

# Microecology research: a new target for the prevention of asthma

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## Abstract

The incidence and prevalence of asthma have increased remarkably in recent years. There are lots of factors contributing to the occurrence and development of asthma. With the improvement of sequencing technology, it has been found that the microbiome plays an important role in the formation of asthma in early life. The roles of the microbial environment and human microbiome in the occurrence and development of asthma have attracted more and more attention. The environmental microbiome influences the occurrence of asthma by shaping the human microbiome. The specific mechanism may be related to the immune regulation of Toll-like receptors and T cells (special Tregs). Intestinal microbiome is formed and changed by regulating diet and lifestyle in early life, which may affect the development and maturation of the pulmonary immune system through the intestinal-pulmonary axis. It is well-recognized that both environmental microbiomes and human microbiomes can influence the onset of asthma. This review aims to summarize the recent advances in the research of microbiome, its relationship with asthma, and the possible mechanism of the microbiome in the occurrence and development of asthma. The research of the microbial environment and human microbiome may provide a new target for the prevention of asthma in children who have high-risk factors to allergy. However, further study of “when and how” to regulate microbiome is still needed.

**Keywords:** Asthma; Environment; Intestinal microbiome; Respiratory microbiome; Sequence analysis

## Introduction

Asthma, the most common chronic disease in childhood, is a heterogeneous disease characterized by chronic airway inflammation and hyperresponsiveness, which affects 14% of children of the world.<sup>[1]</sup> The onset of asthma is multifactorial. Numerous potential risk factors concerning the development of asthma have been studied.<sup>[2]</sup> Recent advances in gene sequencing technology have expanded our understanding of the microbiome. We found that the microbiome plays an important role in the development of asthma. The external microbiome can influence the immune regulation of skin, airway, and gut.<sup>[3]</sup> Humans can be thought considered a “superorganism.” The internal microbiota in the human body consists of a group of microorganisms that have coexisted and co-evolved with the host immune system for millions of years.<sup>[4]</sup> Microorganisms, which are microscopic organisms and may exist in the form of the unicellular organism or a colony of cells, interact with the immune system, and immune cells can produce microbial products in the intestinal tract of animals and humans. Microbiota and microbial products constitute

internal human microecology, which can regulate the development and function of the host immune cells. This review includes 74 papers and corresponding data related to asthma, human microecology, environmental microecology, and asthma prevention published by March 16, 2020. The relationship between asthma and environmental microecology and human microecology was further analyzed to provide a new perspective for asthma prevention. More and more data have shown that the respiratory microbiome and intestinal microbiome both play important roles in host physiology and the pathology of asthma.<sup>[5]</sup> The purpose of this paper is to review the latest research progress of asthma, summarize the risk factors of asthma, expand our understanding of how microecology affects asthma, discover the critical window time of asthma prevention, and then propose a new strategy for asthma prevention.

## Advances in Research Methods of Human Microecology

In 2000, Joshua Lederberg proposed that the human body is a “superorganism” made up of human cells and the symbiotic microbiomes.<sup>[6]</sup> The microbial community that

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Chinese Medical Journal 2020;133(22)

Received: 28-05-2020 Edited by: Peng Lyu

## Access this article online

Quick Response Code:



Website:  
www.cmj.org

DOI:  
10.1097/CM9.0000000000001127

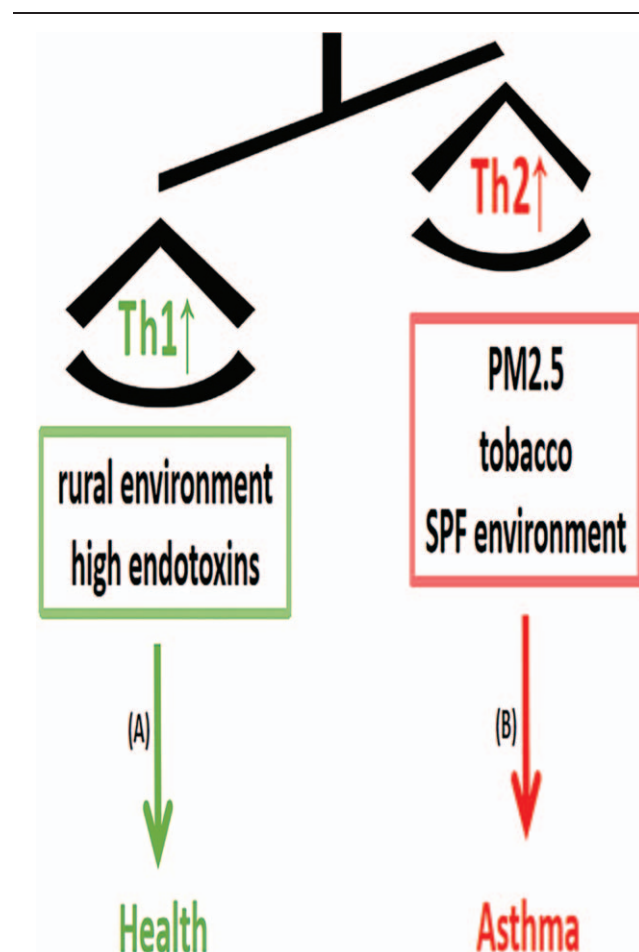
inhabits the human body is a major contributor to the function of this complex micro-ecosystem, and it directly affects health. Compared with macroecology, microecology can capture the biodiversity of habitat and host by sequencing total associated DNA and/or specific systematic marker genes. Different omics techniques can provide researchers with information about diversity and abundance of species, as well as their metabolic capacity and associated symbiotic or pathogenic factors. If we know a person's microbiome, which refers specifically to the collective genomes of resident microorganisms, we will be able to predict the association with certain diseases. If we understand the function of human microbiota, we can further prevent and treat these diseases.<sup>[7]</sup> Considering that different people have different microecological components, we can personalize the treatment for them.

The study of the airway and intestinal microbiota mainly focused on investigating the microbial diversity (including quantity, species, and composition) in the airway and intestinal tract. The original method used in the microbial census is 16S rRNA gene sequencing. In 1977, Sanger pioneered the chain termination sequencing technology,<sup>[8]</sup> which marked the birth of the first generation of DNA sequencing technology. Its disadvantages of high sequencing cost and low throughput affected its large-scale application, so people began to explore better sequencing technology. At present, the next generation sequencing (NGS) technology, also known as second-generation sequencing technology or high-throughput sequencing technology, has been developed. This method is advantageous in terms of being high throughput, high-speed, and economical. However, the reading length of NGS is usually very short. Subsequently, third-generation sequencing technology is developed, which is a kind of single-molecule sequencing technology. Each DNA molecule is sequenced independently without polymerase chain reaction amplification. NGS and the third generation sequencing technology have great impacts on the development of metagenomics research and brought about progress in research methods. Metagenomic research is the sequencing of the DNA of an entire microbiota, which provides broader and more complex information about the microbiota for cataloging organisms, genes, and genomes in the community. The advent of high-throughput sequencing technology makes it possible to conduct a more large-scale macro-genome research to analyze the transcriptome and genome of a species comprehensively and deeply.<sup>[9]</sup>

The development of sequencing technology has given us a more comprehensive and in-depth understanding of the composition and function of microecology. It also allows us to obtain more important information from the microbiome, providing new perspectives on the occurrence and development of diseases, which can further contribute to disease prevention and future personalized medical care.<sup>[10]</sup>

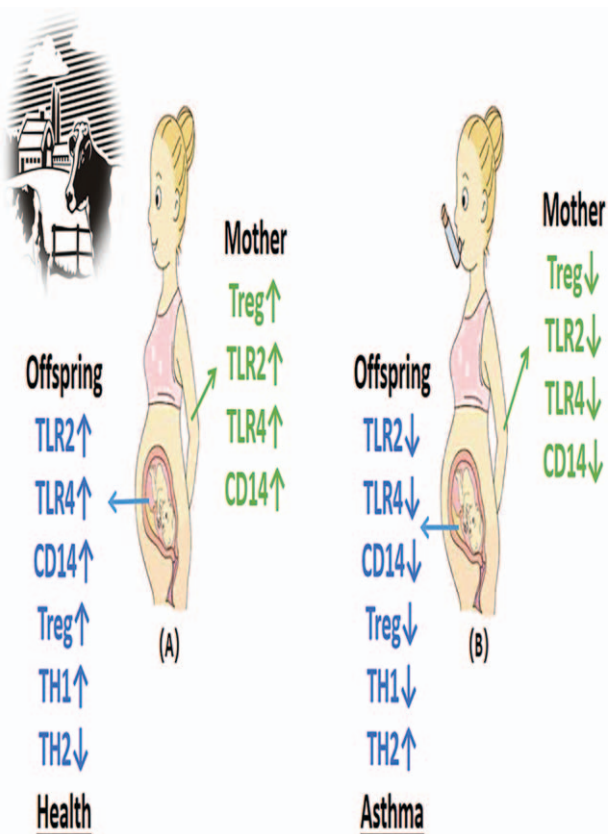
### The External Microbial Environment in Early Life is Crucial to the Formation of Asthma

The emergence of the hygiene hypothesis, which partly explains the reasons for an increased incidence of allergic diseases, has sparked a growing interest in exploring the link



**Figure 1:** T helper cells (Th) can differentiate into two subtypes (Th1 and Th2), and there is a dynamic balance between Th1 and Th2. When the immune response of Th1 is strong, the activity and function of Th2 will be greatly inhibited and reduced, and vice versa. (A) When the organism is exposed to a rural environment and high endotoxin, the secretion function of Th1 increases and the chance of allergic diseases will be greatly reduced. (B) When the body is exposed to PM2.5, tobacco, or non-pathogenic (SPF) environment, the secretion mediated by Th2 increases and further leads to asthma. PM2.5: Particulate matter <math><2.5\ \mu\text{m}</math>; SPF: Specific pathogen-free; Th1: T helper cell-1; Th2: T helper cell-2.

between environmental factors and asthma [Figure 1]. The Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Life Style study (PARSIFAL) group<sup>[11]</sup> found that up-regulated expression of innate immune receptors, such as toll-like receptor 2 (TLR2), TLR4, and the cluster of differentiation 14 (CD14) in fetal cord blood is associated with exposure to rural microbiomes, such as visiting stable/barn and contacting with farm animals. Additional exposure to farm animals increased the expression of TLR2, TLR4, and CD14 by 1.16 (95% confidence interval [CI], 1.07–1.26), 1.12 (95% CI, 1.04–1.2), and 1.10 (95% CI, 1.03–1.23), respectively. Exposure of mothers to the microbiome-rich environment can up-regulate the expression of *TLRs* gene and regulate the intrauterine environment, and affect the development of fetal T cells, which in turn protect against neonatal allergic diseases. A previous study<sup>[12]</sup> also found that mothers living in a rural environment with exposure to high endotoxin can affect neonatal immunization by the TLR2 and TLR4 pathways. The immune response of offspring is regulated by maternal exposure, inducing the intrauterine environment, transmission between maternal



**Figure 2:** (A) Maternal exposure to microbiome-rich-environment can affect the development of fetal T cells. (B) The asthma history of the mother can affect the development of fetal T cells. CD14: Cluster of differentiation 14; TH1: T helper cell-1; TH2: T helper cell-2; TLR2: Toll-like receptor 2; Treg: Regulatory cells.

and infant microflora, or gene regulation. Compared with healthy controls, maternal allergies are associated with lower levels of TLR2, TLR4, and CD14 mRNA in both maternal peripheral blood and fetal cord blood [Figure 2].<sup>[13]</sup> The gene-immune interaction of the TLR pathway affects Treg in early life. Treg protein may be up-regulated in early life to potentially balance the regulation of helper T cell (TH-cell) in healthy immune development.<sup>[14]</sup> Conrad *et al*<sup>[15]</sup> found a functional knockdown of five TLRs in the mother resulted in a loss of protection in offspring against *Acinetobacter lwoffii* F78 asthma, suggesting that prenatal protection from the exposure to *A. lwoffii* F78 required the expression of functional maternal TLR.

Qian *et al*<sup>[16]</sup> found that the longer the mice live in the specific pathogen-free (SPF) environment, the lower the diversity of the intestinal flora will be. And in SPF mice, the level of Th1-specific interferon-gamma (IFN- $\gamma$ ) and the ratio of IFN- $\gamma$ /IL-4 are lower, and the corresponding polarity of Th2 is enhanced, which is associated with susceptibility to asthma.

Moreover, Tregs have received increasing attention in recent years for their roles in the pathogenesis of asthma. Many studies have found that the number and function of Tregs, especially Th2 cells, are reduced in adults and children with asthma.<sup>[17]</sup> And the number and function of regulatory T cells decline in cord blood of high-risk infants

with a family history of allergic diseases, even before Th1/Th2 abnormalities occur.<sup>[18]</sup> The ratio of Th17/Treg, the imbalance between interleukin (IL)-17 and IL-4 responses, and the down-regulation of Forkhead Box P3 (*FOXP3*) are associated with allergic asthma.<sup>[19]</sup>

By examining the association of microbiological levels with asthma status, asthma symptoms, bronchial hyperresponsiveness, and atopy, it is found that there is an association between the protective effects with higher levels of bacterial markers. The results in the study among adults across Europe supported that a high level of bacteria was negatively correlated with asthma symptoms. Gram-positive bacteria in mattress dust may be a potential protective factor of preventing allergy, especially in areas where the level of microbial exposure is generally lower. Muramic acid, which is the main component of the peptidoglycan layer of gram-positive bacteria, activates innate immunity through TLR-2 and participates in immune regulation.<sup>[20]</sup>

Asthma is determined by both genetic and environmental factors. The increasing incidence of asthma in the present-day will make people consider the impact of environmental pollution. Air pollution has a complex chemical component, consisting of a variety of particles. Studies have found that there was a positive correlation between the concentration of components in air pollution and hospitalization in asthma patients. Air pollution is becoming a major risk factor for asthma.<sup>[21]</sup> In a meta-analysis of the correlation between atmospheric particulate matter and the number of hospitalized children with asthma, it was found that as the increase in fine particulate matter PM<sub>2.5</sub> concentration for every 10  $\mu\text{g}/\text{m}^3$  in the air, the number of hospitalized children with asthma increased by an average of 3.45% in the short term.<sup>[22]</sup> A 2019 cohort study<sup>[23]</sup> investigated the association between PM<sub>2.5</sub> and asthma during pregnancy and infancy. This study found that the more exposure to PM<sub>2.5</sub> during pregnancy and the first year of life, the higher incidence of asthma. The critical window period is 6 to 22 weeks postpartum and 9 to 46 weeks postpartum. PM<sub>2.5</sub> enters the placental barrier through the alveoli and directly effects on the fetus or causes systemic inflammation of the mother, reduces the transportation of fetal nutrients and oxygen, and affects fetal lung function. Another study<sup>[24]</sup> using four groups of murine models revealed a significant association between the exposure to PM and the occurrence of asthma. They collected bronchoalveolar lavage fluid (BALF), detected the level of catalase, glutathione, superoxide dismutase, and malonaldehyde (MDA) and then measured the number of cells. Mice in the particulate matter (PM) exposure group had significantly higher numbers of the total cell, particularly the number of inflammatory cells. And the level of oxidative stress indicators in BALF increased, while the content of MDA declined. TH1/TH2 cell measurements showed that the balance of TH1/TH2 polarization was broken. The number of TH1 cells decreased and the number of TH2 cells increased, which skewed the balance towards TH2, and then led to the secretion of IL-4, IL-13, and other substances that stimulate the production of IgE by B cells, which can trigger a series of allergic reaction.

Nowadays, children are actively and passively exposed to tobacco in family life. A longitudinal birth cohort study in

Taiwan, China demonstrated that the higher the exposure dose to paternal tobacco smoke, the higher the methylation of LIM-Domain-Only 2, *IL10*, and glutathione S-transferase M1 genes will be, those are all important for immune function and these changes are associated with risk of asthma. If all three genes were methylated, the risk of asthma is as high as 43.48%.<sup>[25]</sup> At the same time, maternal smoking in pregnancy was strongly associated with reduced lung function and increased risk of asthma (odds ratio, 1.84 95% CI, 1.16–2.92;  $P = 0.01$ ).<sup>[26]</sup> The harmful effects of tobacco on the respiratory system are fully confirmed by both the spirometry and forced oscillation technique results in an Italian study,<sup>[27]</sup> which is a trigger for asthma. The first genome-wide study in 2019<sup>[28]</sup> revealed a significant association between early-life tobacco exposure and asthma. Tobacco releases cytokines and causes the proliferation of airway smooth muscle and inflammatory responses through increasing the *Kelch-like1* gene encoding the calc-regulatory protein.

All these external environmental microbiomes provide a new angle for asthma prevention.

### The Human Microbiome in Early Life is Crucial to the Formation of Asthma

#### Respiratory microbiome

In the past, people thought that the lungs were sterile, but with the development of gene sequencing technology, it was found that the lungs possess their specific microbiota. The pulmonary microflora is a collection of bacteria, viruses, and fungi that live in bronchial trees and lung parenchyma and it may be of great importance for human health.<sup>[29]</sup> Human lungs harbor approximately  $2.2 \times 10^3/\text{cm}^2$  bacterial genomes, which are smaller than that of the colon.<sup>[30]</sup> The main bacteria in healthy lungs are *Proteobacteria*, *Firmicutes*, and *Bacteroidetes*. Microbiomes in healthy lungs involve in the host immune response, disease exacerbation, or protection.<sup>[31]</sup> Because of the airflow, the microbiome of the lungs is more active. During the status of health, resident phagocytes (alveolar macrophages) actively patrol the surface of the alveolar cavity to maintain health.<sup>[32]</sup> The lung microbiome maintains a dynamic balance through inhalation and clearance. When this balance is broken, such as impairment of cilium clearance or regurgitation leading to the increase of bacterial invasion, lung microflora will be dysbacteriosis. The expression of certain microorganisms' is different in diseased or healthy lungs, such as *Proteobacteria*, which is more abundant in diseased than that in healthy subjects. Asthma patients have higher bacterial diversity, which leads to airway hyperresponsiveness. Both of them show a linearly positive trend, mainly *Proteobacteria*.<sup>[33]</sup> A study<sup>[34]</sup> in 2017 using gene sequencing to compare the samples from asthma, rhinitis, and healthy people's throat swabs proved that the microbial diversity and richness of the respiratory tract were negatively correlated with the occurrence of asthma. Besides, several studies have shown that<sup>[35]</sup> microbiota in the airway is dysregulated in the lower airway, which is a characteristic of adult asthma, and eosinophilic inflammation combined with special microbiota is associated with a rapid decline in lung function.<sup>[36]</sup>

#### Intestinal microbiome

The intestinal tract of a newborn is sterile, and bacteria will soon appear in the intestine 1 to 2 h after birth. In the healthy state, intestinal flora and host are in a harmonious, interdependent, and mutually restricted relationship to maintain the balance of microbiome in the human intestinal tract. Human intestinal microbiome is one of the densest microbial communities, with the microbiota of up to  $10^{11}$  CFU/g of luminal content, which plays an important role in metabolism and protection of human health<sup>[37]</sup>: (1) Nutrient metabolism: Gut microbiomes break down carbohydrates to provide energy for the body. (2) Immunomodulation: Intestinal microflora promotes immune regulation through innate and adaptive immunity. After birth, bacteria begin to colonize in the digestive tract, stimulate the immune system, and induce the differentiation and maturation of immune cells through the gut-associated lymphoid tissues. (3) The integrity of the gut barrier and structure of the gastrointestinal tract: the secretion of various metabolites and bacteriocins inhibit the overgrowth of pathogenic bacteria, the invasion, and colonization of foreign pathogenic bacteria.

Healthy intestinal flora mainly consists of *Firmicutes* and *Bacteroidetes*. The intestinal microbiome is the best-studied microbial ecosystem because it is rich in microorganisms and easy to be analyzed through feces. A prospective study<sup>[38]</sup> named the Canadian Healthy Infant Longitudinal Development in Canada found that the content of four bacteria decreased (*Faecalibacterium*, *Lachnospira*, *Rothia*, and *Veillonella*) in feces of infants who were at risk of asthma in the first 100 days after birth. Subsequent animal experiments also confirmed that the above four intestinal bacteria played a protective role in asthma development. A study found that there would be a decrease in the amount of *Bifidobacteria* in long-term asthmatic patients by detecting microbes in the feces of asthmatic patients.<sup>[39]</sup> Abrahamsson TR<sup>[40]</sup> found that low levels of intestinal microbial diversity in 1-month-old infants are associated with high-IgE eczema in early life and with diagnosed asthma before 7 years old. The first 100 days after birth are critical in early life, and intestinal microbial disorders have been linked to the risk of asthma and allergic diseases. Intestinal flora plays an important role in maintaining the balance of intestinal metabolism in infants.

Some studies on Tregs have also found that intestinal microbiota affects the proportion of  $\text{CD4}^+$  cells which produce IL-4 and the relative abundance of  $\text{CD4}^+\text{CD25}^+\text{FOXP3}^+$  cells which affects the development of allergic diseases like asthma in children.<sup>[41]</sup> Metabolites of gut microbes like short-chain fatty acids, can inhibit the expression of Treg-specific *FOXP3* genes and influencing the production and function of Tregs by inhibiting histone deacetylase, some cytokines and chemokines.<sup>[42]</sup> Intestinal microbes in mothers can also affect asthma in offspring by the intrauterine environment or transgenerational epigenetic inheritance.<sup>[43]</sup> The second type of intrinsic lymphoid cells (ILC2s), which are recently discovered population of powerful cells capable of producing Th2 cytokines such as IL-5 and IL-13 play proper regulation of the microbiota on

asthma.<sup>[44]</sup> In recent years, we have found that the proportion of asthma in obese people has risen sharply. We began to observe a special type of asthma, obesity asthma, which is characterized by inflammation of neutrophil and a poor response to inhaled corticosteroid therapy, leading to the aggravation of moderate and severe asthma, which is easy to further develop into refractory asthma.<sup>[45]</sup> The high-fat diet of obesity will change the composition and metabolism of intestinal microbiomes, improve the expression of ILCs in the lungs, and cause allergic inflammation in the airway through the IL-1 signal pathway.<sup>[46]</sup> One study found that the increased risk of asthma caused by obesity began in utero and that maternal weight gain during pregnancy was associated with an increased risk of asthma in offspring.<sup>[47]</sup> The interaction between microbiomes and obesity asthma provides a new strategy for the treatment of obesity asthma and a novel target for the early prevention of neonatal asthma from the perspective of diet and microecology.

In early life, intestinal microbial metabolites can effectively regulate the secretion of sensitizing cytokines (such as thymic stromal lymphopoietin, thymic stromal lymphopoietin (TSLP), and IL-33) in epithelial cells by stimulating G-coupled protein receptors. Besides, the production of IFN- $\gamma$  by activating natural killer family cells (NK [natural killer] and iNKT [invariant natural killer T] cells) can antagonize the release of IL-4 by Th2 cells. Finally, these molecules can induce immune tolerance to allergens mediated by allergen-specific Th1 and Treg.<sup>[48]</sup> Evidence shows that the onset of variant diseases in infants and children with the same cystic fibrosis transmembrane conductance regulator mutation can be explained by differences in the acquisition of microbiomes and interaction between microecology and immune system.<sup>[49]</sup>

### **The interrelationship between the intestinal and respiratory microbiome**

Existing studies have demonstrated that intestinal and pulmonary microbiomes influence the onset of childhood asthma. Microbial communities play a key role in the development of healthy immune responses. Disorders of the airway and intestinal microorganisms can lead to local or systematic diseases.<sup>[50]</sup> The intestines and airways have the same origin from the embryo with similar in structure, they all play important roles in health. Upper respiratory tract, mucus, resident microorganisms, trapped particles, and inhaled microorganisms flow into the gastrointestinal tract with saliva.<sup>[32]</sup> At the same time, the body experiences the condition of reflux many times as to cause bacterial communities to migrate from the digestive tract to the respiratory tract, and then be inhaled to the lungs.<sup>[51]</sup>

At present, the microbiota and immune transmission on the intestinal-pulmonary axis are hotspots of research.<sup>[52,53]</sup> Gut microbiota can influence lung microbiota by modulating lung immunity through the production of bacterial ligands (eg, lipopolysaccharide [LPS]), bacterial metabolites (eg, short-chain fatty acid [SCFAs]), and immune cells (eg, T-cells), which can circulate through lymph or bloodstream to arrive at the lungs. The gut microbiota can directly influence the immune response of

the lung through the circulating cells and their products [Figure 3]. These cells influence the final composition of the microbiota in the lungs, which is important for the shaping and maintenance of innate and immunity. At the same time, innate and acquired immunity can regulate lung microbiota. There is a high consistency between the microorganism genera of the intestinal and that of the respiratory tracts. The study of Madan *et al*<sup>[54]</sup> demonstrated that the majority of the bacteria presented in the respiratory and intestinal tracts are overlapping with eight distinct genera, dominated by *Veillonella* and *Streptococcus*. The intestinal and pulmonary ecosystems link nutritional, respiratory, and digestive health to immune defense through a complex system of interactions.<sup>[51]</sup>

All microbial exposure factors may affect the host by regulating the microbial environment of the intestinal tract and airway, thus avoid the occurrence of allergic diseases, but the specific mechanism still needs to be further studied.

### **The interaction between microbial environment and the human microbiome**

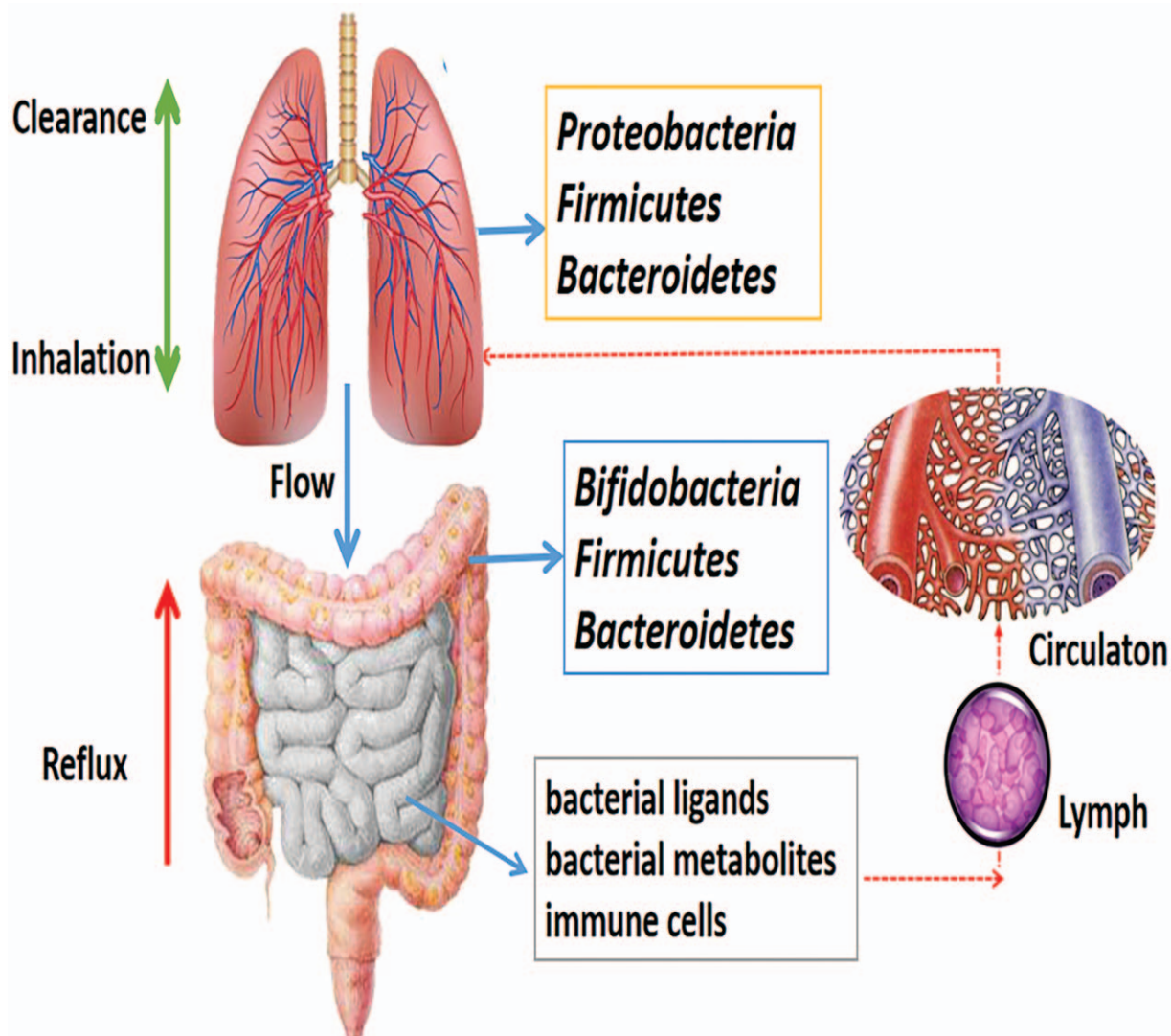
For human beings, there are two ecological levels: macroecology and microecology. The former refers to the macro external environment of the human body, while the latter refers to the internal environment of the human body and its corresponding normal microbiome. There is little research on the connection between the internal environment and the external environment. Skin is the first barrier separating the internal environment from the external environment. The species of transient bacteria and resident bacteria in the skin microenvironment are determined by the characteristics of the distribution area and changes of internal and external factors. Air pollutants and allergens can cause oxidative stress in the skin, leading to dysfunction of the skin barrier, sensitization of skin, and disorders of the immune system.<sup>[55]</sup> We suspect that the external microbiome and human microbiome communicate with each other through the intestinal tract, respiratory tract, and skin, maintaining the stability of the internal environment and the health of the body. To prove this hypothesis, a lot of research experiments are needed in the future.

### **Adjustment of the Microbiome to Prevent Asthma**

#### **The time window for adjustment of the microbiome to prevent asthma**

The development and clinical manifestations of various childhood asthma conditions depend on genetic and environmental determinants that interact at different stages of immune system development, which starts in the uterus. Thus, for many asthmatic patients, the root causes of the disease lie in infancy and early life.<sup>[56]</sup> Epidemiological studies suggested that the immune and respiratory systems are not well developed in early life and it is difficult to maintain homeostasis balance.<sup>[17]</sup>

Newborns with intestinal dysbiosis during the first 50 days after birth had more circulating endothelial cells, activated T cells, and extra patellar peptidase CPA1 in their blood samples during the next 3 months, accompanied with greater heterogeneity, suggesting that the interaction



**Figure 3:** The interrelationship between the intestinal microbiome and respiratory microbiome.

between the immune system and intestinal flora in the first few weeks was important.<sup>[57]</sup> A study found that early exposure to a multi-microbial environment may have a protective effect on the organism and may provide an opportunity to change the host microbiome in the critical time window.

Microbial signals are known to stimulate the development and maintenance of the neonatal immune system. This process begins from the fetus, where there are intrauterine microecology and maternal immune signals transmission. After birth and initial colonization of intestinal microbiota, the immune system can tolerate the food and resident gut microbiomes, but also recognize and respond to pathogens. The immune system can achieve microecology balance through microbial signals and proper nutrition. If imbalances occur in the microecology and immune system, allergic diseases like asthma can be induced.<sup>[58]</sup> Numerous studies have confirmed that proper regulation of the microbiota in early life may play an important role in preventing the development of allergic diseases. And choosing a proper time window for microecology inter-

ventions in high-risk populations is important. Stiemsma and Turvey<sup>[59]</sup> summed up kinds of literature and found that the key time window for preventing asthma is within the first 100 days after birth. Therefore, for children with family allergic history, appropriate adjustment of the microbial environment in early life (eg, embryonic stage) may affect the immune maturity of newborns or infants, which may help to avoid the occurrence of allergic diseases. The research of PARSIFAL team and their previous findings showed that the preventive protection of exposure to environmental microbiomes on allergic diseases can occur during the embryonic phase, or even earlier.<sup>[11,12]</sup> It is becoming increasingly clear that maternal microbiota during pregnancy also plays a key role in the prevention of allergic immune phenotypes in offspring. The mechanism of maternal microbiota on the development of the fetal immune system includes the regulation of the immune status of mothers and infants and the arrangement of microbial metabolites and placental channels of IgG.<sup>[60]</sup>

As we all know, primary prevention is the most important way for disease prevention, and when to start primary

prevention is the focus that we need to pay attention to. The identification of the key window period for asthma prevention is crucial. It may be wise to move the prevention window from postpartum 100 days to the prenatal period.

## The Possibility of Adjusting the Microbiome to Prevent Asthma

### Prevention of asthma based on microbial environment

Several epidemiological studies have shown that children living in the environment exposed to a large diversity of microbiome have less risk of having asthma.<sup>[61]</sup> Some “hygiene environment” factors (including excessively clean living environment, modern lifestyle, urbanized life, small scale family, etc) are all accompanied by the increased incidence of allergic diseases. Thus, the preventive and protective effects of special environmental factors, such as three or more siblings in a family,<sup>[62]</sup> exposure to livestock, high endotoxin load on early-onset allergic asthma are obvious and have been fully confirmed. However, the underlying mechanism is unclear and remains to be explored.

The microecology in early life, which is shaped by early environmental exposures, influences the development of immune and asthma. In some studies,<sup>[63-65]</sup> endotoxin, or low dose of LPS are administered intranasally to mimic over-loading microbial environment to investigate the effects on asthma in mice. Results showed that the high microbial loading can protect against asthma by reducing the airway inflammation induced by the extracts of house dust mites in the asthma model of mice. In a study comparing the cord blood between the infant who exposed to the farm environment and those free of exposure, it was found that the number of Tregs (farm-exposed) is more than that of the control. Tregs are one of the important factors to maintain immune tolerance through actively regulating T cell activation and proliferation in body, inhibiting Th2 to secrete too much stimulation factors such as IL- 4, IL-13, and suppress B cells to produce IgE and then trigger a series of allergic reactions.

Reducing PM2.5 and other air pollution, which increases the inflammatory properties of some allergens, is of great urgency in today’s society because it will reduce childhood asthma and even make great contributions to the whole society.<sup>[66]</sup> Moreover, education campaigns to teach children about the dangers of smoking have significantly reduced passive and active exposure to tobacco and raised awareness of disease prevention.<sup>[27]</sup>

Further epidemiological and experimental studies are needed to explore the mechanisms and further propose new prevention strategies. It is noteworthy that adequate control of harmful environmental changes caused by humans is essential to prevent the growing trend of allergic diseases.

### Prevention of asthma based on the human microbiome

Recent studies of bacterial metabolic products and their effects might provide new strategies for immune modulation in early life. When pregnant mice received a high-fiber

diet or acetate, allergic airways disease (AAD) failed to develop in offspring.<sup>[43]</sup> Feeding mice with a high-fiber diet yielded a distinctive gut microbiota, which increased the levels of the SCFAs like acetate. High-fiber or acetate-feeding led to marked suppression of AAD (a model for human asthma). Intestinal microbiota can ferment dietary fiber to release SCFAs, including formic acid, acetic acid, propionic acid, butyric acid, and valeric acid, which can regulate the production, expansion, and function determination of innate and acquired immune cells.<sup>[67]</sup> For example, butyric acid plays an anti-inflammatory role by inhibiting the aggregation of neutrophils, macrophages, dendritic cells, and effector T cells and increasing the number and activity of Tregs.<sup>[67,68]</sup> Strikingly, the levels of maternal acetate equal to or higher than the median were associated with a significant decrease in the percentage of infants requiring two or more general practitioner visits for cough or wheeze and a trend of reduced parent-reported wheeze.<sup>[43]</sup>

Variations in the composition and functional potential of microbiota in early life such as mode of birth, breastfeeding, dietary behavior, and antibiotic usage have an influence on the onset of asthma and eczema in infants.<sup>[69,70]</sup> Exclusive breastfeeding in the first 6 months of birth, and continued breastfeeding until 2 years old or older, are recognized as the “gold” standard for infant feeding. Breastfeeding is most suitable for the healthy development and survival of infants, because of its rich nutritional components and bioactive factors. Formula-fed infants with altered intestinal microbiota and lower microbiota diversity in the first few weeks of birth show an increased risk of eczema and asthma when compared with breastfeeding infants. Continued breastfeeding may promote the colonization of gut microbe in infants and provide tolerance to food during complementary feeding.<sup>[71]</sup>

Disorder in composition, diversity, and timing of intestinal microbial colonization is associated with an increased risk of allergy. The World Health Organization defines probiotics as live microorganisms that can provide benefits to human health when administered in adequate amounts. Prebiotics are defined as food ingredients that contain non-digestible oligosaccharides, and probiotics and prebiotics are together called synbiotics. The administration of probiotics, prebiotics, and symbiotics is very important in the primary prevention of allergic diseases. The application of probiotics in mothers can reduce the risk of allergic diseases in offspring, which is related to TLR genetic variants.<sup>[72]</sup> Probiotics and prebiotics have been recommended by the World Allergy Organization for the prevention of allergy under certain conditions in the appropriate period for the appropriate groups like non-exclusively breastfeeding infants. Of course, more multi-center and large scale clinical studies need to be further carried out to confirm it.<sup>[73]</sup>

As we know, disease prevention is divided into first, second, and tertiary prevention. For the prevention of asthma, we also hope to reduce the incidence and prevalence of asthma through tertiary prevention. More and more animal and human experiments have proved that intestinal flora plays a key role in immune regulation and the prevention and treatment of allergic diseases such as

asthma. Therefore, intestinal flora has become an important target for asthma prevention. Fecal microbial transplantation is a new treatment for asthma, where the microbiome of a healthy donor is transferred to a disordered microbial ecosystem. Fecal flora transplantation may be more effective than that of probiotics, which can permanently change the intestinal microflora of the recipient, while probiotics can only settle in the intestinal tract for some time.<sup>[74]</sup>

## Conclusions

In summary, with the change of external environment microbiome and internal microbiome, the incidence of allergic diseases like asthma has increased dramatically. To reduce the burden of this disease, early prevention is particularly critical. The role of human microecology in the occurrence and development of asthma has attracted more and more attention, which may provide us with a new strategy for the prevention and treatment of asthma. Appropriate adjustment of human microecology by changing living environment, diet, feeding pattern, adding probiotics and/or prebiotics in early life, even though pregnant mother, need to be further researched and verified to prevent early asthma. Last but not the least, although asthma should be treated with primary, secondary, and tertiary prevention, early intervention is still effective.

## Conflicts of interest

None.

## References

- Azmeh R, Greydanus DE, Agana MG, Dickson CA, Patel DR, Ischander MM, *et al.* Update in pediatric asthma: selected issues: disease-a-month. *Dis Mon* 2019;66:100886. doi: 10.1016/j.disa-month.2019.100886.
- Maslan J, Mims JW. What is asthma? Pathophysiology, demographics, and health care costs. *Otolaryngol Clin North Am* 2014;47:13–22. doi: 10.1016/j.otc.2013.09.010.
- von Mutius E. The microbial environment and its influence on asthma prevention in early life. *J Allergy Clin Immunol* 2016;137:680–689. doi: 10.1016/j.jaci.2015.12.1301.
- Karkman A, Lehtimäki J, Ruokolainen L. The ecology of human microbiota: dynamics and diversity in health and disease. *Ann N Y Acad Sci* 2017;1399:78–92. doi: 10.1111/nyas.13326.
- Kozik AJ, Huang YJ. The microbiome in asthma: role in pathogenesis, phenotype, and response to treatment. *Ann Allergy Asthma Immunol* 2019;122:270–275. doi: 10.1016/j.anai.2018.12.005.
- Lederberg J. Infectious history. *Science* 2000;288:287–293. doi: 10.1126/science.288.5464.287.
- Hornung B, Martins Dos Santos VAP, Smidt H, Schaap PJ. Studying microbial functionality within the gut ecosystem by systems biology. *Genes Nutr* 2018;13:5. doi: 10.1186/s12263-018-0594-6.
- Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. *Proc Natl Acad Sci U S A* 1977;74:5463–5467. doi: 10.1073/pnas.74.12.5463.
- Sun LY, Yang YS. Advances in non-cultivation technology of microorganism and study on intestinal microecology (In Chinese). *China Crit Care Med* 2013;25:573–576. doi: 10.3760/cma.j.issn.2095-4352.2013.09.023.
- Song EJ, Lee ES, Nam YD. Progress of analytical tools and techniques for human gut microbiome research. *J Microbiol* 2018;56:693–705. doi: 10.1007/s12275-018-8238-5.
- Ege MJ, Bieli C, Frei R, van Strien RT, Riedler J, Ublagger E, *et al.* Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. *J Allergy Clin Immunol* 2006;117:817–823. doi: 10.1016/j.jaci.2005.12.1307.
- Schaub B, Liu J, Hoppler S, Schleich I, Huehn J, Olek S, *et al.* Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. *J Allergy Clin Immunol* 2009;123:774–782.e5. doi: 10.1016/j.jaci.2009.01.056.
- Krauss-Etschmann S, Hartl D, Heinrich J, Thaqui A, Prell C, Campoy C, *et al.* Association between levels of Toll-like receptors 2 and 4 and CD14 mRNA and allergy in pregnant women and their offspring. *Clin Immunol* 2006;118:292–299. doi: 10.1016/j.clim.2005.10.003.
- Liu J, Radler D, Illi S, Klucker E, Turan E, von Mutius E, *et al.* TLR2 polymorphisms influence neonatal regulatory T cells depending on maternal atopy. *Allergy* 2011;66:1020–1029. doi: 10.1111/j.1398-9995.2011.02573.x.
- Conrad ML, Ferstl R, Teich R, Brand S, Blumer N, Yildirim AO, *et al.* Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe *Acinetobacter lwoffii* F78. *J Exp Med* 2009;206:2869–2877. doi: 10.1084/jem.20090845.
- Qian LJ, Kang SM, Xie JL, Huang L, Wen Q, Fan YY, *et al.* Early-life gut microbial colonization shapes Th1/Th2 balance in asthma model in BALB/c mice. *BMC Microbiol* 2017;17:135. doi: 10.1186/s12866-017-1044-0.
- Strickland DH, Holt PG. T regulatory cells in childhood asthma. *Trends Immunol* 2011;32:420–427. doi: 10.1016/j.it.2011.06.010.
- Meng SS, Gao R, Yan BD, Ren J, Wu F, Chen P, *et al.* Maternal allergic disease history affects childhood allergy development through impairment of neonatal regulatory T-cells. *Respir Res* 2016;17:114. doi: 10.1186/s12931-016-0430-8.
- Agarwal A, Singh M, Chatterjee BP, Chauhan A, Chakraborti A. Interplay of T helper 17 cells with CD4(+)/CD25(high) FOXP3(+) Tregs in regulation of allergic asthma in pediatric patients. *Int J Pediatr* 2014;2014:636238. doi: 10.1155/2014/636238.
- Valkonen M, Taubel M, Pekkanen J, Tischer C, Rintala H, Zock JP, *et al.* Microbial characteristics in homes of asthmatic and non-asthmatic adults in the ECRHS cohort. *Indoor Air* 2018;28:16–27. doi: 10.1111/ina.12427.
- Liu Y, Wang H-D, Yu Z-X, Hua S-C, Zhou L-T, Peng L-P. Influence of air pollution on hospital admissions in adult asthma in Northeast China. *Chin Med J* 2018;131:1030–1033. doi: 10.4103/0366-6999.230735.
- Ding L, Zhu D, Peng D. Meta-analysis of the relationship between particulate matter (PM(10) and PM(2.5)) and asthma hospital admissions in children (In Chinese). *Chin J Pediatr* 2015;53:129–135. doi: 10.3760/cma.j.issn.0578-1310.2015.02.013.
- Jung CR, Chen WT, Tang YH, Hwang BF. Fine particulate matter exposure during pregnancy and infancy and incident asthma. *J Allergy Clin Immunol* 2019;143:2254–2262.e5. doi: 10.1016/j.jaci.2019.03.024.
- Zhou J, Geng F, Xu J, Peng L, Ye X, Yang D, *et al.* PM2.5 exposure and cold stress exacerbates asthma in mice by increasing histone acetylation in IL-4 gene promoter in CD4(+) T cells. *Toxicol Lett* 2019;316:147–153. doi: 10.1016/j.toxlet.2019.09.011.
- Wu CC, Hsu TY, Chang JC, Ou CY, Kuo HC, Liu CA, *et al.* Paternal tobacco smoke correlated to offspring asthma and prenatal epigenetic programming. *Front Genet* 2019;10:471. doi: 10.3389/fgene.2019.00471.
- Hollams EM, de Klerk NH, Holt PG, Sly PD. Persistent effects of maternal smoking during pregnancy on lung function and asthma in adolescents. *Am J Respir Crit Care Med* 2014;189:401–407. doi: 10.1164/rccm.201302-0323OC.
- Bellisario V, Piccioni P, Bugiani M, Squillacioti G, Levra S, Gulotta C, *et al.* Tobacco smoke exposure, urban and environmental factors as respiratory disease predictors in Italian adolescents. *Int J Environ Res Public Health* 2019;16:4048. doi: 10.3390/ijerph16204048.
- Sugier PE, Sarnowski C, Granell R, Laprise C, Ege MJ, Margaritte-Jeannin P, *et al.* Genome-wide interaction study of early-life smoking exposure on time-to-asthma onset in childhood. *Clin Exp Allergy* 2019;49:1342–1351. doi: 10.1111/cea.13476.
- Moffatt MF, Cookson WO. The lung microbiome in health and disease. *Clin Med (Lond)* 2017;17:525–529. doi: 10.7861/clinmedicine.17-6-525.
- Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, *et al.* Disordered microbial communities in asthmatic airways. *PLoS One* 2010;5:e8578. doi: 10.1371/journal.pone.0008578.
- Caverly LJ, Huang YJ, Sze MA. Past, present, and future research on the lung microbiome in inflammatory airway disease. *Chest* 2019;156:376–382. doi: 10.1016/j.chest.2019.05.011.
- Huffnagle GB, Dickson RP, Lukacs NW. The respiratory tract microbiome and lung inflammation: a two-way street. *Mucosal Immunol* 2017;10:299–306. doi: 10.1038/mi.2016.108.



33. Huang YJ, Nelson CE, Brodie EL, Desantis TZ, Baek MS, Liu J, *et al.* Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. *J Allergy Clin Immunol* 2011;127:372–381.e1-3. doi: 10.1016/j.jaci.2010.10.048.
34. Chiu CY, Chan YL, Tsai YS, Chen SA, Wang CJ, Chen KF, *et al.* Airway microbial diversity is inversely associated with mite-sensitized rhinitis and asthma in early childhood. *Sci Rep* 2017;7:1820. doi: 10.1038/s41598-017-02067-7.
35. Panzer AR, Lynch SV. Influence and effect of the human microbiome in allergy and asthma. *Curr Opin Rheumatol* 2015;27:373–380. doi: 10.1097/BOR.000000000000191.
36. Wang Z, Singh R, Miller BE, Tal-Singer R, Van Horn S, Tomsho L, *et al.* Sputum microbiome temporal variability and dysbiosis in chronic obstructive pulmonary disease exacerbations: an analysis of the COPDMAP study. *Thorax* 2018;73:331–338. doi: 10.1136/thoraxjnl-2017-210741.
37. Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. *World J Gastroenterol* 2015;21:8787–8803. doi: 10.3748/wjg.v21.i29.8787.
38. Arrieta MC, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, *et al.* Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* 2015;7:307ra152. doi: 10.1126/scitranslmed.aab2271.
39. Hevia A, Milani C, Lopez P, Donado CD, Cuervo A, Gonzalez S, *et al.* Allergic patients with long-term asthma display low levels of *Bifidobacterium adolescentis*. *PLoS One* 2016;11:e0147809. doi: 10.1371/journal.pone.0147809.
40. Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. *Clin Exp Allergy* 2014;44:842–850. doi: 10.1111/cea.12253.
41. Fujimura KE, Sitarik AR, Havstad S, Lin DL, Levan S, Fadrosh D, *et al.* Neonatal gut microbiota associates with childhood multi-sensitized atopy and T cell differentiation. *Nat Med* 2016;22:1187–1191. doi: 10.1038/nm.4176.
42. Thorburn AN, McKenzie CI, Shen S, Stanley D, Macia L, Mason LJ, *et al.* Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nat Commun* 2015;6:7320. doi: 10.1038/ncomms8320.
43. Krauss-Etschmann S, Meyer KF, Dehmel S, Hylkema MN. Inter- and transgenerational epigenetic inheritance: evidence in asthma and COPD? *Clin Epigenetics* 2015;7:53. doi: 10.1186/s13148-015-0085-1.
44. Aron JL, Akbari O. Regulatory T cells and type 2 innate lymphoid cell-dependent asthma. *Allergy* 2017;72:1148–1155. doi: 10.1111/all.13139.
45. Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol* 2018;141:1169–1179. doi: 10.1016/j.jaci.2018.02.004.
46. Everaere L, Ait-Yahia S, Molendi-Coste O, Vornig H, Quemener S, LeVu P, *et al.* Innate lymphoid cells contribute to allergic airway disease exacerbation by obesity. *J Allergy Clin Immunol* 2016;138:1309–1318.e11. doi: 10.1016/j.jaci.2016.03.019.
47. Forno E, Young OM, Kumar R, Simhan H, Celedon JC. Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma. *Pediatrics* 2014;134:e535–e546. doi: 10.1542/peds.2014-0439.
48. Park HJ, Lee SW, Hong S. Regulation of allergic immune responses by microbial metabolites. *Immune Netw* 2018;18:e15. doi: 10.4110/in.2018.18.e15.
49. Madan JC. Neonatal gastrointestinal and respiratory microbiome in cystic fibrosis: potential interactions and implications for systemic health. *Clin Ther* 2016;38:740–746. doi: 10.1016/j.clinthera.2016.02.008.
50. Huang C, Shi G. Smoking and microbiome in oral, airway, gut and some systemic diseases. *J Transl Med* 2019;17:225. doi: 10.1186/s12967-019-1971-7.
51. Mathieu E, Escribano-Vazquez U, Descamps D, Cherbuy C, Langella P, Riffault S, *et al.* Paradigms of lung microbiota functions in health and disease, particularly, in asthma. *Front Physiol* 2018;9:1168. doi: 10.3389/fphys.2018.01168.
52. Chung KF. Airway microbial dysbiosis in asthmatic patients: a target for prevention and treatment. *J Allergy Clin Immunol* 2017;139:1082–1083. doi: 10.1016/j.jaci.2017.02.009.
53. Anand S, Mande SS. Diet, microbiota and gut-lung connection. *Front Microbiol* 2018;9:2147. doi: 10.3389/fmicb.2018.02147.
54. Madan JC, Koestler DC, Stanton BA, Davidson L, Moulton LA, Housman ML, *et al.* Serial analysis of the gut and respiratory microbiome in cystic fibrosis in infancy: interaction between intestinal and respiratory tracts and impact of nutritional exposures. *mBio* 2012;3:e00251–12. doi: 10.1128/mBio.00251-12.
55. Ahn K. The role of air pollutants in atopic dermatitis. *J Allergy Clin Immunol* 2014;134:993–999. doi: 10.1016/j.jaci.2014.09.023.
56. Jackson DJ, Gern JE, Lemanske RF. Lessons learned from birth cohort studies conducted in diverse environments. *J Allergy Clin Immunol* 2017;139:379–386. doi: 10.1016/j.jaci.2016.12.941.
57. Olin A, Henckel E, Chen Y, Lakshminanth T, Pou C, Mikes J, *et al.* Stereotypic immune system development in newborn children. *Cell* 2018;174:1277–1292.e14. doi: 10.1016/j.cell.2018.06.045.
58. Houghteling PD, Walker WA. From birth to “immunohealth,” allergies and enterocolitis. *J Clin Gastroenterol* 2015;49 (Suppl 1):S7–S12. doi: 10.1097/mcg.0000000000000355.
59. Stiemsma LT, Turvey SE. Asthma and the microbiome: defining the critical window in early life. *Allergy Asthma Clin Immunol* 2017;13:3. doi: 10.1186/s13223-016-0173-6.
60. Vuillermin PJ, Macia L, Nanan R, Tang ML, Collier F, Brix S. The maternal microbiome during pregnancy and allergic disease in the offspring. *Semin Immunopathol* 2017;39:669–675. doi: 10.1007/s00281-017-0652-y.
61. Stockman JA. Exposure to environmental microorganisms and childhood asthma. *Yearbook of Pediatrics* 2012;2012:25–27. doi: 10.1016/j.yped.2011.06.056.
62. Just J, Belfar S, Wanin S, Pribil C, Grimfeld A, Duru G. Impact of innate and environmental factors on wheezing persistence during childhood. *J Asthma* 2010;47:412–416. doi: 10.3109/02770900903584035.
63. Barboza R, Camara NO, Gomes E, Sa-Nunes A, Florsheim E, Mirotti L, *et al.* Endotoxin exposure during sensitization to *Blomia tropicalis* allergens shifts TH2 immunity towards a TH17-mediated airway neutrophilic inflammation: role of TLR4 and TLR2. *PLoS One* 2013;8:e67115. doi: 10.1371/journal.pone.0067115.
64. Schuijs MJ, Willart MA, Vergote K, Gras D, Deswarte K, Ege MJ, *et al.* Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells 2015;349:1106–1110. doi: 10.1126/science.aac6623.
65. Natarajan S, Kim J, Bouchard J, Cruikshank W, Remick DG. Pulmonary endotoxin tolerance protects against cockroach allergen-induced asthma-like inflammation in a mouse model. *Int Arch Allergy Immunol* 2012;158:120–130. doi: 10.1159/000330896.
66. Acevedo N, Zakzuk J, Caraballo L. House dust mite allergy under changing environments. *Allergy Asthma Immunol Res* 2019;11:450–469. doi: 10.4168/air.2019.11.4.450.
67. Egawa G, Honda T, Kabashima K. SCFAs control skin immune responses via increasing Tregs. *J Invest Dermatol* 2017;137:800–801. doi: 10.1016/j.jid.2016.12.022.
68. Schwarz A, Bruhs A, Schwarz T. The short-chain fatty acid sodium butyrate functions as a regulator of the skin immune system. *J Invest Dermatol* 2017;137:855–864. doi: 10.1016/j.jid.2016.11.014.
69. Hana Kiňová Sepová, Boris Dudík, Andrea Bilková. Gut microbiota: its development and relation to certain diseases [In Czech]. *Ceska Slov Farm* 2018;66:267–273.
70. Leah T, Stiemsma P, Karin B, Michels S. The role of the microbiome in the developmental origins of health and disease. *Pediatrics* 2017;141. doi: 10.1542/peds.2017-2437.
71. Oddy WH. Breastfeeding, childhood asthma, and allergic disease. *Ann Nutr Metab* 2017;70 (Suppl 2):26–36. doi: 10.1159/000457920.
72. Marlow G, Han DY, Wickens K, Stanley T, Crane J, Mitchell EA, *et al.* Differential effects of two probiotics on the risks of eczema and atopy associated with single nucleotide polymorphisms to Toll-like receptors. *Pediatr Allergy Immunol* 2015;26:262–271. doi: 10.1111/pai.12371.
73. West CE, Dzidic M, Prescott SL, Jenmalm MC. Bugging allergy; role of pre-, pro- and synbiotics in allergy prevention. *Allergol Int* 2017;66:529–538. doi: 10.1016/j.alit.2017.08.001.
74. Kang Y, Cai Y. Future prospect of faecal microbiota transplantation as a potential therapy in asthma. *Allergol Immunopathol (Madr)* 2018;46:307–309. doi: 10.1016/j.aller.2017.04.008.

**How to cite this article:** Shi HL, Lan YH, Hu ZC, Yan ZN, Liu ZZ, Kadier X, Ma L, Yu JY, Liu J. Microecology research: a new target for the prevention of asthma. *Chin Med J* 2020;133:2712–2720. doi: 10.1097/CM9.0000000000001127