The UPRosome-decoding novel biological outputs of IRE1 alpha function

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Abstract

Different perturbations alter the function of the endoplasmic reticulum (ER), resulting in the accumulation of misfolded proteins in its lumen, a condition termed ER stress. To restore ER proteostasis, a highly conserved pathway is engaged, known as the unfolded protein response (UPR), triggering adaptive programs or apoptosis of terminally damaged cells. IRE1 alpha (also known as ERN1), the most conserved UPR sensor, mediates the activation of responses to determine cell fate under ER stress. The complexity of IRE1 alpha regulation and its signaling outputs is mediated in part by the assembly of a dynamic multi-protein complex, named the UPRosome, that regulates IRE1 alpha activity and the crosstalk with other pathways. We discuss several studies identifying components of the UPRosome that have illuminated novel functions in cell death, autophagy, DNA damage, energy metabolism and cytoskeleton dynamics. Here, we provide a theoretical analysis to assess the biological significance of the UPRosome and present the results of a systematic bioinformatics analysis of the available IRE1 alpha interactome data sets followed by functional enrichment clustering. This in silico approach decoded that IRE1 alpha also interacts with proteins involved in the cell cycle, transport, differentiation, response to viral infection and immune response. Thus, defining the spectrum of IRE1 alpha-binding partners will reveal novel signaling outputs and the relevance of the pathway to human diseases.

Palabras clave

Palabras clave de autor:IRE1 alpha; UPRosome; ER stress; Cell fate
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