The epithelial barrier hypothesis proposes a comprehensive understanding of the origins of allergic and other chronic noncommunicable diseases

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A steep increase in the prevalence of many chronic noncommunicable diseases occurred during the last 60 years, bringing them to a pandemic size.[1] Our research and efforts to explain the reasons for this rise in their prevalence helped to develop the epithelial barrier hypothesis. This hypothesis posits that disturbance of the epithelial barriers by laundry and dishwasher detergents, household cleaners, surfactants, enzymes and emulsifiers used in the food industry, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles, and microplastics cause tissue inflammation and microbial dysbiosis and play a role in many chronic noncommunicable diseases.[1] The "epithelial barrier hypothesis" proposes mechanisms for the development of diseases of allergic, autoimmune, and neurodegenerative nature, with inflammation and tissue damage in the directly affected organs or distant organs that are not located directly at the skin and mucosal surfaces; accepts and embraces the hygiene and biodiversity hypotheses and links them to epithelial barrier defects and microbial dysbiosis; demonstrates possible ways of prevention of allergic and autoimmune diseases; and suggests future research directions.[1] There is a need to support science and advance the understanding of the factors and molecular mechanisms associated with leaky epithelial barriers and inform policymakers of the detrimental effects of the potential causal or contributing substances. Here, I summarize the molecular and cellular mechanisms of the "epithelial barrier hypothesis" and supporting evidence.

EPIDEMIC INCREASE IN CHRONIC NONCOMMUNICABLE DISEASES CAUSED BY EPITHELIAL BARRIER LEAKINESS

Since the 1960s, history has been marked by a pandemic increase in the prevalence of allergic, autoimmune, and neurodegenerative diseases, affecting more than 2 billion individuals.[1] After 2000, a new wave of diseases, such as food allergy, eosinophilic esophagitis, and drug-induced anaphylaxis, grew into pandemic sizes.[1] The first group of diseases, such as asthma, atopic dermatitis, chronic rhinosinusitis, allergic rhinitis, eosinophilic esophagitis, inflammatory bowel, and celiac diseases, shows that the affected organ's local epithelial tissue is inflamed. The second group consists of metabolic and autoimmune diseases, which are associated with gut or lung epithelial barrier defects, such as obesity, diabetes mellitus, rheumatoid arthritis, multiple sclerosis, fatty liver, autoimmune hepatitis, systemic lupus erythematosus, ankylosing spondylitis, inflammatory bowel, and celiac disease.[1] There have been detailed studies proposing how these diseases may be triggered or aggravated by distant inflammatory reactions in response to dysbiotic changes in the gut or lung immune cells and microbiome.[1-3] In addition, increased intestinal barrier leakiness has been linked with neuropsychiatric disorders such as Parkinson disease, Alzheimer disease, stress-related psychiatric diseases, autism spectrum disorders, and chronic depression[1] (Fig 1).

ENVIRONMENTAL EXPOSURE TO SUBSTANCES THAT CAUSE EPITHELIAL BARRIER DAMAGE

Because of urbanization and modernization, humans started to be exposed to numerous toxins and chemicals after the 1960s (Fig 2). An essential burden to the integrity of the skin and mucosal epithelial barriers was the introduction of anionic surfactants and enzymes in laundry detergents to improve cleaning efficiency and stain removal in the 1960s. Occupational detergent exposure has been linked epidemiologically with asthma, rhinitis, and atopic dermatitis.[1] In experimental models, RNA-sequencing transcriptome of bronchial epithelial cells exposed to 50,000-times-diluted laundry detergent demonstrated an inflamed and disintegrated chronic wound that tries to heal and survive its cells. Together with increased IL-33 expression, the upregulated genes were associated with lipid metabolism, oxidative stress, and cell survival, and the downregulated genes were associated with cell adhesion, extracellular matrix organization, and wound healing.[4] Postrinse fluid collected from towels and clothes at the end of the laundry cycle still contains active detergents and surfactants that can hamper the epithelial tight junction (TJ) barriers.[4] Sodium dodecyl sulfate and sodium dodecylbenzene sulphonate are

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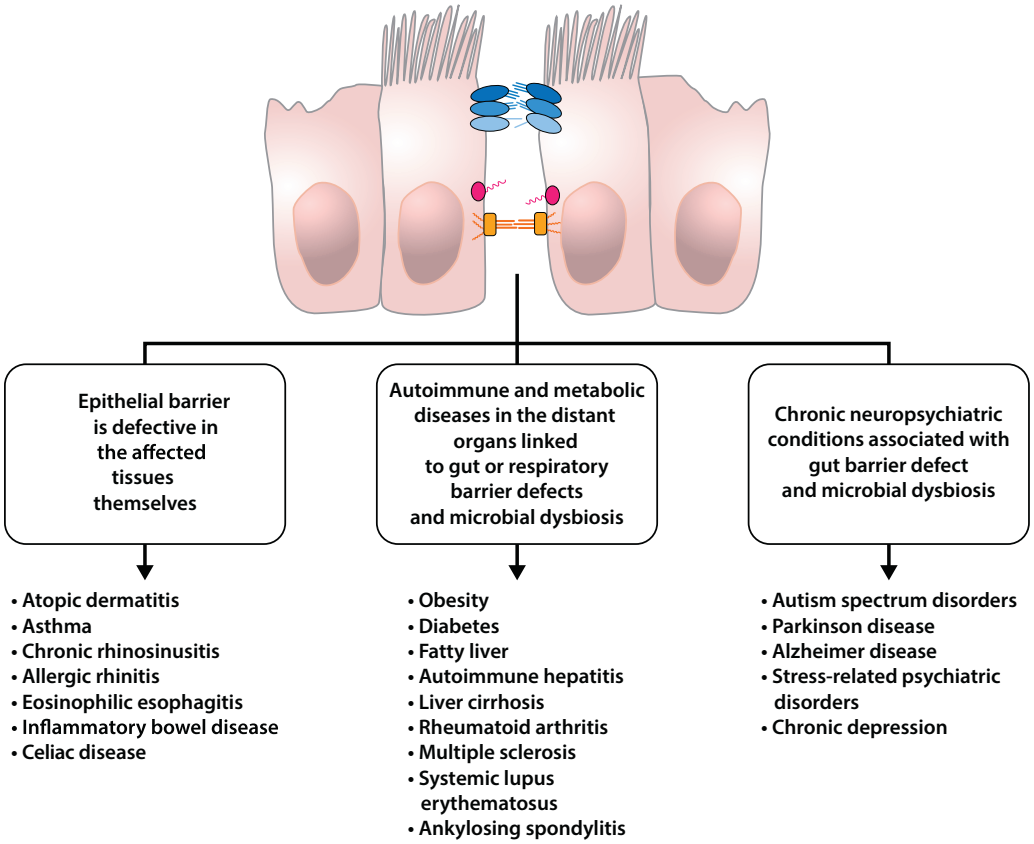


FIG 1. Diseases linked to epithelial barrier defects: Three groups of diseases are associated with epithelial barrier damage and microbial dysbiosis: (1) epithelial barrier defect and microbial dysbiosis in directly affected tissues; (2) distant autoimmune and metabolic diseases linked to gut barrier defects and microbial dysbiosis; and (3) chronic neuropsychiatric conditions linked to a gut barrier defect and microbial dysbiosis.

commonly used surfactants in laundry detergents, soaps, shampoos, cosmetics, and cleaning products. They injure the TJ barrier of the lung and skin epithelium at extremely high dilutions.[5] Unfortunately, daily exposure of healthy individuals and patients to tissue-barrier–damaging doses of laundry detergents, professional dishwashers, and household cleaners is still a threat today.

Increasing evidence also suggests a detrimental effect of the widespread use of emulsifiers in the food industry, a proposed important factor behind the increase in many gut barrier–related diseases. Processed food emulsifiers can increase intestinal permeability, even at low concentrations, leading to mucosal damage observed in villous atrophy in hamsters.[6] Trace amounts of many approved food emulsifiers use pathophysiological mechanisms similar to detergents with surface tension changes and direct cellular toxicity. Emulsifiers may also cause epithelial cell activation due to the dysfunction of the epithelial barrier and bacterial translocation across epithelial cells.

MOLECULAR AND CELLULAR MECHANISMS EXPLAINING THE EPITHELIAL BARRIER HYPOTHESIS

In addition to environmental toxic substances, subepithelial tissue inflammation disrupts epithelial barriers. Epithelial cell activation and release of epithelial cell cytokines, such as the alarmins IL-25, IL-33, and thymic stromal lymphopoietin, play a significant role in causing and exacerbating allergic diseases.[7] Open epithelial TJs in the mucosa help drain subepithelial inflammation while simultaneously allowing the entrance of foreign substances into deeper tissues. Both type 1 and type 2 inflammation affect the skin and mucosal epithelial barriers. Type 1 inflammation below the mucosal surface is marked by an opening of the barrier followed by direct tissue injury by inducing apoptosis of the epithelial cells.[7] Both T_H2 and type 2 innate lymphoid cells play major roles in type 2 inflammation through their cytokines IL-4 and IL-13, which disrupt bronchial, sinus, and skin epithelial barriers, as recently shown.[8-10] A synergistic effect between the aforementioned toxic substances should be considered in addition to an additive effect, because of similar mechanisms of toxicity. Furthermore, exposures to epithelial-disrupting substances are likely to affect barrier physiology at lower concentrations, if the skin or mucosa is inflamed before exposure.

Cascade of events has been proposed as pathogenetic mechanisms linked to the epithelial barrier hypothesis (Fig 2).[1] Microbial dysbiosis resulting from tissue colonization by opportunistic pathogens, followed by transepithelial translocation of opportunistic pathogens and commensals to the subepithelium, results in stimulation of the immune system and subepithelial or submucosal inflammation.[1] Decreased biodiversity develops, because of an adaptive immune response against commensals together with opportunistic pathogens and tissue inflammation. For example, anti–*Staphylococcus aureus* IgE response and *S aureus* epithelial colonization are hallmarks of asthma, atopic dermatitis, and chronic rhinosinusitis currently, which was not

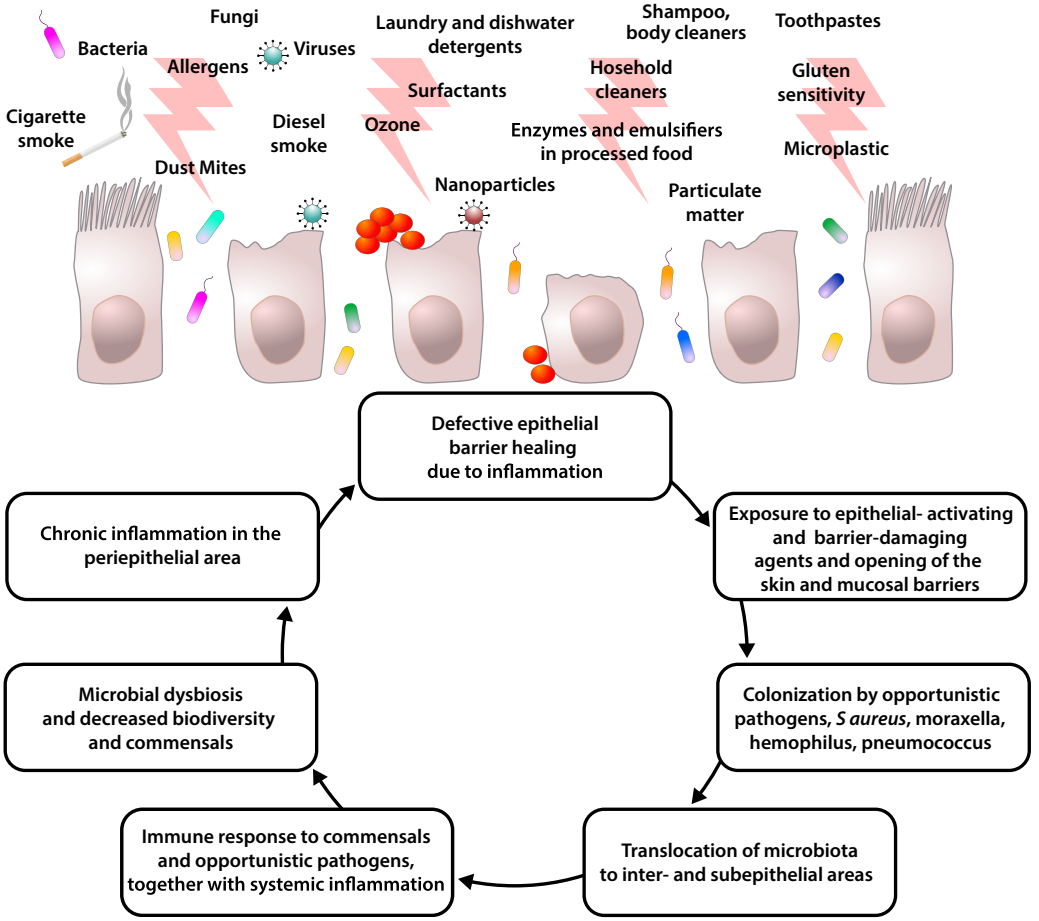


FIG 2. The physiopathology involved in the epithelial barrier hypothesis: The vicious cycle of chronic epithelial barrier dysfunction. Genetic defects in barrier-related molecules or exposure to epithelial barrier–damaging agents cause a disruption of the skin and mucosal TJ barriers. A cascade of events develop that play a role in the pathogenesis of diseases associated with the epithelial barrier hypothesis.

the case in the 1980s. A dysregulated subepithelial immune response, inflammation, and dysfunctional regeneration and remodeling occur through the continuum and chronicity of the local inflammation. Epithelial basement membrane (*Lamina reticularis*) thickening and fibrosis are potentially a mucosal response to develop a secondary barrier following disruption of the primary epithelial barrier. The migration of inflamed cells from leaky barrier areas to other affected tissues and systemic low-level immune activation and microinflammation are potential factors in developing and exacerbating many chronic inflammatory diseases.

CONCLUSIONS

There is sufficient epidemiological evidence in humans and disease models demonstrating that even trace amounts of substances, currently considered safe, can damage epithelial barriers and increase bacterial translocation. Certain members of the population may be at greater risk due to genetic factors. Therefore, avoidance of these substances may be beneficial in reducing the occurrence or the severity of specific chronic noncommunicable diseases. Strategies to reduce illnesses associated with a disrupted epithelial barrier include reduced exposure or complete avoidance of these possibly causal substances. In addition, the epithelial barrier hypothesis may show the importance of more effective screening of new chemicals used in daily life, may stimulate the development of safer products, and may spur the identification of biomarkers to identify and monitor individuals at risk of barrier dysfunction. Finally, studies to develop preventive or therapeutic approaches with interventions through changes in lifestyle, diet, and microbiome are needed.

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