Reviewer’s report

Title: Protocadherin-1 is a glucocorticoid-responsive critical regulator of airway epithelial barrier function

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Reviewer: Pieter Hiemstra

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In this manuscript the authors used a combination of observational studies in patient samples and cultured epithelial cell lines to explore the role of PCDH1 in epithelial barrier function, and show that glucocorticoids increase this barrier function.

Comments:

1. A major drawback of this study is that only immortalized cell lines and tumor cell lines were used to study the function of PCDH1. The extent to which findings on epithelial barrier functions obtained using such cells can be transferred to primary epithelial cells is unknown. This limitation should be discussed in detail.

2. Page 11: Lung tissue samples from asthmatics and controls were obtained from patients undergoing surgery for pneumothorax or lung cancer. The authors should discuss whether and how this could have affected the outcome of the study. Furthermore, it is important to characterize the asthma patients in this study with respect to the severity of their disease.

3. Page 13: Please indicate how the authors determined that the epithelial cultures were indeed polarized as written by the authors.

4. Page 13: Western blotting and the antibody used are not described in the main manuscript. Yet these are important issues that should be part of the main manuscript.

5. Page 14: What evidence do the authors have that the cells used in the siRNA knockdown experiments were differentiated as claimed by the authors in line 212.

6. Page 30: Since the authors did not assess airway hyperresponsiveness and/or reversibility of the asthma patients and controls, it is unclear how asthma was diagnosed.

7. Page 38: What was the control of siRNA PCDH1? Was it a scrambled form?

8. Supplement: Page 2: Were the samples boiled after addition of sample buffer?

9. Supplemental figure, Page 1: This supplemental figure was most likely "damaged" during pdf conversion, but could be evaluated to some extent.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.