Quality control and organelle trafficking: ensuring functional organelles and cells

Julie A. Brill[a,*] and Jared Rutter[b,*]
[a]Cell Biology Program, The Hospital for Sick Children, Toronto, ON M5G 0A4, Canada; [b]Department of Biochemistry, University of Utah/Howard Hughes Medical Institute, Salt Lake City, UT 84112

The Minisymposium on "Quality Control and Organelle Trafficking" featured talks spanning three broad areas: mitochondrial quality control, endoplasmic reticulum quality control, and organelle trafficking.

Mitochondrial quality control

Jason Nielson (Rutter laboratory, University of Utah/Howard Hughes Medical Institute) described a protein quality control system centered on the Vms1-Cdc48 complex. This protein complex translocates to the mitochondrial outer membrane in response to various mitochondrial stresses, particularly those that elicit mitochondrial oxidant production. The search for the mechanism underlying this stress-responsive protein relocalization led to identification of an oxidized sterol that directly binds to Vms1 and is necessary and sufficient for Vms1 localization to mitochondria. This translocation event was hypothesized to support and enhance quality control functions on mitochondria experiencing damaging stressors.

Hagai Abeliovich (Hebrew University) discussed mitophagy, which traditionally involves entire segments or pieces of the mitochondrial network being completely degraded by the autophagic machinery and lysosomes. Abeliovich presented a more complicated picture, showing a much more selective degradative process in which some proteins were degraded and others were spared. Specific protein phosphorylation in the mitochondrial matrix, which led to a "distillation" mechanism and protein segregation, was proposed to account for this protein selectivity.

Adam Hughes (University of Utah) described a similar selective and stress-responsive protein degradation mechanism that centers on the formation of the mitochondrial-derived compartment (MDC) pathway, which selectively eliminates proteins from the inner and outer membranes of mitochondria. MDCs form at sites of endoplasmic reticulum (ER)–mitochondrial contact and use the autophagy machinery to enable the degradation of a subset of mitochondrial proteins, primarily those that are substrates of the mitochondrial import receptor Tom70. These include the large class of mitochondrial nutrient carrier proteins, hinting that the MDC pathway connects intracellular nutrient abundance with degradation of mitochondrial carriers.

Pei-I Tsai (Wang laboratory, Stanford University) focused on a protein that is famous for its role in regulating mitophagy, the PINK1 protein kinase, mutations of which lead to Parkinson's disease. Tsai showed, however, that PINK1 phosphorylates the MIC60 protein, which was previously shown to regulate mitochondrial cristae junctions and energetic efficiency. PINK1 was shown to be required for the maintenance of cristae junctions, specifically in regions of high energetic demand, and MIC60 overexpression rescues the PINK1 loss-of-function phenotype. This function might be conserved in higher eukaryotes, as two MIC60 variants were shown to increase the risk of Parkinson's disease in humans.

ER quality control

Maho Niwa (University of California, San Diego) described a system that appears to have evolved to ensure the inheritance of functional ER into daughter cells before cytokinesis. The ER stress surveillance system prevents entry of ER entry into daughter cells under conditions of ER stress but also supports the maintenance of ER in a recovery-competent state. This appears to be enabled by relocalization of the septin ring to a distinct site in the cell. Using mutants of the Shs1 subunit of the septin ring, Niwa showed that this localization is required to enable cell cycle recovery via the unfolded protein response (UPR) pathway after ER stress-induced arrest.

Amanda Casey (Orth laboratory, UT Southwestern) presented a role for AMPylation of the ER chaperone BiP in *Drosophila melanogaster*. Although BiP is reversibly AMPylated by dFic, and *dfic* mutants exhibit vision defects, it was unclear whether BiP AMPylation is important for vision. Through expression studies in flies, Casey showed that defects in BiP AMPylation resemble loss of *dfic*, including enhancement of vision defects upon exposure to ER stress, indicating that dFic acts through BiP to promote normal visual transduction.

IRE1-dependent UPR activation leads to production of the transcription factor XBP1, which maximizes ER folding capacity. **Jirka Peschek** (Walter laboratory, University of California, San Francisco) described a conserved RNA-intrinsic mechanism for unconventional splicing of *XBP1* mRNA. In vitro reconstitution of the splicing reaction revealed that cleavage of *XBP1* mRNA by IRE1 results in a conformational change in the RNA, accompanied by base pairing–dependent zippering of the resulting exons. This exon zippering promotes ejection of the spliced intron and ensures proper *XBP1* splicing in living cells.

Organelle trafficking

Cell cycle-dependent Golgi disassembly is regulated by reversible monoubiquitination. **Yanzhuang Wang** (University of Michigan) identified the Golgi target–soluble *N*-ethylmaleimide–sensitive

DOI:10.1091/mbc.E16-11-0798
Molecular Biology of the Cell Volume 28 Page 701
MBoC is pleased to publish this summary of the Minisymposium "Quality Control and Organelle Trafficking" held at the 2016 ASCB Annual Meeting, San Francisco, CA, December 6, 2016.

*Address correspondence to: Julie A. Brill (julie.brill@sickkids.ca), Jared Rutter (rutter@biochem.utah.edu).

factor attachment protein receptor (SNARE) syntaxin 5 (Syn5) as the ubiquitinated substrate. In early mitosis, monoubiquitinated Syn5 recruits a complex that includes the deubiquitinating enzyme VCIP135. This complex blocks Golgi reassembly by preventing association of Syn5 with its cognate, vesicle-SNARE Bet1. Activation of VCIP135 later in mitosis releases this block by deubiquitinating Syn5, leading to SNARE pairing and Golgi reassembly.

Cheng-I Jon Ma (Brill laboratory, The Hospital for Sick Children/University of Toronto) described a screen for factors involved in maturation of regulated secretory granules (RSGs) in the *Drosophila* larval salivary gland. The screen revealed a substantial contribution of endocytic and retrograde trafficking factors to RSG maturation. Expression of the tetraspanin CD63 promotes RSG maturation in a manner that depends on a subset of these factors, suggesting that retrograde transport of tetraspanins from early endosomes promotes membrane fusion events needed for RSG maturation.

Amanda Neisch (Hays laboratory, University of Minnesota) reported on a screen for proteins that promote transport of autophagosomes in *Drosophila* neurons. Microtubule-dependent axonal transport allows autophagosomes to fuse with lysosomes. The Striatin homologue CKA and the STRIPAK complex were shown to regulate autophagosome transport in two ways. CKA binds Atg8 and coimmunoprecipitates with dynein, suggesting a direct role in linking autophagosomes to microtubules. In addition, phosphatase activity of PP2A within the STRIPAK complex regulates autophagosome and dense core vesicle transport.