Int J. Basic. Clin. Immunology. 2021: 4 (3-4): 1-3
DOI:
www.internationalsciencepublication.org

Commentary

Anti-IIL-18 immunotherapy for asthma development

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(Received Dec 22, 2021; Accepted Dec 28, 20

Purpose of Study.

This is a commentary on recently published article in *Allergy* entitled as "*Mishra A, Majid D, Kandikattu HK, Yadavalli CS, Upparahalli Venkateshaiah S. Role of IL-18-transformed CD274-expressing eosinophils in promoting airway obstruction in experimental asthma. Allergy. 2021 Nov 20. doi: 10.1111/all.15180*."

Reviewer's Comments.

This article is continuation of previous study with more supportive pieces of evidence to show the critical role of IL-18 in inducing pathogenic eosinophils phenotype in asthma (Venkateshaiah et al., *J Allergy Clin Immunol*. 2018). Asthma is generally accepted as a costly illness, with significant impact on life quality. Asthma is a common chronic inflammatory disease of the lungs characterized by reversible airflow obstruction, hyperresponsiveness, and mucus hypersecretion. It is estimated that asthma is affecting 25 million people in the United States. Major factors involved in asthma pathogenesis are some food and environmental allergens which cause the release of allergic mediators from inflammatory cells and excessive production of cytokines including IL-5, IL-13 and IL-18. IL-18 induction in airway inflammation and airway hyperresponsiveness is reported (Sawada M, et al. *PLoS One*. 2013); however, no effort is made to confirm its critical role in asthma. Sathisha *et al* earlier reported IL-18 role in transforming naïve eosinophils to $CD274^{+}$ expressing pathogenic eosinophils. The current report of Mishra *et al* explored IL-18 and CD274 expressing eosinophil role and unravel the mechanistic aspects. In this study, the investigators used various experimental mouse models. including *Aspergillus. fumigatus*-

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challenged wild type (WT), IL-5$^{-/-}$, IL-18$^{-/-}$, CD2-IL-5 transgenic, IL-5$^{-/-}$/IL-18$^{-/-}$ double gene-deficient, and eosinophil deficient ΔdblGATA. In addition, the study showed that neutralization of CD274 or IL-18 ameliorates allergen-induced experimental asthma and can be used as a future therapeutic approach. Current study by Mishra *et al* provides several evidences regarding the role of IL-18 in transforming naïve eosinophils to pathogenic eosinophils. *Aspergillus fumigatus* was used as an allergen in the study to develop experimental asthma. Accumulation of eosinophils in the peribronchial and perivascular epithelium was noticed in allergen challenged as well as in CC10-IL-18 Transgenic (DOX) mice, whereas in saline-challenged WT mice or CD2-IL-5 Tg mice, eosinophils accumulated in the lung parenchyma. Increased expression of IL-18 and presence of ~97% CD274^{+} eosinophils in the BALF of allergen-challenged WT mice indicate the critical role of IL-18 in pathogenic eosinophils development. In addition, authors noticed that IL-18 levels were higher in allergen-challenged IL-5$^{-/-}$ mice as compared to allergen-challenged WT mice pointing towards the negative regulation of IL-18 by IL-5 which is responsible for the eosinophil accumulation even in IL-5$^{-/-}$ mice following allergen challenge. This allergen challenge leads to accumulation of macrophages in lungs which are source of IL-18 in these mice.

To further delineate the mechanism, Mishra *et al* provided convincing evidence that IL-18 is involved in transforming IL-5-responsive eosinophils to CD274^{+} pathogenic eosinophils that promote asthma development. Administration of recombinant IL-18 in CD2-IL-5 transgenic mice (in which most of the eosinophils are CD274^{-}) showed significantly increased BALF and lungs eosinophils with higher number of CD274^{+} eosinophils when compared to recombinant IL-18 treated WT mice. Moreover, additional asthma related parameters such as airway resistance, MBP^{+}, EPX^{+} eosinophils and PAS-stained goblet cells were increased in recombinant IL-18- treated CD2-IL-5 transgenic mice compared to WT mice. Finally, authors showed that neutralization of CD274 or IL-18 ameliorates allergen-induced CD274^{+} pathogenic eosinophil-mediated induction of experimental asthma. Overall, this study provides several supporting evidences of IL-18 mediated induction of pathogenic eosinophils and propose anti-CD274 and anti-IL-18 immunotherapy as future approach to reduce the severity of asthma.

Conclusion.

The study indicates a need of clinical trials related with anti-CD274 and anti-IL-18 neutralization immunotherapy to extrapolate this

interesting mice data to humans. This study unravels the novel way to differentiate pathogenic eosinophils from healthy eosinophils.

References:

1. *Venkateshaiah SU, Mishra A, Manohar M, Verma AK, Rajavelu P, Niranjan R, Wild LG, Parada NA, Blecker U, Lasky JA, Mishra A. A critical role for IL-18 in transformation and maturation of naive eosinophils to pathogenic eosinophils. J Allergy Clin Immunol. 2018 Jul;142(1):301-305. doi: 10.1016/j.jaci.2018.02.011.*

2. *Sawada M, Kawayama T, Imaoka H, et al. IL-18 induces airway hyperresponsiveness and pulmonary inflammation via CD4+ T cell and IL-13. PLoS One. 2013;8(1):e54623.*