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Review

Environmental Influences and Allergic Diseases in the Asia-Pacific Region: What Will Happen in Next 30 Years?

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ABSTRACT

Asia-Pacific is a populous region with remarkable variations in socioeconomic development and environmental exposure among countries. The prevalence rates of asthma and allergic rhinitis appear to have recently reached a plateau in Western countries, whereas they are still increasing in many Asian countries. Given the large population in Asia, even a slight increase in the prevalence rate will translate into an overwhelming number of patients. To reduce the magnitude of the increase in allergic diseases in next few decades in Asia, we must understand the potential factors leading to the occurrence of these disorders and the development of potential preventive strategies. The etiology of allergic disorders is likely due to complex interactions among genetic, epigenetic, and environmental factors for the manifestations of inappropriate immune responses. As urbanization and industrialization inevitably progress in Asia, there is an urgent need to curtail the upcoming waves of the allergy epidemic. Potentially modifiable risk exposure, such as air pollution, should be minimized through timely implementation of effective legislations. Meanwhile, re-introduction of protective factors that were once part of the traditional farming lifestyle might give new insight into primary prevention of allergy.

Keywords: Asthma; allergic rhinitis; atopic dermatitis; food allergy; prevalence; Asia; environment; pollution; urbanization

INTRODUCTION

Asthma, allergic rhinitis, atopic eczema, food allergy, and other allergic diseases are a large spectrum of clinically observable phenotypes and distinct immunological/molecular mechanisms called endotypes.[1] The pathogenesis of allergic disorders is still not well understood, but this group of highly heterogeneous and multifactorial disorders is most likely due to combinations of genetic, epigenetic, and environmental factors involving redundant and overlapping pathways (**Fig. 1**). The prevalence rates of asthma and allergic rhinitis appear to have reached a plateau in Western countries in the past decade, whereas data from many Asian countries suggest that it is still increasing.[2,3] The recent increase in the prevalence of allergic disorders in Asia cannot be attributed only to major changes in the genetic factors of the population. Previously, great efforts have been launched into genome-wide association studies (GWASs) in pursuit of genes that contribute to risk of

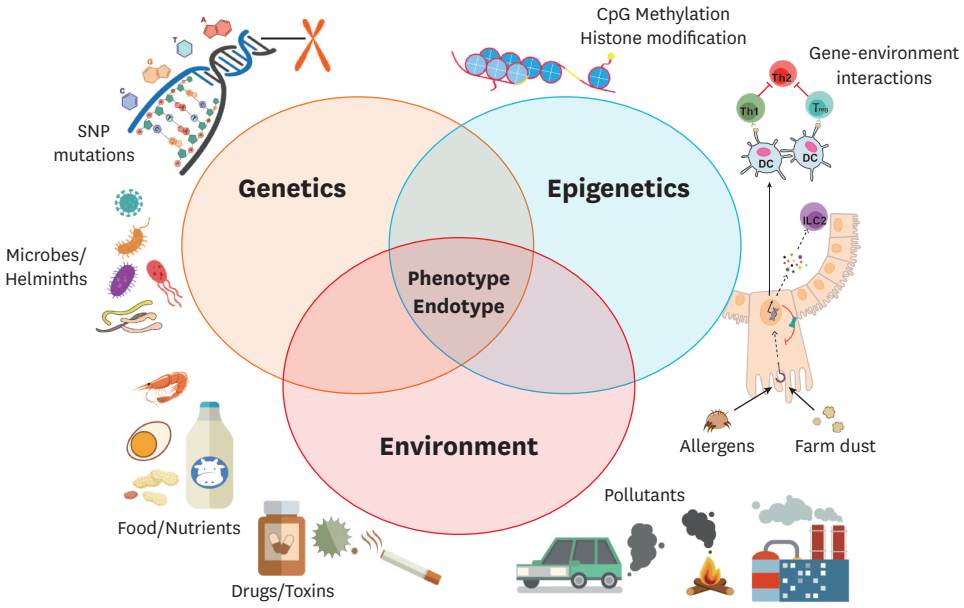

Fig. 1. The complex interactions between genetic, epigenetic, and environmental factors in the development of allergic disorders. Allergic disorders are a group of highly heterogeneous diseases which involve myriads of factors interacting under diverse genetic and immune backgrounds. Environmental exposure may modulate the risk of allergic diseases through the mechanisms of epigenetic control including DNA methylation and histone modification. Convergence of these factors leads to the clinical phenotypes and molecular endotypes of different allergic disorders.
SNP, single nucleotide polymorphism; CpG, consumer packaged goods; Treg, regulatory T cell; Th, T helper; DC, dendritic cell; ILC, innate lymphoid cell.

asthma and allergic diseases. Unfortunately, most of the genetic variants identified by the GWAS approach only have weak effects on asthma,[4] atopic dermatitis,[5] and allergic rhinitis,[6] as reflected by odds ratios very close to one. On a general note, paradigms have shifted increasingly, acknowledging the critical role of environmental factors in development of allergic diseases. The environment harbors not only risk exposure, but also potentially protective factors for host immune homeostasis, especially those related to a traditional rural/farming lifestyle. Because many Asian countries are densely populated, even a slight increase in the prevalence rates of allergic diseases will translate into a large number of affected individuals. Notably, Asian populations may be even more genetically susceptible to the adverse effects of "Westernization."[7-9] As the urbanization of many Asian countries will continue in the foreseeable future, there is an urgent need to develop a novel strategy to curtail the upcoming waves of allergy epidemic. This review provides ideas for countermeasures to reduce the development of allergic diseases in Asian children based on recent findings of epidemiology and mechanistic studies.

EPIDEMIOLOGY OF ALLERGIC DISEASES IN THE ASIAN-PACIFIC REGION

Increasing trends of and wide variations in allergic diseases in the Asian-Pacific region

The past few decades have witnessed an increase in the prevalence of allergic diseases. For epidemiological studies across the world, the standardized survey instruments of the International Study of Asthma and Allergies in Childhood (ISAAC) have been widely used and

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validated at different settings. Recent ISAAC surveys indicated that the increase in childhood allergic diseases is most evident in developing countries.[2] For example, the prevalence rates of asthma and allergic rhinitis among adolescents doubled in Guangzhou, southern China, rising from 3.9% and 17.4% in 1994 to 6.9% and 25.1%, respectively, in 2009.[10] Such increases are most likely attributable to the environmental and lifestyle changes accompanied by economic development and urbanization. In general, asthma and allergic diseases are less common in the Asia-Pacific region than in Western countries. However, wide variations in the prevalence of allergic disorders have been documented among Asian countries and regions with marked differences in the development and environmental exposure.[3,11,12] Not surprisingly, allergic diseases are more prevalent in highly developed countries such as Singapore, Japan, and South Korea than in the other Asian countries. A recent decrease was documented in Japan, with prevalence of current wheeze and atopic dermatitis among children aged 6- to 8-years dropping from 13.6% and 15.8% to 10.2% and 14.6%, respectively, over the 10-year period from 2005 to 2015.[13] A similar decreasing trend was also found in South Korea, where the prevalence of childhood asthma derived from the Korea National Health Insurance claims database decreased from 7.29% in 2010 to 5.95% in 2015.[14] Although the prevalence of allergic diseases may well have reached a plateau in several high-income countries in Asia, the plateau is not as high as that observed in Western countries.[15]

Food allergy and anaphylaxis in the Asia-Pacific region

Food allergy has been emerging over the recent 2 decades as a "second wave" of allergy epidemics.[16] Although the overall prevalence of food allergy is thought to be lower in Asia than in the Western world, substantial variations in the diagnostic criteria of food allergy make accurate comparison rather difficult. Patients, especially those living in rural areas, may have limited access to appropriate diagnostic work-up. Nevertheless, hospitalization for food-induced anaphylaxis, the most severe manifestation of food allergy, provides a proxy measure to facilitate understanding of the epidemiology of food allergy. In Australia, a country with the highest incidence of food allergy across the world, a 3-fold increase in the rates of hospital admissions for food-related anaphylaxis was documented between 1993-1994 and 2004-2005.[17] In particular, most of this increasing disease burden was observed among children under 5 years of age.[17] Comparable to Australian populations, more than 2-fold increase in anaphylaxis incidence over the past decade was observed in Hong Kong.[18] In order to obtain a comprehensive picture of anaphylaxis in the Asia-Pacific region, the Asia-Pacific Academy of Pediatric Allergy, Respirology, and Immunology (APAPARI) Anaphylaxis Study Group reviewed available data on anaphylaxis incidence.[19] Unfortunately, considerable heterogeneity existed regarding methodologies of Asian studies, hindering accurate comparison and interpretation of data between countries. In Western countries, the incidence of anaphylaxis ranged from 1.5 to 7.9 per 100,000 persons per year,[20-22] which is comparable to the estimated incidence rate in Hong Kong (4.68 per 100,000 person-years in 2019).[18] Studies from South Korea (incidence 22 per 100,000 person-years),[23] Singapore (estimated incidence > 2.5 per 100,000 children),[24] Thailand (incidence 4.51 per 1,000 pediatric hospital admissions),[25] Taiwan (12.71 to 13.23 per million population),[26] and Japan (0.006%)[27] also reported a similar incidence (summarized in **Table**), suggesting anaphylaxis may also be an emerging problem in Asia.

The pattern of food allergies can be quite distinct in Asia compared to the Western world, especially in older children and adolescents. For example, wheat and buckwheat are common food allergens in Japanese and Korean children, followed by hen's egg and cow's milk,[28,29] while shellfish allergy is more common in South-east Asian countries such as Singapore,

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Table. Incidence of anaphylaxis reported in the Asia-Pacific region and Western countries

Country	References	Study design	Setting	Data collection years	Age of study population (yr)	Anaphylaxis incidence
Europe	Panesar *et al.* (2013)[20]	Systematic Review	Epidemiological studies of anaphylaxis in Europe	1990–2010	0–80	1.5 to 7.9 per 100 000 person-years
United States	Michelson *et al.* (2020)[21]	Cross-sectional	Emergency department (ED) attendances for anaphylaxis	2008–2016	0–85+	94 ED visits per million person-years (2008) 217 ED visits per million person-years (2016) Increase of incidence rate ratio of 1.14 in children
Australia	Andrew *et al.* (2018)[22]	Retrospective	Emergency medical services (EMS)	2008–2016	0–16	38.7 per 100,000 person-years (2015–2016)
Hong Kong	Li *et al.* (2020)[18]	Retrospective	Clinical Data Analysis and Reporting System (CDARS)	2009–2019	0–98 (median 46)	3.57 per 100,000 person-years per annum Estimated incidence rate of 7.40 per 100,000 person-years for the 0–19 age group (2019)
South Korea	Yang *et al.* (2017)[23]	Retrospective	Korean National Health Insurance (NHI) claims database	2008–2014	0–70	22.01 per 100,000 person-years per annum Crude incidence rate of 21.26 per 100,000 person-years for the 0–19 age group (2014)
Singapore	Liew *et al.* (2013)[24]	Retrospective	Hospital admission, ED visits, Allergy service outpatient clinics in a tertiary hospital	2005–2009	0–18 (median 7.9)	Estimated incidence > 2.5 per 100,000 children per year
Taiwan	Liu *et al.* (2017)[26]	Retrospective	National Health Insurance Research Database	2005–2012	0–80+	12.71 to 13.23 per million population over study period
Thailand	Manuyakorn *et al.* (2015)[25]	Retrospective	Hospital admission in a tertiary hospital	2009–2013	0–18 (mean 8.7)	2.7 per 1000 admissions (2004–2008) 4.51 per 1000 admissions (2009–2013)
Japan	Inoue and Yamamoto (2013)[27]	Retrospective	ED attendances for anaphylaxis	2009–2012	0–14 (mean 4.7)	61/10,030 (0.006%)

Philippines, and Vietnam.[30,31] In contrast, the prevalence of peanut allergy is extremely low in Asia compared to the West.[30] A birth cohort study with follow-up of over 1,000 infants in Korea found that by 1 year of age, 5.3% (n = 62) of the infants developed food allergies, with 2.8% (n = 33) allergic to hen's eggs, 1.7% (n = 20) to cow's milk, and 0.7% (n = 8) to peanuts/nuts.[32] The EuroPrevall consortium was funded by the European commission to evaluate the burden of food allergies using the standardized and validated methodologies. A recent EuroPrevall survey screened more than 35,000 children aged 6-11 years from 3 countries including urban and rural China, India, and Russia.[33] Using the definition of probable food allergy as reporting allergic symptoms within 2 hours after consuming a specific food plus positive results of objective measurement (serum specific immunoglobulin E [IgE] and/or positive skin prick test reaction to specific food), the highest prevalence of food allergy was documented in Hong Kong (1.50%), a highly urbanized city of China, when compared with other participated cities with lesser degree of urbanization including Tomsk (Russia, 0.87%), and Bengaluru and Mysore (India, 0.14%). One notable finding from Hong Kong was that children born and raised in Hong Kong were 4 times more likely to have food sensitization and allergies than those born in mainland China and subsequently migrated to Hong Kong (mean migration age of 5 years). Such findings echoed our previous studies showing that children born in mainland China had a significantly lower prevalence of wheeze than those children born and raised in Hong Kong,[34] underscoring the important role of early-life environmental exposure on the subsequent development of allergies. Furthermore, the high rates of IgE sensitization to common food allergens, such as milk (14.23%), egg (14.05%), shrimp (7.87%), and wheat (7.27%) among Chinese primary schoolchildren, did not translate into a high prevalence of food allergy, suggesting additional factors other than IgE sensitization must be critical for clinical manifestations of food allergy.

One of the most potent risk factors for food allergy is atopic dermatitis, especially for those who developed severe disease early in life.[35,36] The dual-allergen exposure hypothesis proposes that transcutaneous sensitization to food allergens through an inflamed and

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impaired skin barrier resulting from atopic dermatitis may present a sensitizing route bypassing oral tolerance. In the absence of early consumption of food protein to induce oral tolerance, the effect may trigger the development of food allergy.[37,38] Recent evidence has confirmed the presence of peanut allergens in household dust that contributes to the increased risk of peanut allergy in exposed children.[39,40] Atopic dermatitis is often associated with the development of allergic diseases in the sequential order of food allergy, asthma and allergic rhinitis, described as the "atopic march." Findings of the ISAAC Phase III study reported a rise in the prevalence of atopic dermatitis in the Asia-Pacific region compared to the counterparts from Phase I.[12] It is conceivable that a subsequent wave of food allergy may appear following the increase in eczema. There is also evidence that Asian populations may be even more susceptible to allergies when compared to Caucasians. Asian children born in Australia was found to be at higher risk of food allergies, atopic dermatitis, and anaphylaxis compared to those born to Australian-born parents.[7,8] A more recent study directly compared the prevalence of food allergy between Asian children living in Singapore from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort and those living in Australia from the HealthNuts cohort.[9] Despite the ethnic similarities between the 2 cohorts, the prevalence rates of food allergy (15.0% vs. 1.1%) and early-onset atopic dermatitis (30.5% vs. 8.4%) were substantially higher in Asians living in Australia than in Singapore.[9] These findings indicate an amplifying effect of genetic propensity induced by a Westernized environment; oppositely, protective factors in the Asian environment may leverage the risk of exposed children who may be prone to develop allergies.

THE ROLE OF ENVIRONMENTAL FACTORS

Air pollution and childhood asthma

Air pollution remains a major public health concern in Asia, representing one of the most important environmental risk factors for allergic diseases. With the rapid process of urbanization across the world, there has been a shift of major types of ambient pollutants.[41] Traditionally, sulfur dioxides (SO_2) and large particulates derived from burning of sulfur-containing fuels (such as diesel and coal) and biomass are the predominant pollutants. The growing number of automobiles gives rise to traffic-related air pollution (TRAP), which is different in chemical and physical nature to that from the classic air pollution. The representative pollutants are nitrogen dioxide (NO_2) and particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$). A systematic review and meta-analysis of observational studies reported an association between TRAP and childhood asthma, with an overall random-effects risk estimate ranging from 1.03 (95% confidence interval [CI], 1.01-1.05) to 1.08 (95% CI, 1.03-1.14), depending on the types of pollutants.[42] Ambient pollutant exposure is consistently shown to be a potent trigger for asthma exacerbations in both Asian and Western countries.[43] Environmental air pollution might not directly contribute to the inception of allergic disorders, as the levels of ambient air pollutants are exceptionally high in many regions in Asia where asthma prevalence is relatively low. Among all counties in the Asia-Pacific region, ambient $PM_{2.5}$ concentrations were the highest in developing countries, such as Bangladesh, India and China, which were about 5 times higher than the World Health Organization (WHO) guideline values, followed by Thailand, Korea, and Vietnam at twice the WHO recommended cutoff value.[41] When the concentration of $PM_{2.5}$ increased by 10 μg/m^3, the risk of children's hospital admissions or emergency department visit increased by 4.8% (relative risk = 1.05; 95% CI, 1.03-1.07).[44] According to recent global analysis, the largest percentage of pediatric asthma incidence attributable to NO_2 exposure was documented

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in high-income Asia-Pacific countries, with nearly half of the new pediatric asthma cases attributable to NO_2 exposure in Shanghai, China and about 40% in Seoul, Korea.[45]

Indoor air pollution is another intractable problem in Asia. Currently, about half of the Asian population are living in the rural area where open-fire cooking is quite common. Biomass burning for cooking and heating constitutes one of the major sources of indoor environmental pollution. ISAAC Phase III data have revealed that exposure to biomass burning was associated with an increased risk of wheezing and asthma diagnosis in children.[46] The Korean Cohort for Childhood Origin of Asthma and allergic diseases (COCOA) study was set up to determine the critical time windows of various environmental factors on the development of allergic diseases. Recent findings from the COCOA study demonstrated that prenatal exposure to $PM_{2.5}$ and PM_{10}, especially in the first trimester, was significantly associated with early-onset atopic dermatitis.[47,48] An additive effect was further observed in those with lower cord blood vitamin D levels, representing an important epigenetic mechanism mediated by placental DNA methylation in physiological response to $PM_{2.5}$ and PM_{10}. Air pollutants can act on the genome inducing epigenetic changes, which function as critical effectors of exogenous insults. Asthmatic children from highly polluted areas have shown increased DNA methylation at CpG sites of the genetic loci of forkhead box P3 (FOXP3) and interleukin (IL)-10, resulting in impaired regulatory T-cell function.[49] Moreover, exposure to TRAP was associated with lower levels of DNA methylation in the promoter regions of nitric oxide synthase (NOS3) in children with asthma.[50] Given the robust evidence for the association between air pollution and childhood asthma, governmental policies are required to reduce environmental pollutants for mitigating their effects on respiratory health.

Lessons from the rural environment

The "hygiene hypothesis" proposed that respiratory infections associated with overcrowding and unhygienic conditions confer an element of protection on hay fever and atopy.[51] The hypothesis has been pushed forward by various comparative studies conducted in different regions across the globe showing that children living in a rural/farming environment had much lower prevalence of allergies than those in urban areas,[52-58] representing one of the strongest and most consistent protective factors against development of allergic diseases. Two main pillars of the "farm effect" in central Europe are exposure to livestock and consumption of raw farm milk. In Asia, however, consumption of unprocessed milk is rather rare and manual labor is still the prevalent form of practice over mechanized farming. Our previous study has demonstrated that agriculture farming environment in northern China conveyed protection against asthma and allergies, similar to dairy or livestock farming in central Europe.[59] Early-life exposure to diverse microorganisms related to the rural environment may cause the immune system to distinguish between harmful and harmless microbes, thereby boosting immune maturation and programming the immune system toward a more tolerogenic state. Further research in the rural regions of Asia will bring new perspectives on the understanding of protective factors in our environment.

The "farm effect" was further elucidated by the 2 United States farming populations, the Amish and the Hutterite, who share similar genetic background and lifestyle, but distinct farming practice (traditional among the Amish and industrialized among the Hutterite). The prevalence of asthma and atopic sensitization, however, was 4- to 5-fold higher in Hutterite children (21.3% and 33.3%, respectively) than that of Amish children (5.2% and 7.2%, respectively).[55] Further mechanistic studies revealed that the large disparity in the prevalence rates of asthma

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and allergy between Amish and Hutterite children could be explained by the difference in household endotoxin levels, which were 6.7-fold higher in the Amish home than in the Hutterite home.[55] Intriguingly, dust extracts from Hutterite barn conferred the protection similar as the Amish barn dust, implying the increased asthma risk in Hutterite children is due to insufficiency of protective exposure.[60] In the absence of microbial instruction, environmental risk factors, such as allergens, pollutants (*e.g.*, vehicle exhaust and industrial waste gases), and pathogenic microbes, can perturb epithelial barriers located at the surfaces of different organs, such as the skin, gut, upper and lower respiratory tract, allowing penetration of environmental insults into the tissues (**Fig. 2**). Disrupted epithelial cells initiate Th2-mediated immune responses through the release of alarmin cytokines, such as IL-33, IL-25, and thymic stromal lymphopoietin (TSLP), resulting in eosinophilic infiltration, mast cell degranulation, and production of IgE as well as pathological changes including activation of fibroblasts and endothelium, and smooth muscle hyperplasia. These inflammatory responses lead to the manifestation of various allergic disorders such as atopic dermatitis, food allergy, and asthma.

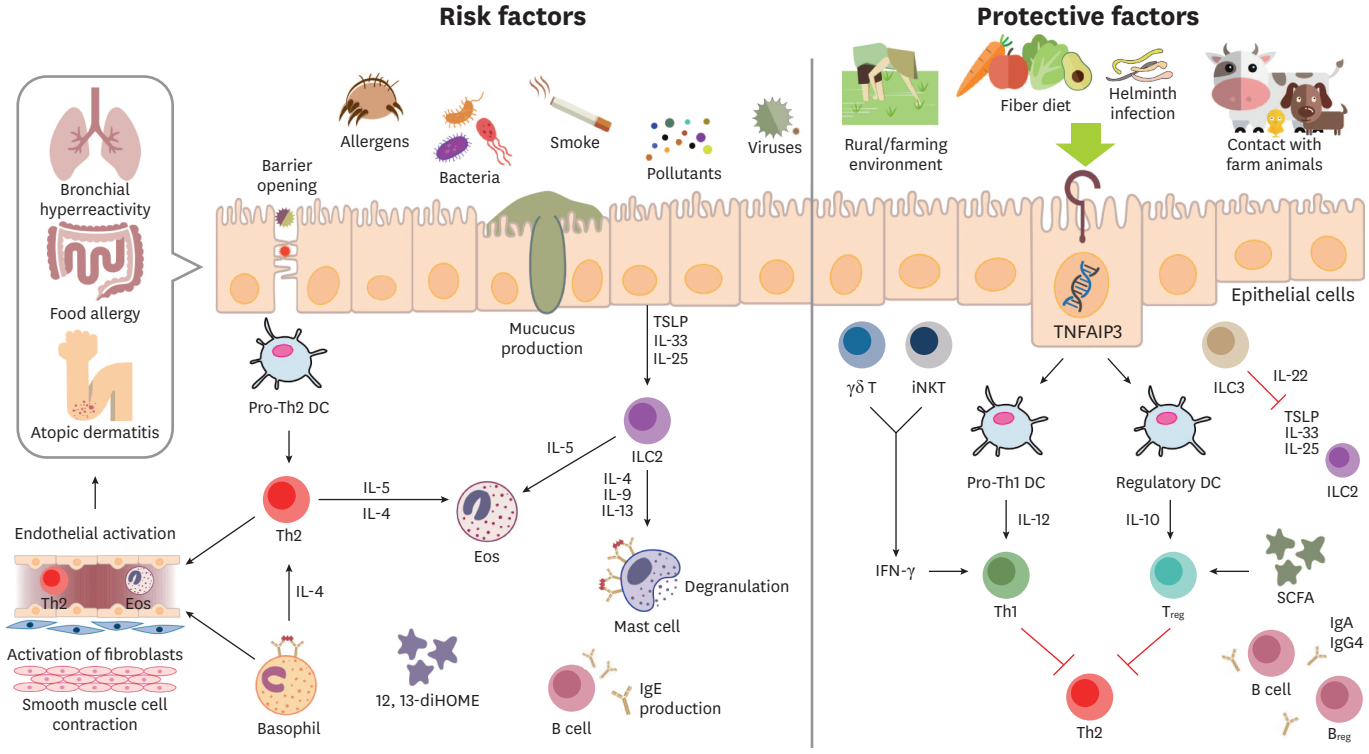

Fig. 2. The crosstalk between environmental factors and immune responses in allergic inflammation. Microbial compounds and immunomodulatory molecules acting directly on the mucosal surfaces of the lungs, gut, and skin can exert biological effects systemically. Environmental risk factors, such as allergens, pollutants (*e.g.*, vehicle exhaust and industrial waste gases) and pathogenic microbes, can perturb epithelial barrier functions (left panel). Damaged epithelial cells allow the penetration of environmental insults, promoting the proliferation of tissue-resident ILC2s through the release of alarmins such as IL-33, IL-25 and TSLP. After capturing the antigen, DCs prime the naïve T cells to differentiate into Th2 cells. Cytokines secreted by ILC2s and Th2 cells drive Th2-dominated immune responses characterized by IL-4, IL-5, IL-9, IL-13, IL-25, and IL-33. Eosinophilia is induced by IL-5, IL-25, and IL-33. IL-9 and IL-13 contribute to the activation of mast cells and mucus production, while IL-4 induces IgE class switching in B cells. Cross-linking of IgE leads to mast cell degranulation and release of histamine, tryptase, prostaglandins, leukotrienes, and cytokines. These molecules and immune effectors cells contribute to pathological changes including activation of fibroblasts and endothelium, and smooth muscle hyperplasia in the skin, gut, upper and lower respiratory tracts, resulting in various inflammatory conditions such as atopic eczema, food allergy, and asthma. In contrast, environmental microbes (rich in traditional rural/farming environment) and regulatory signals from the gut (*e.g.*, helminth infection and high fiber diet) can drive immune responses away from allergic inflammation (right panel). For example, microbial compounds can be identified by TLRs and up-regulate the expression of TNFAIP3 by the epithelial cells. Regulatory and suppressive effects of downstream signaling pathways are characterized by IFN-γ, IL-10, TGF-β, IgG4, and IgA produced by innate-like cell populations, such as DCs, γδT cells, iNKT and ILC3, as well as adaptive immune cells including Tregs, Bregs, and B cells.
ILC2, type 2 innate lymphoid cell; DC, dendritic cell; IL, interleukin; TSLP, thymic stromal lymphopoietin; TLR, innate toll-like receptor; Ig, immunoglobulin; TNFAIP3, TNF-α-induced protein 3 (A20); IFN-γ, interferon-γ; iNKT, invariant natural killer T cells; TGF-β, transforming growth factor-β; ILC3, type 3 innate lymphoid cell; Treg, regulatory T cell; Breg, regulatory B cell.

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The loss of protective factors associated with the rural environment may therefore partially explain the increasing prevalence of allergic diseases in places where the process of urbanization is escalating. In support of this, recent findings from the Copenhagen Prospective Studies on Asthma in Childhood 2010 ($COPSAC_{2010}$) have shown that an urban living environment during infancy increased the risk of asthma, atopic dermatitis, and allergic sensitization in childhood.[61] Furthermore, migration may also impact immune homeostasis by changing microbial exposure and lifestyle factors. Immigrants from Thailand to the United States experienced a shift of gut microbiome diversity, function, and strain composition toward a more Westernized state.[62] Summing up current evidence, the environment plays a complex and dual role in both the development of and the protection from allergic disorders.

Mechanisms underlying rural protection against allergies

A thorough understanding of protective factors in the rural environment and the underlying mechanisms could allow for gaining the necessary insight into allergy prevention. Rural exposure may exert the allergy protective effect through microbial translocation and colonization, thereby altering the compositional structure and metabolic functions of the human microbiome. Part of the immune-regulatory process is achieved via epithelial barrier enhancement of mucosal surfaces located in different organs such as the airways, skin, and intestinal tract (**Fig. 2**). For example, stimulation of human primary bronchial epithelial cells with farm dust increased barrier resistance and antiviral responses,[63] representing one common thread linking the protective farm effect in epidemiologic observations. One possible mechanism is regulated through the ubiquitin-modifying enzyme TNF-α-induced protein 3 (TNFAIP3, or A20). TNFAIP3 can inhibit the downstream signaling pathways of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), one of the central triggers of inflammation activation. The asthma-protective effect of farm dust extracts was abolished in mice devoid of myeloid differentiation primary response gene 88 (*MyD88*) or Toll/interleukin-1 receptor domain-containing adaptor inducing IFN-β (TRIF) and epithelial signaling pathways led by TNFAIP3.[55,64] Previous studies from our team have demonstrated that stimulation with microbe-rich farm dust or its main component lipopolysaccharides (LPS) restored gene and protein expression of TNFAIP3 along with the negative regulator dual-specificity phosphatase-1 (DUSP1) of mitogen-activated protein kinase (MAPK) signaling pathway in asthmatic patients to healthy levels and shifted toward an anti-inflammatory state.[65,66] Interestingly, a gene-environment interaction was detected for a single nucleotide polymorphism (SNP) in the TNFAIP3-encoding gene showing protection against asthma in farm children.[64] Of note, in children at risk of asthma characterized by carrying the risk alleles at chromosome 17q21, a more than 80% reduction in risk was observed in those with exposure to animal sheds.[67] Collectively, these findings reflect the heterogeneity and complex pathogenesis of asthma and allergies, of which the genetic predisposition is also susceptible to environmental influences.

Murine studies have identified several bacterial strains isolated from cowshed dust with immunomodulatory effects *in vivo*. These include the gram-negative bacteria *Acinetobacter lwoffii* F78[68] as well as gram-positive *Lactococcus lactis* G121[69] and *Staphylococcus sciuri* W620.[70] Despite distinct characteristics, there are several common signaling events that shared among different bacteria including activation of dendritic cells, utilization of intracellular receptors, *i.e.*, NOD2, and up-regulation of costimulatory molecules including CD40, CD80 and CD86. Unique signaling events triggered by individual strains are also depicted in **Fig. 3**. Not only do microbial components related to a traditional lifestyle appear to be allergy-protective, but non-

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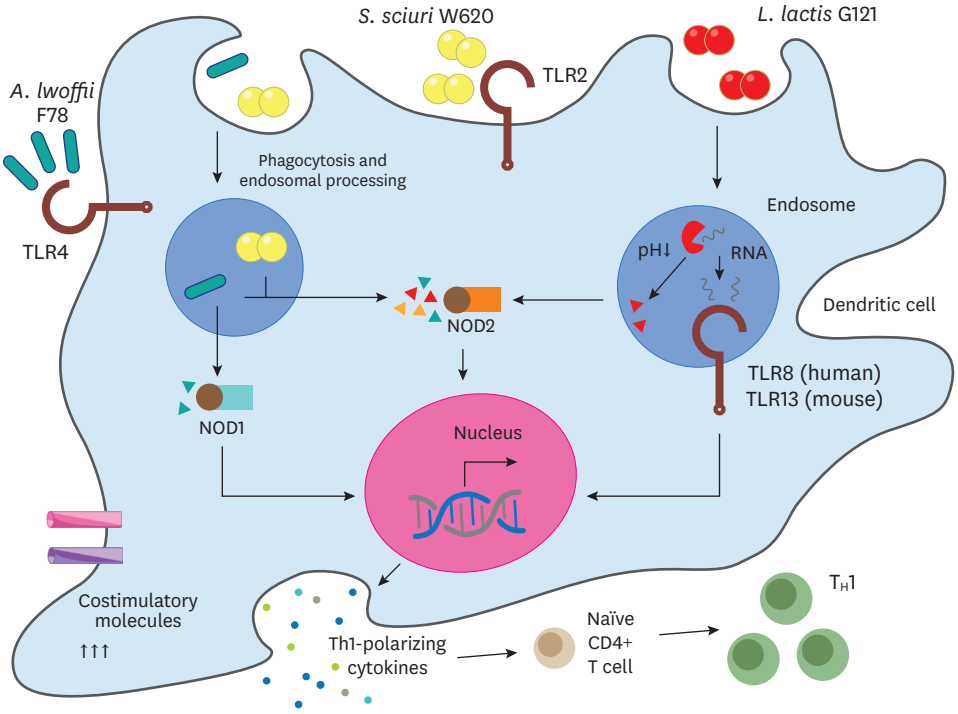

Fig. 3. Signaling pathways mediated by various bacterial strains polarizing Th1 immunity. Gram-positive *S. sciuri* W620 can activate dendritic cells through the cell surface receptor TLR2 and intracellular NOD2, whereas the gram-negative *A. lwoffii* F78 is recognized by TLR2 and TLR4 as well as NOD1 and NOD2. For the recognition of *L. lactis* G121, bacterial uptake is not only necessary to activate dendritic cells, but also endosomal acidification is required. Moreover, *L. lactis* G121 RNA appears to be the major bacterial component mediating protection against experimental asthma and signals through TLR13 in mice and probably through TLR8 in human subjects.
Th, T helper; TLR, innate toll-like receptor.

microbial signals delivered by rural/farm living also convey an element of protection. Farm children have increased levels of circulating antibodies against the mammalian-produced sialic acid N-glycolylneuraminic acid Neu5Gc, a molecule capable of blocking allergic airway inflammation in murine models.[71] These findings suggest that higher exposure to non-microbe-derived Neu5Gc might also contribute to the lower risk of childhood asthma in the rural/farming environment. Recent evidence suggested that communities of microbes, rather than single strains or molecules, are more strongly related to protection against allergic diseases such as asthma.[72] Of note, the indoor dust microbiota composition appears to be a definable, reproducible predictor of asthma risk. Children living in German non-farm homes with an indoor microbiota more resembling Finnish farm homes had decreased asthma risk.[73] Hence, allergy-protective farm effect can be reproduced in non-farm settings, implying a potential target for preventive strategies.

Typically, residents living on family-based farms in the rural area also eat considerable amounts of plant-based fibers. The immunomodulatory activity of the microbiome is partially accomplished via the production of metabolites, especially short-chain fatty acids (SCFAs). High levels of dietary fibers (rich in fruits and vegetables) can change the compositional structure of the gut and airway microbiome, and increase the concertation of circulating SCFAs. Children with high amounts of SCFAs, especially butyrate and propionate, in feces at 1 year of age were less likely to be sensitized and develop asthma by 6 years of age.[74] In mice, SCFAs have been shown to protect mice from allergic lung inflammation through alterations in bone marrow hematopoiesis and repopulation of dendritic cells (DCs) with an

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impaired ability to activate Th2 effector cells through the G-protein-coupled receptor (GPR) 41-dependent signaling pathway.[75,76] More specifically, maturation of the gut microbiome during the first year of life may contribute to the asthma-protective farm effect, partially through the production of SCFAs, especially butyrate.[77] Likewise, helminth infections, which are ubiquitous in rural areas and associated with poor socioeconomic status, can activate immunomodulatory processes and prevent overshooting of inflammatory responses of the host to ensure their long-term survival.[78,79] In a murine model of helminth and respiratory syncytial virus (RSV) coinfection, attenuated pulmonary inflammation and decreased viral load were observed.[80] While the pro-inflammatory metabolites, such as the oxylipin 12,13-diHOME, were enriched in the feces of neonates at high risk of developing allergies.[81] Recent evidence has shown that intra-abdominal treatment of mice with 12,13-diHOME prior to airway challenge exacerbated pulmonary inflammation and decreased lung regulatory T cells in a cockroach antigen-induced airway inflammation model.[82] These findings provide a remarkable example of the concept of "the gut-lung axis,"[83] where perturbation of the microenvironment in the gut can influence the immune homeostasis of the lungs.

INTERVENTIONS FOR ALLERGY PREVENTION

The Benjamin Franklin axiom that "an ounce of prevention is worth a pound of cure" best describes the focus for allergy research, given that there is currently no cure for allergic diseases. The Finnish Asthma Programme (1994-2004) is a vivid example of how nationwide implementation of public health measures can reduce the socioeconomic burden of allergic diseases. Through this campaign, the proportion of patients with severe or uncontrolled asthma had halved, with overall annual costs per patient decreased by 72%.[84,85] The recent Finnish Allergy Programme (2008-2018) was launched to transform the strategy from avoidance to tolerance with a focus on primary prevention of allergy, especially in children.[86] Nonetheless, the experience in Finland might be different from that in the Asia-Pacific region, where burden of allergies is rapidly increasing. On one hand, we should learn from Finland success to reinforce allergy management; on the other hand, we still need to explore approaches tailored for our populations to prevent the onset of disease in the first place.

Microbiome-based interventions

With growing evidence that microbial exposure related to rural/farm living can shape an individual's trajectory toward or away from allergic diseases, microbial immunostimulants may represent a promising option for prospective prevention strategies. The idea that administration of probiotics and prebiotics might positively influence the microbiome development and therefore possibly alter the risk of allergic disorders. However, the causal relationship has yet to be established. It is still largely unknown whether allergic conditions lead to dysbiosis, whether alterations in microbiome occur before development of allergies, and whether these changes are associated with environmental exposure. Germ-free (GF) mice represent a model system to study the sequential effect of colonized microbes on host physiology. Inoculation of GF mice with the bacterial genera *Lachnospira*, *Veillonella*, *Faecalibaterium*, and *Rothia* that depleted in the gut microbiota of infants at risk of asthma ameliorated airway inflammation in their adult progeny.[87] Intranasal instillation of probiotics, such as *Lactobacillus rhamnosus* GG, significantly decreased bronchoalveolar lavage eosinophil counts, levels of IL-13 and IL-5, and airway hyperreactivity in a mouse model of birch pollen-induced allergic asthma.[88] Oral application of *Lactobacillus johnsonii* also efficiently protected recipient mice from airway inflammation via the reprogramming of circulating

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metabolic environment, including docosahexanoic acid (DHA) enrichment.[89] In addition, oral administration of SCFAs to mice during pregnancy and weaning significantly reduced allergic airway inflammation in the offspring.[74] These results obtained from murine studies raise the possibility that early-life patterns of microbial colonization are capable of altering immune responses at various mucosal surfaces and therefore influence the subsequent development of allergic diseases.

Strategies deployed in early infancy to modulate the microbiota or emulate its downstream effects have shown some promise in prevention and treatment. One of the immunostimulants is OM-85 (Broncho-Vaxom), a standardized bacterial lysate derived from 21 respiratory pathogenic strains from 5 genera (*Moraxella*, *Hemophilus*, *Klebsiella*, *Staphylococcus*, and *Streptococcus*), found in human airways. Oral administration of OM-85 has been shown to reduce wheezing episodes triggered by acute respiratory tract infection in children.[90] The ongoing ORal Bacterial Extract (ORBEX) Trial (NCT02148796) has been set up to investigate whether orally applied OM-85 can increase the time to occurrence of the first wheezing episode in lower respiratory tract illness in infants at increased risk of asthma.[91] Meanwhile, we are awaiting the results of Milk Against Respiratory Tract Infections and Asthma (MARTHA) trial,[92] in which over 3,000 infants (6-12 months old) will be recruited from the general population and receive mildly pasteurized milk or commercially available milk until the age of 3 years. The primary outcome in this MARTHA trial is to evaluate whether consumption of minimally processed milk is effective to prevent development of respiratory infections, asthma, and allergies at age 5 years. These prospective interventions will help us elucidate the role of immunomodulatory agents on the development of allergies in the general population at high risk.

Oral tolerance induction approaches

Promising data from epidemiological observations and murine studies have founded the basis for randomized controlled trials (RCT). The developmental atopic march generally starts with atopic dermatitis and food allergy. Therefore, there has been a growing body of RCTs targeted at food allergy to induce immune tolerance in early childhood. Although peanut allergy is not common in Asia, the Learning Early about Peanut Allergy (LEAP) study has provided an encouraging example for a preventative approach for allergies. The LEAP study demonstrated that early introduction of peanut resulted in a substantial reduction in risk of developing peanut allergy at 60 months of age among high-risk infants.[93] A similar finding has been repeated in the Japanese prevention of egg allergy in high-risk infants with atopic dermatitis (PETIT) study, where introduction of heated egg in a stepwise manner along with aggressive eczema treatment proved to be safe and favorable to prevent hen's egg allergy in high-risk infants.[94] These findings emphasize the significance of active tolerance induction and immune resilience, rather than passive avoidance, of potentially allergenic foods to prevent allergic immune responses. Whereas early introduction of allergenic foods has been shown to be an efficacious allergy prevention strategy in a high-risk population, the evidence in the general population is less compelling. The Enquiring about Tolerance (EAT) Study enrolled children from the general population in the United Kingdom found a trend toward reduction in allergy, but the difference did not reach statistical significance intention-to-treat (ITT) analyses.[95] In contrast, the Hen's Egg Allergy Prevention (HEAP) study that included infants from the general population found increased risk of allergic reactions, including anaphylaxis, in the egg consuming group.[96] In addition, differences in the form of allergenic food (pasteurized raw egg white powder in the HEAP study) may account for the discrepancies between studies. For tolerance induction, there may be a therapeutic window

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of opportunity between 4 to 6 months of age, typically before multiple allergic sensitizations occur.[97] There is still a paucity of clinical trials on food triggers specific for the Asian population, considering distinct dietary preferences.

FUTURE PERSPECTIVES

We need to interpret with caution that the environmental factors discussed above are explicit representatives of myriads of potentially relevant elements. The precise protective mechanisms of these factors require in-depth mechanistic studies. The asthma-protective mechanisms related to a rural/farming lifestyle are emerging as a potential target for precision medicine, including treatments specifically stratified for the preexisting immunological and genetic background, already identified host-environment interactions, or a combination of these. Large-scale cohort studies recruiting pregnant women from areas where the traditional rural lifestyle still retains and following up their offspring for longitudinal sampling for immune maturation, microbial development and exposome evaluation would help fill current research gaps.

Management of allergies can be rather challenging in Asia for several reasons. For example, Asia is renowned for its unique dietary practice with a wide variety of food ingredients. Asian delicacies, such as edible bird's nests, insects (silkworm pupa, locusts, and cicadas), bullfrogs, and turtles, can be the causes of anaphylaxis,[98,99] rendering the diagnosis difficult. To comprehensively evaluate the trends, triggers, and management of anaphylaxis across Asian countries, the APAPARI Anaphylaxis Registry was established in 2018, and initially participated countries were Hong Kong, Japan, Singapore, South Korea, and Thailand. Data from the APAPARI Anaphylaxis Registry collected by standardized methodology will form the basis for further exploration of factors influencing anaphylaxis prevalence and preventive strategies. In addition, the problem of under-recognition and under-reporting still exists in some developing or underdeveloped countries in Asia.[100] Structured training of specialists in the field of pediatric allergy and clinical immunology is therefore required to improve the level of clinical care and research in areas with underdeveloped diagnostic expertise.

CONCLUDING REMARKS

Given the large childhood population, wide variations in economic development across countries and regions, along with the pronounced differences in dietary practice and environmental exposure, the Asia-Pacific region provides ample opportunities for allergy research ranging from large-scaled epidemiological observational studies and prospective interventions to in-depth mechanistic investigations. As urbanization, westernization, and industrialization will inevitably continue in the region, we can anticipate a major rise in allergic diseases in this densely populated region. Abating potentially modifiable risk exposure, such as air pollution, should be prioritized in both developing and developed countries in the Asian region. In this regard, the government must implement adequate legislations to reduce the detrimental components of the exposome and minimize their effects on human health. Meanwhile, re-introduction of protective factors that were once part of the traditional farming lifestyle might provide new insight into allergy prevention. Current cumulating evidence is derived from epidemiological observations as well as murine studies and requires translation into prospective interventions and clinical applications. A

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single "magic bullet" seems unlikely to account for allergy protection, but rather it will be a combined effect derived from complex interactions among various environmental and genetic factors as well as epigenetic adaptation promoting balanced immune homeostasis. Birth cohort studies with long-term follow-ups and multi-omics approaches are needed to address when, why, and how environmental drivers alter each individual's immunological maturation profile and genetic predisposition in allergy development. Better understanding of the phenotypes, endotypes, genotypes and environmental determinants of allergic disorders and the interplay among these factors is critical for the implementation of precision medicine and development of novel primary preventive strategies.

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