Mitochondrion 21 (2015) 11

Contents lists available at ScienceDirect

Mitochondrion

journal homepage: www.elsevier.com/locate/mito

Shedding light on molecular mechanisms and identity of mPTP

Mitochondrial ATP synthase displays features that are characteristic of the mPTP. Its activity is inhibited by the concurrent binding of the two mPTP inhibitors ADP and Mg^{2+}, whereas the mPTP inducer inorganic phosphate abolishes this block. A strategic component of the mPTP, cyclophilin D (CypD), interacts with the peripheral stalk of ATP 1synthase, reducing its catalytic activity. This activity is restored when cyclosporine A (a mPTP inhibitor) displaces CypD (Giorgio et al., 2009). Finally, Bcl-Xl, which inhibits the mPTP, interacts with ATP synthase and promotes its activity (Alavian et al., 2011).

Moreover, it has been demonstrated that the c subunit of mitochondrial ATP synthase (the only transmembrane subunit of the ATP synthase with a gating capacity when oligomerized as c-ring (McGeoch and Palmer, 1999)) is a fundamental regulator of mPTP activity (Bonora et al., 2013, De Marchi et al., 2014). This idea was supported by a subsequent study describing currents that were sensitive to mPTP regulators and generated by isolated c subunits on artificial bilayers and in isolated mitochondria (Azarashvili et al., 2014).

The proposal that the c-ring forms the core of the mPTP is now supported by a recent work by Alavian et al. that demonstrates how the c-ring can generate a non-specific current ascribable to the mPTP (Alavian et al., 2014).

This fascinating study raises new questions concerning a potential mechanism that can transform an evolved enzymatic complex into a non-specific and detrimental channel. First, the precise mechanisms involved in forming this pore are unclear. Alavian et al. showed that rearrangement of the c-ring occurs during mitochondrial permeability transition. The authors suggested that through this mechanism, the c-ring diameter should increase, generating non-specific channels. It should be noted that in other species, the stoichiometry of the c-ring can vary widely, by as much as 15 monomers for one ring (Pogoryelov et al., 2007). Nevertheless, no MPT-like activity was observed in this study, suggesting that an increase in the c-ring diameter is not sufficient for inducing MPT-like activities.

Other intriguing questions are what mechanism could isolate the c-ring from the complex and what molecular factors are required for these events to occur. In the study by Alavian et al., they proposed that this event requires CypD activity, but they did not propose a molecular mechanism through which this activity could be transmitted to the c subunit.

Despite the many questions that remain unanswered, these findings add a new piece to the complicated puzzle of the mPTP structure.

Acknowledgments

The Italian Association for Cancer Research (AIRC, IG 14442); Telethon Foundation (GGP11139B), the Italian Ministry of Education, University and Research (COFIN: 20129JLHSY_002, FIRB: RBAP11FXBC_002, and Futuro in Ricerca: RBFR10EGVP_001) and local funds from the University of Ferrara to Paolo Pinton.

References

Alavian, K.N., Li, H., Collis, L., Bonanni, L., Zeng, L., Sacchetti, S., Lazrove, E., Nabili, P., Flaherty, B., Graham, M., Chen, Y., Messerli, S.M., Mariggio, M.A., Rahner, C., McNay, E., Shore, G.C., Smith, P.J.S., Hardwick, J.M., Jonas, E.A., 2011. Bcl-xL regulates metabolic efficiency of neurons through interaction with the mitochondrial F1FO ATP synthase. Nat. Cell Biol. 13, 1224–1233. http://dx.doi.org/10.1038/ncb2330.

Alavian, K.N., Beutner, G., Lazrove, E., Sacchetti, S., Park, H.-A., Licznerski, P., Li, H., Nabili, P., Hockensmith, K., Graham, M., Porter, G.A., Jonas, E.A., 2014. An uncoupling channel within the c-subunit ring of the F1FO ATP synthase is the mitochondrial permeability transition pore. Proc. Natl. Acad. Sci. U. S. A. http://dx.doi.org/10.1073/pnas.1401591111 (1401591111).

Azarashvili, T., Odinokova, I., Bakunts, A., Ternovsky, V., Krestinina, O., Tyynelä, J., Saris, N.-E.L., 2014. Potential role of subunit c of F0F1-ATPase and subunit c of storage body in the mitochondrial permeability transition. Effect of the phosphorylation status of subunit c on pore opening. Cell Calcium 55, 69–77. http://dx.doi.org/10.1016/j.ceca.2013.12.002.

Bonora, M., Bononi, A., De Marchi, E., Giorgi, C., Lebiedzinska, M., Marchi, S., Patergnani, S., Rimessi, A., Suski, J.M., Wojtala, A., Wieckowski, M.R., Kroemer, G., Galluzzi, L., Pinton, P., 2013. Role of the c subunit of the FO ATP synthase in mitochondrial permeability transition. Cell Cycle 12, 674–683. http://dx.doi.org/10.4161/cc.23599.

De Marchi, E., Bonora, M., Giorgi, C., Pinton, P., 2014. The mitochondrial permeability transition pore is a dispensable element for mitochondrial calcium efflux. Cell Calcium 56, 1–13. http://dx.doi.org/10.1016/j.ceca.2014.03.004.

Giorgio, V., Bisetto, E., Soriano, M.E., Dabbeni-Sala, F., Basso, E., Petronilli, V., Forte, M. a, Bernardi, P., Lippe, G., 2009. Cyclophilin D modulates mitochondrial F0F1-ATP synthase by interacting with the lateral stalk of the complex. J. Biol. Chem. 284, 33982–33988. http://dx.doi.org/10.1074/jbc.M109.020115.

McGeoch, J.E., Palmer, D.N., 1999. Ion pores made of mitochondrial ATP synthase subunit c in the neuronal plasma membrane and Batten disease. Mol. Genet. Metab. 66, 387–392. http://dx.doi.org/10.1006/mgme.1999.2822.

Pogoryelov, D., Reichen, C., Klyszejko, A.L., Brunisholz, R., Muller, D.J., Dimroth, P., Meier, T., 2007. The oligomeric state of c rings from cyanobacterial F-ATP synthases varies from 13 to 15. J. Bacteriol. 189, 5895–5902. http://dx.doi.org/10.1128/JB.00581-07.

Massimo Bonora
Paolo Pinton*
Section of Pathology Oncology, Experimental Biology Laboratory for Technologies of Advanced Therapies (LTTA), Department of Morphology, Surgery, and Experimental Medicine, University of Ferrara, Ferrara, Italy
*Corresponding author at: Dept of Morphology, Surgery and Experimental Medicine, Section of Pathology, Oncology and Experimental Biology, University of Ferrara, Via Fossato di Mortara 70 (c/o CUBO), 44121 Ferrara, Italy.
E-mail address: pnp@unife.it.

16 August 2014
Available online 12 October 2014

http://dx.doi.org/10.1016/j.mito.2014.10.001