Organelles and spatial organization of the cell: organelle homeostasis and turnover

Alexander van der Bliek* and Xinnan Wang

*Department of Biological Chemistry, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA 90095; 
†Department of Neurosurgery, Stanford University School of Medicine, Stanford University, Palo Alto, CA 94305

Talks in the “Organelle Homeostasis and Turnover” Minisymposium covered a broad range of topics, including the formation of bacterial magnetosomes, a new understanding of endoplasmic reticulum (ER) protein translocation, the mechanisms for mitochondrial turnover, and phase transition in amyotrophic lateral sclerosis (ALS) protein aggregates.

CONSTRUCTING UNUSUAL ORGANELLES

Two talks described mechanisms for the formation of unusual organelles. The talk by Elias Cornejo (Komelí laboratory, University of California, Berkeley) described the remodeling of bacterial membrane to form a series of evenly spaced invaginations. Iron oxide crystallizes into magnetic particles inside these membrane invaginations. The spacing and formation of the membrane invaginations do not depend on iron oxide crystallization; however, the size of the membrane invagination appears to facilitate the crystal formation process. If a crystal is not made, the membrane invagination will stall at a diameter of ~50 nm. Once crystal formation has initiated, the membrane invagination can expand to significantly larger sizes and accommodate mature magnetic particles.

In another talk, Avinash Patel (Hyman laboratory, Max-Planck-Institute, Dresden, Germany) showed results from biochemical experiments aimed at dissecting the mechanisms of liquid-to-solid phase transition of the ALS protein FUS. This protein normally has a disordered domain that can loosely associate with similar proteins to form a non-membrane-bounded compartment with liquid properties. These liquids exhibit phase separation from the surrounding aqueous environment akin to the separation of oil and water droplets. Given enough time, the concentrated protein solution can also convert to fibrous aggregates. This conversion to aggregates is accelerated by mutations associated with ALS, which leads to the intriguing suggestion that aberrant phase transitions are key to ALS and other age-related diseases.

KEEPING TABS ON PROTEIN SYNTHESIS AND ON TARGETING PROTEINS TO ORGANELLES

Three talks covered the gamut of protein synthesis, targeting, and turnover. Stirling Churcman (Harvard University, Cambridge, MA) described how the expression of nuclear-encoded genes and mitochondrial-encoded genes are coordinated to yield dual-origin protein complexes with appropriate stoichiometry. The transcription rates of nuclear genes and mitochondrial genes are not synchronized; protein expression is instead coordinated at the translational level. Additional experiments using ribosome profiling and selective translation inhibitors showed that cytosolic translation exerts unidirectional control over the translation of proteins by mitochondrial ribosomes.

Naama Aviram (Schuldiner laboratory, Weizmann Institute, Rehovot, Israel) described new proteins involved in signal recognition particle (SRP)-independent protein targeting to the ER. These proteins, called SND1, -2, and -3, associate with the Sec61 complex. Elegant genetic analysis of these proteins in yeast led to the novel idea that there is overlap and partial redundancy among the three main pathways for protein import into the ER. On one end of the spectrum lies the traditional SRP-dependent targeting pathway, used primarily for nascent proteins with an N-terminal targeting sequence, and on the other end of the spectrum lies the GET-dependent targeting pathway used for proteins with a C-terminal targeting sequence. The SND proteins can be thought of as straddling SRP-dependent and GET pathways. The SND pathway normally accepts proteins with internal targeting sequences, but it can also be partially redundant with the SRP-dependent and the GET pathway, as shown by mutations in those pathways.

Sven Truckenbrodt (Rizzoli laboratory, University of Gottingen, Gottingen, Germany) showed that synaptic vesicles have finite lifespans, limited by the number of times these vesicles fuse with the plasma membrane and are recycled. During these cycles, synaptic vesicles are gradually contaminated with proteins that normally reside on the plasma membrane. Accumulating too much of these proteins on vesicles ultimately prevents them from fusing again to the plasma membrane. In this way, synaptic vesicles are inactivated long before their proteins are damaged and the vesicles are degraded.

FLESHING OUT MITOCHONDRIAL TURNOVER

Four talks were focused on the mechanisms of mitochondrial degradation and their physiological consequences. Two key players in mitophagy—the PINK1 and Parkin proteins—were originally identified through recessive patient mutations that cause Parkinson’s disease. Genetic and cell biological analyses showed how these proteins affect mitophagy, but it has been difficult to study this process under more physiological conditions because mice with PINK1 or
Parkin mutations have no discernible phenotypes. **Alicia Pickrell** (Youle laboratory, National Institutes of Health, Bethesda, MD) showed that Parkinson’s phenotypes are greatly enhanced in Parkin-knockout mice when these mice have a mitochondrial DNA polymerase A257G mutation (Mutator mice). These phenotypes include motor coordination defects and the selective degeneration of dopaminergic substantia nigral neurons. Mutator mice have increased levels of phosphorylated ubiquitin compared with wild-type mice. This increase suggests that the stress caused by damage to mitochondrial DNA activates PINK1 and Parkin-dependent mitophagy, because ubiquitin is a PINK1 kinase substrate. These results explain the heightened sensitivity of Mutator mice to mutations in the Parkin gene.

**Zu-Hang Sheng** (National Institutes of Health, Bethesda, MD) showed that autophagosomes in distal axons gain endosome-loaded dynein motor complexes through fusion with late endosomes to form intermediate organelles known as amphisomes. SNAPIN–dynein complexes drive retrograde transport of amphisomes from distal processes to the soma, where mature acidic lysosomes are relatively enriched. Such a mechanism enables neurons to efficiently reduce autophagic stress in distal axons and at synapses, thus maintaining axonal homeostasis. Blocking dynein recruitment to late endosomes by disrupting SNAPIN–dynein coupling impairs the movement of amphisomes toward the cell body. Reducing the ability of autophagosomes to fuse with late endosomes results in aberrant accumulation of immobile autophagic compartments in axon terminals. Thus the study reveals the motor-adaptor sharing mechanism that allows two different organelles to take the “ride-on service” for long-distance trafficking by forming hybrid intermediate organelles.

**Xinnan Wang** (Stanford University, Palo Alto, CA) showed results uncovering Miro degradation as a crucial element of Parkinson’s disease (PD). Miro is a GTPase on the surface of mitochondria that controls mitochondrial motility through interactions with the kinesin and dynein motor complexes. Mutations in Pink1 and Parkin proteins prevent proteolytic degradation of Miro, thus allowing for continued mitochondrial transport and the resulting interference with mitochondrial degradation through mitophagy. Surprisingly, Miro degradation is also impaired in other types of PD unrelated to Pink1/Parkin, and mitochondrial motility and mitophagy are disrupted in induced pluripotent stem cell–derived neurons from PD patients. This suggests that this pathway may be commonly affected in PD.

**Alexander van der Bliek** (University of California, Los Angeles) described results from a collaboration with the Youle laboratory (National Institutes of Health) showing that the mitochondrial fission protein Fis1 is also involved in mitophagy. Mutations in this protein and in its binding partner, the Rab7 GTPase-activating protein TBC1D15, cause the formation of large LC3-containing membrane aggregates. The formation of these aggregates is suppressed by Rab7 small interfering RNA, suggesting Fis1 and TBC1D15 are needed on mitochondria to attenuate Rab7 function during mitophagy. Without this attenuation, the autophagy machinery generates excessive amounts of isolation membrane and is unable to efficiently remove defective mitochondria.

Taken together, these talks provided a colorful snapshot of research focused on cellular processes that control organelle homeostasis and turnover.