

Asthma and autoimmunity: a complex but intriguing relation

Expert Rev. Clin. Immunol. 4(6), 767–776 (2008)

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Asthma and autoimmune diseases apparently have little to share except for the involvement of the immune system in both types of disorder. However, epidemiological studies have shown that asthma and Type 1 diabetes, a typical autoimmune disease, are associated at the population level, and some experimental findings have suggested that autoimmune mechanisms might be operating in asthma as well. Female preponderance, increased incidence of antinuclear autoantibodies and detection of autoantibodies against either bronchial epithelial antigens or endothelial antigens in patients with nonallergic asthma suggest that the disease may have an autoimmune basis. Approximately 50% of patients with nonallergic asthma react to intradermal injection of autologous serum, indicating the presence of circulating vasoactive factors and suggesting an autoreactive mechanism. Recent findings in experimental animals support the involvement of an autoreactive mechanism in allergic asthma as well, indicating that human α -nascent polypeptide-associated complex, identified as an IgE-reactive autoantigen, has the potential to sensitize and induce immediate skin reactions and airway inflammation. In summary, asthma is a heterogeneous disorder characterized by chronic inflammation of the respiratory airways that can be triggered by allergen exposure or by other mechanisms, possibly autoreactive/autoimmune. The autoimmune hypothesis is further, indirectly, supported by the response to immunosuppressive drugs.

KEYWORDS: asthma • autoantibody • autoimmunity • nonallergic asthma

Asthma is a complex respiratory disease in which allergy is believed to play an important role, especially in the younger population. This belief is supported by the observation that asthmatic symptoms are often provoked by allergen exposure and associated with, or preceded by, other allergic manifestations, such as allergic rhinitis. Generally, it is believed that asthma and autoimmune disorders have little in common. Different immune mechanisms are thought to underlie asthma and autoimmune disorders; in fact, allergen-induced IgE-mediated mast cell activation is the key event leading to allergy symptoms, whereas a role for IgE and mast cells in autoimmune disorders has not been clearly identified. Furthermore, a predominant Th2 response has been detected in allergic asthmatics, whereas a Th1-driven response has been found in most patients with autoimmune disorders. However, in recent years, some epidemiological and experimental findings have suggested that there is not a clear dichotomy between asthma and autoimmune disorders [1–4]. A break in immunological tolerance with impairment of Tregs underlies both types of

disorder. Epidemiological studies have clearly shown an association at the population level between asthma and Type 1 diabetes [1]. In addition, an autoimmune mechanism might contribute to asthma, in particular, so-called nonallergic asthma, in which the etiology and pathomechanisms remain obscure. In order to understand why there may be a connection between asthma and autoimmunity, it is necessary to recall the classification and pathomechanisms of asthma. Two broad categories of asthma have been identified since the classification of Rackeman in 1947: ‘extrinsic’ asthma, which is triggered by exposure to exogenous causes, in particular, aeroallergens, and ‘intrinsic’ asthma, in which allergy cannot be demonstrated and asthmatic symptoms are not clearly related to exogenous agents [5]. Recently, the terms ‘extrinsic’ and ‘intrinsic’ have been replaced with ‘allergic’ and ‘nonallergic’, respectively. This last term, in fact, hides the poor knowledge of the pathomechanisms involved, since the disease is characterized only by a negative attribution (i.e., the lack of allergy). On the other

hand, some epidemiological and experimental findings suggest that allergic and nonallergic asthma are not clearly distinct immunopathological entities [6,7].

Both allergic and nonallergic asthma are characterized by inflammatory alterations of the respiratory airways, and IgE antibodies might be involved in both disorders. However, the role of IgE has only been defined clearly in allergic asthma. In fact, it is recognized that in allergic asthmatics, the main event triggering bronchial inflammation is IgE-mediated allergen-induced mast-cell degranulation, followed by recruitment and activation of other inflammatory cells, including eosinophils, basophils and T lymphocytes [8,9]. A role for IgE antibodies in nonallergic asthma has been proposed but their possible contribution to the disease pathomechanism has not yet been elucidated. Burrows *et al.* showed a strong association between high levels of total serum IgE and asthma, both in allergic and nonallergic asthmatics [10]. Elevation of total serum IgE was found to be associated with asthma in non-allergic individuals, supporting the role of IgE as a risk factor for asthma, independent of allergy [11]. Furthermore, local IgE production and class-switch recombination to IgE have been detected in the bronchial mucosa of allergic and nonallergic asthmatics [12,13]. On the other hand, some clinical and immunopathological findings allow the distinguishing of allergic and nonallergic asthma; for example, nonallergic asthma has a later onset in life, female preponderance, a more frequent association with nasal polyposis and a more severe clinical course [14]. Additionally, analysis of blood and bronchoalveolar lavage cells as well as bronchial biopsies from allergic asthmatics have revealed a predominant activation of Th2 lymphocytes, with enhanced production of IL-4, IL-5 and IL-13 [15]. Conversely, cytokine production in nonallergic asthmatics is not so clearly Th2 oriented; in fact, an increased production of either IL-2 (a Th1 cytokine) or IL-5 (a Th2 cytokine) has been detected [16]. In summary, allergic and nonallergic asthma share a common background, characterized by inflammatory changes of the respiratory airways, and the immunopathological differences that can be detected are quite subtle. However, it is clear that in allergic asthma, bronchial inflammation and respiratory symptoms are triggered by allergen exposure and consequent IgE-mediated mast cell activation, whereas in nonallergic asthma, the initiating event is still elusive.

Epidemiological data on the association between asthma & autoimmune diseases at the population level

The International Study on Asthma and Allergy in Childhood has shown large variations in the prevalence of asthma, with industrialized and English-speaking countries showing the highest prevalence [17]. International studies regarding the occurrence of autoimmune disorders have been performed mainly for Type 1 diabetes and have demonstrated that, except in some areas, such as Sardinia and Madeira, where genetic conditioning probably plays a heavy role, the incidence of Type 1 diabetes is higher in industrialized than developing countries, with Scandinavian countries showing the highest prevalences [18,19]. In the last few decades, an increase in asthma prevalence has occurred in industrialized countries and has been paralleled by an increase in the incidence of Type 1 diabetes.

This observation is surprising since asthma and allergy are considered to be inflammatory disorders mediated by Th2 lymphocytes, whereas Type 1 diabetes is considered to be a Th1-mediated autoimmune disease. However, at the population level, a positive correlation between the prevalence of asthma symptoms and the incidence of Type 1 diabetes has been found [1]. A possible explanation could be the presence of common risk factors for asthma and Type 1 diabetes [2,20]. Interestingly, Type 1 diabetes and asthma are positively associated with the gross national product (GNP) at the population level, and countries with low infant mortality rates tend to have higher incidences of these immune-mediated diseases [21]. Similar data deriving from epidemiological reports indicate that for other autoimmune disorders, such as multiple sclerosis and inflammatory bowel diseases, the incidence rate is again higher in industrialized than developing countries, with affluence being a possible risk factor [22–24]. Although GNP reflects many societal and lifestyle differences, it is notable that a high socioeconomic status implies a reduced or delayed exposure to infectious agents. The reduced pressure of infectious agents on the immune system throughout life might contribute to an increase in the susceptibility to asthma, Type 1 diabetes and other autoimmune diseases.

The hygiene hypothesis has been proposed to explain the rising trend of Th2-mediated diseases, such as asthma and allergies, in industrialized and affluent countries [25,26]. According to this theory, changes in the exposure to infectious diseases and microbial products is associated with the increased prevalence of allergic diseases observed in recent decades. It has been suggested that limited exposure to bacterial and viral pathogens during early childhood results in insufficient stimulation of Th1 cells, which, in turn, cannot counterbalance the expansion of Th2 cells, and predisposes to allergy [27]. More recent observations point to a reduced generation of Tregs [28].

Association of asthma & autoimmune diseases at the individual level: a controversial issue

Data regarding the association of asthma with autoimmune disorders, such as Type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, inflammatory bowel disease and multiple sclerosis are controversial. Autoimmune disorders are mediated by a predominant Th1 response, whereas asthma and allergies are characterized by a predominant Th2 response. According to the Th1/Th2 paradigm, allergy and autoimmune diseases should be mutually exclusive at the level of the individual. A reduction in the frequency of allergic symptoms was described in children with Type 1 diabetes by Caffarelli *et al.* [29]. In a recent epidemiological survey carried out using cross-sectional data from the Israeli Defense Force, asthma status was found to affect the prevalence of major autoimmune disorders in military recruits and pre-existing asthma seemed to protect against the development of autoimmune disorders [30]. By contrast, an increased prevalence of asthma symptoms in children with Type 1 diabetes, rheumatoid arthritis and celiac disease was reported by other authors [31]. Analysis of adult data from the third National Health and Nutrition Examination Survey in the USA demonstrated that physician-diagnosed common allergic disorders were positively

associated with reports of physician-diagnosed auto-immune disorders [32]. It is also interesting to note that bronchial hyper-reactivity and respiratory symptoms are common in patients with autoimmune disorders, such as Sjögren's syndrome, rheumatoid arthritis and systemic sclerosis [33–35]. In these patients, bronchial hyperreactivity is likely to be a consequence of structural changes and infiltration of inflammatory cells [36].

Infections, IgE & autoimmunity: hypotheses on the pathomechanisms of nonallergic asthma

The strong association between high levels of total serum IgE and asthma, either in allergic or nonallergic asthmatics, has led to the hypothesis that IgE antibodies are involved in the disease pathomechanism [10]. However, the role of IgE-mediated mast-cell activation in precipitating asthma attacks in patients with allergic asthma is well known, whereas it is still unclear how IgE and mast cells participate in nonallergic asthma. It has been proposed that nonallergic asthmatics produce specific IgE for exogenous or endogenous antigens rather than conventional aeroallergens [37]. Among these antigens, a promising candidate is the enterotoxin of *Staphylococcus aureus*, but other bacterial, fungal and viral antigens have also been considered [38]. The production of specific IgE for respiratory syncytial virus was demonstrated several years ago and it is possible that a similar mechanism operates in asthma exacerbations induced by different viruses [39]. Several lines of evidence indicate that infections are important in both exacerbation and inception of nonallergic asthma. In addition to the production of virus-specific IgE antibodies, epithelial injury, polymorphonuclear-dependent inflammation and enhanced mediator release may be responsible for asthma exacerbations induced by infectious agents [40]. Ten Brinke *et al.* have observed that persistent airflow limitation in adult-onset nonallergic asthma is associated with serologic evidence of *Chlamydia pneumoniae* infection [41]. However, the role of *C. pneumoniae* seems prominent in the acceleration of the loss of lung function in asthmatics rather than in asthma onset. A longitudinal study by Pasternack *et al.* suggested that chronic *C. pneumoniae* infection promotes the development

of airflow limitation in adults with nonatopic asthma, but at the population level, any possible effect of *C. pneumoniae* infection on asthma incidence is of minor significance [42]. If *C. pneumoniae* does not have a causative role in asthma, it is worth remembering, however, that nonallergic asthmatics often report influenza-like illness preceding their disease onset. This has led us to suppose that nonallergic asthma is the consequence of autoimmunity or autoallergy, triggered by an infectious agent through the mechanism of molecular mimicry. A similar mechanism has been hypothesized for other autoimmune disorders in which exposure to an infectious agent is supposed to induce an autoimmune response in genetically predisposed subjects. Airway inflammation and damage in nonallergic asthmatics might be due to cell-mediated cytotoxicity and/or to direct effects of autoantibodies, as happens in most disorders recognized as autoimmune.

Increased frequency of autoantibodies in patients with allergic & nonallergic asthma

Increased levels of autoantibodies have been detected in most autoimmune disorders. An autoimmune pathomechanism has long been suspected, especially in nonallergic asthma, and circulating autoantibodies were, therefore, assayed by several authors (Box 1). Anti- β_2 -adrenergic receptor autoantibodies were suspected as the cause of β -adrenergic hyporesponsiveness in patients with allergic rhinitis and asthma [43]. In the 1960s, antinuclear and anti-lung antibodies were detected in asthmatic patients by Leopold *et al.* [44,45]. Subsequently, an increased frequency of antinuclear antibodies was detected by Lidor *et al.* in patients with nonallergic asthma [46]. Szczeklik *et al.* found an incidence of antinuclear antibodies in 55% of patients with aspirin-induced asthma, 39% of patients with allergic asthma, 41% of patients with nonallergic asthma and 11% of normal controls [47]. In a recent investigation, we detected antinuclear antibodies at a titer of at least 1:160 in 15 out of 32 patients with nonallergic asthma (47%), a significantly higher incidence than reported in the general population (6–15%) [48]. We believe, however, that antinuclear antibodies do not have a direct pathogenic role in asthma, but simply indicate a propensity towards

Box 1. Main studies on autoantibodies in asthmatic patients.

- Venter *et al.* Autoantibodies to β_2 -adrenergic receptors in allergic rhinitis and asthma [43]
- Leopold *et al.* Antinuclear antibodies in bronchial asthma [44]
- Leopold *et al.* Autoimmune antibodies to human lung in bronchial asthma [45]
- Lidor *et al.* Increased frequency of antinuclear antibodies in patients with nonallergic asthma [46]
- Szczeklik *et al.* Presence of antinuclear antibodies in 55% of patients with aspirin-induced asthma, 39% of patients with allergic asthma, 41% of patients with nonallergic asthma and 11% of normal controls [47]
- Comi *et al.* Increased frequency of antinuclear antibodies in patients with nonallergic asthma [48]
- Nahm *et al.* Increased levels of circulating autoantibodies to human bronchial epithelial cells in adult patients with nonatopic asthma [49]
- Nahm *et al.* Identification of cytokeratin 18 as a bronchial epithelial autoantigen associated with nonallergic asthma [50]
- Nahm *et al.* Detection of IgG autoantibodies against bronchial epithelial cell-derived α -enolase in patients with severe asthma [51]
- Lassalle *et al.* Circulating IgG autoantibodies, directed against a common 55-kDa antigen shared by platelets and cultured endothelial cells, were found in 34 out of 97 asthmatic patients. These autoantibodies were mainly restricted to patients with negative cutaneous prick tests and corticosteroid-dependent asthma and correlated with disease severity [52]
- Inganäs *et al.* Anti-IgE antibodies in human serum: occurrence and specificity [54]

autoimmune phenomena due to an immune system dysregulation, in particular a reduced efficiency of Tregs, which should prevent immune responses against autoantigens. In addition to antinuclear antibodies, other autoantibodies have been found in asthmatic patients, including antibodies against bronchial epithelial cells, endothelial antigens, platelets and IgE [49–54]. Circulating autoantibodies against the bronchial epithelial antigen cytokeratin 18 were detected in 43% of patients with nonallergic asthma versus 11% of patients with allergic asthma [49,50]; moreover, bronchial epithelial cell-derived α -enolase was identified as an autoantigen associated with severe asthma. In fact, IgG autoantibodies to α -enolase were proposed as a biological marker for severe asthma [51]. Circulating IgG autoantibodies, directed against a common 55-kDa antigen shared by platelets and cultured endothelial cells, were found in 34 out of 97 asthmatic patients by Lassalle *et al.* [52]. These autoantibodies were mainly restricted to patients with negative cutaneous prick tests and corticosteroid-dependent asthma, were often associated with T-cell reactivity to the same 55-kDa antigen and correlated with disease severity [52]. It has been suggested that these antibodies might contribute to airway inflammation and damage, but their role has not been definitely proven (FIGURE 1). However, it is worth mentioning an interesting report by Lassalle *et al.*, describing a patient with severe corticosteroid-dependent asthma associated with autoantibodies to platelets, who was successfully treated with plasmapheresis [53]. Significantly raised levels of anti-IgE antibodies were found in patients suffering from allergic asthma, as compared with nonallergic blood donors, but their role in the pathomechanism of the disease has yet to be defined [54].

An animal model supporting the role of autoreactivity in asthma

Recently, Bunder *et al.* demonstrated that BALB/c mice sensitized to human α -nascent polypeptide-associated complex, recently identified as an IgE-reactive autoantigen in patients with severe forms of atopy, developed immediate skin reactions and airway inflammation, accompanied by eosinophil and neutrophil accumulation, airway hyperresponsiveness and perivasculitis of lung veins following antigen challenge [55]. The authors concluded that sensitization with a foreign antigen mimicking a self antigen can induce an allergic immune response of a mixed Th2 and Th1 profile that is associated with autoreactivity. It has been proposed that immune mechanisms induced either by molecular mimicry or as a consequence of chronic allergic inflammatory processes may contribute to the perpetuation of allergic immune responses, even in the absence of exogenous allergens, and may contribute to the development of autoimmune diseases [55,56].

Histamine-releasing & vasoactive factors as possible contributors to nonallergic asthma

In recent years, chronic urticaria, formerly considered to be 'idiopathic' in the vast majority of patients, was shown to be an autoimmune disorder in a significant proportion of cases [57]. Recognition of chronic urticaria as an autoimmune disorder stemmed from the observation that intradermal injection of autologous serum caused a wheal-and-flare reaction in 30–60% of patients, whereas it was devoid of any effect in most normal subjects [58]. Sera from chronic urticaria patients were shown to induce histamine release

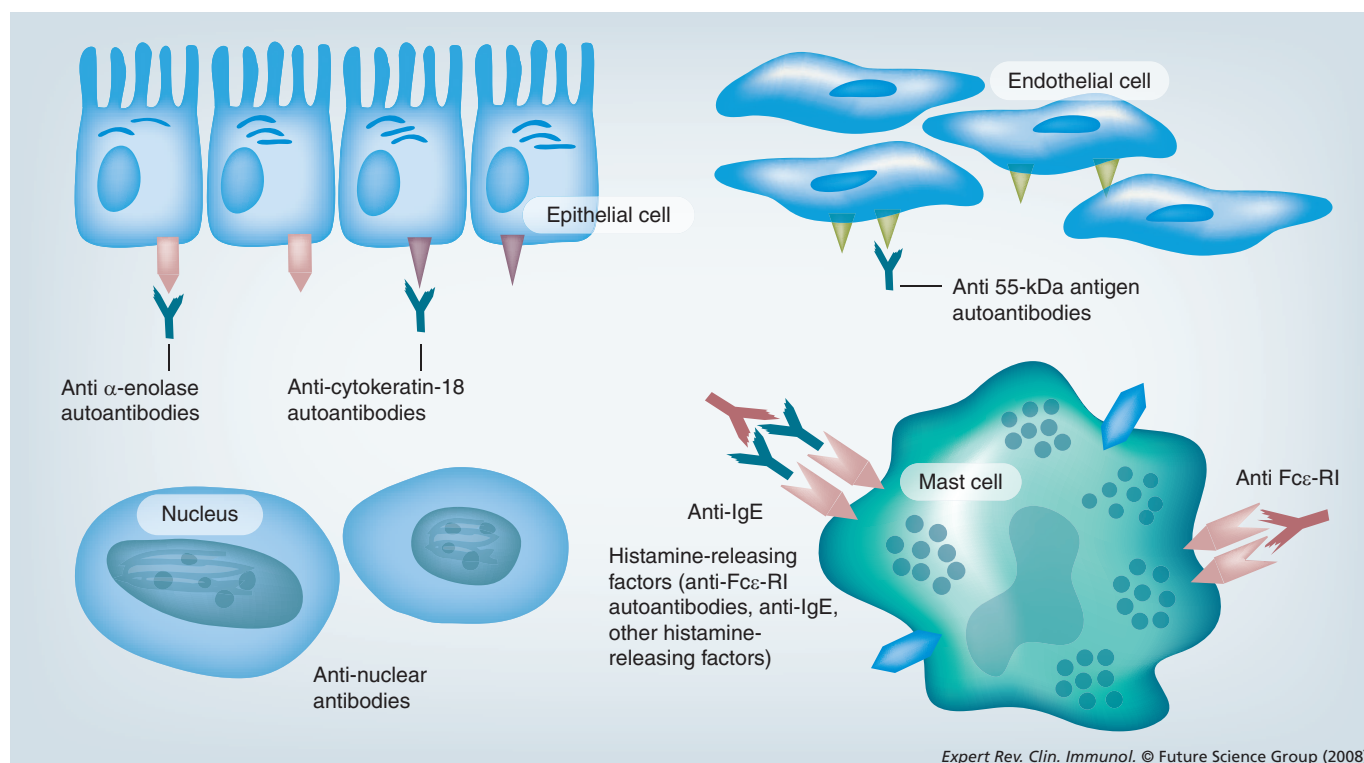


Figure 1. Autoantibodies and histamine-releasing factors that might be involved in the pathomechanism of nonallergic asthma.

from basophils and dermal mast cells *in vitro*, and this histamine-releasing activity was mainly associated with IgG autoantibodies directed against the high-affinity receptor for IgE (FcεRI) or against IgE [59]. We hypothesized that a similar mechanism might be operating in nonallergic asthma and decided to perform autologous serum skin test (ASST) in these patients. We observed that approximately 50% of the patients with nonallergic asthma showed skin reactivity to intradermal injection of autologous serum, but only a minority of patients' sera induced *in vitro* histamine release from autologous basophils or from normal donors' basophils [48,60]. Indeed, ASST positivity in most nonallergic asthmatics cannot be ascribed to the presence of circulating histamine-releasing autoantibodies, which can be detected in only a small group of patients. ASST positivity might be due to other, as yet undefined, vasoactive factors. Activation of the coagulation cascade with thrombin generation has been demonstrated in chronic urticaria patients showing skin reactivity to autologous serum and plasma [61], and thrombin is able to induce edema through an increase in vascular permeability [62,63]; an effect that, notably, is much reduced by antihistamines and totally abolished if mast-cell granules are depleted [64]. Perhaps, also in asthmatics, skin reactivity to autologous serum and plasma is related to the activation of the coagulation cascade and the generation of vasoactive factors. The observation of ASST and basophil histamine-release positivity in some nonallergic asthmatics suggests that, at least in some cases, histamine-releasing or vasoactive factors may play a contributory role. In line with this hypothesis is the observation that skin reactivity to autologous serum is related to airway hyperresponsiveness in patients with asthma [65]. A possible pathogenic role for aberrant autoantibodies against FcεRI or IgE is also supported by the observation that bronchial hyperreactivity is common in patients with chronic urticaria [66]. Circulating histamine-releasing factors, mainly represented by autoantibodies directed against FcεRI or IgE, can be detected in almost half of chronic urticaria patients and are supposed to activate skin mast cells. These histamine-releasing factors might also activate bronchial mast cells, causing bronchial hyperreactivity, which has been frequently been observed in chronic urticaria patients.

Common features of asthma & inflammatory bowel diseases

Asthma is a chronic inflammatory disease of the respiratory airways and asthmatic patients usually present respiratory, and not gastrointestinal, symptoms. However, inflammatory changes of the gastrointestinal mucosa are common in asthmatic patients, and increased numbers of intraepithelial lymphocytes, eosinophils and mast cells can be detected in duodenal biopsies [67]. Accordingly, intestinal permeability is increased in asthmatic patients, suggesting a general defect of the mucosal system [68]. Inflammatory bowel diseases are characterized by predominant intestinal inflammation, and bronchial hyperreactivity and subclinical respiratory abnormalities are common [69]. It has been suggested that these abnormalities are due to a latent inflammation of the bronchial mucosa, as also indicated by the detection of eosinophilic infiltration in the absence of overt pulmonary disease [70].

In addition to the inflammation of the respiratory airways and gastrointestinal mucosa, asthma and inflammatory bowel diseases share other features, such as the possible role of autoimmunity and the increased frequency of autoantibodies specific for various antigens, including bronchial and intestinal antigens [71,72]. This particularly holds true for nonallergic asthma; whereas, in allergic asthma, the main pathomechanism is allergen-induced IgE-mediated mast-cell activation.

Expert commentary & five-year view

For decades, extrinsic (allergic) and intrinsic (nonallergic) asthma has been considered as distinct pathological entities, but it is now clear that both disorders represent two faces of an inflammatory process affecting the respiratory airways. In allergic asthma, bronchial inflammation is triggered by IgE-mediated mast cell activation, whereas in nonallergic asthma, bronchial inflammation is triggered by complex mechanisms, probably also involving IgE and, perhaps, autoimmunity. Asthma therapy currently relies on the use of local steroids, alone or in combination with long-acting β_2 -agonists and leukotriene agonists [73]. This treatment allows asthma control in 90–95% of patients, but has not been proven to prevent respiratory airways remodeling. However, there is a small group of patients with severe disease who need additional therapy consisting of oral corticosteroids and theophylline [101]. In the past, various immunosuppressive and experimental drugs, including methotrexate, ciclosporin, gold salts and troleandomycin, have been used in patients with severe steroid-dependent asthma but most studies have failed to demonstrate an acceptable risk–benefit ratio [74–79]. Methotrexate has been the most widely-used steroid-sparing agent in patients with severe asthma, but the conclusion of the Cochrane database systematic reviews has been that the small potential to reduce the impact of steroid side effects is probably insufficient to offset the adverse effects of methotrexate [76].

In recent years, a monoclonal anti-IgE antibody, omalizumab, has been made available and has been successfully employed in patients with allergic asthma, reducing asthma exacerbations and the use of inhaled corticosteroids [80,81]. Recent controlled multicenter studies have shown that omalizumab as an add-on therapy can reduce the rate of asthma exacerbations and emergency visits in patients with severe-persistent asthma who are inadequately controlled despite best available therapy with high-dose inhaled corticosteroids and long-acting β_2 -agonists [82]. So far, targeting IgE has proven to be an effective strategy in patients with allergic asthma, but the potential clinical applications of omalizumab are rapidly expanding. In fact, monoclonal anti-IgE antibodies have been employed with benefits in patients with chronic urticaria refractory to conventional treatment [83], in patients with Churg–Strauss syndrome [84] and in order to prevent anaphylactic reactions in patients with food allergy, systemic mastocytosis and hymenoptera venom allergy [85–87]. Omalizumab has not been tested in patients with nonallergic asthma, but several findings provide the rationale for its use in these kinds of patients. Elevation of total serum IgE was found to be associated with asthma in nonallergic individuals, supporting the role of IgE as a risk factor

for asthma, independent of allergy [10,11]. Furthermore, local IgE production has been demonstrated in bronchial biopsies from non-allergic asthmatics [12]. A role for IgE and mast cells in nonallergic asthma is probable, although the pathomechanism of nonallergic asthma has not yet been fully elucidated. Since omalizumab has the capacity to bind circulating IgE and prevent mast cell activation, it might also have therapeutic efficacy in patients with severe steroid-dependent nonallergic asthma and elevated IgE levels.

In addition to omalizumab, several novel anti-inflammatory therapies are in different stages of clinical development. Other options in clinical development either target proinflammatory cytokines (e.g., IL-4, IL-5, IL-13 and TNF- α) or inflammatory cells (e.g., Th2 cells and eosinophils) [88]. Of particular interest is the use of TNF- α antagonists in patients with severe steroid-dependent asthma. Increased expression of membrane-bound TNF- α , TNF- α receptor 1 and TNF- α -converting enzyme by peripheral blood monocytes was found in patients with refractory asthma, compared with patients with mild-to-moderate asthma and controls, and the administration of the soluble TNF- α receptor, etanercept, was of benefit in these kinds of patients [89]. Indeed, TNF- α can be considered as a therapeutic target in patients with steroid-dependent severe asthma, and clinical experience with TNF- α antagonists will increase in the near future [90]. However,

the few studies concerning anti-TNF- α therapy in severe asthmatics have shown a marked heterogeneity in response, suggesting that only a small subgroup of patients is likely to benefit from this therapy. In general, what appears mandatory in a modern approach to the asthmatic patient is to characterize the asthma phenotype in order to identify the best therapy, and to evaluate the individual risk–benefit ratio of the proposed treatments [91]. For example, steroids are active on eosinophilic inflammation, whereas they are scarcely active on neutrophilic inflammation, which can be detected in patients with the most severe forms of asthma. Careful evaluation of a patient's characteristics, including sputum examination, evaluation of blood eosinophilia and measurement of exhaled nitric oxide and total serum and specific IgE levels, allows the best therapeutic approach to be delineated. Indeed, we are headed towards more patient-tailored asthma treatment.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Epidemiological studies suggest a link between asthma and autoimmune disorders.
- The increase in asthma prevalence, which has occurred in affluent industrialized countries in the last few decades, has been paralleled by an increase in the incidence of autoimmune/immune-mediated disorders, such as Type 1 diabetes, multiple sclerosis and inflammatory bowel diseases.
- A positive correlation between the prevalence of asthma symptoms and the incidence of Type 1 diabetes has been found at the population level, suggesting the existence of common risk factors.
- A high socioeconomic status implies a reduced and delayed exposure to infectious agents, leading to an impaired generation of Tregs and favoring a break in immune tolerance. The reduced pressure of infectious agents on the immune system throughout life might increase the susceptibility to asthma, Type 1 diabetes and other autoimmune diseases.
- IgE-mediated mast cell activation plays a fundamental role in allergic asthma and probably participates in the pathomechanism of nonallergic asthma. However, an autoimmune/autoreactive mechanism may also underlie asthma, in particular asthma of the nonallergic type.
- Animal models support an autoreactive/autoimmune mechanism in asthma; BALB/c mice sensitized to human α -nascent polypeptide-associated complex, recently identified as an IgE-reactive autoantigen in patients with severe forms of atopy, develop immediate skin reactions and airway inflammation, accompanied by eosinophil and neutrophil accumulation and airway hyperresponsiveness.
- An increased frequency of autoantibodies has been demonstrated in patients with allergic and nonallergic asthma.
- Anti- β_2 -adrenergic receptor autoantibodies were suspected to be the cause of β -adrenergic hyporesponsiveness in patients with allergic rhinitis and asthma.
- An increased frequency of antinuclear antibodies was detected in patients with either nonallergic or allergic asthma. These autoantibodies probably do not have a pathogenic role, but reflect a propensity toward autoimmune phenomena due to immune-system dysregulation.
- Autoantibodies against bronchial epithelial cells (e.g., cytokeratin 18 and α -enolase), endothelial antigens and platelets were detected in patients with asthma, in particular nonallergic and corticosteroid-dependent asthma.
- Approximately half of patients with nonallergic asthma show skin reactivity to intradermal injection of autologous serum, suggesting the presence of circulating vasoactive factors. Positivity of an autologous serum skin test is associated with bronchial hyperresponsiveness.
- Demonstration of the involvement of IgE antibodies and mast cells in nonallergic asthma may provide the rationale for the additional use of omalizumab in this form of disease, particularly in patients with high IgE levels and steroid-dependent asthma.
- Identification of an autoreactive/autoimmune mechanism in allergic and nonallergic asthma may reinforce the use of the immunosuppressive approach towards patients with severe asthma.
- Characterization of the asthma phenotype and elucidation of the molecular mechanisms may lead to patient-tailored therapy.

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