Lipid regulation and transport in membrane remodeling

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"Lipid Regulation and Transport in Membrane Remodeling" covered topics ranging from how lipids are distributed between membrane sites and organelles within the cell, to new methods designed to spatially detect specific lipid pools, to the machinery involved in lipid enzyme regulation of discrete cellular functions, and the consequences on membrane trafficking, metabolism, and disease.

Many lipids are synthesized at the endoplasmic reticulum (ER) or taken up by endocytosis; therefore, they require transfer mechanisms to populate other membranes. Recent studies have discovered nonvesicular lipid transport at membrane contact sites, often facilitated by lipid gradients. Three presentations reported on lipid transport at ER membrane contact sites. **Francesca Giordano** (Institute for Integrative Biology of the Cell, Gif-sur-Yvette, France) showed that ORP5/8 transported phosphatidylserine (PS) from the ER to mitochondria at membrane contact sites, doing so in cooperation with the Mitochondrial Intermembrane space Bridging (MIB) complex with which they interacted. Interestingly, an ORP5-specific interaction with the MIB complex also negatively regulated calcium import into mitochondria with significance to cell senescence (Rochin *et al.,* 2019). **Candice Kutchukian** (Dickson lab, University of California, Davis) explained the importance of lysosomal cholesterol homeostasis for controlling the phosphatidylinositol (PI) 4-phosphate (PI4P) gradient between the *trans*-Golgi network (TGN) and ER necessary to maintain countertransport of cholesterol from the ER to the Golgi. Using models of Niemann-Pick Type C1 (NPC1) disease (Vivas *et al.,* 2019), they showed that altered lysosomal cholesterol homeostasis results in elevated Golgi PI4P as a consequence of enhanced TGN-localized PI4P-producing kinases and relocalized Sac1 PI4P-phosphatase at ER–TGN contact sites. **Yasunori Saheki** (Lee Kong Chian School of Medicine, Singapore) discussed an evolutionarily conserved family of ER-anchored lipid transfer proteins, namely GRAMD1 proteins, that help cells maintain cholesterol homeostasis. GRAMD1s bind one another, sense a transient expansion of the accessible pool of plasma membrane (PM) cholesterol, and facilitate cholesterol transport to the ER at ER–PM contact sites (Naito *et al.,* 2019).

While probes exist to follow the phosphorylated forms of PI, there is no means to detect the shared PI precursor of phosphoinositide (PPIn) lipids in live cells. **Josh Pemberton** (Balla lab, NICHD, Bethesda, MD) described the use of modified bacterial PI-specific phospholipase C enzymes as tools to define the subcellular distribution of PI. Interestingly, they found low steady-state levels of PI at the PM and at endosomes, highlighting the role of sustained PI resupply from the ER for the maintenance of PPIn pools (Pemberton *et al.,* 2019).

Bacteria also require lipid transport. **Damian Ekiert** (New York University School of Medicine) described structural work from his and Gira Bhabha's labs on a protein called LetB, which forms a striking tube sufficiently long to span the gap between the *Escherichia coli* inner and outer membranes. Interestingly, phospholipids bind within a hydrophobic tunnel at the center of the complex, suggesting that LetB acts as a conduit for lipid transport across the bacterial envelope (Isom *et al.,* 2019).

Membrane lipid composition, which directs localized signaling and remodeling, is under tight dynamic control of regulatory enzymes involved in lipid synthesis, modification, and turnover. Physiologically significant to most cellular processes are the vast family of enzymes involved in phospho-regulation of the low-abundance PPIn lipids that define membrane identity and functions. **Yu-Ju Chen** (Liou lab, UT Southwestern Medical Center, Dallas, TX) revealed that PM levels of PI (4,5)-bisphosphate ($PI(4,5)P_2$) can be maintained by a late endosomal/lysosomal pool generated by a RAS association domain family 4 (RASSF4)-activated ARF6 small GTPase pathway (Chen *et al.,* 2017). Acute manipulation and live-cell imaging experiments indicated that $PI(4,5)P_2$ produced by this pathway at intracellular vesicles is delivered to the PM, with importance for numerous $PI(4,5)P_2$-dependent physiological functions. **Blanca Diaz-Rohrer** (Levental lab, University of Texas Health Science Center, Houston, TX) demonstrated that certain protein associations within ordered membrane microdomains, that is, lipid rafts, are sufficient for the recycling of transmembrane proteins to the PM (Lorent *et al.,* 2017). Using screens for lipid raft protein distribution, they found that the small GTPase Rab3 orchestrated this recycling, and abrogation of this pathway disrupted functional PM homeostasis.

Different spatial pools of the same PPIn species can have widely distinct cellular functions, as do different members of PPIn kinase and phosphatase families with overlapping selectivity, respectively. **Amy Kiger** (University of California, San Diego) showed how Class II PI 3-kinase (PI3KC2) and myotubularin (Mtm) PI 3-phosphatase coregulated PI 3-phosphate (PI3P) levels and autophagy (Velichkova *et al.,* 2010). Intriguingly, they found a wild-type PI3KC2 "short" splice variant (PI3KC2-S) lacking catalytic activity that interacted with

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PI3KC2 and Mtm in vivo. Wild-type PI3KC2-S inhibited both PI3KC2 and Mtm catalytic activities and autophagy-repressive functions, thus promoting autolysosome maturation and autophagy levels. **Noah Steinfeld** (Weisman lab, University of Michigan, Ann Arbor) discussed how changes in PI3P levels, using novel hyperactive mutations in the sole yeast PI 3-kinase, Vps34, can selectively alter downstream processes. Elevated PI3P levels led to induced retrograde transport of Atg27 and ESCRT function, but had no effect on autophagy initiation and inhibited a late step in autophagy. Thus, stimulus-induced PI3P is a potential regulator of downstream pathways.

Finally, enzymes that regulate fatty acid synthesis have profound significance for cell health and disease. **Shirin Bahmanyar** (Yale University, New Haven, CT) reported a link between increased de novo fatty acid synthesis and micronuclei, two hallmarks of cancer. Disruption of ER lipid homeostasis through transcriptional activation of fatty acid synthase expands the ER network, which invades spindle microtubules during mitosis, leading to chromosomal missegregation and micronuclei formation.

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