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Editorial overview: Organelles: Finding new uses and creating new structures

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Prof. Pedro Carvalho received his Ph.D. from the University of Porto (Portugal) from work performed in the lab of David Pellman (Dana Farber Cancer Institute/Harvard Medical School). He was a Jane Coffin postdoctoral fellow with Tom Rapoport at Harvard Medical School, a group leader at the Center for Genomic Regulation (Barcelona, Spain) and recently joined the University of Oxford as the EP Abraham Professor of Cell Biology. His research focuses on understanding quality control mechanisms underlying organelle identity, function and architecture, with a particular focus on the endoplasmic reticulum.

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Dr. Davis Ng did his undergraduate work at UC Berkeley with research under the guidance of Richard Calendar. His PhD work was performed at Northwestern University with Robert Lamb in cell biology and virology. He was a postdoctoral fellow with Peter Walter at the UC San Francisco Medical School where he studied protein translocation and the unfolded protein response. He started his independent research group at the Pennsylvania State University where he attained the rank of Associate Professor with tenure. From there, his group moved to Singapore where he is currently a Temasek Senior Investigator at the Temasek Life Sciences Laboratory with appointments at the National University of Singapore and Duke-NUS Graduate Medical School. His current research focuses on the ER stress response and protein homeostasis.

The development of cellular organelles was a monumental evolutionary achievement. By segregating functions into physical compartments, cells could evolve their activities in extent and diversity far beyond simple prokaryotes. This biological innovation was critical in enabling the development of complex multicellular organisms. The textbook view of organelle evolution seems rather settled because of the strong compositional similarities between organelles and their probable progenitors. However, there exists scarce biological records to formulate detailed mechanisms nor are there experimental models that can replicate the phenomena. Modern ongoing processes may provide a real time glimpse. Endosymbiotic bacteria that occupy cell cytosol of sap feeding insects are in the midst of evolving a deepening codependence with their hosts (McCutcheon). Ongoing studies of this remarkable relationship may provide unprecedented insight into organelle evolution. These endosymbionts join the vast literature of organellar studies where host–pathogen interactions and unique organelles of pathogens themselves have brought about important breakthroughs. This issue emphasizes research that continues this tradition as well as notable recent advances in organelle function.

Parasites often evolve specialized organelles or modify common ones to better survive and proliferate in their hosts. Ciliates are characterized by hair-like extensions of membrane called cilia that are shared by some cells of hosts. Advances into the composition and structures of these unique organelles provide new insights into their primary function of coordinated force generation (Verhey and Yang). The lysosome related acidocalcisome, prominent in Trypanosomes but also found in other eukaryotes and bacteria, are membranous stores of multiple ions. These unusual organelles are used for diverse cellular activities, with many likely yet to be discovered (Docampo and Huang). A common pathogen modus operandi is to secrete or inject factors into host cells, to make them more compliant. Apicocomplexan parasites secrete an array of protein factors into the host, many with specialized modifications (Coffey *et al.*). Even within this group, the mechanisms that put pathogen proteins into host cells can be remarkably diverse. Once in, proteins tend to exploit existing pathways to their destinations. Bacterial toxins are masters of exploiting the endomembrane systems of host cells (Williams and Tsai). Their study revealed new insight into membrane trafficking and the remarkable biochemistry of the toxins themselves.

It is perhaps the field of virology that shares the greatest synergy with organelle cell biology. For decades, the study of viral membrane proteins built the foundation to our understanding of protein folding and quality control, vesicle mediated protein transport, and organelle dynamics. In turn,

the detailed understanding of organelle biology and the tools created in the process aided the development of new principles of how viruses hijack the cell for their replication, assembly and transmission (Sewald *et al.*). A classic example is the ESCRT machinery of multivesicular bodies (MVB), which was first described in yeast (Katzmann et al., 2001. Cell. 106:145–155). Although it is now well known that a variety of enveloped viruses recruit ESCRT and associated proteins for budding, recent studies have shown broad cellular roles beyond their function in protein sorting and formation of MVBs (Campsteijn *et al.*). Similarly, during herpes virus infection, the nucleocapsid assembled in the nucleus must be transported into the cytoplasm by egress through the nuclear envelope for further maturation and virus budding from the cell. Although the mechanism was first observed for viruses, nuclear enveloped budding appears to be used for export of large endogenous ribonuclear complexes (Fradkin and Budnik). Remodeling of internal organelles is becoming a common theme in viral replication cycles. Hepatitus C virus rearranges ER and associated lipid droplets to create specialized stations for genome replication and virus assembly (Meyers *et al.*). Thus, viruses not only borrow cellular machineries for their proliferation but can also act as engineers bringing new blueprints to modify existing structures.

In a sense, the revelations from the herpes virus studies are not entirely unexpected. Mechanical stability of the nuclear envelope, which in many cells is underlined by stiff lamin filaments, is critical for nuclear organization and function. However it is becoming more and more apparent that global nuclear envelope integrity requires a variety of spatially restricted remodeling events (King and Lusk). During mitosis the nuclear envelope dynamics takes a whole different scale, when this structure is dismantled. This can happen to different extent and in animal cells is completely disassembled (Makarova and Oliferenko). Like clockwork, the highly dispersed fragments reassemble after chromosome segregation into two perfect double-membrane, sphere-like structures pockmarked with pore complexes. Like the nucleus, the double membrane structure of the mitochondria has fascinated biologists for over a century. Although the mitochondrial structure function relationships are well known, how the intricate cristae are maintained despite the constant fission and fusion events are relatively new revelations (van der Laan *et al.*). During cell division organelles are also shared between the two daughter cell. Over the years many studies focused on how chromosomes are shared during cell division, however it is becoming apparent that the partition of organelles, such as peroxisomes is also very tightly controlled (Rachubinski *et al.*).

The recent technological advancements in single-particle cryo-eletron microscopy have made solving high-resolution structures of large macromolecular complexes almost commonplace. Nowhere is this revolution more impactful than in the endoplasmic reticulum (ER), where much of the lipids and proteins used to build the cell are synthesized. Several views of the ribosome/nascent chain/translocon complex have revealed remarkable insight to the earliest steps of secretory and membrane protein synthesis (Voorhees and Hegde). Unlike other parts of the cell, such proteins can be heavily modified in the ER by N-linked and O-linked glycosylation. Ironically, the more complex modification (N-linked) (Cherepanova *et al.*) is better understood functionally than the relatively enigmatic O-mannosylation event (Neubert and Strahl) even though both are highly conserved. Nevertheless, there is tremendous functional diversity known for both modifications with new functions surely to arise. The ER is also the major site of synthesis of lipids, one of the two major classes of molecules comprising all organelles. It is critical that their composition is carefully calibrated in each to maintain function (Barelli and Antonny). Although each molecule class has been studied intensely by themselves, the precise coordination of protein and lipid synthesis in the ER is critical for the viability of all eukaryotes. How this is accomplished remains a mystery.