

diagnosis and those with IPF. Clearer case definition should improve understanding of how specific disease features impact choice of treatment and anticipated response to therapy.

As demonstrated by the two perspectives in this issue of the *Journal*, as we seek to develop an international consensus on diagnosis and classification of HP, there will be a wide range of differing opinions. There is an urgent need to resolve such differences and to find consensus for the benefit of those individuals suffering with and dying from HP. Looking to the future, it is critically important that steps are taken to move research forward in this disease area. The development of definitive guidelines will, like IPF and the IIPs beforehand, be an iterative process driven by research findings arising from initial attempts at consensus classification. A quote from Winston Churchill (speech, November 1942) perhaps best exemplifies where the perspectives of Salisbury and colleagues and Vasakova and colleagues lead us: "Now this is not the end. It is not even the beginning of the end. But it is perhaps the end of the beginning." Let this be a call to arms for the international ILD community to focus on the important and growing clinical challenge presented by the many faces of HP and to do so for the benefit of our patients. ■

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Group 2 Innate Lymphoid Cells Are the Earliest Recruiters of Eosinophils in Lungs of Patients with Allergic Asthma

Protection against helminths, as well as immune response to allergens, in atopic subjects not only consists of adaptive responses orchestrated by type 2 T helper (Th2) cells but also involves the activation of a recently discovered subset of innate immunity cells (1). These cells, the group 2 innate lymphoid cells (ILC2s), have been recently characterized in both mice and humans and represent a cell subset of the innate immunity specialized in the induction and maintenance of type 2 inflammation (2). Because of their similarities in the function and requirement of transcriptional machinery, it is considered that both Th2 cells and ILC2s collaborate during type 2 immune responses, including

protection against parasites and the genesis of allergic inflammation. ILC2s preferentially localize to the interface between the host and the environment (lung, intestine, and skin), and this strategic localization allows them to represent a critical link between the innate and adaptive components of type 2 immunity (3). ILC2s differ from Th2 cells mainly because of the lack of a T-cell receptor (TCR), but they can be activated by several factors, including cysteinyl-leukotrienes, PGD₂, IL-2, IL-4, IL-7, IL-15, and some toll-like receptor ligands (4). Beyond these factors, the epithelial-derived cytokines IL-25, IL-33, and thymic stromal lymphopoietin represent the major source of their activation (4, 5). Once activated, ILC2s are capable of producing IL-4, IL-13, and large amounts of IL-5, whose production is considered to be a hallmark of their function. Indeed, ILC2s have been shown to accumulate at the site of eosinophilic

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inflammation, including nasal polyps and sinus mucosa in subjects with chronic rhinosinusitis, skin lesions in atopic dermatitis, and of course in lungs of patients with bronchial asthma (6).

In this issue of the *Journal*, Chen and colleagues (pp. 700–712) stressed the role of ILC2s as initiators of eosinophilic inflammation in allergic asthma, thanks to *in vivo* experiments performed in subjects with asthma challenged with the sensitizing allergen (7). The experimental approach allowed the authors to evaluate the biologic effects of allergen challenge, in both the site of inflammation and peripheral blood, and finally, in bone marrow, where eosinophils are generated. The first main novelty emerging from this interesting manuscript consists of the identification of the dynamic of different inflammatory subset activation, with ILC2s the initiators of allergic inflammation and Th2 cells responsible for its maintenance. The early involvement of ILC2s is the direct consequence of the biological mechanisms that determines their activation. Indeed, airway epithelial cells, in addition to functioning as a physical barrier, also secrete cytokines and are able to rapidly activate ILC2s (8). In particular, the epithelial alarmins, different from classical cytokines that are secreted in an active process after pathogens induce their *de novo* synthesis, are constitutively expressed in somatic cells and passively and rapidly released by perturbed airway epithelial cells (9). In particular, the pivotal role of IL-33 in driving the early type 2 response to allergens has been shown in a mouse model of acute airway inflammation that was induced by exposure to the fungus *Alternaria alternata*, which is able to induce a rapid release

of IL-33 by airway epithelial cells and to increase eosinophils recruitment in the lung (10). In this view, it is not surprising that fungal sensitization is frequently associated with asthma (11), and in particular, with the more severe forms of the disease, with acute exacerbations and sometimes with fatal events (12).

The second important finding of the manuscript regards the link between ILC2 activation and eosinophilic inflammation. The recruitment of eosinophils in the lungs of patients with asthma and allergic airway diseases and their local production of toxic mediators are crucial in determining tissue damage and remodeling. In this context, the opportunity to interfere with eosinophilic activation could represent a possible target of new therapeutic approach in bronchial asthma. In past years, several inhibitors of IL-5 have been proposed to treat severe eosinophilic asthma (13). Interestingly, the possibility of acting on ILC2s, the earliest source of eosinophil activation, through neutralization of thymic stromal lymphopoietin has been investigated and proven to be effective only in mild asthma (14), whereas the blocking of IL-25 and IL-33 pathways in humans is currently on the course of evaluation in clinical trials. In addition, Chen and colleagues performed their elegant study in subjects with mild stable atopic asthma, showing that ILC2s are rapidly activated by allergen challenge (7). Taken together, these data allow us to hypothesize that the blocking of ILC2 activation can represent a novel therapeutic strategy in mild to moderate asthma, when this subset plays a crucial role in initiating the allergic inflammation. Once Th2 cells and other cellular elements of allergic phlogosis are activated, it is likely that the blocking of ILC2s is not sufficient to

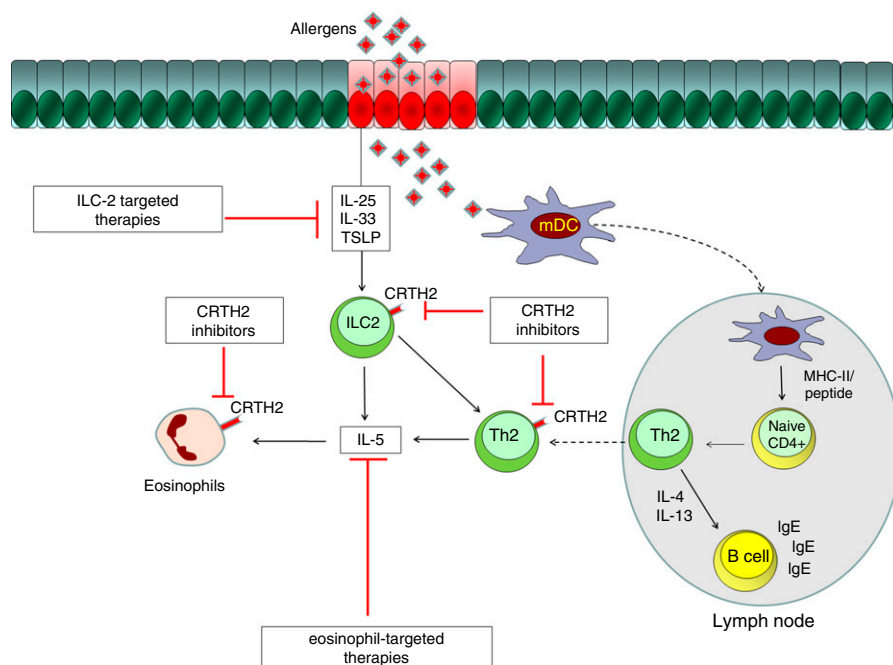


Figure 1. Once activated by allergens, perturbed epithelial cells produce alarmins that activate group 2 innate lymphoid cells (ILC2s), which in turn promote early eosinophil recruitment in lungs and type 2 T helper (Th2) cell activation. Subsequently, Th2 lymphocytes stimulate eosinophils, amplifying the circuit. ILC2-targeted therapies are more probably effective in the initial phase of inflammation, whereas IL-5 inhibition is effective in severe asthma. CRTH2 inhibitors, acting on ILC2s, Th2 lymphocytes, and eosinophils, may act on both the early and late phases of eosinophilic inflammation. CRTH2 = chemoattractant receptor–homologous molecule expressed on Th2 cells; mDC = myeloid dendritic cell; MHC-II = major histocompatibility complex class II; TSLP = thymic stromal lymphopoietin.

dampen the inflammation. The possibility of inhibiting, at the same time, both ILC2 and Th2 activation may represent a possible evolution of asthma treatment, independent in its severity. The DP2 receptor (CRTH2) inhibitor, fevipiprant, which is able to reduce eosinophilic airway inflammation in patients with persistent moderate to severe asthma, could represent a favorable tool in this direction (15). Indeed, CRTH2 ligation by PGD-2 induces both cell recruitment and activation, and more important, this receptor is expressed on several actors of allergic phlogosis, such as ILC2s (1, 4), Th2 lymphocytes, and eosinophils (16).

In conclusion, the inflammatory milieu in eosinophilic asthma is complex, and different players participate in different moments in the induction and maintenance of inflammation. The observation that ILC2s are rapidly activated by the allergen suggests ILC2-targeted therapies are more probably effective in the initial phase of inflammation and in mild to moderate asthma (Figure 1). ■

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Inflammasome Deficiency Makes Pro-resolving Lipid Mediators Great Again

Sepsis is a life-threatening condition associated with organ dysfunction caused by a dysregulated host response to infection (1). Although the infection can often be successfully treated with antimicrobials, and failing organs can be temporally supported by modern intensive care, little progress has been made in the development of clinically effective interventions that therapeutically interfere with the dysregulated immune cascade. Strategies to inhibit proinflammatory cytokines, for examples, have not been successful in clinical trials (2). Sepsis-related morbidity and mortality therefore remain high and might further increase due to an aging population with more comorbidities.

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Sepsis is characterized by consecutive or overlapping hyperinflammatory and hypoinflammatory reactions, which can lead to collateral tissue damage and enhanced susceptibility to secondary infections, respectively (2). The NLR family pyrin domain-containing 3 (NLRP3) inflammasome is believed to play a critical role in inflammation and sepsis, as it serves as a platform for caspase-1-dependent release of IL-1 β , IL-18, and high-mobility group protein B1, as well as cell death in response to infections and noninfectious insults (3, 4). In addition, a previous study indicated that inflammasomes are also able to mediate the production of various proinflammatory eicosanoid lipid mediators. It was demonstrated that intraperitoneal delivery of an NLR family apoptosis inhibitory proteins (NAIP5)/NLR family CARD domain-containing protein 4 (NLRC4) ligand stimulated an

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