



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Biological Chemistry

**Manuscript NO:** 56088

**Title:** Regulation of cytochrome c oxidase contributes to health and optimal life

**Reviewer's code:** 00753114

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** Singapore

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2020-04-16

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2020-06-17 08:00

**Reviewer performed review:** 2020-06-17 12:46

**Review time:** 4 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

The author proposed a potentially interesting hypothesis that NDUFA4, known previously to associate with the respiratory chain's Complex I and Complex IV (CytOX), to switch between the two under conditions of stress or increase energetic demand. The introduction part of the manuscript provide sufficient background, but as a hypothesis paper it is relatively weak in the part that matters, namely the hypothesis itself and how it could be tested. 1. It isn't clear what the major findings are in support of a predominant association of NDUFA4 with complex I under 'normal' conditions, and a switch to associating with CytOX upon stress. This has to be much better elaborated. Are there any direct evidence for a preferential association by NDUFA4 with either complexes that is cytosolic Ca<sup>2+</sup>-dependent, or dependent on energy demand? 2. A Ca<sup>2+</sup>-dependent phosphatase in the mitochondrial IMS seems to reciprocally regulate the affinity of both complexes for NDUFA4. What is the identity of the phosphatase (or any evidence that it is a phosphatase)? 3. Is there any good evidence that CytOX complex preferentially associates with NDUFA4 in its monomeric form? For that matter is there any evidence that NDUFA4 binding will stabilize monomeric CytOX? The author cited Pitceathly et al. (2013) as providing evidence that NDUFA4 acts as a stabilizer of monomeric CytOx. However, in the paper the NDUFA4 mutation resulted in undetectable steady-state NDUFA4 protein levels and loss of CytOX function. If so, does it mean that the CytOX is not functional in its dimeric form? 4. A glaring omission in the manuscript is a detail discussion of how might future work support or refute the author's proposed hypothesis. Any good hypothesis should be falsifiable experimentally. The author should therefore outline the experiments that should be done in the immediate future.



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Biological Chemistry

**Manuscript NO:** 56088

**Title:** Regulation of cytochrome c oxidase contributes to health and optimal life

**Reviewer's code:** 02811953

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2020-04-16

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2020-06-17 11:52

**Reviewer performed review:** 2020-06-30 16:21

**Review time:** 13 Days and 4 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript (56088) entitled "Regulation of cytochrome c oxidase contributes to health and optimal life" is by Bernhard Kadenbach, et al. This is an opinion review. Main comments 1. The title is irrelevant to the content of the paper. The authors have not described the health and optimal health of any animal or organ or cells. They only describe a potential mechanism to control the activities of a component in electron transport chain by NDUFA4 and its relationship to ATP regulation. 2. The first sentence of the abstract is not accurate. There are two ways to generate ATP in a cell, substrate phosphorylation and oxidative phosphorylation. The later only occurs in cells with mitochondria. 3. The abstract does not include sufficient and useful information to support the hypothesis and conclusion. 4. If you believe that ATP functions as an allosteric inhibitor of CytOx, please provide the concentration by which 50% inhibition occurs. In addition, please also indicate how this concentration relates to physiological concentrations of ATP/ADP in the mitochondrion. Please summarize data and include them to support your claim. 5. There are many types of cells that serve variety of physiological functions. Please also elaborate the cell types that your hypothesis may apply to. 6. Please do not quote a lot of sentences from other studies as those are points in other papers. They only work in the context of the paper. Please describe those points in your own language.



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Biological Chemistry

**Manuscript NO:** 56088

**Title:** Regulation of cytochrome c oxidase contributes to health and optimal life

**Reviewer's code:** 03874940

**Position:** Editorial Board

**Academic degree:** DVM, MSc, PhD

**Professional title:** Adjunct Professor, Doctor, Senior Postdoctoral Fellow

**Reviewer's Country/Territory:** Romania

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2020-04-16

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2020-06-24 14:43

**Reviewer performed review:** 2020-07-03 04:09

**Review time:** 8 Days and 13 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

The manuscript "Regulation of cytochrome c oxidase contributes to health and optimal life" discusses in detail the functional structure and the activity of cytochrome c oxidase, and ends with an interesting hypothesis regarding the function nomenclature of NDUFA4 and the suggestion to rename it to „mitochondrial respiratory chain associated factor 1". The manuscript is well written and documented, the quality of information appropriate, although it contains many areas supported mainly on personal opinion. Minor Issues: Based on the title, one would expect to see additional information on the health and disease implications of the cytochrome c oxidase, but the manuscript focuses mainly on the physiological aspects. The overall novelty is unclear, since, besides a hypothesis, their elements of novelty are not clearly stated. Although a scheme regarding the Hypothesis on the variable binding of NDUFA4 to complex I or CytOx is provided (Fig. 1), additional graphical presentations of the content of the manuscript will make the information more comprehensible, easier to follow and finally increase the value of the material. -Please correct the few typos that can be found across the manuscript, as: -"work load" - „Bioenergetics4" - "Villani et al., 1998"



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Biological Chemistry

**Manuscript NO:** 56088

**Title:** Regulation of cytochrome c oxidase contributes to health and optimal life

**Reviewer's code:** 03257477

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Research Scientist

**Reviewer's Country/Territory:** Mexico

**Author's Country/Territory:** Germany

**Manuscript submission date:** 2020-04-16

**Reviewer chosen by:** Ya-Juan Ma

**Reviewer accepted review:** 2020-06-24 18:50

**Reviewer performed review:** 2020-07-11 00:42

**Review time:** 16 Days and 5 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

The title does not reflect the main hypothesis of the manuscript. The review tries to justify the hypothesis that interchange of ATP from low to maximal generation under a stress situation leads to dissociation of NDUFA4 between complex I and CytOx, but it does not have enough evidence to support it. The hypothesis appears to be interesting, however, the review of the previous work is weak. According to the title, background is insufficient to innovate in the field of the cytochrome c oxidase and health.