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Bilayer Tension Induced Unfolded Protein Response Activation

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ABSTRACT

The endoplasmic reticulum (ER) is an organelle that performs various cellular functions including protein folding, lipid synthesis and transport, and calcium storage. Abnormal changes in the ER environment can disrupt these functions, leading to a state called ER stress. When stressed, the ER adopts several homeostatic mechanisms to reduce stress and restore normal functioning. This set of responses, collectively called the Unfolded Protein Response (UPR) is initiated by the clustering of ER membrane proteins IRE1, PERK, and ATF6. While these pathways were originally observed to respond to the presence of misfolded/unfolded proteins in the ER, it has recently been shown that IRE1 is induced by aberrancies in membrane composition independently of misfolded proteins. By altering the thickness of the ER membrane, lipid compositional changes promote IRE1 clustering leading to activation of the UPR. Following this observation, we hypothesize that bilayer tension, another mechanism that directly alters membrane thickness, could lead to activation of the IRE1 signaling pathway. However, the effect of bilayer tension on IRE1 clustering has not been demonstrated. Bilayer tension, an important physicochemical property of ER, has a great influence on lipid droplets budding from ER, which is known to attenuate ER stress. Using MD simulations, we find that bilayer tension in ER membrane regulates the energetic cost of IRE1 clustering. Specifically, lower bilayer tension reduces the energetic cost of IRE1 dimerization, promoting the activation of the UPR. This work establishes a direct biophysical relationship between bilayer tension and UPR activation.