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Effects of different concentrations of opium on the secretion of IL-6, IFN-γ and TGF-β cytokines from jurkat cells

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The accumulation of misfolded proteins in the endoplasmic reticulum (ER) activates a set of adaptive signaling pathways called the unfolded protein response (UPR). The tripartite UPR consists of IRE1-mediated unconventional splicing of XBP1 mRNA, processing of ATF6α to produce a soluble transcriptional activator, and PERK-mediated phosphorylation of eukaryotic translation initiation factor 2 (eIF2α). If protein misfolding is not resolved, cells activate apoptosis, although the mechanism is unknown. To identify signals required for the apoptotic response we have studied the folding and secretion of proteins that fold efficiently or that are subject to misfolding. The findings demonstrate that phosphorylation of eIF2α leads to translation of ATF4 mRNA that subsequently activates transcription of C/EBP homologous protein (CHOP). We show ATF4/CHOP are required to function together to induce genes encoding the translational apparatus and stimulate protein synthesis. The increase in protein synthesis is required to cause oxidative stress, deplete ATP and induce apoptosis. In addition, in response to protein misfolding in the ER, Ca^{2+} leak from the ER causes mitochondrial damage, ATP depletion and superoxide production. Genetic or pharmacological interventions that prevent Ca^{2+} trafficking, increase ATP production or reduce the accumulation of reactive oxygen species (ROS) improve protein folding in the ER and promote cell survival. The findings uncover a feed-forward loop that involves ER protein misfolding, Ca^{2+} leak from ER and uptake into mitochondria, mitochondrial damage, ATP depletion, ROS production and further protein misfolding. The studies identify therapeutic approaches to prevent cell death in response to protein misfolding in the ER.

Biography

Randal J Kaufman received his Ph.D. from Stanford University in 1979 and performed postdoctoral work at MIT. He was a founding scientist at Genetics Institute Inc. In 1994, he became HHMI Investigator and Professor at the University of Michigan School of Medicine. In 2011, he became Director of Degenerative Disease Research at the Sanford-Burnham Medical Research Institute, La Jolla CA. He lists over 400 original publications, has received numerous awards and serves on many scientific review and advisory boards. Kaufman elucidated the critical roles of cellular machinery for protein folding and trafficking that led to the discovery of the unfolded protein response and its importance in metabolic disease.

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