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Review

Important Role of Immunological Responses to Environmental Exposure in the Development of Allergic Asthma

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ABSTRACT

Allergic asthma is a public health problem that affects human health and socioeconomic development. Studies have found that the prevalence of asthma has significantly increased in recent years, which has become particularly pronounced in developed countries. With rapid urbanization in China in the last 3 decades, the prevalence of asthma has increased significantly in urban areas. As changes in genetic backgrounds of human populations are limited, environmental exposure may be a major factor that is responsible for the increased prevalence of asthma. This review focuses on environmental components of farms and rural areas that may have protective effects in reducing the development of asthma. Farm and rural related microorganism- and pathogen-associated molecular patterns are considered to be important environmental factors that modulate host's innate and adaptive immune system to induce protection effects later in life. Environmental microbial-related immunotherapy will also be discussed as the future research direction for the prevention of allergic asthma.

Keywords: Asthma; epidemiology; hygiene hypothesis; environmental exposure; house dust mite

INTRODUCTION

Epidemiological studies have confirmed that allergic asthma becomes more prevalent around the world in the past few decades, and the prevalence of asthma is higher in urban areas than in rural areas. The increased occurrence of asthma is often found to be associated with improvement in hygiene conditions of humans. Thirty years ago, the classic "hygiene hypothesis" stated that crowded and unhygienic living conditions will lead to a decrease in the prevalence of asthma as well as in other allergic disorders including eczema and hay fever.[1] The unhygienic environment increases the opportunities for children to contact microorganisms at the early stages of life. The advent of this hypothesis has increased research on the role of environmental factors in allergic diseases, especially asthma. Currently, reports on asthma-protective factors in the environment have yielded inconsistent findings. Endotoxin has been found to be associated with protection against asthma as a

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recent study reported that the prevalence of asthma was lower in Amish children in a high endotoxin environment.[2] The mechanisms by which environmental factors regulate allergic asthma have been extensively investigated and the findings further expand our knowledge of the interaction between environmental factors and allergic asthma. The aim of the present review is to summarize the research works in China as well as the findings of research groups from other countries in epidemiological surveys on asthma, environmental microorganism factors, immunoregulation mechanisms, and microbial-related immunotherapy. New research directions on relations between environmental factors and allergic asthma are proposed which are expected to guide future studies.

EPIDEMIOLOGICAL TRENDS OF ALLERGIC ASTHMA

Trends in the prevalence of allergic asthma

Since the 1950s, the global prevalence of allergic asthma has been increasing.[3] The International Study of Asthma and Allergies in Childhood analyzed the multicenter survey data on allergic asthma, allergic rhinoconjunctivitis, and eczema at 7-year intervals on average, and the results showed increases in all 3 allergic diseases.[4] Generally, the prevalence of asthma is higher in developed countries, while its increasing trend has slowed down in recent years. However, the asthma prevalence showed remarkably increased in the developing countries with rapid economic growth and urbanization.[5]

In the USA, the prevalence of asthma increased at an annual rate of 1.5% up to 2001, and reached 8.4% in 2010.[6] However, it has shown a steady trend since 2008,[7] with 8.4% in 2016 and 6.7% in 2018, according to the national survey data.[8,9] The prevalence in the UK had also stabilized in recent years (7.2% in 2006 and 6.5% in 2016).[10,11] A high asthma prevalence was found in Canada from 14.3% in 2006 to 16% in 2012.[12] The rate of school-age children with asthma in Sweden was 2.5%, 5.7%, and 7.1% in 1979, 1991, and 2007, respectively.[13] In 2008, 14.9% of children aged 7–11 years in Australia had asthma.[14] In Melbourne, the prevalence in 4-year-old children remained high at 13.8% in 2017.[15] Singapore showed significantly increased prevalence trend from 5.5% in 1967, to 13.7% in 1987, and 20% in 1994,[16,17] and the prevalence continuously went up to 20.7% in 1994 to 27.4% in 2001 for 12- to 15-year-old children.[18] Data from National Health Insurance Sharing Service of Korea revealed a 1.4-fold increase from 1.55% to 2.21% between 2002 and 2015 for asthma prevalence, which was more common in elderly population aged ≥ 60 years.[19]

In China, the prevalence rates of asthma and other allergic diseases have been increasing each year. Pediatric asthma surveys that were conducted in 1990, 2000, and 2010 showed a substantial rise in asthma prevalence in most cities.[20-23] For example, in Beijing, prevalence of asthma in children increased from 0.77% in 1990, to 2.05% in 2000, and to 2.55% in 2010.[21-23] Shanghai children also demonstrated a similar increasing trend in asthma prevalence from 1.50%, to 3.34%, and to 5.73%, respectively.[21-23] A survey in school children from Guangzhou also showed increasing prevalence of asthma from 3.9% in 1994, to 4.6% in 2001, and to 6.9% in 2009.[24] In 1974, 1985 and 1991, Taiwanese showed their prevalence of asthma at 1.3%, 5.07%, and 5.8%, respectively,[25,26] while the prevalence of doctor diagnosed asthma increased dramatically 10 years later at 11.7% in 2001 and 15.7% in 2007.[27] In Hong Kong, however, the prevalence of asthma in 6- to 7-year-old children did not change significantly between 1994 (7.8%) and 2001(7.9%).[28,29]

Difference in the prevalence of asthma between urban and rural populations

In contrast to the high prevalence of asthma in urban areas, asthma is less prevalent in rural regions. Farming and rural environment are proposed to be 2 classic protective factors against asthma in Europe.[30,31] Stein *et al.*[2] compared 30 matched Amish children from traditional farms and Hutterite children from modern farms, and found that although both groups had similar genetic backgrounds and lifestyle habits, the prevalence of asthma was 4 to 6 times higher in the Hutterite population than in the Amish population who were exposed to the high endotoxin levels in house dust. Our study showed that the prevalence of asthma in 13- to 14-year-old children from rural Conghua was significantly lower than that in those from urban Guangzhou (3.4% vs. 6.9%).[32] The prevalence rated of allergic rhinitis and eczema in the 2 groups of children also showed similar rural-urban differences.[32] Similar to the situation observed in southern China, the prevalence of asthma in children from rural regions in northern China was significantly lower than in Beijing city (1.1% vs. 6.3%).[30]

ENVIRONMENTAL AND MICROBIAL EXPOSURE

Environmental exposure and asthma

Asthma pathogenesis is multifactorial and the most important factors are genetics and environmental factors. Since significant changes in genetic background of humans is less likely to occur within several decades, environmental factors might be the major determinants modulating the prevalence of asthma. The "hygiene hypothesis" proposed in 1989 by Strachan[1] suggested that the rapid increase in the prevalence of allergies and autoimmune diseases in humans is due to an overly clean environment. Following the initial "hygiene hypothesis," many epidemiological studies provided direct evidence for the correlation between the prevalence of asthma and living environmental condition in children and explored the underlying immunological and molecular mechanisms.[33-36] In 1999, Braun-Fahrländer *et al.*[37] first found that the risk of atopic constitution and allergies in children who grew up on farms was significantly lower than those who grew up in non-farm conditions. Subsequently, many epidemiological studies that investigated children asthma on European farms,[38-40] traditional and modern farms in the USA,[2] as well as the studies comparing urban and rural environment[32,41-43] have validated the protective effect of a farm environment so called "farm effect."[44] In the southern and northern regions of China, we have also found that the agricultural environment and rural house dust endotoxin have protective effects on childhood asthma.[30,32] It is generally believed that exposure to the farm environment (particularly traditional farms) early in life has significantly reduced the prevalence of asthma in the children compared with those who are not exposed the farm environment. Due to environment diversity, multiple protective environmental factors were found in different studies. The contact factors included livestock, pets,[45] farm crops,[38] unpasteurized milk,[46-48] breastfeeding, farm or village cultivation activities,[32,49] and fishing.[50] The major findings from these studies are summarized in **Table**.[2,30,32,51-57]

Microbial exposure and asthma

Among the complex and diverse factors of the living environment that we are exposed, microbes and their chemical compounds might be the key elements that play roles in the modulation of immune responses and the pathogenesis of allergic diseases like asthma. *Acinetobacter lwoffii* and *Lactococcus lactis* from farms that can induce T-helper 1 cell (Th1) differentiation and mediate protective effects against allergic airway inflammation.[58] Ege *et al.*[59] reported that bacterial and fungal derivatives in house dust had a significant negative

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Table. Studies on environmental exposure and allergies in different countries and regions

Region	Exposure factor	Sample size (No.)	Sample age (yr)	Main findings	Outcomes (onset of allergy)	Ref.
Asia-Beijing, China	Farm livestock and farming behavior	7,077	13–14	Contact with farming and livestock has protective effects.	Reduced	30
Oceania-New Zealand	Traffic at place of residence, drugs, and farm foodstuffs	24,190	6–7; 13–14	Truck traffic, antibiotics or paracetamol exposure during early life, were positively correlated with eczema. Consumption of milk, seafood, eggs, and have a dog in home, were negatively correlated with eczema.	Reduced	51
Europe-Turku, Finland and neighboring regions	Indoor pet exposure during the perinatal period	256	0–2	Fecal *Bifidobacterium longum* counts in non-wheezing infants who were exposed to pets were significantly higher than those of wheezing infants who were not exposed to pets.	Reduced	52
Central Europe-Silesia, Poland	Unpasteurized dairy products and activities related to livestock	1,676	>5	Agriculture-related contact significantly decreased in Silesia and the prevalence of allergies drastically increased within a short period of nine years.	Reduced	53
Northern Europe	Livestock	11,123	Mean age: 53	Subjects who grew up in livestock farms had a lower incidence of asthma (8%) compared to those who grew up in inner cities (11%).	Reduced	54
Asia-Guangzhou, China	Farming environment and endotoxin levels	13,251	13–14	Early contact with crops and high levels of environmental endotoxins may protect children from the effects of asthma.	Reduced	32
North America-USA	Endotoxin levels in homes	60	7–14	High endotoxin levels in traditional Amish farms was a protective factor for asthma, and innate immunity also played an important role.	Reduced	2
North America-Canada	Farming environment	10,941	0–11	The cumulative 14-year asthma incidence in children living in a farming environment was significantly lower than live in non-rural and rural non-farming environments.	Reduced	55
South America-Cordoba rural areas	Contact with livestock, such as dairy farms	1,804	13–14	Residency on dairy farms, including periodic livestock contact reduced allergic rhino-conjunctivitis.	Reduced	56
Africa-Cape Town and Eastern Cape province	Farming exposure, sunlight exposure, pet, antibiotic and probiotic exposure, antihelminth exposure, cigarette smoke and fossil fuel exposure.	1,736	1–3	Farm animal exposure but not unpasteurized milk is the strongest factor to against allergy. Fermented milk produces has a significant effect in urban cohort but not in rural.	Reduced	57

correlation with the incidence of asthma in exposed children. In one Finland study, children who grew up in non-farm families showed decreased risk of asthma, but their family bacterial microbiota composition is similar to that of farm families, suggesting that the microbes are accountable for the farm environment-associated protection against development of asthma.[60]

In addition, high levels of endotoxin in farm and rural environments is related to a low prevalence of asthma and other allergic diseases.[61-63] Endotoxin is a component of the cell wall of gram-negative bacteria and cyanobacteria.[64] A previous study found that the protective effects of endotoxins might be related to the induction of A20 expression in lung epithelial cells.[65] Another investigation revealed that endotoxin levels were 6.8 times higher in traditional Amish farms than in modern Hutterite farms and may regulate innate immune pathways in children to prevent the development of asthma.[2] In addition to the endotoxins, many pathogen-associated molecular patterns (PAMPs), such as extracellular polysaccharides, muramic acid, and glucans, have been shown to be closely associated with the protective effects of farms.[66]

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Antibiotic exposure during maternal pregnancy or early life[67,71] and cesarean delivery[57,72,73] can increase the prevalence of asthma in children by affecting the gut microbiota and other mechanisms. Anti-parasitic therapy is also shown to be associated with increased prevalence of asthma.[74,75] It was also noted that the prevalence of eczema in children would increase when their mothers accepted deworming treatment during pregnancy, while anthelminthic in children had no significant effect on eczema,[76] suggesting that the protective effect of allergies induced by parasite infection might begin in the mother's uterus.

However, it is worthy of noting that some types of microorganisms may have opposite effects on development of asthma. For example, infection with bacterial species like *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* and some virus often aggravates asthma.[77,78]

ENVIRONMENTAL FACTORS AND IMMUNOLOGICAL REGULATION OF ASTHMA

There is still an insufficient understanding of the immunological relationship between the dramatic increase in allergy prevalence and environmental changes. However, in recent years, it has become clear that asthma is a heterogeneous disease in which both innate and acquired immunities are involved. Common factors that promote or inhibit the onset of asthma include allergen exposure and microbial/parasitic infection, oxidative stress as well as environmental and microbial related metabolites. Cells involved in this process include eosinophils, basophils, neutrophils, mast cells, macrophages, dendritic cells (DCs), epithelial cells, natural killer T (NKT) cells, natural helper cells, Th2 cells, T-helper 17 (Th17) cells, group 2 innate lymphoid cells (ILC2), B cells, regulatory T cells (Tregs), and regulatory B cells (Bregs).[79] In **Figure**, we illustrate the environmental factors and immunological regulatory mechanisms involved in the development and prevention of asthma.

Innate immune mechanisms

During human evolution, our immune system is exposed to and interacted with symbiotic surrounding pathogens. The PAMPs on the gut or respiratory microbiota and parasitic worms might be recognized by the pattern recognition receptors on innate immune cells to initiate the immune responses. Study by Lauener *et al.*[80] found that compared with the unexposed children, children with farm exposure had increased CD14/toll-like receptor (TLR) 2 expression levels and that exposure to a farm environment early in life correlates to important regulatory effects on asthma through TLRs. A subsequent study showed that maternal exposure to a microbe-rich environment before delivery resulted in increasing levels of genes expression for the receptors of the innate immune system (*i.e.* TLR2, TLR4, and CD14) in their children. The underlying mechanism for this phenomenon may be related to the intrauterine environment and/or epigenetic changes.[81] TLRs are considered to be key systems in immune response regulation and epithelial cells and DCs play a vital role in linking innate immunity to adaptive immunity. Exposure to appropriate doses of lipopolysaccharide (LPS) weakens signaling pathways required for the production of allergy-related cytokine while retaining double-stranded RNA/DC pathways, thereby activating DCs to promote production of Th1 cytokines but not Th2.[82] In addition, LPS exposure will increase the synthesis of the zinc finger protein A20,[83] thereby inhibiting airway allergic responses to *Dermatophagoides pteronyssinus*.[82] A prospective study showed that maternal exposure to livestock before delivery resulted in significant increases in TLR5 and TLR9 in umbilical cord blood in children while the risk of atopic dermatitis was significantly reduced.[84] Stein *et al.*[2] compared the peripheral

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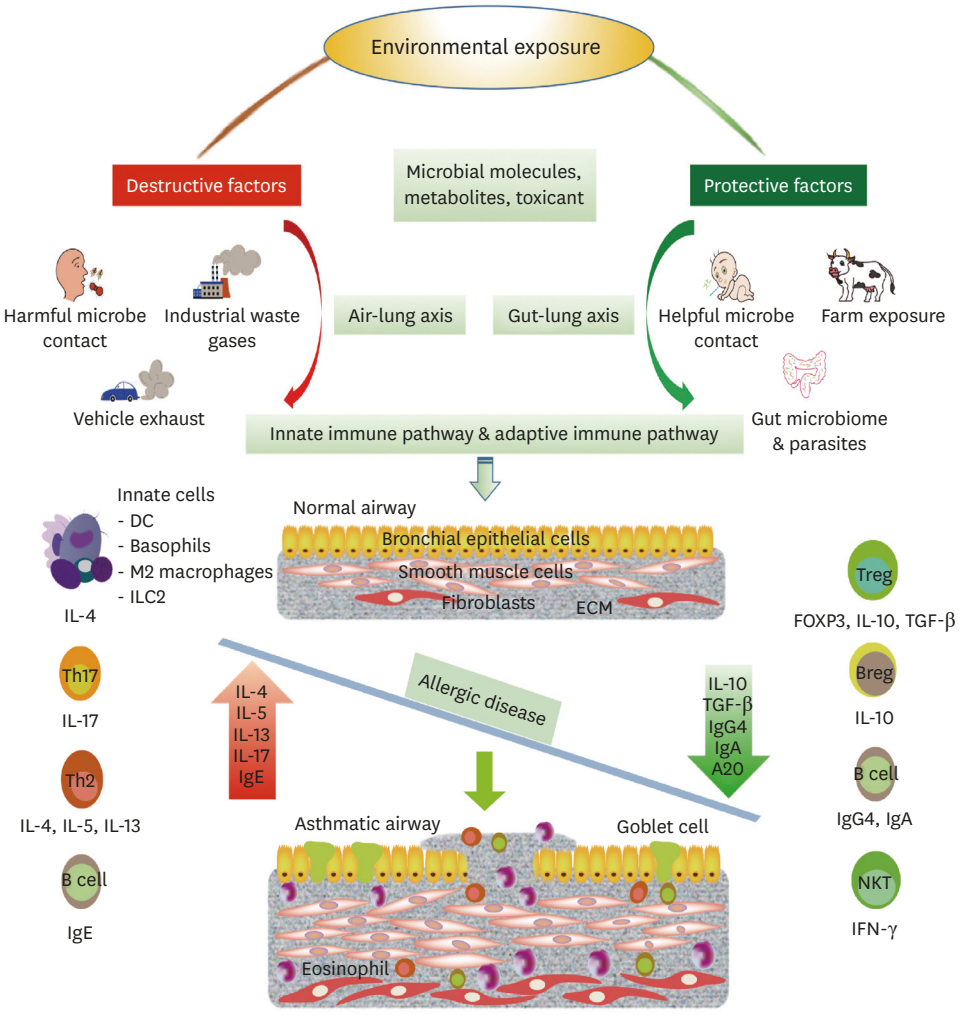

Figure. Potential immunological mechanisms by which environmental factors affect allergic asthma. Environmental microbial molecules and metabolites act on innate and adaptive immune pathways through the air-lung axis and/or the gut-lung axis to exert their immunoregulatory effects. Harmful bacteria, viruses, and industrial waste gases, as well as automobile exhaust, can promote airway inflammation through induction of IL-4, IL-5, IL-13, and IL-17 secretion by innate immune cells (*e.g.*, ILC2, airway epithelial cells, DCs, macrophages, and basophils) and adaptive immune cells (*e.g.*, Th17 cells, Th2 cells, and B cells), resulting in airway mucosal damage, smooth muscle hyperplasia, and fibrotic changes. Conversely, protective environmental factors, such as early life contact with helpful microorganisms, gut parasitic worm infection, gut microbiota, and farm exposure, can result in the production of IL-10, TGF-β, IFN-γ, IgA, and IgG4 by innate (toll-like receptors, airway epithelium, DCs, natural killer T cells), and adaptive immune cells (Tregs, Bregs, and B cells) to protect against allergic asthma.
DC, dendritic cell; ILC2, group 2 innate lymphoid cells; ECM, extracellular matrix; IL, interleukin; TGF-β, transformation and growth factor β; Ig, immunoglobulin; IFN-γ, interferon-γ.

blood cell compositions and the phenotypes of 30 traditional farm and modern farm children, and observed that the percentage of eosinophils was decreased in the traditional farm children and that monocytes exhibited an inhibitory phenotype (lower levels of the human leukocyte antigens DR and HLA-DR as well as higher levels of immunoglobulin-like transcript 3, ILT3). In addition, traditional farm dust extracts had significant protective effects in animal models of asthma. In myeloid differentiation primary response gene 88 (*MyD88*)-deficient mice, this protective effect was drastically reduced. In *MyD88*- and toll/interleukin-1 receptor domain-containing adaptor inducing IFN-β (TRIF)-deficient mice, this protective effect was completely abolished. These 2 molecules are located at the convergence of multiple immune signaling

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pathways. These results suggest that environment microbial factors modulate immune response and induce immune suppression allergic asthma through innate immunity.[2]

It is known that, in addition to endotoxins, diverse microbial products in the environment are effective stimuli for innate immunity.[85,86] Invariant NKT (iNKT) cells are able to recognize glycolipid antigens and some PAMPs may directly activate iNKT cells independently of TLRs. House dust extract (HDE) could promote OVA-induced airway inflammation in asthmatic mice through iNKT cells, but the source of iNKT-related antigens in HDE has not yet been identified.[87] However, a previous study found that influenza A infection in early life could protect adult mice from allergen-induced airway hyperreactivity (AHR), which was associated with a population of NKT cells, enriched for a CD4-CD8-(DN), T-box transcription factor expressed in T-cells (T-bet)-dependent, and interferon-γ (INF-γ)-secreting subset.[88] Chuang *et al.*[89] proposed that early/neonatal infection or antigen stimulation could induce certain NKT subsets, such as $CD38^{hi}$DN NKT cells, in the lung to produce IFN-γ but not IL-17, IL-4, or IL-13, demonstrating that this NKT subset could directly contact and inhibit $CD4^+$ T cell proliferation, thereby blocking allergen-induced AHR.

Acquired immune mechanisms

Study by Gereda *et al.*[90] demonstrated that persistent environmental endotoxin exposure could induce Th1 immune responses resulting in change in the Th1/Th2 equilibrium, thereby reducing allergen sensitivity and protection of infants from allergen sensitization. Asthmatic mice infected with hookworms or whipworms secrete anti-inflammatory protein-2 (AIP-2) and protein P43 that inhibited costimulatory molecule expression in DCs and Th2 response by binding to IL-13.[91,92]

Regulatory $CD4^+$ T cells (Tregs) play a vital role at the sensitization stage in the pathogenesis of allergic asthma and contribute to balancing T-cell differentiation and maturation. The functions of effector $CD4^+$ T cells, including Th1, Th2, and Th17 cells, can be regulated by Tregs, which play an important role in the immunoregulation and suppression of asthma.[93] Many studies have found a correlation between environmental microbial exposure and Treg differentiation/development. McGuirk and Mills[94] and Wilson *et al.*[95] reported that bacteria and helminth infection could facilitate the development of Tregs. Schaub *et al.*[96] found that maternal farm exposure could regulate the immune systems of children, increased the number and functions of Tregs in umbilical-cord blood in newborns, decreased the proliferation of Th2 lymphocytes, and reduced Th2 cytokine levels. They also found that consumption of farm milk by mothers could increase forkhead box P3 (FoxP3) demethylation in their children, thereby reducing their children's risk of asthma during childhood and adulthood. Lluis *et al.*[97,98] reported that during early childhood, farm milk exposure increase FoxP3 demethylation and Treg cell counts through at least 6 different signaling pathways. Our group used a murine gut parasite, *Heligmosomoides polygyrus*, to investigate the immunoregulation mechanism of gut parasites infection against allergic airway inflammation. It was observed that infection with *H. polygyrus* induced prominent response of IL-10-producing regulatory B cells ($IL\text{-}10^+$ Bregs). These Breg cells were able to promote differentiation and proliferation of IL-10-producing and FoxP3 regulatory $CD4^+$ T cells. Cell transfer and depletion experiments demonstrated that $IL\text{-}10^+$Breg, $IL\text{-}10^+$Treg and $FoxP3^+$Treg cells participated in the parasite-induced immunosuppression of allergic airway inflammation.[99]

A birth cohort study showed that contact with livestock or cats during pregnancy could increase secretory immunoglobulin (sIgA) levels in breast milk and reduced atopic dermatitis in their children.[100] Many studies have shown that elevated sIgA and transforming growth factor-β (TGF-β) levels in breast milk have protective effects against asthma in children.[101,102]

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TGF-β secreted by Treg cells is a key factor for survival of IgA+ B cells.[103] IgA limits the responses of microorganisms to host mucosal immunity.[103] These two effects jointly maintain symbiosis with microorganisms in the body, which may be an indirect protective mechanism against allergies.[104] Animal experiments have shown that soluble extracts from nematodes can increase IL-10 and TGF-β levels, thereby inhibiting airway inflammation in asthma.[105]

FUTURE RESEARCH DIRECTIONS

Epidemiological observations provide a mountain of evidence in proving the link between asthma and environmental microbial and parasite exposure.[60,106-110] Human fecal bacteria transplantation, probiotic therapy[111,112] and parasite immunotherapy[76,113] used in clinical trials, and mouse model research[114,115] have enhanced our understanding of the interconnection between environmental microbes,[116] symbionts,[117-123] and asthma. The available data support the negative correlation between exposure to farms and rural environmental microorganisms in early life and that the incidence of allergic asthma and the specific exposure time window could be critical.[110,124] To determine the "best time window" for microbial exposure and to identify the protective microbiome, more cohort observations are needed in the future. Although observational studies help understand the importance of environmental factors in the modulation of allergic asthma, more intervention studies are needed to further elucidate the molecular mechanisms involved in asthma pathogenesis. Animal models are also powerful tolls for the mechanism study of asthma pathogenesis regulated by environmental microorganisms. Furthermore, microbial immunotherapy has been tested as the potential means to protect against allergic asthma; therefor, in-depth studies are needed to characterize the derivatives of symbiotic or infective microorganisms for rational and safe use to control asthma and other allergic diseases.

SUMMARY

It is well established that environmental factors strongly influence the onset and development of asthma and other allergic diseases. The external microorganisms and internal microbiota, and their derivatives have been identified as major components that modulate the immune responses of humans and, in most cases, induce immunosuppression to prevent or alleviate asthma pathogenesis. Research findings have revealed that multiple facets of the immune system are involved in the complex interaction between environmental factors and the prevention of asthma. Further studies on the pathogenesis of allergic asthma, the nature of microorganism derivatives, and immune responses to the bacterial components may result in novel therapies to control and prevent occurrence of allergic asthma in human populations.

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