Reviewer’s report

Title: TRAIL signals through the ubiquitin ligase MID1 to promote pulmonary fibrosis

Version: 0 Date: 03 Mar 2018

Reviewer: Kazuyoshi Kuwano

Reviewer's report:

Collison et al. demonstrated that TRAIL signaling through MID1 to deactivate PP2A plays a role in fibrosis with corresponding lung-function decline, and concluded that TRAIL may be a novel therapeutic target for IPF. This paper is well written but there are several issues to be verified.

Major comments

1. Authors have also shown that TRAIL induces the E3 ubiquitin ligase midline-1 (Mid1) to inhibit the activation status of the protein phosphatase (PP)2A by interacting with the α4 regulatory subunit that is required for the ubiquitin-specific modification and proteasome-mediated degradation of its catalytic subunit PP2Ac. Authors should demonstrate the association of Mid1 and PP2A by western blot and also examine the effect of proteasome inhibitor.

2. The source of TRAIL expression and TRAIL receptor expression should be verified in in vivo. Based on these results, authors should address the mechanisms of fibrosis induced by TRAIL-Mid1-PP2A signaling.

Minor comments

1. Authors should examine the role of TRAIL-Mid1-PP2A signaling in vitro using not only fibroblasts but also lung epithelial cells.

2. Authors should verify which kind of cell is TUNEL positive.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No
**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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