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Coupling and pathway control of coenzyme Q redox state and respiration in isolated mitochondria

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Manuscript submitted 2021-09-15, 2021-11-09 (revision)

Manuscript accepted 2021-11-09

[doi:10.26124/bec:2021-0003](https://doi.org/10.26124/bec:2021-0003)

Reviewer 1

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Manuscript reviewed 2021-10-07

[doi:10.26124/bec:2021-0003.r1](https://doi.org/10.26124/bec:2021-0003.r1)

Reviewer 1

In the manuscript "Coupling and pathway control of coenzyme Q redox state and respiration in isolated mitochondria" Komlódi et al., investigate the use of diffusible Q2 to evaluate, indirectly, the redox state of CoQ pool. The manuscript and the introduction, in particular, is well written and historical discoveries on CoQ function are well detailed and referenced.

Nevertheless, a more recent review of the literature on CoQ biosynthesis, the CoQ synthetic complex assembly, and regulation would improve the quality of the text.

The Q2 state measurements were performed properly. However, I did not identify a control measurement in which Q2 was not added. Can the electrode detect the redox state of the less diffusible endogenous CoQ? It would also be great if they further discuss why the exogenous Q2 did not significantly interfere in the redox state of endogenous CoQ. It would be important to consider that the Q2 and CoQ compete for the same redox sites at CI, CII, and CIII respiratory complexes. Finally, I believe that the measurements of the Q2 redox state should also be performed when added to mitochondria devoid of endogenous CoQ (CoQ biosynthetic mutants). Such control would directly demonstrate the Q2 addition effect.

Authors

1 – We added a paragraph on CoQ synthesis on page 3 with several additional references: "CoQ is endogenously synthesized in all mammalian cells ..."

2 – We added a new Figure 6 (based on previous measurements originally intended for a separate manuscript) on O₂ flux in the absence and presence of 1 μM CoQ₂ mimetic as used in our study. Exogenously added CoQ₂ did not interfere with respiration.

3 – We thank the reviewer for motivating us to carry out a series of new experiments monitoring the signal of the Q-sensor in the absence of externally added CoQ₂, summarized in Figure 7. We added on page 16: “In the absence of CoQ₂ the raw Q-signal detected by the Q-sensor was ~11 % of the raw Q-signal detected with 1 μM CoQ₂ (Figure 7). At such a low signal, the drift becomes a confounding factor, emphasizing the need of adding a Q-mimetic.”

4 –BEC states on the journal website: “BEC reviewers do not have the option to insist on additional experiments, but strictly focus on the quality of the presently provided information. BEC reviewers may suggest additional experiments for future versions, without delay of publishing the actually available and evaluated information” (<https://www.bioenergetics-communications.org/index.php/bec/reviewers>). Experiments with CoQ biosynthetic mutants will be interesting future applications of the Q-Module but are not necessary within the scope of the present manuscript. The new Figure 6 shows that CoQ₂ (1 μM) does not influence respiration suggesting that exogenously added CoQ₂ does not interfere with the endogenous CoQ.