World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(RESEARCH ARTICLE)

Check for updates

The new vision of mitochondrial permeability transition pore opening

Kasumov E.A *, Kasumov R.E. and Kasumova I.V.

Research and Production Center, KORVET, Kryukovo village, building 30, Domodedovo, Moscow region, Russia.

World Journal of Advanced Research and Reviews, 2023, 18(02), 825–828

Publication history: Received on 08 April 2023; revised on 16 May 2023; accepted on 18 May 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.18.2.0913

Abstract

Mitochondria play a fundamental role in the functioning of the body but are also responsible for dysfunction, apoptosis, and death, associated with the mPTP (mitochondrial permeability transition pore) opening. Despite the fact that there are many articles on this topic, none of them solve the problem of PTP identification. The opening of the PTP is elicited by matrix Ca^{2+} and stimulated by binding of cyclophilin D (CyPD), Pi, elevated concentration of reactive oxygen species (ROS), free fatty acids, or diminished transmembrane potential. Nucleotides, Mg^{2+}, and the binding of (cyclosporin A) CsA are known molecular inhibitors of PTP opening, whereas arginine-specific adducts of phenylglyoxal modulate PTP opening in a species and net-charge-dependent manner. It seems to us that the reason for the unresolved problem of mPTP lies in ignorance of the functioning of ATP synthase. According to our mechano-chemiosmotic mechanism we suggest that in ATP synthase two channels are connected, consisting of a c-ring of Fo and, α3β3-hexamer with a cap the oligomycin sensitivity conferring protein (OSCP) subunit of F1 in mitochondria closing a c-ring. In our opinion, OSCP subunit together with α3β3-hexamer act as an analogue of adenine nucleotide translocase (ANT), which can be designated as F1-ANT. It exchanges synthesized 3-ATP molecules in the active center of ATP synthase for 3-ADP molecules from the matrix with the participation of sodium and magnesium ions. Thus, we conclude that both ANT in the membrane and F1-ANT (OSCP subunit together with α3β3-hexamer) in the complex with the c-ring of ATP synthase are jointly involved in the functioning of mPTP.

Keywords: Mechano-chemiosmotic mechanism; Mitochondrial permeability transition pore; OSCP; ANT

1. Introduction

Mitochondria play a fundamental role in the functioning of the body but are also responsible for dysfunction, apoptosis, and death, associated with the mPTP opening. Despite the fact that recently there have been several articles on this topic [1-4], none of them solve the problem of PTP identification. The opening of the PTP is elicited by matrix Ca^{2+} and stimulated by binding of cyclophilin D (CyPD), Pi, elevated concentration of reactive oxygen species (ROS), free fatty acids, or diminished transmembrane potential. Nucleotides, Mg^{2+}, and the binding of CsA are known molecular inhibitors of PTP opening, whereas arginine-specific adducts of phenylglyoxal modulate PTP opening in a species and net-charge-dependent manner [2].

It seems to us that the reason lies in ignorance of the functioning of ATP synthase. We have developed a mechano-chemiosmotic mechanism for coupling ATP synthesis to electron transfer and cyclic low-amplitude swelling-shrinkage of the mitochondria [5-6, animation https://www.youtube.com/watch?v=CeZxSyeDBwk]. Recently obtained experimental data prove the presence of rapid cyclic changes in the intracristae space and slight depolarization [7]. We suggest that in ATP synthase two channels are connected, consisting of a c-ring in Fo and, α3β3-hexamer with a cap the oligomycin sensitivity conferring protein (OSCP) subunit in mitochondria (ATP synthase δ-subunit is a subunit of bacterial and chloroplast F-ATPase/synthase), closing a c-ring (figure 1). In our opinion, OSCP subunit together with α3β3-hexamer is an adenine nucleotide translocase and act as an analogue of adenine nucleotide translocase (ANT) in

* Corresponding author: Kasumov E.A

the membrane, which can be designated as F1-ANT. It exchanges synthesized 3-ATP molecules in the active center of ATP synthase for 3-ADP molecules from the matrix with the participation of ions sodium and magnesium (figure 1, II). This assumption is supported by the effect of cyclophilin (CyPD) on OSCP and PTP activation. It should be noted that F-ATPases lacking δ-subunit generally transport sodium instead of protons. They are proposed to be called N-ATPases, since they seem to form a distinct group that is further apart from usual F-ATPases than A-ATPases are from V-ATPases [8].

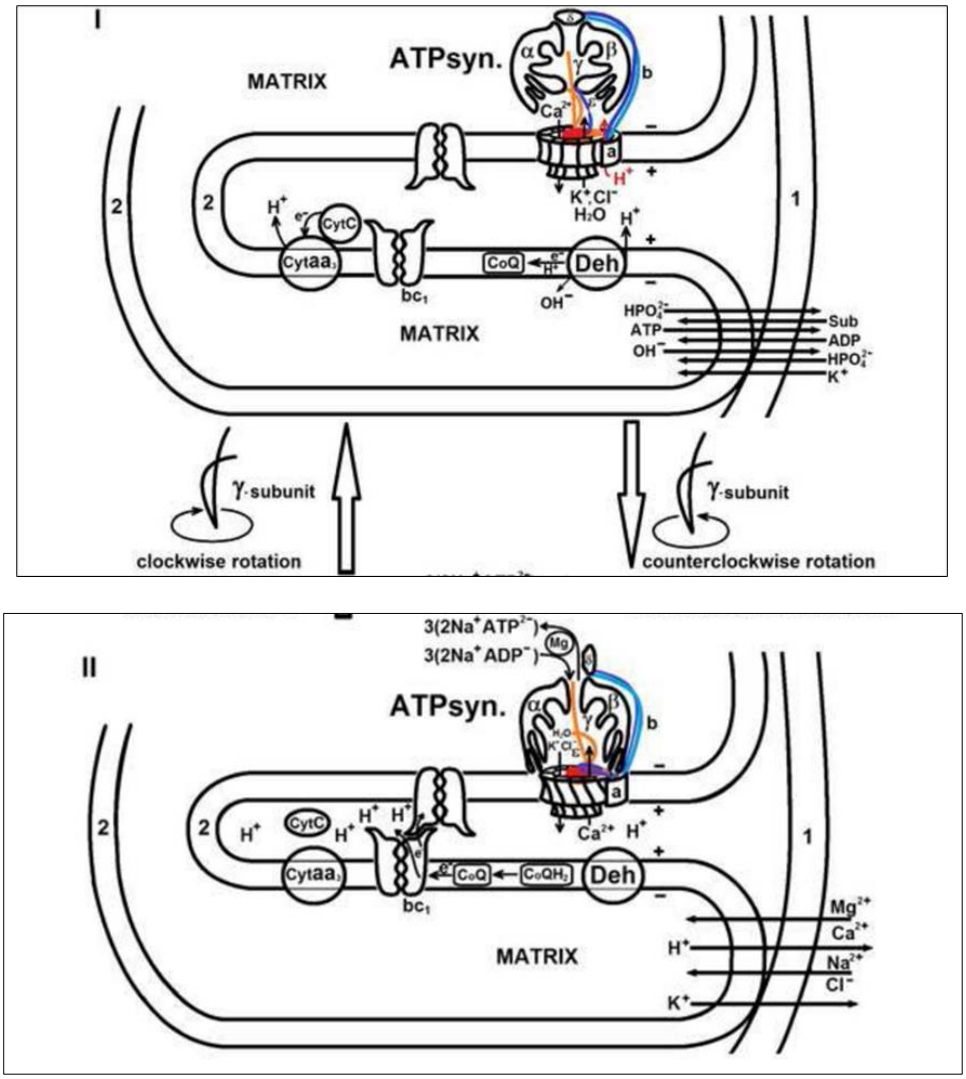

Figure 1 The mechano-chemiosmotic mechanism for coupling ATP synthesis to electron transfer and cyclic low-amplitude swelling-shrinkage of the mitochondria. A cyclic swelling (I) and shrinkage (II) of mitochondria intracristal space associated with the transfer of electrons through the cytochrome bc1 dimers, ion transport in ATP synthase and ATP synthesis; electron transfer from dehydrogenase (Deh) to cytochrome oxidase (Cytaa3) through ubiquinol (CoQH2), dimeric cytochrome bc1 and cytochrome c, 1 - outer membrane, 2 - inner membrane, α, β, γ, δ, ε, b2, a- subunits of ATP synthase. ATP synthase δ-subunit is a subunit of bacterial and chloroplast F-ATPase/synthase. It is known as OSCP (oligomycin sensitivity conferral protein) in mitochondrial ATPase. Schematically shown is the rotation of the γ-subunit counterclockwise direction during energization and clockwise direction in the synthesis of ATP – deenergization. OSCP subunit together with α3β3-hexamer is an adenine nucleotide translocase and act as an analogue of adenine nucleotide translocase (ANT) in the membrane, which can be designated as F1-ANT. It exchanges synthesized 3-ATP molecules in the active center of ATP synthase for 3-ADP molecules from the matrix with the participation of ions sodium and magnesium.

We believe that the functioning of ATP synthase, where positively charged residues of Arg, Lys, and partly His play an important role, occurs in parallel with cyclic swelling-shrinkage of mitochondria, cyclic changes in pH, both of the matrix (from alkaline pH to pH 7 and back to alkaline value) and intracristae space (from acidic pH to pH 7 and back to acidic value). This explains why the permeability transition is strongly affected by matrix pH. In deenergized mitochondria the

pH optimum for PTP opening is 7.4, while the open probability decreases sharply below pH 7.4 [9]. Antoniel et al. showed that the most potent inhibitors of mPTP are matrix protons, with channel block at pH 6.5. Inhibition is reversible, mediated by the highly conserved histidyl residue (H112 in the human mature protein) of oligomycin sensitivity conferral protein (OSCP) subunit of mitochondrial F1Fo (F)-ATP synthase [10]. According to our model the participation of ADP, Pi, protons, potassium, calcium, sodium, magnesium ions, and anions are required for the synthesis of ATP.

During energization of mitochondria γ-subunit rotates anticlockwise due to the binding of phosphate ions to positively charged amino acid residues in the N-terminal γ-subunit in the electric field (membrane potential). The coiled-coil b2 subunits, as we suggest, act as ropes that are shortened by binding of phosphate ions to positively charged lysines or arginines; this process is suggested pulling the α3β3-hexamer to the membrane during the energization process. ATP is then synthesized during the reverse rotation of the γ-subunit by the dephosphatized N-terminal γ-subunit and b2-subunits under the influence of Ca^{2+} ions, which are pumped over from intracristae space, during swelling. It should be borne in mind that the energy balance of mitochondrial functioning depends on the number of charges of phosphate ions (our unpublished data). This is also evidenced by data on the effect of polyphosphates on the behavior of PTP. The short-chain polyP activated mPTP in WT myocytes, to the contrary, long-chain polyP suppressed mPTP activation [11].

The fact that the c-ring is a non-selective ion channel for cations and anions has been substantiated by us in more detail in [5]. Only it is necessary to add that according to recently published data [12], the mitochondrial calcium uniporter (MCU) interacts with the subunit c of the ATP synthase, therefore, the movement of calcium ions in different directions through the c-ring and the calcium uniporter occurs in concert. MCU includes a highly conserved domain comprising two transmembrane regions and an intervening loop enriched in negatively-charged (acidic) residues, forming the mitochondrial Ca^{2+} channel. The opening of this channel for the release of calcium ions from the intracristae space is possible only at pH = 7.0 and more (in order for the residues to acquire a negative charge) with a shrinkage of the intracristae space, where the electrochemical gradient of calcium ions increases several times.

In general, the disruption of the mechano-chemiosmotic mechanism of coupling ATP synthesis to electron transfer and cyclic low-amplitude swelling-shrinkage of mitochondria leads to the opening of PTP. One of the reasons for the PTP opening is the formation of ROS in large quantities. In accordance to the mechano-chemiosmotic mechanism an asymmetric contact of dimers of opposite cyt bc_1 complexes is formed in the intracristae space during shrinkage of organelles, which is a mechanical regulator of electron transfer from the [2Fe-2S] cluster to heme c_1. It should be noted that mROS is formed in swelled mitochondria, and the amount of ROS depends on the time during which the mitochondria are in the swollen state. Another reason for the PTP opening is an increase in the concentration of calcium ions outside the mitochondria, which leads to a strong depolarization of the inner mitochondrial membrane, in contrast to ADP, which causes weak polarization in the mechanism of ATP synthesis. As a result, the calcium concentration in the matrix increases, where calcium homeostasis and the mechano-chemiosmotic mechanism of ATP synthesis are disturbed.

Thus, we conclude that both ANT in the membrane and F1-ANT (OSCP subunit together with α3β3-hexamer) in the complex with the c-ring of ATP synthase are jointly involved in the functioning of mPTP. It is also important to note that the amino acids associated with the active group of OSCP include lysine and arginine, since agents that act on these amino acids inactivate OSCP [13].

Compliance with ethical standards

Acknowledgments

We thank Polozova Victoria for support and helping in preparing the manuscript.

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest. The authors are fully responsible for data collection and extraction, interpretation, and writing of this manuscript.

References

[1] Baines CP, Gutiérrez-Aguilar M. The mitochondrial permeability transition pore: Is it formed by the ATP synthase, adenine nucleotide translocators or both? Biochim Biophys Acta Bioenerg. 1861 (2020) 148249. doi: 10.1016/j.bbabio.2020.148249

[2] Gerle C. Mitochondrial F-ATP synthase as the permeability transition pore. Pharmacol Res. 160 (2020) 105081. doi: 10.1016/j.phrs.2020.105081.

[3] Bernardi P. Mechanisms for Ca2+-dependent permeability transition in mitochondria. Proc Natl Acad Sci U S A. 117 (2020) 2743-2744. doi: 10.1073/pnas.1921035117.

[4] Mnatsakanyan N, Jonas EA. The new role of F(1)F(o) ATP synthase in mitochondria-mediated neurodegeneration and neuroprotection. Exp Neurol., 332 (2020) 113400. doi: 10.1016/j.expneurol.2020.113400.

[5] Kasumov E.A., Kasumov R.E., Kasumova I.V. A mechano-chemiosmotic model for the coupling of electron and proton transfer to ATP synthesis in energy transforming membranes: a personal perspective. Photosynthesis Research, 123 (2015) 1-22. doi: 10.1007/s11120-014-0043-3.

[6] Kasumov E.A., Kasumov R.E., Kasumova I.V. Mild depolarization of the inner mitochondrial membrane is a crucial component of the mechano-chemiosmotic mechanism of coupling. J Nov Physiother Phys Rehabil., 7 (2020) 033-035. DOI: https://dx.doi.org/10.17352/2455-5487.000075

[7] Kondadi A.K., Anand R., Hansch S., Urbach J., Zobel T., Wolf D.M., Segawa M., Liesa M., Shirihai O.S., Weidtkamp-Peters S., Reichert A.S., Cristae undergo continuous cycles of membrane remodelling in a MICOS-dependent manner. EMBO Rep., 21 (2020) e49776, doi.org/10.15252/embr.201949776

[8] Dibrova, DV; Galperin, MY; Mulkidjanian, AY (15 June 2010). "Characterization of the N-ATPase, a distinct, laterally transferred Na+-translocating form of the bacterial F-type membrane ATPase". Bioinformatics. 26 (12): 1473–6. doi:10.1093/bioinformatics/btq234

[9] Bernardi P, Di Lisa F, Fogolari F, Lippe G. From ATP to PTP and Back: A Dual Function for the Mitochondrial ATP Synthase. Circ Res. 116 (2015) 1850-62. doi: 10.1161/CIRCRESAHA.115.306557.

[10] Antoniel, M., Jones, K., Antonucci, S., Spolaore, B., Fogolari, F., Petronilli, V., Giorgio, V., Carraro, M., Di Lisa, F., Forte, M., Szabó, I., Lippe, G., & Bernardi, P. (2018). The unique histidine in OSCP subunit of F-ATP synthase mediates inhibition of the permeability transition pore by acidic pH. EMBO reports, 19 (2), 257–268. https://doi.org/10.15252/embr.201744705

[11] Seidlmayer L.K., Gomez-Garciac M. R., Shibad T., Porter G. A. Jr., Pavlov E.V., Bersg D.M., Dedkova E.N. Dual role of inorganic polyphosphate in cardiac myocytes: The importance of polyP chain length for energy metabolism and mPTP activation. Archives of Biochemistry and Biophysics. 662 (2019)177-189. https://doi.org/10.1016/j.abb.2018.12.019

[12] Huang G, Docampo R. The Mitochondrial Calcium Uniporter Interacts with Subunit c of the ATP Synthase of Trypanosomes and Humans. mBio. 11(2020) pii: e00268-20. doi: 10.1128/mBio.00268-20

[13] Dupuis A, Lunardi J, Issartel JP, Vignais PV. Interactions between the oligomycin sensitivity conferring protein (OSCP) and beef heart mitochondrial F1-ATPase. 2. Identification of the interacting F1 subunits by cross-linking. Biochemistry. 1985 Jan 29;24(3):734-9. doi: 10.1021/bi00324a030.