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# PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 78313

**Title:** Mitochondrial CPT-II Dysfunction: A Possible Novel Mechanism for NAFLD in Hepatocarcinogenesis

**Provenance and peer review**: Unsolicited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02536349
**Position:** Editorial Board
**Academic degree:** MD
**Professional title:** Doctor, Professor
**Reviewer's Country/Territory:** Turkey
**Author's Country/Territory:** China

**Manuscript submission date:** 2022-06-20

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-06-20 05:53

**Reviewer performed review:** 2022-06-29 18:09

**Review time:** 9 Days and 12 Hours

| | |
|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[Y] Minor revision [ ] Major revision [ ] Rejection |
| **Re-review** | [Y] Yes [ ] No |

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|---|---|
| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous<br>Conflicts-of-Interest: [ ] Yes [ Y] No |

**SPECIFIC COMMENTS TO AUTHORS**

A proactive review of pathophysiology which may be linked to treatment modalities of NAFLD. Please correct typographic errors such as: dysfuction (dysfunction), acyltrans- ferases (acyltransferases), malony-CoA(malonyl-CoA), mutanted (mutated), encephalo- pathy (encephalopathy), diseaseallele (disease allele), senother-apeutics

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**Reviewer's code:** 04939517
**Position:** Peer Reviewer
**Academic degree:** MD

**Professional title:** Professor

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

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

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**Reviewer accepted review:** 2022-06-23 05:33

**Reviewer performed review:** 2022-07-04 07:26

**Review time:** 11 Days and 1 Hour

| | |
|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing<br>[Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[ ] Minor revision [Y] Major revision [ ] Rejection |
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|---|---|
| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous<br>Conflicts-of-Interest: [ ] Yes [ Y] No |

**SPECIFIC COMMENTS TO AUTHORS**

Comments to the Author MANUSCRIPT SUMMARY The authors present a review of the progress of CPT-II inactivity with liver fat accumulation as possible novel pathogenesis for NAFLD in hepatocarcinogenesis in the manuscript “Mitochondrial CPT-II Dysfunction: A Possible Novel Mechanism for NAFLD in Hepatocarcinogenesis”. The authors make a strong case that CPT-II inactivity has an important role in the NAFLD malignant transformation. The wording and sentence structure also needs work, but overall, it is an interesting paper. Major points: 1. CPT1 has been recognized as the rate-limiting enzyme of the FAO pathway in the past, and the research on CPT2 is the rate-limiting enzyme of this pathway ware relatively few. The author should increase documents to corroborate the view that CPT2 is the rate-limiting enzyme of the FAO pathway. 2. The first sentence of the second paragraph of the article "1. CPT2 structure" should be pointed out to "facilitates the transfer of what". In previous studies (For example: Current issues regulating treatment of mitochondrial fatty acid oxidation disorders), bezafibrate can be used to treat long-chain FAODs diseases and improve the symptoms of CPT2 deficient diseases. The conclusions inferred in “reference 30” are not particularly consistent with the examples. The author should further enrich the related evidence and merge this paragraph with the “3.1 CPT2 mutation”. 3. In “2. Mitochondrial CPT system”, the theme of "CPT system" should be highlighted, and the content of this part should be further simplified. Moreover, the term "CPT system" is relatively rare, which is generally called "carnitine shuttle system", the author should consider which model is more appropriate. 4. It should be pointed out which "fatal human diseases" are included and whether they are related to HCC induced by NAFLD

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in the last sentence of the second paragraph of 3.3 (Mutation or dysregulation of CPT-II has been linked to many serious, even fatal human diseases, and these data are promising targets for the development of therapeutic agents against NAFLD in future). 5. In the part of "3.4 carnitine level", the level of carnitine is indeed a known key factor affecting the metabolic flux of the FAO pathway, and the decrease of carnitine concentration observed in NAFLD does not directly indicate that CPT2 is related to the pathogenesis of NAFLD. The effect of carnitine on other FAO enzymes or other pathways in the body is worth explaining or pointing out. 6. In "Conclusions and perspectives", it may not be suitable to describe that "… suggesting that CPT-II might become a new mechanism of blocked lipid oxidation for HCC.", because the expression level or enzyme activity of CPT-II is difficult to analyze, which CPT-II is located in the mitochondrial inner membrane of hepatocytes. Is it appropriate to take CPT-II as an early monitoring index of NAFLD malignant transformation? The author should consider a more reasonable expression, or point out the limitations of CPT-II as an early monitoring index. Minor points: Typos and grammatical errors should be corrected, and some expression could be modified. For examples, the expression of singular and plural in the paper; the sentence contains a series of three or more words, phrases or clauses, please insert a comma to separate the elements; "dysfuction" in "Abstract" should be "dysfunction"; "progression" in "Introduction" should be "progress"; the sentence that "Lipid metabolism rearrangements in NAFLD contribute to disease progression that has emerged as one of the most risk for HCC" in "Introduction" should be "Lipid metabolism rearrangements in NAFLD contribute to disease progression that has emerged as one of the most risks for HCC".