Non-canonical function of IRE1 alpha determines mitochondria-associated endoplasmic reticulum composition to control calcium transfer and bioenergetics

Carreras-Sureda, A., Jaña, F., Urra, H., Durand, S., Mortenson, D. E., Sagredo, A., ... & Hetz, C. (2019). Non-canonical function of IRE1α determines mitochondria-associated endoplasmic reticulum composition to control calcium transfer and bioenergetics. Nature cell biology, 21(6), 755-767. <10.1038/s41556-019-0329-y> Accessed 22 Apr 2021.

Abstract

Mitochondria-associated membranes (MAMs) are central microdomains that fine-tune bioenergetics by the local transfer of calcium from the endoplasmic reticulum to the mitochondrial matrix. Here, we report an unexpected function of the endoplasmic reticulum stress transducer IRE1α as a structural determinant of MAMs that controls mitochondrial calcium uptake. IRE1α deficiency resulted in marked alterations in mitochondrial physiology and energy metabolism under resting conditions. IRE1α determined the distribution of inositol-1,4,5-trisphosphate receptors at MAMs by operating as a scaffold. Using mutagenesis analysis, we separated the housekeeping activity of IRE1α at MAMs from its canonical role in the unfolded protein response. These observations were validated in vivo in the liver of IRE1α conditional knockout mice, revealing broad implications for cellular metabolism. Our results support an alternative function of IRE1α in orchestrating the communication between the endoplasmic reticulum and mitochondria to sustain bioenergetics..

Keywords

Calcium signalling, Endoplasmic reticulum, Energy metabolism.