

Ontogenically distinct murine alveolar macrophages modulate cigarette smoke-induced lung inflammation via Spp1

Corresponding Author: Dr Emma Doran

This manuscript has been previously reviewed at another journal. This document only contains information relating to versions considered at Communications Biology.

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

The authors have put significant effort into this revision, and the new experiments and clarifications strengthen the manuscript. However, my conceptual concern regarding the causal link to human disease remains. The data show that these macrophages are induced by cigarette smoke exposure and induce epithelial injury. Yet, data do not demonstrate that these specific macrophages drive the pathology. It is possible that SPP1 macrophages and COPD simply share the same root cause, which is cigarette smoke exposure, without a direct mechanistic connection. The authors must include these causality limitations and discuss them.

credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

In cases where reviewers are anonymous, credit should be given to 'Anonymous Referee' and the source.

The images or other third party material in this Peer Review File are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.

To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>

Round 3

Reviewer #1 (Remarks to the Author):

The authors have put significant effort into this revision, and the new experiments and clarifications strengthen the manuscript. However, my conceptual concern regarding the causal link to human disease remains. The data show that these macrophages are induced by cigarette smoke exposure and induce epithelial injury. Yet, data do not demonstrate that these specific macrophages drive the pathology. It is possible that SPP1 macrophages and COPD simply share the same root cause, which is cigarette smoke exposure, without a direct mechanistic connection. The authors must include these causality limitations and discuss them.

Reply: Thank you very much for the positive feedback and the suggestion. We have now addressed two limitations noted in the Reviewer's comments. First, we agree with the Reviewer that the link to human disease needs to be addressed and we have now done so by adding the following part to the Discussion section (page 15-16): 'We acknowledge that our data do not definitively demonstrate that Spp1+ macrophages drive human COPD pathology. Therefore, future translational studies will be essential to fully clarify the direct causal role of these cell populations in human disease'. Second, we understand the Reviewers' concerns and accordingly, after discussing the potential non-AM effects of the Spp1 blockade, we have now added (page 15): 'This leaves open the possibility that these macrophages and the disease share a root cause, which is cigarette smoke exposure.'