Reviewer 2 v.1

Comments to the Author

Here in this review, Dr Perkins and Dr Oury are presenting a concise review of the paradoxical function of RAGE in the physiopathology of IPF. It should be pointed out that the authors have transmitted clearly and briefly the ideas and facts that has been mentioned regarding this molecule. Nevertheless, I have mayor concerns for this manuscript. Briefly, I summarize some of them:

- First of all, I consider that the title could be so much generalist. It is true that one of the objectives of this review is to bring to clues about the controversial role of RAGE in IPF, if it is part of its pathogenesis or a simple "side effect" of the fibrotic progression. However, it is clear that IL-13 has prominent mentioning (almost 4 pages only for explaining its mechanism and the importance of ILC2). It could be so much interesting to include this cytokine or type 2 immunity as a headline.

- Page 3, Line 66: I am not sure that nintedanib and pirfenidone should be spelled with a capital letter at the beginning, because in the case of pirfenidone, Esbriet® should be the commercial name, which has to be named with an initial capital. Could you please check this?

- Page 5, Line 127: There is mention different lung cell lines, specifically lung fibroblasts. Checking the literature that you mentioned, in the references I've observed the article of Wang et al. (J Allergy Clin Immunol. 2015 May;135(5):1154-62.e1-5), which refers to fibrocytes instead of lung fibroblasts. Could you check this reference?

- Page 5, Line 128: As commented, these two studies (Inghilleri et al. Pulm Med. 2011;2011:421409; and Morbini et al. Mod Pathol. 2006 Nov;19(11):1437-45) suggested that RAGE and its ligand is increased in the fibroblast foci in the lungs with UIP. However, it is also important to mention that these two references showed a great increment of RAGE in the overall lung from IPF patients by immunohistochemistry. This overexpression of RAGE that those articles describe seems to be contrary to the first statement of this paragraph (Page 5, Line 106). Actually, despite Queisser et al. (Am J Respir Cell Mol Biol. 2008 Sep;39(3):337-45) showed that gene expression of RAGE in lung fibroblast is present, they admitted that RAGE is decreased in alveolar epithelial cells and lung fibroblast from IPF patients compared with lung donors. Also Machahua et al (Respir Res. 2016; 17: 144.) showed that RAGE expression was almost missing in fibroblast foci. How could you explain this disagreement?

- Page 6, Line 146: Here I have found another confusing reference. Kyung et al (Int J Clin Exp Pathol. 2013 Dec 15;7(1):221-8) showed that circulating AGE are increased in IPF patients, whereas RAGE is also increased in lung tissue from IPF patients. Although they suggest a correlation, that seems to be positive. Also Machahua et al (Respir Res. 2016; 17: 144.) did not mention a correlation in circulating stage-AGE, but it was mentioned in "Serum AGE/RAGEs as a potential biomarker in idiopathic pulmonary fibrosis" (Respir Res. 2018 Nov 8;19(1):215).

- Page 8, Line 196: In order to add novel insight in re-epithelialization and RAGE I suggest to check the reference “The receptor for advanced glycation end-products enhances lung epithelial wound repair: An in vitro study”, Zhai et al. Exp Cell Res. 2020 Jun 15;391(2):112030.

- Page 9, Line 215: Although this section brings new findings regarding the possible mechanism by RAGE could act, I strongly miss a mention of the intricate relationship of IPF and inflammatory response, as well the immune response. It is true that the inflammatory process could lead to a well-established fibrosis, but the clinical practice and the histopathological findings have demonstrated that the inflammation is not the main character of this disease. How can we manage that RAGE could enhance an inflammatory response, such as in some inflammatory lung diseases, with the implication of some Type 2 immunity, in a disease that do not show clear signs of inflammation? Would we be talking about a subclinical inflammation?

- Page 12, Line 304: Here is still considering the overexpression of RAGE in fibroblast foci with some evidences that could be in the other side, as I mentioned before.

- Page 16, Line 406: In this sentence, I do not observe the contrasted wording. Loss of RAGE could be a secondary mechanism derived from alveolar loss and its gene expression could also decrease by aberrant molecular mechanism. In IPF, the reorganization of the alveolar parenchyma of the fibrotic process is progressive and heterogeneous where the remaining hypertrophy/reactive alveolar epithelial cells had an important role in the maintenance of the pro-fibrotic environment; it is here where a decrease of RAGE could be determinant of an aberrant re-epithelialization. Thus, these two mechanisms that seem to cancel each other, might be supplementary one to another. In the second place, the loss of membrane RAGE could be perfectly related to the lessening in sRAGE, considering that the main source of the soluble isoform is the cleavage of the membrane isoform (Hudson et al. FASEB J. 2008 May;22(5):1572-80), and less than the 7% of sRAGE is endogenous secreted.

- Page 17, Line 412: Missing reference.

- Page 17, Line 413: The problem with associating the RAGE-ligand interaction with the progressive fibrogenesis is the amount of reports that suggested that RAGE is decreased in IPF; thus in a therapeutic approach, when could RAGE inhibitor or antagonist be administrated? It is true that is so much tentative suggesting a role in the pathogenesis of the disease, as another driver process that may trigger the fibrotic response, and that is a good point. The only question about that is if RAGE has a role in progressive fibrosis, why there is no reported changes of RAGE in acute exacerbations for IPF?