Live and let die: is neutrophil apoptosis defective in severe asthma?

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Patients with severe asthma make up a relatively small proportion of the total population of patients with asthma yet account for a disproportional amount of asthma-related morbidity and healthcare utilisation. These patients are usually highly symptomatic, difficult to treat and can be extremely refractory to current treatments. As a consequence, understanding the mechanisms underlying this particular form of asthma is of paramount importance.

Morphological examination of the asthmatic airway reveals epithelial desquamation, thickening of the reticular basement membrane, mucus gland hyperplasia, goblet cell differentiation, angiogenesis and smooth muscle hypertrophy. In addition to these structural changes, an inflammatory cell infiltrate is evident within the airways comprising eosinophils, mast cells, lymphocytes and neutrophils. While eosinophils are the most characteristic inflammatory cell type present in mild to moderate asthma, the neutrophil seems to take centre stage more often in patients with severe disease. In fact, the neutrophil is one of the most characteristic inflammatory cell type present in severe asthma, the neutrophil seems to take centre stage more often in patients with severe asthma.
inbuilt time-dependent) apoptosis when studied in vitro,1 one major puzzle in airways research has been to determine how and why neutrophils persist in such large numbers in the asthmatic airway. It is also uncertain why some patients with severe asthma have an inflammatory response dominated by neutrophils while others have an eosinophil-dominated pattern of disease. Explanations include genetic and epigenetic diversity, unrecognised environmental effects such as occult genetic and epigenetic diversity, unrecognized occupational exposures or viral infection, and inherited or acquired differences in responses to treatment, in particular sensitivity to glucocorticosteroids. Intriguingly, human biopay studies support the concept that inhaled corticosteroids, while highly effective in reducing eosinophilic inflammation in the airways, may be associated with exposure to systemic priming agents that influence the size, shape, deformability and hence pulmonary transit time of this cell. In contrast, granulocytes arriving in the airway wall exit via the bronchial circula-

tion at a post-capillary level and migrate via a classic ‘rolling-tethering’ paradigm involving (1) P-selectin glycoprotein ligand-1, E-selectin ligand-1 and L-selectin mediated rolling; (2) chemokine-mediated cell activation; and (3) β2-integrin-dependent adhesion and diapedesis where granulocytes move into tissues.16 As noted, a significant proportion of neutrophils cross the endothelial barrier by endocytosis, an active RhoG-dependent engulfment process, prior to negotiating the pericyte sheath and passing through ‘pre-perfo-
rated’ regions of the basement membrane.17 The migration of neutrophils into the airway wall may facilitate the subsequent ingress of eosinophils.18 Once recruited into the airway, the neutrophil is left with a limited number of options which include transepithelial migration into the airway lumen, a process which some authors have suggested may represent a regulated and active disposal route for airway granulocytes19; migration back into the circulation (either directly or indirectly via lymphatics); trans-
differentiation into macrophage cells20; cell death; or sustained residence. Neutrophil apoptosis (in contrast to necrosis) results in recognition and engulfment by macro-
phages, which is rapid and in itself promotes the resolution of inflammation and the restoration of normal tissue archi-
tecture.21 The removal of neutrophils in this way serves to prevent the release of cytotoxic contents and thus protect host tissues. The precise timing and magnitude of neutrophil apoptosis in the asthmatic airway has been difficult to determine in vivo but offers a plausible exit strategy for these cells and one that has been observed in a number of other conditions charac-
terised by airway neutrophilia. Consequently, factors that prolong the neutrophil lifespan by blocking apoptosis or impairing the clearance of apoptotic cells may be detrimental to this process and contribute towards the intense neutrophilic inflam-
mation observed. Indeed, in the case of the eosinophil, it has been extremely difficult to identify any evidence of apoptosis within the microenvironment of the airway wall, despite the fact that these cells undergo apoptosis readily once they escape into the airway lumen.22

Unsurprisingly, neutrophil apoptosis turns out to be a highly regulated process. Recognised ‘survival factors’ include lipopolysaccharide, granulocyte-macro-
phage colony-stimulating factor, type I and II interferons, survivin and, rather surprisingly, hypoxia and glucocorticosteroids.23–26 With regard to the signalling pathways implicated in neutrophil survival, the PI3-kinase/AKT, NF-κB, HIF-1α and Mcl-1 pathways all seem to play substantial and context-
specific roles (see Cowburn et al27). Any or all of these mediators may contribute to an ‘apoptosis-resistant’ granulocyte pheno-
type which, if operational in the airway wall of patients with asthma, might severely impede neutrophil clearance.

The presence of eosinophil- or neutro-

phil-specific survival factors within the airways of such patients has been much debated but little explored. In this issue of Thorax, Uddin and colleagues confirm, using induced sputum, that a proportion of patients with severe atopic asthma have predominantly neutrophilic rather than eosinophilic inflammation (see page 684).27 Moreover, far fewer apoptotic neutrophils were evident in the former group, inferring a survival advantage for neutrophils in this cohort of patients. They were also able to show that the sputum sol phase recovered from the neutrophil-dominated patient group delayed apoptosis of naive blood-derived neutrophils. Unfortunately, experiments using a series of blocking antibodies and a panel of ‘best guess’ pharmacological inhibitors were unable to characterise the survival factor(s) further. Such clinical studies are challenging at the best of times, and the group deserves considerable credit for generating this data set. There are inevitable caveats including the intersubject variability in the number of apoptotic airway neutrophils observed, the use of induced sputum which provides only an indirect readout of the cellular microenvironment within the airway, the lack of biopsy data to examine the tissue rather than luminal compartment, and the very low numbers of apoptotic cells present at any one time (<4% in this study). Critically, this study—in common with other reports—offers no insight into the true kinetics of neutrophil and eosinophil trafficking, nor any quantification of neutrophil clearance. It is possible, for instance, that the elevated level of neutrophil apoptosis seen in the severe ‘neutrophilic’ group reflects a failure of apoptotic cell recognition and removal (efferocytosis) rather than a true defect in apoptosis onset, as has been reported in the context of cystic fibrosis. The study is important, however, as it lends support to the view that neutrophil apoptosis and/or clearance may be defective in patients with asthma and shows that survival factors exist in the airway lining fluid which are specifically enriched in the
context of severe asthma. Identifying the neutrophil survival factor(s) present in this patient group is clearly an important next step and, if targetable, may form the basis of a new therapeutic approach for this difficult-to-treat patient group. While this study provides further evidence that neutrophil apoptosis may be deregulated in severe asthma, a number of key questions remain. We need to understand the dynamics of cell migration into and out of the airway wall and determine the true residency times and the relative contribution of apoptosis and, indeed, other non-apoptotic death mechanisms such as autophagy, NETosis and cytolysis in granulocyte clearance. We also need to understand the signals that block apoptosis in the airway wall (yet seemingly not in the airway lumen) and to determine what drives the switch from eosinophil- to neutrophil-dominated inflammation. Drugs which target the removal rather than the arrival of granulocytes in tissues are now emerging, and such agents may offer an important adjunct to current asthma treatments.

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REFERENCES


British Thoracic Society Pleural Disease Guidelines - 2010 update

Nick Maskell, on behalf of the British Thoracic Society Pleural Disease Guideline Group

INTRODUCTION

Pleural disease remains common, affecting over 3000 people per million population each year. It therefore presents a significant contribution to the workload of respiratory physicians. These guidelines attempt to summarise the available evidence to aid the healthcare professional in delivering good quality patient care.

AIMS AND OBJECTIVES OF THE GUIDELINE

Since the last BTS pleural disease guidelines were published in 2003 a large number of good quality primary research papers have been published and the guidelines need to reflect this new data. In addition, there was a need to develop new sections on local anaesthetic (LA) thoracoscopy and thoracic ultrasound to reflect changes in clinical practice.