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REVIEW

Current Challenges and Future Directions in Mitochondrial Potassium Transport Research

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Abstract—Maintenance of ionic homeostasis, particularly the balance of potassium ions as the major cations in the cytoplasm, is critically important for mitochondrial function. Uncontrolled cation influx and the subsequent osmotically-driven water accumulation in the matrix could lead to swelling and eventual membrane rupture. Paradoxically, despite the critical importance of potassium channels and exchangers and their extensive research history, molecular identity of the key potassium transport systems such as the K^+/H^+ exchanger and the ATP-dependent potassium channel remains a subject of ongoing debate. Within this review and analysis of scientific publications, we outline a number of unresolved issues related to potassium transport in mitochondria: incomplete knowledge of structural and functional rearrangements in mitochondria upon potassium ion influx and swelling; ambiguity surrounding molecular identity of the key potassium transport systems – the K^+/H^+ exchanger and the ATP-dependent potassium channel, as well as uncertain role of ATP synthase in ion transport; and the apparent underestimation of the role of the lipid component of the membrane in direct potassium transport and its regulation. We highlight that accumulation of lysocardiolipin, a derivative of the key mitochondrial lipid cardiolipin, in the membrane may represent a missing link crucial for constructing a comprehensive explanation of mitochondrial osmotic regulation mechanisms. Lysocardiolipin can form lipid pores that significantly enhance membrane conductance for cations. Accumulation of lysocardiolipin could be stimulated by lipid peroxidation, could alter membrane properties, and modulate assembly and function of the proteinaceous ion transporters. Accounting for the changes in physical (pressure, lipid packing) and chemical properties of the membrane (peroxidation, deacylation) during conditions that activate osmotic regulation systems is necessary for forming a holistic understanding of potassium transport mechanisms.

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INTRODUCTION

According to the Mitchell's chemiosmotic theory, electrochemical potential on the inner mitochondria membrane is an intermediate step in accumulation and transformation of energy [1]. Evidence of the electric field presence and further development of the Mitchell's theory was presented by V. P. Skulachev, E. A. Liberman, and their co-authors. The presence of a negative charge in mitochondria, generation of electric field on the membrane by the respiratory chain complexes, as well as the possibility of blocking ATP synthesis by uncouplers, which are protonophores, was shown in their studies [2-4]. Largely due to these studies and numerous studies of the researchers at that time inspired by the works of P. Mitchel and

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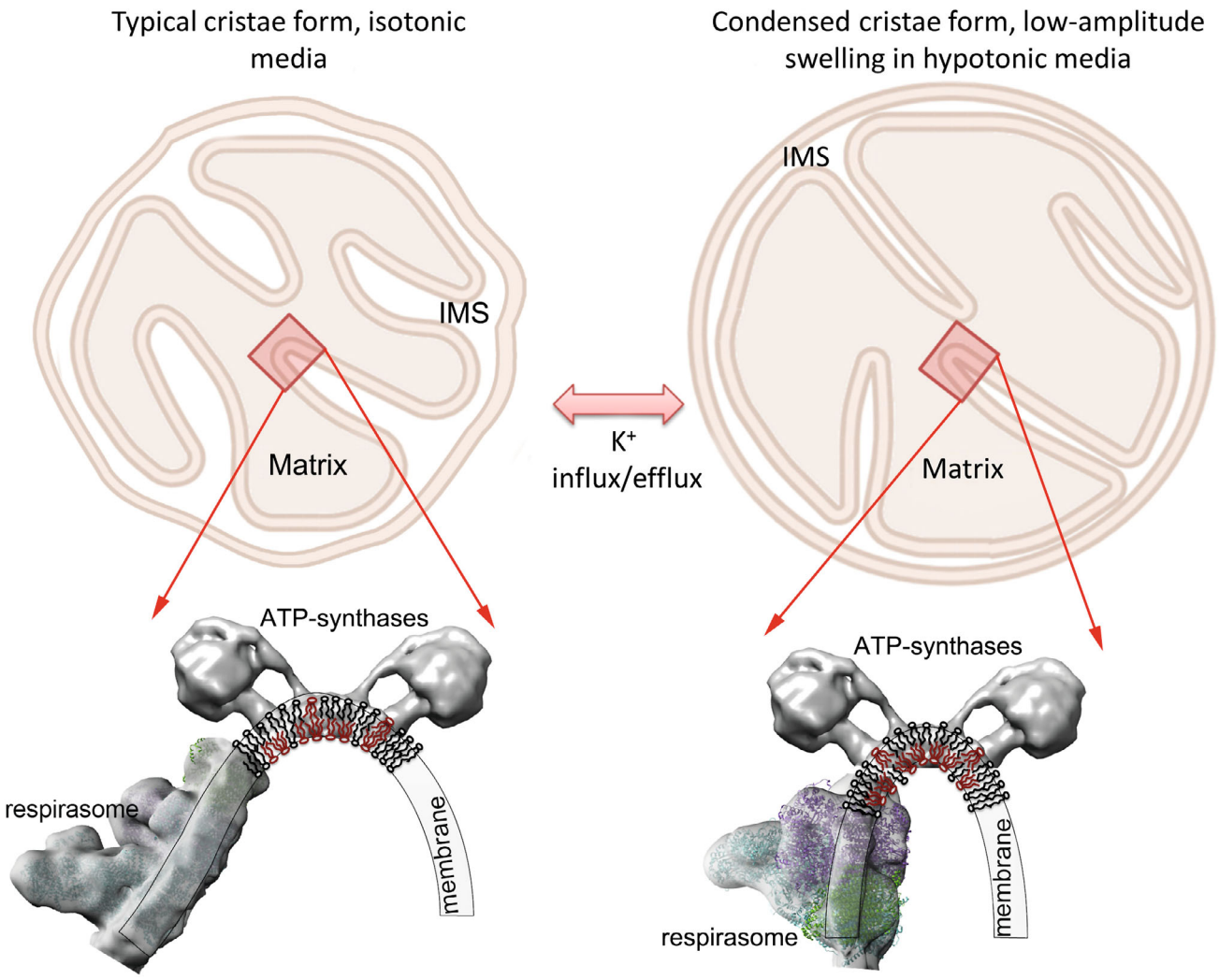

Fig. 1. Two states of mitochondria with transitions between them induced by potassium transport inside the mitochondria matrix or outside of it. Changes in configuration of the inner membrane and its curvature in the process affect supramolecular structure of the membrane proteins associated with oxidative phosphorylation, changing the degree of coupling between respirasomes and ATP-synthases. Changes in the membrane curvature also cause changes in the lipid composition of the membrane – conic lipids such as cardiolipin are re-distributed, and phospholipases could be activated in order to adapt to the new physical properties of the membrane. IMS, mitochondrial intermembrane space.

V. P. Skulachev, this specialized area of science that combines biochemical and biophysical approaches was termed 'bioenergetics'.

Oxidative phosphorylation requires rather high electrical potential on the membrane, which for most of the investigated organisms reaches 160-190 mV. That is why, one of the key objections to this theory was transport of cations to the mitochondrial matrix under the action of electric field, which could cause the compensatory influx of water into the matrix, increase of osmotic pressure, and rupture of mitochondria. Indeed, cation flow to the matrix depends exponentially on electric potential, and influx of potassium ions along the potential could cause mitochondria swelling by approximately 15% per minute [5]. In order to prevent mitochondria rupture, presence of the specialized transporters is necessary in the membrane that in exchange for protons or in symport with OH^- expel cations outside thus maintaining osmotic balance and mitochondria volume [6]. The recently published studies even demonstrate the possibility of potassium ion transport through ATP synthase, which significantly complements the established notions [7, 8]. Despite the fact that the presence of potassium transport in mitochondria has been known for a long time, this, surprisingly, remains one of the most controversial issues in the mitochondria research.

In this review, we present a brief description of the existing problems and controversies, and suggest the most promising, in our view, solution. The key problems include lack of consensus regarding

molecular identity of the K^+/H^+-exchanger and ATP-dependent potassium channel. We suggest a conceptual solution of the existing problems involving shifting of the focus of studies from the protein component to the role of lipids in the processes of direct transport (formation of lipid pores), as well as in the processes of regulation of transport systems activity of which depends significantly on composition and structure of the lipid membrane. It is our opinion that the more comprehensive and complex approach considering biophysical properties of the lipid–protein membranes, their rearrangement under pressure during mitochondria swelling or under the action of other stress factors such as calcium ions, peroxidation, activation of phospholipases is necessary to move forward with providing solutions to the accumulated problems regarding the key aspects of potassium transport and ion transport as a whole.

PROBLEM 1. EFFECT OF POTASSIUM TRANSPORT ON STRUCTURE AND FUNCTIONS OF THE OXIDATIVE PHOSPHORYLATION SYSTEM

Transport of potassium ions, the main ion in cytoplasm of eukaryotic cells, is inextricably linked with the issue of osmotic regulation and mitochondria swelling. The studies of rat liver mitochondria in a hypotonic medium under conditions of low-amplitude swelling (that does not cause membrane rupture and is not associated with opening of a mitochondrial permeability transition pore (mPTP)) conducted in our laboratory revealed that during swelling the system of oxidative phosphorylation could turn into the mode local coupling [9-13]. Comparison of these data with the newest data of cryo-electron tomography [14, 15] supports the hypothesis [12] on the possibility of clustering of the oxidative phosphorylation system during mitochondrial cristae compression. Changes in the membrane and changes in local curvature of the membrane in the vicinity of the ATP-synthase dimers cause changes in optimal orientation of the respiratory chain supercomplexes (respirasomes), which changes both the average distance between the proton pumps and ATP-synthases, and leakage of protons to endogenous uncouplers [16]. Two above-mentioned states of mitochondria – classic state and low-amplitude swelling state – are shown in Fig. 1.

It is worth also mentioning that the changes in tension and curvature of the membrane create local stresses and defects, which is one of the triggers of phospholipase activation, the purpose of which is lipid adaptation to maintain bilayer integrity. Due to this, concentration of free fatty acids, which are endogenous uncouplers, in the membrane could change, and lysoforms of lipids also could accumulate. Considering that the membrane curvature is higher in the compressed state, this state corresponds to the highest possible concentration of cardiolipin molecules, which have a conic shape required for stabilization of the curved sites of the membrane. Transition to the less compressed state could cause partial deacetylation of cardiolipin resulting in a temporal increase in concentration of lysocardiolipin and free fatty acids. We consider testing this hypothesis as one of the promising approaches for investigation of the role of lipids in the structural-functional rearrangements in mitochondria.

It is also worth mentioning that the change in mitochondrial matrix swelling results in the increase of the free water volume and decrease of macromolecular crowding, which could modify functioning of enzymatic systems under stress conditions [17]. Such decrease in the density of matrix proteins could be required for rearrangement of metabolic clusters with the change of the main substrate. In particular, it is known that the complex I could be associated with pyruvate dehydrogenase complexes or with the complexes of fatty acid beta-oxidation. In the process of the preferrable substrate change during transition between anabolic and catabolic states [18] mitochondrial swelling caused by temporal energy stress could also cause, in addition to clustering of the membrane proteins of oxidative phosphorylation system, increase of mobility of matrix proteins, which is required for reorganization of metabolic complexes – detachment of the unfunctional dehydrogenases from the complex I and attachment of the functional ones. Following normalization of ATP synthesis, matrix compression would fix the formed bond until the next stress-related swelling. Interestingly, the effect of membrane fluidity increase on transition to the metabolically active state has been reported also in bacteria [19], which implies possible universality of the suggested principle, although mechanisms of these phenomena could differ. Testing this hypothesis could also be a promising direction for future studies.

PROBLEM 2. UNKNOWN MOLECULAR IDENTITY OF K^+/H^+-EXCHANGER

First evidence of Na^+/H^+ and K^+/H^+ antiport existence in mitochondria was obtained by Mitchell and Moyle [20]. Discovery of the fact that swelling of mitochondria causes efflux of potassium ions from them in the case of potential availability was the first step in providing proof of existence of the K^+/H^+-exchanger [21]. It was also shown that the K^+/H^+-exchanger differs from the Na^+/H^+-exchanger [22]. It was shown in a number of studies that the mitochondrial K^+/H^+-antiporter could be reversibly inhibited

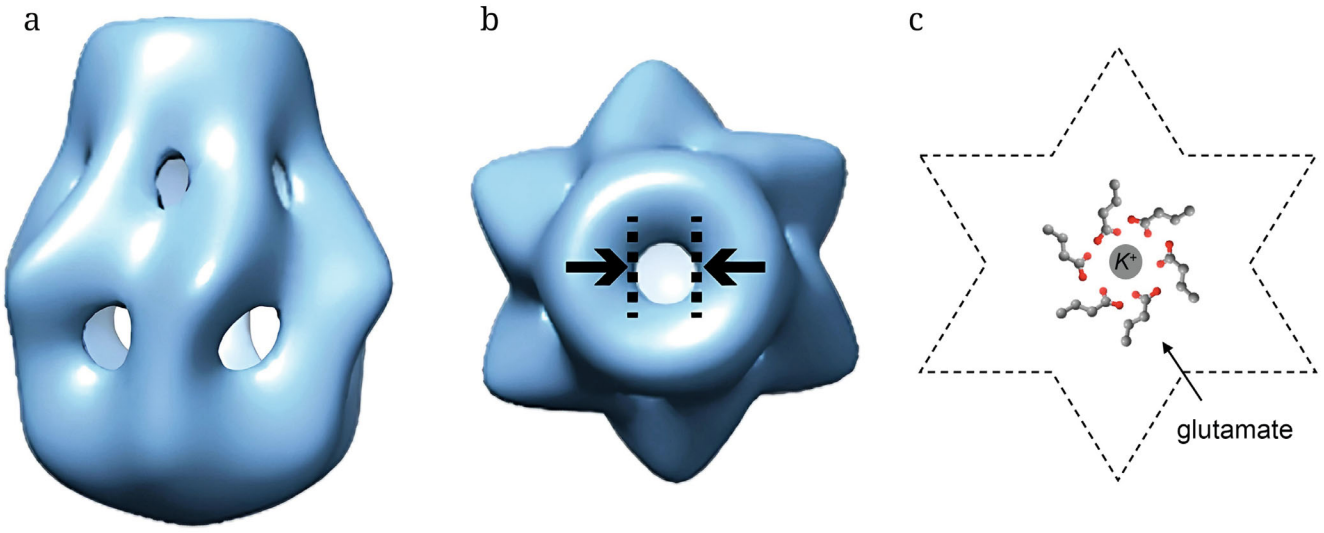

Fig. 2. Suggested hexamer structure of the cation /H^+-exchanger LETM1. a and b) Electron microscopy image of LETM1 hexamer in negative contrast fixed at pH 8. The figure is adapted from the paper by Shao et al. [26]. c) Possible structure of the LETM1-based cation channel.

by Mg^{2+}, protons (matrix acidification), and amphiphilic amines, and irreversibly inhibited by 1,3-dicyclohexylcarbodiimide (DCCD) (see details in the review by Garlid and Paucek [5]). Presumably, the mitochondrial K^+/H^+-antiporter is a protein with mass 82 kDa [23]. This corresponds to the known ion exchanger NHE7, but this protein does not have mitochondrial localization. One of the likely candidates for his role, protein LETM1 (Leucine zipper-EF-hand containing transmembrane protein 1; encoded by the *LETM1* gene), that has high homology with the yeast cation/H^+-exchanger mdm38 [24, 25], was found to be only the $Ca^{2+}/2H^+$-exchanger [26], as well as regulator of the membrane structure [27, 28], while its ability to transport potassium ions *in vitro* was not confirmed. At the same time, the *in vivo LETM1* knockdown results in accumulation of potassium ions in mitochondria and disruption of K^+/H^+- and Na^+/H^+-exchange, as well as its functioning is suppressed by magnesium ions, and in its absence is blocked by quinine, as could be expected for the mitochondrial K^+/H^+-exchanger [29]. A model of one of the functional forms of the LETM1 oligomer (performing $Ca^{2+}/2H^+$-exchange) with low structural resolution was obtained by averaging the data of electron microscopy with negative contrasting as well as using computer modeling (Fig. 2). Although, to the best of our knowledge, no effects of DCCD (binding of which with K^+/H^+-exchanger is known) on LETM1 was reported, presence of carboxyl groups (E222 in the human protein) forming an ion channel ring in the membrane part of LETM1 hexamer structure was suggested [25] (Fig. 2c), which comprise a suitable binding target for DCCD. Despite this, a final experiment with isolated LETM1 on liposomes testing its ability to perform K^+/H^+-exchange has not been conducted yet [30], hence, alternative explanations of the effect of this gene knockout on potassium transport are possible assuming indirect effects. Many aspects of functioning and regulation of LETM1 remain poorly understood, and some data are controversial [31].

At the same time effect of the lipid composition of the membrane on the LETM1 function was established, including, in particular, requirement of cardiolipin for its functioning [32], which emphasizes importance of investigating activity of this protein in the membranes with natural lipid composition corresponding to the inner mitochondrial membrane. It should be also mentioned that there is uncertainty in evaluation of the molecular mass of the functional form of LETM1. Total predicted protein mass is around 83 kDa (based on UniProt data for human and bovine protein), which, considering experimental errors, is in good agreement with the earlier estimation of the mass of K^+/H^+-exchanger 82 kDa [23]. At the same time, the monomer mass in composition of hexamer (in Fig. 2) is only around 67 kDa [26], and according to other data, the functional form is assembled in liposomes without first 115 aa residues and has mass of 74 kDa [32]. The oligomeric form of the exchanger is also questionable; according to the data reported in one study [26], it is a hexamer with mass 404 kDa, and according to other publications the 300-kDa form is predominant, and forms with mass 500-600 kDa also exist [33]. Hence, molecular identity of the K^+/H^+-exchanger in mammals has not yet been identified fully – there is no full confidence that this is exactly protein encoded by the *LETM1* gene,

final form of the protein formed as a result of splicing, proteolysis, or posttranslational modifications has not been clarified, as well as degree of oligomerization; moreover, it is not known whether the homooligomers are formed *in vivo* or the heterooligomers with some other proteins such as the known protein partner, TMBIM5 [34].

At the same time, the data on the effects of lipid composition on the calcium ion transport through LETM1 demonstrate the possible role of lipid rearrangements in regulation of this antiporter. This regulation could occur either through the effect on LETM1 oligomerization, or due to participation of cardiolipin molecule as a cofactor in ion transport. Rearrangement of charged lipids between the membrane parts also could affect potassium channels [35]. Hence, one cannot rule out the possibility that rearrangement of lipids or their modifications are required for the LETM1 to become a K^+/H^+-exchanger. Existence of such regulation could be a reason why the K^+/H^+-exchange activity was not observed in the *in vitro* experiments with model membranes.

Hence, the necessary step in resolving the issue of the identity of K^+/H^+-exchanger is investigation of the ability of all possible protein candidates to mediate K^+/H^+-exchange *in vitro* in the liposomes containing physiological concentrations of cardiolipin, lysocardiolipin, and free fatty acids under conditions of different osmotic pressure on the membrane in order to model natural conditions of the K^+/H^+-exchanger functioning in mitochondria. These investigations should answer a question on the molecular identity of this exchanger and its oligomeric structure; moreover, high-resolution structure of this oligomeric form with the help of cryo-electron microscopy (cryo-EM) should be obtained.

PROBLEM 3. UNKNOWN MOLECULAR IDENTITY OF THE ATP-DEPENDENT POTASSIUM CHANNEL

Another uncertainty regarding the key component of potassium transport in mitochondria is the issue of molecular identity of the potassium ATP-dependent channel (mitoK(ATP)). This channel is activated in mitochondria under conditions of ATP deficit in the matrix, i.e., under conditions of energy stress. Such stress could be caused by the deficit of substrates, by inhibitors of the respiratory chain or ATP-synthase, by the membrane damage. The main physiological state, when mitoK(ATP) is activated, is hypoxia, including ischemia-induced hypoxia. Similar to the case of K^+/H^+-exchanger, pharmacological activators and inhibitors of mitoK(ATP) have been reliably identified, as well as its physiological significance, which is manifested, among other things, in ensuring ischemic preconditioning, protection against oxidative damage, and participation in osmotic regulation [36].

The existing uncertainty in understanding the structure of this channel is quite surprising, because this channel is one of the acknowledged and key therapeutic targets in treating ischemia [37, 38]. Despite the direct fixation of ATP and K^+-dependent ion flows corresponding to activity of mitoK(ATP) in the mitochondrial membrane established with the help of patch-clamp technique [39], for some time even the existence of such channel was questioned (see review by Garlid and Halestrap [40]) mainly due to the lack of knowledge on its molecular identity.

A mitochondria protein capable of inducing potassium conductivity in the lipid membranes was isolated already in 1980s [41]. It was shown later that the ion transport through this 55-kDa protein is sensitive to ATP, and antibodies against this protein block transport of potassium ions in mitochondria, which allowed considering this protein as a candidate for the role of mitoK(ATP) [42]. Moreover, a notion dominated scientific literature for a long time that the channel part of mitoK(ATP) could be formed by the Kir6 proteins, and its regulatory ATP-binding part – by the mitoSur proteins of the ABC family [43]. Nevertheless, this hypothesis contradicts some experimental data [44]. It was also assumed that the ROMK protein could form the channel part of mitoK(ATP) [45, 46], but the experiments with knockout mice did not confirm this [47]. At the same time, it was shown that the protein with mass 45 kDa (and its splice variant with mass 34 kDa) encoded by the *CCDC51* gene and termed by the scientists MITOK, fully correspond to the assumed properties of the mitoK(ATP) subunit, and, presumably, could form its channel part [48]. It was possible finally in this study to resolve numerous issues, including to identify gene of this protein and to demonstrate absence of the effects of known inhibitors and activators of mitoK(ATP) on the potassium transport in the mitochondria derived from the mice with knockout of this gene. Nevertheless, even the authors of this study noted the possibility of the presence of alternative forms of mitoK(ATP) in other tissues. Although, the question remains open on the existence of other systems transporting potassium ions similar in properties with mitoK(ATP), presence of which is difficult to determine on the background of its activity. For example, according to the data reported in a few studies [7, 8], the ATP synthase with the bound IF1 factor could perform the mitoK(ATP)-like functions. If these methodologically thorough experiments will be confirmed by the independent research groups and will not provide any alternative interpretation, this would require reconsideration of the whole paradigm of mitochondria structure [49].

Therefore, despite the existence of recent fundamental studies investigating mitoK(ATP), and that its practical significance in medicine does not raise any doubts, the situation exists currently, when the new fundamental data not only do not provide answers to the existing questions, but create more uncertainty. In particular, discovery of the new MITOK protein only increased the number of new entities (according to Occam's razor principle) but did not provide answers on the functions of the previous protein-candidates for the role of mitoK(ATP), which are located in mitochondria and affect potassium transport. Existence of different forms of mitoK(ATP) with varying tissue-specificity or operating in different metabolic/stress conditions (such as mitochondrial localization of the potassium channel Kv1.3 [50]) also cannot be ruled out.

Impossibility of recreating certain features in the model systems and uncertainty of molecular identity of the key potassium transporters makes one to assume that the lipid component of the membrane and its modifications could be a significant factor affecting potassium transport. Thus, the issue on precise structure of mitoK(ATP) has been transformed into the issue on existence of other potassium channels, which is one of the promising topics in the development of fundamental bioenergetics. One of the possible ways to resolve the issue of uncertainty of the status of protein-candidates is the use of cryo-EM for determining their structure [51]. The issues described above are closely associated with the following problem addressed below in a special section due to its high significance.

PROBLEM 4. UNCERTAINTY OF THE ROLE OF ATP-SYNTHASE SUBUNITS IN POTASSIUM TRANSPORT AND NON-SPECIFIC CONDUCTIVITY

The main fact that raises fundamental doubts in functioning of ATP-synthase as a potassium uniporter [7, 8] is that in the previous studies ability of this protein to transport potassium was not observed, and transport of even smaller in radius sodium cation required, as is well-known, modification of the structure of c-subunits of the synthase. At the same time, the issue with mitoK(ATP) reminds of the problem with the search of another elusive mitochondrial structure usually associated with transport of calcium ions, but also playing the most important role in osmotic regulation, which is vital in the processes of cell death and induction of inflammation – mitochondrial permeability transition pore, mPTP. It was shown in the recent experiments that the c-ring of ATP synthase could induce permeability expected for mPTP [52], but, at the same time, modeling demonstrates impossibility of pore formation by the central part of the c-ring [53]. At present, the question of mPTP structure is one of the most controversial issues in bioenergetics.

As an alternative version, which is rarely mentioned, it could be suggested that the c-subunit of ATP-synthase induces non-bilayer lipid packing. It allows to assume that disruption of the dense packing of the F_O-factor of ATP-synthase destabilizes the bilayer [54] similarly to the case of cobra toxin [55], and, therefore, could cause formation of the lipid defects or even pores, conductivity of which could explain both nonspecific and potassium transport. Interestingly enough, existence of the mPTP-like lipid pores is a well-known fact [56]. It could be reliably concluded that mPTP is not a purely lipid structure, however, considering that the majority of scientist do not accept the possibility that mPTP is a hybrid lipid-protein structure may be a reason for the failure to finally identify its nature. The hybrid protein-lipid nature of the pore in general does not contradict the established understanding that formation of a pore with participation of ATP-synthase requires dissociation of the synthase dimers and certain, not understood at present, reorganization of the c-ring structure [57]. In other words, the pore is formed when the c-subunits have a non-native structure. Formation of defects in bilayer under these conditions could be quite possible.

We believe that elucidation of molecular mechanisms of interactions of ATP-synthase with lipids, and effect of this protein complex on transmembrane transport is at the moment the most urgent problem in bioenergetics, solution of which would be comparable in significance with chemiosmotic theory, because it potentially could provide answers to two questions – structure of mPTP and mitoK(ATP). In order to achieve this, it is necessary to test the existing dominating hypotheses, including to investigate in detail the effect of ATP-synthase, its oligomeric forms, as well as its partially destabilized membrane subunits under various conditions with emphasis on the role of lipids in these processes, such as during oxidation/deacetylation of cardiolipin, accumulation of free fatty acids, and excess of calcium ions (that significantly changes lipid packing).

PROBLEM 5. EFFECT OF LIPID MODIFICATIONS AND PHYSICAL PROPERTIES OF THE MEMBRANE ON POTASSIUM CONDUCTIVITY

Destabilization of lipid bilayer structure in the process of lipid peroxidation. As has been

mentioned above, state and composition of the lipid membrane itself are the most important factors in ion transport. Primarily, these include presence of lipid pores or defects, as well as degree of order and saturation of acyl chains that create barrier for ions. It is known that the increase of a number of double bonds in lipids is accompanied by the increase of a number of defects in the membrane and increase of the membrane permeability for ions, including potassium ions [58]. At the same time, lipid peroxidation also increases permeability of the mitochondrial membrane lipids for potassium and calcium [59], which is in good agreement with the fact that peroxidation disrupts structure of the membrane, increases surface area per one lipid molecule, because the peroxidized sites with acyl chains are prone to contacts with water [60] and be exposed to interface [61].

Indeed, disruption of the membrane structure is a known factor that increases membrane permeability for cations as, for example, under conditions close to lipid phase transition [62]. At the same time, presence of the peroxidized lipid forms in both layers of the membrane bilayer is required for the increase of membrane permeability in the process of accumulation lipid peroxides, which indicates likelihood of cluster mechanism of ion transport with their participation [63]. However, lipid peroxidation in mitochondria causes increase of the relative activity of phospholipase A2 [64, 65], which, most likely, is associated exactly with localization of fatty acid chains of these lipids closer to interface, where phospholipase is located. Hence, under natural conditions (in the presence of phospholipase A2) oxidative stress is the most important factor that increases membrane permeability, which occurs through at least three mechanisms: destabilization of the structure, which causes increase of spontaneous permeability; accumulation of lipid peroxidation products and formation of clusters from them, which facilitate cation transport; accumulation of lysophospholipids, which also are capable of cation transport (see details below).

Lysocardiolipin as a mediator of potassium conductance. It was shown in the earlier studies [66, 67] that lysocardiolipin increases permeability of artificial membranes for potassium ions, similar to ionophores such as valinomycin or nigericin. Further detailed studies demonstrated that other lysolipids, such as lysophosphatidylethanolamine, also increase potassium permeability, although they are less effective in comparison with lysocardiolipin [68]. The mechanism of transport of potassium and other ions by lysocardiolipin, same as other lysolipids, suggests coordination of the ion with the phosphate and hydroxyl groups in the lipid head. Interaction of the ion simultaneously with several lysolipids would be optimal for shielding the ion charge. The same collective mechanism is known for ion transfer by peroxidased lipids. Similar to the lipids subjected to peroxidation, lysolipids also disrupt the established structure of bilayer, have higher mobility, and could be located closer to interface, because they have a smaller hydrophobic region (lower number of acyl chains). Due to the lower hydrophobicity of lysocardiolipin in comparison with cardiolipin, its binding to the membrane proteins is weaker [69], and it does not form large domains [70]. This facilitates its higher mobility and free movements between the membrane layers. It was shown that the transport of potassium ions by lysocardiolipin involves formation of individual channels with the highest conductivity for potassium ions [71]. Interestingly, this kind of conductivity could be induced in the lipids extracted from mitochondria by pre-incubation of mitochondria in the medium with high KCl content, which indicates formation of lysocardiolipin or other lipid modification occurring under these conditions. Considering that the long-term incubation in the medium with high potassium content results in influx of potassium into the mitochondrial matrix followed by their swelling, which also corresponds to the conditions for activation of the K^+/H^+-exchanger, this indirectly suggests probable association of lysocardiolipin accumulation with activation of the K^+/H^+-exchange.

A suggested approximate structure of the potassium ion bound to lysocardiolipin is presented in Fig. 3a. A large variety of the ways of the lipid tails and heads packing for cardiolipin is possible depending on the environment (same as, likely, for lysocardiolipin), therefore, establishing of exact structure requires modeling in accordance with the particular environment. The structure of nigericin, known antibiotic inducing K^+/H^+-exchange in the membranes, is presented in Fig. 3b. General similarity between these structures is obvious – both lysocardiolipin and nigericin coordinate potassium ion and shield its charge by the oxygen atoms. Such structure of the lipid head could facilitate dehydration of potassium ions at the interface and decrease the energy barrier of crossing hydrophobic zone of the channel by the potassium ions.

It is important to note that the main feature distinguishing the K^+/H^+-exchanger nigericin from the potassium ionophore valinomycin is presence of carboxyl group in the former, which provides the possibility of protonation. In the case of lysocardiolipin only phosphate groups are present, which are strong acids making the ability of lysocardiolipin to K^+/H^+-exchange very unlikely. Moreover, the presence of at least two (in dilysocardiolipin) acyl chains makes its flip-flop to the other side of the membrane difficult. That is why the most probable mechanism of potassium transport with participation of lysocardiolipin

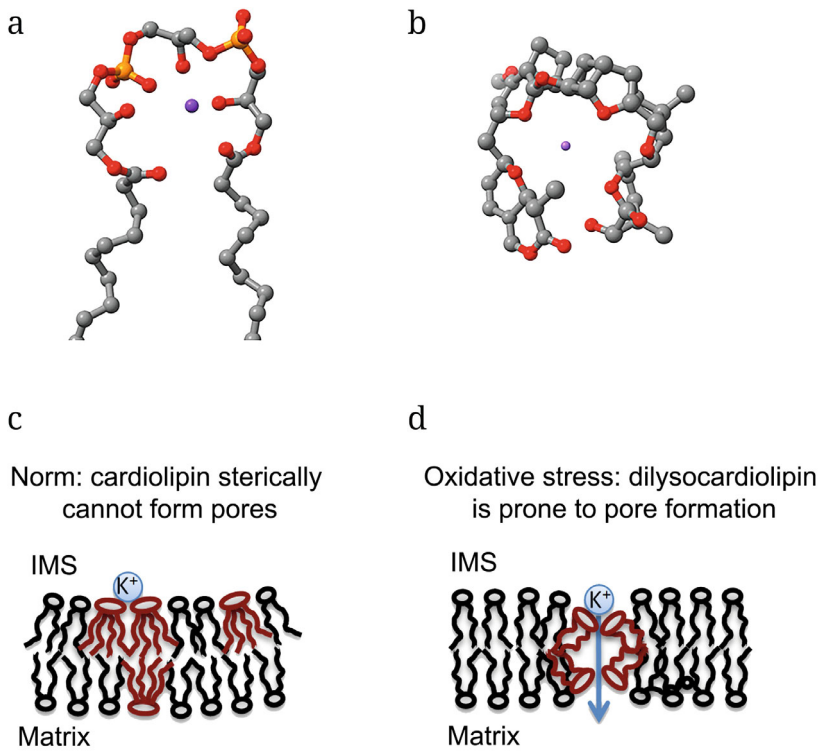

Fig. 3. Possible role of lysocardiolipin in transport of potassium ions. a) Image of lysocardiolipin molecule with potassium ion (only parts of acyl chains of lipids (gray) are shown). Oxygen atoms are shown in red color, sulfur atoms – in orange, single-valent cation – in purple. b) Demonstration of similarity in coordination of cation in the nigericin molecule. c) Normal state of the membrane without lysolipids – cations interact with cardiolipin head, but its conic shape prevents pore formation. Cardiolipins are shown in red. d) State of the membrane under oxidative stress – dilysocardiolipin with high surface area of the head and small tail area (shown in red) is prone to pore formation, which is optimal for cations due to the negative charge of phosphate groups. Direction of the cation transport is determined by the gradient and electric field (in the case of its availability). IMS, intermembrane space.

is formation of lipid pores in the membrane, which carry negative charge and facilitate cation conductance. It is worth mentioning that cardiolipin with its conical shape cannot form such pores due to the steric limitations. Loss of one or two tails makes monolysocardiolipin, or even more so dilysocardiolipin, optimal for formation of the negatively charged lipid pores. In the process, the heads of lysocardiolipin molecules could shield potassium cation during crossing the hydrophobic zone of the membrane, while the lipid itself does not cross to the other side of the membrane.

Lipid pores as an alternative to protein channels. The information presented above is summarized in Fig. 4. It is specified that oxidative stress could be considered as a universal factor activating increase of potassium conductance across the inner mitochondrial membrane. Specialized enzymes, acyltransferases, are present in mitochondria that replace the damaged acyl chains (which are cleaved by phospholipase A2) with the new ones. The acyltransferase tafazzin is specific for cardiolipin; it is functioning both at the stage of synthesis of this lipid replacing the saturated acyl chains with the unsaturated ones (mainly with linoleic acid) and at the stage of accumulation of lysocardiolipin as a consequence of oxidative stress. Disruption of tafazzin functioning could result in the development of serios pathologies such as Barth syndrome [72]. Interestingly, there is another acyltransferase that modifies lysocardiolipin, however, its activity, on the contrary, is associated with increased oxidative damage and diseases [73, 74].

In addition to accumulation of lysocardiolipin, changes in the membrane tension or its phase state, accumulation of fatty acids, as well as increase of calcium ion concentration causing significant changes in the bilayer structure could play roles of signals initiating formation of lipid pores and, in general, lipid bilayer defects [75]. Owing to this mechanism, conductivity of the membrane could be controlled thus exhibiting certain similarities with the properties of K^+/H^+-exchanger or mitoK(ATP). Formation of lipid pores induced by palmitic acid or calcium ions is a mechanism of regulation of the mitochondrial membrane conductance operating simultaneously with the classic cyclosporin-dependent pore mPTP and plays an important role in protecting cells against stress (see review by Mironova and Pavlov [76]).

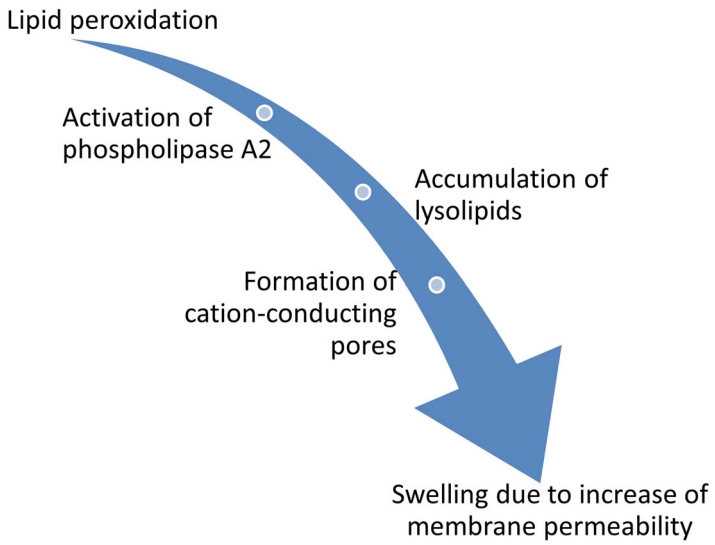

Fig. 4. Schematic representation of events leading to the increase of cationic conductance of the membrane without participation of protein channels, which is induced by the lipid peroxidation and causes mitochondria swelling.

Formation of lipid pores for cations could be stimulated by the membrane swelling (due to increase of membrane tension [77]), by oxidative stress (accumulation of lipid peroxides and lysolipids). Changes in concentration of the two-valent ions, calcium in particular, also is an important factor changing surface of the lipid membranes and leading to clustering of anionic lipids [78], which also could facilitate pore formation, especially in the cases of fluctuating electric potential [79]. Loss of potential on the inner membrane allows efflux of the part of calcium from the mitochondrial matrix, where it is accumulated during the mitochondria functioning, especially in the case of insufficient rate of K^+/H^+-exchange (for example in the case of increased permeability of the membrane to potassium or dysfunction of the K^+/H^+-exchanger). This makes the lipid-based regulation system associated with formation of lysocardiolipin a potential mechanism duplicating the functions of the ATP-dependent potassium channel, and, to certain degree, functions of the K^+/H^+-exchanger (prevention of membrane rupture during swelling). The lipid-associated regulation system could be a less effective evolutionary precursor of the more specialized protein-based systems.

Another factor that must be taken into consideration during formation of lysocardiolipin mediated by phospholipase A2, is the release of free fatty acids that can transport protons across the membrane [80]. Certain transport proteins such as UCP, ANT, and glutamate-aspartate transporter participate in the proton transport induced by fatty acids [80]. A mechanism of modulation of fatty acid transport has been described for ANT [81]. That is why physiological formation of lysocardiolipin with participation of phospholipase is accompanied by the appearance of free fatty acid, hence, the potassium transport is accompanied by the proton transport. Under condition of very high potassium concentration in the matrix at which the transmembrane potential of potassium ions is higher than the electrical potential, combined operation of the potassium-conducting lipid pore and ANT could cause movement of ions corresponding to the K^+/H^+-exchange. Indeed, efflux of the excess of potassium ions from the matrix into the external medium could create, for a short time, electric field sufficient for ATP synthesis [82]. Hence, explosive efflux of potassium due to the opening of potassium channels hypothetically could support membrane potential under extreme conditions. However, for ATP synthesis this would require formation under the effect of electric field of a very large difference in potassium concentration between the matrix and cytosol (three orders of magnitude difference for reaching 180 mV potential), therefore realization of this mechanism *in vivo* under conditions of very high concentration of potassium ions in cytosol is impossible, and changes in potential associated with the efflux of potassium ions could play only a regulatory role (for example in the processes associated with apoptosis and transport).

CONCLUSIONS

Hence, in this review we presented at least five fundamental problems in bioenergetics that are closely associated with the processes of potassium transport: unclear effect of swelling on the system of oxidative phosphorylation; unknown or multiple molecular identity of the key transporters –

K^+/H^+-exchanger and mitoK(ATP); uncertain role of ATP synthase in potassium transport and in opening of mPTP; extremely low knowledge on how lipid modification and physical properties of the membrane affect potassium conductivity. In addition to these problems discussed in detail, lack of comprehensive mathematical models of ion transport should be also noted, however, we did not focus on this problem, because it is impossible to develop such model without answering the questions presented above. As a conceptual solution for the emerging crisis in bioenergetics associated with ion transport, we suggest shifting attention of the researchers from the protein-based transporters to complex consideration of protein–lipid membranes with emphasis on the lipid components of the membrane. Among other things, this implies transition to more physiologically justified models of the mitochondrial membrane containing cardiolipin and lysocardiolipin, as well as conducting investigation with varying viscosity, phase state, fatty acid composition, and other parameters of the membrane.

Abbreviations

DCCD	1,3-dicyclohexylcarbodiimide
mitoK(ATP)	mitochondrial ATP-dependent potassium channel
mPTP	mitochondrial permeability transition pore

Contributions

S. V. Nesterov – preparation of the main test and illustrations; S. V. Nesterov, E. G. Smirnova, and L. S. Yaguzhinsky participated in collecting and analyzing the data, in editing of the manuscript.

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Ethics approval and consent to participate

This work does not contain any studies involving human and animal subjects.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

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