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The body's true portals of entry: Structure, defenses, and failure of soft epithelia in host–pathogen interactions

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Abstract The human body is constantly exposed to a vast diversity of microorganisms present in the external environment, yet invasion of internal tissues and life-threatening infection are relatively uncommon. This apparent paradox can be understood by examining the organization of the body surface as a protective interface. Most of the body surface is covered by keratinized skin, which forms a dry, mechanically robust, and largely impenetrable barrier to microbial entry. In contrast, a limited number of body surfaces must remain permeable in order to support essential physiological functions such as gas exchange, nutrient absorption, secretion, filtration, excretion, and sensory perception. These surfaces are lined by soft, non-keratinized epithelia and collectively constitute the largest interface between the internal body and the external environment. This review develops a unifying conceptual framework in which soft epithelial surfaces are recognized as the body's true portals of entry for pathogens. Although structurally vulnerable by necessity, these surfaces are protected by a multilayered defense architecture that includes mucus barriers, tight junctions, epithelial turnover, antimicrobial molecules, secretory immunoglobulin A, metal sequestration, commensal microbiota, and mechanical clearance mechanisms. Together, these defenses generally prevent sustained microbial growth, epithelial penetration, and systemic spread despite continuous exposure to microorganisms. The review further examines how a limited number of pathogens overcome these defenses through specialized strategies such as adhesion, mucus modification, toxin production, epithelial invasion, and nutrient acquisition. Even when epithelial barriers are breached, powerful systemic immune mechanisms usually prevent widespread dissemination, making bacteremia and deep tissue infection rare events. Persistent internal infections typically require antimicrobial therapy, highlighting the limits of natural immunity once multiple defense layers have failed. By framing soft epithelia as necessary but defended vulnerabilities, this review integrates concepts from epithelial biology, mucosal immunology, microbial ecology, and clinical infectious disease, and provides a coherent explanation for why most infections remain superficial while severe invasive disease is the exception rather than the norm.

Keywords: Colonization resistance, Epithelial barrier function, Host–pathogen interactions, Keratinized skin, Pathogen entry mechanisms, Soft epithelial surface.

Introduction: Life in a microbial world and the body surface as an interface

The human body is continuously exposed to a vast array of microorganisms, including pathogens, yet their entry into internal tissues is relatively uncommon. This apparent contradiction can be explained by the organization of the body's surface barrier system. The external environment is teeming with bacteria, fungi, and viruses, but the internal milieu of the body is normally protected by specialized epithelial coverings that separate the internal tissues from the outside world.

The body surface functions as a continuous interface between the internal body and the external environment. This interface is not uniform. Some regions are covered by keratinized skin that forms a highly resistant barrier to microbial penetration, whereas other regions must remain permeable in order to perform essential physiological functions. These latter regions are lined by soft, moist epithelia.

Keratinized skin provides an effective external shield that is dry, mechanically resistant, and largely impermeable to microbial penetration. Microorganisms usually gain access

to tissues beneath the skin only when this barrier is breached by injury, injections, or insect vectors. In contrast, body surfaces that must exchange gases, absorb nutrients, permit filtration, or receive external signals in the form of light, taste, smell, or physical contact cannot be lined by keratinized epidermis. Such surfaces are instead lined by soft epithelia that enable these physiological functions.

Although soft epithelia are restricted to a limited number of body surfaces, such as those of the mouth, intestinal tract, lungs, urinary tract, and genital tract, their combined surface area constitutes the largest interface between the internal body and the external environment. Owing to their non-keratinized and physiologically permeable nature, these epithelial surfaces have long been recognized as the primary entry points for many infectious agents, including respiratory viruses, enteric bacteria, sexually transmitted pathogens, and opportunistic fungi (Mowat and Agace, 2014; Peterson and Artis, 2014; Iwasaki and Medzhitov, 2015)

In this review, the term *soft epithelial surfaces* is used to denote the non-keratinized epithelial regions of the body surface that are selectively permeable to the exchange of matter and that support sensory functions. Many of these surfaces correspond to what are traditionally described in the literature as mucosal surfaces. The review examines why these surfaces are biologically necessary yet structurally vulnerable, how they are protected by multiple layers of defense, and how a limited number of pathogens overcome these defenses to cause infection.

Two structural extremes of the body surface: Keratinized skin and soft epithelia

The body surface is composed of two fundamentally different types of epithelial barriers: keratinized skin and soft epithelia. Although both are exposed to microorganisms and support resident microbial communities, they differ profoundly in structure, permeability, and vulnerability to pathogen entry**.**

Structure and barrier properties of keratinized skin

Keratinized skin is a highly specialized barrier designed to prevent penetration. The epidermis consists of multiple layers of stratified squamous epithelial cells that undergo terminal differentiation as they migrate toward the surface. During this process, keratinocytes accumulate large amounts of keratin, lose their nuclei and organelles, and form flattened, tightly packed corneocytes. These dead cells are embedded in a dense lipid matrix composed of ceramides, cholesterol, and free fatty acids, creating a water-resistant and mechanically robust barrier.

The outermost layer of the skin, the stratum corneum, is therefore not a living tissue but a hardened, chemically hostile cover that is largely impermeable to bacteria and viruses. Tight junctions and desmosomes in the deeper epidermal layers further reinforce cohesion between cells. The absence of free water limits microbial metabolism, restricting microbial growth (Madison, 2003). As a result, microorganisms residing on the skin surface are generally confined to superficial niches such as hair follicles and sweat gland openings and do not penetrate into viable tissues. Normal skin microbiota, including Staphylococcus epidermidis, Cutibacterium acnes, and Corynebacterium species, thrive on surface-derived nutrients, including lipids and sweat components, without breaching the barrier.

True penetration of intact skin by pathogens is rare. Most microbial invasion through the skin requires mechanical disruption, such as injuries, insect bites, injections, or surgical procedures. An important partial exception is fungi, particularly dermatophytes, such as Trichophyton rubrum and Microsporum species, which can extend filamentous hyphae into keratinized structures. Even in this case, growth is largely restricted to the non-living keratin layer, and invasion of deeper tissues is uncommon unless host defenses are compromised.

Structure and vulnerability of soft epithelial surfaces

In contrast, soft epithelial surfaces are structurally designed for exchange rather than exclusion. These epithelia are composed of a single layer or a few layers of living cells that remain metabolically active and hydrated. They lack keratinization and are maintained in a moist environment by secretions such as mucus, saliva, or other fluids. Their thinness and physiological permeability are essential for functions such as gas exchange, nutrient absorption, secretion, filtration, and sensory perception.

Soft epithelia are sealed by tight junctions that regulate paracellular permeability, but these junctions must remain dynamic to permit physiological transport. Unlike the stratum corneum of the skin, the epithelial surface itself is alive and directly exposed to the external environment. Mucus and other secretions provide an additional protective layer, but this layer is not absolute and can be penetrated, degraded, or modified by microorganisms, such as *Helicobacter pylori* and *Entamoeba histolytica.*

Because soft epithelia provide warmth, moisture, and access to nutrients, they support dense microbial populations. Normal microbiota can persist and even flourish on these surfaces, contributing to colonization resistance. At the same time, the same structural features that allow commensal survival also make these tissues susceptible to pathogen attachment, growth, and, in some cases, invasion. Unlike skin, where penetration is exceptional, soft epithelia represent sites where microbial contact with living cells is unavoidable and must therefore be actively managed by multilayered defense mechanisms.

Soft epithelia as a biological necessity

Although pathogens may occasionally cross soft epithelial surfaces because of their structural properties, these properties represent a functional necessity rather than a failure of evolutionary design. In the lungs, gas exchange requires that oxygen and carbon dioxide diffuse across a minimal barrier. Even modest thickening of the alveolar epithelium, such as occurs in pulmonary oedema or fibrosis, significantly impairs gas transfer, demonstrating that a keratinized surface would not facilitate respiration (Hammad and Lambrecht, 2021).

Similarly, the small intestine must absorb nutrients, electrolytes, and water across a specialized epithelial surface equipped with transporters, enzymes, and microvilli, whereas a keratinized barrier would block these functions (Allaire et al., 2018). The oral cavity and nasal passages rely on soft epithelia for sensory perception. Taste receptors must directly interact with dissolved chemicals, and olfactory neurons depend on exposure to volatile molecules. Although the oral surface must withstand mechanical stress from chewing and speaking, this strength is achieved through stratification rather than keratinization (Şenel, 2021).

The genital tract and lower urinary tract similarly require non-keratinized epithelia to permit secretion, lubrication, and sensation, while renal tubules depend on soft epithelial linings to mediate filtration and reabsorption. In all these organs, softness and physiological permeability are essential for normal function. At the same time, these same features render the tissues vulnerable to microbial contact.

Soft epithelia as the body's true portals of entry: A unifying concept

Although organ systems such as the intestinal tract, lungs, and urogenital tract serve very different physiological roles, they share a common structural characteristic: they are lined by thin, moist epithelia that are physiologically permeable. This review adopts a unifying conceptual framework in which these soft epithelial surfaces are regarded as the body's true portals of entry for pathogens.

Within this framework, infection is understood as an event that must begin at sites where physiological permeability is unavoidable. Evidence indicates that respiratory, gastrointestinal, and urogenital epithelia serve as the entry points for the majority of human pathogens (Mowat and Agace, 2014; Peterson and Artis, 2014; Iwasaki and Medzhitov, 2015;

Song et al., 2024). These tissues collectively form a vast, exposed interface whose structural nature creates inherent vulnerability.

By grouping all soft epithelia under a single conceptual umbrella, the diverse mechanisms that protect them, as well as the ways in which pathogens exploit or breach these defenses, can be understood within a coherent biological narrative linking epithelial biology, microbiology, and infectious disease.

Why soft epithelia are vulnerable entry points

Soft epithelia are unique in that they are simultaneously essential and exposed. Their permeability allows physiological exchange of matter but also permits transient microbial survival and potential entry. These surfaces are maintained at body temperature and are hydrated by secretions, conditions that may favor microbial survival (Peterson and Artis, 2014).

Some soft epithelial surfaces are subject to continuous mechanical forces, such as airflow, swallowing, and peristalsis. While these forces contribute to host defense by limiting microbial residence, they also create selective pressures that favor microorganisms adapted to attachment and growth under dynamic conditions. The intestinal epithelium exists in proximity to trillions of microorganisms, separated only by mucus (Tian et al., 2024). The respiratory tract is continually exposed to airborne microorganisms, such as influenza viruses, Mycobacterium tuberculosis, and Streptococcus pneumoniae, that deposit on epithelial surfaces (Parker and Prince, 2011). The oral cavity undergoes frequent mechanical and chemical disturbances yet remains exposed to foodborne and salivary microbes (Şenel, 2021).

Despite these vulnerabilities, most microorganisms that reach soft epithelia fail to adhere, are rapidly removed, or are destroyed by local defenses. This indicates that structural vulnerability is compensated by highly evolved protective systems operating at and beneath the epithelial surface.

Multilevel defense mechanisms at soft epithelial surfaces

Soft epithelia remain functional and safe because they are protected by several coordinated defensive mechanisms. These defenses operate simultaneously at physical, chemical, microbiological, and mechanical levels.

Physical structures

The first level of protection is the mucus barrier, composed of heavily glycosylated mucins forming a hydrated gel overlying the epithelium. In the gastrointestinal tract, mucus limits direct microbial contact and traps microorganisms for clearance. Alterations in mucus composition can significantly affect susceptibility to infection (Breugelmans et al., 2022). In the intestine, the glycocalyx provides an additional buffer, and its disruption increases permeability and facilitates microbial penetration (Johansson and Hansson, 2016).

Epithelial cells are joined by tight junctions that restrict uncontrolled paracellular passage of solutes and microorganisms. Pathogens such as enteropathogenic *Escherichia coli*, *H. pylori*, and *Clostridioides difficile* produce virulence factors that disrupt tight junction integrity and increase epithelial permeability (Peterson and Artis, 2014**).** Rapid epithelial turnover further limits pathogen establishment by eliminating damaged or infected cells (Tian et al., 2024).

Chemical and molecular defenses

Soft epithelia secrete a wide variety of antimicrobial molecules. Defensins disrupt microbial membranes or interfere with essential microbial processes (Xu and Lu, 2020; Fu et al., 2023). Secretory immunoglobulin A binds pathogens and prevents adhesion, shaping microbial communities and restricting access to epithelial cells (Pietrzak et al., 2020; León et al., 2022).

Lysozyme cleaves bacterial cell walls. Lactoferrin and transferrin bind iron, restricting microbial growth, while calprotectin limits zinc and manganese availability, a process known as

metal sequestration (Murdoch and Skaar, 2022). These mechanisms help suppress the growth of microorganisms such as Salmonella enterica, Pseudomonas aeruginosa, and Candida albicans, which require metal ions for metabolism and virulence. Lactoferrin also modulates immune responses at epithelial surfaces (Actor et al., 2009; Kell et al., 2020). Local pH conditions further limit microbial survival, as in the stomach and vagina (Şenel, 2021).

Soft epithelial cells are not passive barriers but active participants in immune surveillance. Epithelial cells express pattern-recognition receptors such as Toll-like receptors (TLRs), NOD-like receptors, and C-type lectin receptors that recognize conserved microbial structures, including lipopolysaccharides, flagellin, peptidoglycan fragments, viral nucleic acids, and fungal β-glucans. Recognition of pathogens such as S. enterica, influenza viruses, and C. albicans

activates intracellular signaling pathways that stimulate cytokine secretion, antimicrobial peptide production, recruitment of immune cells, and strengthening of epithelial defenses (Iwasaki and Medzhitov, 2015). These mechanisms enable epithelial surfaces to detect invading pathogens rapidly while maintaining tolerance toward commensal microbiota.

Microbiological defenses: Colonization resistance

Soft epithelial surfaces contain limited nutrients that permit temporary microbial survival. These nutrients are consumed by commensal microbiota, which occupy ecological niches, compete for resources, and produce inhibitory metabolites. Colonization resistance emerges from integrated microbial competition and host–microbe interactions rather than from individual species (Caballero-Flores et al., 2023; Woelfel et al., 2024).

For example, commensal intestinal bacteria inhibit colonization by pathogens such as *C. difficile*, *S. enterica*, and pathogenic *E. coli* through nutrient competition, production of antimicrobial metabolites, and modulation of host immune responses. Disruption of the microbiota increases vulnerability to infection (Chen et al., 2024; Dethlefsen and Relman, 2011).

Mechanical removal

Mechanical forces such as peristalsis, mucociliary clearance, coughing, sneezing, and urine flow prevent prolonged microbial contact with epithelia. Diarrhea, although unpleasant, contributes to pathogen clearance during enteric infections caused by pathogens such as Vibrio cholerae, rotaviruses, and enterotoxigenic E. coli (Hodges and Gill, 2010; Keely, 2022).

Coordinated ciliary movement in the respiratory tract removes mucus containing trapped microorganisms such as influenza viruses and S. pneumoniae toward the pharynx, where it is swallowed or expelled (Parker and Prince, 2011). In the urinary tract, continuous urine flow prevents bacterial adhesion and microbial colonization, particularly by uropathogenic E. coli (Hooton, 2012; Johnstone and Herzberg, 2022).

How pathogens overcome epithelial defenses

Only a minority of pathogenic microorganisms possess specialized strategies to breach epithelial defenses. Adhesins enable stable attachment, mucus modification permits closer access, toxins disrupt epithelial function, and some pathogens invade epithelial cells or exploit M cells to reach deeper tissues.

Uropathogenic E. coli use fimbrial adhesins to bind urinary epithelial cells, Neisseria gonorrhoeae uses pili and opacity-associated proteins to attach to genital epithelia, while V. cholerae expresses toxin-coregulated pili that facilitate intestinal colonization (Upadhyay, 2023). These adhesion mechanisms allow pathogens to resist mechanical clearance and maintain prolonged contact with epithelial surfaces.

Several pathogens modify or penetrate the mucus barrier. For example, H. pylori alters local pH through urease activity and moves through gastric mucus using flagellar motility, whereas E. histolytica secretes proteases that degrade mucins

and facilitate epithelial access (Breugelmans et al., 2022). Other pathogens produce toxins that impair epithelial integrity. Enteropathogenic E. coli alters tight junction proteins, while C. difficile toxins damage epithelial cells and increase paracellular permeability.

Some pathogens invade epithelial cells directly. S. enterica, Shigella flexneri, and Yersinia enterocolitica exploit M cells in Peyer's patches to cross the intestinal epithelium and gain access to subepithelial tissues. Intracellular pathogens such as Listeria monocytogenes and various respiratory viruses enter epithelial cells and replicate within them, thereby avoiding some extracellular defense mechanisms.

Other pathogens counter chemical defenses through nutrient acquisition systems. Siderophore production by bacteria such as E. coli, S. enterica, and P. aeruginosa allows iron sequestration from host iron-binding proteins, thereby overcoming nutritional immunity mechanisms mediated by lactoferrin and transferrin. Biofilm-forming organisms, including P. aeruginosa, S. aureus, and C. albicans, establish attached microbial communities that resist antimicrobial molecules and immune clearance.

Pathogen strategies can be distinguished according to the depth of interaction with the epithelial barrier, ranging from surface colonization to paracellular penetration, intracellular invasion, and transcellular passage into underlying tissues. Many pathogens cause disease without breaching the epithelial barrier, whereas only a few achieve systemic spread.

Rare breaches: Entry into the blood and deep tissues

Even if a pathogen succeeds in crossing a soft epithelial barrier and entering the bloodstream or deep tissues, it encounters powerful systemic defenses. Neutrophils, monocytes, and macrophages rapidly mobilize to sites of infection and attempt to eliminate invading organisms. Complement proteins contribute to pathogen destruction and tag microbes to facilitate phagocytosis. Circulating antibodies further enhance clearance by neutralizing microbial toxins and promoting opsonization, thereby increasing the efficiency of phagocytic uptake. The liver and spleen filter the blood and remove microbial cells, immune complexes, and toxins (Mowat and Agace, 2014).

These systemic responses usually prevent widespread dissemination. Only pathogens with specialized virulence factors, such as capsules that resist engulfment by phagocytes, intracellular survival mechanisms, or immune-modulating toxins, are capable of persisting in circulation or establishing infections in deep tissues. For example, *S. pneumoniae* and *N. meningitidis* possess polysaccharide capsules that inhibit phagocytosis, while *M. tuberculosis* survives within macrophages by interfering with intracellular killing mechanisms. *S. aureus* may evade immune clearance through biofilm formation and toxin production.

Even then, infections often remain localized as abscesses or granulomas rather than progressing to systemic disease. Clinically manifested bacteremia or sepsis, therefore, represents an uncommon failure of multiple defense layers at epithelial and systemic levels. The rarity of such events underscores the effectiveness of both soft epithelial and systemic immunity in maintaining the near-sterility of internal tissues despite constant exposure to environmental microbes

Why do persistent internal infections usually require medicines

Once pathogens establish themselves in otherwise sterile internal tissues, host immune mechanisms may be insufficient for complete clearance. Microorganisms may reside within intracellular compartments, abscesses, or biofilms, where immune cells have limited access. Some pathogens replicate more rapidly than adaptive immune responses can expand, while others alter surface antigens or inhibit intracellular killing mechanisms (Fu et al., 2023).

Intracellular pathogens such as *M. tuberculosis*, *L. monocytogenes*, and certain viruses can persist within host cells, whereas

biofilm-forming organisms such as *S. aureus* and *P. aeruginosa* become difficult to eradicate because antimicrobial agents and immune cells penetrate biofilms poorly.

In these situations, inflammation and fever may help limit disease progression but may not be sufficient to eliminate infection. Antimicrobial medicines, therefore, become essential. Antibiotics, antivirals, and antifungals disrupt critical microbial processes, reduce pathogen loads, and may reach locations that immune cells cannot effectively penetrate. Clinical evidence indicates that invasive infections such as meningitis, endocarditis, or severe sepsis carry high mortality in the absence of timely antimicrobial therapy.

From the perspective of this review, medicines become necessary only after pathogens have successfully exploited the vulnerability of soft epithelia, bypassed their defenses, and survived systemic immune responses. Their role highlights the limits of natural immunity once the body's primary portals of entry have been breached.

Conclusion

Soft epithelia are physiologically essential because they support gas exchange, nutrient absorption, secretion, excretion, and sensory perception. Their structural properties cannot resemble those of keratinized skin without compromising these functions. Consequently, they remain thin and moist, and potentially susceptible to microbial penetration, which makes them the body's true portals of entry for pathogens.

This inherent vulnerability is compensated for by an extensive defense architecture, including mucus layers, tight junctions, antimicrobial peptides, SIgA, lactoferrin, commensal microbiota, and mechanical clearance. Although these defense systems may allow pathogens to survive briefly on soft epithelia, they generally prevent uncontrolled multiplication or passage into deeper tissues.

Only a small number of pathogens possess the capabilities required to overcome these barriers. Pathogens such as *H. pylori*, *S. enterica*, *M. tuberculosis*, *N. gonorrhoeae*, and influenza viruses possess specialized mechanisms that permit epithelial colonization, invasion, immune evasion, or systemic dissemination. Even so, the successful invasion of deep tissues remains relatively uncommon because of the combined effectiveness of epithelial and systemic immunity. When such events occur, antimicrobial therapy is usually required because natural immunity alone cannot eradicate pathogens that have entered internal compartments.

This conceptual framework unites findings from epithelial biology, mucosal immunology, microbial ecology, and clinical infectious disease. By recognizing soft epithelia as necessary vulnerabilities, it becomes clearer why infections begin on these surfaces, why most remain superficial, and why severe invasive disease is the exception rather than the norm.

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Author contributions

MG conceptualized the review, conducted the literature analysis, and wrote, revised, and approved the final manuscript.

Conflicts of interest

The author declares that there are no conflicts of interest regarding this work.

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