

The laws of attraction: chemokines, neutrophils and eosinophils in severe exacerbations of asthma

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A possible new therapeutic strategy for preventing exacerbations

Asthma is an extremely common illness which affects an estimated 300 million people of all ages and ethnic backgrounds worldwide with significant costs for healthcare systems.¹ The clinical course of the disease is characterised by acute episodes of worsening of symptoms and decrease in lung function known as exacerbations. Prevention of exacerbations has been the goal of most therapeutic interventions developed so far because exacerbations seriously affect the quality of life of patients and their families.² The clinical presentation of asthma exacerbations may be extremely heterogeneous; they can be rapid in onset or occur more gradually. The severity of asthma exacerbations is also extremely variable, ranging from mild episodes to severe attacks which result in respiratory failure and may ultimately lead to death.

Airway inflammation is a characteristic feature consistently present in patients with asthma from the early stages in children³ to elderly people.⁴ The inflammatory process has been extensively investigated in stable conditions, showing an increased infiltration of eosinophils, mast cells and CD4 T lymphocytes characterised by a Th2 profile, with release of cytokines such as interleukin (IL)-4, IL-5, IL-13, eotaxin and RANTES.⁵ Conversely, little is known about the cellular mechanisms activated during exacerbations and, in particular, in severe exacerbations.

In this issue of *Thorax* (see p 475), Qiu *et al*⁶ investigated the inflammatory response in bronchial biopsy specimens taken from patients admitted to hospital with a severe exacerbation of asthma and who required intubation for respiratory failure. They found that, during severe exacerbations, there was an increase in eosinophils and an even greater increase in neutrophils, resulting in similar final numbers of the two granulocyte subtypes infiltrating the airways. These results confirm previous observations on sputum⁷ and bronchoalveolar lavage fluid in acute severe asthma.⁸ A unique quality of the study by Qiu *et al* is that, unlike the other

studies, it examined bronchial biopsy specimens obtained during exacerbations. This provides direct information on the airway tissue where inflammatory responses take place and interact with smooth muscle and mucus-secreting cells, thus contributing to airway narrowing.

Tissue inflammation in severe exacerbations of asthma has been evaluated previously, but only at post mortem examination. The pathological abnormalities observed in the airways of subjects who suffered a fatal asthma attack included both eosinophil and neutrophil infiltration.⁹ In particular, neutrophils predominated in those patients who died suddenly after onset of the attack, while eosinophils were more frequent in fatal events with a slow onset.^{10 11} It has been proposed that these differences in the inflammatory profile may reflect the dynamics of inflammatory cell recruitment in the airways, with the neutrophil being the predominant cell in the early phase following an inflammatory stimulus and the eosinophil being the predominant cell in the late phase.¹¹ However, it was unclear whether these observations truly reflected the cellular mechanisms underlying the severe exacerbation or were rather due to death-related events. The study by Qiu *et al* sheds some light on this issue by confirming that infiltration of neutrophils and eosinophils are indeed characteristic features of severe exacerbations of asthma.

Interestingly, in a previous paper the same authors reported that both granulocyte subtypes were increased even in severe exacerbations of chronic obstructive pulmonary disease (COPD).¹² Moreover, they showed that airway neutrophilia in COPD was driven by upregulation of the chemoattractants CXCL5 (ENA-78) and CXCL8 (IL-8) and of their type I receptor (CXCR1). When they tested the hypothesis that these chemoattractants may also be crucial in exacerbations of asthma, they found that only CXCL5 was significantly upregulated during exacerbations compared with stable

asthma. While CXCL8 binds to both CXCR1 and CXCR2, CXCL5 binds preferentially to CXCR2¹³ and, indeed, the increased expression of CXCL5 was paralleled by upregulation of CXCR2 in this study. These observations suggest that activation of the CXCL5/CXCR2 axis is a crucial event in the pathogenesis of asthma exacerbations and identifies a new potential target for anti-inflammatory strategies.

One of the most intriguing findings in this study is that, at variance with COPD, in exacerbations of asthma CXCL5 and CXCR2 were correlated with the number of eosinophils infiltrating the airways rather than with neutrophils. Of interest, human eosinophils may produce CXCL5 *in vitro*, an effect that is particularly evident after prolonged incubation with tumour necrosis factor α (TNF α).¹⁴ Since there is evidence that TNF α is increased in severe asthma,^{15 16} and especially in status asthmaticus,¹⁷ it can be hypothesised that even *in vivo* TNF α may induce CXCL5 upregulation by eosinophils. This in turn would drive activation of CXCR2-bearing cells such as neutrophils, thus promoting their recruitment at sites of inflammation. In this context, there is promising evidence that therapeutic strategies aimed at interfering with TNF α signalling may be beneficial in patients with refractory asthma,^{15 16} especially by reducing exacerbations,¹⁸ although this requires confirmation in larger controlled studies.¹⁹

We should be careful in interpreting the findings of Qiu *et al* for several reasons. First, patients with an exacerbation received corticosteroids intravenously as part of the exacerbation management and most of them had been treated with inhaled or oral corticosteroids before the exacerbations. Moreover, the subjects examined were not well matched with regard to age, since patients with an exacerbation were older than those with stable asthma and were mechanically ventilated before biopsy sampling. All these factors could have potentially enhanced airway neutrophilia.^{20 21}

More importantly, this is a cross-sectional rather than a longitudinal study, so the possibility that neutrophilia was already present in those subjects before occurrence of severe exacerbations cannot be ruled out. Indeed, most of the patients with an asthma exacerbation had severe disease treated with high doses of inhaled or oral corticosteroids, while patients with stable asthma had mild disease controlled only with β_2 -agonists on an as needed basis. This difference in the degree of severity may have influenced the inflammatory cell profile in the patients with stable asthma since there

is evidence that tissue neutrophilia is more frequent in severe asthma.²²

Despite these unavoidable limitations, the report by Qiu *et al* is important because it promotes a better understanding of the events contributing to the development of severe exacerbations. Indeed, this study provides the framework for the cellular changes occurring in the airway tissue and the molecular mechanisms responsible for inflammatory cell recruitment. As a consequence, these observations will encourage new research into therapeutic strategies to prevent exacerbations, one of the most important aims of asthma management.

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Dietary supplements and asthma

Dietary supplements and asthma: another one bites the dust

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No effect of selenium supplementation on symptoms of asthma

Throughout history, clinical observation and clinical trials have identified links between nutritional deficiency and disease. For example, scurvy was described by Hippocrates over 2000 years ago, and native cultures have known its cause and cure for centuries. The first intervention study to demonstrate the successful treatment of scurvy with citrus fruits was published in 1753 by Captain James Lind in “*A Treatise of the Scurvy*”. Moving forward to the 20th century, one of the resounding achievements in this field has been identification of the importance of folic acid supplements in the prevention of spina bifida, leading to an overall reduction in incidence in the

Western world. The possibility that nutritional factors may play a similarly important role in the aetiology of chronic respiratory disease is therefore intriguing and has recently attracted a great deal of interest.

The aetiology of asthma remains unclear, but it is widely accepted that environmental factors play a major role and, of these, diet is a potentially important contender. Evidence for this arises from the observations that the prevalence of asthma increases as societies move from a rural subsistence towards a more Western lifestyle; this is associated, among other factors, with a change in dietary pattern including adoption of a

more processed and “convenience-orientated” diet. The result of this dietary change is an overall increase in the intake of refined sugars, fats and additives, and a relative reduction in the intake of complex carbohydrates and micronutrients. This change is a relatively modern phenomenon, occurring in the UK since the end of wartime rationing and also resulting from increased industrialisation of the food supply chain.

There is now an extensive literature on the relationship between diet and respiratory disease.^{1–3} In asthma, observational studies have shown encouraging evidence of a protective effect of several nutrients on disease prevalence and symptoms, including vitamin C,^{4–5} vitamin E,⁶ selenium⁷ and magnesium.⁸ However, and disappointingly in view of early promise with vitamin C,⁹ these findings have not generally translated into consistently positive outcomes in intervention studies. For example, in a recent randomised placebo-controlled trial of vitamin C, magnesium or placebo in 300 patients, we found no effect of either supplement on clinical asthma control.¹⁰ Similarly, an intervention study of vitamin E in adults with asthma also showed no evidence of a benefit.¹¹ While fish oil supplements have been