CELL BIOLOGY

Emerging roles for organelles in cellular regulation

Nancy R. Gough*

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This Editorial Guide describes the emerging confluence of cellular regulation and organelle biology. The signals and molecular machineries that regulate organelle function, dynamics, and replication and the signals produced by organelles are beginning to be discovered.

Our understanding of eukaryotic and prokaryotic cells continues to evolve. Even our understanding and definition of organelles have evolved. There are the well-recognized membrane-bound organelles, such as the endoplasmic reticulum (ER), mitochondria, lysosomes, endosomal compartments, autophagosomes, chloroplasts, vacuoles, nuclei, and peroxisomes. Now, the concept of organelles has been extended to include macromolecular complexes that are stable structures performing specific functions, such as stress granules and centrioles. The jury is still out on whether scaffolded macromolecular regions, such as the postsynaptic density, plasma membrane–associated platforms, and certain cytoskeletal structures, are "organelles." Primary cilia, the single cilium that protrudes from many mammalian cells, are hybrid organelles with a membrane surrounding the portion that extends from the cell and a portion that is contiguous with the cytoplasm. Many of the membrane-less organelles have long been considered important for cellular regulation: The primary cilium functions as a sensory protrusion to detect the morphogen Hedgehog; stress granules sequester mRNAs to control translation (see Kosik and Krichevsky); and many plasma membrane–associated platforms, such as the immune synapse and the cytoskeletal structures that enable cell migration, are intimately involved in responding to extracellular signals (see Astro and de Curtis). The role of membrane-bound organelles as sources of signaling molecules is less well understood. The Editors' Choice section of *Science Signaling* has many examples of exciting findings at the intersection of organellar biology and cellular regulation. A few recent examples are highlighted in the Related Resources.

Each organelle or organized functional macromolecular complex could have an entire article devoted to it. Indeed, relevant subareas have been covered in *Science Signaling* in Focus Issues, such as the one on the ER calcium–refilling channel ORAI and its role in cells of the immune system. Here, just a sample of the many papers *Science Signaling* has published throughout the years is mentioned. Most of the highlighted studies focus on the membrane-bound organelles, but we are also interested in research into regulation of the dynamics and function of the membrane-less structures, which may produce signaling intermediates that affect cellular behavior. Another area of interest is that of specialized vesicles and membrane compartments, as exemplified by vesicles that reside near the Golgi but traffic to the immune synapse to deliver molecules necessary for T cell receptor signaling (see Srikanth *et al.*) or vesicles that are located beneath the forming immune synapse and deliver molecular components necessary for the formation of this complex, dynamic structure (see Purbhoo *et al.*). Whether these vesicles represent distinct organelles remains to be determined.

Organellar membranes not only define the intraorganellar space and maintain organelle identity, but also serve as platforms for organizing regulatory complexes. Alexia *et al.* found that components of the complex that controls the activity of the proinflammatory transcription factor nuclear factor κB (NF-κB) interacted with the protein metadherin at the cytosolic face of the ER and that this interaction was necessary for efficient activation of NF-κB in B and T cells responding to cytokines or stimulation of antigen receptors. Endosomal membranes also serve as signaling stations as proteins traffic from the cell surface to internal endosomal, recycling, or lysosomal compartments. Naguib describes how waves of lipid-mediated signaling that activate the kinase AKT occur as growth factors traffic through the endosomal system. As highlighted in the article by Er *et al.*, growth factor–mediated signaling stimulates AKT to promote epidermal growth factor receptor (EGFR) trafficking and degradation.

Furthermore, the site at which receptors signal, the cell surface or the endosome, can influence the outcome as described for Toll-like receptor 7 (TLR7) signaling in neurons by Winkler *et al.* and for TLR4 by Cheng *et al.* Endosomes can also control the amount of activity produced by receptors, as reported for cytokine receptors and NF-κB signaling by Mamińska *et al.*, and the type of signal transduced, a property that can been leveraged for therapeutic benefit with regard to biased agonist signaling by G protein–coupled receptors (GPCRs) (see Zimmerman *et al.*). Receptor dimerization can also affect the trafficking of GPCRs into the endosomal pathway, as described by Nishimura *et al.* for purinergic $P2Y_6$ receptors and angiotensin AT1 receptors, which is relevant for angiotensin-induced hypertension.

Mitochondrial membranes also serve as key platforms for immune responses and cell death signaling. The antiviral signaling pathway involving MAVS (mitochondrial antiviral signaling) is affected by conditions that alter mitochondrial membrane potential and mitochondrial fusion dynamics (see Koshiba *et al.* and Yasukawa *et al.*), demonstrating that cells can detect changes in organellar status. Indeed, how mitochondria signal back to the nucleus to regulate gene expression, a process called retrograde signaling, was investigated by Chae *et al.*, who determined that retinoic X receptor α (RXRA) was important for mediating the transcriptional response that enables cells to cope with mitochondrial dysfunction.

The ER, mitochondria, and lysosome (or vacuole in yeast) perform essential functions in calcium homeostasis and signaling. The ER contains ligand-activated receptors that trigger calcium release, whereas mitochondria and lysosomes (or vacuoles) serve as sinks. However, this sink function is not without cost, and each organelle must maintain calcium within certain limits to maintain their other functions. Shanmughapriya *et al.* discovered that two types of calcium signals—calcium released from the ER through the calcium-permeable IP_3 receptors and calcium influx through store-operated calcium channels—were important for expression of the gene that encodes the mitochondrial calcium uniporter MCU. Without either of these calcium signaling pathways, the activity of the transcription factor CREB, which bound to the *MCU* promoter, and the expression and abundance of MCU were reduced, mitochondrial

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calcium uptake was compromised, and mitochondrial metabolism was altered.

Calcium also has a role in the Golgi apparatus, which is an organelle involved in the maturation of proteins destined for the cell surface, secretion, or lysosomes. Yang *et al.* found that the Golgi also functioned as a cAMP (adenosine 3′,5′-monophosphate)–regulated calcium store responsive to β-adrenergic receptor signaling. In heart cells, signaling through the β-adrenergic receptor stimulated the release of calcium from the Golgi, which enhanced the delivery of vascular endothelial growth factor receptor 1 (VEGFR1) to the cell surface. As with most membrane-bound organelles, the Golgi also serves as a platform for cellular signaling, as highlighted in an Editor's Choice by VanHook.

Lysosomes are acidic compartments that also sequester calcium and provide key signaling mediators. Studying organellar biology and intracellular channel activity can be challenging. The Protocol by Schieder *et al.* describes the steps and conditions for performing patch clamp analysis of lysosomes. The endolysosomal system contains channels of the two-pore channel (TPC) family (reviewed by Patel). These channels drive trafficking of cargo through the endolysosomal system, and dysregulation of this trafficking may contribute to disorders, such as Parkinson's disease, fatty liver disease, and Ebola infection. Pitt *et al.* found that H^+ was the preferred ion that passed through human TPC1, and they identified calcium and NAADP as intracellular signaling messengers that stimulated TPC1 and affected the relative ability of different positively charged ions to flow through the channel. The exact function of the released H^+ remains an open question.

Molecules within or released by lysosomes regulate the activity of the energy- and nutrient-responsive protein complex mTORC1, which is associated with the lysosomal surface. Lysosome biogenesis and the process of autophagy need to be coordinated because lysosomal fusion with autophagosomes is how the degradative components are provided for the autophagy process. Roczniak-Ferguson *et al.* and Martina *et al.* identified transcription factors that control lysosomal biogenesis through mTORC1 signaling. Indeed, because of the importance of the lysosome for regulating mTORC1 activity and the importance of mTORC1 in regulating autophagy, signals mediated by mTORC1 and signals that regulate it fall into the category of organellar signaling and regulation. Oliveira *et al.* combined phosphoproteomic and metabolomic analyses to understand how changes in nutrient quality or inhibition of TORC1 altered yeast metabolism and to infer the effect of phosphorylation on metabolic enzyme activity. Laxman *et al.* also studied yeast to investigate how cells controlled TORC1 activity to avoid aberrant metabolism of glutamine.

Autophagy provides a key cellular function that enables cells to properly handle excess lipids, aggregated proteins, or damaged organelles. DeBosch *et al.* discovered a mechanism by which the plant carbohydrate trehalose induced autophagy, thereby preventing hepatic steatosis (lipid accumulation) in mice. Macrophages that accumulate in atherosclerotic plaques have impaired autophagy and instead rely on sequestration of proteins in inclusion bodies, including the proinflammatory cytokine interleukin-1β (IL-1β) (see Sergin *et al.*). Some may argue that such inclusion bodies are membrane-less organelles. Thus, autophagy (a process involving membrane-bound organelles) and the formation of inclusion bodies (membrane-less organelles) are coordinated processes.

Groenendyk *et al.* determined that ER stress caused by depletion of ER calcium triggered a reduction in the abundance of a microRNA that enabled an oxidoreductase to accumulate, which mediated a specific ER stress response. Finger and Hoppe discuss the connection between calcium, microRNAs, and ER stress. The ER stress response is complicated and involves multiple pathways; however, advances in understanding this process have led researchers to discover ways to potentially use ER stress therapeutically. Singh *et al.* reported that some breast cancer cells depended on an adaptive increase in the ER stress response to survive and that blocking this adaptive pathway sensitized these cells to growth factor inhibitors. Philippe *et al.* discovered that, in muscle undergoing ischemia (low-oxygen conditions), the ER stress response–activated kinase PERK mediated an increase in the translation of growth factors that trigger angiogenesis. Administration of a PERK inhibitor to mice before ischemia prevented the translation of the mRNAs for VEGF and FGF-2 (fibroblast growth factor–2), raising the possibility that PERK manipulation could be used to increase blood flow in ischemic tissues.

The response to cell stress is a continuum, with adaptive responses enabling survival at one end and cell death at the other. ER remodeling is one such adaptive response. Hatakeyama *et al.* found that the ER structural protein reticulon 4A (Rtn4A), which is involved in ER remodeling, reduced degradation of the growth factor receptor ErbB3 by sequestering the E3 ubiquitin ligase Nrdp1 within ER tubules away from ER sheets, which are the site of synthesis of proteins destined for the plasma membrane. Cultured breast cancer cells depended on Rtn4A to maintain ErbB3 abundance and responsiveness to the ErbB ligand NRG1β. These results suggest that ER remodeling may promote cell survival by enhancing the ability of cells to detect survival signals at the surface. Kanekura *et al.* found that ER stress resulted in permeabilization of the ER membrane by Bax and Bak, proteins that also permeabilize the outer mitochondrial membrane during apoptotic cell death. The catalytic activity of the kinase IRE1 prevented ER permeabilization and cell death in response to ER stress. Tissues from mice with experimentally induced stroke or heart attack and from mice that are a model for Wolfram syndrome, an inherited disease that is characterized by ER stress, had evidence of ER permeabilization. Depending on the disease context, drugs that enhance the kinase activity of IRE1 and limit cell death or drugs that promote this activity and enhance cytotoxicity in cells experiencing ER stress may be beneficial.

In terms of emerging areas in organellar biology and cellular regulation, the area of organelle dynamics in response to changes in intraorganellar conditions, cellular conditions, or extracellular signals is particularly exciting. The signals and molecules that control and coordinate organelle biosynthesis (or division) and how cells properly sort organelles into daughter cells during cell division are important areas of investigation. We anticipate that signals produced by organelles and the functions of these signals will proceed quickly as markers and components that participate in the various processes are identified and as technologies for imaging live cells improve and gain increasingly high resolution in time and space.

Most, if not all, membrane-bound organelles serve multiple functions, performing internal functions within the organelle and serving as platforms for multimolecular complexes. We anticipate that new organelles will be identified, that organelles will be found to be more dynamic and plastic than was previously appreciated, and that signals mediating the flow of information among various cellular compartments will be discovered. Researchers working on the basic cell biology of these processes or on the translation of such information for understanding disease pathology or developing treatment strategies are encouraged to submit to the journal.

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