

## Bronchial immunoglobulin E production in intrinsic asthma

## Production bronchique d'immunoglobulines E dans l'asthme intrinsèque

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**Abstract**

Asthma is widely regarded as a clinical manifestation of atopy. Especially pertinent in infants, this notion is less evident in adults, where there is a classic distinction between atopic (“extrinsic”) asthma and non-atopic (“intrinsic”) asthma. The latter occurs later in life, mostly in females, and nasal polyposis, aspirin sensitivity and cortico-dependence are common in patients with non-atopic asthma. In this patient population, there is no history of allergy, skin prick tests are negative for all aeroallergens tested, and serum levels of total as well as specific immunoglobulin E are within the normal range. The majority of publications on this subject point nevertheless to the existence of clinical and biological markers of “allergic inflammation”, taken here in the broadest sense, in asthmatics in general, including those with apparently intrinsic asthma. In particular, recent work has demonstrated the possibility of increased production of IL-4, IL-13, I $\epsilon$ , C $\epsilon$ , and Fc $\epsilon$ RI in both allergic and non-allergic asthmatics.

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**Résumé**

Il est largement admis que l'asthme est une manifestation clinique de l'atopie. Particulièrement pertinente chez l'enfant, cette notion est moins évidente chez l'adulte où existe la classique distinction entre asthme « extrinsèque » (allergique) et « intrinsèque » (non allergique). L'asthme intrinsèque est volontiers tardif, une prédominance féminine est classique, de même que l'association à une polyposse nasosinusienne, une intolérance à l'aspirine et une moindre corticosensibilité imposant le recours plus fréquent à une corticothérapie orale. Ces patients n'ont pas d'antécédents allergiques, les tests cutanés sont négatifs pour les aéroallergènes et les concentrations d'IgE sériques totales et spécifiques sont basses. La majorité des travaux publiés soulignent néanmoins l'existence de marqueurs cliniques ou biologiques d'inflammation « allergique » au sens large chez l'asthmatique, même d'apparence intrinsèque. En particulier des travaux récents ont montré la possibilité d'une production bronchique accrue d'IL-4, d'IL-13, d'immunoglobulines E et de son récepteur de haute affinité f $\epsilon$ RI chez l'asthmatique allergique ou non allergique.

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Atopy is a disorder characterized by sustained, inappropriate IgE responses to common environmental antigens (“allergens”) encountered at mucosal surfaces [1]. Atopy is a very common feature in asthmatics: atopic asthma is characterized by infiltration of the bronchial mucosa with eosino-

phils and Th2-type cells, circulating specific IgE antibodies and positive skin tests to common aeroallergens, and airway hyperresponsiveness [2]. Stimulation of IgE synthesis by B cells and mobilization of eosinophils is believed to be driven by a complex network of cytokines and chemokines including interleukin-4 (IL-4) and IL-5 [3]. Since Rackeman's clinical classification of asthma, it has been widely accepted that a subgroup of asthmatic patients is not demonstrably

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atopic—the so-called “intrinsic” variant of the disease [4]. Intrinsic asthmatics show negative skin tests and there is no history of allergy [4,5]. Furthermore, serum total IgE concentrations are within the normal range and there is no evidence of specific IgE antibodies directed against common allergens [5]. These patients are usually older than their allergic counterparts, and have onset of symptoms in later life, often with a more severe clinical course [4,5]. There is a preponderance of females and the association of nasal polyps and aspirin sensitivity occurs more frequently in the non-atopic form of the disease [4,5]. Whereas some authors suggest that around 10% of asthmatics are intrinsic, the Swiss SAPALDIA survey (8357 adults, 18–60-years-old) found that a third of total asthmatics were non-allergic [6].

Ever since the first description of intrinsic asthma there has been debate about the relationship of this variant of the disease to atopy [7]. Our recent studies support the concept that although intrinsic asthma has a different clinical profile from extrinsic asthma it does not appear to be a distinct immunopathological entity [5].

In contrast with the general agreement that eosinophils and activated T-lymphocytes may play a role in asthma in both clinical settings, the possible role of IgE and IgE-mediated mechanisms, especially (but not exclusively) in intrinsic asthma, is less clear [5]. Based on the relationship, at the population level, between total serum IgE concentrations and the incidence of asthma/airway hyperresponsiveness, some authors have questioned the existence of intrinsic asthma, suggesting that all asthmatics have an IgE-dependent component to their disease [7]. This relationship need not, however, be causal, and could equally well reflect the possibility that individuals who have a propensity to develop asthma also have a predisposition to produce IgE inappropriately. However, we and others have confirmed that non-atopic asthmatics have elevated total serum IgE concentrations as compared with non-atopic controls, despite the fact that, as a group, non-atopic asthmatics tend to be older than their allergic counterparts and that IgE serum concentrations tend to decline with age [5,8].

Th2-type cytokine-induced B-cell activation and subsequent IgE production is believed to be a critical characteristic of patients with atopy. Interaction of environmental allergens with cells sensitized by binding of surface Fc receptors to allergen-specific IgE is assumed to play a role in the pathogenesis of atopic asthma. IL-4 or IL-13 are absolutely required for IgE-switching in B cells, a prerequisite for elevated IgE synthesis, and thus atopy [9,10]. Evidence for local IgE synthesis has been demonstrated in CD20+ B cells in the nasal mucosa of patients with hayfever [11]. In patients with bronchial asthma compared to normal controls, despite comparable numbers of CD20+ B lymphocytes within the bronchial mucosa, we detected elevated numbers of cells expressing the  $\epsilon$  germline gene transcript (I $\epsilon$ ) and cells expressing C $\epsilon$  which detects either the sterile transcript or mature  $\epsilon$  heavy chain messenger RNA (Fig. 1). These elevations were detected in biopsies from both atopic and non-

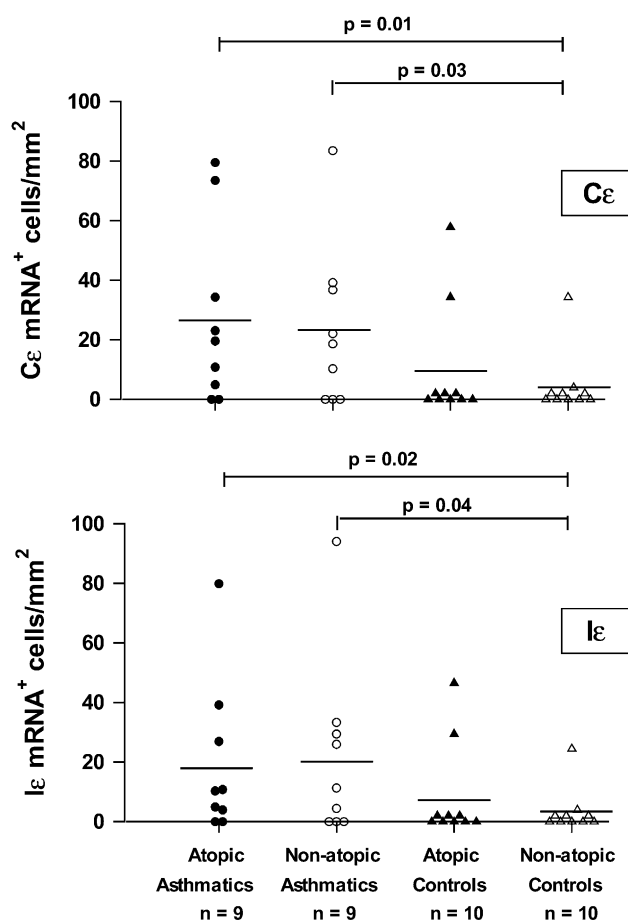


Fig. 1. Local IgE synthesis in the airway mucosa in non-atopic asthma. Cell counts of cells expressing mRNA for the  $\epsilon$  germline transcript (I $\epsilon$ ) and mature IgE heavy chain (C $\epsilon$ ) in bronchial biopsies from atopic and non-atopic asthmatics (from reference [12]).

atopic asthmatics but not in biopsies from atopic non-atopics compared to those from non-atopic normal healthy control subjects [12]. Furthermore, there was an association between the number of C $\epsilon$  and I $\epsilon$ + cells and the number of cells expressing IL-4 mRNA indicating that these changes may be at least in part under the regulation of IL-4 [12]. This suggests that local bronchial mucosal IgE production may indeed occur in so-called intrinsic asthma. This, along with the elevated numbers of cells expressing Fc $\epsilon$ RI in these patients [13], suggests the possibility of local IgE-mediated processes in the absence of detectable systemic IgE production. Thus, non-atopic, as well as atopic asthma may be associated with the production of IgE directed against as yet unidentified allergens or antigens. These results are also compatible with a possible role for virus-specific IgE [14] or IgG autoantibodies to Fc $\epsilon$ RI in non-atopic asthma, as previously suggested in chronic idiopathic urticaria, a disease characterized by basophil and mast-cell release of histamine and other vasoactive mediators in the absence of any clear allergic, infectious, drug-induced, or physical cause [15]. Other autoantibodies have been detected in intrinsic asthmatics, including a circulating IgG autoantibody directed against a common 55 kDa antigen shared by platelets and cultured

endothelial cells [16]. Its role in pathophysiology of asthma has not been elucidated.

In conclusion, inappropriate IgE-mediated mechanisms might occur in asthma, irrespective of its atopic status, as suggested by elevated serum IgE concentrations and bronchial mucosal expression of cells positive for FcεRI, IL-4, IL-13, Iε and Cε. In general, these findings support the concept that these subtypes of asthma, despite showing distinct clinical features, share many common immunopathological mechanisms. Promising future directions of research regarding intrinsic asthma include the possible identification of novel allergens or antigens and the detailed description of local bronchial mucosal IgE production.

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