Feb 20, 2016

Dear Editor,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript “Inhibitory Effect of miR-125b on HCV Core Protein-induced TLR2/MyD88 signaling in THP-1 cells”(ID: 23858). We have studied editor’s and reviewer’s comments carefully and have made revision which marked in yellow in the paper.

1. A running title and author contributions were added.
2. The statements of “Ethics approval, Institutional animal care and use committee, Biostatistics statement, Conflict-of-interest statement and Data sharing statement” were added. Of note, no animals were used in this study. Therefore, the “Animal care and use statement” was not indicated.
3. The expression of abstract is more refined after summarized.
4. The core tip was added.
5. The audio core tip was in the attachment.
6. The background, research frontiers, innovations and breakthroughs, applications, terminology and peer review of comment section were added.
7. Formation of the references were adjusted according to the guideline.
8. All figures have been changed to supplementary and submitted as PPT format. The aligning in the figures was improved in the revision.
9. The language and grammar have been polished by Biomedworld.com, revisions were marked in yellow in the manuscript.
10. We carefully corrected the errors and the abbreviations has been added in the revision.
11. Please find enclosed the edited manuscript in Word format (file name: 23858-Revised manuscript).
12. “Response to reviewers” was showed as follows.

Response to reviewers

Dear reviewers,

We greatly appreciate for the thorough review and positive evaluation of our work. We revised the manuscripts according to your suggestions. The responses to your comments are listed as follows.

Answers to reviewer 503082:

"The authors tested the role of MiR125b in the regulation of macrophage inflammatory activation induced by HCV core protein. Activation of THP-1 cells correlated with decrease in MiR125b levels and overexpression of MiR125b resulted in the suppression of MAPK and NF-kB activity and cytokine production. I think the manuscript is well organized and the results are sound whit respect to the integrity of the paper. One minor point is that the figures and characters in the figures are sometimes hard to read and sometimes not aligned very well."

Re: All figures have been changed to supplementary and submitted as PPT format. The aligning in the figures was improved in the revision.

Answers to reviewer 71717

"Authors investigated the possible role of miR-125b in regulating monocyte immune responses induced by HCV core protein. They found that cytokine production was up-regulated and miR-125b expression was down-regulated by HCV-core protein through TLR2/MyD88 signaling in THP-1 cells. In general, this research is novel, manuscript presentation and readability is good. Some concerns occur; 1-There are some erratum that should be corrected. 2-The abbreviations should be mentioned in the text where it's first used."

Re: We carefully corrected the errors and the abbreviations has been added in the revision.

Answers to reviewer 00068251

1. "Material and Methods 1- The cells differentiated are original functional cells, and produce pro-inflammatory and anti-inflammatory cytokines secretion. In the study, THP-1 macrophage cells are used without being differentiated; this means that macrophage function was not tested. The lack of methodological procedure in the study needs to be explained. "

Re: The THP-1 cell line is a human monocytic leukaemia cell line and resembles primary monocytes and macrophages in morphology and differentiation properties [1]. THP-1 cells adhere to the culture plate and differentiate into macrophages after exposure to phorbol-12-myristate-13-acetate (PMA, also known as TPA, 12-Otetradecanoylphorbol-13-acetate). However, THP-1 cells express distinct monocytic markers and can produce pro-inflammatory and anti-inflammatory cytokines with the stimulation of TLR ligands and some viral proteins including HCV core protein even without differentiation upon PMA exposure. As the reviewer mentioned, macrophage function was indeed not tested in this study. The reason is that we focused on that the effect of HCV core protein on monocytic functions of THP-1 cells. Therefore, THP-1 cells used in this study did not experience differentiation with PMA stimulation.

2. "Discussion 2- There are various studies on MIR-125b. (e.g. miR-125b is overexpressed in several types of cancer and contributes to tumor resistance to chemotherapy, inhibiting apoptosis). As a result, how selective effect in HCV treatment with MIR-125b can be maintained should be mentioned."

Re: As the reviewer mentioned, the previous studies has shown that miR-125b could have opposite roles in the tumorigenesis. Moreover, the modulation of miR-125b expression is also complicated during the process of HCV infection. It was reported that miR-125b expression was reduced in monocytes but increased in serum of HCV infected patients compared to healthy control persons. Thus, HCV does not only inhibit miR-125b expression in monocytes but also stimulate other cells to express higher level of miR-125b what is yet not characterized. Our present study only focused on the monocytes and inflammation, further studies are needed to elucidate the effect of miR-125 in HCV infection in other field such as oncogenesis, vial persistent infection, etc.

3. "References 3- It should be modify the name of the journal as abbreviation according to index medicus."

Re: Following the reviewer's comment, the name of the journal as abbreviation has been corrected in the revised manuscript and highlighted.

4. "General suggestions 4- English grammar should be checked carefully."

Re: Following the reviewer's comment, English grammar has been carefully checked and corrected in the revised version.

Reference

[1]W Chanput，V Peters，H Wichers. THP-1 and U937 Cells. Springer International Publishing, 2015:147-159

We would like to express our great appreciation to you!

Thank you and best regards.

Yours sincerely,

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