Author’s response to reviews

Title: The overexpression of peroxiredoxin-4 affects the progression of idiopathic pulmonary fibrosis

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Version: 2 Date: 30 Nov 2019

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BMC Pulmonary Medicine

Editor-in-Chief

David Noel O'Dwyer
November 30, 2019

Prof. Dr. O'Dwyer,

We deeply appreciate your interest in our manuscript and your courteous reply with the opportunity to respond to the comments from you and the reviewer regarding our manuscript entitled, “The overexpression of peroxiredoxin-4 affects the progression of idiopathic pulmonary fibrosis” by Hanaka et al. We deeply appreciate your interest in our manuscript and your courteous reply. We have read the comments from you and reviewer and have revised our manuscript accordingly as below.

We hope that our responses are satisfactory and that our revised manuscript is now acceptable for publication in BMC Pulmonary Medicine. We are looking forward to your favorable consideration.

Respectfully yours,

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RESPONSE TO TECHNICAL COMMENTS

1. Please move the Declarations heading to come after the Abbreviations.

Response: Thank you very much for your suggesting, and we moved the Declarations heading to come after the Abbreviations accordingly.
2. In the section 'Funding', please also describe the role of the funding body/bodies in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Response: Thank you very much for your suggestion, and we modified it as follows.

Before
Page 29, line 522:
UOEH Research Grant for Promotion of Occupational Health (grant number: 915) supported this study in analysis.

After
Page 30, line 537:
UOEH Research Grant for Promotion of Occupational Health (grant number: 915) supported data analysis and did not play a role in study design, data collection, interpretation, and manuscript writing.

RESPONSE TO EDITOR COMMENTS

1. Please explain the nature of your healthy volunteer population, they are not age matched and appear to have a reduced mean FVC?

Response: Thank you very much for your comments. In relation to the nature of healthy volunteers, they were publicly recruited in our university, and all of them had no medical histories. It was very unfortunate that the backgrounds such as age and smoking history of healthy volunteers and those of IPF patients were not matched. In addition, pulmonary function tests were not performed in the healthy volunteers.
In relation to pulmonary function changes, it was very unfortunate that we could not evaluate pulmonary function in all participants at follow-up periods. We therefore added comments on this issue in the limitation.

According to your comments, we revised our manuscript as follows.

Before

Page 9, line 159:
In addition, serum samples of 15 healthy adult volunteers (32-47 years old) were also collected.

After

Page 10, line 169:
In addition, serum samples of 15 healthy adult volunteers (32-47 years old) with no medical histories were also collected.

Before

Page 25, line 469:
This study has several limitations. First, the human study was a single-center retrospective study with a limited number of patients with S-IPF and AE-IPF for detecting serum and BALF PRDX4 protein levels. Second, cross-reaction of the anti-human PRDX4 antibody with mouse PRDX4 can be observed as the amino-acid sequences of human and mouse PRDX4 are highly homologous [25]; therefore, immunohistochemical staining of lungs of WT mice revealed human PRDX4-positive cells. Third, only male mice were used in this study, similar to our previous research [19, 20, 24, 25], and we were unable to evaluate the gender differences in the pathogenesis of IPF in Tg mice.
This study has several limitations. First, the human study was a single-center retrospective study with a limited number of patients with S-IPF and AE-IPF for detecting serum and BALF PRDX4 protein levels. Second, the backgrounds such as age, gender and smoking histories of the healthy volunteers and those of IPF patients were not matched. Third, we were unable to assess changes between baseline and follow-up period in pulmonary function, because many patients did not undergo a pulmonary function test during the follow-up period, therefore, we could not evaluate the relationship between serum PRDX4 and the change in pulmonary function. Fourth, cross-reaction of the anti-human PRDX4 antibody with mouse PRDX4 can be observed as the amino-acid sequences of human and mouse PRDX4 are highly homologous [25]; therefore, immunohistochemical staining of lungs of WT mice revealed human PRDX4-positive cells. Eventually, only male mice were used in this study, similar to our previous research [19, 20, 24, 25], and we were unable to evaluate the gender differences in the pathogenesis of IPF in Tg mice.

2. A major risk factor for AE is impaired physiology, yet you have not employed statistical models to account for changes there might be between your S-IPF and AE-IPF in baseline lung function and in follow up decline. If you are not able to carry out these statistical adjustments as a result of missing data (which appears to be the case) then please highlight this in the discussion section of your manuscript.

Response: Thank you very much for your comments. Pulmonary function test was not measured in all patients at baseline, and more than half of the patients did not undergo second pulmonary function test during the follow-up period. Therefore, it was very unfortunate that we were unable to assess the changes of pulmonary function between baseline and follow-up in all of the participants.

Therefore, we added related comments in the limitation as follows.
This study has several limitations. First, the human study was a single-center retrospective study with a limited number of patients with S-IPF and AE-IPF for detecting serum and BALF PRDX4 protein levels. Second, cross-reaction of the anti-human PRDX4 antibody with mouse PRDX4 can be observed as the amino-acid sequences of human and mouse PRDX4 are highly homologous [25]; therefore, immunohistochemical staining of lungs of WT mice revealed human PRDX4-positive cells. Third, only male mice were used in this study, similar to our previous research [19, 20, 24, 25], and we were unable to evaluate the gender differences in the pathogenesis of IPF in Tg mice.