New pathways for endoplasmic reticulum stress response and resolution

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This presentation will address the roles of LRH-1 in response to metabolic and proteotoxic liver stresses. Balance of labile methyl groups is important for normal liver function. Quantitatively, a significant use of labile methyl groups is in the production of phosphatidylcholines, which are LRH-1 ligands. We studied the role of LRH-1 in response to the methionine and choline-deficient (MCD) diet, which depletes methyl groups. MCD diet-fed, liver-specific LRH-1 knockout mice do not show the expected decrease in the methyl-pool, and are resistant to hepatitis and fibrosis. Adaptive responses observed in wild-type mice on the MCD diet are present in LRH-1 knockout mice on a normal diet, indicating that such responses are a consequence of decreased LRH-1 activity. These results indicate that LRH-1 functions as a methyl pool sensor.

Secreted and transmembrane proteins undergo processing and folding in the endoplasmic reticulum (ER) prior to their transit through the secretory pathway, and disruption of this process results in a highly conserved ER stress response. We have previously found that LRH-1 is essential for resolution of ER stress in mice. Although this pathway is not conserved in Caenorhabditis elegans, new results show that NR5A-family nuclear receptors in both C elegans (NHR-25) and mice (LRH-1) regulate a novel stress resolution pathway in which ubiquitin ligases direct misfolded proteins through the secretory pathway to the lysosome for degradation. Loss of this pathway in both species results in protein aggregation and toxicity, implicating NR5A nuclear receptors as drug targets for controlling protein degradation.

Keywords:
NR5A, LRH-1, NHR-25, unfolded protein response, endoplasmic reticulum stress, methyl pool, 1 carbon metabolism