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Molecular dynamics simulations shed light on critical events in the early stages of human IRE1 activation

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The inositol-requiring enzyme 1 (IRE1) serves as a highly conserved stress sensor within the endoplasmic reticulum (ER), crucial for mitigating the cytotoxic effects resulting from the accumulation of unfolded proteins. Dysregulation of the unfolded protein response (UPR), a network of signaling pathways aimed at alleviating ER stress, is implicated in various human pathologies including diabetes, and cancer. IRE1, a transmembrane protein, relies on its core luminal domain (cLD) to sense misfolded protein accumulation and initiate downstream signaling events. While the involvement of IRE1 in recognizing unfolded proteins is well-established, the precise mechanism underlying this process in human cells remains contentious. To address this, we conducted extensive molecular dynamics (MD) simulations to explore how the dimeric cLD of human IRE1 (hIRE1) directly interacts with unfolded polypeptides at the atomic level. Our investigations revealed that hIRE1 cLD dimers are stable under non-stress conditions, with peptide binding occurring predominantly on the surface of the dimer rather than within its central MHC-like groove, as observed in the yeast homolog. These novel findings support a model wherein the direct interaction between IRE1 and unfolded proteins represents a crucial early event in the assembly of supramolecular complexes associated with activated IRE1. Insights from this study into the molecular mechanisms governing IRE1 activation hold potential implications for the development of therapeutic strategies targeting the UPR pathway.

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