Control of cellular homeostasis: organelles take the pilot’s seat

Sharon Tooze a and Roberto Zoncu b
a London Research Institute, Cancer Research UK, London WC2A 3LY, UK; b Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, CA 94720

The minisymposium “Organelle Dynamics and Crosstalk in Health and Disease” covered novel, exciting aspects of organelle function related to nutrient homeostasis. Metabolism occurs in space and time. Inside every cell, specialized membranous compartments handle specific anabolic or catabolic processes. Therefore, close coordination among these different compartments, mediated by either chemical or physical means, is emerging as a core aspect of cellular homeostasis. However, the molecular players that mediate this cross-cell communication are only beginning to be identified.

Molecular mechanisms of autophagy

The early molecular events that trigger autophagy, and the role of specific membrane compartments in scaffolding the nascent autophagosome remain the subject of intense investigation.

Sharon Tooze (Cancer Research UK) presented new insight into the role of WIPI proteins during the early stages of autophagosome formation. Through a combination of live microscopy, ultrastructural analysis, and biochemical assays, it was shown that WD-repeat protein interacting with phosphoinositide 2 (WIPI2) binds to Atg16L1 at the omegasome, a phosphoinositide 3-phosphate (PI3P)–rich domain of the endoplasmic reticulum thought to be the “cradle” for phagophore formation. By simultaneously binding to PI3P and Atg16L1, WIPI2 plays a critical role in the recruitment of Atg12–Atg5–Atg16L1 to the membrane of the nascent phagophore. In turn, this event enables the subsequent lipidation of LC3 and the completion of the mature autophagosome. The critical role of the WIPI2-Atg16L1 interaction in cellular homeostasis was underscored by the observation that, when WIPI2 is depleted, cells fail to form autophagosome membranes in order to neutralize an invading intracellular pathogen, Salmonella.

Another outstanding question is how, during selective autophagy, autophagosome formation is directed around specific targets. Michael Mandell (University of New Mexico) reported that the TRIMs, which are a large family of proteins containing a RING domain, a B-box, and a coiled-coil domain, participate in the initiation and regulation selective autophagy. In addition to their role in scaffolding the Beclin 1 complex toULK1, an obligate step for Beclin 1 phosphorylation byULK1, several TRIMs are now shown to bind to LC3 on autophagosomes. In particular, the binding of TRIM5-alpha to LC3 was shown to be essential for the degradation of retroviral capsids and to restrict infection by HIV-1. Thus, TRIM proteins emerge as novel mediators of resistance against pathogens and, more broadly, as key players in selective autophagy.

The lysosome in cellular homeostasis

Traditionally regarded as the cell’s waste processor, the lysosome has recently earned a new life as a dynamic, key signaling center that regulates growth and catabolism. Roberto Zoncu (University of California, Berkeley) presented new evidence on the role of the vacuolar H+ ATPase (V-ATPase) in communicating amino acid availability to the master growth regulatory kinase, mechanistic target of rapamycin complex 1 (mTORC1). Through a combination of in vitro assays on purified organelles and detailed biochemical studies in cells, it was shown that the V-ATPase undergoes a conformational change that modulates the association between the V0 (proton-pumping domain) and V1 (ATP-hydrolyzing domain). This conformational change was mapped to a region of the V-ATPase facing the lysosomal lumen, and it occurred specifically in response to arginine, an amino acid that is absolutely required for mTORC1 activation. This work sheds light on how mTORC1 may detect amino acid levels, a key event in cellular metabolic regulation.

In addition to sensing nutrients, the lysosome also provides “smart storage” for important ions. Andrea Ballabio, presenting on behalf of Roman Polishchuk (Telethon Institute for Genetics and Medicine, Naples, Italy), reported that, in liver cells, the copper transporter ATP7B moves from the Golgi to the lysosome in response to elevated copper levels. At the lysosome, ATP7B becomes competent for transport and moves excess copper into the lysosomal lumen. This is only the first leg of a two-stage journey, in which copper-filled lysosomes subsequently travel toward the apical membrane of hepatocytes and fuse with it, releasing copper into the bile. These findings reveal yet another function of the lysosome in the regulation of cellular metal levels and suggest novel therapeutic avenues in Wilson’s disease, a liver disease that stems from mutational inactivation of ATP7B.

Role of mitochondria in nutrient homeostasis

The mitochondrion also earned the center stage. In addition to its traditional role as the cell’s power plant, this organelle engages in homeostatic processes such as nutrient sensing and lipid catabolism. These functions are enabled by the remarkable ability of mitochondria to modify their morphology, trafficking, and physical

DOI: 10.1091/mbc.E14-12-1589

Molecular Biology of the Cell Volume 26 Page 1009

MBoC is pleased to publish this summary of the Minisymposium “Organelle Dynamics and Crosstalk in Health and Disease” held at the 2014 ASCB/IFCB Meeting, Philadelphia, PA, December 8, 2014.

Address correspondence to: Roberto Zoncu (rzoncu@berkeley.edu).

© 2015 Tooze and Zoncu. This article is distributed by The American Society for Cell Biology under license from the author(s). Two months after publication it is available to the public under an Attribution–Noncommercial–Share Alike 3.0 Unported Creative Commons License (http://creativecommons.org/licenses/by-nc-sa/3.0).

“ASCB®,” “The American Society for Cell Biology®,” and “Molecular Biology of the Cell®” are registered trademarks of The American Society for Cell Biology.
association with other organelles. Using novel fluorescent probes that enable tracking of fatty acids in living cells, Angelika Rambold (Lippincott-Schwartz laboratory, National Institutes of Health) presented evidence that lipid droplets, the main storage site for neutral lipids, receive fatty acids from autophagy and transfer them to mitochondria for beta-oxidation. Intriguingly, in order to accept lipid droplet-derived fatty acids, mitochondria had to be highly fused and located in physical proximity to the lipid droplets. Thus, physical positioning and morphological changes are critical aspects of mitochondrial function in metabolism. Gulcin Pekkurnaz (Schwartz lab, Harvard Medical School) presented intriguing evidence that, in neurons, glucose regulates mitochondrial trafficking via O-GlcNAcylation of Milton, an adaptor protein that links mitochondria with microtubule-bound molecular motors. O-GlcNAcylation of Milton by O-GlcNAc transferase inhibited mitochondrial movement, whereas removal of Milton by O-GlcNAcase stimulated it. Thus, this work uncovers a direct link between glucose flux and mitochondrial traffic that may be key in providing a steady energy supply to metabolically active synaptic terminals.

**Other organelles**

Although autophagosomes, lysosomes, and mitochondria took the center stage, other organelles were shown to play important roles in fine-tuning cell metabolism and function. Combining mass spectrometry with mathematical modeling, Nikolai Slavov (Massachusetts Institute of Technology) reported an unexpected modulation in the stoichiometry and composition of ribosomal particles, which occurs in response to variations in the growth conditions and the overall translational activity. This remarkable plasticity of the ribosome may provide a molecular basis for dynamic changes in the proteome that occur during embryonic stem cell differentiation. The plasma membrane is also a site of active remodeling. Through elegant biochemical and structural experiments, Jeremy Baskin (De Camilli laboratory, Yale Medical School) showed that FAM126A/hyccin, a poorly characterized protein implicated in the pathogenesis of a disorder of myelination (hypomyelinating leukodystrophy), physically associates with and regulates phosphatidylinositol 4-kinase type III-alpha complex at the plasma membrane. These results were corroborated by crystallographic studies carried out in collaboration with the laboratory of Karin Reinisch. Baskin and coworkers propose that FAM126A is implicated functionally in the production of PI4P at the plasma membrane of oligodendrocytes, a cell type whose specialized function involves a massive expansion of the plasma membrane. These findings add a new piece of evidence to a connection between phosphoinositide metabolism and myelin deposition that could have important implications in certain demyelination diseases.