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OPEN PEER REVIEW

Lycopene Promotes NK Cell Cytotoxicity Towards Non-small Cell Lung Carcinoma via Regulating NF-κB Signaling

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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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Contents

1 Original submission Reza Hosseini 2
2 Revision 1 3
Authors' reply to reviewers 4
Reviewer and editor comments 8
3 Revision 2 9
Authors' reply to reviewers 10
Reviewer and editor comments 12

1 Original submission

1 comment · 14 Apr 2024

Reza Hosseini Reviewer

MINOR REVISION 14 Apr 2024

Dear Editor-in-Chief, IJCM

I would like to thank you for inviting me to review the manuscript titled "Lycopene Promotes NK Cell Cytotoxicity towards Non-Small Cell Lung Carcinoma via regulating NF-κB signaling". The authors have shown that the addition of lycopene could improve NK cell-mediated lysis of NSCLC cells. However, the following points should be clarified before this manuscript is published.

1- The authors have shown that although lycopene has somewhat cytotoxic effects on NSCLC cells, it can induce the proliferation of NK cells. They showed that NF-kB is activated upon treatment of NK cells with lycopene. Hence, the authors should clarify how lycopene treatment can induce these opposite effects (cytotoxicity vs proliferation) on cancer and NK cells.
2- In the methods, the authors should add more details, especially about cell culture, NK cell preparation and their treatment with lycopene. Time intervals and doses should be clarified.
3- In Figure 2, it is stated that NK cells are cultured with/without lycopene for 7 days to induce their proliferation/cytotoxic activity, while Figure 3 shows that NK cells and cancer cells are treated for only 4 hours! Hence, the authors should justify how lycopene can induce NK cell cytotoxicity in 4 hours. It is also not clear whether the tumor cells/NK cells are pretreated with lycopene or not.
4- In the figure legends, it should be mentioned which cancer cells are used in the experimental assays, or which cell line the figure is representative of.

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.

Point-to-point letter for manuscript ID: ID-146781

Lycopene Promotes NK Cell Cytotoxicity towards Non-Small Cell Lung Carcinoma via regulating NF-κB signaling

Dear Editor,

Thank you for forwarding us the reviewers' comments on our manuscript, and we find that the comments and suggestions from the reviewers are very helpful. Followed their suggestions, we have performed additional amendments and revised the manuscript to address all the concerns of the reviewers, which that you can see from the point-to-point response to reviewers described below. Revised portion are marked in red in the revised paper.

Thanks again for your consideration. We are looking forward to your favorable responses.

Sincerely,

Hui Zhang

Reviewer 1:

Dear Editor-in-Chief, IJCM

I would like to appreciate your invitation for reviewing manuscript titled" Lycopene Promotes NK Cell Cytotoxicity towards Non-Small Cell Lung Carcinoma via regulating NF-κB signaling". The author has shown that the addition of Lycopene could improve NK cells-mediated lysis of NSCLC cells. However, the following points should be clarified before publishing this manuscript.

1- The authors have shown that although lycopene has somehow cytotoxic effects on NSCLC cells but can induce the proliferation of NK cells. They showed that NF-kB is activated upon treatment of NK cells with lycopene. Hence, the authors should clarify how lycopene treatment can induce these opposite effects (cytotoxicity vs proliferation) on cancer and NK cells?

Response: Thank you for your careful work and questions. Since the hall markers of cancer cells and immune cells are different. P53 is known to mutated in NSCLC and lycopene has been reported to target P53 related proliferation pathway to exert anti-proliferative effect [1]. In our research, lycopene activated the NF-κB signaling in NK cells, which is an important signal pathway regulating NK cell proliferation. Therefore, the mechanism of lycopene in treating tumor cell and NK cells is different, which can explain why the opposite effects were induced. We further noted this difference in our discussion part. Thank you for your suggestion.

2- In methods, the authors should add more details specially into the cell culture, NK cells preparation and their treatment with lycopene. Time intervals doses should be clarified.

Response: Upon requests, we supplemented the details about cell culture NK cell preparation and so on. As you can see the amended part marked in red in our revised manuscript.

3- in Figure 2, it has been declared that NK cells are cultured with/without lycopene for 7 days to induce their proliferation/cytotoxic activity, while Figure 3 shows that NK cells and cancer cells are treated for only 4 hours! Hence, the authors should justify how lycopene can induce NK cells cytotoxicity in 4 hours? it is also not clear whether the tumor cells/NK cells are pretreated with lycopene or not.

Response: Thank you for your careful work here. We are sorry if we have made it confuse to display our results. As shown in Figure 2, we showed that lycopene supplement (10μM) protected NK cells from apoptosis after 7-day *in vitro* culture. It has been reported that oxidant stress is one of the reasons causing NK cell apoptosis during *in vitro* culture. So, we speculate that lycopene might exert anti-oxidant effect on NK cells to protect them from apoptosis. In this part, we didn't refer to the cytotoxicity of NK cells. While in Figure 3, since NK cell cytotoxicity towards cancer cells is non-MHC dependent. The killing effect happens in a fast manner as other research groups use the same treatment time [2]. Here, the NK cells using for experiments were harvested from 7-day *in vitro* culture with or with our lycopene treatment. I think this should be mentioned in our manuscript which you can see the marked part in revised manuscript to avoid the confusion. Thank you for pointing out the confusion part.

4- In figure legends it should be mentioned that which cells cancer cells are used in experimental assays, or which cell line the figure is representative for.

Response: As requested, we supplemented the missing information to make legends more clearer.

Reference:

[1] P. Palozza, R.E. Simone, A. Catalano, M.C. Mele, Tomato lycopene and lung cancer prevention: from experimental to human studies, Cancers (Basel), 3 2333-2357.
[2] Y. Li, D.L. Hermanson, B.S. Moriarity, D.S. Kaufman, Human iPSC-Derived Natural Killer Cells Engineered with Chimeric Antig en Receptors Enhance Anti-tumor Activity, Cell Stem Cell, 23 181-192.e185.

2 Revision 1

0 comments

No public comments in this round.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

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Point-to-point letter for manuscript ID: ID-146781

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Dear Editor,

Thank you for forwarding us the reviewers' comments on our manuscript, and we find that the comments and suggestions from the reviewers are very helpful. Followed their suggestions, we have further polished our manuscript with the help of native English speaker. Revised portion are marked in red in the revised paper.

Thanks again for your consideration. We are looking forward to your favorable responses.

Sincerely,

Reviewer 1:

Dear Editor-in-Chief, IJCM

1. The manuscript is much improved now but it needs a significant language revision to be more fluent before the publication.

Response: Thank you for your work. As requested, we further polished our manuscript which you can see the marked changes in our revised manuscript.

3 Revision 2

0 comments

No public comments in this round.