The mechanisms and functions of interorganelle interactions

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Organelles communicate indirectly through signaling pathways and directly through membrane contact sites (MCS). These interactions can regulate organelle biogenesis, membrane trafficking, and metabolic pathways. Talks at the Minisymposium on “Organelle Contact Site and Biogenesis” discussed new and exciting findings regarding the mechanisms and functions of interorganelle interactions.

Because most mitochondrial genetic information has been transferred to the nuclear genome, regulation of mitochondrial biogenesis, health, and functionality depend on the existence of anterograde and retrograde signaling pathways between mitochondria and the nucleus. Valentina Perissi (Boston University School of Medicine) presented interesting results about a novel mediator of the mitochondrial retrograde signal that is required for the regulation of mitochondria biogenesis in adipsose tissue. Perissi’s results indicate that, upon translocation from the mitochondrial outer membrane to the nucleus, this factor regulates nuclear-encoded mitochondrial genes via modulation of histone methylation and chromatin accessibility. Organelle contacts also play a direct role in the transmission of genetic information. Samantha C. Lewis (Nunnari lab, University of California, Davis) talked about the role of endoplasmic reticulum (ER)–mitochondria contact sites in guiding the replication and inheritance of the mitochondrial genome (mtDNA; Lewis et al., 2016). A key finding was that licensing of mtDNA synthesis occurs at the subunit set of ER–mitochondria contact sites destined for mitochondrial division before apparent constriction or division machine recruitment, consistent with a cellular program for the specific distribution of nascent mtDNA.

The ER also makes functional contacts with endosomes. Rui Dong (De Camilli lab, Yale University/Howard Hughes Medical Institute) demonstrated that ER–endosome contacts affect the lipid composition of endosomal membranes. She showed that vesicle-associated membrane protein–associated protein (VAP), an ER-resident protein, directly interacts with a retromer subunit; these MCS function to restrict the distribution of phosphatidylinositol 4-phosphate (PI4P) on the endosomal membrane. When VAP is depleted, PI4P and actin accumulate on endosomal membranes, and this significantly reduces the efficiency of retromer-dependent cargo sorting (Dong et al., 2016). Melissa Phillips (Voeltz lab, University of Colorado Boulder) described her strategy to identify proteins that regulate endosome fission at ER contact sites. Phillips targeted a promiscuous biotin ligase to a MCS protein, and this allowed her to purify MCS proteins that regulate the ability of ER tubules to be recruited to the site of endosome budding and fission.

Michael Schrader (University of Exeter, United Kingdom) discussed molecular aspects of peroxisome–ER MCS. His group identified a molecular tether in mammalian cells that regulates peroxisome–ER associations. They showed that ACBD5, a peroxisomal acyl-CoA-binding membrane protein, directly interacts with ER-resident VAPB; loss of peroxisome–ER association perturbs peroxisome membrane expansion and increases peroxisome movement (Costello et al., 2017). Amit Joshi (Prinz lab, National Institutes of Health) presented findings on connections between the ER and peroxisome biogenesis. Using a genetic approach, he found two novel ER-shaping proteins, Pex30p and Pex31p, which have reticulin-like membrane domains. Pex30p and Pex31p localize to subdomains of the peripheral ER that are depleted of reticulons and are the sites for generation of preperoxisomal vesicles (Joshi et al., 2016).

Yu-Ju Chen (Jen Liou lab, University of Texas Southwestern Medical Center) discussed the exciting discovery of RASSF4, which regulates the function and formation of ER–plasma membrane (PM) junctions. By affecting PM phosphatidylinositol 4,5-bisphosphate levels, RASSF4 regulates the targeting of the ER Ca2+ sensor STIM1 to ER–PM junctions and the activation of store-operated Ca2+ entry. RASSF4 also regulates the ER–PM tethering function of extended synaptotagmins E-Syt2 and E-Syt3, affecting the number and stability of ER–PM junctions.

Mitochondria also contact the PM, and Lauren Kraft (Lackner lab, Northwestern University) presented her recent findings on Num1, a mitochondria–PM anchor. Kraft found that mitochondria drive the assembly of Num1 into clusters, which serve to stably anchor the organelle as well as dynein to the PM. Disrupting mitochondrial-driven Num1 assembly led to defects in dynein-mediated spindle positioning. Thus, the mitochondria-dependent assembly of a dual-function cortical anchor integrates the positioning of two essential cellular structures and expands the function of organelle contact sites.

Nadav Shai (Maya Schuldiner lab, Weizmann Institute of Science, Israel) presented a new approach for tracking contact sites in yeast. It relies on a split fluorescence reporter in which the membrane of one organelle is labeled by one half of a fluorophore and the membrane of another organelle is labeled by the other half. MCS provide areas of close proximity and allow a fluorescence signal to be seen.

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Using this approach, Shai demonstrated the existence of contact sites between most cellular organelles, including several novel contact sites.

Bo Huang (University of California, San Francisco), the recipient of the Early Career Life Scientist Award, described his group’s effort to create libraries of cell lines expressing endogenously tagged proteins for fluorescence microscopy, as well as for biochemical isolation. Taking advantage of the split fluorescent protein system (Kamiyama et al., 2016) and clustered regularly interspaced short palindromic repeats/Cas9-mediated gene editing, the Huang lab has developed a scalable method for the robust, scarless, and cloning-free tagging of endogenous human genes with fluorescent proteins, demonstrated by the generation of a 30-cell-line minilibrary (Leonetti et al., 2016). Using this minilibrary, they have analyzed the spatial organization of a series of ER-shaping proteins. This method paves the way for the large-scale generation of endogenously tagged human cell lines for the proteome-wide analysis of protein localization and interaction networks in a native cellular context.

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