Essentially all aspects of eukaryotic cell physiology depend on their compartmentalization and on membrane flux between these compartments mediated by small GTPases and their regulators, as well as by specific membrane lipids (Behnia and Munro, 2005). Talks at the Minisymposium on “Membrane Traffic: Dynamic and Regulation” featured how Rab-and Arf-family GTases, together with diverse phospholipids, most notably phosphoinositides (Balla, 2013), control key cell functions ranging from plasma membrane compartmentalization to organelle contacts, endosomal fission, cell motility, intracellular signaling, and cell cycle progression.

Phospholipids in plasma membrane organization, deformation, and signaling

Blanca B. Diaz-Rohrer (Levental lab, University of Texas Health Science Center, Houston) used giant plasma membrane vesicles from cultured mast cells to dissect how transmembrane proteins preferentially localize at the plasma membrane. She reported that the integral single-pass plasma membrane protein LAT strictly depends on sterol and sphingolipid rafts for its localization at the plasma membrane. Abrogation of raft partitioning by shortening the transmembrane domain led to mistargeting to late endosomes/lysosomes and to subsequent degradation, suggesting that raft association is necessary and sufficient for plasma membrane sorting of this protein (Diaz-Rohrer et al., 2014).

Helène Barelli (Antony lab, Institute of Molecular and Cellular Pharmacology, Valbonne, France) used a combination of in vitro assays, molecular dynamics simulations, and experiments in cells to demonstrate a role for polyunsaturated phospholipids in facilitating plasma membrane deformation and fission by endophilin and the GTPase dynamin. Lipids with polyunsaturated acyl chains facilitated fission of endocytic pits from the plasma membrane (Pinot et al., 2014). This likely is of particular relevance in neurons, where polyunsaturated lipids are particularly abundant (i.e., in synaptic vesicles), and might facilitate fast endocytosis in nerve terminals. Chi-Lun Chang (Liou lab, University of Texas Southwestern Medical Center, Dallas) extended his previous finding regarding phosphatidylinositol(4,5)-bisphosphate (PtdIns(4,5)P_2) homeostasis at the plasma membrane (Chang et al., 2013). After receptor-activated phospholipase C (PLC)-mediated hydrolysis of PtdIns(4,5)P_2 into diacylglycerol and inositol 1,4,5-triphosphate, the plasma membrane pool of PtdIns(4,5)P_2 must be replenished. Chang described how the two PtdIns transfer proteins Nir2 and Nir3 are implicated in this process at contact sites between the endoplasmic reticulum and the plasma membrane. Interestingly, PtdIns(4,5)P_2 homeostasis was regulated differentially by Nir2 and Nir3, depending on the accumulation of phosphatidic acid produced following PtdIns(4,5)P_2 hydrolysis by PLC and phosphorylation of diacylglycerol.

Rab GTases in endosomal trafficking, cell polarization, cell migration, and intraflagellar transport

Rab GTases are key regulators of membrane trafficking from yeast to humans (Behnia and Munro, 2005). Arnaud Echard (Institut Pasteur, Paris, France) described how the endosomal Rab35 GTase controls PtdIns(4,5)P_2 homeostasis at an early step in the endocytic pathway. While PtdIns(4,5)P_2 is essential for clathrin-coated-vesicle formation, its rapid hydrolysis is required for coat disassembly and endosomal fusion postinternalization. Echard presented new data regarding the important question of how PtdIns-modifying enzymes are recruited to newly made endocytic vesicles at the right time and place after fission from the plasma membrane. Anthony Mangan (Prekeris lab, University of Colorado Anschutz Medical Campus, Aurora) described how FIP5 and other Rab11 effectors play a key role in the apical/basal polarization of epithelial cysts (Li et al., 2014). In particular, he described how Rab11/FIP5 endosomes that deliver apical markers are targeted during apical lumen formation occurring right at the time of the first cell division.

The function of small GTases is controlled by guanine nucleotide exchange factors that, in the case of Rab5, contain so-called DENN domains. Maria Ioannou (McPherson lab, Montreal Neurological Institute, McGill University) reported that the DENN domain protein DENND2B activates Rab13 on the plasma membrane at the leading edge of migrating cells and this is required for cell migration. Furthermore, she demonstrated that loss of function of Rab13 not only impaired cancer cell invasion in vitro but also greatly reduced tumor metastasis in mice in vivo (Ioannou et al., 2015). A similar mechanism occurs during exit of the BBSome, a complex of eight conserved Bardet-Biedl syndrome proteins, from primary cilia, as Maxence V. Nachury (Stanford University School of Medicine, Stanford) reported. In this case, the Rab-like GTase...
IFT27/RABL4, a component of the intraflagellar transport machinery, binds and activates the Arf-related small GTPase ARL6 to promote exit of ciliary cargo (Liew et al., 2014).

Lipids at the interface between nutrient signaling, growth control, and lysosomal function

An emerging topic during the minisymposium was the question of how membrane compartmentalization by lipids and small GTPases regulates cell signaling and thereby controls key cellular functions such as cell cycle progression. Andrea Marat (Haucke lab, Leibniz Institute for Molecular Pharmacology, Berlin, Germany) provided evidence that nutrient signaling by mTOR is under control of specific PtdIns lipids that reciprocally regulate mTOR activity and lysosomal localization and function. Moreover, Yui Jin (L. S. Weisman lab, University of Michigan, Ann Arbor) showed that the key nutrient signaling kinase TOR genetically interacts with components of the lysosome/vacuole to regulate cell cycle progression in yeast.

These examples illustrate hitherto unknown physical and functional links between nutrient signaling, endolysosomal membrane traffic, and cell cycle progression, and may consequently pave the way for future studies.

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