

Dear Editor:

Please find the edited manuscript in Word format (file name: 9746-review.doc). The manuscript has been revised according to the suggestions of reviewers and Editor. Five figures are added to outline the concepts and experimental procedures as suggested. All the new additions/corrections are yellow highlighted in the text.

Title: Functional Roles of Lysosomal Acid Lipase in Myeloid-derived Suppressive Cell Development and Homeostasis

Author: Cong Yan and Hong Du

Name of Journal: *World Journal of Immunology*

ESPS Manuscript NO: 9746

Response to the reviewers

Reviewer 02445858

“The review entitled “Functional roles of Lysosomal Acid Lipase in Myeloid Derived Suppressive Cell Development and Homeostasis” by Yan and Du, have written nicely about the lysosomal acid lipase. Authors gathered several informations. Basically, well written. However, to make easier for readers, I would like to suggest including cartoons or figures.”

[Reply: Five Figures have been included to illustrate the importance and connection of research works outlined in this review article.](#)

Reviewer 00506409

“In this manuscript a detailed review is presented about lysosomal acid lipase (LAL) and its function with respect to the development and activities of myeloid derived suppressive cells (MDSC). Arguments are presented that the formation of cholesterol and free fatty acids under influence of LAL influences in particular myeloid cells. Most of the work in this area is done in LAL-deficient mice, which manifest an increase in MDSCs, that infiltrate in lymphoid organs and hence affect lymphocyte development and function. Downstream of LAL function are inflammatory processes and tumorigenesis facilitated, which is described in detail for the lung and lymphoid system. This is a relevant topic that appears to be adequately reviewed. The text is clear and the complex issue is well presented. Although immune function and lymphoid organ is only one of the targets, this reviews fits with the scope of an immunology journal. The only comment regards the presentation of the complex pathways in which LAL and downstream processes affect MDSCs, which in turn affect multiple processes and metabolic pathways.”

- 1) It would be advised to summarize the processes and pathways and their components affected in the form of a table, and even better in the form of figures. This would highly facilitate the messages in the text.

Reply: Figures are included as suggested.

- 2) It is also advised to conduct a final check of the English, since there are a few minor typographical errors.

Reply: English has been thoroughly checked by our native English speaking colleagues.

Reviewer 02446204

This review is very well written, providing a comprehensive explanation about the involvement of LAL in the differentiation of MDSCs along with in-depth explanations on its molecular mechanisms. I believe that this review will make a large contribution to an understanding of the impact of lipid metabolism on the regulation of hematopoiesis.

Nevertheless, this manuscript requires some minor revisions before publication in World Journal of Immunology.

- 1) The discussion in the section “MDSCs development and differentiation” (page 9, line 1 - page 10, line 8) is very interesting. The contents of this section are accurate and very much worth reading. Nevertheless, I do hope that authors would make a further discussion regarding the relationship between cell-autonomous and non-cell-autonomous defects in the hematopoiesis in *lal*^{-/-} mice. For example, how cell-autonomous defects would possibly provoke environmental skews in hematopoiesis.

Reply: The relationship between cell-autonomous and environment has been expanded in the text as suggested, Page 11, “After MDSCs infiltration into distal organs.....secretion of Stat3-induced pro-inflammatory cytokines in epithelial cells reversed mature myeloid lineage cells to MDSCs”

- 2) There is an error in the pagination of the reference #67. “J Appl Physiol 2004, 97: In press” should be corrected as “J Appl Physiol 2004, 97: 1543-1548”

Reply: Corrected.

- 3) There are some unclear descriptions regarding the citation of the references. In page 8, line 12, there are no descriptions of the citation. To make it easier for readers to access the original papers, “ under the control of the 7.2 kb c-fms promoter/intron2 regulatory sequence” should be rewritten as “ under the control

of the 7.2 kb c-fms promoter/intron2 regulatory sequence ^{[31], [33]} ". In page 8, lines 18 – 22, it would be better to rewrite the sentences "Expression of hLAL in myeloid lineage cells of this c-fms-rtTA/(tetO)7-CMV-hLAL;lal-/- triple mouse model significantly reduces systemic MDSCs accumulation, ameliorated pathogenic phenotypes and reversed aberrant gene expression, supporting a concept that cholesteryl ester and triglyceride metabolism is essential for the normal biological function of myeloid cells ^[31]." as "Expression of hLAL in myeloid lineage cells of this c-fms-rtTA/(tetO)7-CMV-hLAL;lal-/- triple mouse model significantly reduces systemic MDSCs accumulation ^[33], ameliorated pathogenic phenotypes and reversed aberrant gene expression ^[31], supporting a concept that cholesteryl ester and triglyceride metabolism is essential for the normal biological function of myeloid cells."

Reply: All have been changed as suggested.

- 4) In title, it would be better to rewrite "Myeloid Derived Suppressive Cell" as "Myeloid-Derived Suppressive Cell".

Reply: Changed as suggested.

- 5) In page 19, line 1, it would be better to rewrite the words "cell autonomous" as "cell-autonomous".

Reply: Changed as suggested.

- 6) In page 20, line 20, it would be better to rewrite the words "a macrophage specific elastase" as "a macrophage-specific elastase".

Reply: Changed as suggested.

- 7) In page 20, line 21, it would be better to rewrite the words "AT II cells" as "alveolar type II (AT II) cells".

Reply: Changed as suggested.

- 8) In page 20, line 22, it would be better to rewrite the words "migrating and residential cells" as "macrophages and lung epithelial cells".

Reply: Changed as suggested.

- 9) In page 21, line 6, it would be better to rewrite the words "activated-MMP12" as "activated MMP12".

Reply: Changed as suggested.

- 10) In page 21, line 15, it would be better to rewrite the words "MMP12 overexpression"

as “MMP12-overexpressive”.

Reply: Changed as suggested.

- 11) In page 21, lines 18-19, it would be better to rewrite the words “cell autonomous” as “cell-autonomous”.

Reply: Changed as suggested.

- 12) In page 22, line 9, it would be better to rewrite the words “second to” as “secondary to”.

Reply: Changed as suggested.

- 13) In page 23, line 9, it would be better to rewrite the words “inflammation induced” as “inflammation-induced”.

Reply: Changed as suggested.

- 14) In page 23, line 12, the words “block MDSCs homeostasis and function” should be written as “normalize MDSCs homeostasis and functions”.

Reply: “Normalize” is a wrong word to use.

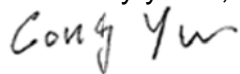
- 15) In page 23, lines 12-13, it would be better to rewrite the words “More detail characterization” as “More detailed characterization”.

Reply: The sentence has been rewritten.

Editorial Comments

PMID numbers and DOI info are added on the cited references.

Sincerely yours,



Cong Yan, Ph.D.

Professor of Pathology and Laboratory of Medicine

Member of IU Simon Cancer Center

Member of the Center for Immunobiology

Indiana University School of Medicine

975 W Walnut Street, IB424G

Indianapolis, IN 46202-5121

Phone: 317-278-6005

E-mail: coyan@iupui.edu