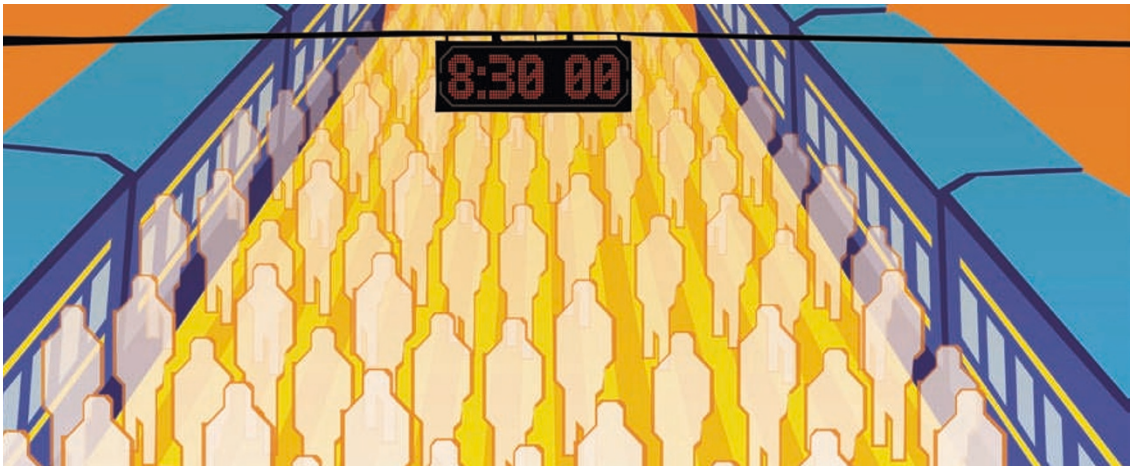
Nature Reviews Molecular Cell Biology | AOP, published online 8 January 2009; doi:10.1038/nrm2622



CELL SIGNALLING

An efficient and timely getting together

> …Ire1 forms supramolecular structures… in discrete stress signalling sites…

Inositol-requiring enzyme 1 (Ire1) — an endoplasmic reticulum (ER) bifunctional transmembrane kinase and endoribonuclease — senses misfolded protein accumulation in the ER lumen and subsequently activates the transcription factor X-box-binding protein 1 (XBP1; Hac1 in yeast) in the cytosol. Ire1 excises an intron from *HAC1* (or *XBP1*) mRNA, which is translated into the active transcription factor upon re-ligation. This unconventional mRNA splicing event initiates the unfolded protein response (UPR), a transcriptional programme that relieves ER stress. But how is Ire1 activated? And how does it regulate UPR signalling to ensure an adequate response to ER stress?

Two reports from the group of Peter Walter now show that yeast Ire1 forms supramolecular structures that form discrete stress signalling sites and recruit *HAC1* mRNA. Korennykh *et al.* show that the cytosolic region of Ire1 undergoes spontaneous oligomerization, which activates the RNase function for signalling the UPR. Using a small-molecule kinase inhibitor that functions as a potent activator of the Ire1 RNase activity, they obtained a 3.2 Å crystal structure of the oligomer. This revealed a helical rod assembly that positions the kinase domain of Ire1 for *trans*-autophosphorylation, orders the RNase domain and creates an interaction surface for binding of the mRNA substrate. The authors further present a model in which oligomers formed by the ER-luminal domain of Ire1 and the cytoplasmic domains are arranged to give similar periodicity of monomers on both sides of the ER membrane. The resulting mesh could provide a platform for the formation and growth of supramolecular Ire1 foci in the plane of the membrane. It is suggested that such an assembly would allow a cooperative response to unfolded proteins and adequate timing for mounting and extinguishing the UPR.

In a second paper, Aragón *et al.* show that, in response to ER stress, Ire1 molecules cluster *in vivo* into foci of higher-order oligomers, and that oligomeric Ire1 recruits unspliced *HAC1* mRNA. A conserved element contained in the 3′ untranslated region (UTR) serves as the targeting element that guides *HAC1* mRNA to Ire1 foci to allow splicing and cell survival under ER stress. Disruption of either Ire1 clustering into foci, or *HAC1* mRNA recruitment to these foci, impairs UPR signalling. The *HAC1* 3′ UTR element is sufficient to target any mRNA to Ire1 foci, as long as its translation is repressed. For *HAC1* mRNA, translational repression is afforded by a base-pairing interaction between the intron and the 5′ UTR.

The authors conclude that robust Ire1 oligomerization and *HAC1* mRNA targeting serve to concentrate both key UPR components into foci to ensure efficient and timely RNA processing and ER stress signalling. Recruitment of mRNA to signalling centres provides a new paradigm for the control of eukaryotic gene expression.

Ekat Kritikou

ORIGINAL RESEARCH PAPERS Aragón, T. *et al.* Messenger RNA targeting to endoplasmic reticulum stress signalling sites. *Nature* 14 Dec 2008 (doi:10.1038/nature07641) | Korennykh, A. V. *et al.* The unfolded protein response signals through high-order assembly of Ire1. *Nature* 14 Dec 2008 (doi:10.1038/nature07661)