

Mechanisms of intrinsic asthma

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Purpose of review

The phenomenon of intrinsic or nonatopic asthma continues to raise questions about the possible role of IgE-mediated mechanisms in asthma pathogenesis. With the current availability of anti-IgE therapy for asthma, clarification of this issue has never been more timely and relevant.

Recent findings

This article summarizes recent studies for and against the proposition that IgE-mediated mechanisms play a critical role in asthma pathogenesis. These data comprise epidemiological studies and recent molecular studies, suggesting that IgE synthesis may take place in the bronchial mucosa of patients with nonatopic asthma, despite the fact that allergen-specific IgE is not detectable in the periphery by standard skin prick testing.

Summary

At present, available data do not allow a firm conclusion to be made as to whether or not IgE-mediated mechanisms play an obligatory role in asthma pathogenesis. Implications for the future therapy of nonatopic asthma in either case are discussed, as well as some suggestions for further research.

Keywords

intrinsic asthma, nonatopic asthma, immunoglobulin E

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Introduction

Rackeman [1] first introduced the terms 'extrinsic' and 'intrinsic' asthma in 1947. He recognized the propensity of allergens to trigger symptoms in some patients with asthma but not others. At this time, nothing was known about the cellular and molecular pathophysiology of asthma, and he considered the disease in nonallergic patients to be caused by an unknown, 'intrinsic' process. Even at this early stage he noticed that patients with 'intrinsic' asthma tended to have onset of symptoms later in life, they were more commonly female, they had disease that was more difficult to control, and they more frequently had rhinosinusitis.

Nowadays, the diagnosis of allergy is based on the propensity of certain individuals inappropriately to produce IgE antibodies against certain antigens ('allergens') encountered at the mucosal surfaces of the respiratory and gastrointestinal tracts. This propensity is formally defined by skin prick testing and radioallergo-sorbent tests, which identify the presence of circulating IgE specific for common aeroallergens [2]. In theory it is impossible to rule out the presence of atopy using these tests, since it is always possible to argue that a patient may have mounted a specific IgE response to an obscure allergen not included even in an extensive panel of skin prick tests. One example of this is the recognition that many 'nonallergic' patients may be sensitive to the fungus *Trichophyton* which causes tinea cutaneous infections, and which is not routinely included in panels of allergen solutions for skin prick testing [3]. In practice, however, 95% of atopic patients can be identified by positive skin prick tests to just a small range of aeroallergens such as grass pollen, cat dander and house and dust mite.

The clinical distinction between atopic and nonatopic asthma has been ratified by more modern epidemiological studies such as the Epidemiological study on the Genetics and Environment of Asthma, Bronchial Hyper-responsiveness and Atopy [4]. Such studies [5•] have shown that, in random samples of patients with asthma identified by validated questionnaires, increased age, female sex, the presence of chronic rhinosinusitis and more severe impairment of lung function are associated with an elevated chance of the patient being nonatopic. Conversely, the presence of other atopic diseases, such as hayfever, seasonal exacerbation of symptoms in line with the pollen season and earlier onset of disease increase the chance that the patient will be atopic. Even so, such studies have highlighted anomalies not easily

explicable in terms of the presence or absence of IgE-mediated responses to allergens. For example, both atopic and nonatopic patients report symptoms of rhinitis with equal frequency [5•], suggesting that nonatopic patients may have some preexisting abnormality of the respiratory mucosa that allows these symptoms to develop even in the absence of mediator release from IgE-sensitized mast cells within the nasal mucosa.

Why is it important to identify nonatopic asthma as a separate disease entity?

Asthma is characterized by bronchial hyperresponsiveness, or the propensity of the airways to constrict in response to a variety of stimuli that would not cause such constriction in patients without asthma. In atopic patients, the release of histamine and other mediators into the airways secondary to cross-linking of surface-bound, allergen-specific IgE is one such stimulus. In fact, histamine hypersensitivity of the airways forms a basis of the 'gold standard' diagnostic test for asthma. It is not surprising, therefore, that allergen exposure of atopic individuals is associated with an increase in asthma symptoms, bronchial reactivity and deterioration in lung function [6,7]. Interestingly, it has proven difficult to demonstrate that allergen avoidance conversely improves asthma in atopic individuals [8]. This may be because studies have been poorly designed, or underpowered, or because clinically relevant allergen avoidance is in practice impossible. Nevertheless, most clinicians would agree that atopic patients should avoid allergens to which they are sensitized, whereas in nonatopic patients such avoidance is irrelevant.

From a physician's point of view, therefore, this is where the story ends. From a scientist's point of view, however, this is where it begins. The key question here is whether or not IgE and IgE-dependent mechanisms play an indispensable role in asthma pathogenesis. If so, then it is relevant to include the propensity for inappropriate manufacture of IgE in epidemiological and genetic searches for the causation of asthma. If not, then strictly such studies are irrelevant.

A further complication is introduced by the distinction between the production of total IgE and 'allergen-specific' IgE. It has long been known from epidemiological studies [9] that, although serum total IgE concentrations fall with age, they remain a predictor of lung function in more elderly patients, regardless of whether or not the patients have asthma. A more recent study [10] showed that, in a large, unselected cohort of patients defined as atopic or nonatopic on the basis of skin prick testing, asthma was more prevalent and airways obstruction more severe in nonatopic patients with total serum IgE concentrations in excess of the 'normal' cut-off (150 IU/ml) compared with those

patients with concentrations within the 'normal' range. Overall, multivariate analysis in the entire study population showed a greater than fivefold risk of asthma in the nonatopic individuals with total serum IgE concentrations greater than 150 IU/ml. These data support the hypothesis that inappropriate IgE production is a risk factor for asthma independent of classical, IgE-mediated allergic responses to allergens. What promotes the production of this IgE? It is hard to envisage that this is a nonspecific, 'bystander' effect on B cells exposed to IgE-switching cytokines such as IL-4 and IL-13 in the course of ongoing allergen-specific allergic responses, since these patients show no evidence of such responses. Is the IgE specific for 'allergens', external or internal, which have yet to be recognized? An alternative hypothesis is that the propensity to develop asthma and the propensity to develop inappropriate IgE responses, allergen-specific or otherwise, are independent traits that are commonly juxtaposed in individuals. An extension of this hypothesis is that such traits reflect linked, but distinct intrinsic, perhaps genetically determined abnormalities. Until recently, most studies on genetic predisposition to asthma centred on polymorphisms of those genes, or their promoters, thought to play an important role in asthma process, such as the gene for IL-5, but also inevitably on those thought to play an important role in the pathogenesis of allergy and IgE production, such as IL-4 and IL-13. If the development of allergy is irrelevant to the development of asthma, then these studies have perhaps been misguided. It is to be hoped that, with the advent of new positional cloning techniques, in which genes predisposing to asthma can be identified regardless of their a priori assumed importance in the asthma process, new light may be thrown on which genes are really important, and more significantly whether different genes govern predisposition to asthma as opposed to atopy. It is of interest in this regard that the first gene to be identified using this technique [11••], ADAM33, encodes a metalloproteinase expressed by a variety of normal lung cells, including bronchial smooth muscle and fibroblasts, but not by inflammatory leukocytes. This observation immediately suggests the hypothesis that alterations in the activity or abnormal expression of 'normal' genes such as ADAM33 in the lung may underline abnormalities in airway function, rather than the immunological components more traditionally associated with atopy and asthma.

Another fact to be considered is the possibility that the atopic status of patients with asthma may change with time. Few if any epidemiological studies have been directed specifically at this question in patients with asthma, but a recent study on children with atopic dermatitis [12] showed that a number of nonatopic children, as defined by skin prick testing, with 'atopic' dermatitis developed positive skin prick tests within the

follow-up period of 10 years. Again this raises the question of whether these processes are inextricably linked or whether they simply commonly occur together. Interestingly, positive patch test reactions to aeroallergens can be induced in some patients with 'atopic' dermatitis who have negative skin prick tests to these aeroallergens [13*]. Does this reflect an IgE-independent, T-cell-mediated reaction to allergens, or is IgE somehow involved? This leads us to the final element of the current conundrum: do negative skin prick tests definitely exclude the possibility of allergen-specific IgE synthesis, perhaps locally in the affected target organs? This theme will be taken up again in the final section of this article.

Cellular and molecular studies of intrinsic asthma

Asthma is characterized by a relatively specific bronchial mucosal infiltrate with eosinophils, and evidence of local T-cell activation, with elevated expression of eosinophil-active chemokines and cytokines. Regarding the cellular infiltrate, early comparisons of atopic and nonatopic asthma showed that this was remarkably similar save for an increased number of tissue macrophages in the bronchial mucosa of the nonatopic patients [14,15]. Despite the apparent absence of inappropriate IgE synthesis in nonatopic asthma, it was somewhat surprising to find equivalent, elevated expression not only of the key eosinophil-active cytokine IL-5, but also the cytokine IL-4, which switches B cells to make IgE, in the bronchial mucosa of both atopic and nonatopic patients as compared with atopy-matched controls, at the level of expression of both mRNA and protein [16,17], with a similar cellular distribution of these cytokines in T cells, eosinophils and mast cells in both groups of patients. Elevated mucosal expression of IL-13, the only other human cytokine causing B-cell IgE switching, at least at the level of mRNA, was also a feature of nonatopic as well as atopic asthma [18]. Furthermore, submucosal expression of mRNA encoding the α -subunit of the IL-4 [19] and IL-5 receptors [20] was elevated, compared with controls, in both patient groups. One difference between the groups in terms of cytokine receptor expression was the increased number of cells expressing the α -subunit of the granulocyte macrophage colony-stimulating factor receptor in nonatopic compared with atopic patients, reflecting the elevated numbers of tissue macrophages [21]. Mucosal expression of the eosinophil chemotactic cytokines eotaxin, eotaxin-2, RANTES, monocyte chemoattractant protein-3 and -4, as well as the expression of the CC chemokine receptor CCR3, a ligand for these chemokines expressed on eosinophils and Th2-type T cells, was also similarly elevated, at least at the level of mRNA, compared with controls, in both atopic and nonatopic patients [22,23], and these mediators again showed a similar cellular

distribution (predominantly epithelial cells, endothelial cells and macrophages in contrast to the cytokines). Despite the similarity of expression in the bronchial mucosa, elevated numbers of induced sputum cells (predominantly macrophages, eosinophils and epithelial cells) showed eotaxin mRNA production and immunoreactivity in patients with nonatopic asthma, but not in those with atopic asthma, compared with controls [24], and concentrations of RANTES in bronchoalveolar lavage fluid from these patients were also elevated [25].

Overall then, in terms of the bronchial mucosal cellular infiltrate and cytokines and chemokines involved in the T cells/eosinophil axis, both atopic and nonatopic asthma show remarkable similarities. What of IgE-mediated mechanisms? As we have seen, expression of IL-4, a key cytokine promoting B-cell switching to IgE synthesis, in the bronchial mucosa appears to be equivalent in atopic and nonatopic patients. One caveat to this observation is the recent finding of deficient STAT-6 mRNA expression in the mucosa of nonatopic patients [26], suggesting that IL-4 signalling may be deficient. Nevertheless, key recent findings have provided tantalizing evidence that local IgE synthesis may indeed occur in the bronchial mucosa of nonatopic patients. As in patients with atopic asthma, these patients show elevated expression of the high-affinity IgE receptor Fc ϵ RI on inflammatory cells in the bronchial mucosa compared with controls [27]. Since IgE upregulates expression of its own receptor, this is indirect evidence of IgE synthesis. More compelling evidence has come from the demonstration of elevated expression of C ϵ germline gene transcripts, as well as mature IgE heavy chain transcripts, in the bronchial mucosa of nonatopic as well as atopic patients compared with controls, in the absence of elevated overall numbers of B cells [28]. C ϵ germline gene expression is characteristic of B cells in the process of switching to IgE synthesis. These findings add weight to the possibility that local IgE synthesis may indeed occur in the bronchial mucosa of nonatopic patients, although it remains to be demonstrated that mature IgE is actually released. It also remains to be seen whether this synthesis could at least partly account for the elevated total serum IgE concentrations seen in some of these patients, and indeed whether some of this IgE may be allergen-specific, even though it is not detectable in the periphery by conventional skin prick tests.

Conclusion

In terms of the bronchial mucosal cellular infiltrate and local expression of cytokines and chemokines that are thought to be important in disease pathogenesis, atopic and nonatopic asthma are very similar diseases. This fact, along with the epidemiological evidence discussed above, allows the hypothesis that IgE-mediated mechanisms involving specific allergen play no critical role in the

pathogenesis of asthma (but do serve to exacerbate disease in sensitized, atopic patients). If this is so, then epidemiological and genetic studies based on the pathogenesis of atopy, rather than asthma, may be clouding, rather than clarifying our understanding of asthma pathogenesis. The close epidemiological link between overall IgE synthesis and obstructive airways disease in atopic and non-atopic patients does suggest some sort of link, perhaps in the form of distinct, genetic predispositions to both inappropriate IgE synthesis and asthma that are commonly inherited together. Conversely, recent molecular findings suggest that we cannot discard the possibility that IgE-mediated mechanisms are fundamental to asthma pathogenesis, even in patients with negative skin prick tests. Further studies, particularly directed at whether IgE is in fact produced in the bronchial mucosa of nonatopic patients and what its allergen specificity might be, along with continued genetic studies unbiased by preconceptions of disease mechanisms, will doubtless serve to clarify these questions. At a time when anti-IgE therapy is readily available for asthma treatment [29•], it has never been more important to clarify the role of IgE in asthma, since it may prove that such therapy is of therapeutic and even prophylactic benefit in both atopic and nonatopic patients alike. Conversely, abandonment of the shackles of an obligatory role for inappropriate IgE synthesis in asthma may open the door to a new appreciation of disease mechanisms and therapeutic avenues.

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