, one such bad consequence is the accumulation of unfolded or misfolded proteins in the endoplasmic reticulum (ER), the cell's protein-making factory. To carry out their many biological functions, proteins must be precisely folded in the correct shape. The body's answer to excessive cell stress and accompanying misshapen proteins is the unfolded protein response. The UPR kicks in and restores normal ER-folding capacity by adjusting certain cellular processes. If this fails, the UPR instructs the cell to self-destruct, a process known as programmed cell death or apoptosis.

Wilkinson describes the UPR pathway as a double-edged sword. “In a large number of diseases, ranging from cancer to ALS, major stress occurs in the affected cells, leading the UPR pathway to be triggered,” he said. “And that’s meant to be helpful. But if the stress isn’t relieved in a timely fashion, it triggers cell death. A limited amount of cell death is normal, but if too many cells die, especially critical cells, then it’s a problem. Chronic UPR activation and excessive cell death has been implicated in brain disorders like Alzheimer’s and Parkinson’s disease.”

In their study, Wilkinson, with first author Rachid Karam, PhD, and colleagues found that the NMD pathway plays a critical role in shaping the activities of UPR. Specifically, they discovered that NMD prevents inappropriate activation of the UPR and also promotes its timely termination to protect cells from prolonged ER stress. “Because of the important role of UPR in regulating cell life/death decisions, it is critical that mechanisms are in place to prevent unnecessary UPR activation in response to innocuous or low-level stimuli,” said Wilkinson. “In this report we demonstrate that the NMD pathway serves in this capacity by raising the threshold for triggering UPR and also promoting its shut off at the appropriate time.”

He added that NMD doesn’t deter the UPR if an important stress comes along where more action is needed. “Although NMD normally represses the UPR, our paper and previous work have shown that it gets out of the way if there’s a real problem,” Wilkinson noted.

Previous studies from the Wilkinson group and others have established that NMD has two broad roles. First, it is a quality control mechanism used by cells to eliminate faulty messenger RNA (mRNA) – molecules that are essential for transcribing genetic information into the construction of proteins critical for life. Second, NMD degrades a specific group of normal mRNAs.

The latest study shows that NMD suppresses inappropriate UPR activities by driving the rapid decay of several normal mRNAs encoding proteins critical for the UPR. “We demonstrate that NMD directly targets the mRNAs encoding several UPR components, including the highly conserved UPR sensor, IRE1-alpha, whose NMD-dependent degradation partly underpins this process,” said Wilkinson. “Our work not only sheds light on UPR regulation, but demonstrates the physiological relevance of NMD’s ability to regulate normal mRNAs.”

Co-authors include Chih-Hong Lou, Heike Kroeger, Jonathan H. Lin, all at UC San Diego; Lulu Huang, formerly of UC San Diego and now at ISIS Pharmaceuticals.

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