

Editorial

Emerging targeted therapeutics underscore immunologic heterogeneity of asthma

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Asthma is a chronic inflammatory disorder of the lower airways that results in sustained coughing and shortness of breath. In addition to greatly affecting quality of life and posing a major burden on the health care system, severe forms of asthma can result in death. Asthma is heterogeneous and can be subclassified into a diverse array of phenotypes and endotypes.¹ An increasingly recognized way to categorize asthma is based on levels of type 2 (T2) inflammation.

T2 inflammation is an important driver of asthma in many patients. It is widely appreciated that environmental stimuli such as allergens, pollutants, and viruses promote release of the epithelial cell–derived alarmin cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) in asthma. Downstream of these alarmins, numerous immune cells such as group 2 innate lymphoid cells and T_H2 cells are activated, and in turn, they produce the effector type 2 cytokines IL-4, IL-5, and IL-13. Collectively, these cytokines exert their effects on target tissues via their receptors through the activation of intracellular Janus kinase (JAK) (Fig 1). Asthma pathologies associated with the proinflammatory type 2 cytokine response include recruitment and activation of eosinophils, epithelial thickening, mucous overproduction, smooth muscle hypercontractility, and IgE production. Given their central role in asthma pathogenesis, epithelial cell–derived alarmin and effector cytokines have become the targets of current and emerging therapeutic approaches.

It is estimated that about 50% of patients with asthma are classified as T2-high.² Biomarkers for this population include high levels of eosinophils in the blood and sputum as well as high levels of fractional exhaled nitric oxide (FENO).³ Current biologic agents approved for asthma treatment are generally indicated for T2-high patients. These include mAbs that target signaling of T2 effector cytokines—specifically, a mAb against the shared receptor subunit for IL-4 and IL-13 (IL-4R α , dupilumab) and those that bind IL-5 (mepolizumab and reslizumab) and its receptor (benralizumab).⁴ In contrast, T2-low patients lack biomarkers. Indeed, the cellular and molecular mechanisms

that underlie this population are poorly defined, although the inflammation appears to be more neutrophilic in nature. Indeed, it is likely that this classification consists of a mix of multiple disease endotypes.¹ Notably, there are limited treatment options for T2-low patients, as they exhibit weaker clinical responses to inhaled corticosteroids and there are no approved treatments specifically targeting this population. Overall, the focus of the 2 studies highlighted here is on investigation of therapies that intervene upstream or downstream of effector cytokines in specific subtypes of asthma.

In the first study, Kelsen et al present a randomized, double-blind, placebo-controlled, dose-ranging study (ZENYATTA) to evaluate the efficacy of astegolimab, a mAb directed against the IL-33 receptor (ST2) in severe asthma.⁵ The rationale for this study was that blocking upstream alarmin signals may limit exacerbations in asthma, as these mediators are likely central activators of downstream type 2 inflammation. The primary endpoint was annualized asthma exacerbation rate (AER) at week 54, and this was met by astegolimab treatment. The therapeutic benefit of astegolimab on the secondary therapeutic endpoint quality of life (as measured by the Asthma Quality of Life Questionnaire) was modest compared with the reduction in AER, whereas no significant improvement in lung function and asthma control (as measured by the Asthma Control Questionnaire) was found. Notably, patients were additionally stratified by blood eosinophil counts (<150, $\geq$ 150 to <300, and $\geq$ 300 cells/ μ L) for prespecified exploratory analyses. Surprisingly, the reduction in AER was significant not in the T2-high population ($\geq$ 300 cells/ μ L) but rather in the T2-low population (<300 cells/ μ L). However, the most consistent signal across the different treatment doses was seen in the group with blood eosinophil counts ranging from 150 to 300. Further, whereas T2-high patients did demonstrate reductions in blood eosinophil count, no reductions in FENO level following treatment were observed in *post hoc* analyses. Together, these findings suggest that blocking ST2 may be more effective in the setting of T2-low asthma, although more highly powered studies are needed to further clarify the therapeutic effectiveness of astegolimab on these different subgroups. Further, why blocking an alarmin would have unique efficacy in this endotype remains to be clarified.

The observation that ST2 blockade may be more effective in T2-low settings evokes the hypothesis that the blockade of epithelial cell–derived alarmins may have unique therapeutic properties beyond simply limiting robust T2 inflammation. A multicenter, randomized, double-blind, placebo-controlled phase 3 clinical trial (NAVIGATOR) found that in addition to the IL-33 pathway, tezepelumab (a mAb against the alarmin TSLP) reduced exacerbation rates across both T2-high and T2-low patients.⁶ However, in contrast to ST2 inhibition, tezepelumab broadly improved blood eosinophil counts, FENO level, 6-item Asthma Control Questionnaire score, Asthma Quality of Life Questionnaire score, and IgE level more effectively in T2-high patients than in T2-low patients. These findings suggest

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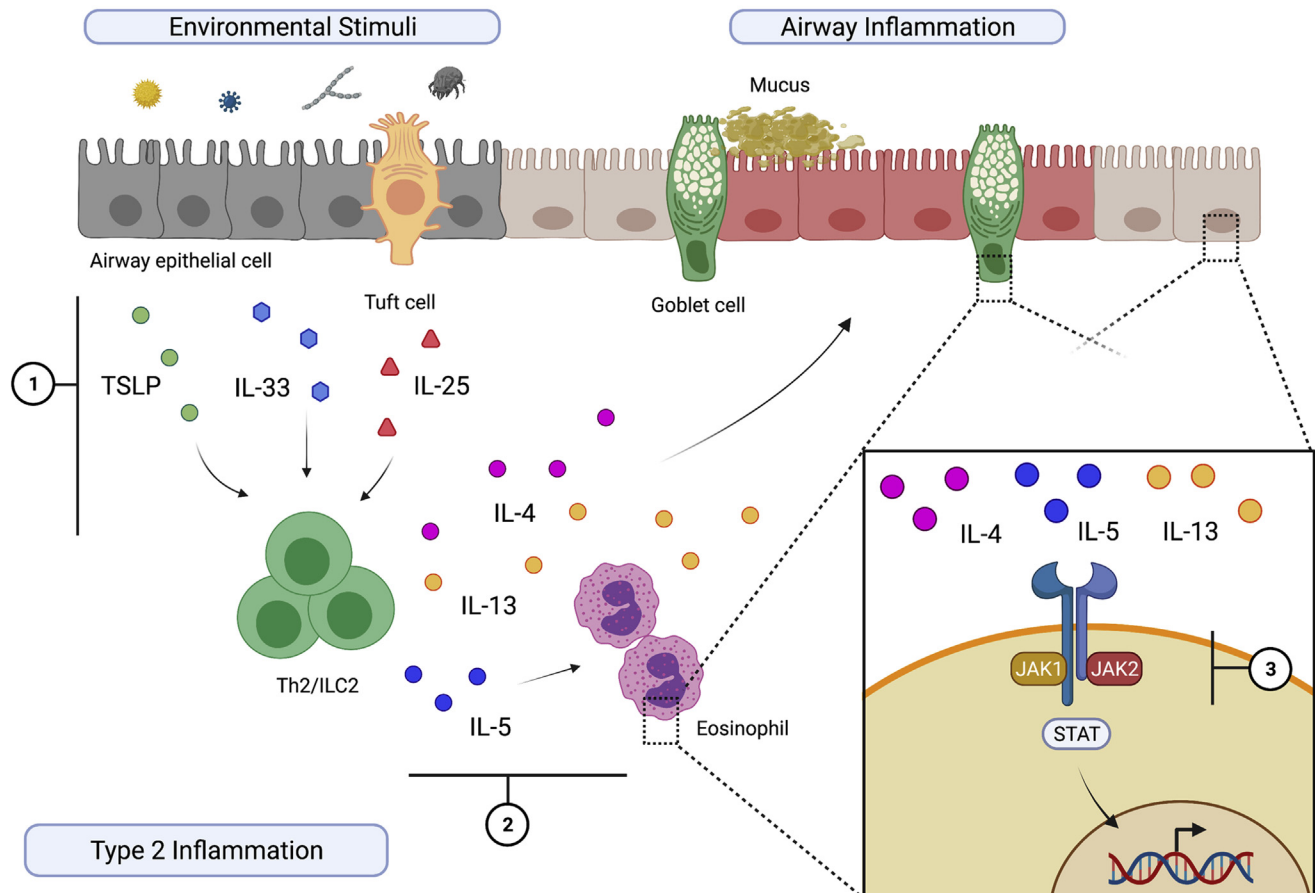


FIG 1. The epithelial-immune circuit of asthmatic inflammation in the lung. Exposure to environmental stimuli, such as pathogens and allergens, leads to epithelial barrier dysfunction, which in turn results in the release of alarmin cytokines such as TSLP, IL-33, and IL-25 (alarmin cytokines). These molecules directly stimulate lymphocytes such as group 2 innate lymphoid cells (ILC2s) and T_H2 cells to release type 2 cytokines (the effector cytokines IL-4, IL-5, and IL-13). These cytokine receptors are expressed on various cell types, including ILC2s, T cells, eosinophils, airway epithelial cells, goblet cells, and sensory neurons; they induce type 2 airway inflammation through JAK family (JAK1, JAK2, JAK3, and TYK2) signaling (downstream signaling). Emerging therapeutics target the following molecules: (1) the alarmin cytokines: tezepelumab (an anti-TSLP mAb), etokimab/itepekimab/MEDI3506 (anti-IL-33 mAbs), and astegolimab (an anti-ST2 mAb); (2) the effector cytokines lebrikizumab/tralokinumab (anti-IL-13 mAbs), mepolizumab/relizumab (anti-IL-5 mAbs), dupilumab (an anti-IL-4R α mAb), and benralizumab (an anti-IL-5R α mAb); and (3) downstream signaling (GDC-0214 [a JAK inhibitor]). Figure created with Biorender.

that the TSLP pathway may preferentially influence T2-high inflammation. What influences these differences remains an exciting area of future inquiry. It is possible, for example, that different environmental stimulants can trigger distinct alarmins to activate unique downstream inflammatory pathways (Fig 1). The findings from such inquiries have the potential to influence therapeutic approaches across a broad spectrum of allergic diseases associated with T2 inflammation.

Given the well-established therapeutic role of effector T2 cytokines in asthma, an alternative strategy is to target downstream JAKs (Fig 1). The second study that we highlight is a double-blind, placebo-controlled, phase 1, proof-of-activity study to evaluate the ability of the inhaled small molecule JAK inhibitor GDC-0214 to reduce inflammation, as assessed by FENO level in patients with mild asthma.⁷ Strikingly, Braithwaite et al⁷ report that inhaled GDC-0214 reduces FENO level in a dose-dependent manner. Further, no severe adverse

events were reported. By utilizing the inhaled approach, it is possible that the safety of JAK inhibitors can be improved by avoiding systemic exposure. A similar approach involving use of the topical JAK inhibitor ruxolitinib cream for atopic dermatitis is currently under way.⁸ Taken together, these results suggest that this agent may be an effective therapeutic strategy. Interestingly, in contrast to ZENYATTA, which enrolled patients with severe asthma and placed considerable focus on T2-low patients, this study was performed in patients with mild disease, but it required a minimum FENO level of greater than 40 ppb. Thus, it seems possible that GDC-0214 could be targeted more toward patients with higher T2 endotypes, although this needs to be explored further. A major weakness of the GDC-0214 study was that it examines a surrogate clinical end point, namely, FENO level, rather than disease symptom outcome. Further, given that the study focuses on a population with mild asthma, it would be helpful to know how GDC-0214

compares with standard-of-care therapeutic agents such as inhaled corticosteroids.

Traditionally, asthma has been considered a classic type 2 inflammatory disease. However, it is also well recognized that there is considerable heterogeneity in terms of pathophysiology. Indeed, new understanding of the immunologic pathways that regulate asthma suggests that different therapeutics may be more suited for different endotypes, phenotypes, and severities of asthma. Additionally, it is possible that the effects of these therapeutics may extend beyond their mere anti-inflammatory properties in relation to immune cells. For example, it is increasingly appreciated that both ST2 and JAK1 are also expressed by sensory neurons and may thereby influence disease outcomes.^{9,10} Whether these therapeutics exert their effects by modulating innervating neurons or other cell types to influence airway hyperactivity and inflammation is an active area of investigation. The studies highlighted herein demonstrate how emerging targeted therapeutics continue to unveil new frontiers of investigation into asthma biology.

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