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Review

The Impact of the Exposome on Epithelial Barriers: New Approach Methodologies for Translational Research

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ABSTRACT

Environmental exposures experienced throughout life, collectively referred to as the exposome, play a fundamental role in shaping epithelial barrier integrity, repair capacity, and vulnerability to disease. These exposures encompass a broad spectrum of chemical, physical, biological, and lifestyle-related factors. Despite growing recognition of their importance, a key unresolved challenge is understanding how single exposures and, more importantly, complex real-world exposure mixtures jointly disrupt epithelial organization, stem and progenitor cell niches, and immune-epithelial communication across different organs. This review consolidates current evidence on environmentally relevant exposomes that directly affect epithelial barrier function and examines their consequences for tissue architecture, niche stability, and frontline defense mechanisms. We further discuss recent advances in new approach methodologies, including organ-specific epithelial barrier models, organoids, organ-on-a-chips, and interconnected multi-organ platforms. By synthesizing evidence across organ systems, we highlight convergent biological processes, such as oxidative stress, inflammatory signaling, disruption of intercellular junctions, and impaired epithelial survival or regeneration, as shared pathways linking environmental stressors to barrier failure. We hope that this review will help bridge exposure science, epithelial biology, and bioengineered human-based models to define critical knowledge gaps and key translational priorities for the field.

KEYWORDS: Epithelial barrier, environmental exposome, NAMs, organ-axis models

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INTRODUCTION

Epithelial barrier integrity has emerged as a fundamental determinant of immune homeostasis and disease susceptibility; the epithelial barrier hypothesis proposes that progressive disruption of barrier integrity by environmental stressors drives chronic inflammation and disease.[1] The human body is in continuous interaction with a wide range of environmental stimuli from the earliest stages of life until death. This complex and dynamic network of interactions is captured by the concept of the exposome, which encompasses all environmental exposures experienced across the lifespan and provides a critical framework for understanding the origins of human disease and for identifying potential therapeutic strategies.[2] According to the European Academy of Allergy and Clinical Immunology guidelines, the exposome-which integrates indoor and outdoor factors, such as air, water, and soil pollution, wildfires, dust storms, nutrition, pathogens, and radiation, with internal biological processes including metabolism, inflammation, DNA damage responses, and oxidative stress–fundamentally shapes the trajectory of health and disease.[3-6]

The principal epithelial tissues of the human body include those that line the respiratory tract, the gastrointestinal system, and the skin. Beyond their structural roles, epithelial barriers regulate molecular transport, activate immune responses, and help maintain microbial tolerance, thereby coordinating frontline defense mechanisms against environmental challenges.[7-9] According to the epithelial barrier hypothesis, increasing environmental pressures associated with climate change and extreme atmospheric conditions have intensified exposure to a broad spectrum of agents that compromise barrier integrity. These include airborne pollutants, particulate matter (PM), volatile organic compounds (VOCs), ozone, household chemicals, micro- and nanoplastics (MNPs), aeroallergens, bioaerosols, pollen, diesel exhaust emissions, and dietary components such as food emulsifiers that directly damage epithelial barriers.[10-12] Such exposures rarely occur in isolation; rather, they manifest as complex mixtures that collectively disrupt the tightly regulated architecture of epithelial tissues across multiple organ systems. The emergence of an increasingly aggressive and difficult-to-control exposome is largely driven by rapid technological advancement and modern lifestyle factors, including the widespread consumption of ultra-processed foods and the routine use of chemically complex household cleaning and cosmetic products. In parallel, the exponential growth of electronic waste and its largely informal recycling have introduced a poorly regulated and inequitable source of environmental exposure at the global level.[13] Notably, this complex exposome landscape coincides with a marked global rise in chronic non-communicable diseases, including obesity, cardiovascular disorders, cancer, respiratory diseases such as asthma, autoimmune conditions, mental health issues, and neurodegenerative disorders, including Alzheimer's disease, as well as preterm birth in infants.[3,14-16] Accumulating epidemiological and experimental evidence links this trend to cumulative exposure (exposome) and its long-term effects on epithelial barrier integrity and immune regulation. Addressing the complexity of exposome-driven epithelial dysfunction requires experimental systems that extend beyond reductionist approaches. In this context, *in vitro* organotropic and microphysiological models have emerged as indispensable tools for mechanistic and translational research. New approach methodologies (NAMs), including organoids and organ-on-a-chip (OoC) platforms, enable reconstruction of three-dimensional (3D) *in vivo*-like architecture and modeling of functional epithelial barriers under biologically relevant exposure conditions.[17,18] Importantly, this technological shift is being reinforced by evolving regulatory frameworks; recent U.S. Food and Drug Administration (FDA) initiatives, including the FDA Modernization Act reforms and subsequent NAMs-oriented guidance, which were further expanded by updates such as Act 3.0, approved in early 2026 are accelerating the adoption of human-relevant experimental systems by encouraging the integration of artificial intelligence, organoid-based assays, and microphysiological platforms.[19]

Main Points

- Lifelong environmental exposures collectively shape epithelial barrier integrity, repair capacity, and susceptibility to disease.
- Complex real-world exposome mixtures disrupt epithelial organization, stem cell niches, and immune-epithelial interactions across organs.
- Oxidative stress, inflammation, and junctional dysfunction represent common pathways linking environmental stressors to epithelial barrier failure.
- Human-relevant new approach methodologies, including organoids and organ-on-a-chip platforms, enable mechanistic and translational investigations into exposome-driven epithelial dysfunction.

In this review, we provide a comprehensive overview of environmental exposomes related to epithelial function and the physiological roles of epithelial barriers examine how *in vitro* microphysiological tools are used to interrogate the complexity of the exposome-driven interactome. We then survey the established and emerging molecular mechanisms underlying epithelial barrier damage and discuss how these processes influence disease initiation and progression. Building on this framework, we synthesize evidence across organ systems to examine how single exposures and complex, real-world exposure mixtures disrupt epithelial organization, niche stability, and immune-epithelial communication, to highlight convergent pathways linking environmental stressors to barrier dysfunction, and to explore how next-generation NAMs can be used to move the field from descriptive associations toward mechanistic and predictive understanding (Figure 1).

ENVIRONMENTAL EXPOSOMES RELEVANT TO EPITHELIAL FUNCTION

Epithelial tissues constitute the primary interface of the human body with the external environment and are therefore continuously exposed to a wide range of environmental stressors. The concept of the environmental exposome has provided a comprehensive framework to understand how lifelong exposure to chemical, physical, and biological factors influences epithelial barrier integrity, tissue regeneration, and disease susceptibility.[20] Rather than acting as passive barriers, epithelial surfaces actively sense environmental cues and

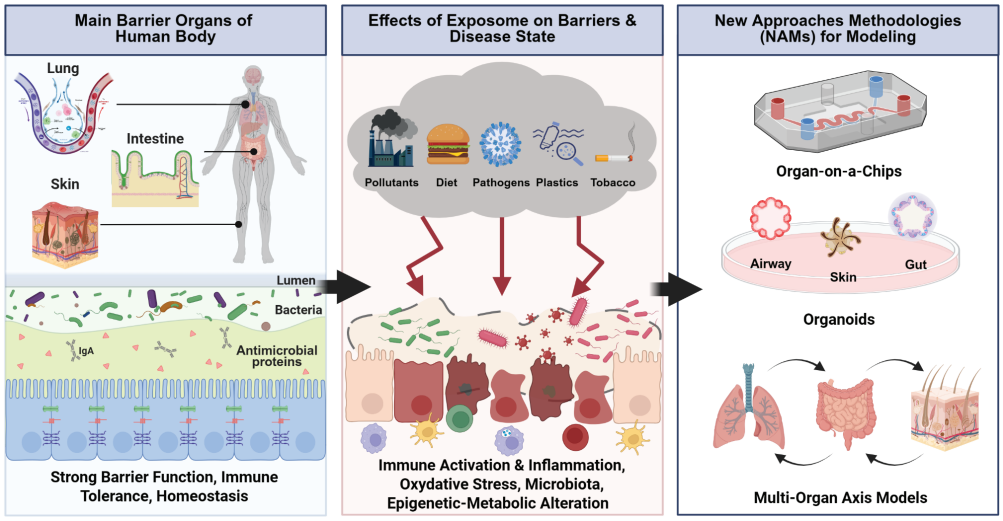

Figure 1. Overview of how environmental exposures compromise healthy epithelial integrity to drive chronic inflammation, and the application of NAMs as OoC and organoids to model these interactions. Created with BioRender.com

NAMs: new approach methodologies, OoC: organ-on-a-chip

translate them into molecular and cellular responses that shape immune activation, metabolic adaptation, and repair processes. The biological consequences of this co-exposure reality are therefore rarely captured by single-agent experimental paradigms, which may substantially underestimate the cumulative and often synergistic impact of the real-world exposome.

Airborne PM is among the most extensively studied exposome components affecting epithelial function. While PM2.5 mass concentration has historically served as a regulatory metric, accumulated evidence suggests that epithelial toxicity is driven primarily by particle composition and chemical reactivity rather than by particle mass alone.[21] Studies have demonstrated that specific PM2.5 species and ultrafine particle fractions are associated with distinct metabolomic signatures, reflecting differential biological reactivity linked to metal-rich and organic aerosol components.[22] In our previous study, we comparatively evaluated the impact of respirable inorganic <PM2.5 silica particles on airway epithelial barrier integrity using a biomimetic airway epithelial barrier-on-chip platform and *ex vivo* human bronchial tissue slices under static and dynamic conditions. Short-term exposure to extremely high concentrations of PM2.5 disrupted epithelial permeability, adhesion, junctional markers, and induced robust proinflammatory responses, particularly under dynamic flow, demonstrating the translational relevance of lung-on-chip systems for modeling environmentally realistic particulate exposures.[12] Additionally, Kaya and Yesil-Celiktas,[23] developed a human lung epithelium-on-a-chip platform incorporating a flexible, transparent ionic liquid-based membrane and a mechanically actuated air-liquid interface to recapitulate breathing-associated mechano-stress. PM0.5 silica particle exposure under dynamic conditions, in combination with mechanical strain, modulates epithelial viability, cytotoxicity, and proinflammatory signaling, emphasizing the importance of biomechanical cues in exposome-relevant lung toxicity assessment.[23]

These findings underscore that epithelial responses to PM exposure depend on source-related physicochemical properties, which modulate oxidative stress pathways, inflammatory signaling, and cellular metabolism.[24] Moreover, at the epithelial surface, PM exposure has been shown to disrupt barrier integrity through oxidative stress-dependent mechanisms. Studies have demonstrated that PM induces the generation of reactive oxygen species (ROS), leading to tight junction (TJ) disassembly and increased epithelial permeability, thereby facilitating pathogen invasion and sustained inflammatory responses.[25,26] Such barrier dysfunction is particularly relevant in airway epithelia, where chronic exposure to ambient particles may impair mucosal defense and predispose to infectious and inflammatory airway diseases.[27]

In addition, VOCs represent a major component of the exposome, especially in indoor environments. Certain VOCs, such as formaldehyde, directly impair epithelial barrier function by inducing oxidative stress and disrupting TJ protein organization.[28] In human airway epithelial models, formaldehyde exposure has been shown to increase ROS production and compromise barrier integrity, highlighting the vulnerability of epithelial tissues to gaseous chemical stressors.[29] These effects are often exacerbated in the presence of co-exposures, reinforcing the concept that epithelial injury arises from cumulative and interactive environmental insults. In line with this perspective, exposome-oriented analytical studies have demonstrated that indoor VOC mixtures, including BTEX (benzene, toluene, ethylbenzene, xylenes), can be sensitively detected by advanced monitoring strategies, enabling a more accurate assessment of epithelial exposure burdens.[30]

Beyond air pollutants, the exposome also encompasses household chemicals, detergents, surfactants, and other daily-use compounds that come into direct contact with epithelial surfaces.[31] These agents exhibit a high affinity for lipid membranes and TJ complexes, leading to increased epithelial permeability and altered immune signaling. Integrative reviews

led by Celebi Sozener et al.[7] and Mitamura et al.[32] from Akdis group, have synthesized compelling evidence that chronic exposure to such environmental agents drives epithelial barrier breakdown, promotes alarmin release, and facilitates type 2-skewed immune responses. This body of work culminated in the formulation of the "*epithelial barrier hypothesis*", which proposes that sustained barrier disruption represents a unifying mechanism linking environmental exposures to the rising prevalence of allergic, autoimmune, and chronic inflammatory diseases.[1]

Recently, MNPs have emerged as a novel and increasingly relevant class of environmental contaminants with direct implications for epithelial health. Due to their small size and high surface reactivity, these particles can interact intimately with epithelial cells, inducing oxidative stress, apoptosis, and disruption of TJs.[33] Experimental evidence demonstrates that MNPs compromise the intestinal epithelial barrier function through ROS-mediated mechanisms, leading to increased permeability and epithelial cell death.[34] Broader reviews suggest that microplastic exposure perturbs epithelial–microbiome interactions and metabolic homeostasis, potentially contributing to chronic inflammatory and systemic disease processes.[35]

Epithelial surfaces are continuously exposed not only to chemical pollutants but also to pollen, fungal spores, bacterial fragments, viruses, endotoxins, and complex aerosol mixtures formed by their interactions.[5,36,37] Pollen and fungal spores are recognized as potent biological agents capable of directly modulating epithelial barrier function through their associated proteins, lipids, polysaccharides, and secondary metabolites.[37] In particular, it has been reported that pollen- and fungal-derived aerosol fractions interacting with environmental stressors induce distinct alterations in metabolomic profiles, resulting in metabolic reprogramming of epithelial cells and activation of inflammation-related signaling pathways.[38] Collectively, these findings underscore that bioaerosols should be considered not only in the context of allergy and infection but also within the broader framework of exposome-driven chronic inflammation, epithelial regeneration, and disease susceptibility.

Collectively, these findings highlight that environmental exposomes relevant to epithelial function exert their effects through shared mechanistic pathways, including oxidative stress, barrier disruption, immune activation, and metabolic remodeling. The biological impact of environmental exposures is shaped not only by exposure intensity but also by chemical composition, co-exposure patterns, and tissue-specific susceptibility. Understanding how diverse exposome components converge on epithelial barriers is therefore essential for elucidating the origins of chronic disease and for developing preventive strategies that reflect the complexity of real-world environmental exposures.

EPITHELIAL BARRIERS AND THEIR PHYSIOLOGICAL ROLES

Epithelial barriers are continuous cellular interfaces that line the skin and mucosal surfaces, including the gastrointestinal, respiratory, and urogenital tracts, where they physically separate host tissues from the external environment while permitting controlled exchange with it.[39] Across organs, epithelial barriers share a conserved architectural framework consisting of polarized epithelial cells interconnected by specialized intercellular junctional complexes that define apical-basolateral organization and paracellular sealing. The junctional apparatus comprises TJs, adherens junctions (AJs), and desmosomes, which together establish epithelial cohesion and mechanical resilience.[40] TJs are formed by claudins, occludins, and junctional adhesion molecules, which are linked to cytoplasmic scaffolding proteins such as zonula occludens-1 (ZO-1), ZO-2, and ZO-3, creating a selectively permeable seal at the apical border.[41] AJs, built around E-cadherin-catenin complexes, stabilize cell-cell adhesion and support epithelial polarity, while desmosomes reinforce tissue integrity under mechanical stress.[42]

Barrier architecture is further specialized according to tissue function. In the gastrointestinal tract, a single-layered epithelium is overlaid by a mucus layer rich in gel-forming mucins that spatially segregates luminal contents from epithelial cells.[41] In contrast, the skin barrier relies on a stratified, cornified epithelium in which terminally differentiated keratinocytes form the stratum corneum, a structure essential for preventing transepidermal water loss and chemical penetration.[43] These tissue-specific adaptations illustrate that epithelial barrier structure is tightly aligned with physiological demands rather than uniform across organs.[44]

Epithelial barriers are dynamic systems sustained by continuous cell turnover driven by tissue-resident stem cell populations. In the intestine, epithelial renewal is organized along the crypt–villus axis, where intestinal stem cells located at crypt bases generate differentiated lineages, including absorptive enterocytes, goblet cells, enteroendocrine cells, and Paneth cells.[45] In barrier tissues affected by chronic inflammation, stem cell function and differentiation programs are altered, which are associated with impaired regeneration and barrier fragility. These observations indicate that epithelial stem cell niches contribute to barrier physiology beyond their role in epithelial renewal.[7,46] A core physiological function of epithelial barriers is the regulation of selective permeability, permitting the exchange of nutrients, ions, and gases while restricting the passage of pathogens, toxins, and allergens.[47] TJs serve as dynamic regulators of paracellular transport, adjusting permeability in response to physiological cues rather than functioning as static seals. Disruption of junctional organization results in increased epithelial permeability, commonly referred to as barrier leakiness, which facilitates the translocation of microbes and antigens into subepithelial tissues.[48] Experimental and clinical studies have reported that increased epithelial permeability frequently accompanies and, in some contexts, precedes chronic inflammatory conditions in different tissues, suggesting that barrier dysfunction may contribute to inflammatory pathogenesis.[49-51] Environmental agents, including detergents, emulsifiers, and airborne pollutants, have been shown experimentally to disrupt TJ integrity, reduce transepithelial electrical resistance, and induce a heterogeneous distribution of junctional proteins in epithelial models.[52] These findings highlight barrier integrity as a vulnerable and actively regulated physiological property.[10,36]

Epithelial barriers function as immunologically active tissues that directly participate in host defense. Epithelial cells express pattern recognition receptors that detect microbial products and environmental signals, activating intracellular pathways such as nuclear factor kappa B (NF-κB), inflammasomes, and autophagy to reinforce barrier defenses.[53] Upon barrier perturbation, epithelial cells release alarmins, including thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and IL-33, which initiate coordinated immune responses by activating dendritic cells, innate lymphoid cells, and macrophages.[54,55] This epithelial-driven signaling links physical barrier disruption to immune activation and tissue remodeling. In the gut, macrophages are key effector cells in epithelial barrier maintenance. Tissue-resident macrophages secrete IL-10 and growth factors such as epidermal growth factor and transforming growth factor-beta, which stabilize TJs and promote epithelial repair following injury. These mechanisms are experimentally supported and contribute to the restoration of barrier integrity during post-inflammatory and post-infectious states.[44]

Epithelial barriers are central regulators of tissue homeostasis through their role in controlling host-microbiota interactions.[56,57] The mucus layer and epithelial antimicrobial peptides spatially confine commensal microbes and prevent direct contact with the epithelium. Microbial metabolites, including short-chain fatty acids and tryptophan derivatives, modulate epithelial metabolism, TJ expression, and inflammatory tone, reinforcing barrier function under homeostatic conditions.[58,59] Barrier disruption is associated with microbial dysbiosis and increased transepithelial microbial translocation, which can amplify immune activation and further compromise barrier integrity. Such feed-forward interactions have been described in allergic, autoimmune, and metabolic conditions, emphasizing the broad physiological relevance of epithelial barrier function.[60] Taken together, epithelial barriers function as integrated systems coordinating structural containment, selective permeability, immune signaling, and metabolic interactions. Beyond passive protection, epithelial barriers contribute to the regulation of stem cell niches, immune responses, and host-microbiota interactions.[61,62] Together, these observations establish epithelial surfaces not merely as passive physical boundaries, but as metabolically active, immunologically instructive tissues whose integrity is continuously negotiated with the surrounding environment.[63,64]

MECHANISMS OF EXPOSOME-INDUCED EPITHELIAL BARRIER DISRUPTION

The exposome compromises epithelial barrier integrity through both direct mechanisms of cellular injury and indirect effects on immune responses, microbiota composition, epigenetic regulation, and metabolic processes. Numerous studies have demonstrated that the environmental exposome disrupts epithelial structure and function across various barrier surfaces, including the skin, respiratory tract, and gastrointestinal system.[16,65] This disruption occurs through complex biological pathways involving oxidative stress, activation of inflammatory signaling, weakening of intercellular junctional complexes, dysbiosis, and epigenetic alterations in epithelial and immune cells.[66] Taken together, these pathways form an interconnected biological network in which oxidative and inflammatory signals initiate epithelial injury, while microbial, metabolic, and epigenetic alterations contribute to the maintenance and progression of barrier dysfunction over time.[43,67,68]

One of the major mechanisms underlying epithelial barrier dysfunction is the destabilization of TJ and AJ complexes, which maintain epithelial cohesion. Experimental studies have demonstrated that pesticide exposure impairs epithelial barrier integrity by disrupting the organization and function of intercellular junctions. Exposure to chlorpyrifos and imidacloprid has been shown to compromise intestinal epithelial barrier properties through alterations in key TJ components, including occludin, claudins, and the adaptor protein ZO-1, resulting in increased paracellular permeability.[69,70] Similarly, deltamethrin exposure has been reported to modulate epithelial barrier function by altering monolayer integrity and permeability, indicating a functional disturbance of junctional complexes.[71] Surfactants and detergents disrupt epithelial barrier integrity primarily by perturbing membrane lipid protein interactions, thereby promoting degradation and mislocalization of TJ components. Experimental studies employing primary human airway epithelial cultures have demonstrated that household cleaning products, including dishwashing detergents and rinse aids, directly injure epithelial cells and induce pronounced junctional breakdown, characterized by disrupted ZO-1 and occludin continuity, reduced barrier resistance, and increased paracellular permeability at concentrations relevant to daily exposure.[72-74] MNPs further compromise epithelial stability by interacting with the apical membrane and disrupting membrane protein organization, thereby weakening barrier integrity.[43] Beyond these surface-level effects, MNPs have been shown to translocate across both airway and intestinal epithelia and, during epithelial passage, trigger oxidative stress and inflammatory signaling, which further amplify junctional disruption and may contribute to systemic exposure.[20,75]

Air pollutants such as PM2.5, PM10, diesel exhaust particles, and ozone similarly impair epithelial barrier function by activating cytoskeletal contraction pathways, resulting in destabilization of tight and AJ complexes and enhanced epithelial permeability.[70,76] Long-term environmental monitoring studies have demonstrated that PM concentrations frequently exceed guideline thresholds in urban and industrialized regions, underscoring the relevance of chronic low-dose exposure scenarios.[77] Recent source-apportionment analyses indicate that PM2.5 derived from industrial and traffic emissions is enriched in transition metals such as nickel, vanadium, and zinc, as well as in carbonaceous fractions (elemental and organic carbon), which are strongly associated with oxidative stress-driven epithelial injury and barrier dysfunction.[78]

Another mechanism contributing to epithelial barrier dysfunction is oxidative stress, which has been consistently observed across epithelial models following diverse environmental exposures. Experimental evidence from human epithelial models demonstrates that pesticide exposure induces excessive intracellular ROS generation, leading to mitochondrial dysfunction and activation of intrinsic apoptotic pathways, characterized by increased Bcl-2-associated X protein/B-cell lymphoma 2 ratios and caspase-3/9 activation.[79]

Air pollutants similarly provoke ROS-dependent epithelial injury, resulting in disruption of junctional organization and increased epithelial permeability, thereby linking oxidative stress to functional barrier impairment.[50] In parallel, oxidative stress–driven mitochondrial dysfunction has been shown to compromise epithelial barrier function by reducing cellular energy availability and weakening barrier integrity, even in the absence of overt junctional protein loss.[80]

Environmental exposures frequently trigger the release of epithelial-derived alarmins, including IL-33, IL-25, and TSLP, which initiate potent type 2 inflammatory responses at barrier surfaces. Experimental studies in human epithelial models have demonstrated that the release of epithelial alarmins is closely associated with impaired barrier integrity, characterized by disrupted TJ organization and increased epithelial permeability.[64,81] These alarmins activate dendritic cells, T helper 2 cells, and group 2 innate lymphoid cells, leading to increased production of IL-4, IL-5, and IL-13 cytokines, which further destabilize TJs and promote mucus hypersecretion, thereby deepening barrier dysfunction.[82-85] Sublethal epithelial damage has been shown to promote the release of nuclear alarmins such as high-mobility group box 1 (HMGB1), which functions as a central danger-associated molecular pattern amplifying inflammatory signaling following epithelial stress. HMGB1-mediated damage-associated molecular pattern signaling has been implicated in sustaining epithelial-immune crosstalk and perpetuating inflammatory feedback loops, thereby linking epithelial injury to chronic, type 2–skewed inflammation and progressive weakening of barrier function across tissues.[43,84-87] Climate change–related increases in pollen burden further compromise epithelial defense mechanisms. Elevated pollen exposure suppresses type III interferon lambda production, an essential antiviral mechanism, thereby increasing susceptibility to virus-induced epithelial injury and potentially augmenting alarmin release during allergen encounter.[65] Processed foods increase exposomal pressure. Emulsifiers such as polysorbate-20 and polysorbate-80 weaken epithelial cohesion, increase paracellular leakiness, and induce inflammatory responses within the gut.[88,89] In addition, advanced glycation end products generated during high-temperature processing of ultra-processed foods activate epithelial danger-signaling pathways, disrupt TJ integrity, and increase susceptibility to allergic sensitization.[46]

Alterations in gut microbiota represent an additional consequence of exposome exposure. Pesticides, including imidacloprid and chlorpyrifos, alter the microbial composition by reducing beneficial *Lactobacillus* spp. and promoting the expansion of *Escherichia coli* pathobionts. These compositional changes are associated with reduced production of short-chain fatty acids, which are essential metabolites for epithelial energy balance and immune regulation, and may impair Aryl hydrocarbon receptor-dependent signaling pathways involved in mucosal homeostasis. Barrier disruption facilitates the translocation of microbial products, such as lipopolysaccharide, which has been associated with enhanced NF-κB-mediated inflammatory signaling in epithelial and immune cells.[50,66,90] Beyond these compositional alterations, the gut microbiota actively regulate epithelial barrier permeability by continuously modulating TJ architecture. Interactions between commensal bacteria, their metabolites, and epithelial cells influence the expression, localization, and assembly of junctional proteins, including claudins, occludin, and ZO-1, thereby dynamically controlling paracellular permeability. Dysbiosis-associated depletion of short-chain fatty-acid-producing bacteria compromises epithelial energy metabolism and TJ reassembly, resulting in increased epithelial permeability and a heightened susceptibility to inflammatory stress.[91] Importantly, epithelial barrier breach enables sustained activation of innate microbial sensing pathways, including Toll-like receptor-myeloid differentiation factor 88 (MyD88) signaling, establishing a feed-forward epithelial-immune-microbiota loop that stabilizes chronic inflammation and reinforces long-term barrier dysfunction, as demonstrated in mucosal tissues.[68]

Exposome-associated epigenetic and metabolic alterations further compromise epithelial integrity. Environmental toxicants induce DNA methylation changes, histone modifications, and chromatin remodeling that affect epithelial differentiation, barrier formation, and immune gene regulation.[92] Metabolic dysfunction in immune cells has also been implicated in secondary epithelial stress and injury. In individuals living with human immunodeficiency virus, reduced peroxisome proliferator-activated receptor gamma expression in colon-resident cytotoxic T lymphocytes ($CD8^+$ T-cells) impairs fatty acid oxidation and mitochondrial function, increasing their uptake of epithelial lipids and amplifying epithelial stress responses and apoptotic susceptibility.[67] Notably, single-cell transcriptomic and integrative bioinformatics analyses provide critical insights into how exposome-related stressors shape cellular heterogeneity, immune crosstalk, and tissue regeneration. High-resolution omics approaches reveal that chronic microenvironmental cues induce stable, disease-associated transcriptional programs in immune cells, particularly macrophage subsets characterized by enhanced lipid metabolism, responses to hypoxia, and immunoregulatory signatures. The persistence and expansion of these transcriptional states reflect long-term metabolic and transcriptional remodeling within stressed tissues, which may indirectly compromise epithelial barrier integrity and repair by sustaining inflammatory and metabolic pressure on epithelial cells, thereby contributing to disease-associated tissue remodeling.[93,94]

Collectively, these findings demonstrate that the exposome reshapes oxidative, inflammatory, microbial, epigenetic, and metabolic pathways within epithelial and immune cells, establishing a persistent and multifactorial mechanism that undermines epithelial barrier integrity across organ systems.

ORGAN-SPECIFIC EPITHELIAL BARRIER MODELS: NAMS AND ORGAN-AXIS APPROACHES

Traditional *in vitro* cell culture and *in vivo* animal models have significant limitations in recapitulating human epithelial barrier function, multi-organ communication, and long-term responses to environmental exposures.[95,96] These limitations have driven the adoption of NAMs as the methodological backbone of modern exposome research, offering human-relevant platforms that bridge reductionist cell culture and ethically constrained animal experimentation[17,73,97,98] These systems may integrate

cutting-edge bioengineering tools: microfluidics, genetically engineered cell sources, biomaterials, and tissue-specific architecture, enabling the study of epithelial barriers under conditions that closely mimic *in vivo* physiology.[99-102]

OoC platforms represent advanced micro-bioengineering technologies that enable high-quality *in vitro* modeling of human organ functions by recapitulating the mechanical and chemical microenvironment through microfluidic and tissue engineering approaches. These systems offer considerable potential for evaluating disease mechanisms, predicting drug efficacy and toxicity, and capturing patient-specific responses. However, they still face several challenges related to scalability, standardization, reproducibility, real-time measurement, and regulatory acceptance, which are currently being addressed through bioengineering-based strategies.[100,103,104] OoC platforms, such as lung-on-a-chip, skin-on-a-chip, gut-on-a-chip, and blood-brain barrier-on-a-chip, recreate key structural and functional features of real tissues using one or more cell types from a specific tissue, including spatio-temporal structure, TJ formation, cellular polarity, mechanical stretch, and vascularization.[12,97,101,102,105-108] OoC platforms have also been developed for the retina, liver, kidney, placenta, and other organs, providing tools to investigate organ-specific responses to environmental stressors. These models are particularly valuable for exposome research because they allow controlled studies of the effects of chemical, physical, and biological exposures on barrier integrity and function.[98,109,110]

In recent years, organoids, self-organizing "stem cell-derived miniature tissues", which function as 3D *in vitro* culture systems derived from tissue stem cells, progenitor cells, or induced pluripotent stem cells (iPSCs), have enabled studies that reflect human genetic variation and person-to-person differences, and have become essential tools for remodeling human organ physiology, epithelial barriers, regeneration, and disease processes.[95,111,112] Organoid-based systems can recapitulate the cellular diversity, architecture, and many functional aspects of native tissues reproduce the histopathology, molecular profiles, and responses to therapies of their primary counterparts, and offer substantial advantages over traditional 2D immortalized cell culture and patient-derived xenograft mouse models.[112,113] In addition to existing organoid models for all organ systems, recent advances in lung, intestinal, brain, and liver organoid models underscore the increasing importance of 3D human-relevant systems for studying tissue homeostasis, regeneration, and disease. Lung parenchymal tissue or bronchoalveolar lavage fluid-derived airway and alveolar organoids enable detailed interrogation of epithelial progenitor states, lineage plasticity, and early oncogenic events,[112,114] while intestinal organoids provide mechanistic insights into stem cell metabolism, niche signaling, and diet-driven tumorigenesis.[111,115,116] In parallel, unguided, guided, and assembled brain organoids recapitulate key features of human neurodevelopment, including enriched cellular diversity, functional neuronal networks, and progressive tissue maturation[117-119] and liver organoids faithfully model hepatic heterogeneity, multi-zonal architecture, and disease-specific molecular traits with high translational relevance.[120,121]

While organoids alone offer great promise, their capabilities are further enhanced when combined with OoC technologies, resulting in systems termed "organoid-on-chip" (OrgoC) that provide controllable microphysiological environments for mechanistic toxicology, including the assessment of environmental exposures and exposome effects on human tissues.[73,122] OrgoC approaches further enhance physiological relevance by combining the multicellular complexity of organoids with the dynamic control of microfluidic systems. These platforms aim to emulate not only the cellular and architectural complexity of tissues but also the dynamic microenvironment: flow, shear stress, oxygen/nutrient gradients, vascularization, and multi-compartment barrier interfaces.[101]

Multi-organ or organ-axis platforms enable investigation of organ-to-organ communication, systemic metabolite exchange, and the effects of barrier impairment. Recent studies demonstrate that these models can capture complex scenarios, including environmental pollutant-induced organ barrier disruption and consequent neuroinflammatory responses.[96,108,123] Among these systems, the brain-lung-liver-intestine axis constitutes a critical multi-organ network orchestrating systemic responses to environmental and chemical insults.[124] Inhaled pollutants can trigger inflammatory and oxidative signaling within the lung epithelium, with mediators subsequently disseminated via the circulation to distal organs such as the liver and brain, thereby eliciting secondary organ-specific effects.[125,126] Likewise, orally ingested MNPs or pharmaceutical compounds undergo intestinal absorption and hepatic biotransformation, processes that may generate bioactive metabolites capable of crossing physiological barriers and influencing central nervous system function.[127] Critically, single-organ models are inherently unable to capture what happens downstream of an initial exposure event; when the lung epithelium responds to an inhaled pollutant, the resulting inflammatory mediators enter the systemic circulation and may elicit secondary responses in distal organs such as the liver, gut, or brain, producing effects that a lung model alone will miss entirely.[128,129] Multi-organ axis platforms allow observation of these propagated cross-organ consequences within a single connected human-relevant system, revealing systemic vulnerabilities that single-organ models cannot structurally detect.[130]

Despite the recognized importance of mixture-based exposures, most NAM studies to date have employed single-agent or binary exposure designs, which inadequately reflect the complexity of real-world environmental conditions.[131,132] Translating this complexity into experimental NAM platforms is methodologically feasible. For example, differentiated primary human nasal epithelial cells cultured at ALI have been used to model multi-allergen exposures, including birch, timothy grass, and ragweed pollen, delivered as aqueous extracts, suspensions, or particle aerosols, using dedicated aerosolization systems.[133] Similarly, ALI-based epithelial models have enabled the study of complex environmental co-exposures such as fungal spores combined with grass pollen allergens, demonstrating how epithelial barrier responses can be interrogated under environmentally relevant multi-agent exposure conditions.[134] Beyond aeroallergens, co-exposure protocols combining PM with VOCs, dietary contaminants, or microbial components can be implemented within existing organoid and OoC platforms to generate ecologically relevant exposure scenarios; emerging evidence already demonstrates that exposures to mixtures elicit biological responses qualitatively distinct from those produced

by individual agents alone.[135] Considerations of dose realism and temporal dynamics are equally critical, as acute high-dose designs capture fundamentally different biology than the chronic, low-level, and sequential exposure patterns that define human environmental experience. Key unresolved challenges include the lack of standardized mixture protocols across platforms, the difficulty of attributing specific biological effects to individual constituents within a mixture, and the poorly understood role of synergistic and antagonistic pollutant interactions at epithelial surfaces.[130] Addressing these challenges through the integration of multi-omics profiling and computational toxicology with NAM-based mixture experiments represents a tractable path forward, the translational implications of which are discussed further in Section 6.[110]

The choice of NAM platform should be guided by the experimental question at hand. Organoids are best suited to questions concerning stem cell dynamics, progenitor niche regulation, or long-term differentiation trajectories, where the system's self-organizing capacity is a key advantage.[136,137] OoC platforms, by contrast, are preferred when the design requires real-time barrier monitoring, fluid shear stress, cyclic mechanical stretch, or gas-liquid interfacing conditions that static cultures cannot replicate.[138,139] Multi-organ axis systems become necessary when the scientific question demands cross-organ communication, for instance, when investigating whether a pollutant absorbed in the lung epithelium triggers secondary neuroinflammatory or hepatic responses via the circulation.[140,141] OrgoC platforms, next-generation human organ avatars, can potentially reflect the complex, detailed human-relevant organ structures and immune cell circulation within fluid flow.[142] Despite these advances in NAMs, reproducing the full cellular diversity across laboratories, long-term culture stability, immune cell interactions, scalability, and organ-to-organ connections remains technically demanding.[18,143] Standardization of design across platforms, media formulations, biological validation, regulatory qualification, and read-out metrics is still limited, particularly in multi-organ systems.[144] Together, these gaps define the methodological frontier of the field. Nevertheless, human iPSC-derived NAMs and NAMs based on CRISPR/*Cas9* gene-editing technology offer the potential to incorporate genetic variability, thereby supporting personalized toxicology and disease modeling.[19,145]

Organ-specific OoC, OrgoC, barrier-on-chip, multi-organ-on-a-chip, and body-on-chip platforms provide physiologically relevant, human-based models to study the effects of the exposome on epithelial integrity, regeneration, and disease. They bridge the gap between traditional *in vitro* and *in vivo* approaches, enabling mechanistic insights into both local barrier disruption and systemic organ-axis interactions. Cutting-edge development and validation of these models will be critical to fully realize their potential in environmental health and translational research.

CONCLUSION AND FUTURE PERSPECTIVES

Environmental exposomes function as complex and interacting mixtures that converge on shared oxidative, inflammatory, metabolic, microbial, and epigenetic pathways, ultimately affecting epithelial integrity, regenerative capacity, and disease susceptibility across multi-organ systems. This perspective reframes epithelial barriers as dynamic environmental sensors and integrators that actively determine tissue resilience and systemic vulnerability. Despite increasing recognition of exposome complexity, much of the existing literature remains constrained by single-agent or short-term exposure models that poorly reflect real-world conditions. Addressing this gap will require a decisive shift toward studying multicomponent, low-dose, and temporally dynamic exposure mixtures, including chemical pollutants, bioaerosols, dietary contaminants, and microbiome-modulating agents in combination rather than in isolation. In this context, next-generation NAMs, particularly organoids, OoC, OrgoC, and multi-organ axis platforms, offer powerful opportunities to model human-relevant exposure scenarios. By integrating epithelial barriers with immune, vascular, and stromal compartments, these systems enable mechanistic interrogation of exposure-driven crosstalk across interconnected organ axes. However, further methodological advances are needed to standardize chronic and sequential exposure paradigms and to capture cumulative and non-linear effects.

Future progress will also depend on the ability to trace exposome components and their transformation products across epithelial barriers into systemic compartments, primarily in the lung-gut-skin organ-axis models. The integration of traceable exposure strategies with high-content imaging, labelling strategies, multi-omics, and computational modeling will be critical for linking exposure dose, barrier penetration, intracellular fate, and functional outcomes. Ultimately, the convergence of exposome science with advanced NAMs holds significant promise for moving beyond associative findings toward causal, predictive, and translational insights that can inform environmental risk assessment, regulatory frameworks, and personalized prevention strategies.

Footnotes

Authorship Contributions

Concept: P.S.M., T.G., Design: P.S.M., B.D., Literature Search: All authors, Writing: All authors.

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