BEC BIOENERGETICS COMMUNICATIONS
Bioenerg Commun 2022.118
https://doi.org/10.26124/bec:2022-0018.r1
Open peer review
Open Access

Open peer review and authors' responses

Impaired Ca^{2+} signaling indicates disturbed mitochondrial function in fibroblasts from patients with sporadic and familial ALS

Authors: Gainutdinov T, Debska-Vielhaber G, Gizatullina Z, Vielhaber S, Orynbayeva Z, Gellerich FN

Bioenerg Commun 2022.18. https://doi.org/10.26124/bec:2022-0018

Reviewer 1: Tuuli Kaambre

Laboratory of Biological Chemistry, National Institute of Chemical Physics and Biophysics, Tallinn, Estonia

Manuscript reviewed 2022-05-18: *Only major points included.*

Reviewer 1

The manuscript is interesting and well written. However, I have a few suggestions.

How the uncoupler facilitated Ca^{2+} release from mitochondria?

Authors

We appreciate the comments of Dr Kaambre. The answer to her question lies in one of the fundamental bioenergetic mechanisms. The mitochondrial Ca^{2+} homeostasis is favored by the electrochemical potential of the mitochondrial membrane potential generated due to the oxidative phosphorylation (P. Mitchell 1969, D.G. Nicholls 2001). To reflect our thoughts, we rewrote the paragraph of the Discussion for clarity and enriched it with an additional description as follows:

The $[Ca^{2+}]_{cyt}$ is finely controlled by the buffering activity of cytosolic Ca^{2+} binding proteins and by its uptake/release from mitochondria. The sequestration of Ca^{2+} by mitochondria stimulates the citric acid cycle enhancing ATP production for cellular needs, including the ATP-driven Ca^{2+} pumps of endoplasmic reticulum and plasma membrane for carrying out the removal of the excess Ca^{2+} from cytosol. Retaining the accumulated Ca^{2+} in mitochondria as much important as its sequestration and depends on the inner membrane potential. Under the situations of heavy depolarization of mitochondria, the mPTP gets activated facilitating leakage of ionized Ca^{2+} from matrix in cytosole. In our experimental setting this was the case of Ca^{2+} overloaded ALS fibroblasts with a resultant sustained mitochondrial energetic depression and inability to hold Ca^{2+}.

Reviewer 1

Figure describing $[Ca^{2+}]$ cyt handling in fibroblasts would definitely make the manuscript better.

Authors

We appreciate the suggestion of Dr Kaambre, however, we think that it would not be easy to implement the one only generalized schematic with many nuances between the mechanisms of sporadic and familiar ALS fibroblasts and thus, will overburden the non-review type article.