

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-1158>

### Reviewer A

*The authors Hua F et al. present a review article on "Development of the dipeptidyl peptidase 4 family and its association with lung diseases". This reviewer has several concerns regarding the quality of the review and the additional value compared to what has been recently published. Overall, this reviewer does not regard this article of enough value to be published at this point unless the focus is specified and elaborated in depth or a much more comprehensive review is conducted with the goal to cover more recently published articles thus summarizing what is the actual state of the art on the topic.*

*One of the primary critiques is that there has been a recent review on DPP4 in lung disease in *Front Pharmacol* by Zhang et al. that is well written and covers the subject. In comparison to that literature review, the authors here appear to not thoroughly cover the literature that has been published in the meantime. Thus, the present review does not meet the criteria of a mere update.*

*In direct comparison, for example in the paragraph covering COPD, the authors here mention none of findings (for example regarding DPP4 and COPD/smoking) nor the literature mentioned in the previous review but largely focus on their own findings. Essential literature from the past years appears to be missing (for example Seys LJM et al., *AJRCCM*, 2017). The soluble form of DPP4 has not been mentioned. It should be referred to in the first paragraph of the manuscript. Also, some evidence should be included regarding the role of DPP4 cleavage on substrates and the associated regulation of substrate receptor preference and activity, thus covering some mechanistical aspects of DPP4 importance that are currently not discussed at all. Examples could be GLP1 itself but also recently identified mechanisms such as procalcitonin particularly acting in the lung (Brabenec et al., *AJRCCM*, 2022). Again, this recent literature is missing. In the chapter regarding the infectious diseases, MERS-CoV virus is missing. However, as DPP4 is can bind MERS-CoV, it should not be missing in a review on DPP4 and lung diseases.*

*Also, language requires revision from a native speaker. Especially, as it is sometimes not clear what is meant or confusion. For example, wording is confusing Line 39 "with proline or alanine". The word targeting should be included at another point of the*

*sentence so this can be understood. The same applies to the DPP9 chapter starting at line 205.*

Comment 1: In the paragraph covering COPD, the authors here mention none of findings (for example regarding DPP4 and COPD/smoking) nor the literature mentioned in the previous review but largely focus on their own findings. Essential literature from the past years appears to be missing (for example Seys LJM et al., AJRCCM, 2017).

Reply 1: We added some data on the association of DPP4 with smoking and added what you have proposed for the literature.

Changes in the text: see Page 3, line 80-84

Comment 2: The soluble form of DPP4 has not been mentioned. It should be referred to in the first paragraph of the manuscript.

Reply 2: We have added some data on the soluble form of DPP4.

Changes in the text: see Page 2, line 55

Comment 3: Also, some evidence should be included regarding the role of DPP4 cleavage on substrates and the associated regulation of substrate receptor preference and activity, thus covering some mechanistical aspects of DPP4 importance that are currently not discussed at all. Examples could be GLP1 itself but also recently identified mechanisms

Reply 3: We added some data on the role of DPP4 on substrates such as GLP1.

Changes in the text: see Page 2, line 60-65

Comment 4: such as procalcitonin particularly acting in the lung (Brabenec et al., AJRCCM, 2022). Again, this recent literature is missing.

Reply 4: We have added some data on procalcitonin acting in the lung.

Changes in the text: see Page 3, line 66-69

Comment 5: In the chapter regarding the infectious diseases, MERS-CoV virus is missing. However, as DPP4 is can bind MERS-CoV, it should not be missing in a review on DPP4 and lung diseases.

Reply 5: We have added some data on MERS-CoV.

Changes in the text: see Page 4, line 140-149

Comment 6: Also, language requires revision from a native speaker. Especially, as it is sometimes not clear what is meant or confusion. For example, wording is confusing Line 39 "with proline or alanine". The word targeting should be included at another

point of the sentence so this can be understood. The same applies to the DPP9 chapter starting at line 205.

Reply 6: We have modified our text as advised.

Changes in the text: see line 54 and 236

## **Reviewer B**

*This review article describes the role of DPP4 and DPP9 in chronic and acute lung diseases. Even though the material in the review is well thought out the authors have not included the information from recently published articles on DPP4. I strongly encourage the authors to revise the manuscript providing the summary of new findings.*

Comment 1: Even though the material in the review is well thought out the authors have not included the information from recently published articles on DPP4. I strongly encourage the authors to revise the manuscript providing the summary of new findings.

Reply 1: We have modified our text as advised.

Changes in the text: see line 61-69, 81-85, 145-149