

Correspondence

Lysis of primed eosinophils in severe asthma

To the Editor:

I read with interest the report by Kano et al¹ on necrotic/lytic death of eosinophils costimulated by IL-5 and sialic acid-binding immunoglobulin-like lectin (Siglec)-8. This work unravels molecular subroutines potentially involved in primary eosinophil necrosis/lysis in diseased tissues. Thus, the work by Kano et al¹ should spark interest in pathogenic potential and pharmacologic control of eosinophil lysis. Severe asthma is an important area for this research.

Kano et al¹ demonstrated that eosinophils, primed by exposure to IL-5, respond to Siglec-8 by necrosis/lysis involving loss of plasma membrane integrity and free extracellular granules (FEGs). In contrast, unprimed eosinophils are made apoptotic by Siglec-8. Muniz-Junqueira et al² reported that propensity of blood eosinophils to lyse and release FEGs increased with increasing severity of asthma in children; proclivity of blood eosinophils to lyse further distinguished 3 levels of severity in children with acute exacerbations. Priming of blood eosinophils may thus be an important biomarker. Together with the observations by Kano et al,¹ early priming of eosinophils² may explain in part the rarity of apoptotic eosinophils in diseased respiratory tissues.³ Flood-Page et al⁴ observed that anti-IL-5 treatment in asthma inhibited blood and sputum eosinophils but apparently did not reduce bronchial tissue levels of cationic protein-releasing FEGs. Hence, other priming factors besides IL-5 studied by Kano et al¹ likely operate in severe asthma.

FEGs were once considered a crush artifact. However, lytic eosinophils and FEGs were demonstrated by brightfield microscopy in wholemount preparations of allergen-challenged airway tissue. Furthermore, it was clear that eosinophil lysis *in vivo* was a primary event without prior signs of apoptosis or piecemeal release of granule proteins (reviewed in Erjefält and Persson³). Lysis was rapidly induced, and the number of FEGs correlated with the extent of allergen-induced epithelial denudation ($r = 0.9$). Eosinophil lysis is induced in human cultured eosinophils bound to sephadex beads and exposed to immunoglobulins,^{3,5,6} plasma,³ and cytokine-mediator soup.⁶ Adhesion through integrins is important,⁵ with lysis being prevented by anti-CD18 antibodies.³ Ueki et al⁶ and Kano et al¹ demonstrate a major role of reactive oxygen species in the lysis process. Further discoveries are awaited now that primary lysis is both an *in vivo* and *in vitro* paradigm of ultimate eosinophil activation.

Lethal asthma has been characterized by severely deranged epithelium associated with numerous cationic protein-releasing FEGs; transmission electron microscopy unravels common occurrence of lytic eosinophils and FEGs in severe asthma despite long-term steroid treatment (reviewed in Erjefält and Persson³). Fattahi et al⁷ now demonstrate that protein-releasing bronchial wall FEGs are significantly correlated with lack of clinical control of asthma and with lack of epithelium. Cationic proteins released from FEGs cause epithelial shedding, contributing to the exaggerated epithelial cell loss in severe asthma. Inferentially, eosinophil lysis would cause exaggerated epithelial repair, which, in turn, causes inflammation and remodeling.³ The need for novel treatments of severe asthma underscores the possibility that the work by Kano et al¹ "might provide therapeutic targets that will be specific to harmful eosinophil functions, leaving innocuous and homeostatic eosinophil functions intact."

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Editor's note: There is no accompanying reply to this correspondence.

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