

Correspondence

A possible differential role of autophagy in asthma?

To the Editor:

Suzuki et al.¹ recently reported that Atg5 deletion in CD11c⁺ cells caused steroid-resistant neutrophilic airway inflammation. They further suggested that refractory severe asthma might be improved by enhancing lung autophagy. Although the findings are interesting, this study has drawbacks in interpretations and study design. The authors had excellently extended the accidental observations (other group) of huge lung neutrophils, increased IL-17A, and IL-1 α in lungs found in uninfected Atg5^{fl/fl} LysM-Cre⁺ mice² toward steroid resistance because steroid-resistant conditions are strongly linked to higher IL-17 response and neutrophils using CD11c-specific Atg5^{-/-} mice. However, the latter strain did not show any increase in neutrophils at basal conditions unlike the former strain. The authors did not explain the reasons for this discrepancy.

Surprisingly, the authors have performed experiments in CD11c-specific Atg5^{-/-} mice without the determination of Atg5 in CD11c cells in asthmatic conditions. This is very much crucial due to the availability of scarce direct Atg5 functional studies in asthma. Although the authors have demonstrated the impairment of autophagy in CD11c⁺ cells in lungs of wild-type mice, they have not shown the status of Atg5 in these cells. There may be a possibility of Atg5-independent impairment of autophagy in these cells.³ In addition, the demonstration of autophagy impairment in CD11c⁺ cells has various pitfalls (Fig 3 in Suzuki et al.¹): (1) β -actin itself is involved in the autophagic process⁴; (2) as a result, there may be a differential β -actin expression between PBS and house dust mite; (3) higher β -actin might also reflect the higher LC3-I and P62 in house dust mite; and (4) thus LC-3 II/LC-3 I may not be valid.

They did not consider or discuss Atg5-independent alternative autophagy pathways such as Ulk1 and phosphoinositol 3-kinase pathways.³ This is crucial in the context of no demonstration of functional autophagic flux in this study because mere accumulation of autophagosomes can occur in both proautophagic and anti-autophagic pathways.⁵

The authors' claim of T_H17 polarization is not strong because there is no naive T-cell experiments and IL-6 increase.

Although the increased numbers of autophagosomes have been shown in bronchial epithelia of those with asthma and Clara cells-specific Atg7^{-/-} had higher airway resistance,⁵ the authors have

neglected the bronchial epithelia in the context of autophagy. Although bronchial epithelium is central to asthma pathogenesis, the authors have used alveolar epithelia-specific knockdown of Atg5 for their claims to emphasize hematopoietic cells. In contrast to their generalized statement of T_H2 cytokine-mediated autophagy inhibition, T_H2 cytokines promote autophagy in airway epithelia and thus lead to the promotion of Atg5-dependent mucin secretion.⁶ Thus, IL-13 seems to have differential effects on macrophages and bronchial epithelia. So autophagy may have a similar differential role in asthma as well as in chronic obstructive pulmonary disease in which increased epithelial autophagy and impairment of autophagic flux in alveolar macrophages have been reported.⁵ This peculiar feature precludes the possibility of selecting autophagy as an effective therapeutic target. In this context, further cell-specific autophagic investigations are required to get a complete picture.

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