Editorial

Do insights from mice imply that combined Th2 and Th17 therapies would benefit select severe asthma patients?

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Asthma is a multi-faceted syndrome, and understanding the key cellular and molecular participants is an important objective, so that clinicians can deliver targeted care. Most asthmatics can be effectively treated through the use of beta-agonists and corticosteroids. However, there remains a considerable percentage of individuals with an asthma diagnosis for whom these conventional therapeutic approaches are ineffective. These patients are considered to have severe disease (1), and severe asthma disproportionately accounts for the socioeconomic impacts of asthma. It has become an important objective for researchers to identify the contributors to severe asthma and to develop approaches to target these events. While allergic asthma is typically caused by an over-exuberant type-2 response (now appreciated to come from CD4 T helper cells and type-2 innate lymphoid cells), in which cytokines including IL-4, IL-5, and IL-13 drive IgE class switching, eosinophil development and survival, and mucus production, the asthma community has for some time appreciated the epidemiological connections between severe asthma and neutrophils. Elevated levels of sputum or bronchoalveolar lavage neutrophils correlate with more severe disease. Mechanistic insight into the cause of elevated airspace/airway neutrophils came from the findings that IL-17 (typically IL-17A and IL-17F) derived predominantly from $CD4^+$ T helper cells (Th17 cells; although type-3 innate lymphoid cells and other leukocytes are producers as well) is an important promotor of neutrophil production and influx in severe asthma. Mouse models of disease demonstrated that Th17 cells were sufficient to cause steroid-refractory disease, and other work demonstrated that Th17 cells were in some instances necessary for several pathophysiological manifestations in asthma models (2). However, the mechanistic contribution of IL-17 and even of neutrophils remains both controversial and contentious. Nonetheless, there are disorders in which IL-17 and neutrophils are important contributors to disease, and IL-17—neutralizing approaches have been developed and are being evaluated clinically. Whether neutralization of IL-17 in selected populations of severe asthmatics will be safe and elicit benefit remains to be fully elucidated, and animal models are an important stepping stone to such definitive clinical trials.

In the August 19th, 2015 issue of *Science Translational Medicine*, Choy and colleagues evaluated the interactions between Th2 and Th17 responses in asthma, with the objective being to assess the effects of neutralizing Th2 and Th17 responses in a mouse model of disease (3). As other groups have done (4,5), these authors exposed normal human bronchiolar epithelial cells to IL-13, IL-17A, TNF (a pro-inflammatory cytokine oftentimes elevated in asthma), or IL-17A + TNF, and identified distinct patterns

of gene expression, including the well-described genes *POSTN*, *CLCA1*, and *SERPINB2* expressed in response to IL-13, whereas the neutrophil growth and survival cytokines *IL8* and *CSF3*, as well as the neutrophil-recruiting CXC chemokines *CXCL1*, *CXCL2*, and *CXCL3*, were induced by IL-17A + TNF. Expression of these genes was then used to evaluate endobronchial biopsy specimens obtained from 51 asthmatic subjects, which allowed the authors to cluster the subjects into three groups: Th2-high, Th17-high, and Th2/Th17-low. Unexpectedly, blood and sputum eosinophils were elevated in both the Th2-high and Th17-high groups. In analyzing the subject phenotypes, the authors found that Th17-high asthma was only present in subjects who were moderate-to-severe, primarily those who were eosinophilic and taking inhaled corticosteroids or a combination of inhaled and oral corticosteroids. The Th17 response appeared to be more pronounced in subjects with more severe disease. These results raise the question, yet again, as to the contribution of the Th17 response in the setting of asthma. In an attempt to provide an answer, the authors turned to a mouse asthma model induced by priming, boosting, and challenging with intranasal house dust mite (HDM) extract and intraperitoneally administering isotype control or Th cytokine-neutralizing antibodies during the challenge phase. Blockade of Th2 cytokines (IL-4 or/and IL-13) decreased airway eosinophils and increased airway neutrophils, while also augmenting lung mRNA expression of *Il17a* and cytokines promoting neutrophil growth and recruitment. A reciprocal interaction between the Th2 and Th17 response suggested that corticosteroids, typically able to diminish Th2 responses, may also augment the Th17 response in the mouse HDM model. Indeed, while dexamethasone effectively reduced several allergic airway disease features, it also promoted increased numbers of neutrophils in the airways and lung expression of neutrophil-recruiting cytokines. However, the long-appreciated effect of corticosteroids to induce neutrophil mobilization (6-8), as well as to prevent their death by apoptosis (9), are as likely to account for these findings as is a switch to a Th17-dominated response. Subsequently, the authors again turned to the HDM model and this time neutralized IL-17A alone or in combination with neutralization of IL-13. While IL-13 neutralization itself profoundly diminished methacholine hyperresponsiveness and expression of mucus-associated genes, it also reduced airway eosinophils and increased neutrophils. Combined IL-17A and IL-13 neutralization yielded the most beneficial effects across the board, reducing AHR and mucus gene expression, while simultaneously preventing the spike in neutrophils that was observed when anti-IL-13 alone was administered. The authors went on to propose that optimal therapeutic benefit in asthma may be achieved through simultaneous Th2 and Th17 pathway-directed therapy, thereby avoiding the emergence of Th17-driven pathophysiologies.

The work of Choy *et al*. is complemented by a paper by Manni *et al*. that appeared earlier this year in the *Journal of Immunology* (10). Manni *et al*. used well-described mouse models of allergic asthma induced by the adoptive transfer of antigen-specific Th2- or Th17-polarized CD4 T cells. This approach had previously been used by the group to demonstrate the corticosteroid-insensitivity of the Th17 response (11). In their new work, the authors used a combination of adoptively-transferred Th2 and Th17 cells, and showed that the inflammation, mucus production, and methacholine responsiveness in these mice were largely unresponsive to dexamethasone. However, when they neutralized IL-13, IL-17A, or the two in combination, there was no impact on inflammation, whereas combined IL-13/IL-17 neutralization had the largest beneficial impact on central airway resistance (Rn), whereas IL-13 neutralization alone was more beneficial to tissue damping (G) and tissue resistance (H), both of which are indicative of events in the lung periphery. Nevertheless, neutralization of IL-13 alone was sufficient to decrease the accumulation of mucus and the expression of mucus-associated genes, without the emergence of neutrophilic airway inflammation. This latter observation contrasts with that of Choy *et al*. (3).

So, where does this leave us regarding the notion of Th2/Th17 counter-regulation in allergic asthma and the possibility that targeting both could elicit benefit in select patients? It seems the jury is still out. As we have described, differences in mouse asthma models may account for the apparent contribution of the Th17 response to pathology (2). Mouse asthma models are chosen based on their recapitulation of the human condition and the potential insight they can provide into mechanisms (12). No model is perfect, and only testing in the patient will reveal the true effects of modulating a specific pathway. Currently, select asthmatics with eosinophilic asthma are being treated with IL-5-neutralizing monoclonal antibodies (13), whereas IL-13 neutralization is still in an experimental stage. In one study, neutralization of IL-13 in severe asthmatics was reported to be of no benefit (14), whereas in another study with a different mAb there was benefit in those patients with a high-periostin Th2 signature (15), and in a third study

with yet another mAb in severe uncontrolled asthmatics there was again benefit (16). Dual neutralization of IL-4 and IL-13 effects using a monoclonal antibody targeting the IL-4 receptor alpha has shown benefit in persistent, moderate-to-severe asthmatics with elevated eosinophil levels (17), as well as when used as an add-on therapy in subjects with asthma that was poorly controlled despite combined medium-to-high dose inhaled corticosteroid and long-acting β-agonist therapy (18). In these papers targeting the Th2 pathologies in asthma, there was no mention of the emergence of a Th17 or neutrophilic phenotype. IL-17A neutralization has not yet been adopted for the treatment of select asthma patients, despite its presumed involvement in severe presentations of disease, especially in fungal allergy. However, in one clinical trial in which a neutralizing antibody targeting IL-17 receptor A (which mediates responsiveness to IL17A, IL-17F, and IL-17E, also known as IL-25) was evaluated in asthmatics, no benefit was reported (19). While mechanistic *in vitro* studies and animal asthma models support an important contribution of IL-17 to severe asthma (20), perhaps additional criteria will need to be used to identify a select patient population in which IL-17 targeting elicits improvement. Whether IL-17/IL-17R neutralization will provide benefit in combination with therapies targeting the Th2 response in asthmatic subjects awaits future clinical trials.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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