Recent advances in the epithelial barrier theory

Pat, Yagiz ; Yazici, Duygu ; D'Avino, Paolo ; Li, Manru ; Ardicli, Sena ; Ardicli, Ozge ; Mitamura, Yasutaka ; Akdis, Mübeccel ; Dhir, Raja ; Nadeau, Kari ; Agache, Ioana ; Ogulur, Ismail ; Akdis, Cezmi A

DOI: https://doi.org/10.1093/intimm/dxae002

International Immunology, Vol. 36, No. 5, pp. 211–221
https://doi.org/10.1093/intimm/dxae002
Advance Access publication 16 January 2024

REVIEW

Recent advances in the epithelial barrier theory

Yagiz Pat[1], Duygu Yazici[1], Paolo D'Avino[1], Manru Li[1], Sena Ardicli[1,2], Ozge Ardicli[1,3], Yasutaka Mitamura[1], Mübeccel Akdis[1], Raja Dhir[4], Kari Nadeau[5], Ioana Agache[6], Ismail Ogulur[1] and Cezmi A. Akdis[1,7]

[1]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland
[2] Department of Genetics, Faculty of Veterinery Medicine, Bursa Uludag University, Bursa, Türkiye
[3] Division of Food Processing, Milk and Dairy Products Technology Program, Karacabey Vocational School, Bursa Uludag University, Bursa, Turkiye
[4] SEED Inc. Co., Los Angeles, California, USA
[5] Department of Environmental Health, T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts, USA
[6] Allergy and Clinical Immunology at Transylvania University, Brasov, Romania
[7] Christine Kühne-Center for Allergy Research and Education, Davos, Switzerland

Correspondence to: Y. Pat; E-mail: yagiz.pat@siaf.uzh.ch

Received 9 October 2023, *editorial decision* 8 January 2024, *accepted* 15 January 2024

Abstract

The epithelial barrier theory links the recent rise in chronic non-communicable diseases, notably autoimmune and allergic disorders, to environmental agents disrupting the epithelial barrier. Global pollution and environmental toxic agent exposure have worsened over six decades because of uncontrolled growth, modernization, and industrialization, affecting human health. Introducing new chemicals without any reasonable control of their health effects through these years has led to documented adverse effects, especially on the skin and mucosal epithelial barriers. These substances, such as particulate matter, detergents, surfactants, food emulsifiers, micro- and nano-plastics, diesel exhaust, cigarette smoke, and ozone, have been shown to compromise the epithelial barrier integrity. This disruption is linked to the opening of the tight-junction barriers, inflammation, cell death, oxidative stress, and metabolic regulation. Consideration must be given to the interplay of toxic substances, underlying inflammatory diseases, and medications, especially in affected tissues. This review article discusses the detrimental effect of environmental barrier-damaging compounds on human health and involves cellular and molecular mechanisms.

Keywords: detergents, exposome, particulate matter, pollution

Introduction

The epithelial barrier theory postulates that the recent increase in chronic non-communicable diseases, including autoimmune and allergic disorders, results from the disruption of the epithelial barriers because of exposure to hazardous environmental agents (1). Since the 1960s, more than 350 000 chemical molecules have been introduced to our lives without concern for their effects on human and animal health. Many of them have ended up as pollutants and even more than 110 000 of them have not been appropriately reported. The harmful impacts of these substances on the body continuously increase due to changes in the human exposome, which is the sum of all the environmental exposures such as diet, microbiome, and pollutants during the lifetime of an individual, driven by industrialization and modernization (2–4). Every day, new potentially hazardous chemicals enter our lives, and this increasing exposure to toxic compounds adversely affects epithelial tissues, the microbiome, the immune system, and human health (2, 5–10). Several studies demonstrate how these environmental factors harm the integrity of the epithelial barriers, leading to chronic diseases (1–4, 6, 7, 9–17). Epithelial barrier damage by environmental toxic compounds results in dysbiosis, translocation of microbiota to subepithelial tissues, opportunistic pathogen colonization, chronic inflammation, local and systemic immune responses, and defective epithelial barrier healing. As a result, disruption of the homeostasis of the epithelial barrier occurs, which is currently associated with various metabolic and autoimmune diseases (1). However, the full impact of these environmental factors on human health remains unknown. A crucial factor to consider is the synergistic impact of environmental toxic compounds, existing inflammatory comorbid diseases, and medications, particularly in inflamed or afflicted tissues. Within this context, we will discuss the homeostasis of epithelial barrier integrity on mucosa and skin, changes in the human exposome in recent decades, and the detrimental effect of environmental toxic agents and diseases associated with epithelial barrier impairment.

Homeostasis of the epithelial barrier integrity

Epithelial tissue covers the inner and outer surfaces of the human body, forming a barrier that protects the structural and functional integrity of the organism. Being the interface between the body and the environment, it is the first line to encounter any potentially dangerous component from the environment. Thus, epithelial surfaces continuously contact with various hazardous factors, including infectious organisms, pollutants, and other environmental antigens. However, the immune regulatory mechanisms of the epithelium have evolved to protect the body against potentially harmful factors while avoiding unnecessary or excessive responses that cause tissue damage and harm the resident microbiota (18). In this context, the primary function of the epithelium is to protect the tissue's functional and structural integrity, contributing to the healthy state of the organism as a whole.

Both the gastrointestinal and respiratory tracts have similar structures and function as selective barriers, allowing the passage of gases or nutrients while maintaining a beneficial relationship with the microbiota and preventing the entry of pathogens. The integrity of the mucosal barrier relies on the intercellular junctions that connect epithelial cells. Tight junctions (TJs), adherens junctions, and desmosomes work together to seal off the space between cells, preventing the movement of soluble substances, proteins, and pathogens between the apical and basolateral surfaces.

The skin's barrier function primarily depends on the outermost layer, known as the stratum corneum, formed through keratinocyte differentiation. Within the stratum corneum, keratinocytes produce essential components like filaggrin (FLG), loricrin, and keratin filaments, which are crucial for maintaining the skin's normal barrier function. The stratified and cornified squamous epithelium of the skin acts as a protective shield, preventing water loss, and blocking the penetration of foreign substances, such as pathogens, allergens, and chemical irritants, from the external environment.

Furthermore, besides their physical barrier properties and the mucociliary clearance mechanism that removes foreign substances, epithelial cells also contribute to chemical defence. They secrete antimicrobial peptides, proteases, and antioxidants, serving as a chemical barrier (19–21). Additionally, epithelial cells express molecular sensors that detect microbial patterns, potentially triggering immune responses throughout the body. Pattern recognition receptors, both on the cell membrane and within the cell, recognize specific ligands present in pathogens, activating signalling pathways that promote the release of proinflammatory cytokines/chemokines. This attracts and activates cells from the innate and adaptive immune systems (22). Disruption of any of these barrier functions in different organs can lead to damage, inflammation, and disease.

Changes in the exposome and exposure to environmental toxic agents

Air pollution-related compounds

Air pollution poses a significant threat to our era, contributing to climate change and being a major cause of respiratory diseases (23, 24). According to the World Health Organization's Global Ambient Air Quality Database, 99% of the global population is exposed to poor air quality (25, 26). Ambient air pollution alone is responsible for an estimated 3.7–4.2 million annual deaths worldwide (27). It is a complex mixture of gaseous and particulate components, including nitrogen oxide (NO), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), carbon monoxide (CO), and ozone, as well as particulate matter (PM) from both natural and anthropogenic sources (27).

Besides outdoor pollution, indoor pollution is a major issue, with pollutant levels often higher indoors than outdoors. It is crucial to consider that people spend a significant amount of time indoors (28). Household air pollution is a major concern, leading to 2.9–4.3 million deaths each year, particularly in low- and middle-income countries (2). This issue is primarily caused by tobacco use and second-hand smoke. Although tobacco use has declined, it is still responsible for more than 8 million deaths annually, mostly in low- and middle-income countries (29, 30).

Natural sources, such as dust, sea salt, desert dust, and forest fires, contribute to air and aquatic PM, while anthropogenic sources like traffic, power plants, and industrial emissions add to the pollution burden (31, 32). Black carbon, aryl hydrocarbons, volatile organic hydrocarbons, polycyclic aromatic hydrocarbons, heavy metals, organic chemicals, minerals, and biological elements make up the majority of PMs (33–37). Over the past four decades, the atmospheric $PM_{2.5}$ concentration increased 38%, especially in China and India (38). In particular, the black carbon concentration, mainly arising from the incomplete combustion of fossil fuels, has significantly increased (39). Exposure to PM_{10} and $PM_{2.5}$ has been associated with higher all-cause, cardiovascular, and respiratory mortality (40). Studies show that air pollution exacerbates cardiovascular and respiratory diseases and is linked to the development of asthma, diabetes, and various neurocognitive disorders (41–43). With the increased use of on-road vehicles, diesel exhaust particulates (DEPs) have become a crucial part of air pollution. It is a complex blend of various substances, present either in gaseous or particulate form. The gaseous components of DEPs comprise CO, nitrogen compounds, sulphur compounds, and a wide array of low-molecular-weight hydrocarbons, including aldehydes, benzene, polycyclic aromatic hydrocarbons and their nitro forms (44).

Volatile organic compounds (VOCs) are carbon-based molecules with a low boiling point and readily vaporize at room temperature. These volatile substances, such as benzene, toluene, and formaldehyde, are cytotoxic and/or carcinogenic solvents found in cleaning products, wallpaper, paints, and plastics (45, 46). These compounds can pose health risks when released into the air. Additionally, certain VOCs can react with NO_2 under ultraviolet light from the sun, leading to the formation of ozone (47).

Micro- and nano-plastics

Micro- and nano-plastic (MPs and NPs) pollution has become a significant environmental concern because of the widespread use of plastics, driven by their low production cost and high durability. However, plastic waste poses a serious threat to nature as most plastics are non-biodegradable.

Globally, approximately 275–350 million metric tons (Mt) of plastic waste were produced due to mismanagement, and 4.8–12.7 Mt of plastic waste find their way into the oceans annually (48–50). It is estimated that 8300 Mt have been produced so far, 60% of them have accumulated in the environment (48). This plastic waste breaks down into small fragments and particles known as MPs (<5 mm) and NPs (1–1000 nm) when entering the environment. The degradation products of plastic pollution can be found in the air, water, and sediment, affecting various ecosystems (51, 52). Studies have shown that both NPs and MPs can be harmful to aquatic species like zooplankton, bivalves, and small fish (52). Furthermore, NPs can penetrate living organisms and may even enter the human food chain, posing potential risks to human health (52, 53). Plastic particles have been detected in the blood, lung, heart, synovial fluid, amniotic fluid, and placenta of humans (54–57).

Detergents, surfactants, and cleaning agents

The term detergent is commonly used for cleaning products. Detergents play a significant role in both industrial and domestic settings. The global detergent industry is substantial, with an annual investment of $60 billion dedicated to detergent production (58). Compounds acting as detergents are amphiphilic substances consisting of hydrophilic (polar) and hydrophobic segments. In an aqueous phase, detergents form micelles, aggregating with hydrophobic parts at the core and polar groups on the surface, shielding them from the surrounding water (59). These molecules are also surfactants because of their ability to decrease the surface tension of water.

Laundry detergents commonly contain surfactants and various enzymes like cellulase, lipase, and amylase (60). Particularly, sodium lauryl (dodecyl) sulphate (SLS or SDS) shows rapid and strong toxicity to epithelial barriers in highly diluted doses (12, 61). Even highly diluted household laundry detergents and SDS can damage the skin epithelial barrier in mouse skin and *ex vivo* human skin. This barrier disruption was induced together with inflammatory responses in epithelial cells (62). Professional dishwasher detergents and rinse compounds have become increasingly popular since the 2000s, primarily due to their ability to streamline operations by reducing the need for manual labour while ensuring efficient cleaning and sanitation of dishware. These machines are now widely utilized in various public food consumption areas, such as restaurants, schools, military barracks, and hotels, where they are employed on a regular basis (17). The cell toxic and inflammatory effects of professional and household dishwashers and rinse agents on cytotoxicity, barrier function, transcriptome, and protein expression in gastrointestinal epithelial cells have been recently reported. A disrupted epithelial barrier, particularly by rinse aid, was observed in liquid–liquid interface cultures, organoids, and gut-on-a-chip, demonstrating decreased transepithelial electrical resistance, increased paracellular flux, and irregular and heterogeneous TJ immunostaining. Notably, alcohol ethoxylates elicited a strong toxic and barrier-damaging effect. RNA sequencing transcriptome and proteomics data demonstrated increased cell death and recovery signals in metabolism, proliferation, and immune and inflammatory responses of epithelial cells. It was exciting to demonstrate that detergent residue on washed and ready-to-use dishware exhibited cytotoxic and epithelial barrier-damaging effects (17). In addition, substances such as bleach, detergents containing ammonia, and disinfectants containing chloramine-T, quaternary ammonium compounds, and ethanolamine can cause irritation to the lungs and worsen asthma, respiratory symptoms, or rhinitis (63–65). Healthcare workers who are exposed to detergents, cleaners, and disinfectants such as formaldehyde, glutaraldehyde, enzymatic cleaners, hypochlorite bleach, and hydrogen peroxide are at a greater risk of developing poorly controlled asthma (66).

Food additives in processed foods

Another significant environmental concern impacting health is the shift in dietary habits, characterized by increased consumption of dietary fatty acids and processed foods, as well as the use of emulsifiers and a decrease in antioxidant content in western-style diets, which are widely consumed (4). These changes in dietary patterns and the introduction of additives in processed foods may have profound effects on human health. In processed foods, the use of food additives such as synthetic colourants, preservatives, stabilizers, surfactants, emulsifiers, and texturisers is common (67, 68). However, mounting evidence suggests that processed foods containing these additives and advanced glycation end-products formed during heat processing can disrupt the integrity of the epithelial barrier (4, 69, 70), damage the microbiome and activate the immune system. The two frequently used food emulsifiers, polysorbates 20 and 80, were recently reported for their cellular toxicity, damage to epithelial barriers, transcriptome alterations, and protein expression in gastrointestinal epithelial cells. Although 1% is allowed, epithelial barrier disruption, upregulation of apoptosis, inflammatory responses, and stress responses were observed at 20 times lower (0.05%) concentrations (71). Moreover, the consumption of processed foods has been linked to various health issues, including all-cause mortality, obesity, metabolic syndrome, and depression (72). Additionally, food contamination can occur through contact with dishware that carries residues from cleaning products like detergents and anionic surfactants (3, 73, 74).

In vivo animal and human studies showed that the higher intake of ultra-processed food was associated with a risk of microvascular diseases such as chronic kidney disease (69) and inflammatory bowel disease (75), and commonly consumed food additives would impact anxiety-related and social behaviours (76). Studies also demonstrated that not only food emulsifier consumption but also detergent exposure was related to obesity (77) and increased the prevalence of cardiovascular disease (78).

Mechanisms and pathological events involved in epithelial barrier damage

The deleterious effects of exposure to compounds inducing damage to the epithelial barriers have been substantiated through methodologies that assess both functional and molecular changes parallel to decreased epithelial barrier

integrity. These compounds exert direct cell death, metabolic and proinflammatory effects, and oxidative stress with disruptive influence on the expression and architecture of epithelial junction molecules. This perturbation is manifested either through modulation of the expression levels of these junctional molecules or direct impairment of the epithelial cells.

For epithelial barrier integrity, mainly the paracellular permeability, the TJ molecules plays a significant role (79). As the primary determinant of paracellular permeability, their disruption causes the uncontrolled flow of apically located environmental factors such as microbiota, pathogens, pollutants, and allergens to the subepithelial tissues (1). The TJs are essential in the maintenance of epithelial cell polarity, regulation of intracellular signalling pathways, cell proliferation, and differentiation. Thus, TJ damage causes disrupted epithelial cell homeostasis (79). TJs are composed of transmembrane proteins (occludin, claudins, and junctional adhesion molecules) and adaptor proteins (Zonula occludens and cingulin). Claudins, which reside in the transmembrane area, are the major controllers of selective permeability (79). Many epithelial barrier-damaging compounds have been shown to alter the expression of these proteins both in RNA and protein levels. In addition, adherence junction proteins such as E-cadherin and catenin can be affected.

Epithelial barrier-damaging compounds can disrupt epithelial barrier homeostasis in a variety of ways. These environmental agents often trigger epithelitis, characterized by the release of proinflammatory cytokines and damage to the epithelial barrier (Fig. 1). Active substances of detergents, like SDS/SLS and similar surfactants, induce significant inflammation, with increased reactive oxygen species (ROS) and interleukin (IL)-33 expression. These agents can lead to eosinophilic inflammation in various tissues, and exposure to them increases the expression of IL-33 and other proinflammatory factors (10, 15, 80, 81). In a recent study, two commercial laundry detergents and two commonly used surfactants for cleaning and cosmetics (SLS and sodium dodecyl benzene sulfonate) were intranasally administered to mice (81). After just four administrations, eosinophilic airway inflammation was induced and was accompanied by increased IL-33 expression and activation of group 2 innate lymphoid cells (ILC2s) in mice. Detergent-induced eosinophilic airway inflammation was significantly attenuated in *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ and *Il33*$^{-/-}$ mice. Experiments in IL-5 reporter mice demonstrated the role of ILC2s in eosinophilia. Detergent-induced IL-33 expression in airways was attenuated by *n*-acetyl cysteine, an antioxidant agent, treatment, both *in vivo* and *in vitro* (81). In another recent study, detergents and SDS/SLS were studied for their role in eosinophilic esophagitis (EoE) because common toothpastes contain relatively high doses of SDS/SLS. Very low doses of SDS (5 μg/ml) decreased epithelial barriers and increased the mRNA expression of IL-33 in cell lines and oesophageal organoids. Mice exposed to SDS showed increased oesophageal inflammation with increased IL-33, basal zone hyperplasia, CD4^{+} cell infiltration, and oesophageal eosinophilia, demonstrating that detergents can be an important trigger of asthma and EoE in the two above-mentioned studies (15).

Air pollutants, including PMs, ozone, NO, NO_2, and DEPs, activate ROS and induce cell death, leading to the secretion of alarmins like IL-33 and driving type 2 inflammation. $PM_{2.5}$, a component of air pollution, triggers various forms of cell death and proinflammatory transcription factors, such as mitogen-activated protein kinases (MAPKs) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), in human bronchial cells, resulting in excessive inflammation, and immune responses (14, 82–84). In addition, DEP and ozone exposure increases alarmin levels in respiratory epithelial cells (13, 85, 86). Additionally, VOC exposure induces transcription factors like NF-κB, activator protein 1, and hypoxia-inducible factor 1-alpha and triggers proinflammatory cytokine release (87). Exposure to oral polystyrene MPs has been linked to the phosphorylation of MAPKs, the induction of proinflammatory proteins like phospholipase A2 and cytochrome c oxidase I, and the release of proinflammatory cytokines, including IL-1β, IL-6, and tumour necrosis factor alpha (TNF-α), in kidney cells in animal models (88, 89). Exposure to polystyrene NPs induces ROS and NLRP3 activation (90). It also causes secretion of IL-8, NF-κB, and TNF-α on lung epithelial cells *in vitro* (91). These findings underscore the concerning impact of both NPs and MPs on inflammatory processes and their potential implications for various organ systems.

Evidently, the epithelial barrier-disrupting substance elicits increased epithelial barrier permeability via the inflammation it causes, apart from its direct effect on the epithelium. Notably, both type 1 and type 2 immune responses contribute to the leakiness of the epithelial barrier (1, 92, 93). The type 1 response causes increased permeability within the epithelial barrier by the cytokines such as TNF-α. The TNF-α not only triggers cell death but also initiates a leakage pathway at TJs. Conversely, the type 2 immune response enhances barrier permeability, particularly through the pore pathway. This effect is mediated by cytokines such as IL-4 and IL-13, which are generated upon the activation of ILC2s triggered by alarm signals [IL-25, IL-33, and thymic stromal lymphopoietin (TSLP)] (92–94).

In addition, damage to microbiota and compromised healthy interaction between the epithelial cells and the microbiome is taking place. In many epithelial barrier dysfunction-related diseases, microbial dysbiosis is commonly observed (95–104). As a result, substances causing damage to the epithelial barrier increase its permeability by direct action on epithelial cells, changes in microbiota and microbial dysbiosis followed by immune system activation inducing cell death, cellular stress, alterations in the expression of cell adhesion molecules and promoting inflammation (Figs. 1 and 2).

Barrier damage leads to microinflammation in epithelial cells called epithelitis by secreting alarmins, TSLP, IL-25, and IL-33, which increase the subepithelial inflammation (Fig. 1). Subsequent to the barrier damage, the microbiota can translocate to the subepithelial tissues (105). It is already known that microbial translocation may cause several autoimmune and chronic diseases such as Crohn's disease (106), chronic HIV Infection (107–109), SARS-CoV-2-related multisystem inflammatory syndrome (110), lupus (111), and fatty liver disease (112–114). Because of dysbiosis (115),

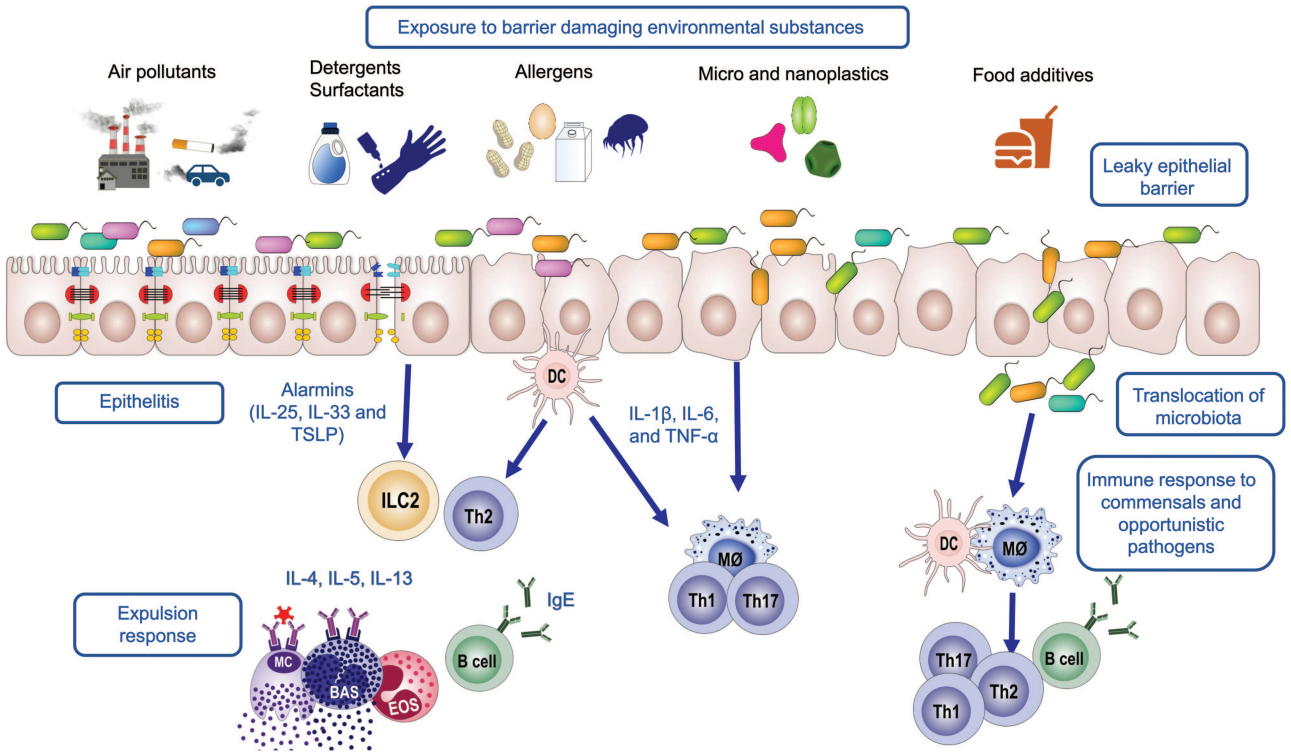

Figure 1. Epithelial barrier impairment by environmental substances. These hazardous factors, including air pollutants (particulate matter, cigarette smoke, volatile organic compounds, etc.), detergents, surfactants, hand disinfectants, allergens (peanut, egg, milk, house dust mite, pollen, etc.), micro- and nano-plastics and food additives such as food colourants, emulsifiers, and sweeteners, cause epithelial barrier impairment and inflammation. Cell death leads to alarmin (IL-25, IL-33, and TSLP) secretion, leading to the development of type 2 inflammation, which is characterized by the presence of ILC2s, Th2 cells, eosinophils (EOS), basophils (BAS), and mast cells (MC). In addition, epithelial cells secrete proinflammatory cytokines such as IL-1β, IL-6, and TNF-α. Translocation of microbiota to subepithelial areas triggers an immune response to commensals and opportunistic pathogens.

some opportunistic pathogens can colonize in the affected tissue, such as *Staphylococcus aureus* in atopic dermatitis (AD) patients (116). Aberrant host microbiota and epithelial barrier interactions lead to abnormal mucosal immune responses, including upregulation of T helper 17 (Th17), Th1 and Th2 type responses, downregulation of T regulatory cells, and dysregulated humoral immunity (117, 118) (Fig. 1). Continuous exposure to exposomes may induce impaired metabolic flexibility of epithelial cells that affects the regenerative capacity of the intestinal tissue (119). As a result of an unhealed epithelial barrier, epithelitis continues and triggers a localized or occasionally systemic inflammatory response. A vicious cycle of connected events takes the lead to persistent peri-epithelial inflammation and barrier leakiness (Fig. 2).

Diseases associated with epithelial barrier impairment

Diseases linked to epithelial barrier impairment consist of three groups. (i) Diseases with local barrier defects such as asthma (120), AD (101), chronic rhinosinusitis (CRS) (121, 122), allergic rhinitis (AR) (123), EoE (124–126), inflammatory bowel (127), and coeliac diseases (128). (ii) Systemic diseases with gut or lung barrier defect and dysbiosis [obesity (129, 130), diabetes mellitus (131, 132), rheumatoid arthritis (133), multiple sclerosis (134), fatty liver (135), autoimmune hepatitis (136), systemic lupus erythematosus, and ankylosing spondylitis (137)]. (iii) Neuropsychiatric diseases with a gut or lung barrier defect and dysbiosis [autism spectrum disorders (138), Parkinson's disease (139, 140), Alzheimer's disease (140, 141), stress-related psychiatric disorders (142), and chronic depression (143)] (1). This list is long, and many other diseases are involved when using the selection criteria for increased prevalence during the last few decades, microbial dysbiosis, epithelial barrier defects in biopsies, and circulating inflammatory biomarkers.

Diseases with a local barrier defect

Systemic type 2 immune responses such as activated, proliferating Th2 cells, and activated ILC2s mainly characterize these diseases. Interestingly, targeting of type 2 cytokines, such as IL-4, IL-5, and IL-13, has been successfully used for the treatment of such as asthma, CRS and AD, and healing of epithelial barriers with these treatments has been reported (144–148). Barrier impairment in the upper airway induces nasal hyperreactivity (145, 149–152). A nasal epithelial barrier dysfunction also triggers the passage of allergens, allergic sensitization, and degranulation of mast cells, even without an inflammatory environment (153). Non-steroid anti-inflammatory drug (NSAID)-exacerbated respiratory disease, as a more severe phenotype of CRS with nasal

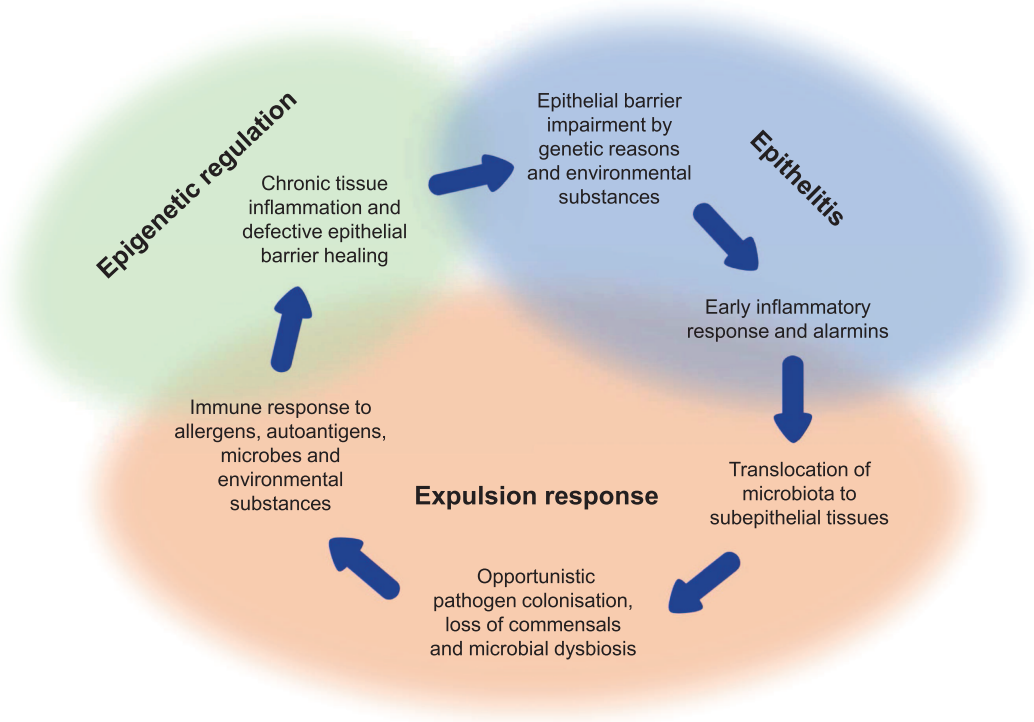

Figure 2. Epithelial barrier-damaging substances cause a vicious cycle. These substances cause epithelitis characterized by an impaired epithelial barrier and by inflammation. Loss of epithelial barrier integrity allows translocation of microbiota to the subepithelial tissues. Ongoing inflammation and epithelial barrier damage lead to dysbiosis and opportunistic pathogen colonization. This triggers the expulsion response, which is the activation of the immune system against allergens, microbes, and environmental substances, to expel them from the subepithelial area. Ultimately, this vicious cycle gives rise to chronic tissue inflammation and defective epithelial barrier healing through epigenetic regulation mechanisms.

polyps, was associated with a distinct dysregulation of epithelial barrier function in nasal polyp tissue (154). The mechanisms of barrier dysfunction in these diseases are not fully understood. Zhang *et al*. (155). showed that mucin-1 deficiency promotes nasal epithelial barrier dysfunction with claudin 1 (CLDN-1) degradation via RBFOX3 (RNA-binding protein, fox-1 homolog 3) shortage, augmenting ubiquitin proteasomal degradation in AR. In addition, Callejas-Díaz *et al*. (156) demonstrated that the genetic transcriptional program responsible for ciliogenesis and cilia function is significantly impaired in epithelium from CRs with nasal polyps and there is altered expression of miR-34 and miR-449 families. Moreover, Gawrysiak *et al*. (157) reported that human rhinovirus HRV16 damages barrier functions and impairs the regeneration of human lung vascular endothelium, leading to uncontrolled exudates of protein-rich extravascular fluid and tissue oedema. In the pathogenesis of EoE, local barrier disruption induced by type 2 inflammation is essential. Alvas *et al*. demonstrated a definitive role for IL-13 signalling via IL-13Rα1 in the EoE mouse model. Moreover, single-cell RNA sequencing analysis of human EoE biopsies showed that EoE signature genes, such as downregulation of FLG, correlated with IL-13 expression compared with IL-4 (158). It has been reported that exposure to common detergents such as SDS triggers IL-33 production, decreasing oesophageal barrier integrity, epithelial hyperplasia, and tissue eosinophilia (15). The laundry detergents and SDS induced eosinophilic airway inflammation *in vivo* through increasing expression of IL-33 from epithelial cells and ILC2 activation. In addition, detergent residues were detected in house dust, suggesting that surfactants are inadvertently inhaled into the airway in daily life (81). AD is a most common type 2 chronic inflammatory skin disease characterized by loss of the skin's barrier function. Recently, Zhang *et al*. (159) showed the clear hallmarks of type 2 inflammatory signatures by single-cell RNA-seq and TCR-seq in AD. In addition, RNA-seq profiles in tape-stripped skin samples identified dysregulation of barrier-related genes with increasing Th2 and Th22/Th17-related markers (160). Moreover, tape strips analysis by liquid chromatography, atomic force microscopy, multiplex immunoassay, and liquid chromatography mass spectrometry showed that children who develop AD have higher levels of sphingoid base chain length and TARC/CCL17 levels (161). Spatial transcriptomics in the lesional AD skin demonstrates the distribution of immune cells such as CCL17-expressing dendritic cells (DCs) and the detailed cell–cell interactions in the leukocyte-infiltrated area in the lesional AD skin (162). In AD pathogenesis, microbial dysbiosis also plays a crucial role since the skin microbiota helps maintain the epithelial barrier permeability. Dysbiosis of the skin microbiota and opportunistic bacteria colonization is common in AD (163). Recent studies found that the opportunistic pathogen *S. aureus* was shown to cause barrier damage via disruption of the lipid composition, which is crucial for skin barrier integrity and causing

inflammation in skin (116, 161, 164, 165). Interestingly, Stuvel *et al.* (166) reported that a rare autosomal disease, Comel-Netherton syndrome, which is characterized by a severe skin disease, atopic diathesis and increased susceptibility for skin infection, is a result of skin barrier disruption rather than an underlying immunodeficiency of the patient.

Systemic diseases with gut or lung barrier defect and dysbiosis

In this group, barrier dysfunction in mucosal tissues allows activated pathogenic immune cells to migrate to the affected organs. For example, fatty liver disease, including non-alcoholic fatty liver diseases (NAFLD), and non-alcoholic steatohepatitis (NASH), have been coupled with increased intestinal barrier permeability and translocation of bacteria into the blood circulation. Linked to this group, Mouries *et al.* (167, 168) reported that the impairment of the gut vascular barrier leads to bacteria translocation into the bloodstream, contributing to NASH development.

Obesity is also an important condition in this group. Obesity impairs the structural and functional integrity of the oesophageal barrier, leading to oesophageal injury (169). A high-calorie and fat-enriched diet affects gut permeability and TJ restructuring in the mouse model (170). Obesity may increase susceptibility to multiple organ disorders through these barrier dysfunctions.

Neuropsychiatric diseases with gut or lung barrier defect and dysbiosis

In the past years, the concept of the gut–brain axis has started to emerge (141, 142). Individuals diagnosed with autism spectrum disorder exhibit altered gut permeability attributed to diminished expression of TJ proteins (138). Indeed, in autism spectrum disorder, blood–brain barrier-related CLDN-5 and CLDN-12 are increased in the brain. In addition, 75% of the autism spectrum disorder samples had reduced expression of TJ family components, such as CLDN-1, OCLN, and TRIC (138). Evidence suggests that acute stress can disrupt the intestinal barrier in animal models (142). Depression has been associated with reduced richness and diversity of gut microbiota. Patients experiencing chronic depression frequently manifest microbial dysbiosis, bacterial translocation in the gut, and an inflammatory response to commensal bacteria (143, 171).

Conclusion

In this era, where human activities have significantly altered the environment of our world, causing considerable harm to human health, it is imperative that we prioritize theories that elucidate disease mechanisms and embrace technologies developed within the framework of emerging paradigms. The epithelial barrier theory, one of the prominent explanations for the development of allergic diseases, has garnered significant support through recent research. With ongoing studies, our understanding of how environmental factors disrupt the epithelial barrier continues to expand. The evidence presented in this review emphasizes that the disruption of epithelial barrier integrity plays a pivotal role in driving microbial dysbiosis, pathological bacterial colonization, immune responses to both opportunistic pathogens, and commensals, as well as tissue inflammation. This cascade of pathological events resulting from epithelial barrier damage significantly contributes to the onset of allergic diseases, autoimmune disorders, and metabolic conditions. To address these challenges, urgent action is required to raise public awareness and implement regulations governing the use of chemicals in both industrial and household products, with a focus on minimizing exposure to toxic substances that harm epithelium. Additionally, there is a pressing need to explore innovative therapeutic and preventive strategies targeting epithelial barrier impairment and its subsequent pathological consequences.

Conflict of interest statement. C.A.A. has received research grants from the Swiss National Science Foundation, European Union (EU CURE), Novartis Research Institutes (Basel, Switzerland), Stanford University (Redwood City, Calif), and SciBase (Stockholm, Sweden); he is the Co-Chair for EAACI Guidelines on Environmental Science in Allergic diseases and Asthma and serves on the Advisory Boards of Sanofi/Regeneron, Novartis, GlaxoSmithKline and SciBase, and is the Editor-in-Chief of *Allergy*. All other authors have no conflicts to disclose.

Funding

None.

References

1. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol* 2021;**21**:739–51. https://doi.org/10.1038/s41577-021-00538-7
2. Pat Y, Ogulur I, Yazici D, *et al.* Effect of altered human exposome on the skin and mucosal epithelial barrier integrity. *Tissue Barriers* 2022;**11**:2133877
3. Celebi Sözener Z, Cevhertas L, Nadeau K, *et al.* Environmental factors in epithelial barrier dysfunction. *J Allergy Clin Immunol* 2020;**145**:1517–28. https://doi.org/10.1016/j.jaci.2020.04.024
4. Celebi Sozener Z, Ozdel Ozturk B, Cerci P, *et al.* Epithelial barrier hypothesis: effect of external exposome on microbiome and epithelial barriers in allergic disease. *Allergy* 2022;**77**:1418–49. https://doi.org/10.1111/all.15240
5. Wang Z, Walker GW, Muir DCG, *et al.* Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. *Environ Sci Technol* 2020;**54**:2575–84. https://doi.org/10.1021/acs.est.9b06379
6. Kucuksezer UC, Ozdemir C, Yazici D, *et al.* The epithelial barrier theory: development and exacerbation of allergic and other chronic inflammatory diseases. *Asia Pac Allergy* 2023;**13**:28–39. https://doi.org/10.5415/apallergy.0000000000000005
7. Mitamura Y, Ogulur I, Pat Y, *et al.* Dysregulation of the epithelial barrier by environmental and other exogenous factors. *Contact Dermatitis* 2021;**85**:615–26. https://doi.org/10.1111/cod.13959
8. Pat Y, Ogulur I. The epithelial barrier hypothesis: a 20-year journey. *Allergy* 2021;**76**:3560–2. https://doi.org/10.1111/all.14899
9. Yazici D, Ogulur I, Kucukkase O, *et al.* Epithelial barrier hypothesis and the development of allergic and autoimmune diseases. *Allergo J Int* 2022;**31**:91–102. https://doi.org/10.1007/s40629-022-00211-y
10. Yazici D, Pat Y, Mitamura Y, *et al.* Detergent-induced eosinophilic inflammation in the esophagus: a key evidence for the epithelial barrier theory. *Allergy* 2023;**78**:1422–4. https://doi.org/10.1111/all.15646
11. Sokolowska M, Quesniaux VFJ, Akdis CA, *et al.* Acute respiratory barrier disruption by ozone exposure in mice. *Front Immunol* 2019;**10**:2169. https://doi.org/10.3389/fimmu.2019.02169
12. Wang M, Tan G, Eljaszewicz A, *et al.* Laundry detergents and detergent residue after rinsing directly disrupt tight junction barrier

integrity in human bronchial epithelial cells. *J Allergy Clin Immunol* 2019;**143**:1892–903. https://doi.org/10.1016/j.jaci.2018.11.016
13. Michaudel C, Mackowiak C, Maillet I, *et al*. Ozone exposure induces respiratory barrier biphasic injury and inflammation controlled by IL-33. *J Allergy Clin Immunol* 2018;**142**:942–58. https://doi.org/10.1016/j.jaci.2017.11.044
14. Xian M, Ma S, Wang K, *et al*. Particulate Matter 25 causes deficiency in barrier integrity in human nasal epithelial cells. *Allergy Asthma Immunol Res* 2020;**12**:56–71. https://doi.org/10.4168/aair.2020.12.1.56
15. Doyle AD, Masuda MY, Pyon GC, *et al*. Detergent exposure induces epithelial barrier dysfunction and eosinophilic inflammation in the esophagus. *Allergy* 2023;**78**:192–201. https://doi.org/10.1111/all.15457
16. Singh N, Diebold Y, Sahu SK, *et al*. Epithelial barrier dysfunction in ocular allergy. *Allergy* 2022;**77**:1360–72. https://doi.org/10.1111/all.15174
17. Ogulur I, Pat Y, Aydin T, *et al*. Gut epithelial barrier damage caused by dishwasher detergents and rinse aids. *J Allergy Clin Immunol* 2023;**151**:469–84. https://doi.org/10.1016/j.jaci.2022.10.020
18. Honda K, Littman DR. The microbiota in adaptive immune homeostasis and disease. *Nature* 2016;**535**:75–84. https://doi.org/10.1038/nature18848
19. Zhang QY, Yan ZB, Meng YM, *et al*. Antimicrobial peptides: mechanism of action, activity and clinical potential. *Mil Med Res* 2021;**8**:48. https://doi.org/10.1186/s40779-021-00343-2
20. Cornick S, Tawiah A, Chadee K. Roles and regulation of the mucus barrier in the gut. *Tissue Barriers* 2015;**3**:e982426. https://doi.org/10.4161/21688370.2014.982426
21. Moens E, Veldhoen M. Epithelial barrier biology: good fences make good neighbours. *Immunology* 2012;**135**:1–8. https://doi.org/10.1111/j.1365-2567.2011.03506.x
22. Li D, Wu M. Pattern recognition receptors in health and diseases. *Signal Transduct Target Ther* 2021;**6**:291. https://doi.org/10.1038/s41392-021-00687-0
23. Manisalidis I, Stavropoulou E, Stavropoulos A, *et al*. Environmental and health impacts of air pollution: a review. *Front Public Health* 2020;**8**:14. https://doi.org/10.3389/fpubh.2020.00014
24. D'Amato G, Akdis CA. Global warming, climate change, air pollution and allergies. *Allergy* 2020;**75**:2158–60. https://doi.org/10.1111/all.14527
25. Tandon A, Kanchan T, Tandon A. The poison we breathe. *Lancet* 2020;**395**:e18. https://doi.org/10.1016/S0140-6736(19)32547-4
26. WHO. Global ambient air quality database. 2021. https://www.who.int/teams/environment-climate-change-and-health/air-quality-and-health/ambient-air-pollution (28 November 2021, date last accessed).
27. Diao P, He H, Tang J, *et al*. Natural compounds protect the skin from airborne particulate matter by attenuating oxidative stress. *Biomed Pharmacother* 2021;**138**:111534. https://doi.org/10.1016/j.biopha.2021.111534
28. González-Martín J, Kraakman NJR, Pérez C, *et al*. A state-of-the-art review on indoor air pollution and strategies for indoor air pollution control. *Chemosphere* 2021;**262**:128376. https://doi.org/10.1016/j.chemosphere.2020.128376
29. Peters A, Nawrot TS, Baccarelli AA. Hallmarks of environmental insults. *Cell* 2021;**184**:1455–68. https://doi.org/10.1016/j.cell.2021.01.043
30. WHO. Tobacco 2021. https://www.who.int/news-room/fact-sheets/detail/tobacco. (31 October 2021, date last accessed).
31. Yang L, Li C, Tang X. The impact of PM(25) on the host defense of respiratory system. *Front Cell Dev Biol* 2020;**8**:91. https://doi.org/10.3389/fcell.2020.00091
32. D'Amato G, Akdis CA. Desert dust and respiratory diseases: further insight on the epithelial barrier hypothesis. *Allergy* 2022;**77**:3490–2. https://doi.org/10.1111/all.15392
33. Bové H, Bongaerts E, Slenders E, *et al*. Ambient black carbon particles reach the fetal side of human placenta. *Nat Commun* 2019;**10**:3866. https://doi.org/10.1038/s41467-019-11654-3
34. Alegbeleye OO, Opeolu BO, Jackson VA. Polycyclic aromatic hydrocarbons: a critical review of environmental occurrence and bioremediation. *Environ Manage* 2017;**60**:758–83. https://doi.org/10.1007/s00267-017-0896-2
35. Zhao CN, Xu Z, Wu GC, *et al*. Emerging role of air pollution in autoimmune diseases. *Autoimmun Rev* 2019;**18**:607–14. https://doi.org/10.1016/j.autrev.2018.12.010
36. Dominici F, Wang Y, Correia AW, *et al*. Chemical composition of fine particulate matter and life expectancy: in 95 US Counties between 2002 and 2007. *Epidemiology* 2015;**26**:556–64. https://doi.org/10.1097/EDE.0000000000000297
37. Thangavel P, Park D, Lee YC. Recent insights into particulate matter (PM(25))-mediated toxicity in humans: an overview. *Int J Environ Res Public Health* 2022;**19**:19.
38. Shaddick G, Thomas ML, Mudu P, *et al*. Half the world's population are exposed to increasing air pollution. *Npj Clim Atmos Sci* 2020;**3**:23.
39. Cao S, Zhang S, Gao C, *et al*. A long-term analysis of atmospheric black carbon MERRA-2 concentration over China during 1980–2019. *Atmos Environ* 2021;**264**:118662.
40. Liu C, Chen R, Sera F, *et al*. Ambient particulate air pollution and daily mortality in 652 cities. *N Engl J Med* 2019;**381**:705–15. https://doi.org/10.1056/NEJMoa1817364
41. Goshua A, Akdis C, Nadeau KC. World Health Organization global air quality guideline recommendations: executive summary. *Allergy* 2022;**77**:1955–60. https://doi.org/10.1111/all.15224
42. World Health O. *WHO Global Air Quality Guidelines: Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide*. Geneva: World Health Organization, 2021.
43. Luo X, Hong H, Lu Y, *et al*. Impact of air pollution and meteorological factors on incidence of allergic rhinitis: a low-latitude multi-city study in China. *Allergy* 2023;**78**:1656–9. https://doi.org/10.1111/all.15469
44. Wichmann HE. Diesel exhaust particles. *Inhal Toxicol* 2007;**19**:241–4. https://doi.org/10.1080/08958370701498075
45. Hendricks AJ, Eichenfield LF, Shi VY. The impact of airborne pollution on atopic dermatitis: a literature review. *Br J Dermatol* 2020;**183**:16–23. https://doi.org/10.1111/bjd.18781
46. Farraia M, Cavaleiro Rufo J, Paciencia I, *et al*. Human volatilome analysis using eNose to assess uncontrolled asthma in a clinical setting. *Allergy* 2020;**75**:1630–9. https://doi.org/10.1111/all.14207
47. Murrison LB, Brandt EB, Myers JB, *et al*. Environmental exposures and mechanisms in allergy and asthma development. *J Clin Invest* 2019;**129**:1504–15. https://doi.org/10.1172/JCI124612
48. Geyer R, Jambeck JR, Law KL. Production, use, and fate of all plastics ever made. *Sci Adv* 2017;**3**:e1700782. https://doi.org/10.1126/sciadv.1700782
49. Lebreton L, Andrady A. Future scenarios of global plastic waste generation and disposal. *Palgrave Commun* 2019;**5**:6.
50. Ashrafy A, Liza AA, Islam MN, *et al*. Microplastics pollution: a brief review of its source and abundance in different aquatic ecosystems. *J Hazard Mater Adv* 2023;**9**:100215.
51. Prata JC. Airborne microplastics: consequences to human health? *Environ Pollut* 2018;**234**:115–26. https://doi.org/10.1016/j.envpol.2017.11.043
52. Lehner R, Weder C, Petri-Fink A, *et al*. Emergence of nanoplastic in the environment and possible impact on human health. *Environ Sci Technol* 2019;**53**:1748–65. https://doi.org/10.1021/acs.est.8b05512
53. Kik K, Bukowska B, Sicińska P. Polystyrene nanoparticles: sources, occurrence in the environment, distribution in tissues, accumulation and toxicity to various organisms. *Environ Pollut* 2020;**262**:114297. https://doi.org/10.1016/j.envpol.2020.114297
54. Ragusa A, Matta M, Cristiano L, *et al*. Deeply in Plasticenta: presence of microplastics in the intracellular compartment of human placentas. *Int J Environ Res Public Health* 2022;**19**:11593. https://doi.org/10.3390/ijerph191811593
55. Khan A, Jia Z. Recent insights into uptake, toxicity, and molecular targets of microplastics and nanoplastics relevant to human health impacts. *iScience* 2023;**26**:106061. https://doi.org/10.1016/j.isci.2023.106061
56. Ragusa A, Svelato A, Santacroce C, *et al*. Plasticenta: first evidence of microplastics in human placenta. *Environ Int* 2021;**146**:106274. https://doi.org/10.1016/j.envint.2020.106274
57. Guan Q, Jiang J, Huang Y, *et al*. The landscape of micron-scale particles including microplastics in human enclosed body fluids.

J Hazard Mater 2023;**442**:130138. https://doi.org/10.1016/j.jhazmat.2022.130138
58. Mousavi SA, Khodadoost F. Effects of detergents on natural ecosystems and wastewater treatment processes: a review. *Environ Sci Pollut Res Int* 2019;**26**:26439–48. https://doi.org/10.1007/s11356-019-05802-x
59. Bothe A, Zouni A, Müh F. Refined definition of the critical micelle concentration and application to alkyl maltosides used in membrane protein research. *RSC Adv* 2023;**13**:9387–401. https://doi.org/10.1039/d2ra07440k
60. Cullinan P, Harris JM, Newman Taylor AJ, *et al*. An outbreak of asthma in a modern detergent factory. *Lancet* 2000;**356**:1899–900. https://doi.org/10.1016/s0140-6736(00)03264-5
61. Xian M, Wawrzyniak P, Rückert B, *et al*. Anionic surfactants and commercial detergents decrease tight junction barrier integrity in human keratinocytes. *J Allergy Clin Immunol* 2016;**138**:890–893.e9. https://doi.org/10.1016/j.jaci.2016.07.003
62. Rinaldi AO, Li M, Barletta E, *et al*. Household laundry detergents disrupt barrier integrity and induce inflammation in mouse and human skin. *Allergy* 2023;**79**:128–41. https://doi.org/10.1111/all.15891
63. Folletti I, Zock JP, Moscato G, *et al*. Asthma and rhinitis in cleaning workers: a systematic review of epidemiological studies. *J Asthma* 2014;**51**:18–28. https://doi.org/10.3109/02770903.2013.833217
64. Medina-Ramón M, Zock JP, Kogevinas M, *et al*. Asthma, chronic bronchitis, and exposure to irritant agents in occupational domestic cleaning: a nested case–control study. *Occup Environ Med* 2005;**62**:598–606. https://doi.org/10.1136/oem.2004.017640
65. Zock JP, Plana E, Jarvis D, *et al*. The use of household cleaning sprays and adult asthma: an international longitudinal study. *Am J Respir Crit Care Med* 2007;**176**:735–41. https://doi.org/10.1164/rccm.200612-1793OC
66. Dumas O, Wiley AS, Quinot C, *et al*. Occupational exposure to disinfectants and asthma control in US nurses. *Eur Respir J* 2017;**50**:50.
67. Shi Z. Gut microbiota: an important link between western diet and chronic diseases. *Nutrients* 2019;**11**:2287. https://doi.org/10.3390/nu11102287
68. Partridge D, Lloyd KA, Rhodes JM, *et al*. Food additives: assessing the impact of exposure to permitted emulsifiers on bowel and metabolic health - introducing the FADiets study. *Nutr Bull* 2019;**44**:329–49. https://doi.org/10.1111/nbu.12408
69. Snelson M, Tan SM, Clarke RE, *et al*. Processed foods drive intestinal barrier permeability and microvascular diseases. *Sci Adv* 2021;**7**:eabe4841. https://doi.org/10.1126/sciadv.abe4841
70. Miclotte L, Van de Wiele T. Food processing, gut microbiota and the globesity problem. *Crit Rev Food Sci Nutr* 2020;**60**:1769–82. https://doi.org/10.1080/10408398.2019.1596878
71. Ogulur I, Yazici D, Pat Y, *et al*. Mechanisms of gut epithelial barrier impairment caused by food emulsifiers polysorbate 20 and polysorbate 80. *Allergy* 2023;**78**:2441–55. https://doi.org/10.1111/all.15825
72. Lane MM, Davis JA, Beattie S, *et al*. Ultraprocessed food and chronic noncommunicable diseases: a systematic review and meta-analysis of 43 observational studies. *Obes Rev* 2021;**22**:e13146. https://doi.org/10.1111/obr.13146
73. Arenas-Jal M, Suñé-Negre JM, Pérez-Lozano P, *et al*. Trends in the food and sports nutrition industry: a review. *Crit Rev Food Sci Nutr* 2020;**60**:2405–21. https://doi.org/10.1080/10408398.2019.1643287
74. Sproesser G, Ruby MB, Arbit N, *et al*. Understanding traditional and modern eating: the TEP10 framework. *BMC Public Health* 2019;**19**:1606. https://doi.org/10.1186/s12889-019-7844-4
75. Narula N, Wong ECL, Dehghan M, *et al*. Association of ultra-processed food intake with risk of inflammatory bowel disease: prospective cohort study. *Bmj* 2021;**374**:n1554. https://doi.org/10.1136/bmj.n1554
76. Holder MK, Peters NV, Whylings J, *et al*. Dietary emulsifiers consumption alters anxiety-like and social-related behaviors in mice in a sex-dependent manner. *Sci Rep* 2019;**9**:172. https://doi.org/10.1038/s41598-018-36890-3
77. Laster J, Bonnes SL, Rocha J. Increased use of emulsifiers in processed foods and the links to obesity. *Curr Gastroenterol Rep* 2019;**21**:61. https://doi.org/10.1007/s11894-019-0723-4
78. Rhodes JM. Dietary exposure to emulsifiers and detergents and the prevalence of cardiovascular disease. *QJM* 2018;**111**:283–6. https://doi.org/10.1093/qjmed/hcx087
79. Zihni C, Mills C, Matter K, *et al*. Tight junctions: from simple barriers to multifunctional molecular gates. *Nat Rev Mol Cell Biol* 2016;**17**:564–80. https://doi.org/10.1038/nrm.2016.80
80. Stefanovic N, Flohr C, Irvine AD. The exposome in atopic dermatitis. *Allergy* 2020;**75**:63–74. https://doi.org/10.1111/all.13946
81. Saito K, Orimo K, Kubo T, *et al*. Laundry detergents and surfactants-induced eosinophilic airway inflammation by increasing IL-33 expression and activating ILC2s. *Allergy* 2023;**78**:1878–92. https://doi.org/10.1111/all.15762
82. Honda A, Inoue KI, Higashihara M, *et al*. Differential pattern of cell death and ROS production in human airway epithelial cells exposed to quinones combined with Heated-PM25 and/or Asian Sand Dust. *Int J Mol Sci* 2023;**24**:10544. https://doi.org/10.3390/ijms241310544
83. Han X, Zhuang Y. PM25 induces autophagy-mediated cell apoptosis via PI3K/AKT/mTOR signaling pathway in mice bronchial epithelium cells. *Exp Ther Med* 2021;**21**:1. https://doi.org/10.3892/etm.2020.9433
84. Wang Y, Zhong Y, Liao J, *et al*. PM25-related cell death patterns. *Int J Med Sci* 2021;**18**:1024–9. https://doi.org/10.7150/ijms.46421
85. Weng CM, Wang CH, Lee MJ, *et al*. Aryl hydrocarbon receptor activation by diesel exhaust particles mediates epithelium-derived cytokines expression in severe allergic asthma. *Allergy* 2018;**73**:2192–204. https://doi.org/10.1111/all.13462
86. Yang FM, Hu MC, Weng CM, *et al*. Loss of PP4 contributes to diesel exhaust particles-induced epithelial barrier integrity disruption and alarmins release. *Allergy* 2023;**78**:1670–3. https://doi.org/10.1111/all.15604
87. Ogbodo JO, Arazu AV, Iguh TC, *et al*. Volatile organic compounds: a proinflammatory activator in autoimmune diseases. *Front Immunol* 2022;**13**:928379. https://doi.org/10.3389/fimmu.2022.928379
88. Wang YL, Lee YH, Hsu YH, *et al*. The kidney-related effects of polystyrene microplastics on human kidney proximal tubular epithelial cells HK-2 and male C57BL/6 mice. *Environ Health Perspect* 2021;**129**:57003. https://doi.org/10.1289/EHP7612
89. Wang W, Guan J, Feng Y, *et al*. Polystyrene microplastics induced nephrotoxicity associated with oxidative stress, inflammation, and endoplasmic reticulum stress in juvenile rats. *Front Nutr* 2022;**9**:1059660. https://doi.org/10.3389/fnut.2022.1059660
90. Chi Q, Xu T, He Y, *et al*. Polystyrene nanoparticle exposure supports ROS-NLRP3 axis-dependent DNA-NET to promote liver inflammation. *J Hazard Mater* 2022;**439**:129502. https://doi.org/10.1016/j.jhazmat.2022.129502
91. Xu M, Halimu G, Zhang Q, *et al*. Internalization and toxicity: a preliminary study of effects of nanoplastic particles on human lung epithelial cell. *Sci Total Environ* 2019;**694**:133794. https://doi.org/10.1016/j.scitotenv.2019.133794
92. Akdis CA, Arkwright PD, Brüggen MC, *et al*. Type 2 immunity in the skin and lungs. *Allergy* 2020;**75**:1582–605. https://doi.org/10.1111/all.14318
93. Pat Y, Rückert B, Ogulur I, *et al*. Differentiation of bronchial epithelial spheroids in the presence of IL-13 recapitulates characteristic features of asthmatic airway epithelia. *Allergy* 2022;**77**:2229–33. https://doi.org/10.1111/all.15279
94. Gauvreau GM, Bergeron C, Boulet LP, *et al*. Sounding the alarmins—the role of alarmin cytokines in asthma. *Allergy* 2023;**78**:402–17. https://doi.org/10.1111/all.15609
95. Chidambaram SB, Essa MM, Rathipriya AG, *et al*. Gut dysbiosis, defective autophagy and altered immune responses in neurodegenerative diseases: tales of a vicious cycle. *Pharmacol Ther* 2022;**231**:107988. https://doi.org/10.1016/j.pharmthera.2021.107988
96. Rath E, Haller D. Intestinal epithelial cell metabolism at the interface of microbial dysbiosis and tissue injury. *Mucosal Immunol* 2022;**15**:595–604. https://doi.org/10.1038/s41385-022-00514-x

97. Gilliland A, Chan J, De Wolfe TJ, *et al*. Pathobionts in IBD: origins, underlying mechanisms, and implications for clinical care. *Gastroenterology* 2023;**66**:44–58.
98. Metwaly A, Reitmeier S, Haller D. Microbiome risk profiles as biomarkers for inflammatory and metabolic disorders. *Nat Rev Gastroenterol Hepatol* 2022;**19**:383–97. https://doi.org/10.1038/s41575-022-00581-2
99. Hülpüsch C, Weins AB, Traidl-Hoffmann C, *et al*. A new era of atopic eczema research: advances and highlights. *Allergy* 2021;**76**:3408–21. https://doi.org/10.1111/all.15058
100. Schwierzeck V, Hülpüsch C, Reiger M. Microbiome of barrier organs in allergy: who runs the world? Germs! *Handb Exp Pharmacol* 2022;**268**:53–65. https://doi.org/10.1007/164_2021_478
101. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet* 2020;**396**:345–60. https://doi.org/10.1016/S0140-6736(20)31286-1
102. Tramper-Stranders G, Ambrożej D, Arcolaci A, *et al*; EAACI Task Force on Conscious and Rational use of Antibiotics in Allergic Diseases. Dangerous liaisons: bacteria, antimicrobial therapies, and allergic diseases. *Allergy* 2021;**76**:3276–91. https://doi.org/10.1111/all.15046
103. Dickson RP. The microbiome and critical illness. *Lancet Respir Med* 2016;**4**:59–72. https://doi.org/10.1016/S2213-2600(15)00427-0
104. Barcik W, Boutin RCT, Sokolowska M, *et al*. The role of lung and gut microbiota in the pathology of asthma. *Immunity* 2020;**52**:241–55. https://doi.org/10.1016/j.immuni.2020.01.007
105. Brenchley JM, Douek DC. Microbial translocation across the GI tract. *Annu Rev Immunol* 2012;**30**:149–73. https://doi.org/10.1146/annurev-immunol-020711-075001
106. Ha CWY, Martin A, Sepich-Poore GD, *et al*. Translocation of viable gut microbiota to mesenteric adipose drives formation of creeping fat in humans. *Cell* 2020;**183**:666–683.e17. https://doi.org/10.1016/j.cell.2020.09.009
107. Dinh DM, Volpe GE, Duffalo C, *et al*. Intestinal microbiota, microbial translocation, and systemic inflammation in chronic HIV infection. *J Infect Dis* 2014;**211**:19–27. https://doi.org/10.1093/infdis/jiu409
108. Sandler NG, Douek DC. Microbial translocation in HIV infection: causes, consequences and treatment opportunities. *Nat Rev Microbiol* 2012;**10**:655–66. https://doi.org/10.1038/nrmicro2848
109. Brenchley JM, Price DA, Schacker TW, *et al*. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* 2006;**12**:1365–71. https://doi.org/10.1038/nm1511
110. Kumar NP, Venkataraman A, Hanna LE, *et al*. Systemic inflammation and microbial translocation are characteristic features of SARS-CoV-2-related multisystem inflammatory syndrome in children. *Open Forum Infect Dis* 2021;**8**:ofab279. https://doi.org/10.1093/ofid/ofab279
111. Ma L, Morel L. Loss of gut barrier integrity in Lupus. *Front Immunol* 2022;**13**:919792. https://doi.org/10.3389/fimmu.2022.919792
112. Gupta B, Rai R, Oertel M, *et al*. Intestinal barrier dysfunction in fatty liver disease: roles of microbiota, mucosal immune system, and bile acids. *Semin Liver Dis* 2022;**42**:122–37. https://doi.org/10.1055/s-0042-1748037
113. Yang Y, Nguyen M, Khetrapal V, *et al*. Within-host evolution of a gut pathobiont facilitates liver translocation. *Nature* 2022;**607**:563–70. https://doi.org/10.1038/s41586-022-04949-x
114. Tilg H, Zmora N, Adolph TE, *et al*. The intestinal microbiota fuelling metabolic inflammation. *Nat Rev Immunol* 2020;**20**:40–54. https://doi.org/10.1038/s41577-019-0198-4
115. Stolfi C, Maresca C, Monteleone G, *et al*. Implication of intestinal barrier dysfunction in gut dysbiosis and diseases. *Biomedicines* 2022;**10**:289. https://doi.org/10.3390/biomedicines10020289
116. Geoghegan JA, Irvine AD, Foster TJ. *Staphylococcus aureus* and atopic dermatitis: a complex and evolving relationship. *Trends Microbiol* 2018;**26**:484–97. https://doi.org/10.1016/j.tim.2017.11.008
117. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014;**157**:121–41. https://doi.org/10.1016/j.cell.2014.03.011
118. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res* 2020;**30**:492–506. https://doi.org/10.1038/s41422-020-0332-7
119. Rath E, Haller D. Intestinal epithelial cell metabolism at the interface of microbial dysbiosis and tissue injury. *Mucosal Immunol* 2022;**15**:595–604. https://doi.org/10.1038/s41385-022-00514-x
120. Heijink IH, Kuchibhotla VNS, Roffel MP, *et al*. Epithelial cell dysfunction, a major driver of asthma development. *Allergy* 2020;**75**:1902–17. https://doi.org/10.1111/all.14421
121. Soyka MB, Wawrzyniak P, Eiwegger T, *et al*. Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN-γ and IL-4. *J Allergy Clin Immunol* 2012;**130**:1087–1096.e10. https://doi.org/10.1016/j.jaci.2012.05.052
122. Zhang N, Van Crombruggen K, Gevaert E, *et al*. Barrier function of the nasal mucosa in health and type-2 biased airway diseases. *Allergy* 2016;**71**:295–307. https://doi.org/10.1111/all.12809
123. Steelant B, Farré R, Wawrzyniak P, *et al*. Impaired barrier function in patients with house dust mite-induced allergic rhinitis is accompanied by decreased occludin and zonula occludens-1 expression. *J Allergy Clin Immunol* 2016;**137**:1043–1053.e5. https://doi.org/10.1016/j.jaci.2015.10.050
124. Simon D, Cianferoni A, Spergel JM, *et al*. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy* 2016;**71**:611–20. https://doi.org/10.1111/all.12846
125. Simon D, Page B, Vogel M, *et al*. Evidence of an abnormal epithelial barrier in active, untreated and corticosteroid-treated eosinophilic esophagitis. *Allergy* 2018;**73**:239–47. https://doi.org/10.1111/all.13244
126. Davis BP, Rothenberg ME. Mechanisms of disease of eosinophilic esophagitis. *Annu Rev Pathol* 2016;**11**:365–93. https://doi.org/10.1146/annurev-pathol-012615-044241
127. Odenwald MA, Turner JR. The intestinal epithelial barrier: a therapeutic target? *Nat Rev Gastroenterol Hepatol* 2017;**14**:9–21. https://doi.org/10.1038/nrgastro.2016.169
128. Verdu EF, Schuppan D. Co-factors, microbes, and immunogenetics in Celiac disease to guide novel approaches for diagnosis and treatment. *Gastroenterology* 2021;**161**:1395–1411.e4. https://doi.org/10.1053/j.gastro.2021.08.016
129. Thaiss CA, Levy M, Grosheva I, *et al*. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. *Science* 2018;**359**:1376–83. https://doi.org/10.1126/science.aar3318
130. Wilbrink J, Bernards N, Mujagic Z, *et al*. Intestinal barrier function in morbid obesity: results of a prospective study on the effect of sleeve gastrectomy. *Int J Obes (Lond)* 2020;**44**:368–76. https://doi.org/10.1038/s41366-019-0492-z
131. Horton F, Wright J, Smith L, *et al*. Increased intestinal permeability to oral chromium (51 Cr)—EDTA in human type 2 diabetes. *Diabet Med* 2014;**31**:559–63. https://doi.org/10.1111/dme.12360
132. Sharma S, Tripathi P. Gut microbiome and type 2 diabetes: where we are and where to go? *J Nutr Biochem* 2019;**63**:101–8. https://doi.org/10.1016/j.jnutbio.2018.10.003
133. Tajik N, Frech M, Schulz O, *et al*. Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. *Nat Commun* 2020;**11**:1995. https://doi.org/10.1038/s41467-020-15831-7
134. Camara-Lemarroy CR, Silva C, Greenfield J, *et al*. Biomarkers of intestinal barrier function in multiple sclerosis are associated with disease activity. *Mult Scler* 2020;**26**:1340–50. https://doi.org/10.1177/1352458519863133
135. Miele L, Valenza V, La Torre G, *et al*. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology* 2009;**49**:1877–87. https://doi.org/10.1002/hep.22848
136. Lin R, Zhou L, Zhang J, *et al*. Abnormal intestinal permeability and microbiota in patients with autoimmune hepatitis. *Int J Clin Exp Pathol* 2015;**8**:5153–60.
137. Ciccia F, Guggino G, Rizzo A, *et al*. Dysbiosis and zonulin upregulation alter gut epithelial and vascular barriers in patients with ankylosing spondylitis. *Ann Rheum Dis* 2017;**76**:1123–32. https://doi.org/10.1136/annrheumdis-2016-210000

138. Fiorentino M, Sapone A, Senger S, *et al*. Blood–brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. *Mol Autism* 2016;**7**:49. https://doi.org/10.1186/s13229-016-0110-z
139. van ISCD, Derkinderen P. The intestinal barrier in Parkinson's disease: current state of knowledge. *J Parkinsons Dis* 2019;**9**:S323–s329.
140. Pellegrini C, Antonioli L, Colucci R, *et al*. Interplay among gut microbiota, intestinal mucosal barrier and enteric neuro-immune system: a common path to neurodegenerative diseases? *Acta Neuropathol* 2018;**136**:345–61. https://doi.org/10.1007/s00401-018-1856-5
141. Köhler CA, Maes M, Slyepchenko A, *et al*. The gut–brain axis, including the microbiome, leaky gut and bacterial translocation: mechanisms and pathophysiological role in Alzheimer's disease. *Curr Pharm Des* 2016;**22**:6152–66. https://doi.org/10.2174/1381612822666160907093807
142. Kelly JR, Kennedy PJ, Cryan JF, *et al*. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Front Cell Neurosci* 2015;**9**:392. https://doi.org/10.3389/fncel.2015.00392
143. Maes M, Kubera M, Leunis JC, *et al*. Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. *J Affect Disord* 2012;**141**:55–62. https://doi.org/10.1016/j.jad.2012.02.023
144. Ferrucci S, Romagnuolo M, Maronese CA, *et al*. Skin barrier status during dupilumab treatment in patients with severe atopic dermatitis. *Ther Adv Chronic Dis* 2021;**12**:20406223211058332. https://doi.org/10.1177/20406223211058332
145. Berdyshev E, Goleva E, Bissonnette R, *et al*. Dupilumab significantly improves skin barrier function in patients with moderate-to-severe atopic dermatitis. *Allergy* 2022;**77**:3388–97. https://doi.org/10.1111/all.15432
146. Wechsler ME. Inhibiting interleukin-4 and interleukin-13 in difficult-to-control asthma. *N Engl J Med* 2013;**368**:2511–3. https://doi.org/10.1056/NEJMe1305426
147. Wenzel S, Ford L, Pearlman D, *et al*. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013;**368**:2455–66. https://doi.org/10.1056/NEJMoa1304048
148. Bachert C, Han JK, Desrosiers M, *et al*. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019;**394**:1638–50. https://doi.org/10.1016/S0140-6736(19)31881-1
149. Velasco E, Delicado-Miralles M, Hellings PW, *et al*. Epithelial and sensory mechanisms of nasal hyperreactivity. *Allergy* 2022;**77**:1450–63. https://doi.org/10.1111/all.15259
150. Pfaar O, Fritzsching B, Wolf H, *et al*. How does allergen immunotherapy-induced tolerance improve the airway epithelial barrier function: a mechanistical-driven hypothesis. *Allergy* 2023;**78**:2577–80. https://doi.org/10.1111/all.15835
151. Castro M, Corren J, Pavord ID, *et al*. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;**378**:2486–96. https://doi.org/10.1056/NEJMoa1804092
152. Pavord ID, Bourdin A, Papi A, *et al*. Dupilumab sustains efficacy in patients with moderate-to-severe type 2 asthma regardless of ICS dose. *Allergy* 2023;**78**:2921–32. https://doi.org/10.1111/all.15792
153. Kortekaas Krohn I, Seys SF, Lund G, *et al*. Nasal epithelial barrier dysfunction increases sensitization and mast cell degranulation in the absence of allergic inflammation. *Allergy* 2020;**75**:1155–64. https://doi.org/10.1111/all.14132
154. Andiappan AK, Asad M, Chua C, *et al*. Neutrophilic inflammation and epithelial barrier disruption in nasal polyps characterize non-steroidal anti-inflammatory drug exacerbated respiratory disease. *Allergy* 2022;**77**:1297–9. https://doi.org/10.1111/all.15198
155. Zhang C, Wang Y, Liao W, *et al*. MUC1 deficiency induces the nasal epithelial barrier dysfunction via RBFOX3 shortage augment ubiquitin-proteasomal degradation in allergic rhinitis pathogenesis. *Allergy* 2022;**77**:1596–9. https://doi.org/10.1111/all.15235
156. Callejas-Diaz B, Fernandez G, Fuentes M, *et al*. Integrated mRNA and microRNA transcriptome profiling during differentiation of human nasal polyp epithelium reveals an altered ciliogenesis. *Allergy* 2020;**75**:2548–61. https://doi.org/10.1111/all.14307
157. Gawrysiak M, Gajewski A, Szewczyk R, *et al*. Human rhinovirus HRV16 impairs barrier functions and regeneration of human lung vascular endothelium. *Allergy* 2021;**76**:1872–5. https://doi.org/10.1111/all.14671
158. Avlas S, Shani G, Rhone N, *et al*. Epithelial cell-expressed type II IL-4 receptor mediates eosinophilic esophagitis. *Allergy* 2022;**78**:464–76. https://doi.org/10.1111/all.15510
159. Zhang B, Roesner LM, Traidl S, *et al*. Single-cell profiles reveal distinctive immune response in atopic dermatitis in contrast to psoriasis. *Allergy* 2023;**78**:439–53. https://doi.org/10.1111/all.15486
160. Pavel AB, Renert-Yuval Y, Wu J, *et al*. Tape strips from early-onset pediatric atopic dermatitis highlight disease abnormalities in nonlesional skin. *Allergy* 2021;**76**:314–25. https://doi.org/10.1111/all.14490
161. Rinnov MR, Halling AS, Gerner T, *et al*. Skin biomarkers predict development of atopic dermatitis in infancy. *Allergy* 2023;**78**:791–802. https://doi.org/10.1111/all.15518
162. Mitamura Y, Reiger M, Kim J, *et al*. Spatial transcriptomics combined with single-cell RNA-sequencing unravels the complex inflammatory cell network in atopic dermatitis. *Allergy* 2023;**78**:2215–31. https://doi.org/10.1111/all.15781
163. Rapin A, Rehbinder EM, Macowan M, *et al*. The skin microbiome in the first year of life and its association with atopic dermatitis. *Allergy* 2023;**78**:1949–63. https://doi.org/10.1111/all.15671
164. Kim J, Kim BE, Berdyshev E, *et al*. *Staphylococcus aureus* causes aberrant epidermal lipid composition and skin barrier dysfunction. *Allergy* 2023;**78**:1292–306. https://doi.org/10.1111/all.15640
165. Yin H, Qiu Z, Zhu R, *et al*. Dysregulated lipidome of sebum in patients with atopic dermatitis. *Allergy* 2023;**78**:1524–37. https://doi.org/10.1111/all.15569
166. Stuvel K, Heeringa JJ, Dalm V, *et al*. Comel-Netherton syndrome: a local skin barrier defect in the absence of an underlying systemic immunodeficiency. *Allergy* 2020;**75**:1710–20.
167. Mouries J, Brescia P, Silvestri A, *et al*. Microbiota-driven gut vascular barrier disruption is a prerequisite for non-alcoholic steatohepatitis development. *J Hepatol* 2019;**71**:1216–28. https://doi.org/10.1016/j.jhep.2019.08.005
168. Portincasa P, Bonfrate L, Khalil M, *et al*. Intestinal barrier and permeability in health, obesity and NAFLD. *Biomedicines* 2021;**10**:83. https://doi.org/10.3390/biomedicines10010083
169. Gibbens YY, Lansing R, Johnson ML, *et al*. Effects of central obesity on esophageal epithelial barrier function. *Am J Gastroenterol* 2021;**116**:1537–41. https://doi.org/10.14309/ajg.0000000000001196
170. Ahmad R, Rah B, Bastola D, *et al*. Obesity-induces organ and tissue specific tight junction restructuring and barrier deregulation by Claudin Switching. *Sci Rep* 2017;**7**:5125. https://doi.org/10.1038/s41598-017-04989-8
171. Kelly JR, Borre Y, O'Brien C, *et al*. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. *J Psychiatr Res* 2016;**82**:109–18.