Neutrophils and asthma

Is the neutrophil the key effector cell in severe asthma?

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The importance of the neutrophil as the dominant inflammatory cell in many of the non-atopic and more severe phenotypes of asthma is now clear

Eosinophilic inflammation has long been considered one of the most distinctive pathological hallmarks of asthma[1] and features in many contemporary definitions of this disease. A plethora of studies published from the mid 1990s onwards have suggested, however, that airway eosinophilia is not a universal finding. This has fuelled debate that discrete pathological phenotypes of asthma may exist, with the neutrophil—rather than the eosinophil—dominating in certain circumstances.[2–4] We present data that support the current renewed interest in the neutrophil as a primary driver of airways inflammation, particularly in the most severe forms of asthma. There are also some intriguing data to suggest that, when the eosinophil has been ''red carded'' and disappears from the inflamed airway, the neutrophil may be drawn in and act as the substitute granulocyte.

The hypothesis that the eosinophil is the key effector cell involved in the pathogenesis of asthma has run into trouble for several reasons: (1) eosinophilic inflammation is present in the airway lumen of only 50% of asthmatic subjects;[4] (2) even intense eosinophilic inflammation, as occurs in eosinophilic bronchitis, fails to induce asthma;[5] (3) many asthma exacerbations occur in the absence of airway eosinophilia; (4) specific anti-eosinophil strategies—for example, anti-IL-5 and IL-12—are poorly efficacious in vivo;[6–8] and (5) eosinophilic deficient mice have now been engineered and this modification has little impact on the airway pathology induced in response to ovalbumin sensitisation.[9]

A strong association has now been established between neutrophilic inflammation of the airways and severe asthma,[10–12] corticosteroid resistant asthma,[13–15] asthma exacerbations,[2] nocturnal asthma,[16] ''asthma in smokers'',[17] occupational asthma,[18] and ''sudden onset'' fatal asthma.[19] It is noteworthy that, in the study by Little and colleagues[12] conducted in a group of 59 asthmatics, forced expiratory volume in 1 second (FEV_1) was inversely proportional to neutrophil numbers. These studies analysed neutrophil numbers in all airway compartments including the small airways and, where measured, neutrophil numbers correlated well with markers of neutrophil degranulation which implies that these cells are also activated.[10 12 15 20–22] These findings are of particular importance given the disproportionate health costs associated with treating patients with severe disease.[23]

These data set up a number of critical questions—namely:

- What are the principal drivers of neutrophil influx into asthmatic airways?
- Can any of the existing asthma treatments be implicated in airway neutrophilia?
- How do we quantify neutrophil trafficking in this disease?
- What are the most promising therapeutic options to inhibit this process?

It is now widely argued that certain physical triggers including viruses, lipopolysaccharides, and ozone may be more important inducers of airway neutrophilia than any primary immunological cause,[21 24] and epithelial derived IL-8 again stands out as one of the most likely chemoattractants for neutrophils.[25] While in severe disease eosinophils and neutrophils are usually found together,[13] cross sectional studies suggest that neutrophils may gradually replace eosinophils in proportion to the severity and/or duration of the disease.[10] This view is supported by the study of Hauber and co-workers[26] who took bronchial wall and transbronchial biopsy specimens from a group of 12 asthmatics before and after treatment with HFA-flunisolide. They found a dramatic fall in the number of IL-5 and eotaxin mRNA positive cells and eosinophils in both the central and peripheral airways and a corresponding and equally marked rise in the number of neutrophils at these sites. A similar effect has been reported elsewhere[27 28] and may reflect the widely cited capacity of corticosteroids to induce eosinophil apoptosis and phagocytic removal and yet inhibit the same process in neutrophils.[29–31] The possibility that the airway neutrophilia develops as a primary pathological response and hence represents a distinct inflammatory phenotype is supported by studies which show that this subgroup of patients is non-atopic and has an impaired response to inhaled corticosteroids.[14 15]

One intriguing insight into the potential high state of flux of neutrophils in the airway wall is provided by the study of Martin *et al*[16] who performed bronchial lavage in patients with nocturnal asthma and found a greater than threefold increase in the number of granulocytes in bronchoalveolar lavage (BAL) fluid samples at 04.00 hours compared with 16.00 hours. This suggests a high rate of turnover of these cells and implies that neutrophils may have a surprisingly short half life (<8 hours) in asthmatic airways. The plasticity of the airway neutrophilia is further supported by experimental data obtained using an equine model of asthma where complete resolution of the neutrophilic airway response occurred over a matter of a few days following removal of the mouldy hay challenge.[32] In this model the alveolar macrophages appeared to make a significant contribution to the clearance of apoptotic neutrophil corpses from within the airway lumen. Thus, if neutrophils do not reside within the asthmatic airways for protracted periods due to the presence of efficient natural clearance mechanisms, strategies designed to block influx—which presumably occurs at the post capillary venule level within the bronchial circulation—may be highly efficacious. Recent studies have revealed the pivotal role of the enzyme phosphoinositide 3-kinase in controlling neutrophil migration, activation and survival,[33 34] and the discovery of neutrophil specific isoforms makes selective therapeutic targeting with conventional small molecular weight inhibitors a realistic prospect. Certainly, the introduction of a Δp85 phosphoinositide 3-kinase construct delivered using an HIV-TAT based protein delivery system in mice has a dramatic protective effect on ovalbumin induced airways inflammation.[35]

Thus, while the role of the eosinophil in mediating airways inflammation in mild and moderate atopic asthma appears secure,[36 37] the importance of the neutrophil as perhaps the dominant inflammatory cell in many of the non-atopic and more severe phenotypes of

asthma is now equally clear. Corticosteroids are highly effective in promoting the resolution of eosinophilic inflammation but far less so in neutrophilic inflammation and, indeed, may even facilitate the arrival and survival of these cells in the airway wall.

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