Review of: "[Review] Structural and Functional Roles of Non-bilayer Lipid Phase in Mitochondria"

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Potential competing interests: No potential competing interests to declare.

The authors present a very interesting compilation about the role of non-bilayer lipid phases in mitochondria and their importance for mitochondrial respiration. The work as merit and will appeal to researchers interested in Bioenergetics and those interested in the roles of lipid in physiological processes. The authors have compiled interesting information from available literature and built a nice paper that could represent an interesting contribution to the field and a helpful resource to researchers in the field. The issues with the paper are manageable and easy to solve, therefore I find the paper interesting and suitable for publication after the minor revisions proposed.

Main comments:

1) Bibliography seems up-to date at first glance, but the fact that that there is only one reference from 2022 gives the impression that the paper was written a while ago and not updated since. Are there not other recent papers (2022) contributing to the discussion here? If so, you should add them to the paper.

2) Again, regarding the bibliography, the references should be double checked since reference 3 and 7 seem the same.

3) In the section “Non-bilayer lipid, cardiolipin, facilitates ATP synthesis in cristae” I found it confusing where it reads: “The last study is of a particular interest. We suggest that protons inside the coupling membrane could be found on the inner surface of inverted micelle formed in a membrane bilayer same as suggested for inverted micelle with cytotoxin in its inner surface.” Is it you who suggests this mechanism or was it the paper cited before?

4) Figures are well chosen and helpful, but I really think that a scheme of your proposition for how proton flux/currents take place at the cristae level would make it easier to visualize and would greatly improve the paper, even if shown in a very simplified/merely illustrative way. I mean, of course, the mechanism described in: “Due to the high structural tension, inverted micelle releases protons along the concentration gradient of protons to the membrane surface on matrix side from where protons are returned back to the inter-crista space via proton pumps. When inverted micelle releases protons inverted micelle transforms back to bilayer membrane. Then when protons diffuse again along membrane surface back to ATP synthase surrounded by CL, conical shape of CL increases to trigger formation of inverted micelle with protons in the inner surface of micelle which then again releases protons to the matrix. It is quite possible that the reversible polymorphic transitions from bilayer membrane to non-bilayer micelle near the ATP synthase trigger rotation of the ATP rotor needed for ATP synthesis.”

5) The paper should be thoroughly reread and checked in its entirety, preferably by a native speaker prior to submission, in order to avoid English mistakes and syntactic errors. Some examples:

“non-bilayer lipids and cardiolipin may facilitate~~s~~ ATP synthesis in mitochondrial cristae”

“The conclusion was made that” -> “The authors concluded that…”

“This finding allowed one to employ CTI and CTII as the proteins that imitate membranotropic effects of DCCD-DPF.” -> “This finding allowed the use of CTI and CTII as proteins that mimic the membranotropic effects of DCCD-DPF.”

“The further experiments have shown that…” -> “Further experiments have shown that…”

“Both non-bilayer phospholipids contribute greatly not only to maintenance of functionally active states of the respiratory chain proteins, but also to overall membrane morphology of mitochondria [13].” -> “Both non-bilayer phospholipids contribute greatly**,** not only to **the** maintenance of functionally active states of the respiratory chain proteins, but also to **the** overall membrane morphology of mitochondria [13].”