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St. Louis, MO 63121

November 16, 2020

Editor, *World Journal of Biological Chemistry*

Dear Sir/Madam:

We are electronically submitting a submitting a revised manuscript entitled "Inhibition of MMP-9 secretion by dimethyl sulfoxide and cyclic AMP in human monocytes" by Denner, Udan-Johns, and Nichols.

We would like to sincerely thank the reviewers of our manuscript for their careful reading and analysis. Each one of their concerns and comments were carefully considered, and appropriate modifications were made to the revision. The manuscript has been strengthened by their input and it is very much appreciated.

We would be grateful if you would arrange for this revised manuscript to be considered for publication in *World Journal of Biological Chemistry*. No other closely related paper is under consideration elsewhere for publication.

Thank you for your attention.

Sincerely,

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We would like to sincerely thank the reviewers of our manuscript for their careful reading and analysis. Each one of their concerns and comments were carefully considered, and appropriate modifications were made to the revision. The manuscript has been strengthened by their input and it is very much appreciated.

Reviewer #1 Comments: The title reflects the main subject of the manuscript, the abstracts reflect the work described, and give new information of the mechanisms by which DMSO and cAMP inhibited MMP-9 secretion, the study demonstrates cellular and pharmacological mechanisms by which MMP-9 secretion can be regulated the monocytic inflammatory response.

Author Response: We are grateful for the careful review of our manuscript and the positive feedback.

Point 1: However, the manuscript doesn't describe methods in adequate detail, in the lines 89-91 (yellow color), is necessary give details about of the conditions of monocytes cells were treated with E. coli and is important mention the concentration of DMSO used.

Author Response: We would like to thank the reviewer for pointing this out and we have now made extensive changes to "Cellular assays" section of the Methods. Many more details have now been provided explaining the purpose for each type of treatments, LPS concentration, cell exposure times, concentrations of different regulators, and control experiments.

Point 2: The results are present in confuses form, is necessary polish this section and detailed the result appropriately and separated the discussion elements (blue mark in the text).

Author Response: We very much appreciate the constructive feedback. We have identified several areas in the Results that may be considered discussion elements. These passages have been removed and incorporated into the Discussion or, in some cases, the Introduction. The areas where these passages were removed from the Results have also been slightly revised to provide appropriate transitions.

Point 3: Finally, is necessary review the figures legends and homogenize the format of units used.

Author Response: We thank the reviewer for the constructive critique. We have gone back through figure legends and ensured that the same units are used throughout.

Reviewer #2 Comments: Matrix-metalloproteinases are extracellular matrix degrading enzymes with important roles in physiological and pathological processes. The manuscript is about a study concerning the mechanisms of MMP-9 secretion in THP-1 monocytes and their regulations by DMSO and cAMP. This study is certainly well done, interesting and useful, but the manuscript needs to be seriously improved before considering publication.

Author Response: We are grateful for the careful review of our manuscript, the positive feedback, and the constructive criticism.

Point 1: At the end of introduction line 76), the authors write: "(...) previous reports of regulation by both dimethyl sulfoxide (DMSO) [9-11] and the intracellular signaling molecule 3',5'-cyclic adenosine monophosphate (cAMP)": as this is the subject of this article, it would be interesting to have a few words about these studies.

Author Response: We appreciate the careful review of our manuscript and the helpful suggestions. We have added passages that describe and detail the previous studies that were cited. We believed this added information will be helpful to the readers.

Point 2: At the end of the introduction, the purpose of the study needs to be detailed: the sentence "In this report we sought to further examine mechanisms of MMP-9 secretion in THP-1 monocytes and regulation by DMSO and cAMP." needs to be developed.

Author Response: We agree with the reviewer that more could be added at the end of the Introduction to better set up the study. We have inserted several more specifics and sentences to help guide the reader into the current investigation without recapitulating the whole story.

Point 3: Material and methods Lines 90-94, "Cells were treated with E. coli bacterial 026.B6 LPS (...) prior to addition of LPS": different treatments have been performed, but they are not sufficiently clearly explained and it is hard to understand. Please, specify the purpose of each treatment, with or without LPS. The different treatments could be also given in a table.

Author Response: We would like to thank the reviewer for pointing this out and we have now made extensive changes to "Cellular assays" section of the Methods. Many more details have now been provided explaining the purpose for each type of treatments, LPS concentration, cell exposure times, concentrations of different regulators, and control experiments.

Point 4: In the paragraph, no indication is given about the concentration and percentages used like it is given in figures.

Author Response: We thank the reviewer for pointing this out. We have extensively revised the "Cellular assays" section of the Methods and incorporated many of the details from the figure legends into the Methods. We hope the additional detail will make it much easier for readers to understand the experimental aspects of the study.

Point 5: Results In this part, there is a mixture of results and discussion (example: lines 159-163 and others), which makes the text confusing and difficult to understand. The results are not sufficiently detailed even if the reader finds important indications in the legends of the figures or in the figures, where the different concentrations and percentages are given. The "Results" part must be rewritten without the discussion elements but with all the results.

Author Response: We very much appreciate the constructive feedback. We have identified several areas in the Results that may be considered discussion elements. These passages have been removed and incorporated into the Discussion or, in some cases, the Introduction. The areas where these passages were removed from the Results have also been slightly revised to provide appropriate transitions.

Science Editor Comments: This study is certainly well done, interesting and useful. The abstracts reflect the work described, and gives new information of the mechanisms by which DMSO and cAMP inhibited MMP-9 secretion, the study demonstrates cellular and pharmacological mechanisms by which MMP-9 secretion can be regulated in the monocytic inflammatory response. However, the manuscript doesn't describe methods in adequate detail.

Author Response: We are grateful for the careful review of our manuscript, the positive feedback, and the constructive criticism. We have extensively revised the "Cellular assays" section in the Methods to include much more detail explaining the purpose for each type of treatments, LPS concentration, cell exposure times, concentrations of different regulators, and control experiments. Additional details were added to some other sections as well. **Changes throughout the manuscript are highlighted in yellow.**

Point 1: Results: In this part, there is a mixture of results and discussion, which makes the text confusing and difficult to understand. The "Results" part must be rewritten without the discussion elements but with all the results. The questions raised by the reviewers should be answered.

Author Response: We very much appreciate the constructive feedback. We have identified several areas in the Results that may be considered discussion elements. These passages have been removed and incorporated into the Discussion or, in some cases, the Introduction. The areas where these passages were removed from the Results have also been slightly revised to provide appropriate transitions.

Point 2: The authors provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and The ARRIVE Guidelines. The authors need to provide the Biostatistics Review Certificate, the Institutional Review Board Approval Form, and Institutional Animal Care and Use Committee Approval Form. No academic misconduct was found in the CrossCheck detection and Bing search.

Author Response: Thank you for the guidance. It appears the requested forms are completed on the website although it is a bit difficult to tell. There were no animals or humans involved in the current study.

Point 3: 5 Issues raised: (1) I found no "Author contribution" section. Please provide the author contributions.

Author Response: Thank you for pointing this out. We have now added an "Author Contribution Statement" on the Acknowledgements page.

Point 4: (2) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s)

Author Response: Thank you. We have included grant funding in the Acknowledgements section that states "This work was supported by funding from the University of Missouri-St. Louis, Alzheimer's Association (NIRG-06-27267) and the Missouri Alzheimer's and Related Disorders Research Program."

Point 5: (3) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor

Author Response: All original figures have now been provided as high-resolution TIF files. Other formats can be provided as needed by the copy editor.

Point 6: (4) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

Author Response: Thank you for pointing this out. PMIDs and DOIs have now been included in all the references.

Point 7: (5) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.

Author Response: Thank you bringing this to our attention. We have now prepared and included an “Article Highlight” or “Core Tip” section right after the Figure Legends section.

Company Editor-in-Chief Comments: (3) Company editor-in-chief: I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements, and the manuscript is conditionally accepted with major revisions. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors. Before final acceptance, authors need to correct the issues raised by the editor to meet the publishing requirements.