JCB Journal of Cell Biology

SPOTLIGHT

Is the Parkinson's-associated protein TMEM175 a proton channel: Yay or nay?

Spencer A. Freeman[1,2] and Sergio Grinstein[1,2]

The abnormal protein degradation implicated in the pathogenesis of Parkinson's disease was previously attributed to defective H^+ leakage from lysosomes via TMEM175 (https://doi.org/10.1016/j.cell.2022.05.021). In this issue, Riederer et al. (https://doi.org/10.1083/jcb.202501145) demonstrate that TMEM175 is instead a K^+ channel, minimally permeable to H^+.

The acidic nature of lysosomes is thought to be central to their role as a degradative and metabolic supply and regulation hub. Abnormal cleavage of key proteins has been implicated in the pathogenesis of various diseases, notably Alzheimer's and Parkinson's disease (PD); impaired degradation has often been attributed to dysregulation of the lysosomal pH. Specifically, hyperacidification of the lysosomal lumen was proposed to cause the accumulation of α-synuclein in PD (1).

The establishment and maintenance of the lysosomal pH are thought to result from a finely calibrated balance between inward proton (H^+) pumping by vacuolar (V)-type ATPases and outgoing H^+ "leak" pathways (Fig. 1). Each V-ATPase is believed to pump 10 H^+ for every 3 molecules of ATP it hydrolyzes. Based on this stoichiometry and assuming strict coupling, the energy delivered by ATP can generate a ΔpH of 3 full units across the lysosomal membrane (inside acidic). Considering that the cytosolic pH is reported to average 7.0–7.2, the luminal pH of lysosomes could therefore reach 4.0. This predicted $[H^+]$ is 5–10 times greater than the reported physiological values (pH 4.7–5.0).

What accounts for this discrepancy? Because H^+ pumping is electrogenic, the existence of a sizable transmembrane potential (inside positive) could explain the reduced acidification. Regrettably, available methods to measure translysosomal membrane voltage are indirect and inaccurate. On the other hand, the failure to attain the pH predicted on thermodynamic grounds can be explained by the existence of H^+ "leaks," i.e., pathways that enable passive H^+ efflux, counteracting the effectiveness of the V-ATPase pumps. Indeed, the use of pump inhibitors reveals that the V-ATPases are not at thermodynamic equilibrium but rather continuously active yet offset by a countervailing leak. An acute addition of specific blockers of the pump such as bafilomycin or concanamycin causes a gradual lysosomal alkalinization, unmasking the constitutive H^+ leak pathways.

The magnitude of the leak can be estimated from the rate of ΔpH and the lysosomal buffering power. In their widely cited paper, Hu et al. (1) estimated the leak to be 10^4–10^5 ions/sec per lysosome, equivalent to a 0.1–1 pA current. In search of the pathway underlying this sizable current, these authors identified an H^+-conductive channel on the lysosomal membrane. Not only was this channel exquisitely H^+-selective (48,000-fold more permeable to H^+ than to K^+), but it was in addition gated by H^+, ensuring its activation at exceedingly low pH, thereby preventing undue acidification. Using an elegant expression-screening strategy, Hu and colleagues were able to attribute the conductance to TMEM175, formerly thought to be a K^+-selective channel (4, 5). These findings attracted much attention, since TMEM175 was earlier identified as a PD-associated protein (6, 7, 8). Indeed, the link with PD pathogenesis was strengthened by the observation that in cells where TMEM175 was deleted or otherwise inactivated, the lysosomal pH became hyper-acidified (by ∼0.3 pH units) and that under these conditions, proteolysis was impaired, including that of α-synuclein, a hallmark of PD.

These remarkable observations prompted Ren and colleagues, the team that had originally designated TMEM175 as a K^+ channel (4, 5), to rigorously reexamine the ionic selectivity and functional role of the channel. As reported in the article by Riederer et al. in this issue (9), careful reanalysis confirmed that under physiological conditions, TMEM175 is highly K^+-conductive and rather poorly permeable to H^+. Two key differences explain the disparate findings: the experiments leading Hu and colleagues to the conclusion that TMEM175 is highly H^+-selective were largely performed in the absence of K^+. This seemingly led to a change in ionic selectivity, a common consequence of removal of the preferred ion of a channel. Thus, Ca_V channels become nonselective in the absence of extracellular divalent ions (10) and several K^+ channels similarly lose selectivity and/or display impaired conductivity when K^+ is omitted. The altered behavior of TMEM175 under equivalent conditions is therefore not unexpected. Moreover, the high H^+ selectivity estimated by Hu et al. (1) was determined mistargeting TMEM175 to the plasma membrane, where the prevailing lipid composition and bilayer curvature and

[1]Program in Cell Biology, The Hospital for Sick Children, Toronto, Canada; [2]Department of Biochemistry, University of Toronto, Toronto, Canada.

Correspondence to Sergio Grinstein: sergio.grinstein@sickkids.ca.

© 2025 Freeman and Grinstein. This article is distributed under the terms as described at https://rupress.org/pages/terms102024/.

Check for updates

Downloaded from http://rupress.org/jcb/article-pdf/225/1/e202511084/1954150/jcb_202511084.pdf by guest on 12 December 2025

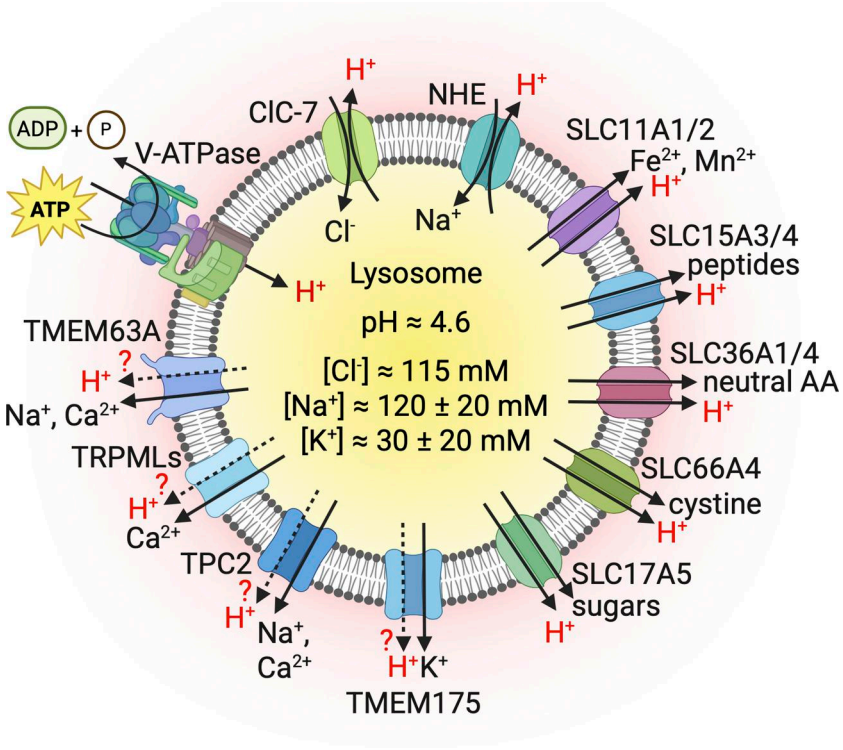

Figure 1. **Proton-transporting systems in lysosomes.** The luminal concentrations of Cl^-, Na^+, and K^+ are rough approximations based on often disparate data. Dotted lines indicate modest, in some instances speculative, permeability to H^+. The stoichiometry of exchangers and cotransporters is not indicated. See references (2, 3) for details.

tension are different from those in lysosomes; some of these experiments used a pH of 3.5, which is much below the physiological level. It would therefore appear that because they were obtained under more physiological conditions, the recent results of Ren's group better reflect the natural selectivity and function of TMEM175. Accordingly, they report that rather than causing hyper-acidification, deletion of the channel is associated with alkalinization of challenged lysosomes.

The need for an H^+-permeable channel to account for the leak is also debatable on theoretical grounds. Unlike the rather large proton leak estimated by Hu et al. (1) to be equivalent to 0.1–1 pA, Riederer et al. arrive at a much lower value based on measurements of the rate of alkalinization induced by inhibition of the pump. Their estimate of ~0.02 fA corresponds to a flux of only ~100 ions/sec. Notably, Riederer et al. concluded that TMEM175 makes no contribution to the leak, which they found to be comparable in wild-type and mutant lysosomes lacking the channel. In this light, it must be borne in mind that H^+ efflux is known to be tightly coupled to the transport of a variety of critical substrates into or out of lysosomes. Thus, the export of amino acids, dipeptides, sialic acid, and iron is driven by the outward H^+ gradient (2), as is the accumulation of luminal Cl^- (3) and likely also of Na^+. Considering the essential need for such coupling, dissipation of the H^+ gradient through an unproductive channel would seem contraindicated. Uncoupled H^+ leakage, e.g., via UCP1, is well suited for thermogenesis in brown fat mitochondria, but may be wasteful in lysosomes.

While its contribution to the H^+ leak is debatable, the role of TMEM175 in PD pathogenesis is unquestionable. Several groups have confirmed independently that TMEM175 deficiency increases α-synuclein aggregation, ultimately leading to the degeneration of dopamine-producing neurons. Transport of K^+ through the channel may underlie these effects by altering the membrane potential and/or the ionic composition of endocytic compartments, but other modes of action of TMEM175 cannot currently be ruled out. Nevertheless, efforts to resolve PD by application of exogenous protonophores to partially dissipate the lysosomal ΔpH may be ill-advised.

Acknowledgments

Spencer A. Freeman was supported by Canadian Institutes of Health Research grants PJT-190244 and PJT-203704. The figure was created with biorender.com.

Author contributions: Spencer A. Freeman: writing—original draft, review, and editing. Sergio Grinstein: conceptualization and writing—original draft, review, and editing.

Disclosures: The authors declare no competing interests exist.

References

1. Hu, M., et al. 2022. *Cell*. https://doi.org/10.1016/j.cell.2022.05.021
2. Freeman, S.A., et al. 2023. *Physiol. Rev.* https://doi.org/10.1152/physrev.00009.2022
3. Scheel, O., et al. 2005. *Nature*. https://doi.org/10.1038/nature03860
4. Cang, C., et al. 2015. *Cell*. https://doi.org/10.1016/j.cell.2015.08.002
5. Lee, C., et al. 2017. *Nature*. https://doi.org/10.1038/nature23269
6. Wie, J., et al. 2021. *Nature*. https://doi.org/10.1038/s41586-021-03185-z
7. Lill, C.M., et al. 2015. *Mov. Disord*. https://doi.org/10.1002/mds.26237
8. Jinn, S., et al. 2017. *Proc. Natl. Acad. Sci. USA*. https://doi.org/10.1073/pnas.1616332114
9. Riederer, E., et al. 2026. *J. Cell Biol*. https://doi.org/10.1083/jcb.202501145
10. Almers, W., and E. W. McCleskey. 1984. *J. Physiol*. https://doi.org/10.1113/jphysiol.1984.sp015352

Downloaded from http://rupress.org/jcb/article-pdf/225/1/e202511084/1954150/jcb_202511084.pdf by guest on 12 December 2025