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Recent advances in the epithelial barrier theory

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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.

REVIEW

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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.

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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

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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),

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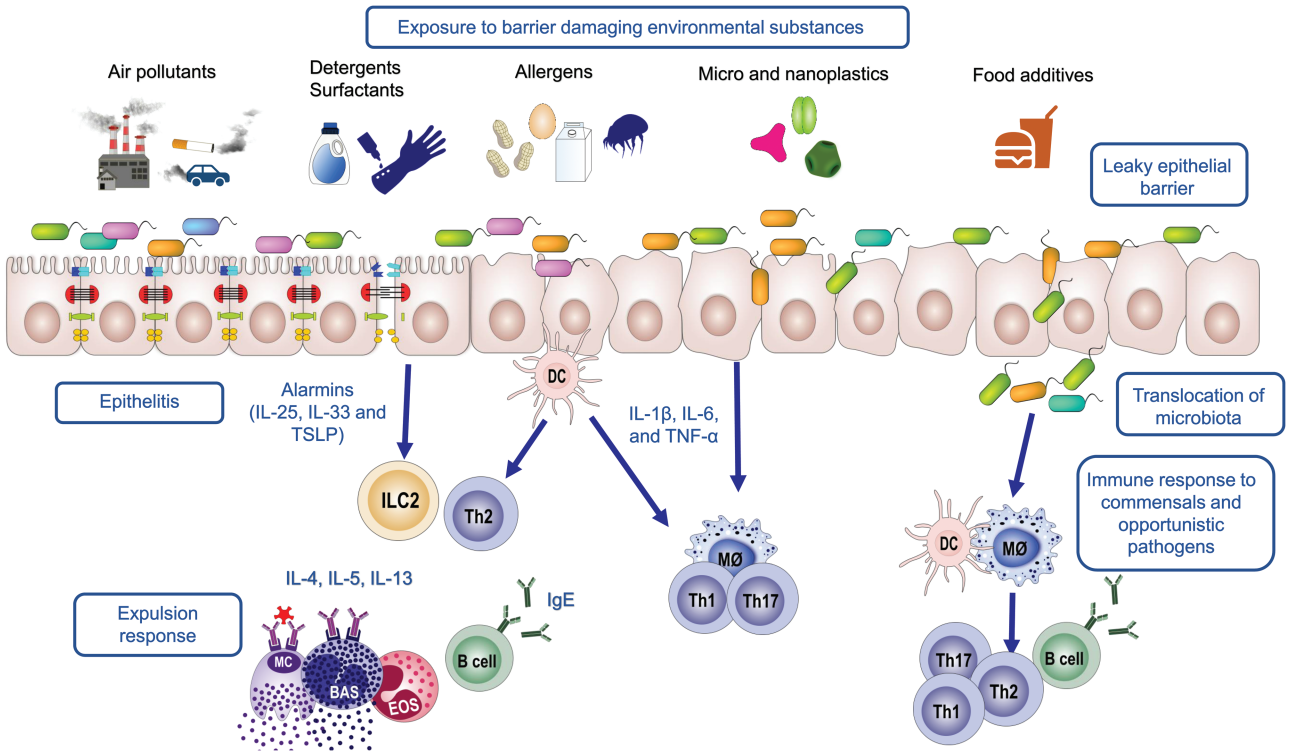


Figure 1. Epithelial barrier impairment by environmental substances. These hazardous factors, including air pollutants (particulate matter, cigarette smoke, volatile organic compounds, etc.), detergents, surfactants, hand disinfectants, allergens (peanut, egg, milk, house dust mite, pollen, etc.), micro- 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

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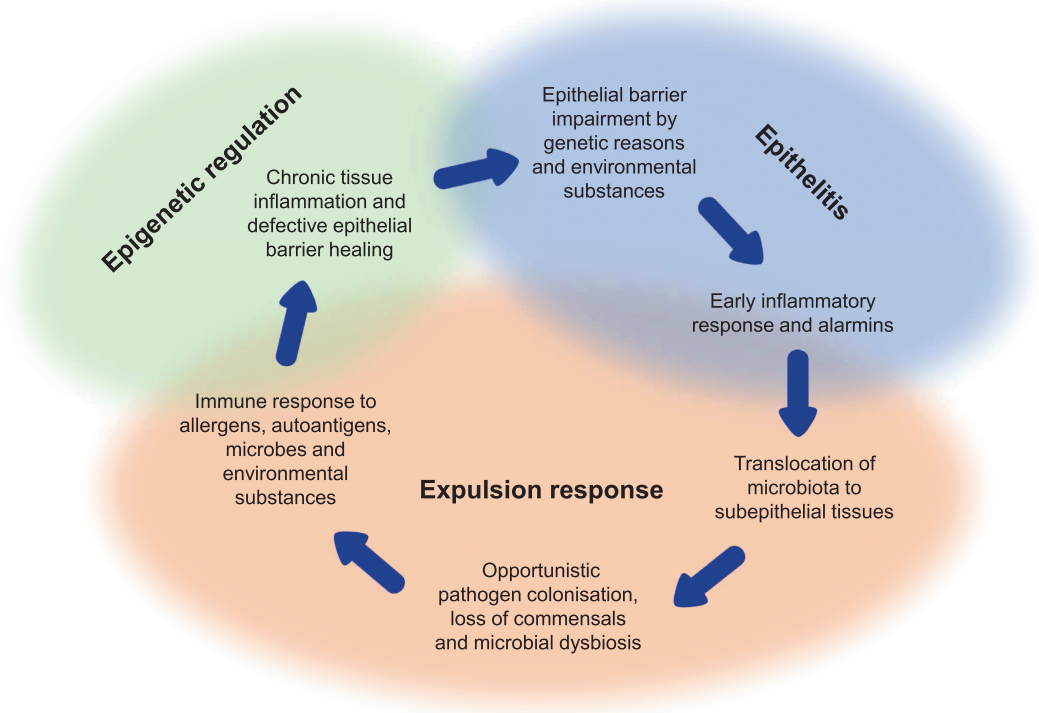


Figure 2. Epithelial barrier-damaging substances cause a vicious cycle. These substances cause epithelitis characterized by an impaired epithelial barrier and by inflammation. Loss of epithelial barrier integrity allows translocation of microbiota to the subepithelial tissues. Ongoing inflammation and 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

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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.

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