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SPOTLIGHT

A pressure relief valve for lysosomes

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Several mechanisms repair damaged lysosomal membranes, but how can lysosomes prevent membrane failure in the first place? Kim et al. (https://doi.org/10.1083/jcb.202509180) uncover a rapid response whereby TMEM63A-dependent ion efflux relieves membrane tension, buying time for slower repair mechanisms to engage.

Lysosomes face threats from both outside and within that can culminate in rupture of their limiting membrane. This is dangerous not only because it disrupts lysosome function but also because it releases lysosome enzymes and inflammatory mediators into the cytosol, potentially triggering cell death. Aberrant lysosome damage responses have been linked to a variety of diseases ranging from microbial pathogenesis to cancer to neurodegenerative diseases (1). These connections have driven a surge of interest in lysosomal membrane injury and repair. Such efforts have defined a growing set of responses that unfold within minutes of membrane lesion, including ESCRT-mediated membrane repair, generation of signaling lipids such as PI4P, and lipid transfer from the endoplasmic reticulum (ER), all of which contribute to restoring membrane integrity (1). However, this focus on repair leaves underexplored a more basic biophysical question: how might lysosomes avoid rupture in the first place?

In this issue, Kim et al. identify the lysosomal mechanosensitive cation channel TMEM63A as part of that first line of defense (2). Rather than repairing a membrane that has already failed, TMEM63A helps prevent catastrophic failure by acting as a pressure relief valve that opens when membrane tension rises and allows efflux of cations from the lysosomal lumen, along with chloride and followed by water (3). The result is reduced hydrostatic pressure, increased membrane flexibility, and a longer window in which slower systems can engage to repair lysosomal membranes (Fig. 1).

Lysosomes are well known for their acidic lumen that is generated by the proton pumping activity of V-ATPases. However, protons are only a small part of the ionic composition of the lysosomal lumen. The lysosomal lumen also contains substantial levels of Na^+, Cl^-, Ca^{2+}, and Fe^{2+}, with approximate concentrations of 120, 115, 0.5, and 0.016 mM, respectively (4). Because biological membranes can stretch only modestly before failing, managing the osmotic effects of these ions poses a mechanical challenge. Furthermore, as lysosomes degrade polymeric macromolecules, the number of osmotically active particles in the lumen increases, which also draws in water and contributes to membrane tension. Lysosomes therefore need to sense and respond to osmotic load to protect the integrity of their limiting membrane. TMEM63A was initially identified for its mechanosensitive properties that provide a stretch-sensitive route for cation release (3, 5). Kim et al. propose that this is a protective process within the context of lysosome membrane damage leading ultimately to an overall reduction in lysosome osmotic pressure that makes lysosomes more resilient.

Intralumenal Ca^{2+} has long been central to models of lysosome damage responses because its leak provides a local damage signal that helps initiate downstream repair responses (4). However, Ca^{2+} is a relatively minor osmotic contributor compared with Na^+, which is present at one to two orders of magnitude higher concentrations inside lysosomes. Consistent with this distinction, although TMEM63A was previously shown to be permeable to Ca^{2+}, Kim et al. found no evidence that Ca^{2+} release is the main basis of TMEM63A-dependent lysosome protection (3, 5). Instead, osmotic stress caused TMEM63A-deficient lysosomes to burst. Blunting the Na^+/K^+ gradient reduced damage susceptibility, implicating these monovalent cations in the protective effect. These results demonstrate a division of labor in which monovalent ion efflux acts acutely to relieve pressure, whereas Ca^{2+} release is more important as a signal to mobilize repair pathways.

One question raised by this new paradigm is how water escapes the lysosome following TMEM63-dependent ion efflux. Although water can cross membranes to a limited extent, a dedicated lysosomal water channel would provide a more efficient means to rapidly reduce luminal volume and relieve osmotic stress. Such a water channel has not yet been identified but could help explain how lysosomes couple ion movement to rapid water efflux during acute mechanical challenges.

TMEM63A may contribute to additional aspects of lysosome damage responses, as it was recently reported to possess lipid scrambling activity (6). If this activity operates in the context of lysosome injury, TMEM63A could, in addition to relieving internal pressure, also help support the

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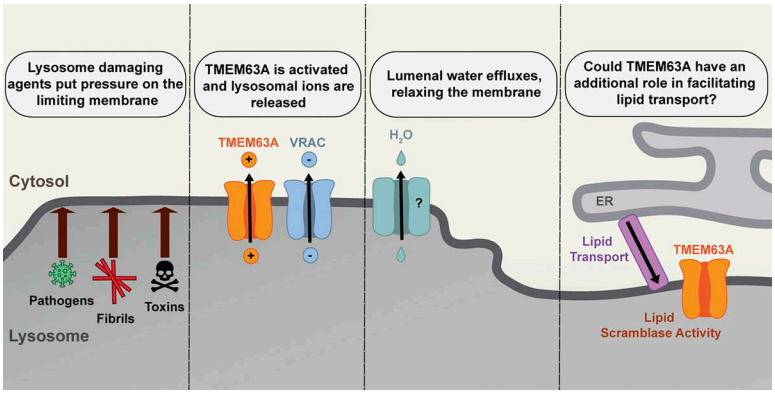

Figure 1. **Lysosomal mechanoresilience prevents membrane rupture.** Lysosome-damaging stimuli (including pathogens, protein fibrils, and toxic chemicals) increase lumenal pressure and thereby elevate tension on the lysosomal membrane. In response to this tension, TMEM63A, a mechanosensitive cation channel, opens and allows cations to exit the lysosomal lumen into the cytosol; anions must follow through channels such as VRAC to maintain ionic balance. Ion efflux drives water out of the lysosome, possibly through a water channel, resulting in an acute reduction in lysosomal volume and hydrostatic pressure. In this way, TMEM63A-dependent solute efflux helps prevent lysosomes from rupture. Because TMEM63A has also recently been reported to possess lipid scramblase activity, it may additionally help facilitate bulk lipid transport from the endoplasmic reticulum (ER) during lysosomal mechanical stress.

influx of lipids that contribute to membrane repair. That possibility is especially compelling because bridge-like lipid transporters, such as VPS13C, acutely respond to lysosome damage and could benefit from a lipid scramblase to equilibrate newly delivered lipids across the lysosome membrane bilayer (7). TMEM63A is therefore well positioned to couple ion flux to membrane remodeling.

The implications extend beyond cell biology into innate immunity. Kim et al. show that TMEM63A protects phagolysosomes challenged by the fungal pathogen *Candida albicans*, whose hyphal growth exerts pressure from within the compartment. This finding highlights mechanoresilience as an adaptive property that may shape host–pathogen interactions. More broadly, lysosome damage contributes to innate immune signaling pathways, so mechanisms that restrain inappropriate rupture are likely to be of broad importance for tuning immune responses (1, 4).

These new insights are also timely in the context of neurodegeneration. Protein fibrils implicated in neurodegenerative disease are increasingly understood to spread through pathways involving lysosome membrane rupture (8). Meanwhile, the lysosome damaging agent leucyl–leucyl-O-methyl-ester (LLOMe) was very recently found to damage lysosome membranes via the growth of amyloid fibrils (9, *Preprint*, 10, *Preprint*). In that sense, LLOMe exposure may mimic aspects of the physical stresses faced by neuronal and glial lysosomes during neurodegenerative disease pathogenesis. As shown by Kim et al., TMEM63A is critical for protecting macrophages from LLOMe-induced rupture. Indeed, lysosomes in TMEM63A KO cells were ∼10× more sensitive to this perturbation. The relationship between LLOMe-induced lysosome damage and amyloid fibrils linked to neurodegenerative diseases (including amyloid β, tau, TMEM106B, and α-synuclein) may broaden the impact of the fundamental principles illuminated by (2).

Good membrane repair is essential, but preventing rupture in the first place is even better. By providing a pressure-induced route for osmolyte escape, TMEM63A lowers lysosome membrane pressure before rupture can occur and thus provides an extra layer to the rapidly growing armament of lysosome defense mechanisms. In this view, lysosomes keep it together because they can bend before they break.

Data availability

No data, protocols, or key laboratory materials were used or generated.

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