Emerging roles of the UPR in membrane homeostasis

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Lipids and proteins shape the physicochemical properties of cellular membranes as a collective, thereby affecting membrane protein function and contributing to organelle identity. Eukaryotic cells face the challenge of maintaining the complex composition of several coexisting organelles. The molecular mechanisms underlying the homeostasis of subcellular membranes and their adaptation during stress are only now starting to emerge. We have studied three membrane property sensors of the endoplasmic reticulum (ER), namely OPI1, MGA2, and IRE1, each controlling a large cellular program impacting on the lipid metabolic network. OPI1 coordinates the production of membrane and storage lipids (Hofbauer et al., 2018), MGA2 regulates the production of unsaturated fatty acids required for membrane biogenesis (Covino et al., 2016), and IRE1 controls the unfolded protein response (UPR) to adjust ER size, protein folding, and the secretory capacity of the cell (Halbleib et al., 2017). Although these proteins use remarkably distinct sensing mechanisms, they are functionally connected via the ER membrane and cooperate to maintain membrane homeostasis.

I am presenting our most recent progress in establishing an immuno-isolation platform for the purification of ER-derived vesicles and subcellular lipidomics. Based on a discussion of the sensing mechanisms and integrative functions of these sensors, we propose that IRE1 can sense the protein-to-lipid ratio in the ER membrane to warrant a balanced production of membrane proteins and lipids via the UPR.

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