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Primary lysis of eosinophils as a major mode of activation of eosinophils in human diseased tissues

Carl Persson and Lena Uller

The current focus on eosinophils coincides with a resurgence of interest in the role of the eosinophil in human disease, especially bronchial asthma. In a timely Review (Eosinophils: changing perspectives in health and disease. *Nature Rev. Immunol.* **13**, 9–22 (2013))[1], Rosenberg and colleagues comprehensively update the biology of viable eosinophils. However, they discuss little regarding the modes of eosinophil death. Eosinophil lysis is mentioned only briefly as a mechanism of granule release, with the authors concentrating instead on 'piecemeal degranulation'.

Recent work, including data from electron microscopy analyses[2,3], suggests that primary eosinophil lysis is a regulated mechanism that is distinct from apoptosis, secondary necrosis, accidental necrosis and crush artefacts[2,3]. It involves chromatolysis and rupture of the cell membrane, causing the release of protein-laden free eosinophil granules[2,3]. Free eosinophil granules that release cationic proteins that are toxic to the epithelium are abundant in bronchial biopsy and sputum samples from patients with asthma[4–8]. Eosinophil lysis also results in the release of cytokines, DNA, damage-associated molecular patterns and lipid mediators[3]. The free eosinophil granules that retain their membrane integrity might have immune functions in the extracellular environment[3].

We draw particular attention to the potential roles of eosinophil lysis in severe asthma. Muniz-Junqueira *et al.*[8] placed whole-blood samples, obtained from healthy and asthmatic children, on glass slides, incubated them for 45 minutes and examined the morphology of eosinophils adhering to the glass. They demonstrated a striking occurrence of eosinophil lysis and release of free eosinophil granules in samples obtained from children with acute asthma, which clearly distinguished this group from children with mild asthma, who, in turn, were clearly distinguished from healthy children. Furthermore, three different levels of severity of acute asthma were distinguished by the propensity of blood eosinophils to undergo lysis and release granules; the level of lysis and granule release increased concurrently with the severity of asthma[9]. These observations suggest that even before their arrival in the bronchial wall, eosinophils in severe asthma have already been primed to readily undergo cytolysis. In addition, it has now been demonstrated that stimuli that are reported to induce eosinophil apoptosis, such as the engagement of eosinophil-expressed sialic acid-binding immunoglobulin-like lectin 8 (SIGLEC8)[1], induce primary lysis of primed human eosinophils[10]. This proclivity of eosinophils to undergo primary lysis might explain why apoptotic eosinophils have not been compellingly demonstrated in human diseased tissues *in vivo*[2]. By contrast, most eosinophils in severe asthma[4–8] and more than 80% of tissue eosinophils in patients with eosinophilic oesophagitis might have undergone primary lysis (G. Gleich, unpublished observations).

The presence of lytic eosinophils and free eosinophil granules that are releasing cytotoxic proteins is positively correlated with increased epithelial cell loss and disease severity in asthma[4–7]. Hence, clinical data suggest that primary lysis of eosinophils is involved in the injury and repair of the airway epithelium that occurs in severe asthma. Furthermore, free eosinophil granules that are releasing cytotoxic proteins persist in diseased tissues in patients with asthma, along with clinical disease, despite the treatment of patients with drugs that are known to deplete eosinophils, such as inhaled glucocorticoids and interleukin-5-specific biologicals[4–8]. If anything, this should encourage researchers to further explore the biology and the pharmacology of primary eosinophil lysis.

We agree that eosinophil lysis does not occur in current mouse models of asthma[1]. However, mouse eosinophils *in vivo* can undergo primary lysis[11]. It would be desirable for future mouse models of asthma to recapitulate eosinophil lysis, as well as the pathological injury and repair of the epithelium that is seen in human disease. The availability of such models should improve our understanding of the immunology of severe desquamative asthma, for which medical need is unmet.

Carl Persson is at the Department of Clinical Pharmacology, Laboratory Medicine, University Hospital of Lund, S-22185 Lund, Sweden.

Lena Uller is at the Department of Experimental Medical Science, Unit of Respiratory Immunopharmacology, BMC D12, Lund University, 22184 Lund, Sweden.

e-mails: carl.persson@med.lu.se; lena.uller@med.lu.se

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Competing interests statement
The authors declare no competing financial interests.