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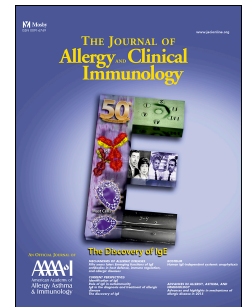
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Is IL-1 β inhibition the next therapeutic target in asthma?

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In this month's issue of the journal, there are two clinical studies that are related by the finding of neutrophils in the airway and the identification of increased airway concentrations of cytokines that are involved in the development of the CD4 Th17 phenotype.

In the first study by Weimin Liu and colleagues from National Jewish Health in Denver, the authors performed bronchoalveolar lavage (BAL) on 60 outpatients who had asthma and utilized flow cytometry with intracellular cytokine staining to identify three immune endotypes of asthma.⁽¹⁾ These were: 1) Th2-predominant asthma, 2) Th2/Th17-predominant asthma, and 3) Th2/Th17-low asthma. These groups were defined by the relative percentage of lymphocytes expressing IL-4 and/or IL-17 by intracellular flow cytometry compared to the total lymphocyte population in the BAL fluid. In a previous publication, this group reported that the subjects in the Th2/Th17 category had the most severe asthma as defined by significantly reduced FEV₁ and lower methacholine PC₂₀, while the subjects in the Th2/Th17-low category had the mildest asthma.⁽²⁾ In cells expressing both IL-4 and IL-17, there was co-expression of GATA3, the transcription factor that is the master regulator of Th2 cells, and ROR γ t, the transcription factor that is the master regulator of Th17 cells.⁽³⁾ In the article in this month's Journal, these authors then sought to determine the association of the BAL fluid levels of the cytokines that are known to polarize CD4⁺ cells toward Th17 development with the frequency of airway lymphocytes expressing IL-17. In addition, they explored associations of the Th2/Th17-predominant endotype with the inflammatory cell phenotype in the BAL fluid. They report that the BAL fluid from the Th2/Th17-predominant asthma category had elevated IL-1 β , IL-6, IL-23, C3a, and serum amyloid A. IL-1 β , IL-6, and IL-23 have been identified as important factors that drive Th17 polarization,⁽³⁾ so it is certainly possible that these cytokines might be responsible for the

Th17 phenotype. However, given that only one BAL was performed on each subject, it is not known whether these cytokines predate the development of the Th17 cell phenotype, so a cause and effect relationship is unknown. Liu and colleagues did performed in vitro studies in which they were able to inhibit the development of Th2/Th17 cells using the IL-1 β receptor antagonist anakinra. However, there are no clinical studies to date examining the use of this agent in asthma, but anakinra did reduce airway neutrophilia in a mouse model of asthma.⁽⁴⁾

Unfortunately, the subjects in the study by Liu and colleagues were not stratified based on severity of illness, nor was information provided about the smoking status or gender of the subjects, factors that also likely regulate CD4⁺ T cell differentiation. For instance, estrogen and progesterone decreased let-7f microRNA and increased IL-23/IL-23 receptor signaling and IL-17A production in patients with severe asthma,⁽⁵⁾ suggesting that female hormones enhance Th17 polarization. In addition, these investigators did not perform an analysis to determine the association of IL-4 or IL-13 on the development of dual Th2/Th17 cytokine producing T cells as both IL-4 and IL-13 inhibited Th17 development, in human T lymphocytes in vitro,⁽⁶⁾ as well as in mouse T cells in vitro and in vivo.⁽⁷⁻⁹⁾ These studies raise the possibility that pharmacologic agents that inhibit IL-4/IL-13 signaling, such as the IL-4 receptor antagonist dupilumab, might increase neutrophilia since the Th17 cytokines IL-17A and IL-17F lead to pulmonary neutrophil recruitment by inducing airway epithelial cell production of CXCL1 and CXCL8, chemokines highly chemotactic for neutrophils. However, results in this study by Liu and colleagues raises an alternative scenario where antagonism of Th2 cytokines directly causes an increase in epithelial cell production of CXCL8, independent of IL-17-mediated CXCL8 secretion. They found that the patient group that had the highest frequency of neutrophils in the BAL fluid was

not the Th2/Th17-predominant group, but instead the Th2/Th17-low group, the category of subjects that had the highest CXCL8 in BAL fluid. This result suggested that Th2 cytokines such as IL-4 and IL-13 might inhibit CXCL8 protein expression in the airway. To test this, the authors determined the effect of IL-4 and IL-13 on LPS-induced CXCL8 production in the immortalized human airway epithelial cell line, BEAS-2B, following LPS treatment. They found that both IL-4 and IL-13 significantly inhibited LPS-induced CXCL8 *in vitro* and also reported that there is a negative correlation between IL-4 and CXCL8 *in vivo*. In addition, G-CSF and GM-CSF, but not IL-17A, were elevated in Th2/Th17-low asthma, raising the possibility that these cytokines might also be inhibited by IL-4 or some other factor produced by Th2 cells. Early clinical studies blocking IL-4 and/or IL13 signaling have not yet been noted to result in a neutrophilic airway phenotype;⁽¹⁰⁾ however, the possibility that Th2 cytokines may be inhibiting neutrophil recruitment is plausible based on the studies described above and there needs to be vigilance that such phenotypes do not develop with the use of pharmacologic agents that antagonize the IL4/IL-13 production or signaling axis. While there is associative evidence that IL-17 might be involved in asthma pathogenesis, inhibition of IL-17 signaling using an IL-17 receptor antagonist did not improve asthma outcomes,⁽¹¹⁾ therefore, identifying a biomarker that identifies who might have Th17-driven asthma pathogenesis is critical to determine the patient population who would benefit from either a more potent IL-17 antagonist, or dual Th2/Th17 antagonism.

In the second study by Paula Busse and colleagues at Mount Sinai, inner city residents with asthma who were greater than 60 years old had significantly worse asthma control and lower pulmonary function compared to inner city subjects with asthma whose age was 21-40 years.⁽¹²⁾

The older group of asthma subjects had greater number and a 3-fold increase in the percentage of cells that were neutrophils (23% vs 7%) compared to the younger subjects. In addition, there was also a 3-fold increase in both the number and percentage of total cells that were eosinophils (3.8% vs 1.2%) in the older compared to the younger subjects. These authors did not measure CD4 cell subsets in the airway by intracellular cytokine staining as did Liu, but they report higher sputum levels of IL-6 and IL-8 in the older subjects, suggesting that these cytokines might be regulating airway inflammation. They also found that increased sputum concentrations of IL-6 and CCL20 were significantly associated with worsened asthma control in the older group of subjects. CCL20 is a chemokine produced by Th17 cells that binds to CCR6.⁽¹³⁾ CCR6 is expressed on dendritic cells, B cells, and Th17 cells; therefore, T cell production might be a positive feedback mechanism for the recruitment of more Th17 cells, thus propagating neutrophilic airway inflammation. Finally, they also reported that in older subjects that increased sputum levels of IL-1 β , IL-6, and CCL20 was associated with hospitalization. These results would suggest that inhibiting Th17 development with an antagonist of IL-1 β signaling might have therapeutic benefit, but clearly a clinical trial must be performed to gauge effectiveness since IL-6 inhibition so far has not been effective in asthma. Such a trial would also have to seriously assess the risk/benefit ratio for an IL-1 β antagonist in asthma, as it may be much narrower compared to the other conditions currently treated by this class of medications. As with all biologics, it will be important to carefully phenotype and select patients based on the best current knowledge of endotype development, as well as follow such patients after the initiation of specific biologic therapy to assess whether the endotype being targeted is actually being affected. Such studies as those reported by Liu and Busse in this issue are important to

determine the predominant inflammation in specific populations so that they can be considered for targeted biologic therapies.

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