Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?

Cezmi A. Akdis[1,2]

Abstract | There has been a steep increase in allergic and autoimmune diseases, reaching epidemic proportions and now affecting more than one billion people worldwide. These diseases are more common in industrialized countries, and their prevalence continues to rise in developing countries in parallel to urbanization and industrialization. Intact skin and mucosal barriers are crucial for the maintenance of tissue homeostasis as they protect host tissues from infections, environmental toxins, pollutants and allergens. A defective epithelial barrier has been demonstrated in allergic and autoimmune conditions such as asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, eosinophilic esophagitis, coeliac disease and inflammatory bowel disease. In addition, leakiness of the gut epithelium is also implicated in systemic autoimmune and metabolic conditions such as diabetes, obesity, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis and autoimmune hepatitis. Finally, distant inflammatory responses due to a 'leaky gut' and microbiome changes are suspected in Alzheimer disease, Parkinson disease, chronic depression and autism spectrum disorders. This article introduces an extended 'epithelial barrier hypothesis', which proposes that the increase in epithelial barrier-damaging agents linked to industrialization, urbanization and modern life underlies the rise in allergic, autoimmune and other chronic conditions. Furthermore, it discusses how the immune responses to dysbiotic microbiota that cross the damaged barrier may be involved in the development of these diseases.

Prior to the first description of hay fever (allergic rhinitis) in 1819 by John Bostock[1] and the first case series published in 1873 by Charles Blackley[2], there was little awareness of allergic diseases. At that time, an increase in grass pollen allergy, leading to hay fever, was recognized and later attributed to a high dose of allergen exposure due to the introduction of heavily pollinating grasses to make hay for dairy herds in Europe and due to increased ragweed growth on and around ploughed fields in the USA[3,4]. Representing the first wave of allergy epidemics, allergic rhinitis was already common in the late nineteenth century, and its prevalence continued to increase throughout the twentieth century. The incidence of allergic asthma and atopic dermatitis started to grow to epidemic proportions after the 1960s[3,5–8] (BOX 1). Since 2000, the prevalence of food allergy, eosinophilic esophagitis and drug-induced anaphylaxis has risen to epidemic proportions[9–11]. In addition, a substantial increase in autoimmune and metabolic conditions, such as diabetes, obesity, rheumatoid arthritis, multiple sclerosis and coeliac disease, has been recorded in industrialized countries since the 1960s and this trend is still continuing today[6,12,13]. During the same period, a significant increase in the prevalence of specific IgG and IgE against allergens was observed. Allergen-specific IgG antibodies were rarely detected in the 1970s and 1980s whereas, in 2018, milk-specific and egg-specific IgG antibodies were detected in almost all babies tested at the age of 1 year[14–17]. Currently, allergen-specific IgE prevalence (to any allergen) exceeds 50% of the population in Europe, Northern America and Australia (BOX 1).

The relatively recent onset of the epidemics of allergic, autoimmune and metabolic conditions leads to the question as to what might underlie their development. Genetic predisposition, lifestyle changes due to urbanization and modernization, increased rates of birth by caesarean delivery, increased early use of antibiotics, a westernized diet and obesity all play important roles[18]. A prominent hypothesis is the hygiene hypothesis, which proposes that certain microorganisms protect against

[1]*Swiss Institute of Allergy and Asthma Research (SIAF), University Zurich, Davos, Switzerland.*

[2]*Christine Kühne-Center for Allergy Research and Education, Davos, Switzerland.*

e-mail: akdisac@siaf.uzh.ch

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Box 1 | **The increase in allergy and asthma, specific antibody responses to environmental antigens, and immune responses to *Staphylococcus aureus***

The beginning of the allergy and asthma epidemic in the 1960s

- Increase in incidence of asthma observed in Finnish army recruits in 1961 (REF.[185])
- Increase in patients of all ages with asthma observed in the UK in the early 1960s[186]
- Almost 10-fold increase in hospital admissions of children with asthma in Australia, the UK, New Zealand, Canada and the USA between 1965 to 1980 (REF.[187])
- Asthma prevalence doubled in Swedish army recruits (particularly those from urban areas) between 1971 and 1981 (REF.[188])
- Low prevalence of allergic diseases in East Germany in 1989, but it became comparable to that in West Germany after reunification[189,190]

Increased IgG and IgE responses against allergens from the 1970s until present

- Very rare or no IgG antibody response in healthy individuals to environmental antigens in the 1970s and 1980s[14,17]
- Increase in allergen-specific IgE and IgG against environmental antigens observed after the 1970s[14,15,191,192]
- Increased allergen-specific IgE in frozen serum samples from 1998 as compared to samples from 1990, when analysed with the same assay[192]
- 49.8% of Norwegian children aged between 10 and 16 years had IgE sensitization against at least one environmental allergenic protein in 2015 (REF.[193])
- IgG against grass pollen, olive/ash pollen, birch pollen or house dust mites in most adults in 2017 (REF.[194])
- IgG antibodies against milk and egg in almost all babies at the age of 1 year in 2018 (REF.[16])
- IgE against one of the allergens in a broad panel of 64 aeroallergen components were detected in more than 90% of individuals with rhinitis, conjunctivitis and asthma in 2019 (REF.[195])

Increased IgE response to *S. aureus* after the 1980s

- No *S. aureus*-specific IgE detected in serum in individuals in a study conducted in 1985, if there is *S. aureus* colonization in the skin[143]
- Only 12% *S. aureus*-specific IgE in serum, if the patients have *S. aureus*-infected skin pustules in 1985 (REF.[143])
- In 2019, *S. aureus*-specific IgE was found in 39% of healthy controls, in 58% of patients with mild asthma and in 76% of patients with severe asthma[141]
- Currently, up to 90% of patients with atopic dermatitis and chronic rhinosinusitis have *S. aureus* colonization and *S. aureus*-specific IgE[89,196]

inflammatory diseases and that their loss, due to hygiene measures, results in an increase in allergy, asthma and autoimmunity[19–21]. Several extensions to the hygiene hypothesis have been proposed. One is the 'old friends' hypothesis', which suggests that some microbial species have co-evolved with humans and their surrounding animals and have protective functions[22] (BOX 2). Another is the biodiversity hypothesis, which proposes that an enriched human microbiome promotes immune balance and protects from allergy and other inflammatory disorders[23] (BOX 3). These three hypotheses focus on the role of the microbiota in conditions involving inappropriate immune responses and postulate that changes in the composition of the microbes we encounter are the main reason for disease development and pathology.

The first connections between microbiota, epithelial disruption and inflammatory disease were made in the late 1980s/early 1990s with the discovery of the link between a dysregulated gut barrier and inflammatory bowel disease and coeliac disease[24–28]. Later, defective epithelial barriers were demonstrated in affected organs in asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis (CRS) and eosinophilic oesophagitis[29–36].

Several therapeutic strategies have been developed that aim to prevent the loss of epithelial barrier integrity or to restore barrier dysfunction. These include the targeting of barrier-disrupting molecules[37], agents that function through the epigenetic regulation of barrier integrity[34,38], various types of healing modalities for defective barriers[30,39,40], and efforts in the prevention of eczema and food sensitization in birth cohorts such as the use of emollients and environmental exposure control measures to protect the skin barrier[41–43]. Moreover, efficient methods for the detection of barrier leakiness are being developed[44–47]. In 2017, Pothoven and Schleimer proposed the 'barrier hypothesis' for type 2 inflammatory diseases, which postulates that epithelial barrier dysfunction can result in allergy development[37].

Here, I extend the previously postulated hypotheses for the increase in the prevalence of allergic and autoimmune diseases by arguing that environmental changes caused by industrialization, urbanization and a westernized lifestyle affect the epithelial barrier of the skin, upper and lower airways, and gut mucosa. The development of leaky epithelial barriers then leads to microbial dysbiosis and the translocation of bacteria to interepithelial and subepithelial areas and the development of tissue microinflammation. As an extension of the barrier hypothesis proposed by Pothoven and Schleimer[37], I propose that these processes underlie not only the development of allergy and autoimmune conditions in barrier-damaged tissues but also a wide range of diseases in which immune responses to translocated bacteria have systemic effects.

Overall, conditions that are caused or exacerbated by damaged epithelia fall into three categories: (1) chronic conditions where local barrier defects cause pathology in affected skin and mucosal tissues such as in allergic diseases, inflammatory bowel disease and coeliac disease[24–43,45,48–58]; (2) chronic autoimmune and metabolic conditions in which leaky barriers and microbial dysbiosis in the gut contribute to disease onset and exacerbations such as in type 1 and type 2 diabetes, obesity, rheumatoid arthritis, multiple sclerosis, ankylosing spondylitis, hepatitis and systemic lupus erythematosus[47,59–76]; or (3) chronic conditions in which gut barrier defects and microbial translocation are associated with neurodegenerative or psychiatric conditions such as autism spectrum disorder, chronic depression, stress-related psychiatric disorders, Parkinson disease and Alzheimer disease[77–83], although causal relationships remain to be proven (TABLE 1).

This review first discusses the environmental changes over the past decades that have led to an increase in epithelial barrier insults. It then examines the involvement of epithelial cells in inflammatory responses and the regulation of epithelial barriers by immune responses as well as the involvement of the microbiota in this process. Finally, chronic diseases and their connection with epithelial barrier damage are reviewed.

Agents that cause epithelial barrier damage

A number of allergens, pathogens and environmental toxins can damage the epithelial barrier. These include allergens derived from dust mites, certain bacteria, fungi, viruses, and toxins contained in laundry, dishwashing

Type 2 inflammatory diseases
Allergic diseases, including asthma, allergic rhinitis, atopic dermatitis, chronic sinusitis with nasal polyps and helminth infections, which are characterized by type 2 immune responses.

Microbial dysbiosis
Microbial imbalance due to the gain or loss of microbial species and changes in the relative abundance.

Microinflammation
Describes a cell or a tissue that shows upregulated pro-inflammatory proteins detected by molecular analyses methods without systemic signs of inflammation.

Type 2 responses
Eosinophilic immune responses with a dominance of T helper 2 cells, type 2 innate lymphoid cells and cytokines such as IL-4, IL-5 and IL-13. These mainly take place in allergies and anti-helminth responses.

and household cleaning agents. Moreover, surfactants, enzymes and emulsifiers in processed food, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles and microplastics have been shown to damage the epithelial barrier[50–55,84–94] (TABLE 2). A large number of these substances are encountered by humans as a consequence of industrialization, urbanization and modernization. In particular, detergents used in laundry, dishwashing and household cleaning agents have been shown to be directly toxic for epithelial cells[84,85]. An increased usage of detergents in general and the addition of surfactants and proteolytic enzymes to commercial detergents has significantly increased the daily exposure of the public to epithelial barrier-damaging agents[95,96]. Numerous studies demonstrate epidemiological evidence for a connection between detergent exposure and the development of asthma and atopic disease[49,51–55,97–100].

The epithelial barrier damage caused by laundry detergents on human skin and bronchial epithelial cells was recently investigated in two studies[84,85]. Even at high dilutions, exposure to laundry detergents disrupted the epithelial barrier function of human skin and bronchial epithelial cells. An analysis of the transcriptome of bronchial epithelial cells exposed to 50,000-times diluted laundry detergent demonstrated an upregulation of genes involved in lipid metabolism, oxidative stress and cell survival, a downregulation of genes involved in cell adhesion, extracellular matrix organization and wound healing, and increased IL-33 expression. The two most commonly used surfactants in detergents, soaps, shampoos and many other cleaning products, that is, sodium dodecyl sulfate and sodium dodecylbenzenesulfonate, damage the tight junction (TJ) barrier of the lung and skin epithelium even at dilutions as high as 100,000 times in air–liquid interface cultures of human primary cells[84]. Post-rinse fluid collected from laundered towels and clothes have been shown to still contain active detergents and surfactants that can damage the epithelial barrier[85].

There is also accumulating evidence for a detrimental effect of emulsifiers in processed food[62,101], which have been shown to increase intestinal permeability even at low concentrations. Some of the approved food emulsifiers are surfactants that behave like detergents, and even trace amounts of these agents markedly increase bacterial translocation in mouse models[102]. All of these aforementioned substances may show synergistic effects even at low concentrations and chronic epithelial inflammation may further increase their effects.

Box 2 | **The hygiene hypothesis and the 'old friends' hypothesis**

The hygiene hypothesis was proposed in 1989 by Strachan for atopic dermatitis[19], then extended to allergic diseases, asthma[20,197,198] and autoimmune diseases[6,21]. It proposes that the incidence of allergic diseases is reduced by prenatal and childhood infections and that this protective effect is a result of a lack of hygiene practices within a household, leading to the increased transmission of infectious agents[6,21,197–199]. The protective effect of growing up on a farm in the development of asthma and allergies has received the most attention in this context and a significant number of studies have substantiated the early findings[20]. For example, it was found that children in Amish communities in the United States, where traditional dairy farming is practiced, are highly protected from asthma and allergies[200]. By contrast, Hutterites communities practice industrialized farming with extensive cleaning measures and have a significantly higher prevalence of asthma and allergies in children[200]. The Amish community uses homemade detergents and cleaning materials, made of washing soda (Na_2CO_3) as the main ingredient, and do not use any commercial cleaning products that may contain barrier-toxic surfactants and enzymes.

The hygiene hypothesis was reframed as the 'old friends/microbiota hypothesis' by Graham Rook in 2003, implicating non-pathogenic commensal microorganisms that have been present throughout human existence as the source of the immunomodulatory signals necessary to prevent immune-mediated chronic disorders[22].

Regulation of epithelial barriers

The epithelial barrier in the airways, gut and oesophagus consists of mucus, microbiota, surface liquids and junctional complexes between adjacent epithelial cells that comprise TJs and adherens junctions. Interepithelial junction molecules bind through homotypic and heterotypic interactions, establish cell–cell contact, and regulate the passage of molecules and small particles between cells[48]. In the skin, the stratum corneum forms a physically stronger barrier than mucosal membranes due to the expression of proteins such as the filament-forming filaggrin and the structural protein loricrin, its interacting partner involucrin and the profilaggrin-like protein hornerin[33,103]. Epithelial cells also play a role in innate immune responses by facilitating mucociliary clearance, producing antimicrobial peptides, cytokines and chemokines, activating intraepithelial and subepithelial cells, and recruiting these to tissues, thereby supporting a physical, chemical and immunological barrier[48,104,105].

The ability of the epithelium to control the balance of tissue damage and repair signals is essential to limit tissue injury and to control the resolution of inflammation during tissue repair. Studies performed on the gut, skin, oesophagus, bronchus and sinus have demonstrated that inflammatory responses can be induced as a consequence of an opening of the epithelial barrier, leading to a vicious cycle where the subepithelial inflammation itself continues to maintain damaged and open barriers[106] (FIG. 1). Closed epithelial TJs in the mucosal epithelium protect against the exposome, including allergens, pollutants, microbes, and their enzymes and toxins. Open epithelial TJs in the mucosa help to drain immune cells and pro-inflammatory molecules from the subepithelial inflammation but simultaneously allow the entrance of foreign substances to deeper tissues[106]. Overall, a series of pathological events takes place in chronic barrier disruption, including microbial dysbiosis and translocation, colonization, and an immune response to opportunistic pathogens as well as the development of chronic T cell responses, particularly type 2 responses in allergic diseases (FIG. 1).

Microbial dysbiosis and translocation. When the microbiota that is normally located on the surface of the epithelium translocates to the deeper layers beneath epithelial cells, it stimulates the immune system, contributing to inflammatory processes[70,107]. Microbial dysbiosis and transepithelial translocation of commensal microbes as well as further colonization by opportunistic pathogens is a hallmark of barrier-damaged tissues. Microbial translocation through the damaged gut mucosa has been reported in many diseases (TABLE 1).

Box 3 | **Biodiversity hypothesis and microbial dysbiosis**

The biodiversity hypothesis as proposed by Tari Haahtela states that the observed increase in allergies is due to a loss of symbiotic relationships with bacteria and dysbiosis caused by changes in the microbiome of the gut, skin and respiratory system[23]. Healthy microbiota on the surface of the mucosal barrier regulate many aspects of barrier homeostasis such as the modulation of barrier permeability, tight junction expression, angiogenesis, vascular permeability, local microinflammation and mucosal tolerance[157,201]. A reduced biodiversity and alterations in the composition of the gut and skin microbiota are associated with various inflammatory conditions, including asthma, allergic diseases, inflammatory bowel disease, diabetes and obesity[21,64,65,78,79,148,157,202]. Dysbiosis of the microbiota has been characterized by an under-representation of certain bacterial taxa that may produce immune regulatory and barrier healing factors such as short-chain fatty acids[202]. Young children at risk of developing allergies have been shown to suffer from gut microbiome dysbiosis with an overall reduced microbiome diversity[203].

As discussed above, this can lead to a vicious circle promoting both inflammation and barrier damage. The development of a chronic wound scenario is an important consequence of microbial translocation characterized by chronic local inflammation[108]. Primary epithelial cells originate from basal epithelial cells, which divide, differentiate and synthetize barrier molecules. Immune cells, such as dendritic cells, macrophages, innate lymphoid cells (ILCs) and T cells, and their cytokines in the chronic inflammatory environment are critical in the regeneration of stem cells and the epithelial barrier[109,110]. In this scenario, the reconstitution of a healthy epithelium is hampered because epithelial stem cells cannot build a strong barrier in an inflammatory microenvironment as has been shown for bronchial, sinus and skin epithelial stem cells[30,32,34,40]. Ex vivo experiments have shown that primary epithelial cells harvested from barrier leaky tissues cannot restore barrier integrity but instead contribute to the maintenance of the leaky barrier[30,32,34,40]. In Crohn's disease, a previously unknown protective mechanism that prevents the systemic dissemination of translocated bacteria was recently identified. The phenomenon is called 'creeping fat', where mesenteric adipose tissue with a rich pro-fibrotic and pro-adipogenic capacity migrates to sites of gut barrier dysfunction, leading to the development of an adipose tissue barrier trying to compensate for the deficiency of the epithelial barrier[111]. Leakiness of the epithelial barrier appears to be epigenetically encoded in barrier-defective tissues. In a mouse model of respiratory inflammation and in air–liquid interface cultures of primary human bronchial epithelial cells, it was shown that histone deacetylase inhibition can restore barrier integrity[34,38].

Regulation of epithelial barriers by local immune responses. A type 2 immune response is the essential default mechanism for defence against parasites and venoms. It opens the epithelial barrier and represents a very specific immune response to kill or expulse helminths, while simultaneously limiting tissue injury, maintaining tissue homeostasis, and contributing to tissue regeneration and fibrosis[112–114]. In 1932, Willem Löffler described eosinophilic pneumonia directed against helminths[115,116]. During their life cycle, fertilized eggs of helminths are ingested and hatch in the intestine and the larvae, which are ~0.5 mm in size, migrate to the lungs. However, helminths such as the roundworm ascaris grow to an adult size of 15–20 cm. In the lung, a strong type 2 expulsion response with eosinophilic pneumonia, together with opening of the epithelial barriers, ensures that the larvae are fully expulsed before they grow too big. They reach the gastrointestinal tract where the parasites can continue to grow. Similarly, an expulsion-like pathophysiology also occurs in the immune response to skin parasites such as scabies[117]. As a default immune response against skin parasites, it is likely that one of the main functions of a type 2 response in the skin is to expulse the 'danger' away from the deep tissues. This can result in severe itching, scratching and transepidermal drainage through and out of the inflamed skin, as observed in atopic dermatitis[117–119].

Conditions such as asthma, CRS and atopic dermatitis are characterized by systemic type 2 immune responses with activated, proliferating T helper 2 (T_H2) cells and activated type 2 ILCs, and the targeting of type 2 cytokines, such as IL-4, IL-5 and IL-13, has been successfully used for the treatment of these diseases[120–122]. Activated circulating immune cells that can migrate to various tissues have been found in the peripheral blood of patients with various chronic inflammatory diseases[123,124]. Circulating allergen-specific memory T cells in allergic diseases have been reported in the frequency of 1 in 10^4 to 10^5 T cells[125]. However, a type 2 immune response in individuals with allergies or asthma is not solely confined to allergen-specific T cells — it also includes a general skewing of the immune response towards the development of cutaneous lymphocyte-associated antigen (CLA^+)-expressing, skin-homing type 2 T cells, chemokine receptor T_H2 ($CRTH2^+$)-expressing T cells, type 2 ILCs, B cells and $CRTH2^+$ eosinophils[113,123,126,127]. The migration of activated T cells to other organs, where they then cause inflammation, has been demonstrated for food allergen-specific and skin-homing T cells that are sensitized in the gut and migrate into the skin, where they cause atopic dermatitis[124]. The extensive activation of T cells due to leaky epithelial barriers could be a mechanism responsible for the atopic march of allergic diseases in the sequential order of atopic dermatitis, food allergy, asthma and allergic rhinitis during childhood[128,129].

In addition to type 2 responses, type 1 responses below the mucosal surface are characterized by an opening of the epithelial barrier followed by the induction of apoptosis in epithelial cells, causing tissue injury. Interferon-γ (IFNγ), FAS, FAS-ligand, tumour necrosis factor (TNF) and TNF-like weak inducer of apoptosis (TWEAK) have been reported as molecules responsible for skin keratinocyte death in eczema, mucosal epithelial cell death, and shedding in asthma, CRS and colitis[130–132]. The potential direct barrier-opening effects of IL-17 and IL-22 have not been demonstrated so far[34]. By contrast, recent studies suggest a barrier-protecting role for T_H17-type and T_H22-type responses[133,134]. Interestingly, T_H17-type CD161-expressing innate immune cells were suggested to protect the gut barrier in an inflammation and

Type 1 responses
Cell-mediated immune responses, typically against intracellular bacteria and protozoa as observed in autoimmunity, delayed type hypersensitivity and tuberculosis. Typically involves $CD8^+$ T cells and T_H1 cells that produce IFNγ.

Table 1 | **Conditions in which epithelial barrier disruption has been linked to pathogenesis**

Disease	Level of evidence for epithelial barrier disruption and its role in disease	Refs
Epithelial barrier defect and microbial dysbiosis in directly affected tissues		
Atopic dermatitis	Studies in humans implicate filaggrin mutations and tight junction deficiency in disease and show that barrier-protecting agents may prevent disease	32,33,41–43,45
Asthma	Studies in humans correlate occupational asthma to contact with detergents and their constituents	30,34,48–55
Chronic rhinosinusitis	Biopsy samples of sinus tissues in humans and air–liquid interface cultures show defects in barrier integrity in sinus mucosa	31
Allergic rhinitis	Studies in nasal biopsy samples of humans demonstrate barrier defects in allergic rhinitis; occupational rhinitis is frequently observed in individuals working as domestic cleaners, and the incidence of rhinitis was found to correlate with exposure to household or professional cleaning agents	35,38,49,54
Eosinophilic oesophagitis	Biopsy samples of affected oesophageal tissues in individuals with eosinophilic esophagitis showed decreased expression of filaggrin, claudin, occludin and desmoglein	36,56
Inflammatory bowel disease	Biopsy samples of affected tissues demonstrated a decreased expression of genes encoding proteins that are involved in maintaining barrier integrity; the expression of barrier-related genes was restored after treatment with TNF-specific monoclonal antibody treatment; multiple studies in humans and animal models examined the molecular and cellular mechanisms of gut barrier disruption	27,57,110
Coeliac disease	Multiple studies in humans showed that larazotide, a drug that targets zonulin, has beneficial effects when given as a supplement to a gluten-free diet	26,58,182,183
Autoimmune and metabolic diseases linked to gut barrier defects and microbial dysbiosis		
Diabetes	Clinical evidence shows that intestinal permeability precedes the onset of type 1 diabetes; zonulin and insulin resistance linked to intestinal barrier defect were found to play a role in this process; gut microbial dysbiosis and breaching of intestinal barriers and/or tight junctions have been linked to the development of insulin resistance in type 2 diabetes; in mouse models, a disturbance of gut barrier integrity was shown to induce islet cell-reactive T cell-mediated autoimmunity	59–63
Obesity	Clinical evidence shows that changes in epithelial barrier function, microbial dysbiosis and dysregulated inflammation can affect the regulation of body weight and glucose homeostasis	64,65
Non-alcoholic steatohepatitis	Clinical evidence and animal models show that a disruption of the intestinal epithelial and vascular barrier and gut microbial dysbiosis are early events in the pathogenesis of non-alcoholic steatohepatitis	66,67
Autoimmune hepatitis	Clinical evidence shows that individuals with autoimmune hepatitis have increased intestinal permeability with microbial dysbiosis and bacterial translocation, the level of which correlated with the severity of disease; this process also explains the link between autoimmune hepatitis and coeliac disease	66,68,69,166
Liver cirrhosis	Increased local and systemic inflammation can render the gut more permeable and allow the translocation of bacteria, bacterial products and fragments into the portal circulation, perpetuating an abnormal local and systemic inflammatory response; both leaky gut and bacterial dysbiosis are involved in the development of liver cirrhosis in a vicious circle	66,70,71
Rheumatoid arthritis	Increased levels of serum zonulin as well as a leaky intestinal barrier, microbial dysbiosis and inflammation are observed in patients with rheumatoid arthritis; restoration of the intestinal barrier using butyrate, a cannabinoid type 1 receptor agonist, or treatment with the zonulin antagonist larazotide acetate inhibited the development of arthritis in mouse models of rheumatoid arthritis	47
Multiple sclerosis	Altered biomarkers of intestinal barrier leakiness correlated with disease severity in patients with multiple sclerosis; high levels of zonulin correlated with rapid disease progression and blood–brain barrier breakdown in patients with progressive multiple sclerosis	72,73
Systemic lupus erythematosus	Gut barrier defects linked to microbial dysbiosis have been observed in patients and in mouse models of systemic lupus erythematosus	74,76
Ankylosing spondylitis	Patients with ankylosing spondylitis have altered gut epithelial and vascular barriers, microbial dysbiosis, and increased zonulin concentrations in the blood	75
Chronic neuropsychiatric conditions linked to gut barrier defect and microbial dysbiosis		
Autism spectrum disorders	Post-mortem histopathology studies show reduced tight junction barriers in individuals with autism spectrum disorders	77
Parkinson disease	Intestinal biopsy samples from individuals with Parkinson disease show barrier defects and increased concentrations of zonulin in the blood and faeces	78–80
Alzheimer disease	Enteric inflammation, barrier defects and microbial dysbiosis are observed in individuals with Alzheimer disease	79,81
Stress-related psychiatric disorders	Evidence that acute stress can induce gut barrier disruption in animal models; microbial dysbiosis and translocation are frequently observed in individuals suffering from stress-related psychiatric disorders	82
Chronic depression	Patients with chronic depression often show microbial dysbiosis, bacterial translocation in the gut and an immune response to commensals	83

Table 2 | **Epithelial barrier-damaging substances introduced by industrialization and urbanization that are linked with chronic inflammatory conditions**

Condition associated with damaged epithelial barrier	Substance	Evidence	Refs
Occupational asthma (employees in the detergent industry)	Cellulase and lipase enzymes	Allergic sensitization to enzymes in patients	53
Occupational asthma (employees in the detergent industry)	Amylase	Allergic and non-allergen-specific bronchial hyperreactivity in patients	52
Occupational asthma and chronic bronchitis (individuals working as domestic cleaners)	Bleach and other irritants	Case–control study	99
Occupational asthma (employees in modern detergent factory)	Different enzymes in laundry detergents	Investigation of 342 workers showed upper respiratory or chest symptoms in 19% and 16% of the workers, respectively	51
Asthma and rhinitis	*Bacillus subtilis* enzyme	Allergic and direct tissue-destructive activity observed in employees of detergent factory	54,98
Asthma	Different cleaning products	Evidence laid out in consensus document of the EAACI	97
Asthma	Medical disinfectants	4,102 nurses were included in the study; poor asthma control was observed in nurses exposed to medical disinfectants	55,97
Asthma	Proteases of *Alternaria alternata*	Air–liquid interface cultures from patients with asthma show increased barrier disruption	93
Chronic rhinosinusitis	*Staphylococcus aureus*	Human sinus biopsy explant cultures	184
Atopic dermatitis	*S. aureus*	Human skin biopsies	89

EAACI, European Academy of Allergy and Clinical Immunology.

ageing model in rhesus monkeys[133]. Here, the production of IL-17 and IL-22 by CD161$^+$ T cell subsets and natural killer cells was impaired, whereas IFNγ production and gut permeability were increased. As additional mechanisms in barrier disruption, inflammasome activation and the response to severe cellular stress, such as burn injury, cause barrier leakiness, microbial dysbiosis and bacterial traslocation[76,135].

Immune response to the dysbiotic microbiome and opportunistic pathogens. An important feature of chronic mucosal inflammation is the development of an immune response towards newly colonizing facultative pathogens. This is typically an expulsion response mediated by a type 2 inflammatory response, as discussed above, but can also be a mixed response including the inflammatory components of type 1 and type 17 responses, depending on local and systemic factors[136]. It has been demonstrated that both type 1 and type 2 inflammatory processes can occur beneath the epithelium and lead to an opening of the TJ barrier[31,106]. It is important to emphasize that most mouse models of mucosal inflammation, such as asthma, rhinitis and colitis, are created by using a barrier-damaging agent such as papain, cholera toxin, lipopolysaccharide, dextran sodium sulphate or oxazolone[137–139].

A typical example of an opportunistic pathogen that induces a type 2 response in allergic inflammatory tissues is *Staphylococcus aureus*, which is the most abundant bacterium that colonizes barrier-damaged tissues in the skin and upper respiratory mucosa. A breach of the epithelial barrier by *S. aureus* has been associated with asthma, CRS and atopic dermatitis, and a high prevalence of IgE antibodies specific to *S. aureus* antigens correlates with severity and disease exacerbation in the same patients[140–144] (BOX 1). *S. aureus* colonization further compromises the mucosal barrier if the epithelium has already been disturbed. As discussed above, and similar to the default parasite larvae expulsion response, type 2 responses may also result in the expulsion of microbes that translocate to subepithelial tissues. However, translocated bacteria cannot easily be expulsed and the barrier cannot be closed in this type of chronic mucosal inflammation, likely because signals from commensal microbes and newly colonizing facultative pathogens are too weak to stimulate an appropriate anti-bacterial response followed by full tissue healing. In addition, a type 2 response typically does not involve a neutralizing immune response against microbes, and therefore it is more likely to lead to chronicity rather than to elimination of the microbe.

In addition to *S. aureus*, certain facultative pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, have also been associated with the development of asthma[89,145,146]. An overgrowth of such facultative pathogens also leads to a decrease in the local biodiversity of the microbiome, which may contribute to the development of allergic diseases as postulated by the hygiene hypothesis. Interestingly, it was shown that children with asthma exhibit an aberrant immune response to opportunistic pathogens before they develop asthma. At this point, T cells can be detected in blood and have been shown to produce IL-5, IL-17 and IL-10 in response to experimental incubation with *H. influenzae*, *M. catarrhalis* and *S. pneumonia* as well as with commensal bacteria[147,148]. Segmental filamentous bacteria can induce T_H17 cell responses[149], which play a role in controlling bacterial invasion into deeper tissues; on the other hand, these immune responses can lead to the development of autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis[148].

Inflammasome
Multi-protein complexes that activate caspase 1 to induce the processing of pro-IL-1β and pro-IL-18, which can induce cell death.

Type 17 responses
IL-17-dominated immune response to extracellular bacteria and fungi, observed in autoimmune diseases such as psoriasis.

Chronic diseases linked to barrier damage

The mechanisms of damage and regulation of the epithelial barrier and its link to chronic diseases have been an exciting research focus for several decades. A significant number of chronic non-communicable diseases have been reported to include epithelial barrier defects and microbial dysbiosis in their pathogenesis. These can be classified as conditions due to direct inflammation in the affected tissues, autoimmune and metabolic diseases associated with airway or gut barrier defects, or neuropsychiatric diseases linked to microbial dysbiosis and barrier leakiness in the gut (TABLE 1).

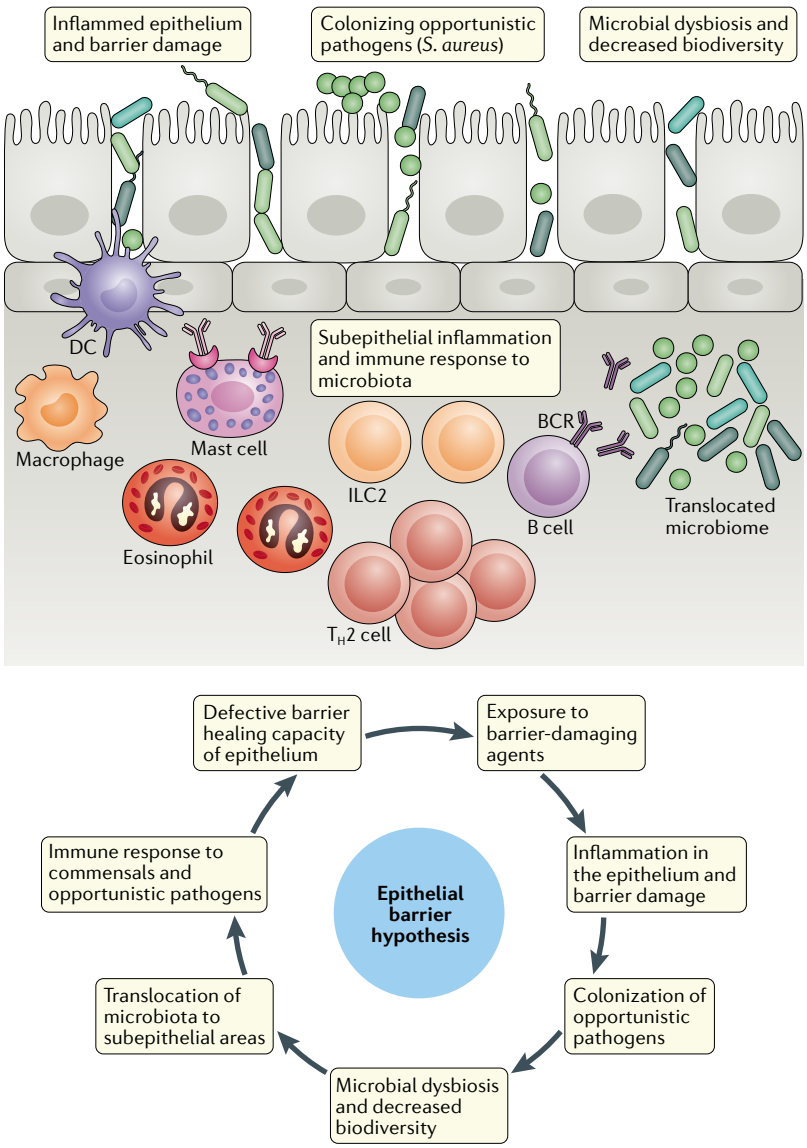

Fig. 1 | **Exposure to barrier-damaging agents or genetic deficiency in barrier molecules cause the colonization of opportunistic pathogens and epithelial inflammation.** Microbial dysbiosis and the translocation of commensals and opportunistic pathogens across epithelial barriers is typically followed by a type 2 immune response, characterized by a predominance of T helper 2 (T_H2) cells, type 2 innate lymphoid cells (ILC2s) and eosinophils. Mast cells, macrophages and antibody-producing B cells can also be involved in this response. The epithelium cannot fully repair and close the barrier, instigating a vicious circle of leaky barriers, microbial dysbiosis and chronic inflammation. DC, dendritic cell.

Chronic diseases with local barrier defects. Epithelial barrier damage in the affected tissues is a hallmark of a broad range of allergic inflammatory diseases. These include asthma, atopic dermatitis (eczema), CRS, eosinophilic esophagitis, food allergy and allergic rhinitis[24–43,45,48–58].

Filaggrins, which form a key component of the stratum corneum, and TJs in the stratum granulosum, provide two layers of skin barrier, and genetic defects in both layers have been associated with atopic dermatitis[32,33]. Skin barrier leakiness due to filaggrin mutations have also been associated with a broad range of allergic diseases and IgE sensitization, suggesting that compromised epithelial barriers lead to many chronic inflammatory diseases[33,150]. Particularly, the link between skin barrier impairment and many allergic diseases suggests that an early diagnosis of barrier defects and protection of the skin barrier would have beneficial effects in the prevention of disease[151]. Exposure to many of the agents listed in TABLE 2 and TABLE 3, such as detergents, food emulsifiers, particulate matter, ozone and allergens, in early childhood could well be relevant to the development of allergen sensitization in the first years of life in addition to already existing mutations in barrier molecules and bacterial dysbiosis[102,150,152,153]. Representing another group of diseases with local inflammation in the affected tissues, gut barrier defects have been linked to inflammatory bowel disease and coeliac disease[24,25,27,28].

Epithelial barrier defects in systemic autoimmune and metabolic diseases. The second group of conditions in which pathology has been associated with barrier leakiness and microbial dysbiosis includes autoimmune and metabolic diseases that affect organs distant from the site of barrier leakiness. These include rheumatoid arthritis, multiple sclerosis, ankylosing spondylitis, several types of hepatitis, systemic lupus erythematosus, type 1 and type 2 diabetes, and obesity[47,59–76] (TABLE 1).

One of the characteristic pathogenetic events in this group of conditions appears to be the activation of pathogenic immune cells in mucosal tissues with disrupted barriers, which then migrate to the affected organs (FIG. 2). For example, air pollution and exposure to airborne particulate matter is associated with increased disease activity in multiple sclerosis together with an increase in $CCR6^+$ $CD4^+$ T cells with migratory properties that can allow them to pass through the blood–brain barrier. In addition, there is an increase in the number of myeloid dendritic cells that express cytokines such as IL-1β, IL-6 and IL-23, which stimulate the development of T_H17 cells[154] (FIG. 2). In a rat model of autoimmune encephalomyelitis, it was shown that myelin-specific T cells do not directly enter the central nervous system. Instead, they first become 'licensed' in the lungs, which then allows them to enter the central nervous system, where they induce the development of multiple sclerosis-like inflammation[155]. Although this study did not specify barrier disruption, disease in this model was induced by administering autoantigen together with lipopolysaccharides and Freund's complete adjuvant, both of which can disrupt tissue barriers.

Table 3 | **Animal and in vitro models of barrier disruption**

Substance	Evidence	Refs
Polystyrene microplastic	Mouse models show effect of polystyrene microplastics on gut barrier	92
Ozone	Mouse models show respiratory barrier injury through ozone	91
Cigarette smoke	Mouse models show that cigarette smoke causes acute lung injury	94
Particulate matter	Ex vivo experiments with human and rat alveolar epithelial cells show that particulate matter affects the distribution of occludin and the alveolar barrier; PM2.5 causes defects in the nasal epithelial barrier in non-inflamed nasal biopsy samples of patients with sinusitis; PM10 stimulates myeloid dendritic cells to induce T_H17 cells with brain-homing property in vitro	87,90,154
Diesel exhaust particulates	Human and rat alveolar epithelial cells exposed to diesel exhaust particulates show low occludin expression and barrier leakiness	87
Nanoparticles	Human cell cultures show that nanoparticles disrupt intestinal barrier homeostasis	88
Anionic surfactants and commercial detergents	Human skin keratinocyte cultures show that anionic surfactants and commercial detergents decrease tight junction barrier integrity	84
Detergent residue	Human bronchial epithelial cell air–liquid interface cultures show that detergent residues disrupt tight junction barrier integrity in human bronchial epithelial cells even at low concentrations	85
Emulsifiers in processed food	Emulsifiers increased damage to the structure of hamster small intestine in vivo and the translocation of *Escherichia coli* across M-cells in vitro	102,152

PM2.5, particulate pollutant that is 2.5 μm or smaller in size; PM10, particulate pollutant that is 10 μm or smaller in size; T_H17, T helper 17.

A link between distant inflammation in the disease area and gut barrier leakiness was also reported in a mouse model of arthritis. Here, effector T cells were found to migrate from the lamina propria of the leaky gut towards the synovium, where they caused pathology[47]. This study demonstrated the key aspects of the extended barrier hypothesis, in that the gut barrier defect caused microbial dysbiosis, which, in turn, caused inflammation at a distant site (FIG. 2). Further supporting this hypothesis, it was shown that restoration of the intestinal barrier using butyrate, a cannabinoid type 1 receptor agonist, or treatment with the zonulin antagonist larazotide acetate, inhibited the development of arthritis in this mouse model[47]. Although defective barriers in the lungs and gastrointestinal mucosa have been demonstrated as sites for cellular activation, including the activation of antigen-presenting cells, further research is needed to study how immune cells with potential pathogenic function are activated in these tissues.

When epithelial barriers in the intestinal or respiratory tract break down, the disruption of other barriers, such as the blood–brain barrier or other vascular endothelial barriers such as in the eye, can ensue, and permeability defects in these barriers can lead to immune cell recruitment and activation. This process may underlie the development of various metabolic and autoimmune disorders[156–160].

A number of studies have investigated whether a leaky gut or a disrupted respiratory barrier are the initiators or consequences of disease development. In type 1 diabetes, recent studies point to a leaky gut as the initiator given that subclinical intestinal barrier dysfunction can be detected in individuals before the clinical onset of disease[60]. Moreover, in a rat model of spontaneous type 1 diabetes, increased gastric and small intestinal permeability occurred before insulitis and clinical diabetes[161]. Notably, epithelial barriers are also regulated by metabolic mechanisms, for example, high tissue glucose concentrations due to insulin resistance can negatively affect the tightness of epithelial barriers[63,162]. In airway epithelial cell cultures it was shown that high glucose levels can lead to the downregulation of TJ proteins by decreasing connexin 43 expression[163], suggesting a positive feedback mechanism for the continuation of dysregulated gut barrier in diabetes. In parallel to metabolic changes and gut barrier defects in diabetes, perturbation of the intestinal microbiota together with a persistent low-grade inflammatory response in the gut and fat tissue is also observed in obesity[64,65].

Several bacterial toxins, such as *S. aureus* enterotoxins, zonula occludens toxin of *Vibrio cholera*[58] and *Bacillus subtilis*[52–54,98] toxins, have been shown to damage the epithelial barrier. Zonulin is a precursor of the haptoglobin protein, a human analogue of zonula occludens toxin of *V. cholera*, that downregulates TJ function. This protein has been proposed to play a role in several autoimmune diseases[47,58]. In a rat model of type 1 diabetes, it was shown that a zonulin inhibitor can reverse the manifestations of disease and microbial translocation in the gut[63]. In patients with rheumatoid arthritis, increased serum zonulin levels have been linked to a leaky intestinal barrier and represent a target for treatment[47]. Similarly, in patients with multiple sclerosis, increased zonulin concentrations were linked to an opening of tight junctions and a breakdown of both the intestinal barrier and the blood–brain barrier in response to gut dysbiosis, presenting a direct link between disease pathology and the intestinal barrier[72].

Several studies have also linked disturbed epithelial barriers to other autoimmune diseases. For example, patients with ankylosing spondylitis often have gut epithelial and vascular barrier damage, bacterial dysbiosis and increased serum zonulin levels together with bacterial ileitis[75]. For systemic lupus erythematosus, barrier

Zonulin
A precursor of the haptoglobin protein, which downregulates tight junction function and reflects intestinal barrier permeability as a marker of an impaired gut barrier.

defects linked to microbial dysbiosis have been observed in humans and mouse models[76,164].

Different types of liver diseases, including fatty liver disease (non-alcoholic steatohepatitis), autoimmune hepatitis and liver cirrhosis, have been linked to gut barrier defects. The incidence of fatty liver disease has reached epidemic levels, with a 25.4% global prevalence, showing a strong comorbidity with obesity and diabetes[165]. Disruption of the intestinal epithelial and vascular barriers and gut microbial dysbiosis were found to be early events in the pathogenesis of fatty liver disease in mouse models and in patients[66].

Autoimmune hepatitis is an immune-mediated, inflammatory, chronic and progressive liver disorder. Increased intestinal permeability, derangement of the microbiome and bacterial translocation, all of which correlated with the severity of the disease, were observed in patients with autoimmune hepatitis[166]. Liver cirrhosis profoundly alters the gut barrier, rendering it more permeable and allowing the translocation of bacteria, bacterial products and fragments into the portal circulation, thus perpetuating an abnormal local and systemic inflammatory response. Both leaky gut and bacterial dysbiosis are involved in the development of liver cirrhosis in a vicious circle[70].

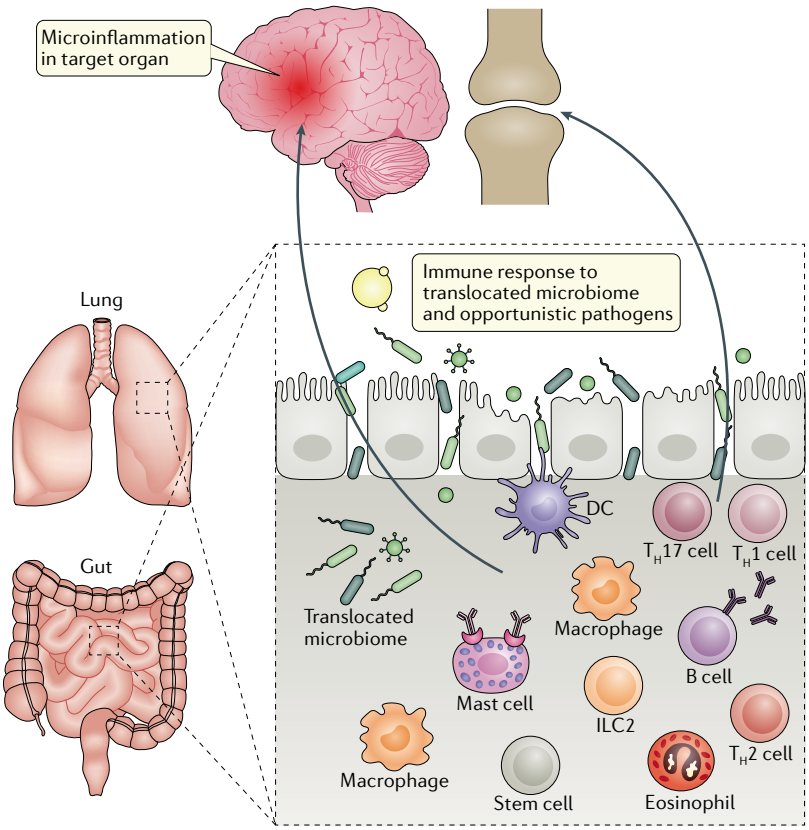

Fig. 2 | **Immune cells activated in the leaky gut or lung can migrate and contribute to inflammation in distant organs.** For several autoimmune conditions, a connection between a disruption of the epithelial barrier in the gut or lung and inflammation in distant organs has been demonstrated. For example, a link between gut barrier disruption and distant inflammation was recently reported in a mouse model of arthritis. In this study, T helper 1 (T_H1) and T_H17 effector T cells accumulated in the lamina propria of the leaky gut and migrated to affected joints, causing pathology[47]. Similarly, barrier disruption due to environmental exposure, such as particulate matter in the lungs, may cause distant inflammation in multiple sclerosis[87,90,154]. In a mouse model of multiple sclerosis, disease was induced by intratracheal administration of the autoantigen myelin basic protein together with a barrier-damaging adjuvant. Autoantigen-specific effector T cells were shown to be 'licensed' in the airways for migration to the brain, where they caused multiple sclerosis-like inflammation[155]. Dendritic cells (DCs), macrophages, innate lymphoid cells, T cells and their cytokines in the chronic inflammatory environment interact with stem cells and are critical for both the damage and regeneration of the mucosal epithelial barriers[109,110]. B cells, mast cells, eosinophils, type 2 innate lymphoid cells (ILC2) and T_H2 cells are also typically involved in the response to the translocated microbiome.

Epithelial barrier defects in neurodegenerative and psychiatric diseases. The link between the onset and progression of neurodegenerative diseases and chronic sterile inflammation is an active topic of debate[167]. Several recent studies in animals and humans suggest a connection between increased intestinal barrier leakiness and neurodegenerative and psychiatric disorders such as Parkinson disease[168], Alzheimer disease, autism spectrum disorders[169] and chronic depression[170] (TABLE 1). These conditions have substantially increased in prevalence during the same time period as allergic and autoimmune diseases[168–171].

Analyses of gut-wall barrier function in humans can be performed through in vivo permeability tests, gut biopsies and in situ immunohistology staining of TJ proteins as well as using ex vivo mucosal permeability tests. In addition, serum biomarkers of barrier leakiness, such as zonulin and proteins detectable in faecal samples, can be analysed[78–80]. Such studies point to gut barrier leakiness and a microbial dysbiosis-driven systemic microinflammatory state, migrating pro-inflammatory cells and defects in the blood–brain barrier leading to neuroinflammation as key pathogenetic mechanisms in this group of diseases[82].

For example, a post-mortem analysis of gut samples demonstrated that 75% of individuals with autism spectrum disorder had a reduced expression of barrier-forming TJ components (claudin 1, occludin and tricellulin), and 66% had an increased expression of pore-forming claudins (claudins 2, 10 and 15) in the gut epithelium as well as mild levels of gut mucosal inflammation[77,172]. There is also evidence for an association of Alzheimer disease with leaky barriers. In a mouse model of Alzheimer disease, dysfunction of the intestinal epithelial barrier and vascular amyloid-β deposition in the intestinal mucosa were shown before cerebral amyloid-β aggregation was detectible[173]. In addition, an increase in pro-inflammatory proteins in microglial cells, blood–brain barrier endothelial cells and circulating immune cells in individuals with Alzheimer disease was identified[167]. However, most studies of the relationships between a leaky intestinal epithelial barrier, microbial dysbiosis, and neuroinflammation and neurodegeneration are correlative in nature, and a full causal relationship remains to be demonstrated.

Conclusion

Several shortcomings of the hygiene, old friends and biodiversity hypotheses have been discussed during the past decades and suggest that these hypotheses do not fully explain the increase in prevalence of allergic and autoimmune diseases. These shortcomings include the

fact that water sanitation was established in many western cities in the 1920s but allergy and asthma epidemics only started in the 1960s. The protective role of parasite infections that increase biodiversity has been questioned for the same reason. In addition, allergic asthma is still on the rise in some cities in Asia and Africa that have low standards of hygiene[174]. Another limitation of the hygiene and biodiversity hypotheses is that probiotics are not viable alternatives for the prevention or treatment of allergies[175]. Moreover, studies of migrants who move from developing countries to affluent regions demonstrate a rapid increase in asthma and allergic diseases as well as autoimmune diseases such as type 1 diabetes and multiple sclerosis[176–178]. It appears that domestic living conditions, increased birth by caesarean sections, antibiotic usage, dietary practices, urbanization and indoor air pollution are more prominent factors than general public hygiene[18,179,180].

The barrier hypothesis as presented here includes mechanisms described by the hygiene, old friends and biodiversity hypotheses. These include the immune regulatory role of infectious agents on the innate immune response, T_H1–T_H2 balance and other complex immune regulatory responses. Once the epithelial barrier is leaky, multiple immune regulatory mechanisms take place to suppress tissue inflammation in barrier-damaged tissues. Some allergic diseases, such as allergic rhinitis, as well as certain types of asthma and food allergy can be treated with allergen-specific immunotherapy, which induces regulatory T and B cells and suppresses inflammation in barrier-damaged tissues[181]. One may question why diseases that are linked to defective epithelial barriers can show vastly different clinical manifestations. However, given that epithelial damage can occur in very different anatomical locations and considering the complexity of the microbiota and microbial dysbiosis as well as the complexity of immune responses and immune regulation, it is not surprising that the consequences of epithelial damage can play a role in many different diseases.

The barrier hypothesis suggests a need for avoidance of environmental triggers and warrants further studies on safe levels of exposure to potentially harmful substances such as inhaled and ingested detergents, ingestion of processed foods containing emulsifiers, exposure to particulate matter, diesel exhaust, microplastics and certain nanoparticles. As Paracelsus said in 1493, "*sola dosis facit venenum*", all substances are poisons, everything has the potential to become toxic, it merely depends on the dose. It is recommended that patients with the chronic non-communicable diseases listed in TABLE 1 avoid exposure to these substances (TABLE 3).

There is a need to continue research into the epithelial barrier to advance our understanding of the factors and molecular mechanisms associated with 'leaky barriers'. Experimental models should be developed and validated to monitor the trafficking of environmental antigens across a leaky epithelial barrier; this will inform approaches for the prevention, early intervention and development of novel therapeutic approaches. Possible strategies to reduce diseases associated with a disrupted epithelial barrier include the avoidance and dose control of all of the above mentioned products, the development of safer, less-toxic products, the discovery of biomarkers for the identification of individuals with a leaky barrier, the development of novel therapeutic approaches for strengthening the tissue-specific barrier molecules as well as other components of the mucosal barrier, blocking bacterial translocation, avoiding the colonization of opportunistic pathogens, and interventions through diet and the microbiome.

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