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REVIEW ARTICLE

Epithelial barrier hypothesis: Effect of the external exposome on the microbiome and epithelial barriers in allergic disease

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Abstract

Environmental exposure plays a major role in the development of allergic diseases. The exposome can be classified into internal (e.g., aging, hormones, and metabolic processes), specific external (e.g., chemical pollutants or lifestyle factors), and general external (e.g., broader socioeconomic and psychological contexts) domains, all of which are interrelated. All the factors we are exposed to, from the moment of conception to death, are part of the external exposome. Several hundreds of thousands of new chemicals have been introduced in modern life without our having a full understanding of their toxic health effects and ways to mitigate these effects. Climate change, air pollution, microplastics, tobacco smoke, changes and loss of biodiversity, alterations in dietary habits, and the microbiome due to modernization, urbanization, and globalization constitute our surrounding environment and external exposome. Some of these factors disrupt the epithelial barriers of the skin and mucosal surfaces, and these disruptions have been linked in the last few decades to the increasing prevalence and severity of allergic and inflammatory diseases such as atopic dermatitis, food allergy, allergic rhinitis, chronic rhinosinusitis, eosinophilic

esophagitis, and asthma. The epithelial barrier hypothesis provides a mechanistic explanation of how these factors can explain the rapid increase in allergic and autoimmune diseases. In this review, we discuss factors affecting the planet's health in the context of the 'epithelial barrier hypothesis,' including climate change, pollution, changes and loss of biodiversity, and emphasize the changes in the external exposome in the last few decades and their effects on allergic diseases. In addition, the roles of increased dietary fatty acid consumption and environmental substances (detergents, airborne pollen, ozone, microplastics, nanoparticles, and tobacco) affecting epithelial barriers are discussed. Considering the emerging data from recent studies, we suggest stringent governmental regulations, global policy adjustments, patient education, and the establishment of individualized control measures to mitigate environmental threats and decrease allergic disease.

KEYWORDS
air pollution, climate change, epithelial barrier, exposome, nutrition

1 | INTRODUCTION

Research over the years shows growing evidence that environmental factors play an increasingly dominant role in human health.[1,2] As the genetics of allergic diseases have not thoroughly explained the considerable increases observed in the past decades, gene-environment interaction studies, as well as Mendelian randomization techniques, underline the basis of environmental triggers for allergic diseases, making them primarily considered to be environmental diseases.[3] The exposome encompasses all environmental exposures such as chemicals, pollutants, tobacco smoke as well as lifestyle factors, dietary habits, and infectious agents that a person encounters throughout their lifetime, from conception to death.[4-6] The concept was first introduced by Wild in 2005 to highlight the impact of the entire environment on human health by complementing the genome.[7] Wild classified the individual's contact with external environmental factors as the *eco-exposome* and the internal effects that occur after interaction with the exposome as the *endo-exposome*.[8] Afterward, three overlapping domains have been defined as *general external environment* (climate, biodiversity, urban environment, and socioeconomic factors); *specific external environment* (allergens, microbes, diet, tobacco, and pollutants); and *host-dependent internal environment* (metabolic factors, inflammation, and oxidative stress).[2,4,9] Further, as a novel but a potentially broader explanatory approach, Renz et al. put forth the concept of the *meta-exposome*, which takes into consideration the bidirectional effect of the environment on human subjects and influence of humans on all other living systems and their genomes.[10] Species diversity in the natural environment in which humans live is of great importance in enriching the human microbiome, ensuring immune balance, and for preventing the development of allergic and inflammatory diseases.[11]The recently introduced *'epithelial barrier hypothesis'* proposes that exposure to the urban environment and significant changes in the urban exposome by modernization, industrialization, and urbanization damages and initiates inflammation of the epithelium, the cellular layer that covers the surface of the skin, as well as the respiratory, urogenital, and gastrointestinal tract.[12] The epithelial barrier concept is initially introduced by assigning the epithelial tasks of keeping away the noxious environmental insults, such as the epithelial barrier, secretory IgA, and lamina reticularis thickening. The second set of events consist of washing away the inflammation by draining from tissues toward the lumen, ciliary movement, mucus production, and the immune regulatory function exerted by various regulatory cells, their cytokines, and cell surface factors.[13] Activation of epithelial cells and release of epithelial cell cytokines, such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), followed by type 2 inflammation play major roles in the development and exacerbation of allergic diseases.[14] Local epithelial damage to the skin and mucosal barriers lead to type 2 inflammation in the tissues and development of allergic conditions presenting as atopic dermatitis (AD), asthma, allergic rhinitis (AR), chronic rhinosinusitis (CRS), and eosinophilic esophagitis. These diseases and the epithelial barrier damage always develop in association with changes in microbiome.[12] In the gut, leaky epithelial barriers and microbial imbalance may contribute to the onset or development of many chronic autoimmune and metabolic diseases, such as diabetes, obesity, rheumatoid arthritis, multiple sclerosis, or ankylosing spondylitis.[12] These diseases may be triggered or aggravated by distant inflammatory responses and changes in the gut or lung microbiome. Moreover, defective epithelial barriers have also been linked to neurodegenerative and psychiatric diseases such as Parkinson's disease, Alzheimer's disease, autism spectrum disorders, and chronic depression.[12] Environmental exposures can directly disrupt the epithelial barriers of the gut, skin, and respiratory tract and alter the structure of the microbiome. Thus, leaky epithelium and impaired immunoregulation in the affected organs influence the development of a chronic ongoing inflammation.[9,15] Furthermore, changes and loss of microbial biodiversity in urban environments secondary to delivery by cesarean section, early antibiotic exposures, reduced

exposure to farm-life, and lack of pets in the houses leading to low endotoxin exposures have been suggested to increase allergic diseases due to the development of microbial dysbiosis in early life.[16,17]

The industrial revolution in the 19th century affected our planet leading to drastic changes in environmental homeostasis, which is defined as the healthy interrelationship of living organisms with their environment. Humans have been exposed to more than 200,000 new molecules since the industrial revolution, particularly during the last 60 years, without a clear understanding of their toxicity or means to mitigate their effects. The concepts of chronic exposure, molecular and microscopic changes, epigenetic changes, and their synergistic and additive affects were not considered for regulation of these new molecules.[18-20] Various emerging health threats including dramatic increases in air pollutants such as particulate matter (PM), diesel exhaust, nitrogen dioxide (NO_2), ozone (O_3), and tobacco smoke, the alarming effects of global warming, changes and loss of biodiversity, and the complex interactions between all these factors are affecting all living beings.[15,19] Recent studies have shown that climate change and global warming have many consequences on respiratory health by increasing airborne allergen concentrations (i.e., pollen,[21,22] fungi,[23]) and allergenicity,[24,25] duration of pollination, and season length of airborne pollens.[26,27] Another important environmental insult that negatively affects health is the change in dietary habits due to increases in the consumption of dietary fatty acids and processed foods, usage of emulsifiers, and decrease of antioxidant content in western-type diet, which is widely consumed (Figure 1).

Here, we discuss the impacts of climate change and the exposome, the relationship between the microbiome of skin, gut, oropharynx, lung, and exposome; the effect of increased fatty acid consumption due to the changes in dietary habits; environmental agents (detergents, disinfectants, household cleaners, airborne pollen, PM, O_3, microplastics, nanoparticles, and tobacco) that affect epithelial barriers and finally the epithelial barrier hypothesis. We review the changes in the external exposome within the last decades and their effects on epithelial barriers in relation to allergic diseases.

2 | GLOBAL WARMING, CLIMATE CHANGE, AND EXPOSOME

Climate change refers to any change in climate and weather patterns altered for an extended time period. Some authorities (Framework Convention on Climate Change) define climate changes as that which attributable directly or indirectly to human activities which alter the composition of the global atmosphere, in natural climate variability observed over comparable time periods.[28,29] It is noteworthy that although it took nearly a century to convince the scientific authorities that human actions could alter the climate of the entire world, there is now consensus on the levels of carbon dioxide (CO_2), methane (CH_4), nitrous oxide (NO), and fluorinated gases that are increased as a result of industrialization, urbanization, and population growth and are accumulating in the atmosphere trapping heat leading to the greenhouse effect and anthropogenic climate change.[30,31] Anthropogenic global warming and climate change are considered the major growing threats to global biodiversity and ecosystems, leading to the extinction of thousands of species over the next century.[32]

The greenhouse effect and air pollution together increase average temperatures around the world.[33] Air pollution is defined as a major driver for global warming. As a consequence of a warmer Earth, water temperatures of the oceans increase, glaciers melt, sea levels rise, and the snow and ice cover in the Northern Hemisphere diminish.[34-41] Ozone layer depletion and climate change also impact ultraviolet (UV) radiation.[42-44] Extreme weather events, such as heatwaves, droughts, floods, blizzards, thunderstorms, sandstorms, wildfires, and hurricanes, are happening more frequently and intensely due to climate change.[34,45-48] Urbanization is linked to the rising levels of pollutants in the air, as well as water and soil. These environmental changes are modifying spatial and transient dissemination of aeroallergens such as pollens and dust mites causing recurrence of respiratory allergic diseases over a long period of time in most industrialized countries as well as in developing countries.[19,33,49,50]

It is well documented that climate change negatively affects many aspects of human health, both physically and mentally[51,52] (Figure 2). In the perspective of allergic disease, this phenomenon alters the timing, dispersion, quantity, and quality of aeroallergens classified as bio-contaminants, leading to an increase in the frequency and severity of allergies.[9] Higher temperatures have been shown to prolong the pollen season, and higher CO_2 levels lead to an increase in the biomass of pollen and pollen production, which makes the plants produce more pollen and allergens. Likewise, the overall pollen season of all pollen types has been indeed extended. Most pollen types have shifted toward earlier times of the year for pollen outputs (i.e., ragweed), possibly aggravating the burden on pollen-allergic patients.[21,53] Air pollutants, especially NO_2, which is more prevalent in urban locations, also collaborate with airborne allergens and alter the biological functions of pollens by decreasing viability, altering the physicochemical characteristics of the pollen surface, and increasing their allergenic potential through pro-inflammatory properties by acting as an adjuvant, and therefore pose a greater risk for the development of atopic sensitization and symptoms in sensitized individuals.[24,54] Elevated pollutants have been shown to change the transcriptome of the ragweed pollen.[54,55] Proteases derived from pollens irreversibly damage the airway epithelial barriers by disrupting intercellular junctions and anchorage of respiratory epithelial cells[56] (Figure 3).

It is even claimed that climate change may have played a pivotal role in the emergence of COVID-19 by forcing species to change their habitats and their geographic range, and serving as a tool to bring wild animals closer to humans and farm animals.[57] It was mentioned that SARS-CoV-2 cell entry factor (SCEF) is important for the entrance of COVID-19 virus to the upper airway epithelium, while in smokers it was also shown that SARS-CoV-2 can easily penetrate both the upper and lower airways epithelium.[58] Moreover, a significant positive correlation between COVID-19 infection and airborne pollen concentration

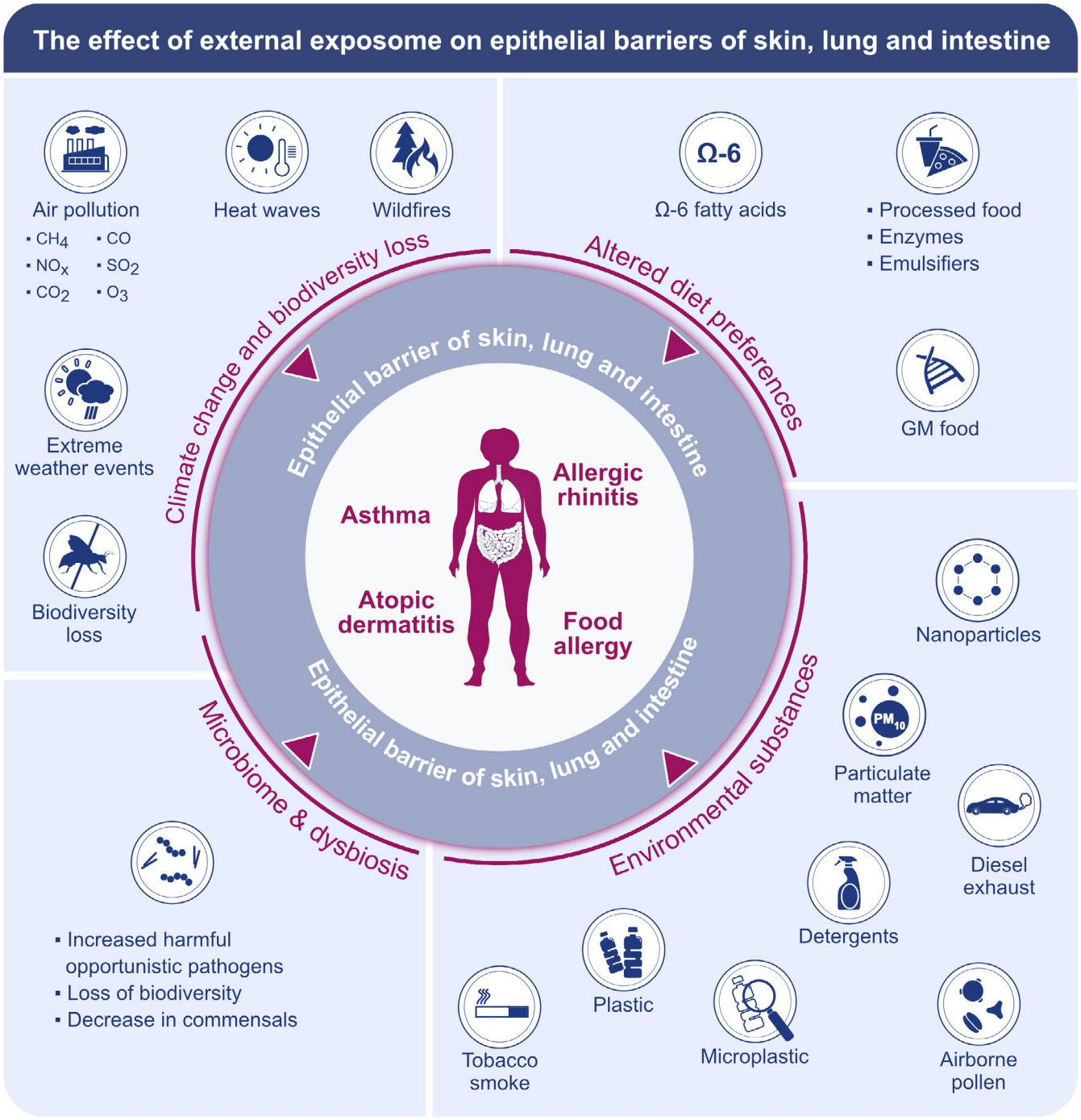

FIGURE 1 Effect of external exposome on epithelial barriers of skin, lung, and intestine. Extreme weather events, wild fires, global warming due to the climate change, air pollution and changes and loss of biodiversity; increased consumption of processed foods, n-6 fatty acids and genetically modified food; exposure to environmental substances; and the increase in harmful opportunistic pathogens, loss of microbiome diversity and decrease in commensals; disrupts the barriers of skin, lung, and intestine and causes allergic diseases such as asthma, atopic dermatitis, food allergy, and allergic rhinitis. CH_4: methane, NOx: nitric oxides, CO_2: carbon dioxide, CO: carbon monoxide, SO_2: sulfur dioxide, O_3: ozone, GM: genetically modified

was reported by Damialis et al. The authors have mentioned that the interaction of the coronavirus and pandemic viruses with similar potential in the future may be exacerbated by the increased abundances of airborne pollen, because pollen exposure weakens antiviral immune response.[59] The association between climate change and infectious disease is well established, but burden of the effects and affected pathogens remain under-studied. In 2017, McIntyre et al. published the first large-scale systematic assessment of climate effects on pathogens, concluding that zoonotic pathogens may be more climate sensitive as 75% of emerging diseases are zoonotic.[60]

There is scientific evidence suggesting that it is crucial to take timely action against air pollution and greenhouse gas production to control

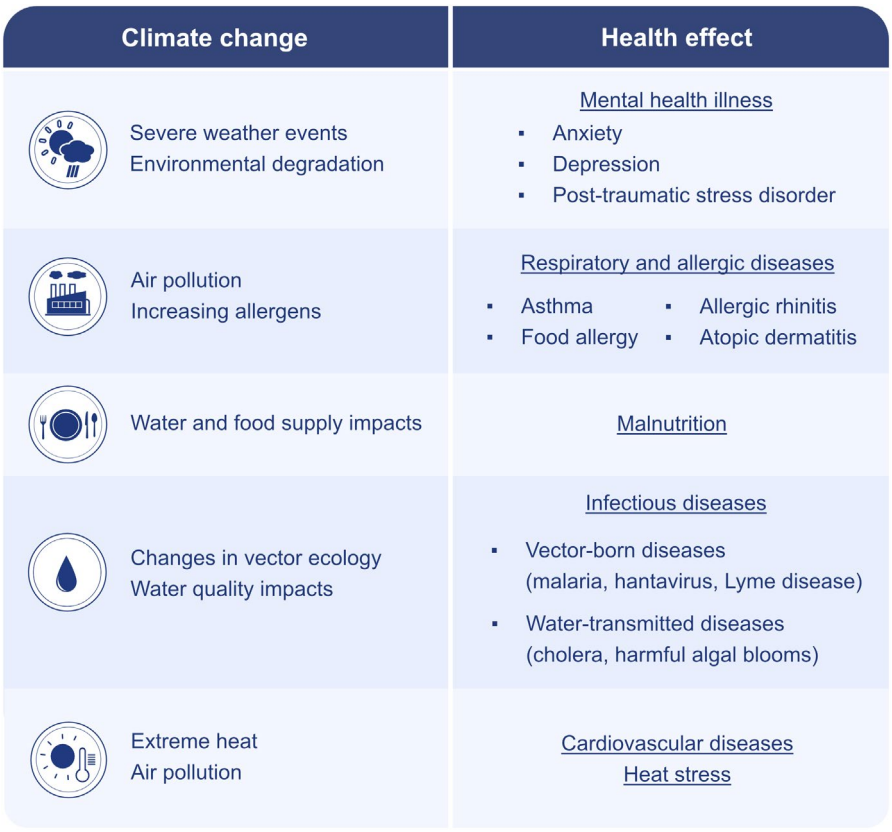

FIGURE 2 Health effects of climate change. Climate change causes mental health illness such as anxiety, depression, and post-traumatic stress; causes respiratory and allergic diseases through air pollution and increased allergens; causes malnutrition through affecting water and food supplies; causes infectious diseases such as vector-borne (malaria, hantavirus, lyme disease) and water transmitted diseases (cholera, harmful algal blooms); causes cardiovascular diseases, and heat stress due to extreme heat and air pollution

urbanization-induced climate change and biodiversity loss and change, which will contribute to the higher burden of allergic diseases in the near future.[61] Healthcare facilities as well as healthcare professionals should play significant roles as practitioners, and role models against this threat.[52] Healthcare professionals should now take leadership and responsibility to guide policy decision makers for bringing solutions to lessen the harm to our exposome in an evidence-based manner. Any attempt to reduce PM and CO_2 emission would address both air pollution and climate change, which can be achieved by strict policy decisions to obtain long-lasting health effects. Moreover, appropriate controls for reducing greenhouse gases and air pollution may also diminish the negative health aspects of changing bioaeresols (i.e., pollens, fungi). In addition, artificial plantation and transportation of new species may also increase the negative health risks associated with bioaeresols. This issue can be discussed in the future larger reports. It is also crucial to prioritize the surveillance for pathogens that may respond to climate change and contribute to strengthening climate change resilience for infectious diseases in order to act against new epidemics such as Zika virus in South America or even the COVID-19 pandemic.

3 | EFFECTS OF CLIMATE CHANGE ON ASTHMA AND ALLERGIC RHINITIS

Climate change poses a significant threat to respiratory health by directly generating or exacerbating pre-existing respiratory disorders. It is vital to highlight that the prevalence of asthma has risen in recent decades and is expected to rise further.[62] Besides, aeroallergens play important roles in the pathophysiology of AR, and their distribution varies by geographical regions depending on the type of climate. Therefore, it can be assumed that the impact brought about by global warming will affect the distribution of aeroallergens and pollen mass, thus, these may effect the prevalence of asthma and AR.[63,64] A recent study in Georgia, USA, showed that the concentration of several tree pollen taxa increased over the last 27 years, and multiple species started to release their pollens earlier. The authors have concluded that early pollen discharge of some species could be associated with warmer temperatures.[65] In a retrospective analysis of datasets lasting 20 years or longer from 17 locations in the northern hemisphere showed that increases in daily minimum and maximum temperatures over time were associated with increases in both pollen load and duration of pollen season.[66] In another study, an approximately twenty days earlier start date in pollen season, lengthening of the pollen season by about eight days over the same period and an increase of pollen concentration by twenty-one percent across North America were found and those findings were associated with increased temperatures.[67] However, it was also reported that a significant increase in the annual amount of airborne pollen for many taxa in urban areas in Europe was not associated with temperature increase.[68]

Another effect of climate change can be observed on molds. In contrast to the strong relationship between global warming and increased pollen counts, fungal spores have been shown to decrease with increased temperatures.[23] On the other hand, it is envisioned that climate change may increase the amount of indoor and outdoor molds by increasing humidity in the buildings due to increasing floods

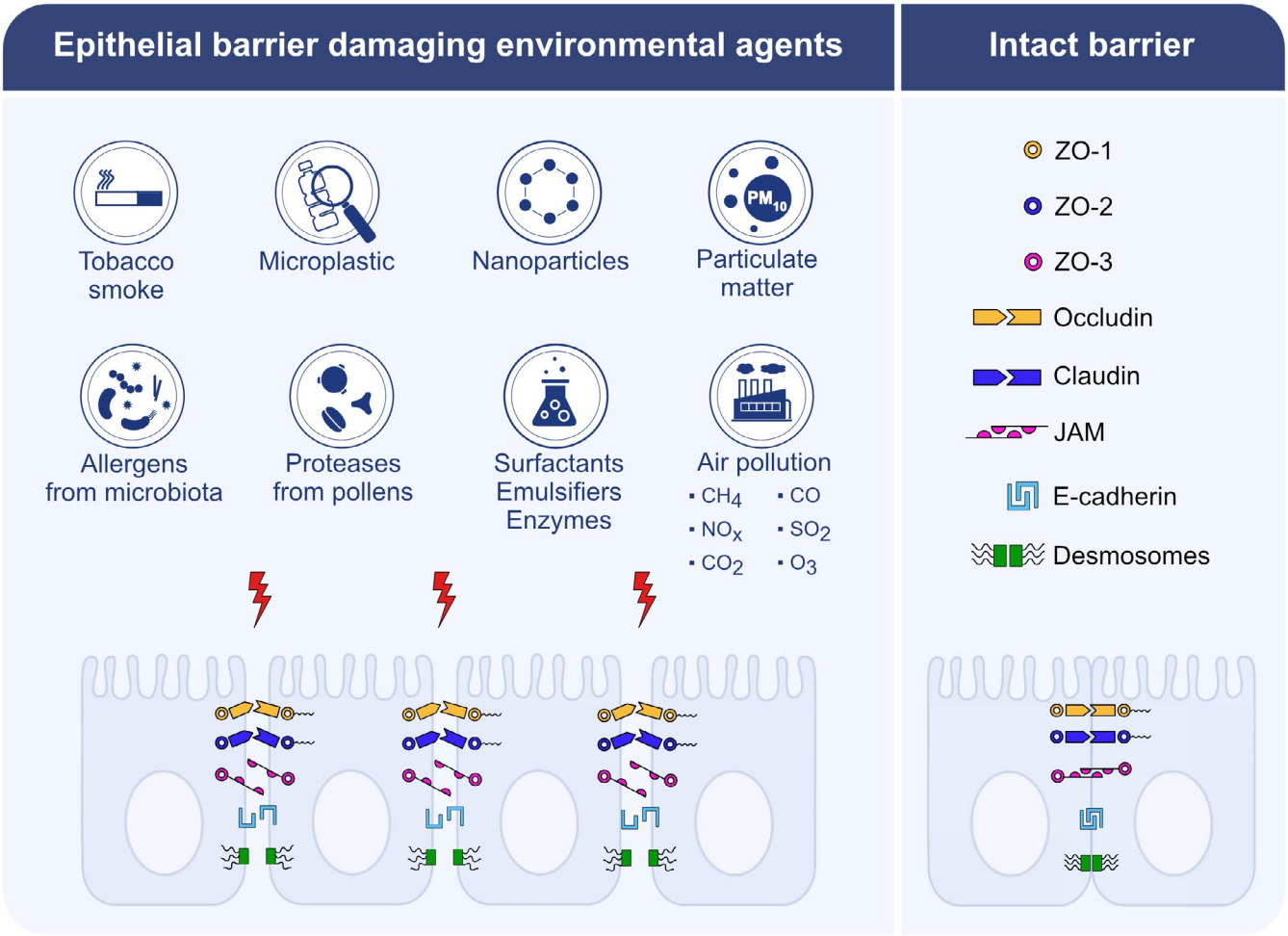

FIGURE 3 Epithelial barrier damaging agents from the environment. Allergens derived from bacteria, virus, and fungus; protease activity of allergens; surfactant, emulsifiers, and enzymes used as food additives; cigarette smoke, nanoparticles, particulate matter, and pollutant gases including nitric oxides, sulfur dioxide, carbon monoxide, carbondioxide, methane, ozone; microplastics irreversibly damage epithelial barriers by disrupting intercellular connections and anchoring of epithelial cells. Zonula occludens 1–3, occludin, claudins, junctional adhesion molecules, E-cadherin and desmosomes are depicted as damaged epithelial molecules. CH_4: methane, NOx: nitric oxides, CO_2: carbondioxide, CO: carbon monoxide, SO_2: sulfur dioxide, O_3: ozone, ZO: Zonula occludens, JAM: junctional adhesion molecules

and heavy rains. Although, there are not enough studies to validate these associations, in 2005, after the aftermath of hurricanes Katrina and Rita in New Orleans, the levels of mold spores were detected extremely high in the water-damaged houses. Endotoxins and fungal glucans of predominantly *Aspergillus niger*, Penicillium spp., Trichoderma, and Paecilomyces. were also high in the environment and were found to be associated with health effects.[69] In another study on fungal exposure of workers participating inpost-hurricane renovation in the same area, the workers were exposed to increased levels of fungi, but their levels dropped significantly in the first year after hurricanes. Therefore, although the burden of molds increases due to climatic reasons, there are no data showing that this change is permanent.[70] In addition, a study from the San Francisco Bay Area in the USA used time series regression models and noted season length for the most frequent outdoor molds has increased over the last two decades. Finally, the authors suggested that mold spore and pollen activity are connected to variations in observed climate change factors.[71]

Increased urbanization and global warming have created a warmer and more humid environment, which is ideal for the growth of house dust mites (HDM).[72] Sensitization to HDM has been most prominent among urbanized Asian regions due to their fast industrialization.[73] A retrospective study from China evaluated a total of 5,486 patients over a 10 years period and demonstrated that HDMs comprised the most common aeroallergen in Guangzhou, which is a rapidly industrializing region.[74]

Unfortunately, the concerning outcomes of industrialization, global warming, and climate change are not limited to variations seen in aeroallergens. Air pollution and climate change are inextricably linked. Fossil fuels, the primary source of CO_2 emissions, are also major air pollutant that contribute to climate change. A case-crossover study from Belgium reported that air pollutants cause more severe AR.[75] The results of this study are consistent with the international expert consensus of the World Allergy Organization published in 2020, which in brief, states that pollutants are linked to inflammation and exacerbate allergic airway diseases.[76] The

notorious invasive common ragweed (*Ambrosia* spp), which is a highly allergic species is anticipated to become more widespread and allergenic due to the increase in atmospheric CO_2 especially in the Northern Hemisphere.[66,77,78] Khreis et al. conducted a study across 18 European countries including 63,442,419 children and reported that nearly one-third of all childhood asthma cases might be linked to exposure to air pollution. Based on their findings, the authors hypothesized that adherence to the recommendations of World Health Organization Air Quality Guidelines could prevent up to 11% of childhood asthma cases each year.[79,80] A prospective birth cohort study from the Netherlands analyzed data of 3,687 participants and found a link between the incidence of asthma and exposure to air pollutants from birth.[81] In addition to these recent studies, many older ones establish a connection between exposure to air pollution in early life and developing asthma.[78,82-88]

Common limitations mentioned in these studies include the heterogeneity and complexity of asthma, the existence of confounders such as smoking, parental atopy, breastfeeding, and challenges in diagnosing asthma, especially in children. However, over the past decades, some natural disasters like thunderstorms, dust storms, and wildfire smokes have created an opportunity to observe patients with already diagnosed asthma, free from some of these confounding factors during a climate change-driven event[89] (Figure 4). Thunderstorm-related asthma epidemics are good demonstrative *in vivo* models for the impact of heavy rain on pollen's capacity to trigger asthma symptoms whether the patient had symptoms or not in the past. Many studies have shown that thunderstorms increase asthma exacerbations and therefore the number of hospital admissions due to the increased airborne pollen grains and fungal spores.[90-98] Current hypothesis indicates a mechanical effect with thunderstorms with heavy rain, wind, lightnings, or both, fragmenting pollens into smaller allergenic particles. Sub-pollen particles 'attract' humidity and create droplets, and then descend to the ground drops of water containing potentially allergenic small particles quickly hit the ground and are sprayed into the air, contributing to the creation of bioaerosols. These tiny particles can then easily penetrate deeper into the airways to trigger asthma attacks.[9,99,100] A study supporting this hypothesis demonstrated that increasing pollen fragment concentrations were associated with thunderstorms, strong downdrafts, and high rates of rainfall and that pollen fragments persisted in the atmosphere for several hours after the storms.[101] The most recent and probably the most catastrophic thunderstorm asthma epidemic struck Melbourne, Australia, in 2016. There was more than a sixfold increase in respiratory-related presentations to public hospitals in 30 h. A study that evaluated the risk factors for hospital admissions found higher odds ratio among patients with known asthma.[97] Aside from thunderstorms, inhalation of fine particles in smoke during wildfires can induce lung irritation. An analysis in California, USA, showed that the October 2017 wildfires were responsible for over 300 asthma and cardiovascular-related hospital

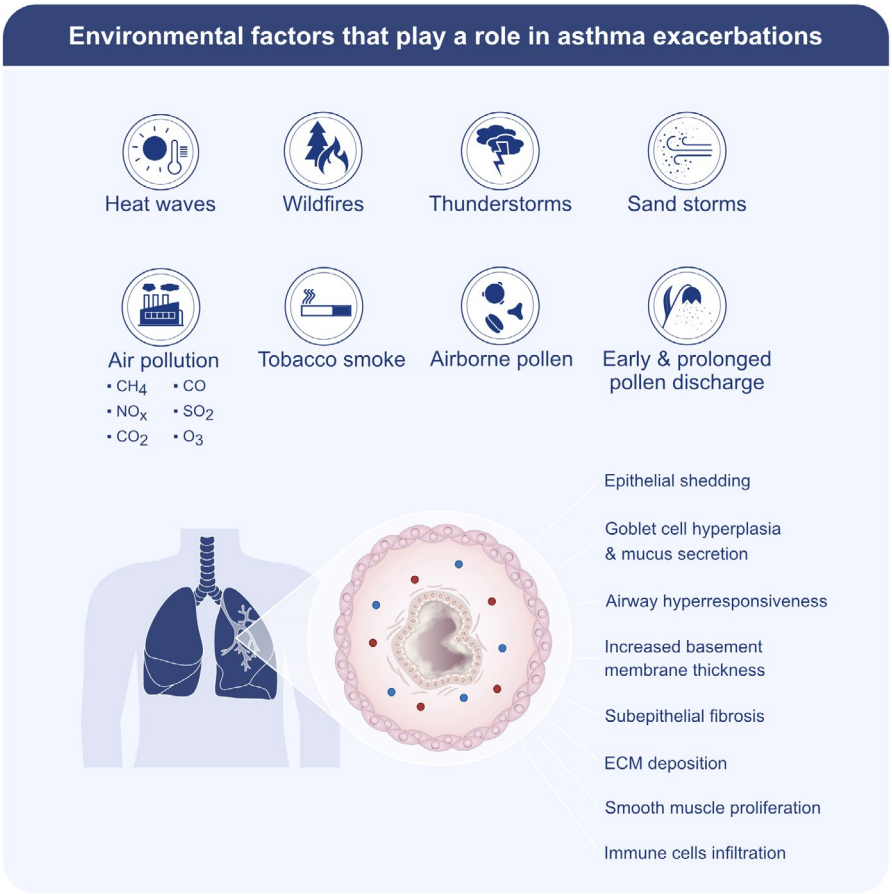

FIGURE 4 Environmental factors that play a role in asthma exacerbations. Air pollution with gases (NO_x, SO_2, O_3, CO_2, CO, CH_4) and particulate pollutants (PM2.5 and PM10) emitted from industrial smog and wildfire smog, environmental tobacco smoke, heat waves, sandstorms, and airborne pollen cause asthma exacerbations. Moreover, extreme heat causes early and prolonged pollen discharge, and thunderstorms cause bioaerosols containing potentially allergenic small particles due to the rapid hit of water droplets to the ground. All of these factors may have a direct or indirect effect on epithelial shedding, goblet cell hyperplasia, airway hyperresponsiveness, increased basement thickness, subepithelial fibrosis, extracellular matrix (ECM) deposition, smooth muscle proliferation, and immune cell infiltration in the airways and exacerbate asthma

admissions.[102] In addition, a recent meta-analysis reported that exposure to fire smoke in both children and adults increased hospital admissions and emergency room visits due to asthma attacks, with a higher incidence in adults.[103,104] Air-liquid interface cultures of bronchial epithelial cells demonstrated that wildfire smoke induces epithelial barrier dysfunction by disrupting tight junction (TJ) proteins, increasing paracellular permeability.[105] Particles found in dust storms are larger than those in wildfires, but they can still induce strong inflammatory responses.[106] A study conducted in Crete, Greece, concluded that extreme desert dust storms increase hospital visits for respiratory symptoms[107] (Figures 3 and 4, Table 1).

4 | CLIMATE CHANGE AND FOOD ALLERGY

The evidence for the relationship between global climate change and an increase in food allergies (FA), such as peanut allergy, is weaker in comparison with other allergic disorders. Peanut and tree nut allergies appear to be on the rise.[108-110] It is still uncertain whether this increase could be attributed to the increases in atmospheric CO_2 concentration and temperature. A few studies have investigated the impact of elevated CO_2 concentration on peanuts and demonstrated that they are responsive to these factors and suggest that their allergenic characteristics could also be influenced.[110] A study published the first evidence that increased CO_2 concentrations can result in a rise in the concentration of the major peanut allergen (Ara h 1).[111] A recent study examined the changes in allergic diseases in asthmatic children over a 25 years period in France and determined that FA with tree pollen sensitization increased.[112] Further research is needed to explore the relationship between climate change and other common causes of food allergies such as egg, shellfish, soy, and cow's milk (Table 1).

5 | CLIMATE CHANGE AND ATOPIC DERMATITIS

Compared to other allergic diseases, it is seen that different consequences of climate change, such as UV lights, cold and dry weather conditions, and floods, have more influence on AD. Global warming is thought to be causing floods by melting polar ice caps, rising sea levels, and heavier rains. Floods have been shown to have an impact on childhood AD flare-ups, according to a retrospective study conducted in Taiwan.[113] The study hypothesized that increased levels of molds in the indoor environment and prolonged exposure to contaminated water could trigger an AD flare-up in sensitized children. In an observational study, 60 patients with AD were followed for 18 months and high levels of air pollutants such as PM10, NO_2, and O_3, as well as an increased pollen counts were found to exacerbate AD symptoms.[114] However, a limitation of the study was a lack of a report of other confounding factors such as UV lights. A recently published retrospective study suggested that UV exposure is beneficial in most patients with AD lesions.[115] This finding is consistent with the literature that supports phototherapy with UV light for AD to reduce inflammatory response in the skin.[116] Although global climate change could allow more harmful UV-B to reach the Earth's

TABLE 1 Climate change and environmental exposures associated with allergic diseases

Allergic disease	Exposure	The effects on disease	Ref.
Asthma and Allergic rhinitis	Global warming	Increase in the prevalence of asthma and AR Pollen concentrations increase as temperature rise Pollen season length increased Fungal spores decrease as temperature rise With more humid and warmer environments HDM allergy increased AR prevalence increased	[63] [65-67] [21,22] [23] [72-74]
	Floods	More severe asthma due to mold proliferation	63,69
	Rising $CO_{2\ levels}$	Ragweed pollens elicit a stronger allergic lung inflammation and becoming more widespread	[55,77,78]
	Air pollutants	1/3 of childhood asthma cases may be linked to air pollution Increase incidence of asthma in children and young adults Expose to pollution in early life causes asthma development Causing AR to be more severe Cause Ragweed more common and allergenic	[79,80] [81] [82-88] [75,76] [24,54,77,78]
	Thunderstorms	Trigger asthma exacerbation Increased hospital admissions	[9,99,100] [90-97]
	Wildfires	Exacerbate asthma Induce epithelial barrier dysfunction	[102-104] [105]
	Dust storms	Strongly induce inflammatory response Increase respiratory symptoms	[106] [107]
Food allergy	Rising CO_2 levels	Rising peanut and tree nut allergies	[110-112]
Atopic dermatitis	Floods	Flare-up of childhood AD	[113]
	Air pollutants	Increase in the severity and development of AD	[114,117]

surface by decreasing stratospheric O_3, combined with industrialization and urbanization, it may also decrease UV light penetration by increasing cloud cover, dust, smoke from wildfires, and other airborne particles. A comprehensive study examined the link between air pollution and allergic diseases and found that exposure to oxidants such as O_3 and NO_2 at birth increased the risk of developing asthma by 17% and eczema by 7%[117] (Table 1).

6 | THE EXTERNAL EXPOSOME AND THE MICROBIOME OF SKIN, GUT, OROPHARYNX, AND LUNG

The contribution of the microbiomes of the skin, gastrointestinal and respiratory tracts to health and disease is well established. Studies on allergic diseases and microbiota and external exposome (Cesarean section, feeding with formula, use of prebiotics or probiotics, diets high in fat and low in fiber content, early antibiotic usage in infancy, etc.) have identified that human microbiota has a central role in the regulation of this process.[118] Due to the drastic changes in modern environments, hygiene, and lifestyles, the variance of content of gut and skin microbiota may contribute to the development of various chronic inflammatory diseases including asthma, and other allergic diseases, and may trigger autoimmunity.[9,119]

Human DNA is assumed to represent only a small percentage of all DNA in the human body. A much higher percentage of the genetic contribution is made by the so-called human microbiome, which consists mostly of bacteria, fungi, viruses, archaea, and other microorganisms.[120] Host-microbiota interactions are essential for the evolution of the immune system. While the immune system eliminates the pathogens, it also tolerates the beneficial microbiota that maintains a symbiotic life with the host.[119] The effect of microbiota on immunity-related diseases is known not only on naturally colonized microorganisms at the barrier sites, such as the gut, skin, lung, and other mucosal surfaces, but also on non-barrier organs such as liver, kidneys, joints, lungs, eyes, and brain.[119]

Microbial dysbiosis has always been reported in areas of epithelial barrier dysfunction, such as gut, esophagus, lung, and sinus mucosa.[12,121-127] One of the main events following epithelial barrier damage is the colonization of opportunistic pathogens, such as *Staphylococcus aureus* (*S.aureus*), Moraxella, Hemophilus, and Pneumococcus. *S.aureus* has become the dominating bacterial species in AD skin lesions and chronic rhinosinusitis.[128-132] The percentage of healthy carriers of *S. aureus* increased to 35% from 4% within the last four decades.[133] These percentages increase to more than 90% in CRS and AD.[134] In the barrier-damaged areas were opportunistic pathogens start to dominate, relatively non-inflammatory commensals start to decrease in abundance as well as microbial biodiversity.

Healthy skin consists of different microorganism communities depending on the sampling area. Propionibacterium species are dominant in sebaceous sites, whereas Corynebacterium and Staphylococcus species are found in humid areas.[135,136] Changes in these healthy microbiomes may result in allergic sensitizations.[118] The skin harbors many regions with different bacterial communities; therefore, it may also affect local and systemic immune responses.[119] At birth, regulatory T (Treg) cells dominate the skin barrier, and it is necessary to be exposed to commensals in order to develop tolerance against these microorganisms.[137] The importance of interaction with cutaneous microbiota in early life has been proven by observational studies on cutaneous dysbiosis.[119] In the first years of life, early exposure to protective commensals such as *Staphylococcus epidermidis* prepares tolerogenic Treg cells and contributes to the development of commensal-specific skin-resident memory cells and effector T cells that support the innate microbial defense.[135,136]

Commensals colonizing the oral cavity, a mucosal area of the gastrointestinal system, are well known to contribute to oral health/hygiene and inflammation.[138] Immediately within a few hours of birth, infants undergo rapid colonization of microbiota. Initially, the gut microbiome is generally composed of *Escherichia coli* and Enterococcus species, followed by anaerobes including Bifidobacteria, Bacterioides, and Clostridium spp. that become predominant in line with decreasing oxygen concentrations in the gut.[139] Clostridium species are more dominant than Bifidobacterium species in cesarean-born babies, whereas it is vice versa in babies born vaginally.[140] Breast-fed babies generally have less diversity in the gut in the first few weeks of life and are usually colonized by Bifidobacterium species.[118]

In the lungs, the pulmonary blood-air barrier and colonizing microbiota also play a role in immune-related diseases. It has been shown that T helper 2 (Th2) cytokine release is decreased as the pulmonary bacterial load increases in newborn mice.[141] Moreover, in the lungs of germ-free mice, invariant natural killer T (iNKT) cell levels, producing IL-4 and IL-13, were also found to increase in response to ovalbumin, suggesting a decisive role in the presence and absence of commensal microbiota.[142] Gut-lung axis enables the gut microbiome to influence the lungs and protects the host from asthma by shifting the Th2, Treg (Th2-Treg) balance toward Tregs.[119] Parasitic gut infection is another potential mediator for gut-lung axis via the altered intestinal microbiota and the induction of pulmonary Tregs. This has been suggested partially to explain the high atopy rates in developed countries with low helminthic exposure.[119] However, for example, in New York, USA, since water sanitation started in 1910, parasite burden significantly decreased, whereas asthma started to increase after the 1960s.[143]

Exposure to different microorganisms (bacteria, mold, virus, protozoan, and helminths) may induce epigenetic changes that affect the immune system modulation and result in the development of inflammatory diseases. During the maternal and postnatal periods known as the 'window of opportunity', maternal infections, microbiota, diet, drugs, and environmental exposures such as pollutants have a profound importance for the modulation of the immune system.[144] A recently studied model proposed that environmental exposure during pregnancy may remodel the maternal microbiome and immune functions and thus also affect fetal immunity and microbiome development.[145] These effects educate the innate immunity of the newborn and regulate the response-ability to those microorganisms that pass through maternal vertical transmission and colonize in the body habitats. Depending on the content and

functional features, these preliminary microorganisms remodel the composition and accumulation rate of exogenous microorganisms in the first year of life.[146] Antibiotics are among environmental factors that affect the human microbiome and are well known to alter the incidence and severity of autoimmune and allergic diseases.[147] Diets with different fiber, tryptophan, and fatty acid contents may modulate immune-related diseases through various mechanisms.[119] Furthermore, chemical and physical environmental factors can alter the host-microbiota interactions. For example, sun exposure has been shown to alter antimicrobial peptides via UV radiation because UV can kill microbes and modulate the skin microbiota.[148]

7 | MICROBIOME AND ALLERGIC DISEASES

Studies have shown that human health is closely associated with the balance of the common microbial community, the so-called halobiont homeostasis. Microbial biodiversity and the interactions among various microorganisms have functional outcomes. The change and loss of biodiversity lead to a more unstable and less resistant microbiota, often dominated by one or few microorganisms; this is a phenomenon known as dysbiosis, which can alter the immune balance maintained by the gut, skin, and respiratory microbiomes and cause diseases.[144,149] Biodiversity hypothesis states that the increase in allergic diseases may be due to bacterial dysbiosis and decreased biodiversity of commensals.[150] The healthy microbiota on the mucosal surface regulates various aspects of barrier homeostasis such as barrier permeability modulation, TJ expression, angiogenesis, vascular permeability, local micro-inflammation, and mucosal tolerance (Table 2). On the other hand, dysbiosis together with epithelial barrier leakiness damages immune homeostasis at the affected tissue.[144] In a healthy situation, the microbiome stays above the epithelium to live together, with a homeostatic interaction driven from co-evolution, however, when the epithelial barrier becomes leaky, dysbiotic commensals and opportunistic pathogens migrate in between the affected epithelial cells and translocate beneath the epithelium. This is easily visible in the CRS epithelium by light microscopy and clearly takes place in the affected gut epithelium in colitis.[151-154] Therefore, decreased diversity and the changes in the gut and skin microbiota contents are related to several chronic inflammatory diseases, including asthma, AR, AD, and FA.[12,17,155]

7.1 | Asthma

Asthma is a complex disease and involves several risk factors. Evidence of risk factors in early life that can alter the development of lung immunity associated with dysbiosis, which leads to asthma, was extensively reviewed by Cerata et al.[156] These factors are delivery by cesarean section, usage of antibiotics during the neonatal period, maternal diet, breastfeeding, early-life allergen exposure, pollution, external microbes, and host microbiome.[17,157-159] Some of these risk factors interact with each other to contribute to the pathogenesis of asthma, and some of these interactions are mediated through the microbiome and epithelial barriers.[144,160] Perinatal and/or early-life microbial exposure affects physiological development, and exposure to farming environments, environments with high microbial or allergen loads at this age is associated with a reduced risk of asthma and other allergic diseases in children.[161,162] Regular contact with farm animals increases indoor home endotoxin concentrations, which might explain the protective effect of contact with farm animals on atopic outcomes, and it is hypothesized that the farm environment can provide immunomodulatory stimuli.[163] Endotoxin was shown to be a protective factor for asthma in older children.[164] Additionally, peak exposure to specific allergens, bacteria, and certain environmental microbiota, especially in the first year of life, reduces the likelihood of having recurrent wheeze and allergic

TABLE 2 Microbiome and allergic diseases

Allergic disease	Current concepts	Ref.
Asthma	Reduced risk with perinatal and/or early-life microbial/allergen exposure	[161,162]
	Reduced with endotoxin exposure in childhood	[164]
	Higher abundance of certain gut bacteria was shown in asthmatic subjects	[165,166]
Allergic rhinitis	Alteration in normal nasal mucosal bacterial abundance and diversity was shown	[169,170]
	Reduced risk with early-life exposure to environmental microbiota	[155,171]
Atopic dermatitis	Altered abundance and diversity of skin microbiota compared to healthy skin	[131,175,176,180]
	Early-life skin colonization of certain bacteria in AD	[182]
	Increased risk with dysregulated gut-skin axis	[176,183,184]
	Filaggrin mutation can initiate AD	[177-179]
Food allergy	Increased risk with dysbiosis in gut environment	[189,191]
	Increased risk with lower gut microbiota diversity at early infancy	[190]
	Reduced risk maternal Mediterranean diet during lactation and gestation	[193]
	Reduced risk with diet consisting of high levels of fruits and vegetables during infancy	[194]
	Increased risk with high-sugar, high-fat, low short-chain fatty acid diets	[195]

sensitization.[155] Host microbiota has been primarily linked to asthma pathogenesis via gut microbial metabolites. Having a higher abundance of certain gut bacteria like Faecalibacterium, Lachnospira, Rothia, Bifidobacterium, or Akkermansia, especially during the first month of life, has been associated with protection against allergic sensitization and allergic asthma.[165,166] Additionally, there is growing evidence for the role of the gut and lung axis in the development of chronic lung diseases.[167] It is also thought that the composition and function of the upper respiratory tract microbiome may influence the pathogenesis of asthma.[168] It is clear that many external and host-related factors influence the dynamic nature of the relationship between the host microbiome and asthma (Table 3).

7.2 | Allergic rhinitis

Although there is still a limited link in the relationship between nasal microbiome dysbiosis and the development of AR, the nasal microbiome potentially holds an important role in the modulation of localized immune responses. In the normal nasal mucosa *S. aureus*, Propionibacterium, Prevotella, Corynebacterium, Bacteroides, and Streptococcus are common. However, in AR, the abundance of *S. aureus*, Propionibacterium, Corynebacterium, and Peptoniphilus is considerably increased, whereas the numbers of Prevotella and Streptococcus are decreased.[169] It was shown that in patients with seasonal AR, during the season, the variety of organisms in the middle meatus had significantly increased, and there was a correlation between bacterial diversity and nasal lavage eosinophil counts.[170] In a study, 180 children, aged between 7 and 11 years, from Finnish and Russian Karelia (both have similar climates, the former is a more modernized area and latter is a rural environment) were followed up for 10 years, and atopic sensitization and allergic diseases were found to be up to 10-fold higher in Finnish Karelia. Bacterial and fungal populations in the nasal mucosa were more abundant and diverse in Russian participants than Finnish peers, and it was stated that early-life exposure to environmental microbiota might be biologically related to allergic manifestations at a younger age (Table 3).[171]

7.3 | Atopic dermatitis

According to current knowledge, the pathogenesis of AD is defined by the interplay between genetic background and epithelial barrier defects, epigenetic changes, immunologic factors, dysbiosis in the skin and gut microbiota, and external risk factors.[172,173] It has been demonstrated several times that the composition and diversity of microorganisms on the skin differ between people with eczema and those healthy ones.[131,174-176] It is a major question whether barrier disruption in the affected organs starts first or proceeds microbial dysbiosis (Table 2). In other words, it is still unclear whether dysbiosis of the skin microbiome is one of the pathogenetic factors of AD or the cause of the onset of AD. On the other hand, skin barrier disruption due to genetic defects in barrier molecules such as filaggrin mutations can initiate AD.[177-179] The same question is also valid for asthma and CRS.[177] In atopic skin, there has been a reduction in commensal bacteria and in patients with AD, a higher colonization index and increased pathogen density show a positive correlation with the skin lesions' severity and the severity of the disease.[180,181] Early-life skin colonization may also occur before the disease's clinical manifestations.[182] Gut-skin axis is another potential pathway in the pathogenesis of AD. Gut and skin microbes can interact with each other through immunologic and metabolic pathways.[183] Certain microbial metabolites from the gut have effects on skin microbiota, and gut bacterial dysbiosis has an effect on the skin immune system via a systemic imbalance in the Th2-Treg lymphocyte ratio[173,184] (Table 3).

7.4 | Food allergy

The gut microbiome is a dynamic environment constantly being influenced and modified by external factors, such as diet. Mechanisms of immune tolerance to food antigens appear with these modifications in this process. Disruptions in the immune responses and dysbiosis of the gut microbiome are associated with the development of FA.[185-188] Gut microbiome and bacterial diversity vary with factors such as maternal health, maternal diet, mode of delivery, dietary change with increasing age from the intrauterine stage to the first 3–4 years of life and intestinal colonization during infancy, which may affect the development of FA.[189,190] At 3 months, lower microbiota richness was associated with increased food sensitization by age 1, but microbiota richness was no longer associated with food sensitization after 12 months of age.[190] Although breastfeeding is a major source of immune factors and beneficial bacterial species, the direct relationship between breastfeeding and food sensitization is still unclear.[191,192] A maternal mediterranean diet during lactation and gestation and an infant diet consisting of high levels of fruits and vegetables were found to be protective against the subsequent development of FA.[193,194] In contrast, high-sugar and high-fat diets and diets with low levels of fecal short-chain fatty acids have been associated with the development of FA.[195] In the end, poor food, altered bacterial diversity, and lack of protective factors from certain bacterial species like prevotella may result in allergic diseases, including FA.[191,196] Children with egg allergy were found to have increased diversity and different taxa in the early-life gut microbiome compared to children without allergies.[197] This suggests that the specific microbiota associated with individual food allergies may differ depending on the food (Table 3).

8 | CHANGE IN DIETARY HABITS AND ALLERGIC DISEASES

In recent years, many dietary hypotheses have been put forward in relation to allergic diseases, and changing dietary content is

TABLE 3 Does microbial dysbiosis or epithelial barrier disruption proceeds the development of allergic diseases?

Allergic disease	Evidence for microbial dysbiosis starts first	Evidence for barrier disruption starts first	Ref.
Asthma	Reduced risk of asthma with perinatal and/or early-life microbial/allergen exposure	Increased risk of asthma with epithelial barrier disruption due to exposure to cleaning products	[161,162,164-166,214,215]a [12,159,177]b
	Reduced risk of asthma with increased prevalence of early-life *Faecalibacterium*, *Lachnospira*, *Rothia*, *Bifidobacterium*, or *Akkermansia*	AD patients with epithelial barrier disruption secondary to filaggrin mutation conferred an overall asthma risk	
	Reduced risk of asthma with endotoxin exposure in childhood		
	Higher abundance of certain gut bacteria was shown in asthmatic subjects		
Allergic rhinitis/ CRS	Alteration in normal nasal mucosal bacterial abundance and diversity was shown	Dysregulation of TJs observed both in biopsy specimens and epithelial cultures in the absence of any inflammatory stimulus	[155,169-171]a [124]b
	Reduced risk of AR with early-life exposure to environmental microbiota		
	Increased prevalence of S.*aureus*, *Propionibacterium*, *Corynebacterium*, *Peptoniphilus* and decreased prevalence of *Prevotella* and *Streptococcus* in AR		
Atopic dermatitis	Altered abundance and diversity of skin microbiota compared to healthy skin	Genetic mutations in the epidermal barrier-related genes	[180,182-184]a [127,131,177,178]b
	Early-life skin colonization of certain bacteria in AD	Reduced expression of Claudin−1 in AD might enhance the penetration of altered microbial flora	
	Increased early-life prevalence of *S. aureus* and decreased commensal microbes, eg. *S. epidermidis* in infants with AD	While the correlations do not imply a causative relation, S aureus negatively correlated with TJ genes only in the lesional skin. Further studies needed	
	Gut bacterial dysbiosis has effect on the skin immune system		
Food allergy	Increased risk of FA with dysbiosis in gut environment	Barrier defect secondary to filaggrin mutation is thought to facilitate peanut allergy	[118,140,186-191,193]a [177]b
	Increased early-life prevalence of *Clostridium* species and decreased *Bifidobacterium* and *Lactobacillus* species in FA		
	Increased prevalence of *Clostridium* species over *Bifidobacterium* species in infants born by cesarean section		
	Presence of *Prevotella* in maternal stool is associated with a decreased risk of their infant developing FA		
	Reduced risk of FA with diet consisting of high levels of fruits and vegetables during infancy		[194]a,b
	Increased risk of FA with high-sugar, high-fat, low short-chain fatty acid diets		[195]a,b

[a]References for the first column.

[b]References for the second column.

considered one of the most important environmental factors that cause allergies. Increased consumption of processed and fatty foods as a result of the conversion of the traditional diet to the western diet is often associated with the increase in the prevalence of allergic diseases.[198,199] The effects of fatty acids are contradictory. While n-3 (omega-3) fatty acids have potential protective effects, n-6 (omega-6) fatty acids have potentially harmful effects.[200,201] In a combination study in humans and mouse models to show the counterregulatory actions of docosahexaenoic acid (DHA; C22:6, w-3)-derived protectin D1 (PD1) in allergic airway inflammation, it

was shown that PD1 administration decreased airway eosinophil count, T lymphocyte recruitment, airway mucus, levels of IL-13, cysteinyl leukotrienes, PGD2, and airway hyperresponsiveness to inhaled methacholine. These studies present the importance of PD1 in reducing airway inflammation and the importance of an omega-3-rich diet in terms of maintaining airway homeostasis.[201] In an *in vitro* study, the D-series resolvins PD1 and resolvin D1 derived from the omega-3 (v-3) fatty acid DHA have been shown to have potent pro-resolution activities in allergic airway inflammation by intranasal administration. PD1 and resolvin D1 have been shown to reduce the total number of inflammatory cells and eosinophils in bronchoalveolar lavage and lung tissue and to cause goblet cell metaplasia in the airways of mice.[202] In particular, the increased n-6/n-3 ratio is considered one of the main factors that increase the allergic response.[199,203] The n-6/n-3 ratio of the human diet in the Paleolithic period was 0.79 and remained approximately the same for a long time.[204] However, within the last century, this ratio has increased up to 10–20:1 due to nutritional changes. This rapid change in the n-6/n-3 ratio, which is recommended to be approximately 5:1, also increased the negative impacts of n-6 fatty acids and their metabolites. It is known that arachidonic acid (AA), one of the n-6 fatty acid metabolites, increases the inflammatory response via eicosanoids. The increase in thromboxane A2, prostaglandin E2, and leukotriene B4 eicosanoid levels in the body also increase allergic sensitivity.[205] Unlike n-6, n-3 fatty acids compete with AA and prevent the formation of inflammatory agents. Moreover, eicosapentaenoic acid (EPA)-derived resolvins (especially resolvin E1) induce an anti-inflammatory effect by attenuating NF-κB activation.[206]

Another nutritional factor frequently associated with allergic diseases is antioxidants. In the past, foods were delivered to the consumer shortly after production, but today they are replaced mainly by processed foods.[207] Decreased levels of antioxidant A, C, and E vitamins in processed foods are thought to increase susceptibility to allergic diseases.[208] In addition, genetically modified (GM) organisms, which is the general name given to plants, animals, or microorganisms whose specific characteristics have been modified by transferring genes from species other than their own by biotechnological methods, is another important problem of our era. In recent years, GM plants have been increasingly used for food production and industrial applications. Some studies have suggested that transgenic crops may have allergic effects.[209-211] Although there are no clear results, GM food does not appear to be more allergenic than natural food, and so far there are no data to suggest that GM proteins cause allergies.[212,213] However, it should be noted that the reported studies are limited to short-term follow-ups, and long-term results are unknown. In addition, a new protein is transferred by gene transfer technology, and most of the allergens are in protein structure. Therefore, longer-term studies about the effects of GM foods on humans are needed. Another current issue is that rural life, contact with farm animals, and consumption of non-pasteurized milk at an early age prevent the development of allergic diseases as a result of increased exposure to nonmicrobial-derived N-glycolylneuraminic acid (Neu5GC).[214,215]

Below, the complex interactions between changing dietary habits linked to asthma, AR, AD, and FA will be discussed.

8.1 | Asthma

The increase in the prevalence of asthma in parallel with the increased processed/fast food consumption in recent years has suggested that these two conditions may be related.[216] Especially, in western countries, as a result of the widespread consumption of fast food, the increased use of predominantly n-6 containing vegetable oils is proposed to be one of the main factors in the increase of asthma.[217] High n-6/n-3 ratio and n-6-derived AA metabolites induce asthma by causing airway inflammation and bronchoconstriction.[218,219] In contrast, n-3 fatty acids have beneficial effects by reducing airway inflammation and severity of bronchoconstriction and are also sources of pro-resolving mediators that have been shown to reduce airway inflammation.[220,221] Furthermore, maternal intake of n-3 fatty acids during pregnancy has been shown to have protective effects against asthma in children.[222,223] However, in a systematic review of 8 studies on the consumption of n-3 fatty acids involving 3,366 women and their 3,175 children, the evidence was limited to recommend supplementation of n-3 fatty acids during pregnancy and/or lactation to reduce allergic disease in children.[224] In subsequent studies, maternal fish oil consumption has been reported to increase histone acetylation of anti-inflammatory gene regions (such as *FOXP3*, *IL10RA*, *and IL7R*) and may be protective against asthma; however, further studies are needed.[225-227] In the chromatographic analysis of the fecal samples of 301 one-year-old children, the highest fecal butyrate and propionate levels (≥95th percentile) were associated with less atopic sensitization and development of asthma between 3 and 6 years of age.[228] In addition to the protective effects of n-3 fatty acids, the salicylic acid Neu5GC exposure has been shown to reduce airway inflammation and protect against the development of asthma.[214]

Another factor that plays an important role in the pathophysiology of asthma is oxidative stress.[229] Insufficient intake of antioxidant vitamins (A, C, and E) and the resulting imbalance between antioxidant capacity and reactive oxygen species in the body make individuals more susceptible to asthma.[230] Two systematic reviews and meta-analyses reported that the beneficial effects of vitamins A, D, C, E, and, zinc on asthma outcomes were weak, but low dietary intakes of vitamins A and C were associated with a statistically significant likelihood of asthma and wheezing. Unlike vitamins A and C, vitamin E intake was not associated with asthma.[231,232] Vitamin A is metabolized to retinoic acid (RA) by $CD103^+$ dendritic cells (DCs). This DC-derived RA has significant effects on DC activity, and depending on its concentration, promotes Th17 cells or Tregs. So far, specific microbial strains such as *Bifidobacterium longum subsp infantes* have been shown to promote RA metabolism, fork head box P3 $(FoxP3)^+$ Treg cells, induce mucosal immune tolerance, and protect against inflammatory diseases.[233-235] Moreover, a number of *in vivo* studies demonstrated that vitamin D and RA, inhibit the formation

of inflammatory Th17 and favor the generation of FoxP3 Tregs, and confer tolerogenic responses (Table 4).[236]

8.2 | Allergic rhinitis

Studies on adults and children reported that consumption of junk food/fast food increases the risk of AR.[237] Although the results are unclear, food additives and artificial sweeteners often found in processed foods can trigger AR symptoms.[238-240] Limited number of studies have investigated the effects of dietary fatty acids on AR development. Accordingly, increased n-6/n-3 ratio and n-6-derived AA metabolites have been suggested to play an important role in the pathophysiology of AR.[241] While there is no evidence to support a protective association of fish (n-3 rich) consumption during pregnancy with AR symptoms from infancy to 8 years of age, early intake of fish (before 9 months) has been shown to reduce the prevalence of AR.[242-245] In adults, results are conflicting. Dietary n-3 fatty acid intake showed to be both protective and non-effective.[243,246] However, dietary n-3 fatty acids have been shown to dampen AR in a mouse model.[247] Oxidative stress and low total antioxidant levels also increase the occurrence and symptoms of AR.[248] In some studies, it was observed that serum levels of vitamins A, C, and E were low in individuals with AR, and supplementation of these vitamins reduced AR symptoms.[249,250] However, there are also studies in which the positive effects of supplementation were not observed (Table 4).[251,252]

8.3 | Atopic dermatitis

The prevalence of AD, a common, chronic, and recurrent inflammatory disease characterized by skin barrier impairment, has increased globally across all age groups, and this increase has also been associated with the westernization of dietary patterns and increased consumption of processed food.[253] Processed foods and some food additives such as monosodium glutamate (popular flavor enhancer) could act as pseudo-allergens and increase the occurrence and severity of AD.[254,255] Maternal diet and antenatal nutrition could affect fetal development by altering fetal programming, which may in turn alter immune response and atopy.[256] Nutrition during infancy and childhood is very important for the development of AD, and breastfeeding for the first 6 months is thought to be effective in preventing the development of atopic diseases. A study conducted with 4,089 patients showed that breastfeeding for the first 4 months reduces the risk of eczema in the first 4 years.[257] In addition, it has been pointed out that feeding infants with extensively hydrolyzed formula (eHF) in the first 4–6 months, avoiding cow's milk and dairy products, and starting solid foods after the 4th month prevent the development of AD.[257] However, it was reported that feeding with eHF after the 6th month did not suppress the development of AD.[258]

Studies investigating the effects of dietary fatty acids on AD in adults are quite limited and conflicting. Although some studies have indicated that low n-3 intake is inversely correlated with AD in women and one randomized control trial noted that AD severity decreases after n-3 supplementation; another studies have found no association between n-3 intake and AD, and other clinical studies reported that n-3 supplementation in adults did not show any benefit over placebo in AD.[259-264] Recently, oxidative stress has been shown to induce AD by increasing the pro-inflammatory response.[265] Studies conducted on children and adults have found an inverse relationship between serum vitamin C and E levels with AD, and supplementation of vitamin E reduced AD symptoms (Table 4).[266-268]

8.4 | Food allergy

As a result of changes in diet, the increase in the prevalence of FA is inevitable.[269] Maternal nutrition and consumption of highly processed foods during pregnancy have been shown to increase FA in infants.[270,271] In addition, food additives and preservatives, which are often found in processed foods, increase the susceptibility to food allergies.[272,273] Clinical studies investigating the effect of n-3 fatty acids on FA during pregnancy and/or lactation are contradictory but, starting fish oil supplementation early in pregnancy and continuing during lactation has been shown to reduce allergic sensitization to food proteins in offspring.[274] In a study that measured fatty acids in the feces with high-performance liquid chromatography indicated that children with the highest fecal butyrate levels were less likely to develop food allergies.[228] Antioxidant intake can also affect food allergies through its effects on the immune response. Maternal intake of vitamins A, C, and E together with food has a protective effect against FA in childhood.[275] However, taking these vitamins as supplements did not show similar effects[276](Table 4).

9 | ENVIRONMENTAL SUBSTANCES AFFECTING THE EPITHELIAL BARRIERS

Following the industrial revolution in the 19th century, environmental health threats such as air pollution and chemical hazards have increased worldwide. With the increase in PM, diesel exhaust, O_3, nanoparticles, and cigarette smoke, the air that we breathe has been dangerously polluted. The toxic burden faced by humans has increased with the introduction of cleaning products, detergents, and surfactants, as well as with increases in the use of processed foods and emulsifiers.[277-280]

The steep increase in type 2 inflammatory diseases, that is, asthma and AD, coincide with the usage of surfactants and enzymes in laundry detergents and household cleaners in the 1960s, and food allergy and eosinophilic esophagitis coincide with the use of food emulsifiers and dishwasher detergents after 1990s. Besides, the increasing load of nanoparticles and microplastics in the seas, soils, and nowadays in the indoor and inner-city air pose a significant threat to living beings. Recent research has revealed that environmental exposures, climate change, and global warming adversely affect airborne pollens and increase their allergenicity.[5,281]

TABLE 4 Change in dietary habits and allergic diseases

Allergic disease	Dietary habits	The effects on disease	Ref.
Asthma	High n−6/n−3 ratio	Airway inflammation and bronchoconstriction ↑	[219]
	n−3 fatty acids	Airway inflammation and severity of bronchoconstriction ↓	[201,221]
	Maternal intake of n−3 fatty acids	Protective effects against asthma in children	[222-224]
	Maternal fish oil consumption	Histone acetylation of anti-inflammatory gene regions ↑	[225-227]
	High Butyrate and Propionate	Less atopic sensitization and asthma development between 3–6 years of age	[228]
	Neu5GC exposure	Reduce airway inflammation Protect against development of asthma	[214]
	Vit. A, D, C, E, zinc Low dietary intakes of Vit A and C	Weak beneficial effect on asthma Statistically significant likelihood of asthma and wheezing	[231,232]
	Increased RA, Vit D consumption	Induce mucosal immune tolerance Inhibit Th17, favors the generation of FoxP3+ Tregs Protect against inflammatory diseases	[233-236]
Allergic rhinitis	Consumption of junk food/fast food	The risk of AR ↑	[237]
	Fish (n−3) consumption during pregnancy	The prevalence of AR ↓	[242-245]
	Supplementation of Vit. A, C, and E	AR symptoms ↓ No positive effects on AR	[249-252]
Atopic dermatitis	Processed foods and some food additives	The occurrence and severity of AD ↑	[253,255]
	Breastfeeding for the first four months	The risk of eczema in the first four years ↓	[257]
	Feeding infants with intensive eHF in the first 4–6 months, avoiding milk and dairy products	Prevent the development of AD	[257]
	Feeding eHF after the sixth month	Not suppress the development of AD	[258]
	Monounsaturated fatty acid	Allergic sensitization in females, mostly no significant associations for males	[258]
	High n−6/n−3 ratio	Moderate to severe AD ↑	[260]
	The intake of n−6 fatty acids	Lower in the severe AD group	[261]
	n−3 PUFA docosahexaenoic acid	Beneficial impact on AD	[262]
	Supplementation with polyunsaturated fatty acids of the omega−3	The mean SCORAD improved in 14 of 17 patients by more than 50% after 8 weeks and 16 weeks of treatment	[263]
	Dietary supplementation with very long-chain n−3 fatty acids	No significant difference, the possibility of a placebo effect	[264]
	Vitamin C and E	Protective effects against AD	[266-268]
Food allergy	Consumption of highly processed foods during pregnancy	Food allergies in infants ↑	[270,271]
	Food additives and preservatives	Food allergies ↑	[272,273]
	Starting fish oil supplementation early in pregnancy and continuing during lactation	Allergic sensitization to food proteins in offspring ↓	[274]
	Maternal intake of vitamins A, C, and E together with food	Protective effect against FA in childhood	[275]
	Taking Vit. A, C, and E supplements	Not protective effect against FA	[276]

9.1 | Particulate matter, nanoparticles, nitrogen dioxide, and ozone

Particulate matter is a mixture of solid particles and liquid droplets generated by human activity. Besides, it is formed in the atmosphere through chemical reactions of gases such as sulfur dioxide, nitrogen oxides, and certain organic compounds often emitted from industrial processes, motor vehicle exhaust, diesel and coal combustion, house heating, and wildfires. All types of PM (PM0.1, <0.1 μm in diameter; PM 2.5, <2.5 μm in diameter; PM10, <10 μm in diameter) particles

behave like gases due to their small sizes and cause diseases, especially in the respiratory tract.[282] However, PM2.5 is considered to be the greatest problem, because it can diffuse deeper into the terminal bronchioles and alveoli.[283] It has been demonstrated *in vitro* that PM 2.5 can disrupt the epithelial barrier by degrading TJ proteins in the lower and upper airways, downregulating occludin and claudin-1 expressions, suppressing E-cadherin levels, decreasing transepithelial electric resistance, and increasing paracellular permeability[282,284-286] (Figure 3). Wildfires are a major source of ambient air PM2.5 in different studies and wildfire exposure has been associated with worsening asthma symptoms and increases in emergency room visits.[287] Moreover, short-term and long-term exposures to high levels PM2.5 can cause increased FoxP3 methylation, a key transcription factor in immune tolerance.[288,289] Furthermore, PM2.5 causes increased lysosomal membrane permeability, oxidative stress, and lipid peroxidation at low doses, while at high doses it causes necrosis in airway epithelial cells.[290] *In vivo* and *in vitro* studies have revealed that PM2.5 is also associated with skin diseases such as AD, skin allergies, and eczema by causing DNA damage, irreversible lipid peroxidation, protein carbonation, and loss of structural epidermal proteins such as cytokeratin, filaggrin, and E-cadherin in the skin epithelial barrier.[291-295] On the other hand, PM10 is also a significant contributor causing damage to airway epithelial cells. PM10 was reported to induce alveolar epithelial dysfunction by reducing occludin at the plasma membrane and dissociation of ZO-1 in human and primary rat alveolar epithelial cells.[296] In another recently published study, cellular DNA damage and aberrant gene expression patterns associated with PM10 were shown in the airways cells.[297] Furthermore, PM10 strongly stimulated messenger RNA expression and secretion of the pro-inflammatory cytokines IL-6 and CXCL1 in mouse airway epithelial cells and it induced the expression of IL-6, IL-8, and IL1B in human airway epithelial cells.[298] It must be noted that a link has been reported with PM 10 exposure not only to asthma but also to other inflammatory diseases. Exposure to airborne PM is associated with increases in multiple sclerosis in Stockholm, Sweden. Increased numbers of circulating myeloid DCs that express cytokines such as IL-1β, IL-6, and IL-23, which stimulate the development of Th17 cells, were reported in these patients.[286,296,299] Their findings were associated with an increase in $CCR6^+$ $CD4^+$ T cells with the migratory capacity to pass through the blood–brain barrier. These findings suggest that PM causes chronic respiratory diseases, especially asthma, and exacerbate existing ones. Although the harmful effects of ultrafine particles such as PM0.1 are less well known, in an animal model, it was demonstrated that PM0.1 caused increase of lysosomal membrane permeability, oxidative stress, and lipid peroxidation at low doses and it caused necrosis in airway epithelial cells at high doses.[290] It was also reported that PM0.1 induced autophagic cell death of human neuronal cells.[300]

In recent years, nanoparticles (NPs), organic or inorganic, smaller than 100 nm, are increasingly used in various industries and contribute significantly to air pollution. NPs can produce quantum effects by confining their electrons and entering the human body through inhalation, ingestion, skin, or injection. Inhaled NPs pass through the pores in the alveolar-capillary membrane, enter the interstitium and even into the systemic circulation via the blood and lymphatics.[301,302] Carbon nanotubes directly stimulate epithelial cells, macrophages, and fibroblasts to produce pro-inflammatory and profibrotic mediators, causing increased collagen production and deposition in the extracellular matrix, leading to fibrosis.[303] Titanium dioxide (TiO_2) and silicon (SiO_2), the most ubiquitous NPs, induce unbalanced overexpression of immature neurotrophins and lead to apoptotic death of lung epithelial cells.[304] Moreover, with their high lipid affinity, NPs coat and disrupt phospholipid membranes, interfere with lipid-rich structures in the pulmonary circulation such as surfactants and endothelial cell junctions, and even destabilize lysosomal membranes triggering cell death.[305] Although initial studies reported that TiO_2 did not penetrate the stratum corneum, a recent study indicated that the cubic and about 25nm size sample was cytotoxic to human epidermal keratinocytes.[306] Similarly, acicular TiO_2-NP is shown to interact with human epidermal keratinocytes, induce secretion of pro-inflammatory cytokines and disrupt the skin barrier by altering cell junctions.[307] The intestinal toxicity of NPs is less known, cationic liposome NPs containing ZnO, silver, aluminum, and nickel, as well as TiO_2 and SiO_2 NPs, accumulate across the intestinal epithelial barrier and then translocate by endocytosis by the M-cell, or by disrupting the integrity of the cell membrane, or by phagocytosis by macrophages.[305,308] It has been shown *in vitro* that cellular uptake of Nickel Oxide-NPs causes cytotoxicity by disrupting the mitochondrial and lysosomal functions and TiO_2-NPs lead to increased paracellular permeability in human intestinal epithelium[309,310] (Figure 3).

Nitrogen dioxide (NO_2) is a major component of air pollution, especially an important component of the traffic-related air pollution. However, due to the use of gas stoves, it is accepted as an important indoor pollutant as well as an outdoor pollutant.[80] Exposure to NO_2 is associated with an increased risk of developing respiratory diseases due to its deep penetration into the lungs. This effect is thought to be via epithelial barrier damage. In an *in vitro* study investigating the effect of NO_2 on airway epithelial defense functions; ciliary activity, mucociliary transport velocity, and epithelial permeability were significantly impaired in the NO_2 exposed group of fifty-two healthy rabbits.[311] In another animal model, it was suggested that after exposure to ≤1 ppm NO_2 level, active ion transport across the airway epithelium was significantly increased without change in paracellular pathways for diffusion, and NO_2 altered the cell membrane function.[312] A randomized controlled trial examining the effects of indoor NO_2 in asthmatic children demonstrated that increased NO_2 exposure was associated with a dose-related increase in risk of higher asthma severity score, wheeze, night symptoms, and rescue medication use.[313] NO_2 can cause epithelial barrier dysfunction in the upper as well as the lower airways. In an *in vivo* study evaluating the effects of 2 ppm NO_2 exposure on human nasal epithelium by electron microscopy, the luminal margin membranes of ciliary cells were ultrastructurally altered in six of seven nasal epithelial samples after NO_2 exposure.[314,315]

Ozone gas has a variable lifetime and occurs both in the upper and lower atmospheres, almost at ground level. Ground-level O_3 is

the main component of photochemical smog and is formed in the presence of sunlight by chemical reactions between oxides of nitrogen and volatile organic compounds emitted by motor vehicles, power plants, industrial boilers, refineries, and chemical plants. Even during colder months, O_3 can reach high levels and be carried long distances by wind and spread to rural areas.[316,317] Due to its poor water solubility, inhaled O_3 can penetrate deep into the lungs. Acute exposure can damage alveolar cells, bronchiolar epithelium, and capillary endothelium initially with cell stress, desquamation, followed by protein leakage, neutrophil, and macrophage influx, and production of IL-1α and IL-33 from epithelial and myeloid cells.[318-320] Ehile acute exposure caused airway inflammation and airway hyperresponsiveness, chronic inflammatory process presenting with collagen deposition in epithelial and subepithelial areas led to peribronchial fibrosis and emphysema.[318,321] Recent studies suggest that chronic O_3 exposure is responsible for bronchial hyperreactivity, asthma, asthma exacerbation, chronic obstructive pulmonary disease, and even pulmonary fibrosis and respiratory death[322] (Table 5).

9.2 | Detergents and emulsifiers

At the beginning of this century, the scarcity of oils used in soap production and the desire to find stronger cleaning agents led to the start of work to produce the first synthetic detergent. Within the last several decades, the use of detergents for laundry, dishwashing, household, or industrial area cleaning has tremendously increased, with a change in their formulation, including cosmetics and personal care products. The increase in the incidence of allergic diseases in the same period suggested that detergents may trigger the formation of allergic diseases by affecting the associated epithelial barriers, especially the skin and respiratory tract[9,323] (Figure 3). Surfactants, particularly sulfated anionic surfactants and commercial detergents, have proven to have direct detrimental effects on skin and bronchial epithelial barrier integrity, even in trace concentrations.[278,279] In a clinical trial, the insult of sodium lauryl sulfate, an anionic surfactant, to the stratum corneum was demonstrated by both increased transepidermal water loss (TEWL) and decreased stratum corneum hydration.[324,325] Recently, a study showed that detergents cause high TEWL in cleaning personnel due to reduced barrier function, related to the increased risk of work-related hand dermatitis.[326] Furthermore, it has been observed that with the increased need for hand cleaning during the COVID-19 pandemic, disinfectants worsen the disease in individuals with a previous history of AD or contact dermatitis and even also cause eczema in healthy individuals.[327,328] In addition, isothiazolinone derivatives used in water-based detergents also cause contact dermatitis by direct contact or airborne.[329,330]

The airway epithelial barrier is as sensitive as the skin barrier to detergents. Detergent residues on newly washed clothes and on the surface of the floor can be easily inhaled, and even at very low concentrations, they directly damage TJs and related molecules of the airways.[278] In the same study, RNA sequencing demonstrated an increase in cytokines such as IL-25, IL-33, and TSLP that initiate type 2 immunity, even in 50,000 times diluted commercial laundry detergent damaged epithelial tissue. As a result, as reported in different occupational studies, the development of asthma or exacerbation of respiratory symptoms in adults seems inevitable by inhaling sprays or vapors, namely aerosolized forms of detergents that are widely used in every field.[331,332]

Emulsifiers such as lecithin, carboxymethyl cellulose, and sorbitol monostearate, which are food additives, are frequently used to reduce the surface tension with a detergent-like effect, to maintain a homogeneous dispersion.[333,334] They are thickening the mucosal surface fluid, trapping commensal bacteria, avoiding a healthy interaction between the epithelium and commensals and alter the microbiota and disrupt mucus–bacterial interactions in mouse models to induce intestinal inflammation.[333,335] Dishwasher detergent residue left on rinsed clean dishes when used for food consumption are being currently studied to determine if they are damaging the esophageal or gastrointestinal epithelial barriers[15] (Table 5).

9.3 | Microplastics

Water-insoluble polymeric particles derived from petroleum are called microplastics (<5mm in size) and nanoplastics (1 nm-1μm in size). Due to their cost-effectiveness, small size, light, and compatible nature, these substances are used in many sectors. Secondary microplastics are formed when larger-sized 'macroplastics' found in nature are degraded into smaller-sized fragments by ultraviolet rays from the sun, waves, rain wind, and other decaying organisms. Humans are easily exposed to micro- and nanoplastics in daily life through contact, inhalation, and ingestion from water, soil, and air. These products can easily penetrate tissues and interact with cells and cellular structural molecules.[336,337] The nanoplastic protein interaction causes the proteins to fold, alters their secondary structure and denatures them, and can also interact with lipid bilayers to alter cell membranes.[338,339] In a study with 25 nm and 70 nm nanoplastics, they were shown to induce inflammatory gene transcription, upregulate pro-inflammatory cytokines, and alter the expression of proteins connected with cell cycle and pro-apoptosis.[340] Of the nanoplastic varieties, nano polystyrene induces metabolic changes related to autophagy and endoplasmic reticulum stress, while nano ZnO causes oxidative stress-induced cell death due to mitochondrial dysfunction.[341] Occupational studies have shown that workers in different fields exposed to plastics and their products develop increased respiratory symptoms, decreased lung capacity, interstitial fibrosis, allergic alveolitis, and granulomatous lesions.[336]

The amount of plastic produced per year exceeds 100 million tons and increasing plastic waste load in the seas and oceans poses a threat to the environment and the health of humans and affected animals. Today, increased levels of plastic are detected in fish and sea creatures. Microplastics have been detected even in drinking water, foods such as mussels, shrimp, fish, salt, sugar, honey, and

TABLE 5 Environmental substances affecting the epithelial barriers

Environmental factors	Mechanism	Ref.
PM	Increase Fox P3 methylation (*especially PM2.5)*	[282,284-286,288-298,300]
	Degrade TJ proteins, downregulate occludin and claudin−1 expression, suppress E-cadherin levels (especially PM 2.5 &PM10)	
	Increase paracellular permeability (*especially PM 2.5)*	
	Increase lysosomal membrane permeability, oxidative stress, and lipid peroxidation *(especially PM0.1 & PM 2.5)*	
	Cause DNA damage, protein carbonation (*especially PM 2.5 & PM10)*	
	Cause loss of structural epidermal proteins such as cytokeratin, filaggrin (*especially PM2.5)*	
	Reduce occluding, dissociate ZO−1, stimulate mRNA expression, and secretion of pro-inflammatory cytokines (*especially PM10)*	
	Cause necrosis in airway epithelial cells, at high doses cause autophagic cell death of human neuronal cells (*especially PM0.1)*	
Nanoparticles	Stimulate collagen production and deposition in the extracellular matrix, lead to Fibrosis	[303-305]
	Overexpress of immature neurotrophins and lead to apoptotic death	
	Disrupt phospholipid membranes	
	Destabilize lysosomal membranes and trigger cell death	
	Alter cell junctions and disrupt cell membrane integrity	
	Disrupt the mitochondrial and lysosomal functions and increase paracellular Permeability	
Nitrogen dioxide	Damages upper and lower airway epithelial barrier	[311-314]
	Altered cell membrane functions	
	Dose-related increase in asthma risk due to deep penetration into lungs	
Ozone	Have high penetration in airways	[318-322]
	Lead to cell stress, desquamation, and cell death with oxidative stress	
	Induce IL−1α and IL−33 production from epithelial and myeloid cells	
	Increase protein leakage, neutrophil, and macrophage influx	
	Induce collagen deposition in epithelial and subepithelial areas and cause peri bronchial fibrosis in chronic process	
Detergents and emulsifiers	Have direct detrimental effects on epithelial barrier integrity	[229,230,264,266-276]
	Increase trans epidermal water loss and decrease stratum corneum hydration	
	Damage TJs and related molecules of the airways	
	Induce secreting IL−25, IL−33 and TSLP	
	Alter the microbiota and disrupt mucus−bacterial interactions in intestinal epithelial barrier	
Microplastic	Penetrate tissues and interact with cellular structural molecules	336-341
	Cause the proteins to fold, alter structure, and denaturate	
	Interact lipid bilayers to alter cell membranes	
	Induce inflammatory gene transcription, pro-inflammatory cytokines, and pro-apoptotic protein expression	
	Cause endoplasmic reticulum, mitochondrial dysfunction and induce cell death by oxidative stress	

(Continues)

TABLE 5 (Continued)

Environmental factors	Mechanism	Ref.
Tobacco and e-cigarettes	Disrupt epithelial cell barrier integrity	[344-350]
	Cause rapid lipid peroxidation	
	Increase alveolar epithelial permeability	
	Impair alveolar clearance	
	Alter apoptotic cell recognition receptors and cytokine secretion pathways	
	Cause epithelial cell death and dysfunction of macrophages	
Protease allergens	Increase the permeability of epithelium	[351-359]
	Damage the tight junction molecules ZO–1, occludin, and E-cadherin	
	Stimulate Th2 differentiation and IL–4 and IL–13 secretion	
	Increase the formation of collagen under the epithelial tissue and induce airway Remodeling	

beer. They have a high absorption capacity in the gastrointestinal tract, and the effects of microplastics have been shown both *in vitro* and *in vivo*.[337] In a mouse model, polystyrene microplastics have been shown to reduce intestinal mucus secretion and cause damage the intestinal barrier function[342] (Figure 3). Different sizes of spherical fluorescent polystyrene particles (1, 4, and 10 μm) were used in the culture media, and it was observed that the one μm plastic particle is the most cytotoxic due to its high surface volume ratio. The study concluded that the smallest particles (<1.5 μm) might penetrate the gastrointestinal epithelial barrier[343] (Table 5).

9.4 | Tobacco and e-cigarettes

Tobacco, one of the most common toxic substances in the environment with its content of approximately 5,000 chemicals, causes toxicity especially to the respiratory system. *In vitro* studies have shown that tobacco causes rapid lipid peroxidation in the rat tracheal epithelium and is associated with alveolar epithelial damage in guinea pigs.[344,345] In lung transplantation studies, impaired alveolar clearance in the lungs of a smoker or ex-smoker donor, expressed *ex vivo*, indicated alveolar epithelial damage and was associated with primary graft failure.[346,347] Even though e-cigarettes are marketed as alternatives to aid smoking cessation, there is not enough evidence to show that they help. Moreover, their safety is questionable as they contain a number of toxic chemicals such as benzene, ethanol, iron, aluminum, cadmium, tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, and formaldehyde, in addition to their four main components: nicotine, propylene glycol, glycerol, and food flavorings.[348] An *in vitro* study showed that sub-chronic exposure to e-cigarette aerosols disrupt human bronchial epithelial cell barrier integrity similar to cigarette smoke.[349] Furthermore, flavorings in tobacco products have been shown to cause airway epithelial cell death, apoptosis, and dysfunction of macrophages through altering apoptotic cell recognition receptors and bronchial epithelial cell cytokine secretion pathways[350] (Table 5).

9.5 | Airborne pollens

The protease activity of allergens such as molds, pollens, cockroaches, HDMs, and food contributes to epithelial integrity disruption and initiates the innate immune response[351,352] (Figure 3). Group 1 HDM allergens called Der p 1, Der f 1, Blo t 1, Eur m 1, and Der m 1 have cysteine protease properties that increase the permeability of the epithelium.[353] Stimulation with the cockroach Per a 10 allergen with serine protease activity was found to be detrimental on the TJ molecules zonula occludens-1 (ZO-1) and occludin and stimulated Th2 differentiation in the airway epithelium.[354] It has been found that Der p 3, Der p 6, and Der p 9 destroy ZO-1, occludin, and E-cadherin in lung epithelial cells with trypsin, chymotrypsin, and collagenolytic-like protease effects and are effective in airway remodeling.[355] Asp f 5, an allergen with metalloprotease properties from *Aspergillus fumigatus*, has been shown to increase IL-4 and IL-13 levels in mouse lung tissue and play a role in airway remodeling by changing the amount of collagen under the lung epithelial tissue.[356] Besides, it has been reported that food cysteine proteases impair intestinal barrier function and increase intestinal permeability with mechanisms similar to inhalant allergens in both mice and *in vitro* studies.[357] To conclude, protease active allergens facilitate the presentation of allergens, induce an allergic inflammatory response, thus facilitating sensitivity to secondary allergens[358,359] (Table 5).

10 | EPITHELIAL BARRIER HYPOTHESIS AND ALLERGIC DISEASES

The increase in understanding the underlying multiple and complex immune mechanisms, additional to the development of novel detailed diagnostic techniques and ease of access to comparable data have led to the proposal of several hypotheses explaining the complexity of chronic conditions, including allergic disorders. Such hypotheses can provide a framework toward understanding the relations

between the immune system, allergens, environmental triggers and epigenetics, signs and symptoms of diseases, and demographics in the field of allergy. Among these '*Hygiene hypotheses*' has initially focused on explaining the increase in allergic disorders with decreased incidence of infections in westernized countries, which is mainly based upon epidemiological data. With the evolution of our understanding about innate and adaptive arms of the immune system and its regulation, the impacts of microbiome, exposome, genome, and epigenome, '*atopic march*' have found their illustrative backbones.[360] Precise definition of endotypes, phenotypes, and even theratypes in addition to several biomarkers has advanced existing paradigms into tailored novel approaches including therapies.[361]

Skin, in addition to respiratory and gastrointestinal mucosa, is the contact surface of the host with the external environment lined by epithelial barriers (epidermal barrier and epithelial mucosa). Functional derangement of the epithelial barrier, which acts as a first-line physical defense and active site of the immune response, has been regarded as a factor responsible for the development of many diseases, including allergies and autoimmune diseases. Recently described '*Epithelial barrier hypothesis*' emphasizes that environmental exposure to substances that are mainly toxic and hazardous have deleterious impacts onto these outermost access points, the barriers of the skin, airways, and gastrointestinal mucosa.[12]

11 | REGULATION OF THE EPITHELIAL BARRIERS

Epithelial cells play critical roles in the maintenance of homeostasis through a wide range of physiologic functions. There is a complex

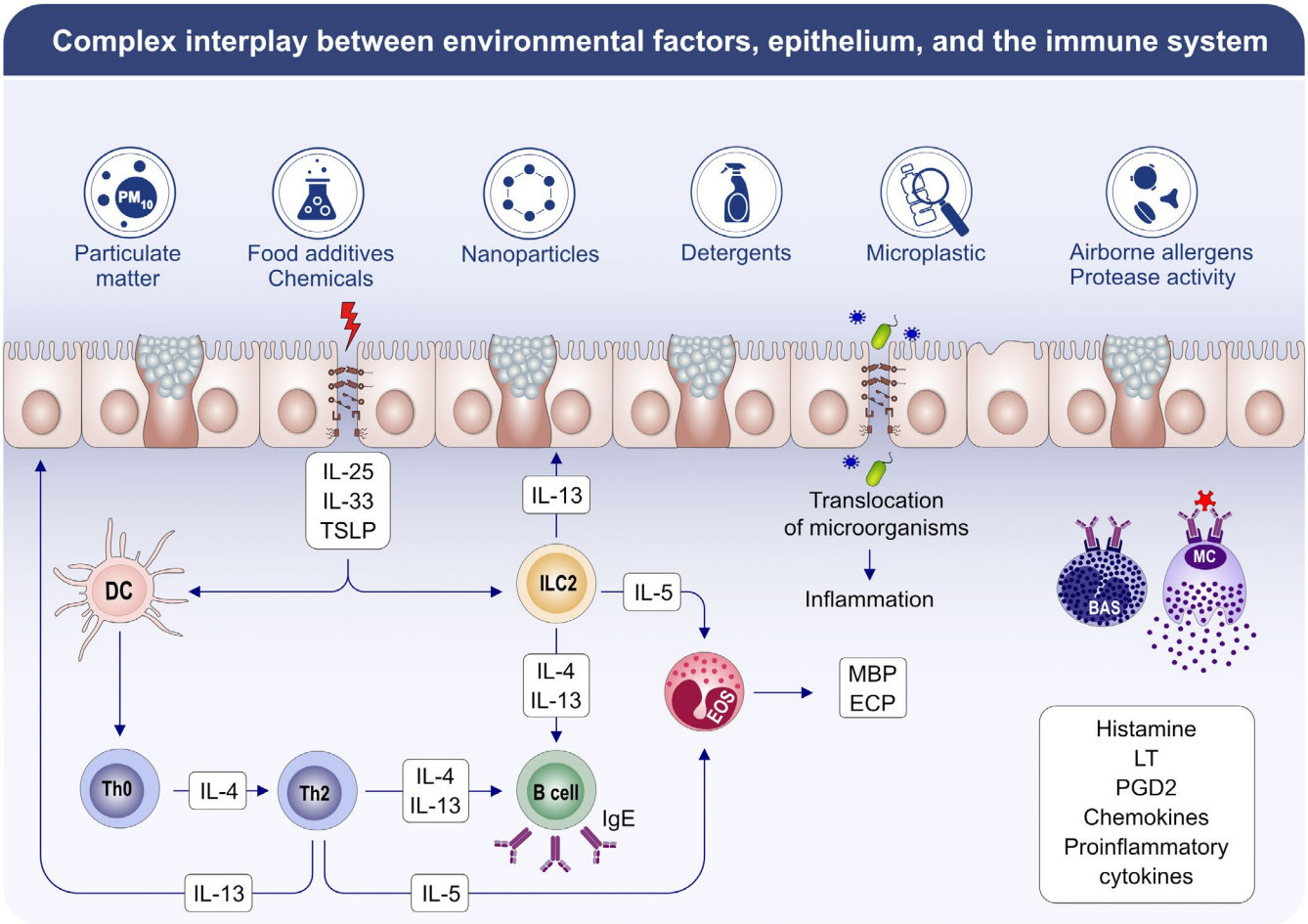

FIGURE 5 Complex interplay between environmental factors, epithelium, and the immune system. Epithelial cells can secrete IL-25, IL-33, and TSLP in response to various stimuli from the environment resulting in a Th2 type shift of the immune response. These cytokines activate dendritic cells and group 2 innate lymphoid cells). ILC2s share many functional similarities with Th2 cells such as the production of IL-5, and IL-13 as well as other effector molecules that enhance the Th2 immune response. Eosinophils, basophils, and mast cells are attracted to the area and degranulate. Dysregulation of the epithelial barrier has been hypothesized to cause a leaky epithelium, which causes dysbiosis of the microbial content, decrease of commensals and increase of opportunistic pathogens. The translocation of microorganisms to interepithelial and subepithelial compartments induces inflammation. IL: interleukin, TSLP: thymic stromal lymphopoietin, DC: dendritic cell, ILC2: innate lymphoid cell-2, EOS: eosinophil, BAS: basophil, MC: mast cell, MBP: major basic protein, ECP: eosinophilic cationic protein, LT: leukotriens, PGD2: Prostaglandin D2, Th0: naive T cell, Th2: T helper 2, Ig E: immunoglobulin E

interplay between environmental factors, epithelium, and the immune system. Epithelial cells can secrete IL-25, IL-33, and TSLP in response to several stimuli, leading to a skewing of the immune response into Th2 type.[362] These cytokines activate DCs and group 2 innate lymphoid cells (ILC2). ILC2s share many functional similarities with Th2 cells, such as the production of IL-4, IL-5, IL-9, and IL-13 as well as other effector molecules potentiating the Th2 immune response.[363] It has been reported that ILC2s disrupt epithelial barrier integrity by IL-13[364] (Figure 5).

It has been postulated that derangement of the epithelial barrier causes a leaky epithelium that results in dysbiosis of microbial content, including commensals and opportunistic pathogens and translocation of this content into interepithelial and subepithelial compartments, which induces micro-inflammation.[12] It is well-accepted that the microbiome plays a crucial role in the shaping of the immune system and tissue homeostasis.

12 | EPITHELIAL BARRIER DAMAGE AND THE LINK BETWEEN ALLERGIC DISEASES

There are several similarities and differences in the structure and function of epithelial barriers between the skin, the gastrointestinal system, and the respiratory tract.[15] A disruption in the epithelial barrier could be a common pathway in the development of multiple allergic conditions.[365,366] The interaction between the epithelium and immune cells in addition to crosstalk with microbiota and environmental factors enroll in the pathogenesis of atopic disorders, including AD, AR, asthma, CRS as well as eosinophilic esophagitis and FA[367,368] (Table 2). Dysbiosis in the gut microbiota has effects on the immunity of distal organs, such as the lungs, in addition to modulating the immune responses of the gastrointestinal tract itself.[369] Increasing evidence has shown the link between gut-lung axis, which suggests that the host-microbe interactions exist beyond the local environment to distal tissues.[370]

In the skin, the epidermal barrier is composed of the stratum corneum and TJs. Change in the composition and dysfunction of lipids (ceramides, free fatty acids, and cholesterol) and structural proteins (filaggrin), elevated skin pH, and loss of microbiome diversity all may lead to impairment of epidermal barrier as seen in patients with AD.[285,371] While the transmembrane proteins including claudins, occludins and adhesion molecules compromising the TJs, their barrier functions are weakened by altered lipid and profilaggrin processing. Filaggrin is a structural protein that is essential for the regulation of epidermal homeostasis. Loss-of-function mutations in filaggrin have been proposed to cause epithelial barrier defects, which reduces epidermal defense against allergens, microorganisms, and other environmental insults and plays a role in the development of AD, as well as bearing risk for FA, AR, and asthma. This defect results in a skewing of immune response into Th2 type immune response with resultant chronic inflammation of the skin.[372] There is reduced expression of the TJ proteins claudin-1 and claudin-23 in patients with AD.[127] The importance of the epithelial barrier can be marked even in the early days of life. It has been revealed that the development of allergy to several foods in the absence of oral feeding may be linked to inflamed and disrupted epithelial barrier in infants with severe AD.[373]

Also, airway epithelial cells not only comprise a physical barrier but also play key roles in immune, inflammatory, repair, and remodeling responses upon encounters with triggers, including inhaled allergens, pathogens, PMs, and chemicals. Additional to mucociliary clearance, epithelial cells can produce antimicrobial peptides, several chemokines, and cytokines that recruit and activate other effector cells and sustain clearance of pathogenic insults.[374] TJs in the airway epithelium have been extensively studied in healthy individuals. Studies have revealed that the airway epithelium in asthma and upper airway diseases is dysfunctional due to disturbed TJ formation.[375] In asthmatic children, expression of claudin-1, occludin, and ZO-1 proteins was significantly reduced compared to non-asthmatic children.[376] Claudin-18 is required for the airway epithelial permeability barrier. Loss of claudin-18 was sufficient to impair epithelial barrier function in human bronchial epithelial cells. IL-13 decreases claudin-18 expression in epithelial cells. Claudin-18 mRNA levels were found to be lower in asthmatics than in healthy controls.[377] It has also been reported that TJ protein expressions were decreased in patients with CRS with nasal polyps, which highlights the role of the defective epithelial barrier in the disease pathogenesis.[124]

Airway epithelium acts as an initial defense barrier to inhaled particulates, including allergens. The protease activity of several allergens may contribute to sensitization by disrupting the integrity of the airway epithelial barrier.[378] It has been understood that the common allergens such as HDMs and several pollens have cysteine and serine proteases that can disrupt the epithelial barrier. Similarly, molds including aspergillus and penicillium exert serine protease activity. Additional insults to these activities have dampened the immune response. A disrupted barrier is a site for dysbiosis in the airway epithelium as well. Change in the content of the microbiome also shapes the altered immune response. Infectious triggers have several impacts on airway epithelium. It is well known that human rhinovirus (HRV) infection is a trigger of asthma exacerbations. It has been reported that HRV increases inflammatory cytokine production, reduces IFN-β production, and plays a role in wound repair by causing defective repair response in the epithelial cells of asthmatic children.[379] Besides, it has been reported that low-dose chronic endotoxin or farm dust exposure has reduced epithelial cytokines that can activate DCs, protecting asthma development in mice models.[380] On the other hand, it has been suggested that chlorination products promote allergic sensitization by compromising the permeability or the immunoregulatory function of epithelial barriers.[381] In animal models of asthma, hypochlorite-induced asthma was linked to impairment of airway barrier to this irritant.[382] It has also been reported that laundry detergents at a very high dilution or detergent residue after rinsing have disruptive effects on the TJ barrier integrity in human bronchial epithelial cells.[278] Detailed discussions related to these are mentioned in this manuscript elsewhere.

The intestinal epithelium is the largest mucosal surface in contact with the external environment. The gastrointestinal epithelial barrier has to defend against the passage of foreign antigens, several microbes, and their toxins, while it has to act as a selective barrier to absorb and exchange essential dietary nutrients, water, and electrolytes.[383] Protein-protein networks that form desmosomes, adherence junctions, and TJs compromise the intestinal epithelial barrier.[383] Early studies have delineated the role of the gut epithelial barrier on the development of inflammatory bowel disease and celiac disease.[384,385] The number of diseases related to the leaky gut has increased within the last few years and now include diseases such as type 1 diabetes, irritable bowel syndrome, and colorectal cancer.[386] It has been proposed that the breakdown of oral tolerance to food could also be associated with a downregulated intestinal barrier function. In several experimental animal models and human clinical trials, the association between food allergy and defects in the intestinal barrier function has been emphasized.[370,386-388] There is also evidence that an abnormal epithelial barrier is also present in patients with eosinophilic esophagitis.[368]

13 | CONCLUSION

The current exposome concept is a promising model to improve the uncertain data on the impact of environmental factors on the development of allergic diseases. External exposome has vital effects on human health related to climate change, air pollution, change and loss of biodiversity, change in dietary habits, and dysbiosis. These external factors that cause damage to the epithelium, and the disruption in the epithelial barrier constitutes a common pathway in the development of multiple allergic conditions. Moreover, the interaction between the epithelium and immune cells in addition to crosstalk with microbiota and environmental factors take part in the pathogenesis of atopic disorders including AD, AR, asthma, and FA. As a result, an increase in the incidence of allergic diseases secondary to external changes is expected in the medium and long term.

In this scenario, the task of scientific society is to give priority to external exposome research and establish the extensive usage of the exposome-based approach for allergic diseases and asthma. The relationship between environmental exposure and allergic diseases should be assessed in longitudinal cohort studies with standardized exposure models. It is essential to understand the risk factors and preventive measures to be taken against them in multifactorial, chronic diseases such as allergic conditions. There is no doubt that these developments will ultimately lead to better prevention strategies.

From a public health perspective, the education of the population and the emergence of governmental decisions to prevent climate change, changes and loss of biodiversity, unhealthy dietary habits, and exposure to environmental substances (detergents, airborne pollen, O_3, microplastics, nanoparticles, tobacco) are urgent measures to be considered throughout the world. In this global fight, mitigation measures can be undertaken to limit the harmful effects of all these threats. Furthermore, adaptation measures should be taken for the impacts of global warming.

These growing environmental threats need actions throughout the world with united forces of all capabilities. The unresponsiveness of governmental institutions, the resistance of the general population, lack of infrastructure, and poverty are all barriers to these efforts. Physicians have the most crucial role in promoting and activating the people on the health effects of environmental changes. A multidimensional approach involving all stakeholders will be necessary to overcome these environmental problems and develop a better future for our planet.

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AUTHOR CONTRIBUTION

ZCS, DM, and CA conceptualized the scope of the article, decided the headings and subheadings, and distributed the tasks among all authors. BOO wrote the part of the environmental substances. PC and SA wrote the part of the effects of climate change. MT and IY wrote the part of microbiome, BG and UO wrote the part of the nutritional factors. CO wrote the part of the epithelial barrier hypothesis. ZCS reviewed and combined the contributions from all authors. ZCS, MA, IO, YM, KN, CO, DM, and CA reviewed the article and figures, contributed different sections, and harmonized the final version.

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