Microbes and asthma: Opportunities for intervention

Hermelijn H. Smits, PhD,[a] Pieter S. Hiemstra, PhD,[b] Clarissa Prazeres da Costa, MD, PhD,[c] Markus Ege, MPH,[d] Michael Edwards, PhD,[e] Holger Garn, PhD,[f] Peter H. Howarth, MD,[g] Tuomas Jartti, MD,[h] Esther C. de Jong, PhD,[i] Rick M. Maizels, PhD,[j] Ben J. Marsland, PhD,[k] Henry J. McSorley, PhD,[j] Anne Müller, PhD,[l] Petra I. Pfefferle, PhD,[m] Huub Savelkoul, PhD,[n] Jürgen Schwarze, MD,[o] Wendy W. J. Unger, PhD,[p] Erika von Mutius, MD, MSc,[d] Maria Yazdanbakhsh, PhD,[a] and Christian Taube, MD, PhD[b] *Leiden, Amsterdam, Wageningen, and Rotterdam, The Netherlands, Munich and Marburg, Germany, London, Edinburgh, Southampton, and Glasgow, United Kingdom, Turku, Finland, and Epalinges and Zurich, Switzerland*

The worldwide incidence and prevalence of asthma continues to increase. Asthma is now understood as an umbrella term for different phenotypes or endotypes, which arise through different pathophysiologic pathways. Understanding the many factors contributing to development of the disease is important for the identification of novel therapeutic targets for the treatment of certain asthma phenotypes. The hygiene hypothesis has been formulated to explain the increasing prevalence of allergic disease, including asthma. This hypothesis postulates that decreased exposure at a young age to certain infectious agents as a result of improved hygiene, increased antibiotic use and vaccination, and changes in lifestyle and dietary habits is associated with changes in the immune system, which predispose subjects to allergy. Many microbes, during their coevolution with human subjects, developed mechanisms to manipulate the human immune system and to increase their chances of survival. Improving models of asthma, as well as choosing adequate end points in clinical trials, will lead to a more complete understanding of the underlying mechanisms, thus providing an opportunity to devise primary and secondary interventions at the same time as identifying new molecular targets for treatment. This article reports the discussion and conclusion of a workshop under the auspices of the Netherlands Lung Foundation to extend our understanding of how modulation of the immune system by bacterial, parasitic, and viral infections might affect the development of asthma and to map out future lines of investigation. (J Allergy Clin Immunol 2016;137:690-7.)

Key words: *Hygiene hypothesis, asthma, sensitization, microbes, microbiome, helminths, viruses, immune regulation*

From the Departments of [a]Parasitology and [b]Pulmonology, Leiden University Medical Center; [c]the Institute of Medical Microbiology, Immunology and Hygiene, Technische Universät München; [d]Dr von Hauner Children's Hospital, Ludwig-Maximilians-Universität of Munich; [e]the Department of Respiratory Medicine & Wright-Fleming Institute of Infection and Immunity, Imperial College London; [f]the Institute for Laboratory Medicine and Pathobiochemistry, Philipps University of Marburg; [g]the Academic Unit of Clinical and Experimental Sciences, University of Southampton Faculty of Medicine, University Hospital Southampton; [h]the Department of Pediatrics, Turku University Hospital; [i]the Department of Cell Biology and Histology, Academic Medical Center, University of Amsterdam; [j]the Institute of Infection, Immunity and Inflammation, University of Glasgow; [k]the Faculty of Biology and Medicine, University of Lausanne, Service de Pneumologie, CHUV, Epalinges; [l]the Institute of Molecular Cancer Research, University of Zurich; [m]Comprehensive Biomaterial Bank Marburg (CBBMR), Philipps University Marburg; [n]the Cell Biology and Immunology Group, Wageningen University; [o]the MRC-Centre for Inflammation Research, Queens Medical Research Institute, University of Edinburgh; and [p]the Department of Paediatrics, Erasmus Medical Center, Rotterdam.

Disclosure of potential conflict of interest: H. H. Smits has received grants and travel support from the Dutch Lung Foundation. P. S. Hiemstra has received travel support from Lung Foundation Netherlands and grants from Boehringer Ingelheim and Galapagos. C. Prazeres da Costa has received travel support from Longfonds, Netherlands. M. Ege has received grants from the German Federal Ministry of Research (BMBF), the German Research Foundation (DFG), the European Commission, the European Research Council, and Friesland Campina and has received royalties from Protectimmun GmbH. M. Edwards is a grant reviewer for NMRC Singapore; has consultant arrangements with Chiesi; is employed by GlaxoSmithKline; has received grants from GlaxoSmithKline, Chiesi, Merck, and Pfizer; has received payment for lectures from Pfizer; and has received travel support from the European Academy of Allergy and Clinical Immunology, the European Respiratory Society, and the American Academy of Allergy, Asthma & Immunology. H. Garn has received a grant from the German Research Foundation (DFG; SFB/TR22) and has received travel support from Lung Foundation Netherlands. T. Jartti has received a grant from the Academy of Finland. E. C. de Jong is employed by AMC, University of Amsterdam. R. M. Maizels is employed by the University of Edinburgh and has received grants from Wellcome Trust and the Rainin Foundation. B. Marsland has received travel support from the Netherlands Lung Foundation. H. J. McSorley has received a grant from Asthma UK. J. Schwarze has received travel support from the Netherlands Lung Foundation; has consultant arrangements with MEDA, GlaxoSmithKline, and Bausch & Lomb; is employed by the University of Edinburgh; has received grants from the Medical Research Council and the Wellcome Trust; has received payment for lectures from Abbvie and Thermo Fisher; and has received support for allergy study days for clinicians from Thermo Fisher Scientific, MEDA Pharmaceuticals, Nutritia, Mead Johnson Nutrition, GlaxoSmithKline, Abbott, IMed-Emerade, Allergy Therapeutics, and Stallergenes. E. von Mutius has received grants from European Research Council, the German Research Foundation, and Friesland-Campina; is on the Editorial Board for the *New England Journal of Medicine*; has served as an Associate Editor for the *Journal of Allergy and Clinical Immunology*; has provided expert testimony for the European Research Council and European Commission, UK Research Excellence Framework, AUKCAR, Messerli Research Institute, and University of Tampere; and has received payment for lectures from Novartis, Mundipharma, DOC Congress SRL, Oekosoziales Forum Oberoesterreich. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 18, 2015; revised January 6, 2016; accepted for publication January 19, 2016.

Corresponding author: Hermelijn H. Smits, PhD, Department of Parasitology, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands. E-mail: h.h.smits@lumc.nl.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2016.01.004

Abbreviations used
DC: Dendritic cell
RSV: Respiratory syncytial virus
TLR: Toll-like receptor
Treg: Regulatory T

In recent decades, there has been a marked increase in the incidence of many noncommunicable diseases, including asthma, which is now estimated to affect 300 million persons worldwide.[1] Patients with asthma experience a variable degree of airflow obstruction, breathlessness, and bronchial hyperresponsiveness associated with chronic airway inflammation and excessive mucus production. Various specific and unspecific triggers have been identified that can lead to an increase in inflammation, obstruction, and symptoms. Traditionally, asthma, especially allergic asthma, has been considered an inflammatory disease associated with T_H2 cells, production of IgE antibodies, accumulation of eosinophils in the lungs, and goblet cell hyperplasia. It is now recognized that asthma is a complex syndrome in which many different phenotypes exist, including early-onset allergic asthma, late-onset eosinophilic asthma, and exercise-induced, obesity-related, and noneosinophilic asthma.[2]

Recently, the definition of asthma has shifted further with the introduction of endotypes, which distinguish asthma variants by their underlying molecular mechanisms. Probably the best described endotype is the type 2–induced form of the disease.[3] Other endotypes are less well defined and include patients without type 2–induced airway inflammation (probably driven by T_H1 or T_H17 cells) and allergic bronchopulmonary mycosis as an asthma endotype.[4]

Most asthmatic patients have a mild form of the disease, which can be managed with inhaled corticosteroids and long-acting β-agonists. However, patients with more severe disease and particularly those with a non-T_H2 endotype might not respond well to currently available therapies. Particularly in asthmatic patients, personalized medicine might open novel approaches to accommodate the heterogeneity of the disease. Better understanding of mechanisms and endotypes will provide opportunities for both prevention and causal treatment.

In the last years, interactions of microbes, including worm parasites, with their host have been identified: exposure to microorganisms not only triggers but also effectively suppresses immune responses, and beneficial effects of microorganisms are increasingly recognized and mechanistically understood. Strategies are emerging to potentially implement these effects in novel interventions to prevent or treat allergic diseases, such as allergic asthma (Fig 1). A better understanding of the disease in its many guises at a basic level is needed to endorse such strategies and improve and refine interventions. In this context a group of clinicians and basic scientists with wide-ranging fields of expertise convened in Amersfoort, The Netherlands, under the auspices of the Netherlands Lung Foundation for a workshop to assess our current understanding of the disease and identify challenges and opportunities for the prevention and treatment of asthma, with microbial intervention as the guiding theme for the workshop.

HYGIENE HYPOTHESIS AND "OLD FRIENDS" HYPOTHESIS

The so-called hygiene hypothesis is frequently invoked to help explain the increasing prevalence of asthma. The hypothesis has its origins in observations published in 1989 by Strachan,[5] who noted that decreasing family size was associated with hay fever in developed countries and suggested that this might be related to a lower degree of sibling-related childhood infections and microbial exposure. In extension of the hygiene hypothesis, Rook[6] has postulated the "old friends" hypothesis, in which many infectious agents and microbes in their coevolution with human subjects have developed mechanisms to modulate and evade the host immune system (Fig 1). Immunomodulatory microorganisms have been described to activate various cells of the regulatory network, such as regulatory T (Treg) cells and regulatory B cells, and to modulate or even reprogram certain antigen-presenting cells, leading to tolerogenic dendritic cells (DCs), alternatively activated macrophages, or both. A more detailed understanding of how these infectious agents accomplish this can provide indicators for primary prevention strategies and might help to identify new molecular targets for novel treatments. This is especially relevant because in patients with various noncommunicable inflammatory diseases, such as asthma, these regulatory networks seemed to be underrepresented and poorly developed.

Rural exposure and "archaic" microbiome

As discussed above, microbes ("old friends") form a central part of the (extended) hygiene hypothesis.[6,7] Interestingly, this has not so much to do with personal hygiene (as often interpreted from the hygiene hypothesis) because a recent study showed that personal or home cleanliness was not associated with a risk of asthma or allergy.[8] The "old friends" mostly represent a group of microbes with which the human race has coevolved and that in the past 50 years were rapidly lost because of changes in lifestyle, living conditions, or occupations. Prime candidates are microbes associated with rural living, such as farming, and various members of an archaic microbiome responsible for a richer composition of our personal microbial hemisphere, which includes compartments such as the gut, lung, and skin. From this perspective, helminths are regarded as a natural and ancient (evolutionary conserved) partner of the microbial community, which is still the case in many parts of the world but no longer in westernized countries. The likelihood that archaic microbes play an essential role in protection against asthma and allergic diseases is framed by several landmark studies.

Several studies noted that living on farms offers a protective effect against atopy, hay fever, and asthma, especially in children.[9] Further analysis suggested a link with increased exposure to a variety of bacteria and fungi related to farming and protection from asthma.[10] Interestingly, several gene-environment interactions were found for early farm exposure. A number of single nucleotide polymorphisms in children living in rural Europe were linked to farming, such as in the genes transcribing CD14 or Toll-like receptors (TLRs).[11] Remarkably, a recent farm study also reports on associations with the asthma risk alleles on chromosome 17q21, suggesting that the same genotype both constitutes a genetic risk to asthma and, at the same time, is susceptible to environmental influences.[12] This would imply options for future preventive strategies.

In addition, in particular, farm exposure during pregnancy seems to influence gene expression patterns by means of DNA methylation in specific asthma- and allergy-related genes, further contributing to its protective effect.[13] In contrast, a higher