Immunoglobulin A in asthma: friend or foe?

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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, including phagocytosis, production of reactive oxygen intermediates, 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 involved in sIgA-mediated eosinophil activation was described by Lamberjhed 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 FcαRI [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 Peckles 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
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.

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References