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Minireview

On the structural possibility of pore-forming mitochondrial F_oF_1 ATP synthase☆

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ABSTRACT

The mitochondrial permeability transition is an inner mitochondrial membrane event involving the opening of the permeability transition pore concomitant with a sudden efflux of matrix solutes and breakdown of membrane potential. The mitochondrial F_oF_1 ATP synthase has been proposed as the molecular identity of the permeability transition pore. The likeliness of potential pore-forming sites in the mitochondrial F_oF_1 ATP synthase is discussed and a new model, the death finger model, is described. In this model, movement of a p-side density that connects the lipid-plug of the c-ring with the distal membrane bending F_o domain allows reversible opening of the c-ring and structural cross-talk with OSCP and the catalytic $(\alpha\beta)_3$ hexamer. This article is part of a Special Issue entitled 'EBEC 2016: 19th European Bioenergetics Conference, Riva del Garda, Italy, July 2–6, 2016', edited by Prof. Paolo Bernardi.

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1. Introduction

Mitochondrial F_oF_1 ATP synthase is a surprising molecular machine. Not only does it utilize electrochemical energy in the form of Mitchell's proton motive force (pmf) to fuel its ATP forming function [1–4], but also does the energy transformation from pmf to ATP occur via mechanical rotation [5–13]. Over the course of more than 20 years and much to everyone's surprise, its active role in membrane bending and cristae formation emerged [14–23] and only very recently, against all anticipation, a horizontal arrangement of the elusive α-helical architecture of the a-subunit was visualized [24–26].

And now labs that investigate the so-called mitochondrial permeability transition pore (ptp) suggest that mitochondrial F_oF_1 ATP synthase could form a large pore in the inner mitochondrial membrane [27–34], a suggestion that is completely contrary to its energy-converting function which requires a proton tight coupling membrane [35,36]. After more than 50 years of active research on the mitochondrial F_oF_1 ATP synthase [37], the addition of a pore-forming function is perhaps too much of a surprise and, predictably, the reaction of the F_oF_1 ATP synthase field has been rather muted [38,39]. In this short review I would like to critically discuss the structural possibility of pore-forming mitochondrial F_oF_1 ATP synthase, including the likeliness of models put forward by myself and others.

2. The mitochondrial permeability transition pore

The mitochondrial permeability transition involves a sudden efflux of matrix solutes of up to 1.5 kDa size, a breakdown of the inner mitochondrial membrane potential ($\Delta\Psi_m$) and an influx of water into the matrix which results in mitochondrial swelling. The mitochondrial permeability transition was first described as a swelling of isolated mitochondria in the 1950s [40,41] and coined permeability transition by Hawthorne et al. in the late 1970s [42–44]. Parallel to this, a mitochondrial megachannel was discovered by patch-clamp experiments on isolated mitoplasts, mitochondria from which the outer membrane was removed through osmotic shock [45,46]. Subsequently it was realized that both the permeability transition (pt) and the mitochondrial megachannel (MMC) have the same underlying molecular base: the permeability transition pore (ptp) [47]. The ptp in its fully open state is highly conductive (~1 nS), with a diameter estimated to be larger

Abbreviations: OSCP, oligomycin sensitivity conferring protein; ptp, permeability transition pore; mpt, mitochondrial permeability transition; pmf, proton motive force; $\Delta\Psi_m$, electric potential across the inner mitochondrial membrane; MMC, mitochondrial mega channel; kDa, 1000 Da; Å, 0.1 nm; nS, nano Siemens; pS, pico Siemens; ROS, reactive oxygen species; P_i, inorganic phosphate solubilized in water; pH, negative decadic logarithm of the proton concentration; CyPD, mitochondrial cyclophilin D; CsA, cyclosporin A; ANT, mitochondrial adenine nucleotide translocator; VDAC, voltage-dependent anion channel of the outer mitochondrial membrane; DAPIT, diabetes sensitive-protein in insulin-sensitive tissue; PS, peripheral stalk; CS, central stalk; PD, p-side density; p-side, positive side of the coupling membrane; n-side, negative side of the coupling membrane; EM, electron microscopy; cryoEM, cryogenic electron microscopy.

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than 14 Å and unspecific to solutes up to ~1.5 kDa [48,49]. For short full openings the ptp remains reversible [50–53], whereas prolonged opening is irreversible and triggers the release of pro-apoptotic factors such as cytochrome *c* [54]. Electrophysiological measurements suggest substates of openings and "flickering" at lower conductance [55]. Molecular modulators that enable or promote ptp opening include matrix Ca^{2+}, a diminished $\Delta\Psi_m$, reactive oxygen specimen (ROS), matrix P_i, fatty acids, pH, polyphosphate and the binding of mitochondrial cyclophilin D (CyPD), a peptidyl-prolyl *cis–trans* isomerase. An inhibiting effect on pore opening is elicited by ADP/Mg^{2+} and binding of cyclosporine A (CsA) to CyPD [56]. Among the plethora of molecular players only CyPD is recognized as a bona fide binding partner of the ptp [57,58]. Thus the recent attention on mitochondrial F_oF_1 ATP synthase as being the possible molecular identity of the ptp is the result of assays screening for potential CyPD binding partners, which identified CyPD to be co-migrating with the mitochondrial F_oF_1 ATP synthase in blue native gels [27] and the subunit OSCP (oligomycin sensitivity conferring protein) as a binding site [29]. However, many other molecular candidates of the ptp that were investigated in the past were later dismissed or become the subject of intense debate, such as ANT, VDAC, TSPO or polyphosphate. As such, skepticism is warranted [59,60]. The mitochondrial F_oF_1 ATP synthase's recycling of ATP from ADP·Mg^{2+} and P_i is the major source of ATP in respiring cells [61]. Its intricate bipartite structure is traditionally divided into the water soluble F_1 domain, comprising subunits α_3, β_3, γ, ε and δ, and the membrane bound F_o domain harboring the proton transporting c_8-ring and subunits a, A6L, b, d, F_6, OSCP (oligomycin sensitivity conferring protein), e, g, f, DAPIT (diabetes-associated protein in insulin-sensitive tissue; also termed AGP) and 6.8 kDa (also termed MLQ) for the bovine enzyme [62,63]. Following its function as a rotational energy converter an alternative denomination is into a rotor part (c_8-ring and the central stalk (CS) subunits γ, ε and δ) and a stator part (α_3, β_3, OSCP, b, d, F_6, a, A6L, e, f, g, DAPIT and 6.8 kDa) with OSCP, b, d and F_6 belonging to the peripheral stalk (PS) that anchors the catalytic $(\alpha\beta)_3$ hexamer to the transmembrane domain of the stator. Mitochondrial F_oF_1 ATP synthase from yeast has a very similar composition, with the exception that in its F_o domain the c-ring contains 10 c-subunits and lacks DAPIT and 6.8 kDa but instead contains the additional subunits j and k [64]. The most detailed structural insights have been gleaned from X-ray crystal structures of mitochondrial F_oF_1 ATP synthase subcomplexes, namely the F_1, the F_1–c_8, the F_1–c_{10}, a peripheral stalk fragment and the F_1–PS fragment subcomplex [65–69]. However, no atomic model of an entire mitochondrial F_oF_1 ATP synthase is available and for some of the F_o subunits location and function are unknown [70, 71]. At present the best structural data on intact mitochondrial F_oF_1 ATP synthases is provided by cryoEM single particle studies, albeit at limited resolution or quality [24,25,72]. This lack of high resolution structural information on the architecture of mitochondrial F_oF_1 ATP synthase leaves a discussion of structural possibilities for pore formation unavoidably speculative though not, it can certainly be argued, meaningless.

3. Potential pore sites of the mitochondrial F_oF_1 ATP synthase

Thus far two main sites of possible pore-formation in mitochondrial F_oF_1 ATP synthase have been proposed: the monomer–monomer interface of the dimer (Fig. 1A) [29,31,33] and the c-ring (also termed rotor ring for its proton transport coupled directional rotation) by itself and in the context of mitochondrial F_oF_1 ATP synthase [30,32] (Fig. 1B, D). The dimer proposal is based on electrophysiological recordings of a black membrane that yielded currents in agreement with the known electrophysiological properties of the ptp after addition of mitochondrial F_oF_1 ATP synthase dimers that were excised and extracted from blue native gels. No ptp-like currents were observed after the addition of monomeric F_oF_1 ATP synthase extracted from the same blue native gel. Given, however, that bovine F_oF_1 ATP synthase comprises 17 different subunits of which the two F_o subunits DAPIT and 6.8 kDa are easily lost during extraction of this fragile multisubunit membrane complex from the inner mitochondrial membrane, a straightforward alternative explanation is the loss of ptp specific subunits during extraction from the excised gel bands or reconstitution into the black membrane. In this context it is worth mentioning that the bovine F_oF_1 subunits DAPIT and 6.8 kDa were recognized as constituents of the full complex only relatively recently [62,71], demonstrating how sensitive the full F_oF_1 ATP synthase complex is to extraction procedures and the loss of native lipid. However, both subunits are essential to the full complex in vivo [73,74] and were present in 2D crystals in which only monomeric bovine F_oF_1 ATP synthase was present [23]. The dimerization interface was visualized for the first time at the α-helical level for the F_oF_1 ATP synthase from the unicellular colorless green algae *Polytomella* spec [24]. The interface does not show any obvious pore-forming site. However, the *Polytomella* spec. interface is unique and to date structures of the dimerization interface of the bovine or drosophila enzyme have not been reported and for the yeast dimer not yet published. Therefore, a more thorough examination of the monomer–monomer interface as a potential pore-forming site remains a task for the future.

An alternative proposal for a pore-forming entity within the components that make up the mitochondrial F_oF_1 ATP synthase is its proton transporting c-ring. This proposal is based on studies that examined ptp formation after depletion of the c-subunit mediated by small interfering RNA knock-down [30]. Fortuitously, the c-ring is structurally the best characterized subcomplex of the F_oF_1 ATP synthase membrane domain, including numerous high resolution X-ray crystal structures [75–81]. F_oF_1 ATP synthase c-rings consist of multiple copies of c-subunits arranged as a circle with a subunit copy number and diameter varying between species (8–15), but not between F_oF_1 ATP synthase complexes of the same species [82]. The lumen of the c-ring is void of protein and proton tightness is enabled by the presence of lipids filling its lumen. The presence of c-ring lumenal lipids has been demonstrated in vivo for the *Escherichia coli* enzyme [83] and in vitro for reconstituted rotor rings [84]. Interestingly, the only high resolution X-ray structure of a rotor ring that visualized some but not all lumenal lipids showed them to be shifted to the p-side of the rotor ring [85]. This finding is in line with the p-side protruding lipid plug in reconstituted c-rings, as detected by atomic force microscopy [84,86], molecular dynamics simulations of membrane embedded c-rings [87] and the density protruding from c-rings in cryoEM single particle reconstructions of intact F_oF_1 ATP synthases [24,25]. The pore like shape of the rotor ring with a diameter roughly matching the predicted pore diameter of the ptp makes the c-ring an obvious candidate for a potential pore-forming site. In this context it is noteworthy that in an evolutionary scenario proposed by Mulkidjanian and colleagues the rotor ring was proposed to have evolved from a polymer conducting pore as part of a RNA translocase, over the pore of a protein translocase to a cation transporting c-ring [88]. This homology pattern based evolutionary scenario has subsequently been bolstered by structural studies on the flagellar motor and the *Thermus thermophilus* V-ATPase [89,90]. However, even though it has been reported that the reconstituted c-ring can form a voltage dependent channel [91], it seems unlikely that the c-ring in itself constitutes the ptp. Any proposal for the c-ring as the ptp itself has to explain how the many modulating molecular players interact with it and importantly how either the lipid plug is removed or the diameter of the c-ring substantially widened; and how all of this occurs in a reversible manner and while exhibiting several substates of conductance. Since CyPD as the only bona fide binding partner of the ptp was not shown to interact with the c-ring, but rather binds to the OSCP, the c-ring by itself appears too simple to allow for regulation and modulation. Therefore, the c-ring in the context of either monomeric or dimeric F_oF_1 ATP synthase is a more likely candidate for a physiological relevant site of pore formation. In the intact mitochondrial F_oF_1 ATP synthase the central stalk (CS) makes tight contact with the c-ring at multiple sites, but it does not seal it off from bulk solution and keeps the c-ring's lumen connected to the matrix [65–67]. That leaves the lipid plug as the only barrier to pore formation. Conformational rearrangement of c-subunits accompanied by diameter widening of

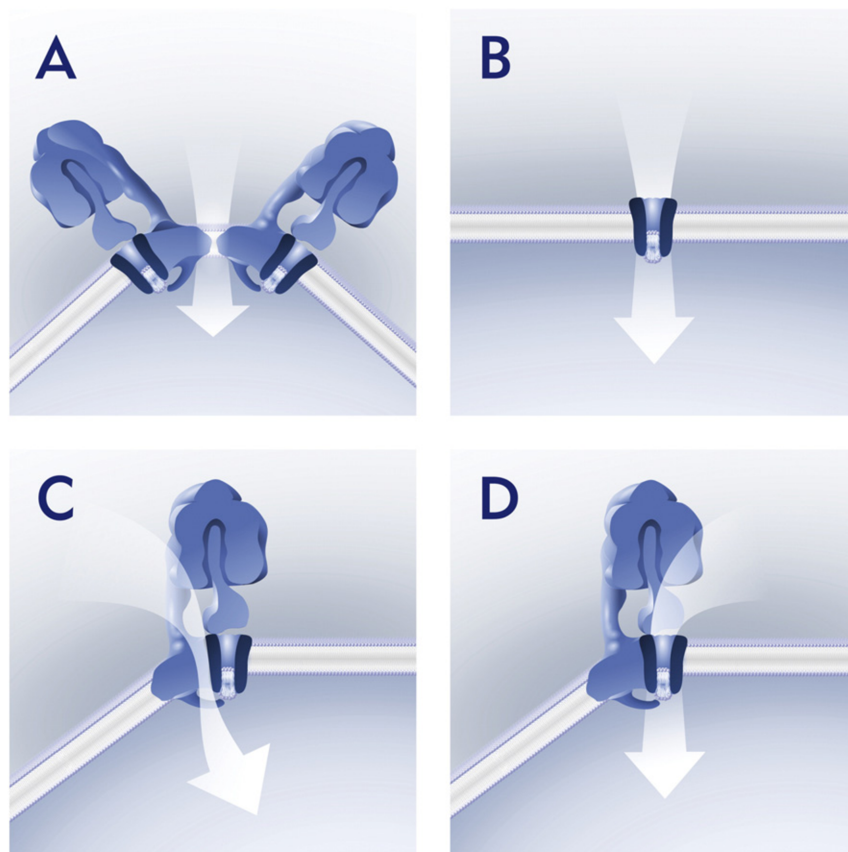

Fig. 1. Potential pore-forming sites of the mitochondrial F_oF_1 ATP synthase. (A) The dimerization interface of the F_oF_1 ATP synthase dimer. (B) The lumen of the lipid plug sealed c-ring by itself. (C) The interface between the c-ring and the aqueous half-channel harboring a-subunit. (D) The lumen of the c-ring in the context of the F_oF_1 ATP synthase.

the c-ring has been suggested as a way to c-ring pore-formation [32]. In line with the idea of a diameter change in the c-ring, large scale rearrangements have been proposed as a way to switch gears for the *T. thermophilus* V-ATPase [92] and normal mode analysis suggests that c-rings are able to deform substantially [79]. Direct structural evidence for both types of flexibility, however, has not been reported yet. On the contrary, X-ray crystallography performed on numerous c-rings in detergent rather suggests c-rings to be rigid in their architecture which does not seem to allow for larger movements of individual subunits or alpha helices. If the crystal structure based perceived rigidity is perhaps at least partially the result of the embedding detergent micelles' high dielectric environment remains to be seen [93].

A further potential site for pore formation is the interface between the a-subunit and the c-ring (Fig. 1C). In the cryoEM structure of the *Polytomella* F_oF_1 ATP synthase dimer deep invagination of the membrane at the interface of the c-ring and the a-subunit have been visualized [94] rendering this idea more appealing. However, mitochondria of ρ^0 cells lacking mitochondrial DNA which encodes the a- and A6L subunits are able to form the ptp [95] and hence it is generally thought that the a- and A6L subunits are not part of the ptp.

4. The death finger model

What could possibly allow the reversible removal of lipids from the lumen of the c-ring at different degrees of completeness while allowing modulation by all known molecular players? Recently, a novel density on the p-side of the bovine F_oF_1 ATP synthase was visualized by single particle cryoEM and proposed to possibly stem from subunit e [25]. This novel p-side density (PD) had not been seen in previous cryoEM single particle reconstructions of the same bovine complex [22,96], but it is reminiscent of a feature observed in EM projection maps of negatively stained bovine F_oF_1 ATP synthase dimers [97]. A simple explanation of why this p-side density had not been visualized in formerly published cryoEM maps of the same enzyme is that it stems from subunits of the complex that are easily lost during detergent extraction and purification from inner mitochondrial membrane or during cryoEM specimen preparation. Indeed, the map in the region of the p-side density is not well defined, suggesting that the occupancy of the subunits underlying the PD in the data set is incomplete. Density in the same region was also visualized, though not described, in an independent recent single particle cryoEM reconstruction of a bovine F_oF_1 ATP synthase preparation that included the subunit DAPIT and 6.8 kDa [72]. The mammalian subunits DAPIT and 6.8 kDa, which escaped investigators' attention for several decades as a consequence of their tendency to easily detach from the complex, are therefore good candidates for being the subunits that form the PD. The PD extends from the rotor ring distal part of the transmembrane F_o domain to the p-side of the rotor ring and appears to be in contact with the lipid headgroups of the lipid plug that is protruding from the p-side of the rotor ring. If anchored to the lipid headgroups of the lipid plug, movement of the PD could then exert mechanical pull on lipids from the c-ring, resulting in partial or full removal from the c-ring and opening of the pore (Fig. 2). The natural propensity of the hydrophobic acyl chains to avoid exposure to bulk water and thus to re-insert into the c-ring lumen would allow reversibility of the process, especially if the lipids are not completely removed. This may also cause the "flickering" of open states modulated by temperature. It might be asked if a contact to lipids filling the c-ring impedes or even stops rotational catalysis. Brownian rotational motion of the c-ring, either idling or biased by gradients of chemical or electrochemical energy, is the result of thermal impact from its surrounding lipid and water molecules [98]. Since the Brownian motion of lipids is several orders of magnitude faster (10^{-7}–10^{-9} s timescale) [99,100] than that of c-ring rotation (10^{-1}–10^{-3} s timescale) [101,102], binding of c-ring lumenal lipids is "invisible" to the c-ring itself. Consequently, binding of

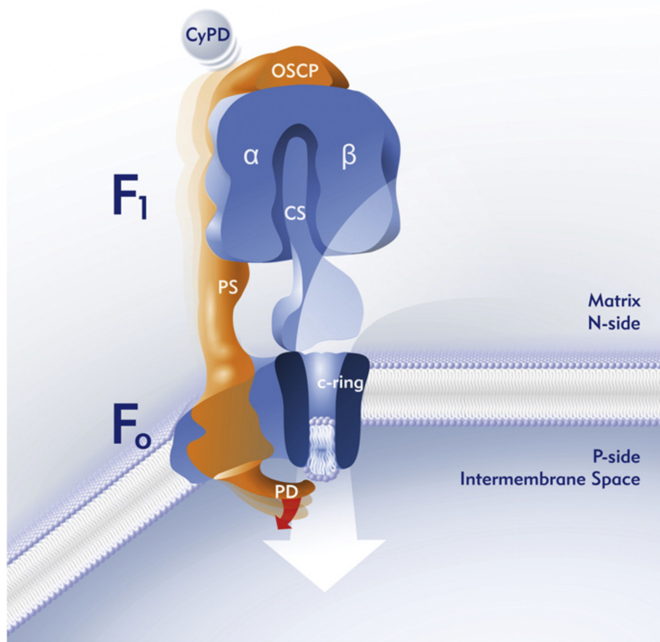

Fig. 2. The death finger model of mitochondrial F_oF_1 ATP synthase pore-formation. Movement of a p-side density (PD) that connects the lipid plug of the c-ring with the c-ring distal membrane bending F_o domain allows reversible opening of a c-ring pore. Structural contact of the transmembrane PD with the peripheral stalk (PS) enables cross-talk with the CyPD binding OSCP and the Ca^{2+} sensing catalytic $(\alpha\beta)_3$ hexamer.

the PD to the lipid plug does not impede rotational catalysis. Another important issue to resolve is how binding of CyPD to the OSCP could possibly influence the opening probability of the ptp in the more than 200 Å distant lipid plug of the c-ring. Contact between the transmembrane domains of the PD and the peripheral stalk (PS) could explain how CyPD binding to the OSCP can influence the opening probability of the ptp through conformational changes that are communicated from the top of the catalytic $(\alpha\beta)_3$ hexamer to the p-side of the c-ring. In addition, contacts between the peripheral stalk and the c-terminal region of the α subunit and the central region of the β subunit have been visualized and described for the bovine enzyme [25,72]. Possibly these contacts allow structural cross-talk between catalytic $(\alpha\beta)_3$ hexamer and the central region of the peripheral stalk. This could convey conformational changes induced by the binding of ATP/Ca^{2+} instead of ATP/Mg^{2+} [103,104] and thus act as a sensor of Ca^{2+} concentration. CryoEM studies on monomeric bovine F_oF_1 ATP synthase as a detergent solubilized complex [22,25] and in 2D crystals of the membrane embedded, complete, fully active and coupled enzyme [23] have suggested and demonstrated that the monomer by itself can bend lipid bilayers. Also, on the basis of molecular dynamic simulations it has been proposed that the formation of rows of dimeric F_oF_1 ATP synthase could be driven by the easing of tension imposed on the membrane in the oligomer relative to an ensemble of isolated F_oF_1 ATP synthase dimers [19]. That is, dimer row formation is envisioned to be driven by an overall lower energetic state of the system instead of specific dimer to dimer contacts. If so, then the strain imposed on a single dimeric or monomeric F_oF_1 ATP synthase will be greater than in the assemblage of a row of dimers. Since it is the rotor distal membrane bending F_o domain which makes the connection to the p-side lipid plug of the c-ring, higher membrane tension may increase the opening probability of the pore by exerting additional pull in a spring-like fashion. In other words, the ratio of oligomeric to non-oligomeric F_oF_1 ATP synthase in the mitochondria as a whole could be a major determinant of mitochondrial permeability transition probability; and thus the oligomerization state of mitochondrial F_oF_1 ATP synthase represents an efficient means of regulating mitochondrial permeability transition. A consequence of this on the cellular level would be a stronger propensity to die for senescent cells, which have been shown to have a high non-oligomer to oligomer ratio in their mitochondria [105,106]. PTP opening and conductance is distinctive in different species ranging from none (brine shrimp *Artemia franciscana* [108]), over relatively low conductance with ~50 pS and no sucrose permeability in *Drosophila melanogaster* [33] to high conductance with 300 pS in yeast [31] and 500 pS in mammals [29]. Structural divergence in the PD itself and the architecture of the peripheral stalk or differences in the degree of membrane bending by F_oF_1 ATP synthase between species [20] could account for these species dependent properties of the ptp. An attractive test of the death finger model would thus be to examine if the F_oF_1 ATP synthase of the brine shrimp *A. franciscana* possesses a PD or not. In summary, on the basis of recent structural findings, the death finger model reconciles seemingly conflicting data on mitochondrial F_oF_1 ATP synthase as the molecular identity of the ptp, while avoiding violation of what is already known from solid crystal structures.

5. Conclusion

In the absence of an atomic model of a F_oF_1 ATP synthase from ptp forming mitochondria, all the above described possibilities remain hard to examine or to test experimentally and are therefore speculative. And despite great advances in cryoEM and X-ray crystallography of intact F_oF_1 ATP synthases in the last year [24–26,72], a high resolution structure that includes water, lipids and ligands does not seem to be around the corner. Studies performed on F_oF_1 ATP synthase in mitochondria will always leave doubt due to its primary function of energy conversion and the concomitant entanglement with the overall mitochondrial state. However, critical assessment at the molecular level is imperative. Therefore, a feasible and important way to test if mitochondrial F_oF_1 ATP synthase is indeed the long sought after molecular identity of the ptp, is in vitro electrophysiology. This would be preferably carried out by patch-clamp of complete, intact, active and fully coupled F_oF_1 ATP synthase complexes reconstituted into artificial lipid bilayers. Single-particle cryoEM is a more and more powerful tool to visualize dynamics of cellular machines, which has been impressively demonstrated for the ribosome [107]. Even though mitochondrial F_oF_1 ATP synthase is a much less suitable specimen for this technique, perhaps it might be possible to use single-particle cryoEM to visualize an open state of the ptp.

It may well turn out that the F_oF_1 ATP synthase will be another case of a potential molecular identity of the mitochondrial permeability transition pore that eventually will be dismissed. But still, as long as there is so much that is unknown about this surprising molecular machine, discounting the idea outright would be ill-considered.

Transparency document

The Transparency document associated with this article can be found in the online version.

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