Open Access
Check for updates
International Journal of Medical Science and Dental Health (ISSN: 2454-4191)
Volume 11, Issue 09, September 2025
Doi: https://doi.org/10.55640/ijmsdh-11-09-12

Physiological Disruption of Epithelial Barrier Integrity by Pathogenic Fungi and Its Systemic Implications

Rosol J. Mohammed

Al_Karkh University of Science, Baghdad, Iraq

Sama Mustafa Mohammed Ali

Al_Karkh University of Science, Baghdad, Iraq

Aeshah A. Ahmed

Al_Karkh University of Science, Baghdad, Iraq

Received: 26 August 2025, **accepted:** 09 September 2025, **Published Date:** 22 September 2025

1. Abstract

Epithelial barriers of the skin, gastrointestinal tract, respiratory tract, and urogenital surfaces provide the first line of defense against pathogenic invasion while supporting diverse commensal microbiota. These barriers rely on tight and adherent junctions, mucosal secretions, and immune surveillance to maintain integrity. Pathogenic fungi overcome these defenses by employing virulence strategies such as adhesion through specialized surface proteins, morphological transitions, biofilm formation, secretion of hydrolytic enzymes, and release of toxins, including the Candida albicans peptide candidalysin. These processes compromise junctional complexes, disrupt epithelial polarity, and trigger inflammatory responses, resulting in increased permeability and barrier dysfunction. While many fungal infections remain superficial, opportunistic pathogens such as C. albicans, Aspergillus fumigatus, and Cryptococcus neoformans can breach epithelial barriers, disseminate systemically, and cause life-threatening disease, particularly in immunocompromised individuals. Host epithelial and immune cells respond to fungal invasion through pattern recognition receptors, cytokine release, and recruitment of phagocytes, yet fungal immune evasion frequently undermines clearance. Understanding the molecular mechanisms of fungal-epithelial interactions and systemic dissemination provides critical insights for developing targeted therapies that preserve barrier function and strengthen antifungal immunity.

Keywords: fungal pathogenesis, epithelial barrier, Candida, Aspergillus, fungal toxins, barrier integrity, systemic infection.

2. Introduction

The host's skin, gastrointestinal tract, and respiratory tract serve as the principal points of interaction with the external environment, where they are continually challenged by pathogenic microorganisms and their toxins. For this reason, these barrier sites are under constant immune monitoring to maintain integrity and prevent infection. Epithelial surfaces, however, are not merely static physical shields; rather, they operate as complex and dynamic barriers incorporating both

chemical and biological defenses. In the gastrointestinal tract, for instance, the acidic environment of the stomach, protective mucus layers, and microbicidal enzymes constitute effective strategies against microbial invasion. At the same time, epithelial surfaces provide niches for vast communities of commensal microorganisms. Collectively termed the microbiota, these organisms play essential roles in digestion, immune regulation, and overall health. Colonization begins immediately after birth, establishing the largest population of symbiotic bacteria within the host and shaping early immune development.[1]

Airway epithelial cells play a crucial role in the innate immune system. In addition to promoting mucociliary clearance, epithelial cells produce antimicrobial substances as well as chemokines and cytokines that recruit and activate other leukocytes [2].

A rise in epithelial permeability is a hallmark of mucosal inflammation, but the molecular pathways contributing to this process have only begun to be elucidated in recent years. Multiple environmental exposures, including airborne pollutants, respiratory viral infections, allergens, and cigarette smoke, have been shown to impair airway epithelial barrier integrity without inducing overt cell death. Mechanistically, these insults are thought to disturb tight junction complexes and promote barrier dysfunction. In support of this, Schamberger and colleagues recently demonstrated that cigarette smoke extract directly compromises epithelial barrier properties, highlighting a key environmental contributor to mucosal inflammation.[3]

Pathogenic bacteria, viruses, and fungi interact with lung epithelial cells by exploiting host surface receptors, thereby enhancing adhesion, promoting cellular invasion, and facilitating infection establishment. Beyond serving as a physical barrier, epithelial cells actively participate in immune surveillance through the expression of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I–like receptors (RLRs). These receptors detect conserved pathogen-associated molecular patterns (PAMPs) on invading microorganisms and initiate signaling cascades that drive the production of chemokines and cytokines. The resulting mediator release not only recruits and activates immune cells but also shapes the magnitude and nature of the host immune response at the mucosal surface.[4&5] . In fungi, mannans or glucans are examples of PAMPs that are recognized by PRRs such as toll-like receptors (TLRs) and dectins [6].

Pathogenic fungi breach or subvert these defenses via adhesion, morphogenesis, enzymatic tissue damage, and immune modulation, often in the context of barrier disruption (e.g., dysbiosis, inflammation, medical devices, immunosuppression). The result ranges from superficial colonization to invasive disease.[7]

This review focuses on a critical evaluation of the strategies by which pathogenic fungi disrupt the structural and functional integrity of epithelial barriers—including those of the skin, oral cavity, gastrointestinal, respiratory, and urogenital tracts—through mechanisms such as enzymatic degradation, toxin release, biofilm development, and evasion of host immune defenses.

3. Fungal Pathogens and Epithelial Barrier Interaction

3.1 *Candida* species

Opportunistic *Candida* species, particularly *C. albicans*, employ morphogenetic switching between yeast and hyphal forms as well as the expression of adhesins and invasins (e.g., Als family proteins) to adhere to and penetrate epithelial barriers [8]. *C. albicans* represents a major fungal pathogen of clinical concern. Although it typically exists as a commensal within the human microbiota, it can transition to a pathogenic state, causing epithelial injury and immune activation [9]. This organism is capable of infecting diverse mucosal and cutaneous sites, including the oral cavity, gastrointestinal tract, vagina, and skin, in both immunocompetent and immunocompromised hosts. More severe manifestations include invasive candidiasis—a systemic infection of the bloodstream, heart, and deep organs—which is particularly prevalent in hospitalized patients and remains associated with substantial mortality rates (~50%), despite the availability of antifungal treatment [10].

A key virulence determinant of *C. albicans* is the recently identified cytolytic peptide toxin candidalysin (CL) [11]. This molecule is secreted during hyphal growth and interacts directly with epithelial cell membranes, leading to disruption of barrier integrity, dysregulated calcium influx, and release of intracellular proteins into the extracellular environment [12]. Such cellular injury initiates host signaling pathways that culminate in the production of pro-inflammatory mediators[12,13], thereby shaping the epithelial immune response to *C. albicans* infection.

Systemic implications. Systemic candidiasis arises when *Candida* disseminates to normally sterile sites, most commonly the bloodstream, and may extend to deep-seated organs such as the central nervous system, liver, spleen, heart, and kidneys. Infection can also localize within the intra-abdominal cavity, with or without concurrent candidemia. Despite the use of antifungal agents, systemic candidiasis remains associated with significant morbidity and persistently high mortality rates.[14].

3.2 *Aspergillus* species

Species of the genus *Aspergillus*, particularly *A. fumigatus*, are responsible for aspergillosis, a spectrum of diseases that predominantly affect individuals with underlying conditions or immune deficiencies [15]. As an environmental filamentous fungus and opportunistic pathogen, *A. fumigatus* can trigger outcomes ranging from allergic responses to invasive, disseminated infections. The infectious process typically begins with inhaled conidia, whose initial interaction occurs with airway epithelial cells (AECs) [16].

The integrity of the airway epithelial barrier plays a pivotal role in host defense. Epithelial cells are interconnected by tight junctions (TJs)[17,18], which maintain a selective and highly regulated barrier that controls the passage of ions, water, and immune cells, while restricting microbial translocation [17]. TJs consist of multiple structural and regulatory proteins, including zonula occludens-1 (ZO-1), junctional adhesion molecule A (JAM-A), occludins, and claudins [18]. Disruption of this barrier by *A. fumigatus* not only facilitates fungal invasion but may also promote excessive neutrophil infiltration and secondary microbial colonization, outcomes with particularly severe implications in patients with chronic pulmonary disease [19].

Systemic implications. *Aspergillus fumigatus* possesses multiple traits that facilitate immune evasion, resistance, and impairment of host defenses. One key factor is the pigmentation of its conidia, which shields fungal cells from reactive oxygen species (ROS) generated by macrophages and neutrophils. This protective mechanism not only dampens oxidative killing but also reduces complement activation, disrupts phagosome maturation, and obscures immunologically relevant cell wall components, thereby limiting recognition by the host immune system [20].

3.3 Other opportunistic fungi

3.3.1 *Cryptococcus*

Cryptococcus species are major causative agents of life-threatening central nervous system (CNS) infections, particularly in individuals with compromised immune systems. *C. neoformans* is capable of breaching the blood–brain barrier and inducing meningoencephalitis, a process thought to begin with interactions between cryptococcal hyaluronic acid (HA) and the host endothelial receptor CD44 [21,22].

A defining virulence attribute of *C. neoformans* is its polysaccharide capsule, composed primarily of glucuronoxylomannan (GXM)[23]. This structure is central to immune evasion and pathogenicity[24]. Genetic studies have identified the *CPS1* gene, which encodes a capsule polysaccharide synthase essential for capsule integrity and host interactions. Deletion of *CPS1* results in ultrastructural defects at the capsule–cell wall interface and markedly reduces fungal adherence to human brain microvascular endothelial cells (HBMECs). Importantly, HA is detectable in wild-type strains but absent in *cps1Δ* mutants, and adherence assays demonstrate that endothelial binding capacity correlates directly with HA levels. These findings establish that *CPS1* functions as an HA synthase, and that HA acts as a cryptococcal adhesion factor facilitating endothelial attachment during CNS invasion.[25,26].

Systemic implications. For *Cryptococcus neoformans* to establish infection within the central nervous system (CNS), it must first traverse the blood–brain barrier (BBB). Following primary infection of the respiratory tract, the fungus disseminates hematogenously and penetrates the BBB, culminating in meningitis or meningoencephalitis, conditions responsible for substantial global mortality each year. Experimental evidence indicates that *C. neoformans* employs multiple routes to breach the BBB, including transcellular passage through endothelial cells, paracellular migration between them, and carriage within infected phagocytes via the so-called “Trojan horse” mechanism. The secretion of diverse virulence factors is critical for promoting fungal dissemination beyond the BBB and enabling the establishment of CNS infection.[27].

3.3.2 Mucorales (e.g., *Rhizopus* spp.)

Mucormycosis is a highly invasive and often fatal infection caused by fungi of the order *Mucorales*, with

Rhizopus oryzae representing the most frequently implicated species[28]. A key step in disease progression is the interaction of fungal elements with vascular endothelial cells. Host endoplasmic reticulum stress induces the upregulation of glucose-regulated protein 78 (GRP78), a transmembrane signal transducer that is also expressed on the surfaces of endothelial and epithelial cells. GRP78 has been identified as an essential receptor exploited by *Mucorales* to mediate host cell invasion. Among the fungal ligands, spore coat protein homologs (CotH), particularly CotH3, function as critical surface antigens that bind to GRP78, thereby promoting adherence and facilitating tissue invasion.[29].

Systemic implications. *Mucorales* are opportunistic fungi that typically cause disease in the context of impaired host defenses. Infections occur most frequently in individuals with neutropenia, hematopoietic or solid-organ transplantation, iron overload, uncontrolled diabetes mellitus—particularly in the setting of diabetic ketoacidosis (DKA)—malnutrition, or as breakthrough infections following prolonged antifungal therapy. Across clinical manifestations, the defining feature of mucormycosis is the capacity for rapid and extensive angioinvasion, leading to vascular thrombosis, tissue necrosis, and subsequent hematogenous dissemination[30].

4. Mechanism of barrier disruption

The harmful impact of compounds that compromise epithelial barriers has been well demonstrated using approaches that evaluate both functional alterations and molecular changes associated with reduced barrier integrity. Such compounds can induce cytotoxicity, metabolic dysregulation, proinflammatory signaling, and oxidative stress, collectively disrupting the expression and structural organization of epithelial junctional molecules. This disruption may occur either through altered regulation of junctional protein expression or through direct injury to epithelial cells[31].

Tight junction (TJ) molecules are key determinants of epithelial barrier integrity, playing a central role in regulating paracellular permeability. Core TJ components such as claudins, occludin, and junctional adhesion molecules, together with scaffold proteins like zonula occludens (ZO) proteins, coordinate to maintain barrier function and regulate selective transport across epithelial layers. Disruption of these complexes is closely linked to impaired barrier integrity and increased susceptibility to inflammation and infection[32]. As the primary regulators of paracellular permeability, TJs prevent the uncontrolled translocation of apical environmental factors—including microbiota, pathogens, pollutants, and allergens—into subepithelial tissues. Additionally, TJs are crucial for maintaining epithelial polarity, coordinating intracellular signaling pathways, and controlling cell proliferation and differentiation. Consequently, TJ damage results in the breakdown of epithelial homeostasis[31]. Numerous epithelial barrier–disrupting compounds have been shown to modulate the expression of tight junction proteins at both the transcriptional and translational levels. Furthermore, components of adherens junctions, including E-cadherin and catenins, may also be compromised, further undermining barrier integrity[32].

Disruption of the microbiota and impaired interactions between epithelial cells and commensal microbes are frequently observed in the context of barrier dysfunction. Microbial dysbiosis is a common feature across numerous diseases associated with compromised epithelial integrity[33,34]. Consequently, agents that impair epithelial barriers enhance permeability through direct injury to epithelial cells, disruption of the microbiota and induction of dysbiosis, and subsequent activation of the immune system. These processes collectively drive cell death, cellular stress, altered expression of adhesion molecules, and the promotion of inflammation[31].

Fungi interact with host epithelial surfaces by binding to cell-associated carbohydrates and proteins, including glycoproteins, glycolipids, and extracellular matrix components such as fibronectin, laminin, and collagen. These interactions are frequently mediated by fungal adhesins, which are specialized surface proteins that facilitate adhesion and colonization[35].

Fungi interact with host epithelial surfaces by binding to cell-associated carbohydrates and proteins, including glycoproteins, glycolipids, and extracellular matrix components such as fibronectin, laminin, and collagen. These interactions are often mediated by fungal adhesins, specialized surface proteins that facilitate colonization. Adherence is further reinforced through biofilm formation, which promotes persistence and enhances resistance to host immune defenses. In *Aspergillus fumigatus*, extracellular polysaccharides such as galactosaminogalactan (GAG) contribute to adhesion as well as immune evasion. In addition, fungi can exploit

epithelial tight junctions and surface receptors to establish attachment, subsequently disrupting barrier integrity and enabling invasion[36].

Fungal infections constitute a major global health challenge, accounting for an estimated 1.5 million deaths annually[37]. Conidia of several pathogenic fungi can attach to alveolar epithelial surfaces, where they germinate and produce invasive hyphae[38]. Interestingly, despite hyphal penetration, epithelial cells frequently maintain their overall morphology, raising debate as to whether invasion necessitates direct cellular damage. Experimental evidence indicates that hyphae may enter bronchial epithelial cells through reorganization of the actin cytoskeleton, without overt disruption of cell shape or barrier integrity[37]. However, the precise molecular mechanisms underlying fungal invasion of epithelial tissues remain incompletely understood[36].

Fungi infecting humans need to have thermal resistance to the human body, locomotion through or around host barriers, lysis and absorption of human tissue, and resistance to immune defenses[39].

Although the pathogenic mechanisms vary between superficial and invasive infections, four core virulence attributes are consistently required. The first step involves fungal adhesion to epithelial surfaces, mediated by cell surface adhesins—such as Hwp1 and Als3—that are closely associated with hyphal morphology. Subsequent epithelial damage arises both from the mechanical force exerted by hyphal extension and from the action of secreted hydrolytic enzymes and toxins[40, 41].

A major advance in the understanding of fungal virulence was the identification of the first peptide toxin from a human-pathogenic fungus, *Candida albicans*. This toxin, termed candidalysin, is a proteolytic fragment derived from the hypha-associated polypeptide Ece1. During hyphal growth, the *ECE1* gene is upregulated, and the Ece1 polypeptide is processed by the Golgi proteases Kex2 and Kex1 before secretion. Among the eight resulting peptides, candidalysin uniquely integrates into host cell membranes, where it induces pore-like lesions and epithelial damage. Beyond its cytotoxic effects, candidalysin also functions as a danger-associated signal, activating host epithelial danger response pathways. This dual role highlights candidalysin as a central factor in the commensal-to-pathogen transition of *C. albicans* at epithelial surfaces[42].

Both innate and adaptive immune responses are essential for controlling and eliminating microbial pathogens. In this context, mucosal barriers, together with resident immune cells, not only shield underlying tissues from infection but also actively participate in microbial recognition and defense. Upon pathogen encounter, mucosal epithelia release cytokines and alarmins that coordinate the recruitment of innate and adaptive immune effectors, including macrophages, neutrophils, dendritic cells, and T cells. However, many mycotoxins exert detrimental effects on mucosal barrier integrity and can suppress cellular immune functions. Such toxin-mediated disruptions of host defense mechanisms may, in turn, heighten susceptibility to infections by opportunistic pathobionts residing within the commensal microbiota[43].

5. Barrier Sites Affected

Fungal dysbiosis has been linked to a range of human diseases across multiple barrier surfaces—including the oral cavity, vagina, skin, lungs, and gastrointestinal tract, where it can predispose to localized infection and, in severe cases, facilitate systemic dissemination.[44].

- **Skin and mucosal epithelium.**

The human host presents diverse and often challenging niches for microbial colonization, including the mucosal surfaces of the oropharyngeal, gastrointestinal, and vaginal tracts. *Candida albicans* has adapted to persist within these environments [45], where initial interactions with the host are predominantly mediated by the yeast form, followed by germ tube emergence and hyphal development. Yeast cells utilize multiple adhesion strategies[46], including conserved tandem repeat domains within adhesin proteins that facilitate binding to a wide array of epithelial ligands and promote yeast–yeast aggregation. Under conditions of impaired mucosal immunity, these adaptations permit fungal penetration into underlying tissues, frequently resulting in severe pathology[47].

- **Gastrointestinal tract.**

The gut microbiota is a key determinant of human health, influencing both immune function and susceptibility to infection. Invasive intestinal candidiasis is closely linked to disruptions in microbial homeostasis. Among fungal colonizers [48], *Candida albicans* is the principal causative agent of invasive disease. Under conditions of intestinal dysbiosis, *C. albicans* can overgrow, undergo yeast-to-hypha transition, upregulate adhesins, secrete toxins, and compromise

the gut mucosal barrier, ultimately breaching into the bloodstream and causing sepsis and multi-organ failure, outcomes frequently associated with high mortality[49].

A central virulence determinant in this process is candidalysin, a cytolytic peptide toxin with dual functionality. It directly damages epithelial membranes by pore formation and simultaneously activates host responses[50]. Most mechanistic insights have been derived from in vitro studies using oral epithelial cell models, where candidalysin has been shown to stimulate the release of cytokines, chemokines, alarmins, and antimicrobial peptides [51]; to induce cellular stress responses such as mitochondrial dysfunction , ATP depletion, and necrosis [52]; and to promote Ca^{2+} influx with disruption of F-actin structures. While these findings highlight the toxin's pathogenic potential [53], it is important to note that the gastrointestinal tract represents the primary reservoir of *C. albicans* [54].

- **Respiratory tract.**

The respiratory epithelium is a structurally and functionally complex barrier, with distinct cellular compositions along the conducting airways and alveoli. Beyond sustaining gas exchange and maintaining pulmonary homeostasis, epithelial cells actively engage with inhaled pathogens. These interactions can be exploited by microbes, which manipulate host signaling pathways to promote adhesion and tissue invasion. In turn, epithelial cells contribute to host defense by secreting cytokines and chemokines that coordinate immune responses and shape inflammatory outcomes [55]. Diseases caused by *Aspergillus* species affect over 10 million individuals worldwide and are responsible for an estimated 200,000 deaths annually [56]. The initial step in infection involves the adhesion of *A. fumigatus* conidia to epithelial cell surfaces or to components of the surrounding extracellular matrix (ECM)[57]. Adhesion is mediated through multiple mechanisms, including binding to host membrane proteins, carbohydrates, and mucins. For example, the conidial lectin FleA recognizes fucosylated structures and binds avidly to lung mucins [58]. Host adhesion molecules such as E-cadherin have also been implicated in facilitating fungal attachment [59]. In addition, the hyphal cell wall polysaccharide galactosaminogalactan has been identified as a key mediator of adhesion to epithelial cells and to ECM components such as fibronectin [60].

- **Urogenital tract.**

The vaginal mucosa represents a common site of fungal infection, most notably vulvovaginal candidiasis (VVC) caused by *Candida albicans*. Successful colonization requires adhesion of the fungus to the epithelial surface, a complex and dynamic process involving multiple interactions between fungal cell wall components and host epithelial proteins. This adhesion underlies both commensal persistence and pathogenic invasion [61].

Host defense mechanisms also contribute to limiting infection. The rapid turnover of squamous epithelial cells within the vaginal mucosa is protected by counteracting fungal adherence and invasion[62], thereby reducing the likelihood of sustained colonization. Genetic factors further influence susceptibility, with polymorphisms in Toll-like receptor 2 (TLR2)—a pattern recognition receptor expressed by innate immune cells—being associated with recurrent vulvovaginal candidiasis (RVVC) [63]. Additionally, variable-number tandem repeats in the *NLRP3* inflammasome gene, which result in exaggerated neutrophil-driven inflammatory responses to *Candida* colonization, appear to play a more critical role in RVVC pathogenesis than generalized immune defects [64-65].

6. Systemic effects

Fungi represent an immensely diverse kingdom, with more than six million species estimated to exist globally; however, fewer than 600 are known to be pathogenic to humans [66,67]. Most human fungal infections remain superficial, yet a subset of species are capable of causing severe, life-threatening disease [66]. Among the most clinically significant opportunistic fungi are *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Candida albicans* [68]. When these organisms disseminate beyond their initial site of colonization, they can give rise to invasive diseases such as meningoencephalitis, invasive aspergillosis, and invasive candidiasis [69]. Because of their small size, fungal propagules can evade the mechanical defenses of the respiratory tract, including cough reflexes and mucociliary clearance, allowing them to reach the alveolar spaces. Within the lungs, *C. neoformans* encounters resident immune cells that typically restrict fungal growth. In immunocompetent hosts, infection is often resolved or maintained in a latent state[70,71]. By contrast, in immunocompromised individuals such as patients with advanced HIV/AIDS, organ transplant recipients, or those undergoing

immunosuppressive therapies *Candida neoformans* can establish symptomatic pulmonary infection, leading to pneumonia, acute respiratory distress syndrome, and dissemination beyond the lungs[72]. Once in the bloodstream, *C. neoformans* exhibits a strong tropism for the central nervous system (CNS). Penetration of the blood–brain barrier (BBB) allows the fungus to invade the brain parenchyma, where it can cause cryptococcal meningoencephalitis. Globally, cryptococcal meningoencephalitis accounts for more than 220,000 cases each year and is responsible for an estimated 180,000 deaths annually[73].

Free fungal cells may also access the circulation directly via mechanisms such as transcytosis, paracellular traversal, or passage through damaged epithelial and endothelial barriers. Once in the bloodstream, host immune components, particularly neutrophils and Kupffer cells, contribute to the clearance of circulating fungi. Notably, fungal pathogens within the vasculature can exploit strategies analogous to those employed during their escape from primary infection sites to facilitate invasion of distant organs. Overall, fungal dissemination is governed by complex host–pathogen interactions that determine the balance between immune containment and systemic spread[71].

The nature of the host immune response is highly dependent on the fungal species involved, with the relative contribution of innate and adaptive defense mechanisms varying according to both the pathogen and the site of infection. Moreover, within a single species, morphological plasticity—for example, the yeast, pseudohyphal, and hyphal forms of *Candida albicans*—can serve as a critical determinant of how the host immune system recognizes and responds to infection[74]. Yeast cells and fungal spores are generally amenable to phagocytic clearance, whereas the larger dimensions of hyphae hinder effective engulfment. To overcome such barriers, pathogenic fungi have evolved diverse strategies to evade or subvert host immune defenses. Certain species exhibit facultative intracellular lifestyles, enabling survival within phagocytes, which they exploit both to resist microbicidal mechanisms and to facilitate dissemination throughout the host. A defining feature of antifungal immunity is the interdependence of innate and adaptive responses, together with the dynamic interplay between host defense pathways and fungal virulence strategies. Notably, several core immune mechanisms are broadly conserved in responses to diverse fungal pathogens[75]. Neutrophils, macrophages, and monocytes constitute central effector cells in antifungal immunity. Resident phagocytes within infected tissues serve as the first line of defense, while additional neutrophils and monocytes are rapidly recruited in response to inflammatory mediators, including cytokines, chemokines, and complement factors. These cells exert antifungal activity primarily through the generation of reactive oxygen species and the release of antimicrobial peptides, leading to fungal damage or killing. The reliance on intracellular versus extracellular effector mechanisms is shaped by the fungal species, morphotype, and the route by which the pathogen enters the host[76].

Table 1 shows fungal pathogens vs mechanisms of action

Fungal Pathogen	Site of Infection	Key Virulence Mechanisms	References
Candida albicans	Mucosal surfaces, bloodstream, systemic	- Adhesins (Als protein family, Hwp1) for epithelial/endothelial binding - Morphological plasticity (yeast–hyphae switching) aiding invasion - Biofilm formation conferring drug resistance and persistence - Secretion of hydrolytic enzymes (SAPs, lipases, phospholipases) degrading host tissue - Immune evasion via β-glucan masking and phenotypic switching	77

Aspergillus fumigatus	Lungs, sinuses, systemic (especially immunocompromised)	- Inhaled conidia resist phagocytosis - Hyphal invasion of epithelial and endothelial barriers - Production of gliotoxin (induces apoptosis, suppresses immunity) - Secretion of proteases and elastases for tissue damage - Resistance to oxidative killing by immune cells	78
Cryptococcus neoformans	Lungs, CNS (meningoencephalitis)	- Polysaccharide capsule inhibiting phagocytosis and complement activation - Melanin production protecting against oxidative stress - Intracellular survival and replication in macrophages (“Trojan horse” mechanism) - Ability to cross the blood–brain barrier	79
Histoplasma capsulatum	Pulmonary and disseminated histoplasmosis	- Survival inside macrophages via altered phagolysosomal pH - Expression of heat shock proteins for intracellular persistence - Cell wall α-glucan masking β-glucan from host PRRs - Modulation of host immune response (suppression of TNF-α, IFN-γ pathways)	80
Blastomyces dermatitidis	Lungs, skin, disseminated infection	- BAD1 adhesin mediating host attachment and immune suppression - Thick yeast cell wall resisting immune clearance - Suppression of Th1 responses, promoting immune evasion	81
Coccidioides immitis / posadasii	Pulmonary coccidioidomycosis (“Valley fever”), systemic spread	- Transformation of arthroconidia into large spherules producing endospores - Secretion of proteases and metalloproteases for tissue invasion - Outer wall glycoproteins mediating immune evasion - Induction of host inflammatory tissue damage	82
Pneumocystis jirovecii	Lungs (Pneumocystis pneumonia, PCP)	- Adhesion to alveolar epithelial cells via major surface glycoprotein (gpA) - Formation of cyst-like structures resisting clearance	83

		- Antigenic variation to evade host immunity - Biofilm-like community persistence in alveoli	
Mucorales (e.g., Rhizopus spp.)	Rhino-orbital-cerebral mucormycosis, pulmonary/systemic	- Aggressive angioinvasion → vessel thrombosis and tissue necrosis - Rapid hyphal growth under hyperglycemia and acidosis (diabetic ketoacidosis) - Iron uptake via siderophores and high-affinity permeases - Evasion of neutrophil killing	84

7. Future Perspectives

Future research should focus on the development of innovative therapeutic strategies alongside the application of advanced experimental models that more accurately recapitulate human barrier physiology.

- **Novel therapeutic strategies (microbiome modulation, immunotherapy, barrier protectants).**

- Microbiome modulation

Microbiome therapeutics refers to the use of microbes, their metabolites, and associated factors to suppress pathogenic communities while promoting the growth of beneficial microorganisms [85]. Unlike conventional drugs, which may have adverse systemic effects, microbial therapies exploit the natural residency of microbes within the human body, offering a more physiological means of disease management. Recent advances include the engineering of microbial strains to enhance their therapeutic efficacy [86].

Within the gut, fungi—particularly *Candida* species—play a sophisticated role in shaping the composition and function of the bacterial microbiome, a key regulator of host physiology. This occurs through mechanisms such as direct cell–cell interactions, competition or cooperation for nutrients, secretion of secondary metabolites and antimicrobial peptides, and modification of the local physicochemical environment. These multifaceted interactions between gut fungi, bacteria, and host immunity are fundamental to maintaining immune homeostasis, and their dysregulation contributes to the balance between health and disease [87-88].

-Immunotherapy

Immunotherapy encompasses therapeutic strategies that modulate or harness the immune system [89]. In the context of fungal infections, monoclonal antibodies (mAbs) generated through hybridoma technology represent a promising approach, providing antibody-mediated protection[90]. Cytokine-based interventions, such as recombinant IFN-γ and GM-CSF, are also under investigation as adjunctive therapies to augment antifungal immunity in immunocompromised hosts[91].

The fungal cell wall, composed primarily of carbohydrate polymers interspersed with proteins, constitutes a major target for opsonizing antibodies. Protective antibodies against *Candida albicans* and *Cryptococcus neoformans* typically recognize glycan structures or surface proteins and are most often IgM or IgG subclass molecules. These antibodies exert protective effects by promoting phagocytic uptake and enhancing phagolysosomal maturation, thereby strengthening antifungal immune responses [92].

-Barrier protectants

The integrity and function of the intestinal barrier are shaped by multiple environmental and host-related factors, including diet and lifestyle. At the molecular level, such influences can modulate the expression of claudins and thereby alter epithelial tight junction (TJ) assembly and permeability[93]. TJs are critical for maintaining epithelial cohesion and are composed of transmembrane proteins such as claudins, occludin, junctional adhesion molecules (JAMs), and tricellulin, together with cytoplasmic plaque proteins including the zonula occludens (ZO) family[94]. Among these, claudins play a central role in establishing and regulating intercellular junctional connections. Notably, dietary components such as fungal mycotoxins and secondary metabolites from diverse fungi can directly affect claudin expression and compromise epithelial barrier function [95].

In addition to structural integrity, epithelial innate defenses provide essential protection against microbial overgrowth. Early responses include the production of antimicrobial peptides (AMPs) and cytokines. Reduced AMP levels, particularly in saliva, are linked to increased susceptibility to oral *Candida* infections. Certain AMPs, such as human β-defensins 1–3, possess direct fungicidal properties, underscoring their importance in epithelial antifungal defense [96].

• Advanced models (organoids, organ-on-chip).

- Organoids

In the past decade and a half, advances in *in vitro* methodologies have enabled the generation of three-dimensional multicellular structures, termed organoids or "mini-organs." These stem cell–derived systems self-organize into differentiated, functional cell types that closely mimic their *in vivo* counterparts, thereby recapitulating essential features of whole-organ physiology. Organoids provide a powerful tool for dissecting the contribution of specific cell types, particularly as they lack immune and endothelial cell populations. In the respiratory system, adult human lung stem cells, crucial for epithelial renewal and repair[97], have been shown to generate 3D lung organoids under defined differentiation conditions. Importantly, patient-derived organoids allow for high-fidelity modeling of host fungal interactions in a physiologically relevant context.

- Organ-on-chip

The emergence of organ-on-chip (OoC) technology represents a major advancement in biomedical research, driven by the need for physiologically relevant models that more accurately reflect human biology, disease mechanisms, and therapeutic responses. By bridging gaps left by conventional *in vitro* systems and reducing reliance on animal models, OoCs provide powerful platforms for translational research. Lung-on-chip and gut-on-chip systems are increasingly being applied to the study of fungal infections, offering valuable insights into barrier disruption and antifungal drug evaluation [98].

A pivotal step toward lung organoid culture was the development of the lung-on-chip device, a microphysiological model that replicates the functional unit of the breathing lung through dynamic communication between alveolar epithelial and endothelial cells across a microporous elastomeric membrane. Similarly, intestine-on-chip models have enabled advanced investigations of microbial colonization and host responses *in vitro*. These systems recapitulate hallmark features of intestinal disease, including elevated proinflammatory cytokine production, reduced expression of epithelial differentiation markers, impaired proliferation, and compromised barrier integrity [98].

References

1. Moens, E., & Veldhoen, M. (2012). Epithelial barrier biology: good fences make good neighbours. Immunology, 135(1), 1-8.
2. Moens, E., & Veldhoen, M. (2012). Epithelial barrier biology: good fences make good neighbours. Immunology, 135(1), 1-8.
3. Rezaee, F., & Georas, S. N. (2014). Breaking barriers. New insights into airway epithelial barrier function in health and disease. American journal of respiratory cell and molecular biology, 50(5), 857-869.
4. Leiva-Juárez, M. M., Kolls, J. K., & Evans, S. E. (2018). Lung epithelial cells: therapeutically inducible effectors of antimicrobial defense. Mucosal immunology, 11(1), 21-34.
5. Barros, B. C., Almeida, B. R., Barros, D. T., Toledo, M. S., & Suzuki, E. (2022). Respiratory epithelial cells: more than just a physical barrier to fungal infections. *Journal of Fungi*, *8*(6), 548.
6. Gow, N. A., Latge, J. P., & Munro, C. A. (2017). The fungal cell wall: structure, biosynthesis, and function. *Microbiology spectrum*, *5*(3), 10-1128.
7. White, T. C., Findley, K., Dawson, T. L., Scheynius, A., Boekhout, T., Cuomo, C. A., ... & Saunders, C. W. (2014). Fungi on the skin: dermatophytes and Malassezia. Cold spring harbor perspectives in medicine, 4(8), a019802.
8. Lopes, J. P., & Lionakis, M. S. (2022). Pathogenesis and virulence of Candida albicans. *Virulence*, *13*(1), 89-121.
9. Ho, J., Yang, X., Nikou, S. A., Kichik, N., Donkin, A., Ponde, N. O., ... & Naglik, J. R. (2019). Candidalysin activates innate epithelial immune responses via epidermal growth factor receptor. *Nature communications*, *10*(1), 2297.
10. Kullberg BJ, Arendrup MC (2015) **Invasive candidiasis***The New England Journal of Medicine* **373**:1445–1456.
11. Moyes, D. L., Wilson, D., Richardson, J. P., Mogavero, S., Tang, S. X., Wernecke, J., ... & Naglik, J. R. (2016).

Candidalysin is a fungal peptide toxin critical for mucosal infection. *Nature*, *532*(7597), 64-68.

12. Naglik, J. R., Gaffen, S. L., & Hube, B. (2019). Candidalysin: discovery and function in Candida albicans infections. *Current opinion in microbiology*, *52*, 100-109.

13. Richardson, J. P., Willems, H. M., Moyes, D. L., Shoaie, S., Barker, K. S., Tan, S. L., ... & Peters, B. M. (2018). Candidalysin drives epithelial signaling, neutrophil recruitment, and immunopathology at the vaginal mucosa. *Infection and immunity*, *86*(2), 10-1128.

14. Pappas PG, Lionakis MS, Arendrup MC, et al. Invasive candidiasis. Nat Rev Dis Primers. 2018. May 11;4:18026.

15. Latgé, J. P. (1999). Aspergillus fumigatus and Aspergillosis. *Clin. Microbiol. Rev.* 12, 310–350.

16. Croft, C. A., Culibrk, L., Moore, M. M., & Tebbutt, S. J. (2016). Interactions of Aspergillus fumigatus conidia with airway epithelial cells: a critical review. *Frontiers in microbiology*, *7*, 472.

17. Denker B.M., Nigam S.K. Molecular structure and assembly of the tight junction. Am. J. Physiol. 1998;274:F1–F9. doi: 10.1152/ajprenal.1998.274.1.F1. [DOI] [PubMed] [Google Scholar]

18. Forster C. Tight junctions and the modulation of barrier function in disease. Histochem. Cell Biol. 2008;130:55–70. doi: 10.1007/s00418-008-0424-9.

19. Dunne, K., Reece, E., McClean, S., Doyle, S., Rogers, T. R., Murphy, P., & Renwick, J. (2023). *Aspergillus fumigatus* Supernatants Disrupt Bronchial Epithelial Monolayers: Potential Role for Enhanced Invasion in Cystic Fibrosis. *Journal of fungi (Basel, Switzerland)*, *9*(4), 490.

20. Chamilos, G., & Carvalho, A. (2020). Aspergillus fumigatus DHN-melanin. *The Fungal Cell Wall: An Armour and a Weapon for Human Fungal Pathogens*, 17-28.

21. Vu, K., Tham, R., Uhrig, J. P., Thompson III, G. R., Na Pombejra, S., Jamklang, M., ... & Gelli, A. (2014). Invasion of the central nervous system by Cryptococcus neoformans requires a secreted fungal metalloprotease. *MBio*, *5*(3), 10-1128.

22. Jong, A., Wu, C. H., Gonzales-Gomez, I., Kwon-Chung, K. J., Chang, Y. C., Tseng, H. K., Cho, W. L., & Huang, S. H. (2012). Hyaluronic acid receptor CD44 deficiency is associated with decreased Cryptococcus neoformans brain infection. *The Journal of biological chemistry*, *287*(19), 15298–15306.

23. Lee, H. H., Carmichael, D. J., Ríbeiro, V., Parisi, D. N., Munzen, M. E., Charles-Niño, C. L., ... & Martinez, L. R. (2023). Glucuronoxylomannan intranasal challenge prior to Cryptococcus neoformans pulmonary infection enhances cerebral cryptococcosis in rodents. *PLoS pathogens*, *19*(4), e1010941.

24. Liu, Y., Zhang, Y., Zhao, X., Lu, W., Zhong, Y., & Fu, Y. V. (2023). Antifungal peptide SP1 damages polysaccharide capsule of Cryptococcus neoformans and enhances phagocytosis of macrophages. *Microbiology Spectrum*, *11*(2), e04562-22.

25. Chang Y. C., Jong A., Huang S., Zerfas P., Kwon-Chung K. J. (2006) CPS1, a homolog of the *Streptococcus pneumoniae* type 3 polysaccharide synthase gene, is important for the pathobiology of *Cryptococcus neoformans*. Infect. Immun. 74, 3930–3938

26. Jong A., Wu C. H., Chen H. M., Luo F., Kwon-Chung K. J., Chang Y. C., Lamunyon C. W., Plaas A., Huang S. H. (2007) Identification and characterization of CPS1 as a hyaluronic acid synthase contributing to the pathogenesis of *C. neoformans* infection. Eukaryot. Cell 6, 1486–1496

27. Al-Huthaifi, A. M., Radman, B. A., Al-Alawi, A. A., Mahmood, F., & Liu, T.-B. (2024). Mechanisms and Virulence Factors of *Cryptococcus neoformans* Dissemination to the Central Nervous System. *Journal of Fungi*, *10*(8), 586.

28. Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. *Clin Infect Dis.* 2012;54(suppl 1):S16–S22.

29. Gunathilaka, S. S., Rajapakse, S., & Bandara, N. (2024). Targeting cell surface GRP78 for the treatment of mucormycosis: potential and promising therapeutic approach. *Reviews and Research in Medical Microbiology*, 10-1097.

30. Farmakiotis, D., & Kontoyiannis, D. P. (2016). Mucormycoses. *Infectious Disease Clinics*, *30*(1), 143-163.

31. Pat, Y., Yazici, D., D'Avino, P., Li, M., Ardicli, S., Ardicli, O., & Akdis, C. A. (2024). Recent advances in the epithelial barrier theory. International immunology, 36(5), 211-222.

32. Zihni, C., Mills, C., Matter, K., & Balda, M. S. (2016). Tight junctions: from simple barriers to multifunctional molecular gates. Nature reviews Molecular cell biology, 17(9), 564-580.

33. Akdis, C. A. (2021). Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?. *Nature Reviews Immunology*, *21*(11), 739-751.

34. Chidambaram, S. B., Essa, M. M., Rathipriya, A. G., Bishir, M., Ray, B., Mahalakshmi, A. M., ... & Monaghan, T. M. (2022). Gut dysbiosis, defective autophagy and altered immune responses in neurodegenerative diseases: Tales of a vicious cycle. *Pharmacology & therapeutics*, *231*, 107988.

35. Brenchley, J. M., & Douek, D. C. (2012). Microbial translocation across the GI tract. *Annual review of immunology*, *30*(1), 149-173.

36. DeHart, D. J., Agwu, D. E., Julian, N. C., & Washburn, R. G. (1997). Binding and germination of Aspergillus fumigatus conidia on cultured A549 pneumocytes. *Journal of Infectious Diseases*, *175*(1), 146-150.

37. Barros, B. C., Almeida, B. R., Barros, D. T., Toledo, M. S., & Suzuki, E. (2022). Respiratory epithelial cells: more than just a physical barrier to fungal infections. Journal of Fungi, 8(6), 548.

38. Brown, G. D., Denning, D. W., Gow, N. A., Levitz, S. M., Netea, M. G., & White, T. C. (2012). Hidden killers: human fungal infections. Science translational medicine, 4(165), 165rv13-165rv13.

39. Köhler, J. R., Hube, B., Puccia, R., Casadevall, A., & Perfect, J. R. (2017). Fungi that infect humans. Microbiology spectrum, 5(3), 10-1128.

40. Hoyer, L. L., Green, C. B., Oh, S. H., & Zhao, X. (2008). Discovering the secrets of the Candida albicans agglutinin-like sequence (ALS) gene family–a sticky pursuit. *Medical mycology*, *46*(1), 1-15.

41. Moyes, D. L., Wilson, D., Richardson, J. P., Mogavero, S., Tang, S. X., Wernecke, J., ... & Naglik, J. R. (2016). Candidalysin is a fungal peptide toxin critical for mucosal infection. *Nature*, *532*(7597), 64-68.

42. Moyes, D. L., Runglall, M., Murciano, C., Shen, C., Nayar, D., Thavaraj, S., ... & Naglik, J. R. (2010). A biphasic innate immune MAPK response discriminates between the yeast and hyphal forms of Candida albicans in epithelial cells. Cell host & microbe, 8(3), 225-235.

43. Brown, R., Priest, E., Naglik, J. R., & Richardson, J. P. (2021). Fungal toxins and host immune responses. Frontiers in microbiology, 12, 643639.

44. Iliev, I. D., & Leonardi, I. (2017). Fungal dysbiosis: immunity and interactions at mucosal barriers. *Nature Reviews Immunology*, *17*(10), 635-646.

45. Hallen-Adams, H. E., & Suhr, M. J. (2017). Fungi in the healthy human gastrointestinal tract. *Virulence*, *8*(3), 352-358.

46. Williams, D. W., Jordan, R. P., Wei, X. Q., Alves, C. T., Wise, M. P., Wilson, M. J., & Lewis, M. A. (2013). Interactions of Candida albicans with host epithelial surfaces. *Journal of oral Microbiology*, *5*(1), 22434.

47. Nikou, S. A., Kichik, N., Brown, R., Ponde, N. O., Ho, J., Naglik, J. R., & Richardson, J. P. (2019). Candida albicans interactions with mucosal surfaces during health and disease. *Pathogens*, *8*(2), 53.

48. Wang, F., Wang, Z., & Tang, J. (2023). The interactions of Candida albicans with gut bacteria: a new strategy to prevent and treat invasive intestinal candidiasis. *Gut pathogens*, *15*(1), 30.

49. Zhong, L., Zhang, S., Tang, K., Zhou, F., Zheng, C., Zhang, K., ... & Zhang, G. (2020). Clinical characteristics, risk factors and outcomes of mixed Candida albicans/bacterial bloodstream infections. *BMC Infectious Diseases*, *20*(1), 810.

50. Russell, C. M., Rybak, J. A., Miao, J., Peters, B. M., & Barrera, F. N. (2023). Candidalysin: Connecting the pore forming mechanism of this virulence factor to its immunostimulatory properties. *Journal of Biological Chemistry*, *299*(2).

51. Richardson, J.P.; Brown, R.; Kichik, N.; Lee, S.; Priest, E.; Mogavero, S.; Maufrais, C.; Wickramasinghe, D.N.; Tsavou, A.; Kotowicz, N.K.; et al. Candidalysins Are a New Family of Cytolytic Fungal Peptide Toxins. *mBio* **2022**, *13*, e03510-21.

52. Blagojevic, M., Camilli, G., Maxson, M., Hube, B., Moyes, D. L., Richardson, J. P., & Naglik, J. R. (2021). Candidalysin triggers epithelial cellular stresses that induce necrotic death. *Cellular microbiology*, *23*(10), e13371.

53. Westman, J., Plumb, J., Licht, A., Yang, M., Allert, S., Naglik, J. R., ... & Maxson, M. E. (2022). Calcium-dependent ESCRT recruitment and lysosome exocytosis maintain epithelial integrity during Candida albicans invasion. *Cell reports*, *38*(1).

54. Alonso-Monge, R., Gresnigt, M. S., Román, E., Hube, B., & Pla, J. (2021). Candida albicans colonization of the gastrointestinal tract: A double-edged sword. *PLoS pathogens*, *17*(7), e1009710.

55. Barros, B. C. S. C., Almeida, B. R., Barros, D. T. L., Toledo, M. S., & Suzuki, E. (2022). Respiratory Epithelial Cells: More Than Just a Physical Barrier to Fungal Infections. *Journal of Fungi*, *8*(6), 548.

56. Ben-Ghazzi, N., Moreno-Velasquez, S., Seidel, C., Thomson, D., Denning, D. W., Read, N. D., ... & Gago, S. (2021). Characterisation of Aspergillus fumigatus endocytic trafficking within airway epithelial cells using high-resolution automated quantitative confocal microscopy. *Journal of Fungi*, *7*(6), 454.

57. Croft, C. A., Culibrk, L., Moore, M. M., & Tebbutt, S. J. (2016). Interactions of Aspergillus fumigatus conidia with airway epithelial cells: a critical review. *Frontiers in microbiology*, *7*, 472.

58. Kerr, S. C., Fischer, G. J., Sinha, M., McCabe, O., Palmer, J. M., Choera, T., ... & Fahy, J. V. (2016). FleA expression in Aspergillus fumigatus is recognized by fucosylated structures on mucins and macrophages to prevent lung infection. *PLoS pathogens*, *12*(4), e1005555.

59. Yan, T., Han, J., & Yu, X. (2016). E-cadherin mediates adhesion of Aspergillus fumigatus to non-small cell lung cancer cells. *Tumor Biology*, *37*(12), 15593-15599.

60. Gravelat, F. N., Beauvais, A., Liu, H., Lee, M. J., Snarr, B. D., Chen, D., ... & Sheppard, D. C. (2013). Aspergillus galactosaminogalactan mediates adherence to host constituents and conceals hyphal β-glucan from the immune system. *PLoS pathogens*, *9*(8), e1003575.

61. Gaziano, R., Sabbatini, S., & Monari, C. (2023). The interplay between Candida albicans, vaginal mucosa, host immunity and resident microbiota in health and disease: an overview and future perspectives. Microorganisms, 11(5), 1211.

62. Netea, M. G., Joosten, L. A., Van Der Meer, J. W., Kullberg, B. J., & Van De Veerdonk, F. L. (2015). Immune defence against Candida fungal infections. *Nature Reviews Immunology*, *15*(10), 630-642.

63. Rosentul, D. C., Delsing, C. E., Jaeger, M., Plantinga, T. S., Oosting, M., Costantini, I., ... & Netea, M. G. (2014). Gene polymorphisms in pattern recognition receptors and susceptibility to idiopathic recurrent vulvovaginal candidiasis. *Frontiers in microbiology*, *5*, 483.

64. Jaeger, M., Carvalho, A., Cunha, C., Plantinga, T. S., Van De Veerdonk, F., Puccetti, M., ... & Netea, M. G. (2016). Association of a variable number tandem repeat in the NLRP3 gene in women with susceptibility to RVVC. *European Journal of Clinical Microbiology & Infectious Diseases*, *35*(5), 797-801.

65. Camilli, G., Griffiths, J. S., Ho, J., Richardson, J. P., & Naglik, J. R. (2020). Some like it hot: Candida activation of inflammasomes. *PLoS pathogens*, *16*(10), e1008975.

66. Naglik, J. R. (2014). Candida immunity. *New Journal of Science*, *2014*(1), 390241.

67. Taylor, D. L., Hollingsworth, T. N., McFarland, J. W., Lennon, N. J., Nusbaum, C., & Ruess, R. W. (2014). A first comprehensive census of fungi in soil reveals both hyperdiversity and fine-scale niche partitioning. *Ecological monographs*, *84*(1), 3-20.

68. Köhler, J. R., Casadevall, A., & Perfect, J. (2015). The spectrum of fungi that infects humans. Cold Spring Harbor perspectives in medicine, 5(1), a019273.

69. Denham, S. T., & Brown, J. C. (2018). Mechanisms of pulmonary escape and dissemination by Cryptococcus neoformans. *Journal of Fungi*, *4*(1), 25.

70. Shoham, S., & Levitz, S. M. (2005). The immune response to fungal infections. *British journal of haematology*, *129*(5), 569-582.

71. Strickland, A. B., & Shi, M. (2021). Mechanisms of fungal dissemination. *Cellular and Molecular Life Sciences*, *78*(7), 3219-3238.

72. Voelz, K., & May, R. C. (2010). Cryptococcal interactions with the host immune system. Eukaryotic cell, 9(6), 835-846.

73. Rajasingham, R., Smith, R. M., Park, B. J., Jarvis, J. N., Govender, N. P., Chiller, T. M., ... & Boulware, D. R. (2017). Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. The Lancet infectious diseases, 17(8), 873-881.

74. Romani, L. (2011). Immunity to fungal infections. Nature Reviews Immunology, 11(4), 275-288.

75. Shoham, S., & Levitz, S. M. (2005). The immune response to fungal infections. British journal of haematology, 129(5), 569-582.

76. Burgess, T. B., Condliffe, A. M., & Elks, P. M. (2022). A fun-guide to innate immune responses to fungal infections. Journal of Fungi, 8(8), 805.

77. Mayer, F. L., Wilson, D., & Hube, B. (2013). Candida albicans pathogenicity mechanisms. Virulence, 4(2), 119-128.

78. Chamilos, G., & Carvalho, A. (2020). Aspergillus fumigatus DHN-melanin. The Fungal Cell Wall: An Armour and a Weapon for Human Fungal Pathogens, 17-28.

79. May, R. C., Stone, N. R., Wiesner, D. L., Bicanic, T., & Nielsen, K. (2016). Cryptococcus: from environmental saprophyte to global pathogen. Nature Reviews Microbiology, 14(2), 106-117.

80. Garfoot, A. L., Shen, Q., Wüthrich, M., Klein, B. S., & Rappleye, C. A. (2016). The Eng1 β-glucanase enhances histoplasma virulence by reducing β-glucan exposure. MBio, 7(2), 10-1128.

81. Dawood, I. R. A., & Tahseen, T. H. (2024). Examination Of The Use Of Picture Card Technology To Help Elementary School Students Develop Their Basketball Skills. International Journal of Cognitive Neuroscience and Psychology, 2(2), 1-7.

82. Tahseen, T. H., Jawad, K. A. H., Dakhil, H. O., Khamis, H., & Abbas, S. (2024). The effectiveness of attention and kinesthetic awareness and their relationship to the accuracy of performing the forehand and backhand stroke in badminton. Sciencia Journal, 1, 77-85.

83. Thomas Jr, C. F., & Limper, A. H. (2007). Current insights into the biology and pathogenesis of Pneumocystis pneumonia. Nature Reviews Microbiology, 5(4), 298-308.

84. Ibrahim, A. S., Spellberg, B., Walsh, T. J., & Kontoyiannis, D. P. (2012). Pathogenesis of mucormycosis. Clinical infectious diseases, 54(suppl_1), S16-S22.

85. Yadav, M., & Chauhan, N. S. (2022). Microbiome therapeutics: exploring the present scenario and challenges. *Gastroenterology report*, *10*, goab046.

86. Ogunrinola, G. A., Oyewale, J. O., Oshamika, O. O., & Olasehinde, G. I. (2020). The human microbiome and its impacts on health. *International journal of microbiology*, *2020*(1), 8045646.

87. Zuo, T., Wong, S. H., Cheung, C. P., Lam, K., Lui, R., Cheung, K., ... & Ng, S. C. (2018). Gut fungal dysbiosis correlates with reduced efficacy of fecal microbiota transplantation in Clostridium difficile infection. *Nature communications*, *9*(1), 3663.

88. Rao, C., Coyte, K. Z., Bainter, W., Geha, R. S., Martin, C. R., & Rakoff-Nahoum, S. (2021). Multi-kingdom ecological drivers of microbiota assembly in preterm infants. *Nature*, *591*(7851), 633-638.

89. Papaioannou NE, Beniata OV, Vitsos P, Tsitsilonis O, Samara P. Harnessing the immune system to improve cancer therapy. Ann Transl Med. (2016) 4:261. doi: 10.21037/ atm.2016.04.01

90. Datta K, Hamad M. Immunotherapy of fungal infections. Immunol Investig. (2015) 44:738–76.

91. Qadri, H., Shah, A. H., Alkhanani, M., Almilaibary, A., & Mir, M. A. (2023). RETRACTED: Immunotherapies against human bacterial and fungal infectious diseases: A review. *Frontiers in Medicine*, *10*, 1135541.

92. Ulrich, S., & Ebel, F. (2020). Monoclonal Antibodies as Tools to Combat Fungal Infections. *Journal of Fungi*, *6*(1), 22.

93. Kozieł, M. J., Kowalska, K., & Piastowska-Ciesielska, A. W. (2020). Claudins: new players in human fertility and reproductive system cancers. *Cancers*, *12*(3), 711.

94. Robinson, K., Deng, Z., Hou, Y., & Zhang, G. (2015). Regulation of the intestinal barrier function by host defense peptides. *Frontiers in veterinary science*, *2*, 57.

95. Kozieł, M. J., Ziaja, M., & Piastowska-Ciesielska, A. W. (2021). Intestinal barrier, claudins and mycotoxins. *Toxins*, *13*(11), 758.

96. Tomalka, J., Azodi, E., Narra, H. P., Patel, K., O'Neill, S., Cardwell, C., Hall, B. A., Wilson, J. M., & Hise, A. G. (2015). β-Defensin 1 plays a role in acute mucosal defense against Candida albicans. *Journal of immunology (Baltimore, Md. : 1950)*, *194*(4), 1788–1795.

97. Huang, S. X., Islam, M. N., O'neill, J., Hu, Z., Yang, Y. G., Chen, Y. W., ... & Snoeck, H. W. (2014). Efficient generation of lung and airway epithelial cells from human pluripotent stem cells. *Nature biotechnology*, *32*(1), 84.

98. Koceva, H., Amiratashani, M., Akbarimoghaddam, P., Hoffmann, B., Zhurgenbayeva, G., Gresnigt, M. S., ... & Mosig, A. S. (2025). Deciphering respiratory viral infections by harnessing organ-on-chip technology to explore the gut–lung axis. *Open biology*, *15*(3), 240231.

99. Huh D, Leslie DC, Matthews BD, Fraser JP, Jurek S, Hamilton GA, et al. A human disease model of drug toxicity-induced pulmonary edema in a lung-on-a-

chip microdevice. *Sci Transl Med.* (2012) 4:159ra147.

100. Lanik, W. E., Luke, C. J., Nolan, L. S., Gong, Q., Frazer, L. C., Rimer, J. M., ... & Good, M. (2023). Microfluidic device facilitates in vitro modeling of human neonatal necrotizing enterocolitis–on-a-chip. *Jci Insight*, *8*(8), e146496.