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Role for lipid droplet biogenesis and microlipophagy in adaptation to lipid imbalance in yeast and in a mouse model for human disease

The immediate responses to inhibition of phosphatidylcholine (PC) biosynthesis in yeast are altered phospholipid levels, slow growth, and defects in the morphology and localization of ER and mitochondria. With chronic lipid imbalance, yeast adapt. We find that lipid droplet (LD) biogenesis is up-regulated in yeast undergoing lipid imbalance and is required for adaptation to lipid imbalance. We confirmed that the Unfolded Protein Response, a stress response pathway that is activated by accumulation of unfolded ER proteins, is activated by this lipid stress. We also find that LDs form at ER aggregates, contain polyubiquitinated proteins and an ER chaperone, and are degraded in the vacuole by a process resembling microautophagy. This process, microlipophagy, is required for restoration of organelle morphology and cell growth during adaptation to lipid stress. Microlipophagy does not require a core macroautophagy gene, ATG7, but does requires ESCRT components. It also requires a newly identified class E VPS protein that localizes to ER and is up-regulated by lipid imbalance. In complementary studies, we detect elevated lipid droplet biogenesis, ER stress, and defects in ER proteins that are essential for excitation contraction coupling in a mouse model for a congenital muscular dystrophy produced by defects in PC biosynthesis. Using super-resolution microscopy, we find that unfolded ER proteins are associated with lipid droplets. Thus, the ER proteostasis pathway that we identified in yeast occurs in mammalian cells and may contribute to protein quality control in human disease

Speaker Biography

Liza Pon studied mitochondrial function in steroid hormone biosynthesis as a pre-doctoral student in the laboratory of N.R. Orme-Johnson at Tufts University (1982-1987). As an NRSA Postdoctoral Fellow with Gottfried Schatz at the University of Basel, she studied protein import into mitochondria (1987 -1990). Dr. Pon established her own laboratory in 1990 at Columbia University, where she is currently Professor of Pathology and Cell Biology and the Institute of Human Nutrition, and Director of the Confocal and Specialized Microscopy Shared Resource. The focal point of her research is organelle quality control, interaction of mitochondria with the cytoskeleton and other organelles, and how these processes affect cellular fitness and lifespan.

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