Open peer review and authors' responses

NUBPL: a mitochondrial Complex I deficiency disorder

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Reviewer 2

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*Only major points from review and responses included.

Reviewer 2

The manuscript is well written and the topic is also very important in terms of Complex I deficiency and neurodegenerative diseases.

In the review, I would like to see the effects of complex I deficiency through genetic transfer vs chemically/ environmentally/age-induced mutation, and their effects on health. I have seen patients with Gulf War syndrome displaying Complex I deficiency, and related cognitive deficits. These service members were exposed to toxins/fertilizers.

Authors

We thank the reviewer for this comment. According to a study published in PLOS ONE (doi:10.1371/journal.pone.0184832), there does not seem to be a difference in Complex I or Complex IV activity between veterans with Gulf War Illness and controls. We have tried to link our manuscript to Gulf War Illness but were unsuccessful. We believe that this comment from the reviewer is out of the scope of this short review on an iron-sulfur-cluster transferring genetic disorder.

Reviewer 2

Q how do the effects of complex I deficiency differ in patients with genetically inherited disorders vs chemically induced? Please elaborate in this review.

Authors

In the clinical manifestations section, we have added a brief paragraph before the table to address this comment (in red font). Nevertheless, it is beyond the scope of this review to elaborate on the differences between genetic complex I deficiency versus

chemically-induced inhibition. The paragraph is as follows: "Like most diseases related to OXPHOS malfunction, NUBPL manifests in several systems with different severities (Table 1). In the brain, genetic deficiency of NUBPL is associated with neurological symptoms and some forms of Parkinson's disease (Kimonis et al., 2021). Interestingly, the use of chemical agents, such as pesticides, has also been implicated in Complex I deficiency and enhanced susceptibility to Parkinson's (Richardson et al., 2019). Pesticides such as rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine are strong Complex I inhibitors and have been used to generate chronic Parkinson's disease mouse models (Zhang et al., 2022). It is unclear whether clinical manifestations of genetic Complex I deficiency differs from chemically-induced inhibition of Complex I. Nevertheless, since the outcome of both is a severely reduced ETS activity and reactive oxygen species generation, it is not farfetched that the manifestations would not be very different."

Reviewer 2

I believe, a review article should be in a bit detail to cover the introduction and location of the enzyme. Its effects on metabolic pathways through genetic vs chemically vs physiologically induced alterations. Available treatments, gaps in knowledge, and future hope.

Authors

For the sake of brevity and the limited space in the inaugural issue, we were limited with our review. In the resubmitted manuscript we have elaborated a little and enhanced the content of this review, however, it is not possible to write a full review on this topic for the issue at hand. As for the available treatments, there are none until now. In the conclusion, we touched upon gaps in knowledge and future hope for this disease.