

Article type : Letter to the Editor

Reply to Comment from Carl Persson

We thank Prof. Persson for his very insightful comments ¹ on our review article ² on the role of IL-33 in the lung, and for bringing these additional studies to our attention.

Prof. Persson points to a series of rarely-discussed papers discussing Creola bodies (clumps of epithelial cells in the airway lumen) which are strongly associated with an increased risk of asthma after RSV bronchiolitis ^{3,4}. These papers strongly support the argument that epithelial damage due to RSV infection, with presumed release of epithelial alarmins such as IL-33, is associated with the development of asthma. It remains to be shown whether Creola bodies are associated with increased IL-33 release, and this is an interesting area for further studies. The clearance of dying epithelial cells may well be critical, as previous studies have shown that mice with defective phagocytosis of apoptotic epithelium show an increased airway IL-33 response, and consequent increased inflammation ⁵. If, as is hypothesised, Creola bodies and IL-33 release are strongly co-associated with the development of asthma, these could be important biomarkers for further interventions a subset of paediatric patients with RSV bronchiolitis, such as anti-IL-33 biologics currently in development.

On Prof. Persson's second point, on the role of IL-33 and TSLP in the regeneration of airways after epithelial sloughing, we agree that these cytokines may well have a role in the aberrant healing and fibrosis of airways after repeated viral damage. Again, this could argue that the release of these cytokines during severe paediatric respiratory viral infections could be a critical point for intervention. However, while too much IL-33 signalling could lead to allergic

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sensitisation and fibrosis, sufficient IL-33 responses are required for efficient healing of the lung ⁶ or the skin ⁷ after injury, therefore blocking this cytokine in those children which have the most injury due to RSV infection could result in defective restoration of the epithelial barrier.

Henry McSorley

Henry.mcsorley@ed.ac.uk

Centre for Inflammation Research

University of Edinburgh

Edinburgh, United Kingdom

Kristina Johansson

Department of Microbiology and Immunology, Sandler Asthma Basic Research Center,

And Department of Medicine,

University of California,

San Francisco, California, United States of America

We declare that we have no conflict of interest

1. Persson C. Comment on Review article by Kristina Johansson and Henry McSorley entitled "Interleukin-33 in the developing lung - Roles in asthma and infection." *Pediatr Allergy Immunol.* 2019;doi: 10.1111/pai.13184.
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