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Severe asthma and allergy: mechanisms, diagnostics and treatment

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Introduction

Severe asthma and allergic disease were the topic of a symposium sponsored by *Journal of Internal Medicine* that was held in Stockholm on 11–12 November 2011. Several of the reviews by internationally recognized speakers are presented in this issue of the journal [1–4].

Asthma and allergy: common and chronic conditions

Asthma and allergic diseases are a public health concern of pandemic proportions, affecting around 300 million patients of all ages and ethnic groups worldwide. In a study of lifetime risk of asthma conducted in Ontario, it was found that one in three individuals had physician-diagnosed asthma. It is interesting that one in five individuals was diagnosed before the age of 20. This demonstrates the long-term pattern of asthma, compared to other chronic diseases such as diabetes and coronary heart disease [5].

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In the majority of subjects with persistent, mild to moderate asthma, the disease can be relatively well controlled by the use of currently available medications [2]. However, 5–10% of patients suffer from particularly severe asthma that is poorly controlled clinically and often refractory to standard treatment. Chronic rhinosinusitis with or without allergy affects more than 10% of the European population, and is often associated with asthma [3]. There is good evidence that both inherited and environmental factors influence the risk of developing asthma. Large-scale analyses of functional genetics, such as gene expression and epigenetic studies, have been made possible by the Human Genome Project. To date, no single gene has been identified that can explain the majority of asthma cases or predict disease prognosis [1]. With respect to treatment, allergen-specific immunotherapy (SIT) is the only currently available medical intervention that has the potential to affect the natural course of allergic disease and reduce the risk of new sensitizations. Moreover, immunotherapy has been shown to have disease-modifying capacities with the ability to prevent the progression of allergic diseases. However, current therapeutic allergy vaccines are still prepared from relatively ill-defined allergen extracts [4].

Genetics of asthma: current research

In the first review from the symposium, a number of important issues regarding the genetics and epigenetics of asthma are discussed by Melén and Pershagen [1]. Examples of genes that have been particularly associated with asthma are *ORMDL3*, *ADAM 33*, *NPSR1* and *IL4RA* [6]. The first genome-wide association study (GWAS) of asthma was published in 2007 and genetic variants regulating *ORMDL3* expression on chromosome 17q21 were identified as strong determinants of asthma susceptibility ($P < 10^{-11}$) [7]. *ORMDL* genes have further been shown to have high sequence conservation between many species, which supports an important role for cellular functions.

Although the genetic association between *ORMDL3* and childhood asthma seems to be very strong across studies and populations, the disease risk association with a single genetic variant was reported to be fairly weak in a meta-analysis by Moffat *et al.* [7]. Twenty-one GWASs of asthma or asthma-related diseases have been published to date, and markers in several reported genes have been identified [8]. Rare variants or mutations are not identified by current GWAS chips and cannot be evaluated in these studies. Furthermore it has been suggested that rare variants are important for several complex diseases [9], but few studies have addressed their role in the pathogenesis of asthma. 'Next-generation sequencing' (NGS) technologies are

currently undergoing rapid development [10]. A major advantage of whole-genome sequencing is the possibility to detect genetic variants other than single-nucleotide polymorphisms, including rare variants. NGS will soon offer large-scale methods for use in genetic studies as well as clinical settings.

The focus of epigenetic analyses (e.g. DNA methylation) within the respiratory field has been on specific candidate genes, and large-scale global methylation analyses are awaited and have yet to be conducted. Thus, the role of methylation status in childhood asthma is still poorly understood, both at a single-gene level and on a global genomic level [11, 12]. New insights into the genetic impact of methylation on the pathogenesis of severe asthma are emerging, but further work is required to fully understand the mechanisms involved.

Severe asthma

In the second symposium review, Kupiec and Wenzel focus on severe asthma [2].

Approximately 5–10% of all asthmatic children and adults have chronic symptoms and/or recurrent exacerbations despite maximum treatment with conventional medications. Severe asthma can be divided into three groups: untreated, difficult-to-treat and treatment-resistant severe asthma (these include asthma for which control cannot be achieved despite the highest level of recommended treatment and asthma for which control can be maintained with adherence to recommended treatment and environmental measures). The authors review the current networks for severe asthma as well as studies to harmonize the phenotyping of patients with the severe form of a heterogeneous disease. In 2006 it was proposed that for phenotypes to become clinically meaningful, pathobiology must be linked to clinical features, genetics, physiology and natural history [13]. More recently, statistical approaches to defining phenotypes have been reported. To describe the heterogeneity of asthma, a cluster analysis was applied to identify phenotypes in asthmatic children with different manifestations of the disease [14]. Four clusters were identified based on 12 variables including demographic data, duration of asthma, FEV1 (Forced Expiratory Volume) before and after inhalation of salbutamol, atopy, exhaled nitric oxide and medication. Children classified as severely asthmatic were present in all clusters, confirming the heterogeneity of the disease, and no cluster corresponded to the 2008 definition of severe asthma from the Global Initiative for Asthma. In addition, Brasier *et al.* [14] identified a pattern of cytokine expression in bronchoalveolar lavage fluid that characterized a distinct subset of patients with severe and bronchial hyper-responsiveness.

Many different risk factors for severe asthma have been recognized; decreased lung function, severe and multiple allergies, exposure to triggering factors and recurrent pulmonary infections

are among the most common. Nevertheless, identifying combinations of genetic disposition and external factors remains a challenge. Dysregulation of lipid mediators, including reduced concentration and receptor expression of lipoxin A₄ [15] as well as reduced concentration of prostaglandin D₂ [16], has also been reported in severe asthma, which may offer additional therapeutic options. Another concern is the limited availability of new drugs for treatment of the currently therapy-resistant patients with asthma.

Rhinosinusitis

Chronic rhinosinusitis (CRS) and airway inflammation are the topics for review in the third symposium presentation by Bachert and Zhang [3]. Phenotypes of CRS can be differentiated based on mucosal remodelling and inflammatory patterns. The authors discuss recent findings that point to staphylococcal superantigens as possible causal agents in the intrinsic form of severe asthma. In addition, they note that an anti-IgE strategy has shown promising therapeutic potential in non-atopic patients with nasal polyps and asthma.

The differentiation of CRS into several subgroups based on specific remodelling and inflammatory cell and cytokine patterns is discussed, along with a summary of the factors that may predict asthma comorbidity in patients with CRS [17]. There is a major difference in asthma comorbidity between CRS patients with and without nasal polyps, which might be related to the inflammatory profile within the mucosal tissue. The authors report the findings of a recent pan-European sinusitis cohort study within the GA2LEN research programme (Global Allergy and Asthma Network of Excellence). It was found that asthma comorbidity was significantly higher in patients with nasal polyps, compared to those without polyps. Thus, in a group of patients with nasal polyps, indicators for asthma comorbidity were identified as the Th2 cytokine interleukin-5 and IgE, specifically IgE antibodies against *Staphylococcus aureus* enterotoxins. These observations are consistent with previous findings of an impact of staphylococcal superantigens on airway disease but also demonstrate an impact of these antigens on the severity of sinus disease and the presence of lower airway involvement. Bachert and Zhang hypothesize that the presence of enterotoxin IgE in serum indicates the involvement of staphylococcal superantigens in the pathophysiology of severe asthma. This involvement is most probably mediated by both superantigen effects on T cell activation and induction of IgE production in mucosal plasma cells. These interesting findings present new treatment possibilities for a group of severely affected asthma patients.

New strategies for allergy vaccines

At present, SIT is prepared using relatively ill-defined allergen extracts. Treatment is based on the repeated administration of the disease-causing allergen in order to modify the allergen-specific immune response so that higher doses of the allergen can be tolerated. It has been shown that SIT is similarly effective in alleviating allergy symptoms compared with pharmacological treatments both for asthma [18] and allergic rhinitis [19, 20]. Furthermore, it induces prolonged clinical remission accompanied by a persistent alteration in immunological reactivity. In the last review from the symposium presented in this issue, Valenta and co-workers provide an overview of the development and mechanisms of SIT. They also review the new forms of therapeutic vaccines, and discuss the future options for this type of treatment for asthma [4].

SIT has developed through knowledge of the structure of the most common allergen molecules, allowing the production of synthetic peptides, pure recombinant allergens and hypoallergenic derivatives. Valenta *et al.* discuss the different possible SIT strategies and report that recombinant allergen-based vaccines may in fact replace allergen extract-based vaccines. In order to make administration of allergen to a patient more convenient and efficient, and eventually allowing self-administration, new routes for allergen delivery have been tested. The intralymphatic route seems to be clinically effective after only a few injections but the need for administration of intranodal injections under ultrasonographic guidance may be a limitation [21].

As a further development of recombinant hypoallergenic allergen vaccines, the authors consider the use of carrier-bound B cell epitope-containing peptides. These peptides are selected to eliminate the side effects of both IgE and T cells, and to induce allergen-specific IgG antibodies. In this respect the use of virus-derived carrier proteins offers an additional opportunity because it may lead to vaccines that induce protective IgG antibodies both against the allergen as well as against infectious diseases [22]. Will SIT become a therapeutic option for prophylaxis and prevention of allergic sensitization? Taking into consideration the time window during which allergic sensitization can occur, the authors discuss two possibilities for prophylactic intervention, pre-natal or early post-natal, and the different treatment strategies that can be used. Thus, today we have the knowledge to create novel types of allergy vaccines for programming the immune system in different ways and with new routes for delivery. Thus SIT is a promising therapeutic option for asthma and allergic diseases.

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Conflict of interest statement

None of the authors has any conflicts of interest to declare.

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- Accepted Article
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