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OPEN PEER REVIEW

Glucose Metabolism in Acute Myeloid Leukemia Cell Line Is Regulated via Combinational PI3K/AKT/mTOR Pathway Inhibitors

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

2 comments · 15 Sep 2023 – 17 Sep 2023

Referee 1 Reviewer

MAJOR REVISION 15 Sep 2023

1- The fact that the investigated glucose metabolism mediators are downstream of PI3K/Akt/mTOR pathways has already been established in various separate studies, but maybe not in the HL-60 cell line. So, proper and sufficient citations to these studies are required.
2- In the method section, the MTT part must be deleted, as you have already published it in
Iran J Allergy Asthma Immunol , April 2022; 21(2):178-188.

3- Irrelevant self-citation is observed in references 9 and 10. The sentence referring to these articles is not relevant to the topic.

5- Do you have any idea about any likely mutation in PI3K, Akt and mTOR molecules in the HL-60 cell line?
4- How do you interpret the finding that inhibiting one and even two molecules in the PI3K/Akt/mTOR axis is not enough to have the desired effects? However, co-administration of three inhibitors can do it.

Associate Editor

MAJOR REVISION 17 Sep 2023

Major revision

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to Reviewers' Comments

Reviewer 1:

Comment 1: The fact that the investigated glucose metabolism mediators are downstream of PI3K/Akt/mTOR pathways has been already found in various and separate studies, but maybe not in HL-60 cell line. So, proper and sufficient citations to these studies are required.

Response: We appreciate the reviewer's insightful comments. So far, the association between glucose metabolism mediators and PI3K/Akt/mTOR pathway in HL-60 cell line has not been investigated. For further clarification, we were used appropriate citation in the discussion section.

Comment 2: In method section, MTT part must be deleted as you have already published it in Iran J Allergy Asthma Immunol , April 2022; 21(2):178-188.

Response: This statement was omitted and the paragraph has been revised based on the Reviewer's comment (Page 6, paragraph 2, line 4).

Comment 3: Irrelevant self-citation is observed by in references 9 and 10. The sentence referring these articles is not relevant to the topic.

Response: According to the Reviewer's comment, Mentioned references were removed, and the entire references was carefully rechecked.

Comment 4: How do you interpretate the finding that inhibiting one and even two molecules in PI3K/Akt/mTOR axis are not enough to have the desired effects? However, co-administration of three inhibitors can do it.

Response: We are really thankful for deep look of the Reviewer. We discussed more about the combinational inhibition of PI3K/AKT/mTOR pathway in the discussion part.

Comment 5: Do you have any idea about any likely mutation in PI3K, Akt and mTOR molecules in HL-60 cell line?

Response: We appreciate the reviewer's comments. Unfortunately, there are not found any data about the mutation of PI3K/Akt/mTOR pathway in HL-60 cell line on the literatures.

Reviewer 2:

Comment 1: Title would be better to indicate the negative or positive regulatory effect of inhibitors on the metabolism as well as the type of metabolism (glucose metabolism) and the importance of combination therapy.

Response: We appreciate the reviewer's insightful comments. We have revised that Title based on the Reviewer's comment (Page 1, line 1).

Comment 2: Add the complete form of all abbreviations before their first use, in abstract and in the main text.

Response: As truly mentioned by the Reviewer, the abbreviations were descripted in the main text.

Comment 3: The sentence of Results in the abstract needs grammatical revision.

Response: The sentence of results in the abstract was thoroughly revised based on the Reviewer's comment.

Comment 4: Complete the method of MTT assay or add an appropriate citation.

Response: This comment has also been dealt with in response to Reviewer 1 (Comment 2). This part was omitted and cite to the appropriate article based on the Reviewer's comment (Page 6, paragraph 2, line 4).

Comment 5: The expression level of proteins was evaluated in which time intervals? It should be indicated in methods and in figures presenting the results.

Response: According to the Reviewer's comment, the time intervals for expression level analysis was added to methods part, and also in figure captions (Page 6, paragraph 2, lines 5 and Page 21 to Page 25).

Comment 6: Indicate the primer sources or design process in methods.

Response: We are really thankful for deep look of the Reviewer. The primer design process was presented in part 3 of Materials and Methods (Page 7, paragraph 1, line 5).

Comment 7: Define the statistical markers in figure captions and as well, indicate what "p=…" presents in figures.

Response: We have improved all figures and figure captions as suggested by the Reviewer's comment (Page 21 to Page 25).

Comment 8: It would be better to discuss the connection paths between PI3K/AKT/mTOR pathway and the key proteins and enzymes studied in discussion. It can be shown in a schematic diagram.

Response: We are really thankful for deep look of the Reviewer. We discussed more about the connection between PI3K/AKT/mTOR pathway and the key proteins of metabolic system in the discussion section.

Comment 9: Generally, a large part of discussion has just introduced the target proteins studied instead of discussing their importance in anticancer therapy. It would be better to revise the discussion part to indicate the impact of this study.

Response: According to the Reviewer's comment, we thoroughly refined the discussion part.

2 Revision 1

2 comments · 29 Sep 2023 – 29 Sep 2023

Referee 1 Reviewer

MINOR REVISION 29 Sep 2023

Thanks for the answers.

Associate Editor

MINOR REVISION 29 Sep 2023

Minor revision

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to Reviewers' Comments

Reviewer 1:

Comment 1: Thanks for the answers.

Response: Thanks for the attention of the Reviewer.

Associate Editor's Comments:

Comment 1: Minor revision

Response: Unfortunately, no comments are visible.

3 Revision 2

2 comments · 2 Oct 2023 – 2 Oct 2023

Referee 1 Reviewer

MINOR REVISION 2 Oct 2023

Thanks for the replies. I think this manuscript still needs grammatical revision. Some examples are "results were showed" in line 144 or "ANOVA following by " in almost all the figure legends, which must be changed to "followed by".
In order to save you time, I suggest sending your manuscript to some reliable companies that provide such services.

Associate Editor

MINOR REVISION 2 Oct 2023

Minor revision

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to Reviewers' Comments

Reviewer 1:

Comment 1: Thanks for the replies. Although I think this manuscript still needs grammatical revision. Some examples are line 144 "results were showed" or almost in all the figure legends "ANOVA following by " which must be changed to "followed by".

In order to save your time, I suggest sending your manuscript to some reliable companies rendering such required services.

Response: We appreciate the reviewer's insightful comments. We thoroughly grammatically revised the entire manuscript.

4 Revision 3

1 comment · 10 Oct 2023

Associate Editor

ACCEPT 10 Oct 2023

Accept