Dysregulation of type 2 innate lymphoid cells and T_H2 cells impairs pollutant-induced allergic airway responses

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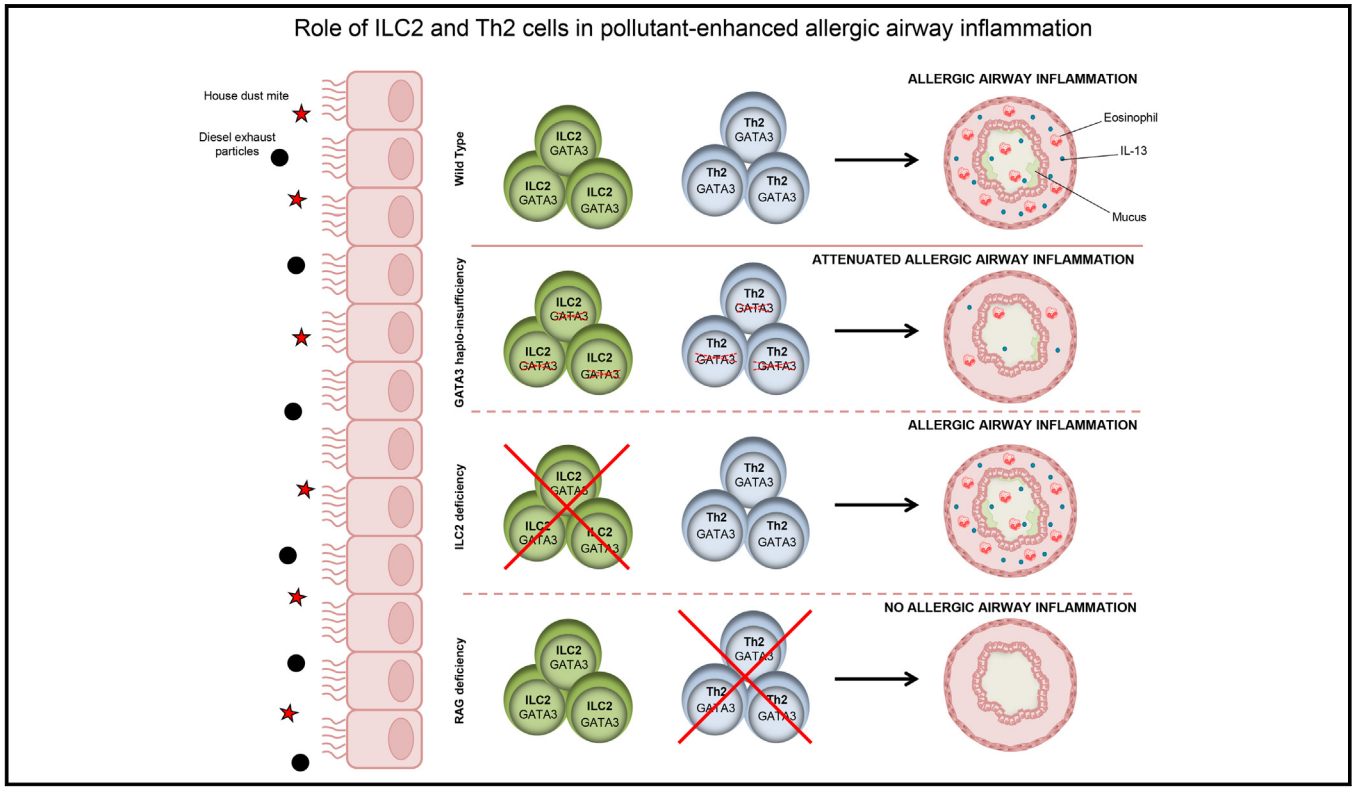
GRAPHICAL ABSTRACT



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Background: Although the prominent role of T_H2 cells in type 2 immune responses is well established, the newly identified type 2 innate lymphoid cells (ILC2s) can also contribute to orchestration of allergic responses. Several experimental and epidemiologic studies have provided evidence that allergen-induced airway responses can be further enhanced on exposure to environmental pollutants, such as diesel exhaust particles (DEPs). However, the components and pathways responsible remain incompletely known.
Objective: We sought to investigate the relative contribution of ILC2 and adaptive T_H2 cell responses in a murine model of DEP-enhanced allergic airway inflammation.
Methods: Wild-type, Gata-$3^{+/nlslacZ}$ (Gata-3–haploinsufficient), RAR-related orphan receptor α (RORα)$^{fl/fl}$IL7R^{Cre} (ILC2-deficient), and recombination-activating gene (Rag) $2^{-/-}$ mice were challenged with saline, DEPs, or house dust mite (HDM) or DEP+HDM. Airway hyperresponsiveness, as well as inflammation, and intracellular cytokine expression in ILC2s and T_H2 cells in the bronchoalveolar lavage fluid and lung tissue were assessed.
Results: Concomitant DEP+HDM exposure significantly enhanced allergic airway inflammation, as characterized by increased airway eosinophilia, goblet cell metaplasia, accumulation of ILC2s and T_H2 cells, type 2 cytokine production, and airway hyperresponsiveness compared with sole DEPs or HDM. Reduced Gata-3 expression decreased the number of functional ILC2s and T_H2 cells in DEP+HDM-exposed mice, resulting in an impaired DEP-enhanced allergic airway inflammation. Interestingly, although the DEP-enhanced allergic inflammation was marginally reduced in ILC2-deficient mice that received combined DEP+HDM, it was abolished in DEP+HDM-exposed Rag$2^{-/-}$ mice.
Conclusion: These data indicate that dysregulation of ILC2s and T_H2 cells attenuates DEP-enhanced allergic airway inflammation. In addition, a crucial role for the adaptive immune system was shown on concomitant DEP+HDM exposure. (J Allergy Clin Immunol 2017;139:246-57.)

Key words: *Diesel exhaust particles, house dust mite, type 2 innate lymphoid cell, T_H2 response, asthma*

Abbreviations used
AHR: Airway hyperresponsiveness
BALF: Bronchoalveolar lavage fluid
DC: Dendritic cell
DEPs: Diesel exhaust particles
HDM: House dust mite
ILC2: Type 2 innate lymphoid cell
MHCII: MHC class II
MLN: Mediastinal lymph node
Rag: Recombination-activating gene
RORα: RAR-related orphan receptor α
TCR: T-cell receptor
TSLP: Thymic stromal lymphopoietin
WT: Wild type

Asthma is a chronic disorder of the conducting airways associated with reversible airway obstruction, chronic airway inflammation, airway remodeling, and airway hyperresponsiveness (AHR).[1] It is a heterogeneous disease in which multiple phenotypes can be distinguished based on clinical characteristics and the inflammatory profile. Asthma that originates during childhood (early-onset asthma) mostly has an atopic component[2,3] and is typically considered a T_H2-driven disease.[4]

In addition to the adaptive immune system, the airway epithelium has gained great importance during initiation and maintenance of the allergic and asthmatic cascade. In particular, it has been shown that on allergen exposure, several epithelial cytokines, such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), are involved in the pathogenesis of asthma.[5,6] Moreover, several genes discovered in genome-wide association studies (ie, IL-33, IL-1RL1, and TSLP) support a key role for these cytokines.[7,8] On the one hand, these epithelium-derived cytokines have the capability to activate the adaptive immune system by stimulating T_H2-polarizing dendritic cells (DC).[5] On the other hand, the recently identified type 2 innate lymphoid cells (ILC2s) also become activated by these cytokines.[9-11] Analogous with T_H2 cells, ILC2s require the transcription factor Gata-3 and are a potent source of the type 2 cytokines IL-5 and IL-13, which are able to induce lung eosinophilia and mucus hypersecretion.[11-15] Studies in recombination-activating gene (Rag)$^{-/-}$ mice have shown that these ILC2s are crucial players in allergic airway responses.[16] Even in the absence of the adaptive immune system, ILC2s were able to mediate eosinophilia, goblet cell metaplasia, type 2 cytokine production, and AHR.[17-19] In addition, mice that were ILC2 deficient because of targeting of the transcription factor RAR-related orphan receptor α (RORα) had decreased type 2 immune responses.[14,20,21] Interestingly, it was reported that ILC2s and T cells interact with each other and that this crosstalk could contribute to the maintenance, proliferation, and activation of both ILC2s and T_H2 cells.[21-23]

In addition to allergen exposure, it has become well accepted that traffic-related particulate matter, such as diesel exhaust particles (DEPs), also contributes to the development and exacerbation of asthma.[24-26] For instance, epidemiologic studies reported a correlation between high DEP levels and the frequency of symptomatic episodes in allergic children.[27] In addition, combined allergen plus DEP administration during controlled human exposure studies resulted in increased allergen-specific immunoglobulin levels and type 2 cytokine responses.[28] Furthermore, concomitant DEP plus house dust mite (HDM) exposure in murine models enhanced eosinophilia, immunoglobulin production, AHR, and remodeling.[29] However, the mechanisms underlying the enhanced effects of DEPs on allergen-induced airway inflammation remain largely unknown. Several studies suggested that the airway epithelium could be an important player because particulate matter was also able to stimulate the release of several epithelium-derived cytokines, such as TSLP and IL-33, which can lead to enhanced DC maturation and T_H2 responses.[30-33] However, whether this also activates ILC2s is unknown.

In this article we investigate the relative contribution of ILC2s and the adaptive immune system in the enhancing effects of DEPs on allergen-induced airway inflammation. We show in a murine model that concomitant exposure to a clinically relevant allergen (ie, HDM) and DEPs enhances several allergic airway responses, including airway eosinophilia, goblet cell metaplasia, increased ILC2 and T_H2 cell numbers, type 2 cytokine production, and AHR. Because Gata-3 is an important transcription factor during the development and function of both ILC2s and T_H2 cells,[34] we