Editorial

Neutrophilic Asthma

Asma neutrofílica

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The goal of systems or personalized medicine is to deliver the optimal drug to the right patient at the right time.[1,2] A prerequisite for this is the correct identification of asthma clinical phenotypes that possess mechanisms that can be targeted by specific drugs. Eosinophilic asthma is one such phenotype which is characterized by elevated levels of circulating eosinophils. These patients have an underlying type 2 T-helper cell (Th2) mechanism, are more responsive to treatment with inhaled corticosteroids (ICS) but conversely appear more susceptible to exacerbations.[1,2] The appreciation of the Th2-based driver mechanism of these patients has driven the use of biological therapies targeted Th2 cytokines. For example, anti-IL-5-directed drugs used to block eosinophil differentiation and activation are effective in patients with high blood eosinophils, severe and recurrent exacerbations already requiring high dose ICS and oral corticosteroids (OCS) [1,2]. Unfortunately, only 40-50% of asthmatics have this phenotype and there is a need to define non-Th2 asthma along with their associated driver mechanisms.

Neutrophilic asthma was first reported in bronchial biopsies [3] but is more often defined as patients with high (40-70%) sputum neutrophil counts. Sputum neutrophilia is linked to severe asthma, a relative lack of response to corticosteroid therapy and chronic airflow obstruction, [3] and is reported to occur in acute exacerbations[3]. A neutrophilic asthma phenotype may arise from the presence of enhanced levels of neutrophilic chemokines such as GROα, interleukin 8, CXCL10, and CCL2 which are all elevated in sputum of these patients.[3]

However, a number of clinical trials directed against neutrophil-associated mediators have not been successful in moderate to severe asthma. These studies include an antibody against TNFα (golimumab), an anti-IL-17 receptor antibody (brodalumab) and with a CXCR2 antagonist.[3] In the latter study, involving 640 patients with uncontrolled persistent asthma, treatment for 6 months with the CXCR2 antagonist AZD5069, that blocks the effects of interleukin 8, had no effect on the rate of severe exacerbations, asthma symptoms, or lung function compared with placebo despite significantly reducing mean blood neutrophil counts.[4]

A recent study, the AMAZES study, from Gibson and colleagues [5] examined the effect of 500 mg azithrpmycin or placebo on 420 adults with uncontrolled persistent asthma despite the use of ICS and long-acting bronchodilator therapy over 48 weeks. In this study, azithromycin reduced asthma exacerbations and significantly improved asthma-related quality of life irrespective of asthma phenotype. These results were in contrast to an earlier study (AZISAST) where evidence for a preferential effect of azithromycin on severe exacerbations and on the rate of lower respiratory tract infections in neutrophilic asthma was observed.[6] The AZiSAST study compared 250 mg azithromycin and placebo over 26 weeks in 109 subjects and also had different inclusion criteria and inflammatory granulocyte classifications which may account for the difference in outcomes. However, the results regarding lower respiratory tract infections in non-eosinophilic asthmatics were similar in the two studies.

These data on the beneficial effect of azithromycin in both eosinophilic and non-eosiniphilic severe asthma correspond to earlier data in murine models of severe steroid refractory allergic asthma whereby clarithromycin suppressed inflammation and airway hyperresponsiveness by distinct mechanisms (reducing Th2-driven eosinophilia and suppression of IL-17 and TNFα) depending upon the models used.[7]

This may suggest that that neutrophils *per se* are not driving a distinct asthma phenotype since raised levels of sputum neutrophils may also result from sub-clinical or clinical infection and environmental pollution.[8] Furthermore, long term high-dose ICS or OCS use may prevent neutrophil cell death resulting in an apparent neutrophilic disease. However, it is evident that blood and sputum neutrophil counts are only weakly correlated and poorly predictive of sputum neutrophilia.[8] Stratification of patients according to blood neutrophils is, therefore, less than optimal and a better marker of neutrophilic asthma is required. Poor patient stratification may result in the failure of many of these trials in neutrophilic asthma as a true airway neutrophilic phenotype was not selected. In addition, the complexity of the chemokine/chemokine receptor system [9] means that targeting a single neutrophil chemoattractant may not be sufficient to have a notable effect.

Analysis of sputum cell transcriptomics between severe and non-severe asthma highlighted the importance of inflammasome activation in neutrophilic asthmatics in the absence of overt

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infection [10]. Inhibition of inflammasome activation in a mouse model of severe asthma indicated cross-talk between eosinophilic and neutrophilic asthma. This was confirmed by Hansbro and colleagues who demonstrated that NLRP3 and IL-1β expression correlated with neutrophilic inflammation, disease severity and steroid resistance in asthma and these features could be induced by IL-1β overexpression in a mouse model of asthma.[11] In addition, IL-1β-induced steroid-resistant airway hyperresponsiveness was suppressed by neutrophil depletion.

Differential sputum cell transcriptomics has also implicated neutrophil-derived TCN1 and MMP9, mucins and oxidative stress response genes as being important in severe neutrophilic asthma.[12] A disease signature, closely associated with sputum T-cells, was defined which included IL-17-inducible chemokines (CXCL1, CXCL2, CXCL3, IL8, CSF3) and neutrophil chemoattractants (IL8, CCL3, LGALS3) which again highlighted the key role for bacterial infection via TLR2 activation in this asthma phenotype. These data are reinforced by the finding that the sputum microbiome in a small number of neutrophilic asthmatics was less diverse and more dissimilar compared with that observed in eosinophilic asthma and correlated with sputum neutrophil cell counts.[13] Neutrophilic asthma was associated with a relatively greater abundance of pathogenic taxa and a lower expression of Streptococcus, Gemella, and Porphyromonas taxa. The data suggests that differences in microbiota composition might influence neutrophilic asthma and impact upon antimicrobial and steroid responses.

It is evident that current biomarkers of neutrophilic asthma are not suitable for use in clinical trials and the discovery of good biomarkers is essential. Sputum colour has been proposed as a biomarker to identify patients with neutrophilic asthma.[14] Although significant, the sensitivity and specificity are below 80% and still requires the production of sputum which is an issue with many subjects with severe asthma. More importantly, Alam and colleagues found 52 biomolecules in BAL fluid that differentiated refractory asthma (RA) from non-RA subjects.[15] 13 out of these 52 molecules correlated with BAL neutrophilia and, in addition, five serum inflammatory analytes (growth and differentiation factor 15 (GDF-15), human epididymis protein 4, MMP7, tetranectin, and von Willebrand factor) were associated with infection-negative neutrophilic RA. These results are exciting and need to be confirmed. Blood biomarkers and non-invasive measures such as exhaled volatile organic compounds (VOCs) should also be investigated.

In addition, it will be important to distinguish the presence of neutrophils with distinct functional phenotypes and immunomodulatory functions.[3] Despite this, the mechanisms underlying neutrophilic asthma as demonstrated above are becoming clear and include delayed neutrophil apoptosis, impaired macrophage phagocytosis, activation of the inflammasome pathway, alterations in the airway microbiome and distinct neutrophil subtypes.[1,3] Systems medicine, which extends beyond a simple omics analysis, combining deep clinical phenotyping is expected to define the many inflammatory pathways that underlie neutrophilic asthma.[1,3] The present challenge is to develop the means to easily identify these sub-phenotypes of neutrophilic asthma in order to stratify patients and enhance the chances of success in clinical trials using anti-neutrophil therapies.

Conflicts of Interests

There are no conflicts of interest.

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