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COMMENTARY

The mitochondrial swelling channel

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Early bioenergeticists who described the principles of chemiosmosis were aware that swelling of mitochondria was a likely and even frequent event, based on the large electrochemical gradient of K+ ions across the mitochondrial inner membrane. Swelling could be measured as a change in electron density by electron microscopy or by spectrophotometry in isolated mitochondria. The mitochondrial permeability transition (mPT) was originally described as an acute swelling change in mitochondria, later determined to be caused by the rapid opening of a pore (mPTP) defined biophysically and pharmacologically as a Ca^{2+}- and voltage-dependent, cyclosporine A-sensitive large-conductance channel. The identity of the pore is controversial, but the ATP synthase c-subunit is a major candidate. In their breakthrough study (Akosah et al. https://doi.org/10.1085/jgp.202613979), they establish a novel dark-field imaging approach, allowing detection of mitochondrial swelling in living cells. Swollen mitochondria exhibit decreased light scattering and, therefore, microscopically "disappear." The cell-based imaging technique enables dissection of two separate processes, mitochondrial swelling, and depolarization. The authors demonstrate that K^+ influx causes swelling but not immediate mitochondrial depolarization in wild-type cells, whereas in ATP synthase c-subunit knockout cells, Ca^{2+}-dependent mitochondrial depolarization occurs without swelling, suggesting a lack of K+ influx. The results suggest that the ATP synthase c-subunit channel is the key member of a channel complex constituting the "swelling channel" of the mPTP.

The causes of mitochondrial swelling have their origins in the tenets of the chemiosmotic theory of Mitchell (1961), mostly centered on potassium ion (K^+) homeostasis. Swelling also gained attention for its role in mitochondrial permeability transition (mPT), which is an acute Ca^{2+}-induced change in mitochondrial osmotic status often signaling cell death (Hunter et al., 1976). Electrophysiological recordings demonstrated that mitochondrial matrix swelling and subsequent rupture of the mitochondrial outer membrane were due to the opening of a voltage-dependent, high-conductance, nonselective channel of the mitochondrial inner membrane, named the "mitochondrial megachannel" or "multiconductance channel" (Kinnally et al., 1989; Petronilli et al., 1989), sensitive to the cyclophilin D (CypD) inhibitor CsA (Szabo and Zoratti, 1991). The opening of the mitochondrial permeability transition pore (mPTP) not only causes irreversible, death-inducing changes to mitochondria, but also regulates many functions not involving cell death, including Ca^{2+} homeostasis and signaling, ATP synthesis efficiency, and cell metabolism (Bernardi et al., 2023). This makes it likely that the mPTP forms a key channel regulating osmotic balance in health and disease.

Here, in Akosah et al. (2026) the molecular identity of the "swelling" channel, previously a candidate for the mPTP, is put forth, and the case is made, and again in this commentary, for its role as the main channel of mPTP, the molecular identity of which is still in question. In the whirlwind of the controversy surrounding mPTP identity, investigators have tended to overlook the fact that the fundamental role of mPTP opening is to alter the osmotic barrier of the mitochondrial inner membrane, modifying the concentration of ions and proteins inside the mitochondrial matrix. The identity of the channel molecule that regulates this process is therefore a critical question in biology. In addition, previous methods to investigate pore candidates failed to address pore opening or swelling *in situ* and therefore may have led to incorrect conclusions. The new technique now demonstrated in Akosah et al. (2026) sets the record straight by extending the ability to study mitochondrial swelling to living cells.

In the past, almost all osmotic changes were gauged as changes in optical density and light scattering in isolated mitochondria (Hackenbrock, 1966; Halestrap, 1989). In the isolated mitochondrial preparation, swelling appears as a decrease in light scattering (Hackenbrock, 1966) detected using a spectrophotometer to measure the decrease in absorbance at a predetermined wavelength (Garlid and Beavis, 1985). Now, to study changes in mitochondrial matrix volume and permeability transition in living cells, Akosah et al. (2026) established a novel dark-field imaging approach. This technique uses an opaque

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ring to block the light path onto a cell in an inverted microscope. Only the most distal or divergent beams of light from the source are bent by the condenser that sits under the cell to illuminate it. If this distal transmitted light passes straight, it misses the lens above the cell, while in contrast, the light scattered by the specimen is sent through the lens to the detector. In this configuration, increases in water content inside mitochondria will keep the light beams straight and cause mitochondria to "disappear." Mitochondrial optical density changes are, thereby, easily detected as changes in visibility of the entire mitochondrial structure.

There is a long history of the study of mitochondrial swelling (Chappell and Greville, 1959). Swelling is related to a breach in the inner mitochondrial membrane that otherwise constitutes a relatively tight energy barrier because of a low permeability to protons, anions, and cations (Mitchell, 1961). During respiration, mitochondrial ATP is produced by utilizing the H^+ electrochemical potential generated by four membrane-localized complexes that carry out oxidoreduction of a series of molecules containing high-energy bonds. The energy released upon breaking these bonds is indeed used to pump H^+ across the mitochondrial inner membrane, developing a large potential difference. Mitchell proposed that K^+ ions, which are very high in the cytosol of most cells, would need to be held out of the mitochondrial matrix, along with H^+ ions, and that the key mechanism to prevent K^+ accumulation and matrix swelling was operation of an electroneutral H^+/K^+ exchange (Mitchell, 1961). He felt that the impermeability to ions is key in preventing K^+ influx. Subsequently, it was surmised that small changes in permeability would produce changes in mitochondrial matrix osmotic state, volume, and inner membrane structure. These alterations could lead to rapid changes in the efficiency of bioenergetics (Appelhans and Busch, 2017). The kinetics of these permeability changes were thought to mostly relate to K^+ cycling since K^+ is the dominant intracellular ion.

Given the high concentration gradient of K^+, the resulting influx or uptake burden of K^+ must be balanced by K^+ efflux to prevent the loss of membrane potential and bioenergetic power in health (Bernardi, 1999). The efflux was effectively shown in 1980, where Azzone et al. demonstrated that the K^+ ionophore valinomycin caused membrane depolarization followed by increases in respiration (H^+ ion pumping by the electron transport complexes), leading to a new "resting" or steady-state (more depolarized) "equilibrium" potential dependent on the concentration of valinomycin (Azzone et al., 1978; Bernardi, 1999). When K^+ was allowed to move into the matrix with valinomycin application, there was an equivalent permeabilization to water so that any net uptake of K^+ was accompanied by osmotic swelling. Confirmed by Garlid's group, the K^+ electrochemical gradient favored continuous K^+ accumulation, leading to matrix swelling that could result in breakdown of the outer membrane and loss of mitochondrial function unless an efflux mechanism, albeit a slow one, were present. Proof of the presence of a K^+/H^+ exchanger postulated by Mitchell was provided by another experiment (Dordick et al., 1980) where chelation of matrix Mg^{2+} removed the "brake" on the endogenous slow K^+/H^+ exchanger, while subsequent pharmacological intervention using the K^+/H^+ exchange reagent nigericin hastened K^+ efflux in exchange for H^+, again activating respiration. In summary, the massive electrochemical potential gradient for K^+ across the inner membrane leads to unavoidable influx of K^+ and its accompanying anions that lead to swelling. One important note is that the anion to balance the K^+ charge is likely to be phosphate in cells, but in early studies of isolated mitochondria, acetate (acetic acid) was used (Bernardi, 1999). It has been proposed that a complex containing Ydl183p and the Mdm38p human homologs Mrs7p, LETM1, and HCCR-1 is involved in the formation of a K^+/H^+ exchanger complex (Zotova et al., 2010).

The new technique developed by Akosah et al. (2026) allows the old valinomycin experimental results to be validated in intact cells. Akosah et al. (2026) show a decrease in light scattering following valinomycin application, and they mirror these changes with electron microscopic imaging. They also demonstrate that not surprisingly, inducing K^+/H^+ exchange pharmacologically with nigericin prevents the decrease in light scattering and, when used on its own, even increases light scattering, reflecting a decrease in matrix volume. For the first time, they also now demonstrate definitively that swelling with valinomycin long precedes mitochondrial depolarization, confirming the dissociation of swelling and membrane potential changes and suggesting operation of the slow endogenous K^+/H^+ exchanger.

Incidentally, a low volume state of the mitochondrial matrix was also observed in the 1960s in early electron micrographs of isolated mitochondria. This electron-dense state was defined as the "condensed state," and it was found to be present while ATP was being synthesized (Hackenbrock, 1966). The "orthodox" state was defined as one with a less electron-dense matrix, occurring in resting mitochondria that had a good membrane potential but were not actively making ATP because ADP had not been provided. Akosah et al. (2026) were able to show that these three states of orthodox, swollen, and condensed accompany kinetic changes in swelling and membrane potential in living cells.

Most exciting in Akosah et al. (2026) is the use of the novel technique to define the molecular identity of the K^+ uptake channel that causes swelling and to determine whether the channel is required for permeability transition (Fig. 1). It is important to note here that swelling during mPT is not caused by Ca^{2+} influx; rather, it is caused by the opening of a Ca^{2+}-sensitive cation channel that conducts K^+ (in addition to Na^+, H^+). If water were to also enter the matrix through the same channel, that channel would constitute a swelling channel. Although the exact molecular identity of "the pore" of mPTP is still in question, the ATP synthase c-subunit has weathered time and criticism to rise to the top of the list as the major candidate. A protein complex containing the c-subunit was first shown to induce pore activity in 2005 (Pavlov et al., 2005). In 2013, Giorgio et al. and subsequently Urbani et al. and Mnatsakanyan et al. suggested that ATP synthase contained the pore for mPTP (Giorgio et al., 2013; Mnatsakanyan et al., 2019; Urbani et al., 2019). Pinton's group genetically knocked down (KD) the c-subunit (Bonora et al., 2013), reducing mPT-induced cell death. Alavian et al. (2014) used patch clamping to record the highly purified c-subunit

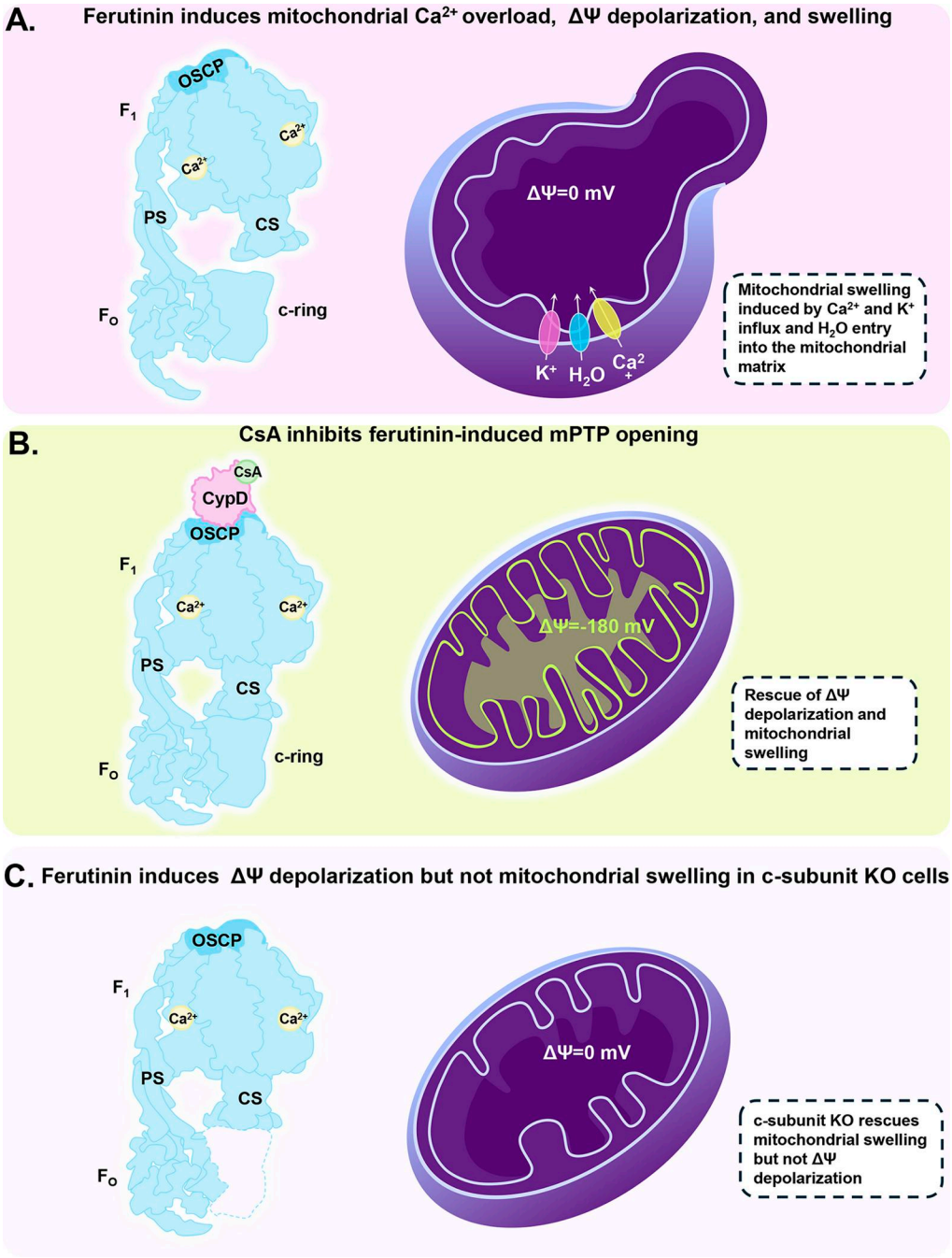

Figure 1. **ATP synthase c-subunit is a key channel required for mPTP-induced swelling. (A)** Left: Schematic illustration of hypothetical conformational changes within the ATP synthase upon activation of the c-subunit leak channel. Right: Ferutinin induces mitochondrial Ca^{2+} overload, ΔΨ depolarization, and mitochondrial swelling via mPTP opening that involves the activation of the ATP synthase leak channel and other mechanisms. **(B)** Left: Schematic illustration of ATP synthase leak channel inhibition by CsA. Right: CsA inhibits ferutinin-induced mitochondrial Ca^{2+} overload, ΔΨ depolarization, and mitochondrial swelling via inhibition of mPTP. **(C)** Left: Schematic illustration of ATP synthase in c-subunit knockout HAP1 cells. Right: Ferutinin induces mitochondrial Ca^{2+} overload and ΔΨ depolarization, but not mitochondrial swelling in c-subunit knockout HAP1 cells.

reconstituted into lipid membranes and redemonstrated that c-subunit KD was protective. The study also demonstrated in patch recordings that a purified mutant c-subunit had a fixed large conductance and that this mutant increased the propensity toward cell death, subsequently confirmed in cardiac patients (Morciano et al., 2021). Mnatsakanyan et al. (2022) used highly purified human ATP synthase c-subunit rings from HEK293 cells and *Escherichia coli* to demonstrate that c-subunit rings form large voltage-dependent ion channels. In this report, c-subunit KD reduced the conductance of the inner membrane and prevented a CsA-sensitive channel activity in patch-clamp recordings. C-subunit KD also prevented Ca^{2+}-induced swelling in light-scattering experiments performed with isolated mitochondria. During glutamate excitotoxic cell death in neurons,

the ATP synthase F_1 domain was separated from the F_O (c-ring) and was degraded, while the c-subunit was then free to exacerbate neuronal death (Mnatsakanyan et al., 2022). Furthermore, purified F_1 closed the purified, reconstituted c-subunit channel in electrophysiological recordings, suggesting that F_1 formed an inactivation gate on the matrix side of the channel. In a recent study, Mnatsakanyan and her colleagues solved the structure of the mPT- and anoxia-resistant ATP synthase of the brine shrimp *Artemia franciscana* and showed that the e-subunit forms another inactivation gate on the intermembrane space side. *Artemia* also has adaptations in OSCP that make the stator stalk resistant to Ca^{2+}-induced conformational changes, thus preventing F_1 dissociation from F_O and channel activation (Kumar et al., 2025).

Despite this wealth of data, the contributing nature of the ATP synthase c-subunit appeared to be refuted by showing that HAP1 c-subunit knockout cells demonstrated similar Ca^{2+} retention capacity (CRC) as wild-type cells (He et al., 2017). However, these cells lack the large-conductance (1.5 nS) mPTP-like activity of the inner membrane as shown in patch-clamp recordings (Neginskaya et al., 2019). They only possess a small conductance (~300 pS), albeit CsA-sensitive channel that is attributed to the ATP/ADP exchanger (AAC). The CRC technique measures membrane potential and Ca^{2+} concentration–dependent Ca^{2+} uptake; thus, cells that demonstrate depolarized mitochondrial membrane potential secondary to high mitochondrial Ca^{2+} have impaired CRC. Akosah et al. (2026) suspected that relying only on CRC measurements to diagnose mPT would fail since the technique would miss changes in swelling. Therefore, they first set out to demonstrate that swelling and membrane potential loss are separable, albeit related events. They showed that valinomycin application induces swelling, which is eventually followed by membrane depolarization, perhaps due to electron transport chain loss of H^+ ions, whereas during mPT caused by application of the Ca^{2+} ionophore ferutinin, the membrane potential is lost first, due to Ca^{2+} influx, followed by swelling. Akosah et al. (2026) show that sometimes even upon complete loss of membrane potential (such as with application of FCCP), the resultant futile H^+ cycling is not associated with swelling, since large K^+ influx does not occur. However, if Ca^{2+} influx induces opening of a large-conductance K^+ (and water) channel, this opening will cause swelling. Regulated or small K^+ influx may not cause complete depolarization even when a small degree of swelling occurs, since K^+ cycling balances influx with K^+/H^+ exchange and respiratory chain activity. In contrast to the scenario with channel opening, if opening does not occur, eventual depolarization of the membrane potential by Ca^{2+} influx even without K+influx-induced swelling is sufficient to impair further Ca^{2+} uptake in the CRC experiment, thus allowing incorrect assumptions regarding mPTP activation.

After defining the parameters, to definitively test whether the ATP synthase c-subunit forms a K^+ channel that causes both mPT and swelling, Akosah et al. (2026) used the same HAP-1 cells that demonstrated the loss of Ca^{2+} retention in the CRC study, then used light scattering in the living cells to test whether ferutinin could induce swelling in a dynamic fashion. They show that the cells lacking the c-subunit are completely resistant to swelling, despite the occurrence of depolarization also previously shown by the Walker group (He et al., 2017). This implies that mitochondria depolarize due to the Ca^{2+} load but are resistant to swelling. It was concluded, therefore, that in the absence of an assembled ATP synthase, the voltage-dependent mPT fails to open even upon full Ca^{2+}-induced depolarization (Fig. 1). Slightly different observations were made upon c-subunit KD in mouse embryonic stem cells (Mnatsakanyan et al., 2022). According to transmission electron microscopy imaging, mitochondria appeared swollen and had disrupted crista morphology at baseline in c-subunit KD compared with WT. This could be explained by the key role of ATP synthase in shaping the cristae folds. However, c-subunit KD cells did not swell further upon ionomycin treatment (Ca^{2+}-overload), similar to observations made in Akosah et al. (2026).

There is emerging evidence that the AAC may still form a channel in addition to the ATP synthase c-subunit, especially when ATP synthase c-subunit channel activity is inhibited or genetically deleted (Neginskaya et al., 2019), supporting the overwhelming physiological importance to cells of mPT. Studies suggest that the CsA/CypD sensitivity observed in HAP1 c-subunit knockout cells was likely caused by AAC forming a channel, supported by recent reports (Karch et al., 2019; Neginskaya et al., 2019). In a recent study (Tommasin et al., 2025), low pH was used to inhibit the ATP synthase channel, causing activation of AAC upon mPT stimulation. In that report, the authors concluded that the ATP synthase and AAC channels reside in a supercomplex.

Conclusion

Akosah et al. (2026) highlight the multifaceted nature of mitochondrial swelling, and its relationship to membrane potential changes, to mPT, and to activation of mPTP. This study also reinforces the need to use direct and comprehensive approaches to evaluate mitochondrial physiology.

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