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Barth syndrome: a genetic ailment with a lipid component and bioenergetic ramifications

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Reviewer 1

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*Only major points from review and responses included.

Reviewer 1

CL can act as H+ trap with its anionic phosphate groups and it may be responsible for the lateral transfer of protons on the surface of cristae membrane. Please discuss it in the manuscript.

Authors

We have included this analysis in the manuscript (in section 2.2).

Reviewer 1

Tafazzin catalyzes reversible transacetylation reaction with no intrinsic acyl chain specificity and is responsible for most of the CL remodeling. However, the existence of the other two enzymes responsible for CL remodeling was not even mentioned. These enzymes are: MLCLAT1 and ALCAT1. Please add their description to manuscript and modify Fig. 4. accordingly.

Authors

We have included this in the resubmitted manuscript and modified the figure accordingly.

Reviewer 1

CL interaction is required for the optimal function of many proteins residing in the inner mitochondrial membrane, not only for the respiratory complexes and ATP synthase, but for other proteins having fundamental roles in mitochondrial bioenergetics such as adenin nucleotide translocase, phosphate carrier, di-, tricarboxylate transporters, etc.

Moreover, recent evidences show that CL is essential for intermediary metabolism, since CL deficiency leads to defects in the TCA cycle, Pyruvate dehydrogenase and Pyruvate carboxylase activity as well. Please add detailed description of the effects of CL non-maturation/deficiency on intermediary metabolism.

Authors

We have included this information in the resubmitted manuscript (in section 2.2).

Reviewer 1

Description of Barth syndrome experimental models (yeast, mouse, patient derived fibroblasts, etc.) is completely missing. Please include it in the manuscript.

Authors

We have not included the experimental models used to study BTHS due to the lack of space and since our scope was to describe the disease in light of bioenergetics. It is very important to include in future reviews.

Reviewer 1

Discussion of potential therapeutic strategies are incomplete. The authors mention elamipretide as promising therapeutic agent, however its efficiency is questionable.

Authors

We have amended this section.

Reviewer 1

Description of functional impacts of tafazzin deficiency on cellular functions is really poor. For example, tafazzin deficiency causes hyperactivation of mTORC1 signaling and defective mitophagy leading to the accumulation of autophagic vacuoles and later apoptosis. Please summarize the potential effects of tafazzin deficiency on cellular function/signaling in a distinct chapter.

Authors

We thank the reviewer for the in-depth analysis of our work and we respond to the comments which have enhanced our content tremendously (in blue in the resubmitted manuscript).