Mucosal IgA Is an Important Moderator of Eosinophil Responses to Tissue-Derived Chemoattractants

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The eosinophil is the principal inflammatory cell mediating bronchial tissue damage in asthma [1,2]. A number of potent eosinophil chemoattractants have been described [3], although their role in eosinophil recruitment to inflammatory sites in vivo is not known. Recent evidence suggests that interleukin-8 (IL-8), a well characterised neutrophil chemoattractant and activator, is also a potent eosinophil chemoattractant [reviewed in ref 4]. The abundant IL-8 revealed by immunocytochemistry in normal bronchial epithelium is increased in asthma [5], and we have measured increased IL-8 in the circulation of severe asthmatics [unpublished data]. IL-8 levels in response to an inflammatory stimulus are distinctly compartmentalised [6] and we therefore further investigated IL-8 expression in bronchial tissue.

In detergent (2% Triton X-100)-extracted homogenates of bronchial biopsy tissue from normal subjects, mildly asthmatic or, for comparison, patients with chronic obstructive pulmonary disease no free IL-8 was detectable using a specific, sensitive ELISA. Free IL-8 was, however, detected in 9/9 severely asthmatic subjects at a concentration of 0.082 ± 0.02 pg/ng secretory component and this was de-

spite high-dose steroid therapy (0-70 mg prednisolone and $3,200 \pm 1,000$ µg budesonide daily).

An IgA autoantibody to IL-8 was previously reported in gastric mucosa at concentrations which correlated with IL-8 production [7]. We therefore established an ELISA to detect IL-8/IgA complexes. In all subject groups, an IL-8/IgA complex was readily detected and the level of the complex was significantly higher in asthmatic compared to normal subjects.

IL-8-induced activation of eosinophils was initially demonstrated by scanning electron microscopy which revealed a shape change response in all eosinophils, indicating no unresponsive subpopulation. Activation by IL-8 was also demonstrated by the IL-8-induced

synthesis of granuloocyte/macrophage-colony-stimulating factor (GM-CSF) 8 pg/106 cells) in 24-hour eosinophil cultures. Further, release of GM-CSF was stimulated in the presence of secretory IgA (sIgA)-coated Sepharose beads, a potent stimulus for the release of granule basic proteins, at a cell-to-bead ratio of 20:1.

The effect of sIgA on IL-8-induced eosinophil migration was investigated in chemotaxis experiments using micro-Boyden chambers. Precoating polycarbonate filters with

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sIgA at 2 µg/ml resulted in a significant ($p=0.002$) increase in the migratory response to IL-8 (10^{-10} A) of highly purified eosinophils from atopic donors compared with the response on bovine serum albumin or plasma-IgA-coated filters. The response to IL-8 on sIgA-coated filters (42.1 ± 8.5 cells per high-power field) was not significantly different to that for IL-5 (3×10^{-9} M) or platelet-activating-factor (PAF) (10^{-7} M). Conversely, there was a significant ($p < 0.01$) 57% inhibition of the neutrophil chemotactic response to IL-8 (10^{-8} M), but not to PAF (10^{-7} M) on filters coated with purified secretory component, but not sIgA.

In summary, the presence of IL-8/IgA complexes in bronchial tissue, synergism between IL-8 and sIgA in eosinophil activation and a switch in the target cell specificity of IL-8 mediated by sIgA and/or secretory component indicated that IL-8 may be an important eosinophil chemoattractant and activator in the bronchial mucosa in asthma.

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