ment, it may be possible to suppress the inhomogeneity of a molecular system and amplify coherent polariton behavior in a realistic material. Alternatively, the strength of light-matter interaction may be increased by leveraging photonic hotspots (localized areas with enhanced electromagnetic fields) or reducing mode volume (spatial concentration of electromagnetic waves). These strategies could enable robust polariton delocalization even in the presence of moderate disorder.

Insights from the study of Yin *et al.* are likely to extend beyond polariton-mediated vibrational energy transfer to other classes of polaritonic systems (such as electronic or excitonic polaritons) in which energetic disorder similarly undermines coherence and transport (*9*–*11*). In organic semiconductors and photovoltaic materials, the balance between light-matter coupling and inhomogeneity within a material may ultimately determine the feasibility of harnessing polaritonic modes for energy or charge transport. Although further experimental validations will be necessary, the quantitative criterion established by Yin *et al.* may serve as a unifying design rule across a wide class of polariton-enabled technologies.

The ability to strategically harness disorder as a design element could open new frontiers for polariton-based applications in optoelectronic, photonic, and quantum technologies. For example, disorder or defects may be deliberately engineered in a system to direct polariton-mediated processes, enabling reconfigurable or programmable energy transport. The study of Yin *et al.* provides a blueprint for realizing this emerging possibility. □

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CELL BIOLOGY

A protein tunnel helps stressed lysosomes swell

The endoplasmic reticulum donates lipids through a tunnel-like protein to help lysosomes expand

Jennifer Lippincott-Schwartz

Membrane-bound organelles such as the lysosome, which is involved in cellular waste management, change their surface area to mediate both beneficial and pathological responses. One mechanism that participates in this process is lipid transfer from other organelles to the lysosome, but the details are not well understood. On page 800 of this issue, Yang *et al.* (*1*) report a lipid signaling pathway from the endoplasmic reticulum (ER) that enables lysosomes to swell (vacuolate) to accommodate the increase in their contents under various stress conditions. This pathway results in the recruitment of a tunnel-like lipid transfer protein called PDZ domain-containing protein 8 (PDZD8) to a contact site between the ER and the lysosome, facilitating ER-to-lysosome lipid flow and enabling the expansion of the lysosomal membrane. This mechanism has broad implications for understanding how interorganelle lipid transfer facilitates organelle size regulation.

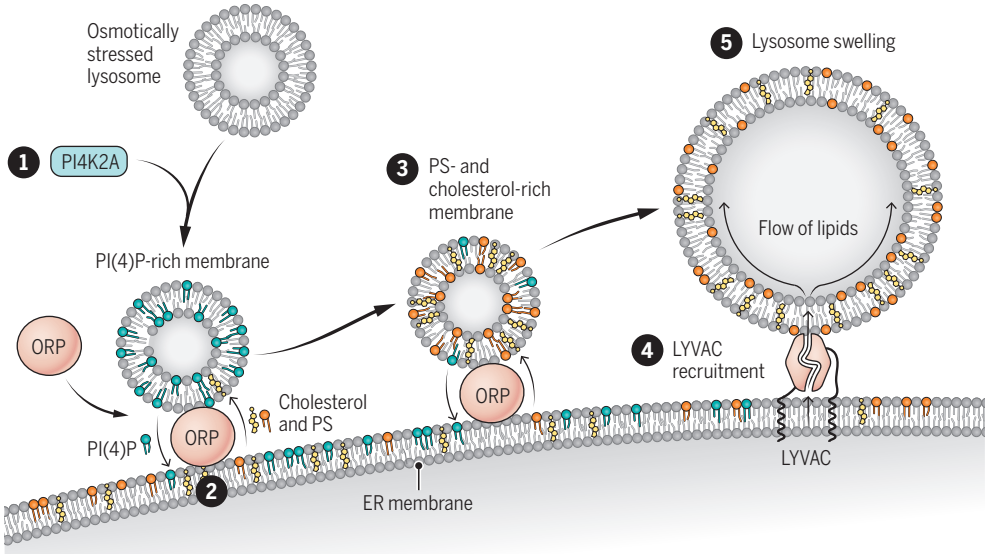
Roughly 30% of the cytoplasm of eukaryotic cells is occupied by membrane-bound organelles (*2*). These organelles (such as the ER, Golgi, mitochondria, lysosomes, and endosomes) specialize in different important cellular functions, including energy production, waste processing, and protein synthesis. Membrane boundaries allow each organelle to maintain a distinctive internal environment, isolating specific chemical reactions and regulating the exchange of substances between the organelle and the cytoplasm. Organelles regulate their size and activities by vesicle budding and fusion or by direct lipid or metabolite exchange at contact sites with neighboring organelles. This allows organelles to grow or shrink in response to input and outflow of internal components, which is critical for maintaining cell homeostasis.

One organelle that undergoes considerable changes in size is the lysosome, which receives materials taken up from the outside of the cell and breaks them down into usable parts for cell growth and survival. Pathologic conditions such as viral infections, chemotherapy treatment, and lysosomal storage disease lead to the accumulation of undigested solutes inside lysosomes, which causes the organelles to draw in water and swell (*3*). For the lysosome to swell or shrink under different conditions, its membrane boundary's surface area must either increase as the lysosome swells or decrease as it shrinks. This requires the regulation of membrane delivery to or removal from the lysosomal surface. Without such regulation, a lysosome under osmotic pressure may not swell sufficiently to avoid rupture, which can release lysosomal enzymes into the cytoplasm, causing inflammation and, in some cases, cell death. Lysosomal storage diseases such as Niemann-Pick, Gaucher, Fabry, and Tay-Sachs are all characterized by persistent lysosomal swelling (*4*) and ongoing inflammation.

Yang *et al.* set out to dissect the pathways that deliver the extra membrane that is needed for lysosomes to swell under osmotic imbalance. Such delivery could be enabled either through vesicle trafficking pathways to the lysosome or by nonvesicular lipid transfer at contact sites between lysosomes and other organelles (*5*, *6*). The authors induced lysosome swelling in cultured human cell lines using apilimod (an inhibitor of the lipid kinase PIKfyve), which causes lysosomal accumulation of chloride ions (Cl^-) and ammonium, resulting in water influx

Steps enabling lysosomal swelling

PI4K2A is recruited to osmotically stressed lysosomes and generates PI(4)P on these membranes (**1**). ORP binds to PI(4)P on the lysosome and initiates a bidirectional exchange with ER-localized PS and cholesterol (**2**), resulting in a lysosome membrane that is rich in PS and cholesterol (**3**). PS on the lysosome then attracts LYVAC, an ER-associated lipid transfer protein (**4**). Sensing of lysosomal membrane tension and cholesterol enrichment leads LYVAC to mediate directional flow of lipids from the ER to the lysosome, allowing the lysosome to swell (**5**).



ER, endoplasmic reticulum; LYVAC, lysosome vacuolator; ORP, oxysterol-binding protein–related protein; PI4K2A, phosphatidylinositol 4-kinase type 2 alpha; PI(4)P, phosphatidylinositol 4-phosphate; PS, phosphatidylserine.

and lysosomal swelling. They then used a proximity labeling method to determine what proteins were preferentially recruited to lysosomes. A major hit was PDZD8, a multidomain ER transmembrane protein with a tunnel-like shape capable of tethering the ER to organelles and mediating lipid extraction and transfer (*7*). Yang *et al.* found that recruitment of PDZD8 to stressed lysosomes preceded lysosome vacuolation. In cells lacking the PDZD8 gene, lysosome vacuolation was inhibited and lysosomal osmotic stress was more likely to cause cell death by lysosome rupturing. These observations implicated PDZD8 and nonvesicular lipid transfer in lysosome vacuolation. Therefore, Yang *et al.* renamed PDZD8 as lysosome vacuolator (LYVAC).

Yang *et al.* next analyzed the role of different subdomains of the LYVAC protein in osmotic-induced lysosomal vacuolation using structural and deletion analyses. Negatively charged lipids such as phosphatidylserine on lysosomal membranes were found to recruit LYVAC to the osmotically stressed membrane via LYVAC's C1 domain. Once there, other low-affinity interactions with lysosomal components such as Rab7, a small guanosine triphosphatase involved in regulating membrane traffic, helped establish close contact between the ER-localized LYVAC and lysosome. This enabled lipid transport between the ER and lysosome through LYVAC's lipid tunnel.

How did osmotically stressed lysosomal membranes become enriched in phosphatidylserine in the first place? And what is driving the flow of lipids from the ER to lysosomes once LYVAC is properly positioned? Yang *et al.* addressed these questions by focusing on other lipid transfer proteins, specifically the oxysterol-binding protein (OSBP)–related protein (ORP) family (*8*), that were also enriched on osmotically swollen lysosomes. ORPs are typically recruited to phosphatidylinositol 4-phosphate [PI(4)P]–enriched membranes, where they act as lipid exchangers (*9*). The authors found that apilimod treatment increased the amount of the PI(4)P-producing enzyme PI4K2A on lysosomal membranes, causing recruitment of ORPs to lysosomes. The ORPs then initiated the exchange of PI(4)P on lysosomes with cholesterol and phosphatidylserine on the ER (see the figure). This suggests that ORP-driven increases in phosphatidylserine and cholesterol on osmotically stressed lysosomes set up conditions for recruiting LYVAC. Supporting this possibility, Yang *et al.* found that genetic ablation of the gene encoding PI4K2A abolished both LYVAC recruitment to lysosomes during osmotic stress and lysosomal swelling.

What makes the transfer of lipids from the ER to the lysosome through the LYVAC tunnel unidirectional? The results of liposome transfer assays and molecular dynamic simulations performed by Yang *et al.* suggest that lipid transfer by LYVAC toward phosphatidylserine- and cholesterol-rich lysosomal membranes is chemically favorable because of their finding that lipids move preferentially from cholesterol-poor to cholesterol-rich environments. At the same time, the transfer was energetically favorable because of the membrane tension gradient between the ER and the swelling lysosome, which could help drive lipid movement (*10*). In their model, enhanced membrane tension and increased cholesterol levels in osmotically stressed lysosomes synergize to enable lysosomes to "pull" ER lipids through the LYVAC tunnel to drive lysosomal membrane expansion.

Future work will need to clarify how lysosome swelling under osmotic stress is attenuated. Normally, lysosome swelling is considered helpful to cells because it prevents lysosome rupture, which can trigger cell death by releasing hydrolytic enzymes into the cytoplasm. However, partial, localized, or transient lysosome rupture can be beneficial or even necessary for proper cell function by activating inflammasomes for immune signaling or causing cancer cells to undergo apoptosis or necrosis (*11*). How cells decide to attenuate or continue lysosome swelling to the point of lysosome rupture is thus important to understand. Another avenue for future work is addressing whether LYVAC facilitates the transfer of lipids from the ER to organelles other than lysosomes. For example, LYVAC is found at ER-mitochondria contact sites (*12*). If LYVAC does facilitate transfer of lipids from the ER to mitochondria, it will be important to establish which ORPs are involved and how they are recruited. □

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