Lipids and proteins mix it up in Philly

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The "Lipids in Signaling and Membrane Organization" Minisymposium featured 10 exciting presentations that addressed the roles of lipids in intracellular protein sorting, organelle biogenesis, and interorganelle lipid transport.

Protein-lipid interactions drive interorganelle sorting of proteins

Experiments presented by **Joseph Lorent** of the Levental lab (University of Texas) define physical properties of integral membrane proteins that determine their inclusion in lipid domains of the plasma membrane (PM) called "rafts." Through analyses of hundreds of transmembrane domains, it was concluded that three properties promote residence in a lipid raft: a small transmembrane domain (TMD) surface area, a long TMD, and palmitoylation of the protein. **Mengxiao (Mandi) Ma** of the Burd lab (Yale University) showed that endosome-to-Golgi retrieval of a yeast SNARE protein, Snc1, depends critically on the sequence of its TMD and two endosomal sorting factors, Snx4 and Atg20, that bind to the cytoplasmic domain of Snc1. Mutations in the TMD ablate recognition by Snx4-Atg20 in vitro and retrieval of Snc1 from the endosome, leading to speculation that specific lipid–TMD interactions underlie proper presentation of the Snc1 retrieval signal.

The lipid droplet (LD) is a storage organelle whose biogenesis and catabolism are governed by enzymes that are targeted to its surface via poorly characterized mechanisms. **Coline Prévost** (Walther-Farese lab, Harvard University) and collaborators used molecular dynamics simulations to identify candidate features of the LD surface that are recognized by an amphipathic helix that confers LD targeting. Their findings suggest that binding is promoted by lipid packing defects within the LD surface that facilitate insertion of bulky hydrophobic amino acid side chains into the LD surface, a result that was confirmed with elegant in vitro reconstitution studies.

The role of the endoplasmic reticulum in organelle biogenesis

Lipid droplets begin as an agglomeration of neutral lipids within the endoplasmic reticulum (ER) membrane bilayer that emerges into the cytoplasm. **Will Prinz's** group (National Institutes of Health) discovered mutations in yeast (*Saccharomyces cerevisiae*) that result in defective LD emergence. The affected proteins (Scs3 and Yft2) localize to sites of LD emergence, where they appear to modify the local lipid composition to promote emergence. A critical protein in this process is an ER integral membrane protein called seipin. **Pedro Carvalho** (University of Oxford) reported that besides the well-established role in LD biogenesis, seipin is also involved in peroxisome biogenesis. He suggested that seipin collaborates with peroxisome biogenesis factors to establish a local lipid environment that is permissive for formation of both LDs and peroxisome precursors. **Rui Dong** (De Camilli lab, Yale University) and collaborators implicated a phosphoinositide phosphatase (INPP5K) in controlling ER architecture, where an ER integral membrane protein, ARL6IP1, recruits INPP5K to ER membranes. INPP5K lipid phosphatase activity plays a role in the dynamics of peripheral ER tubules in cultured human cells and *Caenorhabditis elegans* neurons.

Phosphoinositide signaling modules control nonvesicular transport of lipids

Scott Hansen (University of Oregon) described a two-component phosphoinositide signaling network built around the interconversion between phosphatidylinositol 4-phosphate (PI(4)P) and phosphatidylinositol 4,5 bisphosphate ($PI(4,5)P_2$). Hundreds of parallel reactions employing fluorescent lipid reporters and carried out on micropatterned lipid bilayers illustrated how signaling reactions can be modulated by the geometry of the membrane environment, a process they term "stochastic geometry sensing."

Three colleagues presented their progress investigating nonvesicular lipid transport between organelle membranes at "contact sites." PI(4)P is a lipid that is extracted from the PM or Golgi apparatus (where it is produced) and then delivered to the ER by a lipid transport protein. **Mira Sohn** (Balla lab, National Institutes of Health) showed that PM $PI(4,5)P_2$ regulates the ability of the lipid transfer proteins ORP5 and ORP8 to transfer PI(4)P from the PM to the ER. She reported that ORP8 is recruited to the PM by elevated levels of $PI(4,5)P_2$, exchanging PI(4)P for phosphatidylserine, thereby controlling PM PI(4)P, a precursor to $PI(4,5)P_2$. In nonvesicular lipid transport pathways, PI(4)P is transferred to, but does not accumulate in, the ER, suggesting that it is rapidly dephosphorylated in the ER, which was confirmed in studies by **Gerry Hammond** (University of Pittsburgh). He further showed that the ER-localized PI(4)P phosphatase, Sac1, is capable of dephosphorylating PI(4)P only when it is presented in the ER membrane. **Antonella De Matteis** (Telethon Foundation) reported her group's studies on the identification of tethering factors acting at ER–Golgi contact sites and on the role of these contacts in controlling the levels of PI(4)P in the Golgi complex.

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