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UNFOLDED PROTEIN RESPONSE

Reacting to membrane stress

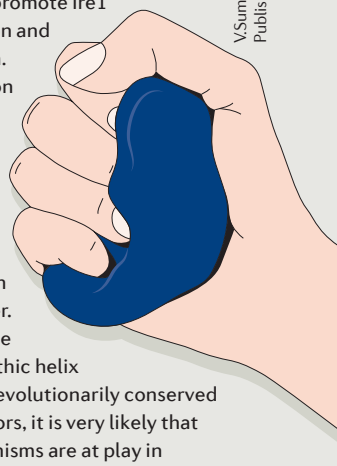
The unfolded protein response (UPR) is a highly conserved pathway of protein quality control in the endoplasmic reticulum (ER), which is activated in response to various cellular stresses. The UPR is activated not only by unfolded proteins, but also by aberrant lipid composition of the ER membrane referred to as lipid bilayer stress. Halbleib *et al*. now provide molecular details of how changes in membrane composition activate the UPR.

Inositol-requiring enzyme 1 (Ire1), which is a transmembrane ER protein, is a conserved activator of the UPR. Ire1 binds to unfolded proteins, which induces its oligomerization and activation, ultimately leading to the production of the transcription activator Hac1. Focusing on the interaction of Ire1 with membranes, the authors identified an amphipathic helix in the sequence of *Saccharomyces cerevisiae* Ire1, disruption of which decreased yeast survival and reduced Hac1 activation in stress conditions that normally induce the UPR. This suggested a role for the amphipathic helix in Ire1-mediated UPR activation.

> “changes in membrane composition associated with lipid bilayer stress promote Ire1 oligomerization and UPR activation”

Next, the authors used liposomes with defined lipid composition into which they inserted the minimal membrane-sensitive domain of Ire1, which comprised the amphipathic helix and the transmembrane helix (TMH). Insertion into membranes with increasing lipid order, a common characteristic of all lipid bilayer stress conditions, was associated with oligomerization of this sensor. Molecular dynamics simulations revealed that the amphipathic helix imposed a kinked and tilted orientation of the TMH region within the lipid bilayer, which enforced local membrane compression, in particular in the thicker, more ordered membrane domains. Such membrane compression is energetically unfavourable and was predicted to be relieved by TMH oligomerization, which may, in turn, facilitate more stable oligomerization of the protein through the dimerization domains present in the ER lumen, thereby leading to Ire1 activation.

Thus, changes in membrane composition associated with lipid bilayer stress promote Ire1 oligomerization and UPR activation. This depends on the presence of the Ire1 amphipathic helix, which regulates the orientation of the TMH within the lipid bilayer. As the presence of an amphipathic helix appears to be evolutionarily conserved in UPR activators, it is very likely that similar mechanisms are at play in other organisms.



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Paulina Strzyz

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