

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 84780

Title: Bioenergetic alteration in gastrointestinal cancers: the good, the bad and the ugly

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04056477

Position: Peer Reviewer

Academic degree: PhD

Professional title: Associate Professor, Deputy Director

Reviewer's Country/Territory: China

Author's Country/Territory: Taiwan

Manuscript submission date: 2023-03-28

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-04-18 02:59

Reviewer performed review: 2023-04-26 03:38

Review time: 8 Days

Scientific quality	<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 Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<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
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This is a complete and timely review relating to the energy metabolism and energy-based therapy in gastrointestinal cancers. I only have some minor suggestions:

1) lonidamine should be abbreviated as LND rather than LDN

Response: We sincerely appreciate the reviewer for bringing this error to our attention. We have taken their feedback into consideration and made the necessary corrections throughout the manuscript.

2) "The roles of remaining subunits in GI cancer is currently unknown...", is should be revised to are

Response: We are grateful to the reviewer for identifying this error and bringing it to our attention. We appreciate the reviewer's diligence, and we have made the necessary correction in the revised manuscript.

3) In the section of glycolytic inhibitors, the following papers can be discussed (2-Deoxy-D-glucose increases the sensitivity of glioblastoma cells to BCNU through the regulation of glycolysis, ROS and ERS pathways: In vitro and in vivo validation. *Biochem. Pharmacol.* 2022, 199, 115029.; Sun, X. D.; Sun, G. H.; Huang, Y. X.; Hao, Y. X.; Tang, X. Y.; Zhang, N.; Zhao, L. J.; Zhong, R. G.; Peng, Y. Z., 3-Bromopyruvate regulates the status of glycolysis and BCNU sensitivity in human hepatocellular carcinoma cells. *Biochem. Pharmacol.* 2020, 177, 113988.; Glycolytic inhibition by 3-bromopyruvate increases the cytotoxic effects of chloroethylnitrosoureas to human glioma cells and the DNA interstrand cross-links formation. *Toxicology* 2020, 435, 152413.)

Response: We appreciate the valuable suggestion provided by the reviewer. However, it should be noted that some of the suggested literature explores the effects of glycolytic inhibitors in non-gastrointestinal cancers, which falls outside the scope of our review. Therefore, we may not be able to include those specific studies in the revised version. Nonetheless, we have identified one relevant study within our scope and have incorporated it into the revision as recommended (See the revised reference 171).

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Title: Bioenergetic alteration in gastrointestinal cancers: the good, the bad and the ugly

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05688164

Position: Peer Reviewer

Academic degree: BSc, MD, PhD

Professional title: Research Fellow

Reviewer's Country/Territory: Hungary

Author's Country/Territory: Taiwan

Manuscript submission date: 2023-03-28

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-04 06:06

Reviewer performed review: 2023-05-08 08:10

Review time: 4 Days and 2 Hours

Scientific quality	<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
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
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Conclusion	<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
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

8 May 2023 Manuscript ID: 84780 Type: Review Title: 'Bioenergetic alteration in gastrointestinal cancers: the good, the bad and the ugly' by Chu YD et al., submitted to World Journal of Gastroenterology Dear Authors, Understanding the bioenergetic alterations in cancer cells may lead development of new therapies to improve cancer diagnosis and treatment. Chu and colleagues in the present review article entitled 'Bioenergetic alteration in gastrointestinal cancers: the good, the bad and the ugly', reviews the latest findings on bioenergetic alterations in various gastrointestinal cancers and discusses potential therapeutic strategies that target these alterations. The main strength of this paper is that it addresses an interesting and timely question, providing a comprehensive review of the latest research on bioenergetic alterations in gastrointestinal cancers and its discussion of potential therapeutic strategies. In general, I think the idea of this review is really interesting and the authors' fascinating observations on this timely topic may be of interest to the readers of World Journal of Gastroenterology. However, some comments, as well as some crucial evidence that should be included to support the author's argumentation, needed to be addressed to

improve the quality of the manuscript, its adequacy, and its readability prior to the publication in the present form. Please consider the following comments:

1. First, I would like the authors to clarify the type of this review article, such as narrative. Please refer to the checklist and make sure there are crucial elements for the review type (<http://prisma-statement.org/PRISMAstatement/checklist.aspx>). Then I would like the authors to address the following questions and clarify them in the manuscript: a) What are some of the bioenergetic alterations that occur in gastrointestinal cancers? b) How do these alterations affect the progression and treatment of these cancers? c) Are there any potential therapeutic targets for these bioenergetic changes?

Response: We appreciate the reviewer's comment and would like to address these questions. This review article is indeed a narrative review that covers the relevant topics. Regarding question (a), the paragraph titled "BIOENERGETIC ALTERATION AND THE WARBURG EFFECT" provides the necessary information. For question (b), the impacts of defects in different molecules on bioenergetic alteration, GI cancer progression, and potential treatment response are summarized in Table 1 to Table 3 and depicted in Figure 3. Question (c) is addressed in Table 4 and Figure 4. We believe these sections provide the desired insights and information.

2. Title: The manuscript's title is its most crucial section. Please use a short, self-explanatory title that captures the essence of this review. Reference:
<https://plos.org/resource/how-to-write-a-great-title/>;
<https://pubmed.ncbi.nlm.nih.gov/35792782/>;
<https://www.developmenttools.com/title-generator/>.

Response: We appreciate the suggestion provided by the reviewer. However, we would like to highlight that the title currently used in this manuscript has been approved by the journal's editorial office during the pre-inquiry stage.

3. A graphical abstract that will visually summarize the main message of the manuscript is highly recommended.

Response: We appreciate the suggestion provided by the reviewer. However, it should be noted that the journal did not request a query for the graphical abstract.

4. Abstract: I recommend the authors reorganize this section with 200–220 words, proportionally presenting the following subsections without headings: the background, a short summary, and the conclusion. The background should include the general background (one to two sentences), the specific background (two to three sentences), and the current issue addressed by this review (one sentence), leading to the objectives. In this subsection, I would like the authors to lay out basic information, a problem statement, and their motivation to break off. The short summary ends with a sentence that puts this subsection in a general context. The conclusion should include one sentence describing the main result using words like “Here we highlight”. The conclusion should describe the potential and the advance this study has provided in the field, and finally, a broader perspective (two to three sentences) readily comprehensible to a scientist in any discipline.

Response: We sincerely appreciate the reviewer's suggestion, and we have carefully incorporated their recommendations into the revised abstract.

5. Keywords: Please list six keywords chosen from Medical Subject Headings (MeSH) (<https://meshb.nlm.nih.gov/>) according to the journal's guidelines (<https://www.wjgnet.com/bpg/GerInfo/217>) and use as many as possible in the title and in the first two sentences of the abstract.

Response: We would like to express our gratitude to the reviewer for their comment. As per their feedback, we have made the necessary changes to the keywords in the revised version.

6. Introduction: The authors need to revise a section of their research paper. This section should be approximately 1000 words in length and include information on key study constructs that would be essential for readers in any discipline to understand. The authors should present the introduction in a specific order, starting with the overall context, then moving on to the specific context and addressing the current problem before presenting the objectives. The key structures should be logically and coherently arranged. To help a reader understand the review paper better, the authors should provide a brief outline of the following sections. In this regard, a general overview of hallmarks of mitochondrial bioenergetics and its resilience involving beyond the tricyclic cycle and electron transport chain, including presentation of signs and symptoms (<https://doi.org/10.3390/cells11162607>).

Response: We sincerely appreciate the valuable suggestion provided by the reviewer. However, it is worth noting that our manuscript already contains a comprehensive introduction section spanning approximately 1000 words. This section aims to provide essential information on key study constructs to ensure readers from various disciplines

can grasp the content. Additionally, we have included an informative overview in Figure 1, illustrating the hallmarks of bioenergetics machinery, encompassing glycolysis, lactate, the tricarboxylic acid cycle, the electron transport chain, and oxidative phosphorylation.

7. Other works that may enhance the value of this manuscript include: doi: 10.3390/ijms222413384; <https://doi.org/10.3390/biomedicines9070833>;
<https://doi.org/10.3390/ijms22094753>; <https://doi.org/10.3390/ijms21175986>;
<https://doi.org/10.3390/biomedicines9080881>.

Response: We sincerely appreciate the suggestion provided by the reviewer. However, it is important to note that the majority of the suggestions were beyond the scope of this article. Nevertheless, we have carefully considered one of the suggestions and incorporated it into the appropriate section in the revised version (See the revised reference 12).

8. Discussion: I would like the authors to present an independent section by opening with an introductory paragraph followed by a summary of the previous sections. Then, I expect the authors to develop arguments clarifying the potential of this study as an extension of the previous work, the implication of the findings of this study, how this study could facilitate future research, the ultimate goal, the challenge, the knowledge and technology necessary to achieve this goal, the statement about this field in general, and finally the importance of this line of research. It is particularly important to present the limitations, merits, and potential translation of this review to clinical practice.

Response: We appreciate the reviewer's comment. All of the recommendations mentioned have been addressed in the original "Conclusion and Future Perspective" section, which has now been revised and renamed as the "Discussion and Future Perspective" section.

9. Conclusion: In my opinion, presenting the conclusion would be better served by a single paragraph outlining some careful and in-depth conclusions made by the authors in their capacity as subject matter experts. It is important for the authors to attempt to explain both the theoretical and practical implications of their research. To fully grasp the significance of this study, I think it would be necessary to discuss theoretical and methodological strands that still require improvement as well as suggestions for a future course.

Response: We appreciate the reviewer's comment. In response to the suggestion, we have included a new section in the manuscript titled "CONCLUSION," as recommended.

10. Overall, the manuscript contains four figures, four tables, and 296 references. I believe that the manuscript may provide valuable insights into the bioenergetic changes that occur in gastrointestinal cancers, which can help clinicians more accurately diagnose and predict the course of the disease and develop new therapies to improve patient outcomes. I hope that, after these careful revisions, the manuscript can meet the Journal's high standards for publication. I am available for a new round of revision of this article. I declare no conflict of interest regarding this manuscript.
- Best regards, Reviewer

Response: We sincerely appreciate the valuable comments provided by the reviewer, as they have significantly improved our manuscript.