Does non-allergic asthma still exist?

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Summary

An old clinical classification distinguished between atopic (IgE-mediated) and non-atopic forms of bronchial asthma. Leaving aside the allergen triggers of extrinsic asthma, the triggers for intrinsic asthma and extrinsic asthma are the same, e.g. exercise, cold air and inhaled irritants. Recently, scientific evidence has challenged the dualistic concept of extrinsic and intrinsic asthma. Biopsies obtained from non-atopic asthmatics showed enhanced expression of high-affinity IgE receptor (FcεRI), probably due to IgE synthesis occurring at least locally in the airways of these patients, despite their having negative skin prick tests and low serum IgE levels.

KEY WORDS: allergy; bronchial asthma; intrinsic asthma; IgE; omalizumab.

Introduction

Asthma is a chronic disease of the airways characterized by inflammatory, structural and functional changes that are responsible for bronchial hyperresponsiveness and airflow limitation. It is now widely accepted that asthma is a heterogeneous disease that includes several different phenotypes, each of which is defined by distinct clinical, functional and pathobiological patterns (1).

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Asthma has almost universally been regarded as an atopic disease involving allergen exposure and allergic (IgE-mediated) sensitization.
Atopy is a condition characterized by sustained, inappropriate IgE responses to common environmental antigens (or allergens) encountered at mucosal surfaces (2).
Since the original description of IgE by Ishizaka et al. in 1966, understanding of its role in the pathogenesis of allergic diseases has greatly increased (3). It is now well recognized that serum levels of allergen-specific and total IgE are strongly associated with the degree of sensitization and disease severity in allergic patients (4).
Determination of total serum IgE levels is used as a screening tool for atopy, and an upper limit of 120-180 U/L is generally accepted as a reasonable threshold for distinguishing atopics from non-atopics.
Besides atopy, elevated IgE levels are occasionally observed in disorders like parasitic infection, myeloma, chronic inflammatory bowel diseases, and human immunodeficiency virus (HIV) infection; in addition, smoking and exposure to diesel exhaust or benzole have been shown to enhance IgE production (5).

Atopic and non-atopic asthma

A minority of asthmatic individuals are not, however, demonstrably atopic by conventional criteria, which has led to the suggestion that asthma may be divided clinically into atopic (extrinsic) and non-atopic (intrinsic) variants (6). According to this old classification, non-atopic (intrinsic) asthma was considered a distinct pathogenetic variant of asthma in which patients are skin prick test-negative and have total serum IgE concentrations within the normal range (7). Recently, there have been major advances in our understanding of the molecular mechanisms of atopic (extrinsic) asthma and other allergic diseases, but relatively little progress in our understanding of non-atopic (non-allergic or intrinsic) asthma. Indeed, the mechanisms of this variant of asthma, in which allergens have no obvious role in driving the inflammatory process in the airways, remain uncertain.

There is less familial association with intrinsic than with extrinsic asthma. In fact, a strong genetic predisposition to allergy is common in extrinsic asthma, but environmental factors are more likely causative agents of intrinsic asthma.

Intrinsic asthma is typically a late-onset condition, more common in females, and it tends to be more severe than the non-intrinsic form, requiring higher doses of corticosteroids for adequate control. Anecdotally, it of-

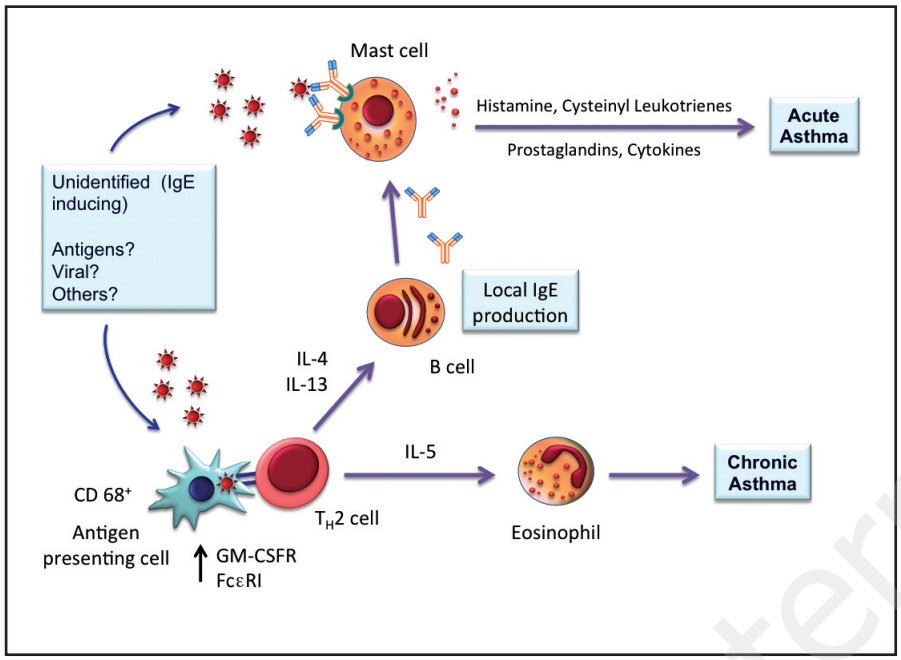

Figure 1 - Immunopathological mechanisms in non-atopic asthma. In the absence of atopy, unknown antigens could presumably trigger local IgE production. Such antigens, as in atopic asthma, lead to the release of pharmacological inflammatory mediators that cause rapid onset bronchospasm and chronic asthma.

ten starts following a severe upper or lower respiratory tract infection. Leaving aside the allergen triggers of extrinsic asthma, the two forms of asthma share the same triggers, such as exercise, cold air and inhaled irritants. In accordance with Rackemann's original classification, there is less familial association in intrinsic than in extrinsic asthma. This is perhaps to be expected, given the strong genetic predisposition both in atopy and in allergies, but it also indicates that environmental factors may be more important in the causation of intrinsic asthma (8).

Nevertheless, in the last two decades several pieces of evidence have challenged the dualistic concept of extrinsic and intrinsic asthma. Inflammatory cytokines IL-4, IL-5, and IL-13 (7, 9) in bronchial biopsies were similar both in allergic and in intrinsic asthmatics, leading to the concept that different phenotypes of asthma have similar patterns with increased T-helper type 2 (Th2) cells, mast cell activation and infiltration of eosinophils, both in allergic and non-allergic patients (Figure 1). Moreover, the finding of enhanced expression of high-affinity IgE receptor (FcεRI) even in bronchial biopsies obtained from non-atopic asthmatics is probably due to IgE synthesis occurring at least locally in the airways of these patients, despite their having negative skin prick tests and low serum IgE levels (10).

Local and peripheral IgE synthesis

The presence of increased local synthesis of IgE also in non-atopic asthmatics has been demonstrated in more recent studies. Ying and colleagues showed (11) local expression of epsilon germline gene transcripts and RNA for the epsilon heavy chain of IgE in the bronchial mucosa in atopic and non-atopic asthmatics, while Takhar et al. (12) elucidated the class switch recombination to IgE in the bronchial mucosa in atopic and non-atopic patients with asthma. Mouthuy and colleagues (13) recently confirmed that local IgE production occurs in the bronchial mucosa in intrinsic asthma and showed, for the first time, that part of this IgE is directed toward house dust mite (Der p) allergens. All these data suggest that, despite the absence of circulating peripheral IgE in non-atopic asthmatics and the lack of systemic sensitization to allergens, non-atopic patients with asthma nevertheless activate the cellular machinery of atopy at least locally in their bronchial mucosa.

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Significantly elevated serum IgE titers have occasionally been observed in non-allergic individuals, both with and without asthma, and little is known about the clinical significance of this finding. Indeed, whereas elevated serum IgE is the hallmark of atopy and contributes to asthma and bronchial hyper-reactivity (BHR) in atopic individuals, the significance of IgE in non-allergic subjects is less clear at present (5). In fact, elevated total circulating IgE (>150 U/mL) has been estimated to be present in approximately one third of asthmatic patients with a negative skin prick test (8). Intrinsic (non-allergic) asthma is now regarded as a clinical manifestation or phenotype of asthma, accounting for about 10% of asthmatics, rather than a distinct disease entity. Few studies have dealt with the potential association of IgE and asthma in the absence of clinical allergy, therefore we can only speculate about the possible contributory role of serum IgE to the

pathogenesis of bronchial asthma in non-allergic individuals.

IgE and non-atopic asthma

The possible association of serum IgE levels with asthma, irrespective of specific allergic sensitization, has long been investigated.
Burrows et al. (14) revealed that, regardless of subject status with regard to atopy, the prevalence of self-reported asthma was closely related to serum IgE levels, suggesting that IgE-mediated mechanisms may play a role even in non-atopic asthmatics with no detectable allergen-specific IgE.

Lung function in non allergic asthmatics with elevated total IgE may be even worse compared with asthmatics with normal circulating IgE, and the extent of obstructive airway disease may closely correlate with IgE levels in non-allergic asthmatics.

Sunyer et al. (15) examined a general population-based sample (including individuals with symptomatic asthma) drawn from five different areas of Spain. They screened the whole population for a diagnosis of bronchial asthma through spirometry, measurement of airway responsiveness to methacholine challenge, and a clinical questionnaire for symptoms, and also measured circulating IgE, either total (PRIST) and specific ones (RAST). The authors found a prevalence of asthma in the individuals with increased levels of IgE, even in those negative for specific IgE to common aeroallergens. Thus, the association between bronchial asthma and total serum IgE levels was irrespective and independent of a specific reactivity to common areoallergens or symptoms of allergy. They concluded that these findings support the existence of a close interrelationship between asthma and total IgE, even in non-atopic subjects.
In a recent study, Beeh and colleagues (5) demonstrated that non-allergic patients with elevated total serum IgE (defined "non-allergic" on the grounds of a negative skin prick test and a lack of history of atopy and specific IgE) have a higher prevalence of asthma than non-allergic subjects with normal IgE (in particular, they reported a more than five-fold increased risk for asthma in non-allergic subjects with IgE > 150 U/L). Moreover, the authors showed that lung function in the non-allergic asthmatics with elevated total IgE was even worse than that of the asthmatics with normal circulating IgE, and that the extent of obstructive airway disease was closely correlated with IgE levels in non-allergic asthmatics as well. The authors did not provide a clear explanation for these findings and the role and the possible mechanisms of the association of increased total serum IgE with asthma in non-allergic patients therefore remains to be fully understood.
Interestingly, recent case reports on the efficacy of the human monoclonal anti-IgE antibody omalizumab even in non-allergic asthma have provided indirect evidence of the role of IgE in the absence of a documented history of allergy. Omalizumab is still best known as a safe and effective add-on treatment in allergic asthmatics, allowing them to achieve better control of the disease, by reducing the number of exacerbations and the use of steroids, and a better quality of life (16).

Anti-IgE in non-allergic asthma

To date, only two case reports have reported effectiveness of omalizumab in patients with non-allergic asthma and high serum IgE levels (17, 18). In both cases, anti-IgE was employed in severe asthmatics, despite the absence of an indication in the international guidelines. During long-term follow-up, the patients benefited from the anti-IgE therapy showing a dramatic improvement of symptoms, QoL score, and no acute exacerbations. The authors concluded that it is currently unknown whether omalizumab may have a beneficial effect in patients with non-allergic asthma who have elevated serum total IgE. Nevertheless, taken together the results of these two reports suggest that in patients with severe asthma and elevated IgE a trial with omalizumab can be performed, regardless of RAST and skin prick test results.

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Another recent study showed beneficial effects of omalizumab in allergic and non-allergic patients with nasal polyps and asthma (19): reduction (similar in allergic and non-allergic subjects) of upper and lower airway symptoms (nasal congestion, rhinorrhea and loss of sense of smell, dyspnea, wheezing and cough). The authors concluded that these findings strongly support the functional role of local polyclonal IgE in airway mucosal tissue also in view of the finding, by others, of eosinophilic inflammation in nasal polyps with increased local tissue IgE levels independently of the allergic status of the patients (20). It has been proved that this polyclonal IgE expression in chronic rhinosinusitis with nasal polyps is driven by *Staphylococcus aureus* (*S. aureus*) colonization of the nasal mucosa, also in absence of a clearly recognized allergic mechanism (21), therefore it is possible the same phenomenon can occur in the lower bronchial mucosa.

Discussion

Contrary to what is commonly thought, IgE can be elevated, even locally, in non-allergic asthmatics. To explain this, we have to consider the possibility of underdiagnosis of allergic patients (i.e. sensitization towards rare, non-tested allergens) and the possibility of a potential bias in various pathological conditions (parasitic infections, myeloma, chronic inflammatory bowel diseases, HIV infection, cigarette smoking). In other words, it is possible that non-allergic subjects with high IgE levels may actually be "pre-allergic" ones destined to develop specific sensitization later on. Total IgE elevation could be also a non-specific reaction secondary to asthmatic inflammation, which might stimulate B-cell

An elevation of serum total IgE levels could be also a non specific reaction secondary to asthmatic inflammation, which might stimulate B-cell production of polyclonal IgE. So, the correlation between asthma severity and total IgE levels may be a surrogate marker of asthmatic inflammation.

production of polyclonal IgE (22). This explanation also correlates asthma severity with total IgE levels, making IgE a surrogate marker of asthmatic inflammation, the latter susceptible, together with lung function, to anti-inflammatory therapy.
An alternative, and attractive, interpretation is supported by genetic linkage analyses, which revealed a possible co-inheritance of the genetic loci representing bronchial hyperresponsiveness and atopy, i.e. a "high IgE phenotype" (23, 24). If this interpretation is correct, the above observations would represent a non-causal, merely associated phenomenon.
IgE could also express a humoral autoimmunity, since specific reactivity against human proteins with structural similarity to allergens has been described (25), in accordance with the late-onset occurrence of intrinsic asthma, seen mainly in females. Anti-nuclear antibodies are more common in patients with asthma than non-asthmatics, but no difference was found between allergic and non-allergic asthmatics (26). Autoantibodies to cytokeratin-18 and enolase-alpha (expressed in epithelial cells) have been described in patients with intrinsic and more severe asthma (27), while autoantibodies to FcεRI have been detected both in allergic and in non-allergic asthmatics (28). Furthermore, the synthesis of human IgE may be directly regulated by basophils and mast cells, independently of the allergen-specific T-cell/B-cell interaction (29).

The superantigen theory

It is well established that respiratory tract virus infections are the most common cause of acute exacerbations in asthmatics (30). However, recent evidence has led to the hypothesis that an unidentified exogenous antigen (without systemic sensitization), infectious agent or endogenous allergen may be responsible for activating a non-specific production of IgE antibodies to epitopes expressed by these unidentified agents. There is some evidence that invasion of airway epithelial cells by *S. aureus* (and other microorganisms) causes the release of staphylococcal superantigens which act on airway B lymphocytes to cause class-switching with the local production of polyclonal IgE, together with IgE directed against staphylococcal antigens (which acts as a superallergen). This causes mast cell activation and release of bronchoconstrictor mediators and sensitizes mast cells to activation by triggers, such as exercise and cold air (via changes in surface osmolarity). Staphylococcal superantigens also cause polyclonal expansion and activation of T cells, resulting in increased T-helper type 2 (Th2) cells. Furthermore they also inhibit the function of regulatory T-cells (T-reg) resulting in further enhancement of Th2 and $CD8^+$ cells. Finally, staphylococcal superantigens may activate Th17 cells, leading to neutrophilic inflammation which shows a lower response to corticosteroids. In this context IL-17 also enhances the expression of glucocorticoid-receptor (GR)-alpha, which is transcriptionally inactive.
Staphylococcal infection of epithelial cells may also lead to damage and exposure of epitopes on epithelial structural proteins, such as cytokeratin-18, resulting in the formation of cytotoxic IgG antibodies, which further damage epithelial cells, making them more susceptible to further microbial colonization (8, 31).
Superantigens are derived not only from *S. aureus*, but also from other bacteria, including *Mycoplasma*, viruses, parasites and fungi, which can act as extremely potent polyclonal T cell mitogens (32).

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The monomeric IgE theory

Is IgE an independent sensitizer of effector cells (mast cells and basophils) triggering bronchial hyperresponsiveness even in the absence of specific sensitizations in non-allergic patients? Several *in vitro* studies have supported this idea showing that bronchial hyperresponsiveness in tracheal segments may occur after incubation with sera of patients with high IgE levels (33). On this basis, it might be reasonable to use monoclonal anti IgE therapy even in non-allergic asthmatics. Similar work has been performed by Khalesnikoff and colleagues (34), who observed that IgE, by binding to its high-affinity receptor (FcεRI), was able, on its own, without allergen cross-linking, to induce intracellular signaling pathways, resulting in the production of cytokines (IL-4, IL-6, IL-13, TNF-α) and the enhancement of mast cell survival (34). In addition, monomeric IgE can also directly bind and activate receptors present on eosinophils, neutrophils and monocytes. It has been demonstrated that monomeric IgE delayed spontaneous apoptosis of primary human neutrophils from asthmatics without allergen cross-linking (35).

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Conclusions

All these data support the role of IgE as a risk factor for asthma, independent of allergy, and further challenge the definition of intrinsic asthma as a "non-specific IgE-mediated" entity. Several studies support the evidence that serum IgE levels are associated with BHR and asthma independently of allergic status and specific allergic sensitization, but further studies are warranted to elucidate whether all these observations represent a causal, pathogenic or a non-causal association.
These observations have important implications, both

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preventive and therapeutic. First of all, the demonstration that intrinsic asthma is associated with local IgE production and, in some cases, with elevated non-specific circulating IgE, suggests that anti-IgE strategies may be appropriate also in non-allergic asthma. It is also possible that inhaled omalizumab, which is ineffective in extrinsic asthma (37), might be effective in patients with intrinsic asthma.

Moreover, if superantigens are involved in the pathogenesis of intrinsic asthma, measures to eradicate microorganisms might be effective. Another approach may be to neutralize the effect of superantigens such as *S. aureus* esotoxins with specific antibody therapy with intravenous immunoglobulin (IVIG), which has been used in the treatment of toxic shock syndrome associated with staphylococcal toxins (37). IVIG has not been specifically studied in intrinsic asthma, but it has been reported to be effective in some patients with severe asthma, although this has been disputed in controlled trials (38). Since autoantibodies to epithelial proteins have been reported, the use of immunosuppressants may be indicated, particularly in those difficult to-treat, steroid-dependent or resistant, intrinsic variants of asthma. Cyclosporine has been disappointing in the treatment of asthma in non-selected patients with severe disease (39), but perhaps might be more effective in patients with intrinsic asthma. New strategies include inhaled immunosuppressants (cyclosporine or tacrolimus), which might also be effective.

In conclusion, all these findings reinforce the evidence that asthma is associated with total IgE even in subjects with negative specific IgE, and that other immunological patterns may be involved, thereby opening up a new and exciting scenario as regards the future clinical management of asthma, particularly with reference to those difficult-to-treat and refractory expressions of the disease.

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