

Review

Current Understanding and Therapy of Asthma Workshop Summary

Kuender D. Yang¹, Yu-Zhi Chen² and Shau-Ku Huang^{3,4}

The prevalence of asthma has increased globally in the past 2 decades. To address this critical issue, a workshop on "Current Understanding and Therapy of Asthma" was recently held in Beijing, as a part of the 10th International Conference of the Society of Chinese Bioscientists in America (SCBA). Several pertinent topics were addressed by leading experts from China, Taiwan, Japan and the US, which include epidemiology, the molecular genetic mechanism, pathogenesis, treatment and prevention of asthma. This article highlights the issues presented and discussed in this ground-breaking symposium emphasizing this important public health problem in the Chinese population. *Cellular & Molecular Immunology*. 2004;1(6):436-439.

Key Words: asthma, prevalence, pathogenesis, therapy, prevention

Introduction

The worldwide prevalence of asthma has dramatically increased in the past 2 decades, but the reason why this is the case remains an unresolved and critical issue. Asthma is a debilitating disease, affecting more than 155 million people in the developed world, and the cost of treating asthma in the USA alone is approximately US \$6 billion per year. This highlights the need for a better understanding of the disease mechanism and for improved therapeutic strategies. To this end, a workshop was recently held with the aim to share clinical experience and exchange scientific ideas about this growing public health problem, especially in the Asian populations. This workshop, which is a part of the SCBA International Conference, is the first of this kind in the entire 18 years history of the SCBA to emphasize this critical disease in the Chinese population.

The mission of the SCBA is to promote the understanding of communication about biosciences among Chinese bioscientists all over the world through, in part, a bi-annual international conference. The 10th SCBA International Conference was held in Beijing between July 18-23, 2004. The symposium on "Current Understanding and Therapy of Asthma" was co-chaired by Professor

Shau-Ku Huang from Johns Hopkins Asthma and Allergy Center, and Professor Nanshan Zhong from Guangzhou Institute of Respiratory Diseases. The scope of this symposium embraced an integrated understanding of the epidemiology, molecular pathogenesis, pathology, therapy and prevention of asthma. Speakers of the symposium came from the United States, Japan, Taiwan, Beijing and Guangzhou. Further, the symposium and attendees were kindly hosted by Professor Yu-Zhi Chen and her colleagues in Capital Institute of Pediatrics, Beijing.

Scope of the asthma symposium

Asthma is a disease defined by an inflammatory airway response mostly elicited by extrinsic allergens or intrinsic factors under the influence of genetic background. The symposium began with an introduction by Professor Shau-Ku Huang, highlighting the prevalence and current understanding of asthma. It is evident that a complex molecular and genetic network determines the expression of atopic asthma, dysregulation of IgE production and Th2-biased inflammatory changes of airways under certain environmental conditions. The newly identified candidate asthma genes, their interactions with environment, and inflammatory mechanisms of bronchial hyperresponsiveness have been the basis for developing therapeutic and preventive strategies for asthma.

Prevalence of asthma in China

The overall prevalence of asthma in China has increased from 0.9% to 1.5% between 1990 and 2000. This was addressed by Professor Yu-Zhi Chen of Capital Institute of Pediatrics, Beijing. The current childhood asthma rate in urban areas of Beijing is 6.3%, while the prevalence is lower at 1.1% in rural areas of Beijing. Looking at allergy sensitization as reflected by positive skin test, she found that the overall positive allergy skin prick test in the urban

¹Chang Gung Children Hospital at Kaohsiung, Taiwan. yangkd@adm.cgmh.org.tw.

²Capital Institute of Pediatrics, Beijing, China. acebc@public3.bta.net.cn.

³Johns Hopkins Asthma and Allergy Center, Maryland, USA.

⁴Corresponding to: Dr. Shau-Ku Huang, Johns Hopkins Asthma and Allergy Center, Baltimore, Maryland 21224, USA. Tel: +01-410-550-2006, Fax: +01-410-550-2527, E-mail: skhuang@jhmi.edu.

Received for publication Oct 8, 2004. Accepted for publication Nov 27, 2004.

area is 36.2%, while the overall positive prick test in the rural area remains lower at 11.2% in school children aged between 13 and 14. This is an interesting finding that supports the "hygiene hypothesis". This hypothesis suggests that urban children living in a relatively germ-free environment are prone to have Th2-related allergy sensitization, while rural children surrounded by a more microbe-rich environment tend to have Th1 reaction that suppresses allergy sensitization.

In acute exacerbation of asthma, physicians like to prescribe antibiotics and herbs in addition to inhaled corticosteroid or systemic corticosteroids in their practice. A combination of antibiotics or herbs with inhaled steroid for asthma management is popular in China. The most common allergen in perennial asthma is *Dermatophagoides farine* while seasonal asthma is frequently associated with pollen-related rhinitis, due to exposure to *Artimisia*, *Humulus* or both pollens. Professor Chen also pointed out that people with good dietary habits, such as daily fruit or vegetable intake, tended to have a lower risk of asthma. She concluded that the increase of asthma prevalence was more related to changes of environment. Children living in rural areas and eating more fruits and vegetables tend to have a lower risk of asthma. A return to a living environment with natural food and housing should be encouraged to halt the rising asthma prevalence.

Molecular pathogenesis of asthma

Asthma is a complex disease with a genetic component. Atopy is by far the strongest risk factor for asthma that has been identified, and is defined by elevated specific IgE and positive skin tests to inhaled allergens. Genetic predisposition to asthma and atopy has been shown in many family and twin studies, and, in fact, more than 23 loci in 17 chromosomes have been linked to asthma. Professor Nobuyuki Hizawa from Hokkaido University, Japan, described a unique model considering the "gene-gene" interaction effect on the development of IgE and hyperresponsiveness, which proves to be more powerful than analyzing a single gene effect in many case-control studies of genetic association with asthma. Dr. Hizawa pointed out that certain IgE regulatory genes co-exist with genes controlling tissue remodeling, and that this combination will ultimately determine the expression of asthma. For instance, he demonstrated that an insertion polymorphism of the gene encoding prothrombin activation inhibitor 1 (PAI1) or a promoter polymorphism of the gene encoding the β subunit of the high affinity IgE receptor (Fc ϵ RI) gene alone was not associated with asthma, whereas a combination of certain genotypes for PAI1 and Fc ϵ RI genes significantly increased the risk for asthma. Apparently, a gene-gene interaction occurs in the development of asthma. These studies suggest that the development of asthma is determined by a complex network of genetic interaction. For example, a cluster of genes, such as IL-13 and Fc ϵ RI, that regulates the IgE production may determine the allergen sensitization and/or hypersensitivity; while another cluster of genes, such as PAI1 and ADAM33, may have a combined effect on tissue remodeling. A variety of genetic backgrounds and

combinations among these two clusters of genes may determine the occurrence and severity of asthma.

Another critical issue involving the gene-environmental interaction on the development of asthma was also described by Dr. Hizawa. He showed that a polymorphism of a chemokine gene, RANTES, is associated with late onset of asthma. The RANTES gene -28 GC polymorphism was associated with asthma only in those subjects whose age was greater than 45 years. Taken together, his studies highlight the fact that asthma is a complex disease involving both gene-gene and gene-environmental interactions. Subjects with different genetic backgrounds under certain environments require individualized strategies to prevent and treat asthma.

New anti-inflammatory therapies of asthma

Focusing on Th2-biased IgE mediated allergic reactions, Professor Bruce Bochner from the Johns Hopkins Asthma and Allergy Center highlighted a series of newly developed anti-inflammatory therapies of asthma that target different levels of the ligand-receptor-signal transduction events. At the ligand level, the humanized anti-IgE monoclonal antibody (Omalizumab) has been marketed for treating patients with moderate and severe asthma. This antibody effectively decreases by 1 to 2 log scales the free serum IgE levels, decreases asthma exacerbations and decreases the necessary dosage of inhaled corticosteroids. It may have a better clinical result if given at higher dosages to suppress free serum IgE levels even further. Another ligand neutralization antibody, anti-IL-5 antibody, may have the potential to control airway remodeling, although clinical trials showed no improvement in clinical symptoms but a decrease of pulmonary eosinophils and tenascin expression in airways was evident. Certain clinical trials with receptor antagonists also proved efficacious. Enbrel, a TNF α receptor competitor, was able to improve asthma symptoms, lung function and methacholine-mediated hyperresponsiveness. Whether this can decrease airway remodeling deserves further study. An alpha 4 integrin antagonist is now in a trial with oral formulation for asthma therapy, although its inhaled formulation has been proven ineffective for this purpose. Some other chemokine receptor antagonists or antibodies are also in early trials to target leukocyte recruitment in the airways.

Another class of newly developed anti-inflammatory drugs for asthma therapy targets the signal transduction pathway for leukocyte activation or leukocyte apoptosis. One such drug is from Rigel, an Syk tyrosine kinase inhibitor that targets the tyrosine kinase coupled to Fc ϵ RI. This compound has been experimentally formulated into a spray or topical regimen for allergic disorders. Another experimental antibody directed against siglec-8 is shown to mediate eosinophil apoptosis. This may also be a candidate to treat eosinophil-mediated disorders.

Research of asthma pathogenesis and therapies in China

Both human and animal studies on the pathogenesis and

therapies of asthma have been actively conducted in China. Professor Nanshan Zhong described a few human and animal trials in this symposium. He demonstrated that cDNA vaccine, BCG component, injected into mouse muscle could modulate asthma attacks, decrease airway inflammation and induce a higher level of Th1 response with higher IFN- γ expression. In a study on the role of chemokine-like factor 1 (CKLF1), a potent airway muscle proliferating factor, his study group demonstrated that CKLF1 appeared to be expressed in the allergic airways, especially on the submucosal muscular layer, suggesting its active role in airway remodeling.

In human trials, he also conducted a randomized trial to prove that one half of the inhaled steroid dosage recommended by GINA guidelines was as effective as the full dose of the recommended dose in Chinese asthma patients. This study may highlight a protocol suitable for Chinese patients that would minimize the side effects and decrease the cost of asthma therapy in China. Similarly, Dr. Zhang also found that a combination of herb medication with inhaled corticosteroids could significantly reduce the asthma symptoms and decrease the use of inhaled corticosteroids. In the studies with mite allergen immunotherapy, he showed that while immunotherapy had only a marginal effect in subjects without the need for inhaled corticosteroids, a significant beneficial effect was obtained in patients who did require inhaled corticosteroid therapy. Taken together, Professor Zhang identified better asthma treatment regimens for Chinese people, which are different from those used for Caucasians. Whether these newly developed regimens in China are suitable for people in other countries deserves further international study.

Induction of oral tolerance and modulation of allergic diseases

Many allergy cDNA vaccines have been developed based on animal studies. However, none has been progressed into clinical trials, because of the safety concerns. Dr. Chin-Hsiang Hsu from China Medical and Pharmacy University, Taichuan, Taiwan, who first published an effective DNA vaccine for asthma prevention in mice in *Nature Medicine*, is now formulating his unique DNA strategy using a recombinant plant that could produce a large amount of house dust mite antigen. One would expect that oral intake of a safe recombinant plant would raise oral tolerance for house dust exposure. This may be suitable for prevention as well as treatment of mite-related asthma or allergic rhinitis.

Currently, Dr. Hsu is promoting the probiotics modulation of allergic rhinitis and asthma in Taiwan. He has isolated a brand new lactobacillus called LP33 from human intestine and testified that this strain can raise mainly Th1 reaction, such as IFN- γ and IL-12 expression, in human leukocytes as shown by a human gene chip analysis. He discarded other strains that did not raise Th1 reaction. He is now amplifying the Th1-inducing strain, LP33, in a unique fermentation factory. The LP33 strain has been formulated into certain healthy food products either in capsule form with 10^{10} cfu/capsule or yogurt with 10^7 cfu/ml for health promotion. They proved that patients

with allergic rhinitis improved significantly after taking the LP33 capsule for 6 weeks, and that the effect could be maintained for another 6 weeks. Dr. Hsu highlighted a new area of therapy to modulate or prevent asthma via induction of oral tolerance by administration of recombinant plant or probiotics.

Early perinatal prevention of asthma

A growing body of evidence suggests that allergic sensitization could occur in utero and might be related to future development of allergic diseases. An experimental study has shown that a specific blockade of the immune braking pathway CTLA-4 (cytotoxic lymphocyte antigen-4; CD154)/CD80; CD86 by CTLA-4 IgG early in the allergen sensitization stage significantly attenuated IgE production. This suggests that certain gene(s) can affect antenatal IgE production under certain prenatal environments. Clarification of the antenatal gene-environmental interaction for IgE production may provide a better regimen for the early prevention of allergy sensitization, resulting in decrease of allergic diseases. Dr. Kuender D. Yang from Chang Gung Children's Hospital at Kaohsiung and his colleagues have conducted a cohort study with 1,200 infants from prenatal to infant and toddler stage to see if genetics, environment, or both is the most important factor in perinatal sensitization in order to guide a better perinatal prevention of asthma. Their preliminary analysis showed that a significant correlation is found between the maternal, but not paternal, atopy and increased levels of cord blood IgE (CBIgE) and 6-month infant IgE levels, as well as the occurrence of infant eczema. Certain gene polymorphisms such as IL-13 and CTLA-4 had an impact on the elevation of CBIgE levels. Maternal but not paternal atopy had an imprint on the gender- and IL-13 polymorphism-linked prenatal sensitization as demonstrated by elevated CBIgE levels.

Comparisons of the effects of breast feeding and different infant formulas found that breast feeding more than 4 months did not decrease food allergy sensitization in infants less than 3 years old, but did significantly decrease the incidence of aeroallergen sensitization in infants older than 3 years old. In contrast, partial protein hydrolyzed formula (Nan HA) did protect infants and toddlers from food allergy sensitization, and partly decreased aeroallergen sensitization in children older than 3 years old. This study suggests that maternal, but not paternal, factors have an impact on early (perinatal) allergic sensitization, for which a better control of allergen exposure, of feeding formula, or of allergic immune response in the perinatal stage may decrease incidence of allergic disorders, particularly in families with maternal history of allergic diseases.

In summary, allergic disorders are probably the most common human diseases in the world, with approximately more than one-third of the population affected. This disorder apparently is a multigene and multifactorial disorder beginning in utero and developing into a number of versatile phenotypes postnatally. To reach a total control of human allergic disorders, we should try to prevent sensitization in the perinatal stage and actively treat those

patients with early symptomatic disease in order to avoid long term sequela based on individual genetic background and environmental conditions, called pharmacogenomics. This symposium generated a good consensus on the direction for prevention and treatment of asthma and allergic diseases, and it is hoped that this type of exchange and dialogue will continue at the next SCBA conference and/or in a dedicated forum that brings together scientists and physicians to address this critical public health problem.

Selected references from speakers' work

1. Chen YZ. National Cooperation group on childhood asthma China. Comparative analysis of the state of asthma prevalence in children from two nation-wide surveys in 1990 and 2000 year. *Zhonghua Jie He He Hu Xi Za Zhi*. 2004;27:112-116.
2. Hizawa N, Yamaguchi E, Konno S, Tanino Y, Jinushi E, Nishimura M. A functional polymorphism in the RANTES gene promoter is associated with the development of late-onset asthma. *Am J Respir Crit Care Med*. 2002;66:686-690.
3. Bochner BS. Verdict in the case of therapies versus eosinophils: the jury is still out. *J Allergy Clin Immunol*. 2004;113:3-9.
4. Hsu CH, Lin SS, Liu FL, Su WC, Yeh SD. Oral administration of a mite allergen expressed by zucchini yellow mosaic virus in cucurbit species downregulates allergen-induced airway inflammation and IgE synthesis. *J Allergy Clin Immunol*. 2004;113:1079-1085.
5. Wang MF, Lin HC, Wang YY, Hsu CH. Treatment of perennial allergic rhinitis with lactic acid bacteria. *Pediatr Allergy Immunol*. 2004;15:1-7.
6. Liu SC, Wang CL, Chuang H, Ou CY, Hsieh TY, Yang KD. Prenatal prediction of infant atopy by maternal but not paternal total IgE levels. *J Allergy Clin Immunol*. 2003;112:899-904.
7. Chang JC, Liu CA, Chuang H, et al. Gender-limited association of cytotoxic T lymphocyte antigen 4 (CTLA-4) polymorphism with cord blood IgE levels. *Pediatr Allergy Immunol*. 2004;15:506-512.