Bioenergetics: Open Access
ISSN: 2167-7662

Gutierrez-Aguilar and Baines, Bioenergetics 2014, 3:1
DOI: 10.4172/2167-7662.1000e119

Editorial Open Access

Mitochondrial ATP Synthase: Is the Molecular Engine of Life also an Efficient Death Machine?

Manuel Gutierrez-Aguilar[1*] and Christopher P Baines[1,2,3]

[1]Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO, USA

[2]Department of Biomedical Sciences, University of Missouri, Columbia, MO, USA

[3]Department of Medical Pharmacology & Physiology, University of Missouri, Columbia, MO, USA

Following the initial studies by Hunter and Haworth on the "Ca^{2+}-induced membrane transition" [1-3], a plethora of studies addressing the pharmacology, bioenergetics and structure of the Mitochondrial Permeability Transition (MPT) pore have allowed us to slowly decipher the pathophysiological relevance of this mitochondrial entity [4-6]. Although most of the MPT pore regulatory aspects were envisaged a few years after its discovery, it has taken decades and different approaches to reveal some of its structural aspects (see below).

Pharmacological inhibition of the MPT pore with Adenine Nucleotide Translocator (ANT) and Cyclophilin D (CypD) ligands led to the long lasting and widespread notion that the MPT pore was formed by the ANT acting as a channel component and CypD as a regulatory factor. In this model, ADP, ATP and the ANT ligand bonkrekate would inhibit pore opening by directly binding to ANT whereas CypD inhibition with Cyclosporin A would inhibit a conformational change mediated by CypD on a proline due to its peptidyl-prolylcis-trans isomerase activity. Although this hypothesis was widely accepted and a plethora of evidence indeed pointed towards a central role of this mitochondrial translocator as a MPT pore constituent [5], experiments with mouse lacking the two major isoforms of ANT demonstrated its dispensability for MPT to ensue [7]. It is important to mention that the pore detected in these knockout animals was insensitive to ANT ligands and threefold more resistant to Ca^{2+}, whereas CsA further inhibited its opening. On the other hand, mitochondria from CypD knockout mice were also resistant to Ca^{2+} (twofold), oxidative stress and desensitized to CsA [8-10]. Overall, these results strongly suggested that ANT and CypD were MPT pore regulatory factors.

In a recent set of studies, two different groups addressed the possibility that ATP-synthase may play an important role on the MPT pore, possibly being the pore itself [11,12]. This finding per se would put an end to a long-lasting search and consequently redirect research efforts to elucidate pore formation mechanisms and potential molecular-selective therapies aiming to dissipate MPT-pore dependent cell pathology while bypassing ATP synthase normal functioning. A note of caution should be stated as more studies in this direction are warranted before precipitous conclusions can be drawn (see above). Although both studies strongly suggest the MPT pore may be composed of ATP synthase subunit(s), the main question still to be addressed is: What is the MPT pore?

In the work by Bonora et al. [11] ATP-synthase subunit c, located in the membrane (F0) sector of the enzyme was shown to be necessary for MPT to ensue. In this study, the authors decreased the expression levels of subunit c and showed a concomitant resistance to Ca^{2+} and H_2O_2- induced MPT pore opening. Antithetical overexpression of subunit c rendered the cells susceptible to MPT pore dependent depolarization and cell death. While these experiments are indeed promising, it is important to mention that ATP-synthase oligomers are thought to confer the particular cristae architecture of the inner mitochondrial membrane and depletion of this oligomers results in mitochondria with onion-like multiple inner membranes [13]. It is thus possible to speculate that genetic manipulation of the c subunit would consequently alter the overall mitochondrial architecture potentially affecting MPT onset indirectly.

In the work by Giorgio et al. [12], the authors used a more direct approach and detected a Multiple Conductance Channel-like activity when purified dimers of ATP synthase were reconstituted for electrophysiological measurements. In these experiments, channel opening was achieved by adding an excess of Ca^{2+} and was preventable with Mg2+, ADP and AMP-PNP but not with CsA or bongkrekate consistent with preparations lacking both CypD and ANT. It is noteworthy to mention that the potent MPT pore inducer phenylarsine oxide did not activate this channel. Furthermore, modulation by other effectors such as diamide or ubiquinone analogues was not tested [14]. In this work, CypD was shown to selectively bind to oligomycin sensitivity conferral protein (OSCP) and consequently modulate the (still undefined) MPT pore through the lateral stalk of ATP synthase. Knockdown of the alleged CypD target (i.e. OSCP) sensitized mitochondria to pore opening. This result requires more attention as OSCP depletion results in the assembly failure of stalk subunits such as a, b and c [15,16] and the consequent ATP synthase dimer disruption. As noted above, this condition considerably impacts mitochondrial ultrastructure potentially affecting the Ca^{2+}threshold of the pore. One interesting finding however was that ATP synthase working as an ATPase increases twofold the Ca^{2+} threshold of the pore. This finding suggests a direct and physiological relationship between ATP synthase and the MPT pore. Finally, the authors did not solve what is the MPT pore and just mentioned that it could be formed at the interface between dimers potentially in the membrane. Although this could explain the sometimes-unruly nature of the pore and its sensitivity to molecules affecting membrane fluidity such as local anesthetics or fatty acids, it could well mean that a still unidentified channel closely interacts with ATP synthase but is not ATP synthase per se.

Hopefully these studies will pave the beginning of a renewed search for answers to an old question. The suggestion that the MPT pore may be formed by discrete subunits of ATP synthase or at least closely interacting with this enzymeis indeed appealing. Nevertheless, more studies are still warranted to truly address what is the MPT pore.

***Corresponding author:** Manuel Gutierrez-Aguilar, Dalton Cardiovascular Research Center, University of Missouri-Columbia, 134 Research Park Dr., Columbia, MO 65211, USA, Tel: 573-884-8767; Fax: 573-884-4232; E-mail: bainesc@missouri.edu

Received December 30, 2013; **Accepted** January 2, 2014; **Published** January 10, 2014

Citation: Gutierrez-Aguilar M, Baines CP (2014) Mitochondrial ATP Synthase: Is the Molecular Engine of Life also an Efficient Death Machine?. Bioenergetics 3: e119. doi:10.4172/2167-7662.1000e119

References

1. Hunter DR, Haworth RA (1979) The Ca^{2+}-induced membrane transition in mitochondria. I. The protective mechanisms. Arch Biochem Biophys 195: 453-459.
2. Haworth RA, Hunter DR (1979) The Ca^{2+}-induced membrane transition in mitochondria. II. Nature of the Ca^{2+} trigger site. Arch Biochem Biophys 195: 460-467.
3. Hunter DR, Haworth RA (1979) The Ca^{2+}-induced membrane transition in mitochondria. III. Transitional Ca^{2+} release. Arch Biochem Biophys 195: 468-477.
4. Rasola A, Bernardi P (2011) Mitochondrial permeability transition in Ca^{2+}-dependent apoptosis and necrosis. Cell Calcium 50: 222-33.
5. Halestrap AP (2010) A pore way to die: the role of mitochondria in reperfusion injury and cardioprotection. Biochem Soc Trans 38: 841-860.
6. Baines CP (2010) The cardiac mitochondrion: nexus of stress. Annu Rev Physiol 72: 61-80.
7. Kokoszka JE, Waymire KG, Levy SE, Sligh JE, Cai J, et al. (2004) The ADP/ATP translocator is not essential for the mitochondrial permeability transition pore. Nature 427: 461-465.
8. Basso E, Fante L, Fowlkes J, Petronilli V, Forte MA, et al. (2005) Properties of the permeability transition pore in mitochondria devoid of Cyclophilin D. J Biol Chem 280: 18558-18561.
9. Baines CP, Kaiser RA, Purcell NH, Blair NS, Osinska H, et al. (2005) Loss of cyclophilin D reveals a critical role for mitochondrial permeability transition in cell death. Nature 434: 658-662.
10. Nakagawa T, Shimizu S, Watanabe T, Yamaguchi O, Otsu K, et al. (2005) Cyclophilin D-dependent mitochondrial permeability transition regulates some necrotic but not apoptotic cell death. Nature 434:652-658.
11. Bonora M, Bononi A, De Marchi E, Giorgi C, Lebiedzinska M, et al. (2013) Role of the c subunit of the FO ATP synthase in mitochondrial permeability transition. Cell Cycle 12: 674-683.
12. Giorgio V, von Stockum S, Antoniel M, Fabbro A, Fogolari F, et al. (2013) Dimers of mitochondrial ATP synthase form the permeability transition pore. Proc Natl Acad Sci 110: 5887-92
13. Paumard P, Vaillier J, Coulary B, Schaeffer J, Soubannier V, et al. (2002) The ATP synthase is involved in generating mitochondrial cristae morphology. EMBO J 21: 221-230.
14. Martinucci S, Szabo I, Tombola F, Zoratti M (2000) Ca^{2+}-reversible inhibition of the mitochondrial megachannel by ubiquinone analogues. FEBS Lett 480: 89-94.
15. Straffon AF, Prescott M, Nagley P, Devenish RJ (1998) The assembly of yeast mitochondrial ATP synthase: subunit depletion in vivo suggests ordered assembly of the stalk subunits b, OSCP and d. Biochim Biophys Acta 1371: 157-162.
16. Devenish RJ, Prescott M, Roucou X, Nagley P (2000) Insights into ATP synthase assembly and function through the molecular genetic manipulation of subunits of the yeast mitochondrial enzyme complex. Biochim Biophys Acta 1458: 428-442.