EDITORIAL

Immunoglobulin A in asthma: friend or foe?

P.S. Hiemstra

In this issue of the Journal, NAHM *et al.* [1] describe the results of an analysis of the levels of immunoglobulin (Ig)G and IgA directed against allergens and bacterial antigens in induced sputum that was obtained from patients with atopic asthma. Sputum induction was performed by inhalation of hypertonic saline, a technique that has gained much attention because it is relatively noninvasive and allows the study of airways inflammation [2]. The authors demonstrate that IgA levels against both *Dermatophagoides farinae* extracts and *Streptococcus pneumoniae* capsular polysaccharide are higher in induced sputum from atopic asthmatics as compared with the levels found in sputum from healthy controls. In addition, IgG levels against *D. farinae* are also higher in asthmatics; in contrast, IgG levels against *S. pneumoniae* do not differ between the two groups. Interestingly, the authors describe that specific IgA levels in sputum correlate with levels of eosinophil cationic protein (ECP), a marker for eosinophil degranulation. These results suggest an involvement of IgA in eosinophil degranulation in the patients with atopic asthma.

IgA is the predominant immunoglobulin isotype produced in the human body. Most IgA present in mucosal secretions, such as those collected by bronchoalveolar lavage (BAL), is present in a polymeric form bound to a secretory component (secretory IgA (sIgA)) [3]. Data presently available indicate that IgA plays a role both in host defence against infections and in inflammatory processes [4–6]. In the lung, its host defence function is achieved in part by the ability of IgA to inhibit the adherence of micro-organisms or viruses to the mucosal surface. In addition, IgA may facilitate the removal of antigens from the submucosa by transporting it through the epithelial layer [6]. Furthermore, binding of IgA to particles facilitates their phagocytosis due to the presence of specific IgA Fc receptors on the surface of phagocytes [7].

In addition to playing a role in host defence against infection, IgA may also contribute to tissue injury. The role of IgA in the pathogenesis of IgA nephropathy has been extensively studied, and deposits of IgA together with complement components are observed in the mesangial area of the kidney [5]. IgA may also cause lung injury, as shown by studies on IgA immune complex-mediated acute lung injury in the rat [4]. The capacity of IgA to trigger the release of mediators from inflammatory cells and to activate the complement system is involved in its role in inflammation [7].

Various cell types have been found to bind IgA. The prototype Fc receptor for IgA is FcαRI (CD89), which is present on neutrophils, eosinophils, monocytes and macrophages (reviewed by MORTON *et al.* [7]). CD89 is a heavily glycosylated transmembrane protein with a 32 kDa protein core, that is a member of the immunoglobulin gene superfamily and closely related to human Fc receptors for IgG and IgE. Binding of IgA or sIgA to FcαRI leads to activation of a variety of effector functions, in-cluding phagocytosis, production of reactive oxygen in-termediates, degranulation and production of cytokines. Various studies have demonstrated IgA-binding and IgA-mediated activation of eosinophils, but IgA binding molecules on eosinophils have been incompletely characterized. As indicated, eosinophils express FcαRI [7]. It has been shown that the degree of glycosylation of FcαRI on eo-sinophils is higher than that on neutrophils [8], but the functional consequences of this difference are not clear. Alternative splice variants of FcαRI messenger ribonucleic acid (mRNA) have also been reported in eosinophils [9], but their role in mediating the eosinophil response to IgA triggering remains to be established. A receptor for the secretory component on eosinophils that may be in-volved in sIgA-mediated eosinophil activation was descri-bed by LAMKHIOUED *et al.* [10]. Whereas the full pattern of IgA binding structures on the eosinophil awaits further characterization, it is clear that IgA has marked effects on eosinophils. These effects include induction of degranulation [11] and cytokine production [12]. There is also evidence that eosinophils from patients with atopic asthma are more prone to the stimulatory effects of IgA, since eosinophils from allergic individuals express more FcαR [8]. In line with this observation, it was recently reported that the T-helper (Th)2-derived cytokines interleukin (IL)-4 and IL-5 increase the binding of IgA-coated beads to eosinophils [13].

In support of these data from *in vitro* studies, several studies including the study by NAHM *et al.* [1] indicate that IgA is involved in degranulation of eosinophils *in vivo*. Firstly, the levels of IgA in BAL fluid from patients with asthma are higher than those in controls [3, 14]. Secondly, a marked correlation between total IgA or sIgA levels and eosinophil cationic protein (ECP) exists in BAL fluid and sputum from asthmatic patients [3, 15]. The results described by NAHM *et al.* [1] on the role of allergen-specific IgA are in line with those reported recently by PEEBLES *et al.* [15] describing a marked correlation between ECP levels in BAL fluid and the levels of ragweed-specific IgA in BAL fluid and serum following segmental allergen challenge. In addition, complexes of IgA and IL-8 have been detected in induced sputum, and the levels of these complexes were higher in atopic asthmatics compared with healthy nonatopic control subjects [16]. In atopic asthmatics, the levels of IgA-IL-8 complexes correlated with

Correspondence: P.S. Hiemstra, Dept of Pulmonology, Building 1 C3-P, Leiden University Hospital, Albinusdreef 2, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Fax: 31 715248118.

sputum ECP levels. Finally, also in patients with chronic eosinophilic pneumonia a correlation between IgA and ECP levels in BAL was reported [17].

Increased IgA levels in pulmonary secretions can be explained by various mechanisms, including increased numbers or activity of mucosal plasma cells that secrete IgA, increased leakage of IgA from the circulation, and increased secretory component-mediated transport of IgA across the epithelium. It has been shown that IgA in BAL and sputum from asthmatics is mainly derived from local synthesis, and that increased IgA levels in these secretions cannot be fully explained by increased vascular leakage. There is evidence from *in vitro* studies that cytokines that have been implicated in the pathogenesis of asthma may enhance the transport of IgA across the epithelium. IL-4 and interferon (IFN)-γ synergistically enhance the expression of secretory component on, and IgA binding to cultured epithelial cells [18]. In line with this observation, IFN-γ and IL-4 were found to increase secretory component-mediated transport of IgA across epithelium in cell culture [19, 20].

In conclusion, the present data support a role for immunoglobulin A in eosinophil-mediated inflammatory processes in the lung in asthma. The contribution of immunoglobulin A-induced activation of other effector cells to airways inflammation remains to be investigated. Increased immunoglobulin A levels and priming for immunoglobulin A-induced stimulation of eosinophils may contribute to eosinophilic inflammation in asthma. The function of FcαRI and other immunoglobulin A receptors needs to be further explored to understand the putative role of immunoglobulin A in asthma.

References

1. Nahm D-H, Kim HY, Park HS. Elevation of specific IgA antibodies to both allergen and bacterial antigen in induced sputum from asthmatics. *Eur Respir J* 1998; 12: 540–545.
2. Kips JC, Fahy JV, Hargreave FE, Ind PW, In 't Veen JCCM. Methods for sputum induction and analysis of induced sputum: a method for assessing airways inflammation in asthma. *Eur Respir J* 1998; 11: Suppl. 26, 9s–12s.
3. Peebles RS Jr, Liu MC, Lichtenstein LM, Hamilton RG. IgA, IgG and IgM quantification in bronchoalveolar lavage fluids from allergic rhinitics, allergic asthmatics, and normal subjects by monoclonal antibody-based immunoenzymetric assays. *J Immunol Methods* 1995; 179: 77–86.
4. Jones ML, Mulligan MS, Flory CM, Ward PA, Warren JS. Potential role of monocyte chemoattractant protein 1/JE in monocyte/macrophage-dependent IgA immune complex alveolitis in the rat. *J Immunol* 1992; 149: 2147–2154.
5. Galla JH. IgA nephropathy. *Kidney Int* 1995; 47: 377–387.
6. Lamm ME, Nedrud JG, Kaetzel CS, Mazanec MB. IgA and mucosal defense. *APMIS* 1995; 103: 241–246.
7. Morton HC, van Egmond M, van de Winkel JG. Structure and function of human IgA Fc receptors (Fc alpha R). *Crit Rev Immunol* 1996; 16: 423–440.
8. Monteiro RC, Hostoffer RW, Cooper MD, Bonner JR, Gartland GL, Kubagawa H. Definition of immunoglobulin A receptors on eosinophils and their enhanced expression in allergic individuals. *J Clin Invest* 1993; 92: 1681–1685.
9. van Dijk TB, Bracke M, Caldenhoven E, *et al.* Cloning and characterization of Fc alpha Rb, a novel Fc alpha receptor (CD89) isoform expressed in eosinophils and neutrophils. *Blood* 1996; 88: 4229–4238.
10. Lamkhioued B, Gounni AS, Gruart V, Pierce A, Capron A, Capron M. Human eosinophils express a receptor for secretory component. Role in secretory IgA-dependent activation. *Eur J Immunol* 1995; 25: 117–125.
11. Abu-Ghazaleh RI, Fujisawa T, Mestecky J, Kyle RA, Gleich GJ. IgA-induced eosinophil degranulation. *J Immunol* 1989; 142: 2393–2400.
12. Nakajima H, Gleich GJ, Kita H. Constitutive production of IL-4 and IL-10 and stimulated production of IL-8 by normal peripheral blood eosinophils. *J Immunol* 1996; 156: 4859–4866.
13. Bracke M, Dubois GR, Bolt K, *et al.* Differential effects of the T helper cell type 2-derived cytokines IL-4 and IL-5 on ligand binding to IgG and IgA receptors expressed by human eosinophils. *J Immunol* 1997; 159: 1459–1465.
14. Van de Graaf EA, Out TA, Kobesen A, Jansen HM. Lactoferrin and secretory IgA in the bronchoalveolar lavage fluid from patients with a stable asthma. *Lung* 1991; 169: 275–283.
15. Peebles RS Jr, Liu MC, Adkinson NF Jr, Lichtenstein LM, Hamilton RG. Ragweed-specific antibodies in bronchoalveolar lavage fluids and serum before and after segmental lung challenge: IgE and IgA associated with eosinophil degranulation. *J Allergy Clin Immunol* 1998; 101 (2 Pt 1): 265–273.
16. Louis R, Shute J, Biagi S, *et al.* Cell infiltration, ICAM-1 expression, and eosinophil chemotactic activity in asthmatic sputum. *Am J Respir Crit Care Med* 1997; 155: 466–472.
17. Boomars KA, van Vlezen-Blad H, Mulder PG, Koenderman L, Lammers JW, van den Bosch JM. Eosinophil cationic protein and immunoglobulin levels in bronchoalveolar lavage fluid obtained from patients with chronic eosinophilic pneumonia. *Eur Respir J* 1996; 9: 2488–2493.
18. Phillips JO, Everson MP, Moldoveanu Z, Lue C, Mestecky J. Synergistic effect of IL-4 and IFN-gamma on the expression of polymeric Ig receptor (secretory component) and IgA binding by human epithelial cells. *J Immunol* 1990; 145: 1740–1744.
19. Loman S, Radl J, Jansen HM, Out TA, Lutter R. Vectorial transcytosis of dimeric IgA by the Calu-3 human lung epithelial cell line: upregulation by IFN-gamma. *Am J Physiol* 1997; 272 (5 Pt 1): L951–L958.
20. Loman, S. Airway epithelial cell functions; relation to inflammation in asthma. PhD Thesis, University of Amsterdam, 1998.