Molecular fingerprints of a stressed endoplasmic reticulum

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Biological Membranes are complex and dynamic assemblies comprising thousands of different lipid and protein species. Physical and compositional properties of membranes determine their identity and functionality in the cellular context.

The endoplasmic reticulum (ER) is the site of activation of the unfolded protein response (UPR), a large-scale transcriptional program crucial for protein and lipid homeostasis. Conditions triggering the UPR are collectively termed ER stress. These include overpopulation of the ER lumen with un- or misfolded proteins or lipid perturbations. Unmitigated ER stress has been linked to diseases like type II diabetes and cancer[1,2]. We investigate the role of the ER membrane in these processes and elucidate the molecular basis of cytotoxicity during prolonged ER stress.

To address this, we have established a versatile immunoisolation strategy for subcellular membranes. Quantitative lipidomics revealed substantial remodeling of the ER membrane lipidome upon ER stress. Based on these data, combined with molecular dynamics simulation, we suggest *in vitro* model systems that mimic the physical properties of the ER membrane better than prevailing ones. Quantitative proteomics reveals that the stressed ER is accumulating proteins of the late secretory pathway, suggesting a general block of secretion as a basis for adverse effects during prolonged ER stress.

1 Peter Walter and David Ron. The unfolded protein response: from stress pathway to homeostatic regulation. Science, 2011

2 Romain Volmer and David Ron. Lipid-dependent regulation of the unfolded protein response. Current Opinion in Cell Biology, 2015.