

EDITORIAL

IgE — a marker of late asthmatic response?

Hersheimer observed in the 1950s that airway responses to allergen inhalation have two distinct components — the early asthmatic response (EAR) and the late asthmatic response (LAR) [1]. Following allergen inhalation, bronchoconstriction occurs immediately and gradually improves over the next 2 h, the early asthmatic response (EAR). In approximately, 50% of adults [2] and 70% to 85% of children [3] with asthma, a second response is seen with maximum bronchoconstriction between 6 and 8 h after allergen inhalation, the late asthmatic response (LAR). Early and late asthmatic responses are typical features of asthma. EAR is clearly dependent on IgE-mediated activation of mast cells through high affinity receptors (FcεRI). The pathogenetic mechanisms responsible for the induction and magnitude of LAR are not fully understood. However, allergen reactive TH2 cells play a central role in the activation and recruitment of IgE producing B-cells, mast cells and eosinophils involved in late asthmatic reaction.

Factors determining the occurrence and severity of LAR have been extensively studied. High circulating IgE antibody or skin sensitivity to the inhaled allergen is said to be an important determinant for the development of LAR [4,5]. However, Durham *et al.* were unable to find an association between total or specific IgE and pattern of asthmatic responses following allergen inhalation [6]. The dosage of the allergen rather than the concentration appears to determine the early and late asthmatic responses after allergen challenge [7]. Increasing the dose of allergen can induce LAR in an asthmatic subject who previously demonstrated only an early reaction [8]. Other major determinants of LAR are nonspecific bronchial responsiveness and size of the early response. A lower value for methacholine PC20 at baseline and a greater fall in FEV₁ during an early response predict the development of a late response [9–11]. However, other investigators have failed to confirm the relationship between the sizes of early and late asthmatic responses [12]. van der Veen *et al.* proposed a model combining PC20 histamine, allergen skin sensitivity and allergen-specific proliferative response of peripheral T lymphocytes *in vitro*, for the prediction of LAR [13].

The late phase inflammatory response involves the recruitment and activation of eosinophils, neutrophils, macrophages and T cells. The most remarkable feature of LAR is an increase in recruitment and activation of the

airway eosinophils [5,14], mediated to a great extent by CD4⁺ T-helper cells. T cells are unique in that they are the only cells that can recognize processed antigens and respond to them. Allergen inhalation induces an immune response through the uptake and processing by antigen presenting cells, which then presents peptide fragments to specific T cells. The polarization towards a TH2 phenotype depends on the secretion of TH2 cytokines, which include IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, and GM-CSF. Pre-existing allergen specific IgE may favour the induction of TH2 responses, both by activating mast cells to produce IL-4 and IL-13 and by facilitating B-cell antigen presentation [15].

Antigen-specific IgE (as determined by allergen-specific IgE levels) response is regulated by HLA class II and T-cell receptors and involve T–B cognate interaction while nonantigen-specific IgE response (as determined by total serum IgE levels) involve noncognate interaction of mast cells, basophils and T cells with B cells [15]. TH2 cells produce IL-4 and IL-13, which are switching factors for IgE and IgG4 isotypes, and IL-5, a potent growth and activation factor for eosinophils [16]. IL-4 is the most important cytokine mediating IgE synthesis and together with IL-13 plays a central role in IgE-dependent allergic reaction. Some of the effect of IgE-dependent focusing of allergen to T cells is perhaps mediated by CD23, the low affinity IgE receptor [17]. The role of IgE in mediating allergic airway reaction is confirmed by the finding that treatment of allergic asthmatic patients with monoclonal anti-IgE antibodies attenuated airway eosinophilia, increased the dose of allergen needed to provoke an early reaction, and reduced the mean maximum fall in FEV₁ during the early and late responses to allergen challenge [18]. Therefore, IgE has a direct role in mediating not only the EAR but also the LAR.

In this issue Peebles *et al.* have demonstrated that presence of allergen-specific IgE and IgA could be an important determinant in the pathogenesis of late phase reactions [19]. Ragweed allergen-specific IgE levels in serum and bronchoalveolar lavage (BAL) fluid directly correlated with the severity of the LAR. The subjects were classified based on whether ragweed-specific IgE was detectable or undetectable in BAL fluid at baseline. It was found that subjects with detectable levels of allergen-specific IgE antibodies had a stronger late reaction and also had higher levels of BAL fluid

fibrinogen and eosinophilic cationic protein (ECP) levels, markers of airway inflammation. Furthermore, the association between ragweed-specific IgA, both in serum and BAL fluid, and the magnitude of LAR was interesting. Although IgA plays an important role in host defence against microbial organisms, its role in the handling of allergens is ambiguous. In an earlier study Nahm *et al.* showed that IgA levels against *Dermatophagoides farinae* extracts and *Streptococcus pneumoniae* capsular antigens were higher in induced sputum from atopic asthmatics as compared to the levels in healthy controls. They also showed specific IgA levels correlated with levels of eosinophilic cationic protein, a marker of eosinophil degranulation [20]. There is also evidence that eosinophils from atopic asthmatics are more prone to the effects of IgA, since these eosinophils express more Fc α R (CD89) receptors [21]. Besides, Th2-derived cytokines IL-4 and IL-5, produced at the site of an allergic inflammatory response, increase the binding of IgA to eosinophils thereby promoting eosinophil degranulation [22]. These findings incriminate IgA in promoting the inflammatory response in asthmatic patients but the extent of the involvement is unclear. In view of these findings, the observation by Peebles *et al.* on the role of allergen-specific IgA in modulating the LAR assumes significance.

While IgE-dependent inflammation plays a major part in allergic asthma, there are many inconsistencies. The SAPALDIA study has demonstrated that total IgE is a poor diagnostic indicator of respiratory allergic diseases [23] and in the African population serum levels of IgE have been reported to be higher in nonasthmatics than asthmatics [24]. Moreover IgE $-/-$ knock out mice when challenged with allergen can elicit inflammatory response of the airways and airway hyperresponsiveness [25]. These studies cast a question mark on the precise role of IgE in allergic disease.

Late asthmatic responses are associated with an increase in airway hyperresponsiveness and this may last for days, weeks or months [26]. As noted earlier, an increase in nonspecific bronchial hyperresponsiveness promotes the development of a late phase reaction [9,13]. Cockcroft proposed that in perennial asthmatics, a vicious cycle could be established by natural allergen exposure leading to airway hyperresponsiveness. The increased airway hyperresponsiveness could further amplify the response to subsequent exposure to allergen [27]. These observations have been supported by a recent study in which atopic asthmatics, following inhalation of doubling doses of allergen, were found to have significant decreases in PC20 methacholine and histamine. These changes were more pronounced in subjects who exhibited late response to allergens [28], suggesting that allergens could cause asthma rather than merely triggering symptoms.

The late phase reaction is considered to be a model system to study the mechanisms of chronic inflammation in asthma. However, the inability to maintain a chronic state of LAR following an allergen challenge is a major disadvantage. A continuing allergen exposure, akin to the natural allergen exposure, is required to induce a state of low-grade chronic inflammation. Repeated exposure to low doses of allergen, where the allergen dose is standardized (in contrast to natural allergen exposure), is a valuable alternative research tool. Previous studies have established that repeated low-dose allergen exposure produced signs of mild exacerbation of asthma, with significant changes in the bronchial reactivity, and hence can provide an attractive model to study the various pathophysiological mechanisms involved in asthma [29,30]. The dose of allergen and the duration of exposure are important determinants, and these have yet to be standardized to yield consistent results. Once standardized, such an experimental model of asthma could provide an excellent tool to study the roles of IgE, growth factors, airway remodelling, the role played by epithelium in the handling of allergen and to evaluate the therapeutic efficacy of novel drugs.

The study by Peebles *et al.* has indicated an involvement of allergen-specific IgE and IgA, in the pathogenesis of LAR. However, there are a number of unanswered questions on the true role of IgE in asthma. In a recent study T-cell epitope peptides of cat allergen were shown to initiate a T-cell-dependent LAR, without the requirement for an early IgE mast cell-dependent response, in sensitized asthmatic subjects [31]. The existence of IL-5-producing helper T cells in the absence of antigen-specific immunoglobulins (IgE, A and G) is sufficient for the development of the eosinophilic inflammation at the bronchial mucosa upon inhalation of the relevant antigen [32]. These studies illustrate that features that are by and large mediated by IgE can be achieved in its absence. Hence, it appears that there exists a missing link to interpret the true role of IgE in asthma. It is possible that the experimental allergen challenge, with large doses of allergen inhaled over a short period of time, is not the best method to study the pathogenetic mechanisms in asthma. Further studies with repeated exposure to low doses of allergen may provide clues to some of the missing links.

References

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