

Reviewer 1 v.1

Comments to the Author

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The authors examined the functional role of CASC2, a long non-coding RNA down-regulated in sera of COPD patients, in human bronchial epithelial cell line 16HBE. Although the manuscript seems to be well-written, it also contains some issues as follows:

1. Authors demonstrated that CASC2 was down-regulated "in sera" of COPD patients (Fig. 1A). However, the functional role of CASC2 was examined "in 16HBE". Why? Authors should show data that serum CASC2 is derived from patients' epithelial cells. Showing data that demonstrate a down-regulation of CASC2 in epithelial cells of the patients would also strengthen the manuscript. Alternatively, at least, a down-regulation of CASC2 secreted in culture medium should be shown in the 16HBE experiments. Similarly, the cell origin of serum miR-18a in COPD patients is unclear.
2. Authors should clearly specify which individual miRNA they analyzed: miR-18a-5p or miR-18a-3p. This information is very important when comparing the presented data with other studies' results. Also, it must be used overall in the manuscript. In addition, detailed information of miR mimic and inhibitor used should be provided (e.g., origin, sequences, etc.)
3. (Page 15, line 5) Down-regulation of IGF1 correlated with the CASC2 level in COPD patients should be shown by the authors.
4. Appropriate control experiments are missing. For example, in Figs. 4 and 5, the effects of miR-18a mimic and inhibitor should also be examined in the CSE-untreated cells.
5. Mechanism of down-regulation of CASC2 induced by CSE is unclear.
6. (Fig. 2E) Mechanism of inhibition of inflammatory cytokine expression by CASC2 is unclear. Does IGF1 also participate in it?
7. (Figs. 2B and 4A) How did the authors distinguish endogenous CASC2 and miR-18a from exogenously applied them?

8. (Fig. 4A, CSE+CASC2 group) The result does NOT support authors' idea that "CASC2 functions as a ceRNA of miR-18a".

Minor:

1. It might be hard to distinguish respective groups among the columns in Figs (e.g., Fig. 4D). Color Figs. would be helpful for readers.

2. Check spelling and English grammar well.