Primary lysis/necrosis of eosinophils and clinical control of asthma

I read with interest the demonstration by Volbeda *et al*¹ that clinical asthma control associates significantly with 'lower activated eosinophil numbers in the bronchial wall, yet only weakly with sputum eosinophils'. I was particularly intrigued by the online supplemental information¹: 'EPX staining showed widely spread distribution of eosinophilic granules, not necessarily in close proximity to EPX+ cells. Therefore, degranulation of eosinophils was determined by quantification of the EPX immunopositive area by computer-assisted image analysis'. This statement suggests to me that the wall eosinophils had largely been activated by lysis of eosinophils that deposits protein-laden eosinophil granules extracellularly in the diseased tissue.²

For a centennium, the occurrence of free eosinophil granules in airway tissues and sputum samples were either ignored or considered an artefact caused by sample handling.³ However, wholemount tissue preparation combined with deep tissue staining of eosinophil proteins clearly demonstrated that free eosinophil granules were a real *in vivo* phenomenon.² Transmission electron microscopy further demonstrated that the granules emanated from eosinophils exhibiting evident lysis/necrosis (chromatolysis, cell membrane rupture, etc). Importantly, the lysis of eosinophils was not preceded by apoptosis, and it happened to eosinophils with little prior piecemeal degranulation.² Intense staining in human diseased airways tissue indicated significant release of toxic eosinophil proteins from the free granules,^{2,3} a process now being explored *in vitro*.⁴ Numbers of free eosinophil granules in the airway wall have also correlated positively with disease activity in asthma and rhinitis.^{2,3} These data, together with the current report,¹ support the notion that eosinophil lysis releasing granules (plus many biologically active nuclear/cytosolic molecules!), may have a causative role in eosinophilic airways diseases.

Transepithelial migration of eosinophils (rather than apoptosis/phagocytosis mechanisms) will eliminate these cells from the diseased bronchial wall. Hence, cell numbers in the lumen may not mirror cell numbers in the wall during important phases of bronchial mucosal inflammation.⁵ In agreement, Volbeda *et al*¹ found that activated eosinophils in bronchial biopsies better than eosinophil numbers in sputum reflect the level of disease control. It would be of interest to learn about location of the free granules; for instance, any association with epithelial fragility in uncontrolled asthma¹? The possibility that ongoing lysis of eosinophils is important for lack of asthma control¹ underscores the need to unravel mechanisms involved in lysis of eosinophils and discover their pharmacological regulation.

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Funding None.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Persson C. *Thorax* 2013;**68**:295.

Received 1 November 2012

Accepted 22 November 2012

Published Online First 15 December 2012

► <http://dx.doi.org/10.1136/thoraxjnl-2012-203023>

Thorax 2013;**68**:295.

doi:10.1136/thoraxjnl-2012-202955

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