

Molecular interplay in CNS fungal invasion: Strategies for Invasion, Immune Evasion, and Host Countermeasures

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Abstract

Fungal infections of the central nervous system (CNS) represent severe clinical threats with high mortality, stemming from intricate molecular interplay between neurotropic fungi and specialized host defenses. This review dissects the mechanisms underpinning fungal CNS invasion—including enzymatic blood-brain barrier (BBB) disruption, transcellular transport, and "Trojan horse" evasion within phagocytes—alongside evolved immune escape tactics such as molecular camouflage by capsular polysaccharides, biofilm-mediated resistance, and immunosuppressive microenvironment shaping. Critically, CNS-resident immune cells including microglia, utilize surface C-type lectin receptors (CLRs) and Toll-like receptors (TLRs) to initiate antifungal immunity through Syk/CARD9-dependent signaling and inflammasome activation. However, fungi subvert these defenses by neutralizing phagosomal acidity, inducing non-lytic expulsion, and hijacking metabolic pathways to enhance virulence and drug tolerance. The dynamic coevolutionary arms race manifests in chronic CNS colonization via Th2 polarization, contrasting with the dual-edged role of adaptive immunity where CD4⁺ T cell responses aid pathogen clearance yet exacerbate neuroinflammation. Overcoming therapeutic challenges, particularly limited antifungal BBB penetration and rising drug resistance, requires deciphering these host-pathogen molecular dialogues to design targeted interventions disrupting immune evasion or bolstering CNS-specific immunity.

Introduction

Fungal infections of the CNS pose a significant clinical burden, characterized by high mortality and poor prognoses [1]. Although less frequent than bacterial or viral counterparts, CNS fungal infections can lead to severe complications such as meningitis, encephalitis, and cerebral abscesses [2-4], posing substantial diagnostic and therapeutic challenges. Survivors frequently suffer persistent neurological sequelae, such as cognitive impairment, seizures, or motor dysfunction [4]. Immunocompromised individuals constitute the core vulnerable cohort, encompassing patients with AIDS, chemotherapy recipients, individuals with diabetic ketoacidosis, and solid organ transplant recipients [5-7]. The incidence of CNS fungal infections rises in parallel with this expanding population, wherein such infections significantly contribute to elevated mortality. Among transplant recipients, CNS fungal involvement occurs in 0.9% of renal, 0.8% of hepatic, 1.4% of pulmonary, and 1.1% of cardiac cases [8], with associated 90-day mortality reaching 20.7%. In AIDS patients, these infections account for >20% of fatalities [5], while cryptococcal meningitis in Africa exhibits mortality rates as high as 44% within two weeks of diagnosis [9]. Furthermore, *Cryptococcus neoformans* causes approximately 7.7% of CNS infections in patients with malignancies [10]. Critically, the immunodeficient state impairs host defense mechanisms, establishing a permissive niche for fungal invasion and immune evasion in the CNS—a pivotal predisposing factor in this pathophysiological interplay.

1. Major Pathogenic Lineages of Invasive Central Nervous System Fungi

Approximately 10–15% of human-pathogenic fungi cause central nervous system (CNS) infections [4]. Major pathogenic groups include yeasts (*Candida* and *Cryptococcus* spp.), filamentous fungi (*Aspergillus* spp.), and dimorphic fungi (*Histoplasma* and *Coccidioides* spp.) [11]. Notably, *Cryptococcus*, *Coccidioides*, *Candida* and *Histoplasma* species also infect immunocompetent hosts, eliciting CNS manifestations[21][22] (**Figure 1**).

Fungal virulence as a prerequisite for CNS infection

Fungal virulence constitutes the foundational prerequisite for successful host invasion, immune evasion, and central nervous system (CNS) colonization. Unlike obligate pathogens, most human-pathogenic fungi are environmental organisms whose virulence traits have evolved primarily for environmental fitness, yet fortuitously enable survival within mammalian hosts. These virulence attributes encompass structural components, metabolic adaptability, stress resistance, and secreted effectors that collectively permit fungi to withstand host-imposed constraints and exploit permissive niches[1].

A defining feature of fungal virulence is the capacity to resist host immune recognition and killing. Cell wall architecture and dynamic remodeling regulate the exposure of pathogen-associated molecular patterns (PAMPs), such as β -glucans, mannans, and chitin, thereby modulating engagement with host pattern recognition receptors. Metabolic flexibility represents another core virulence determinant, allowing fungi to exploit alternative carbon and nitrogen sources, reprogram mitochondrial activity, and modulate lipid metabolism in response to host-derived pressures[2]. These adaptations not only enhance survival within immune cells but also contribute to antifungal drug tolerance and persistence[3]. Collectively, fungal virulence traits establish the biological preconditions for CNS invasion, shaping the downstream processes of BBB traversal, immune evasion, and host–pathogen coevolution discussed in subsequent sections.

***Cryptococcus* spp.**

Cryptococcus species are the primary etiological agents of fungal meningoencephalitis, predominantly *C. neoformans* and *C. gattii*. *C. neoformans* both targets immunocompetent and immunocompromised individuals (notably HIV-positive patients) [12], whereas *C. gattii* exhibits a heightened neurotropism in immunocompetent hosts in china[23]. Inhalation of *C. neoformans*—in animal feces (primarily pigeon excreta) and soil—initiates pulmonary infection, followed by haematogenous or lymphatic dissemination to the CNS. Invasion manifests as severe symptoms including headache, fever, vomiting, altered mental status, meningismus,

visual disturbances, and cranial nerve palsies [2; 12]. Critically, a key virulence factor is its capsular polysaccharide (e.g., glucuronoxylomannan, GXM), which mediates both immune evasion and CNS tropism.

***Candida* spp.**

Opportunistic pathogens causing invasive candidiasis in contexts such as solid organ transplantation, chemotherapy, HIV infection, or trauma. CNS involvement typically arises secondary to neurosurgical interventions or disseminated disease [13]. Incidence in neurosurgical cohorts has increased from 6% to 17% [14]. Approximately 50% of disseminated candidiasis patients develop CNS symptoms, with mortality rates of 10–30% [1]; 18–29% of survivors experience persistent neurological sequelae [15]. Species implicated include *C. albicans*, *C. tropicalis*, *C. lusitaniae*, *C. guilliermondii*, *C. auris* and *C. parapsilosis* [16]. Infants exhibit particular vulnerability : CNS involvement occurs in 66% of neonates with disseminated candidiasis and 80% with *Candida* endocarditis, resulting in meningitis, abscesses, granulomas, vasculitis, haemorrhagic necrosis, and demyelination [17; 18].

***Aspergillus* spp.**

Ubiquitous environmental fungi causing significant morbidity in immunocompromised hosts. High-risk cohorts include bone marrow transplant recipients (32% incidence), patients with haematological malignancies (8%), and those with underlying pulmonary disease (9%) [1], particularly during neutropenia or corticosteroid therapy. While pulmonary involvement predominates, extrapulmonary infection occurs in 40% of cases, with CNS dissemination developing in 10–20% of invasive aspergillosis patients [19; 20]. CNS *aspergillosis* demonstrates geographic predilection , with higher prevalence in tropical/subtropical regions (e.g., India, Sudan, Pakistan, Saudi Arabia, Turkey, USA) [21; 22]. Complications diverge significantly by host immune status: immunosuppressed patients are predisposed to cerebral infarction, haemorrhage, encephalomalacia, cerebrovascular accidents, aneurysms, and solitary or multiple abscesses[19; 23-25], whereas immunocompetent hosts more commonly manifest cranial nerve/cavernous sinus syndromes, orbito-sinus involvement, granulomas, or abscesses

[19; 23; 26]. Critically, the angioinvasive propensity of *Aspergillus* underpins CNS pathogenesis.

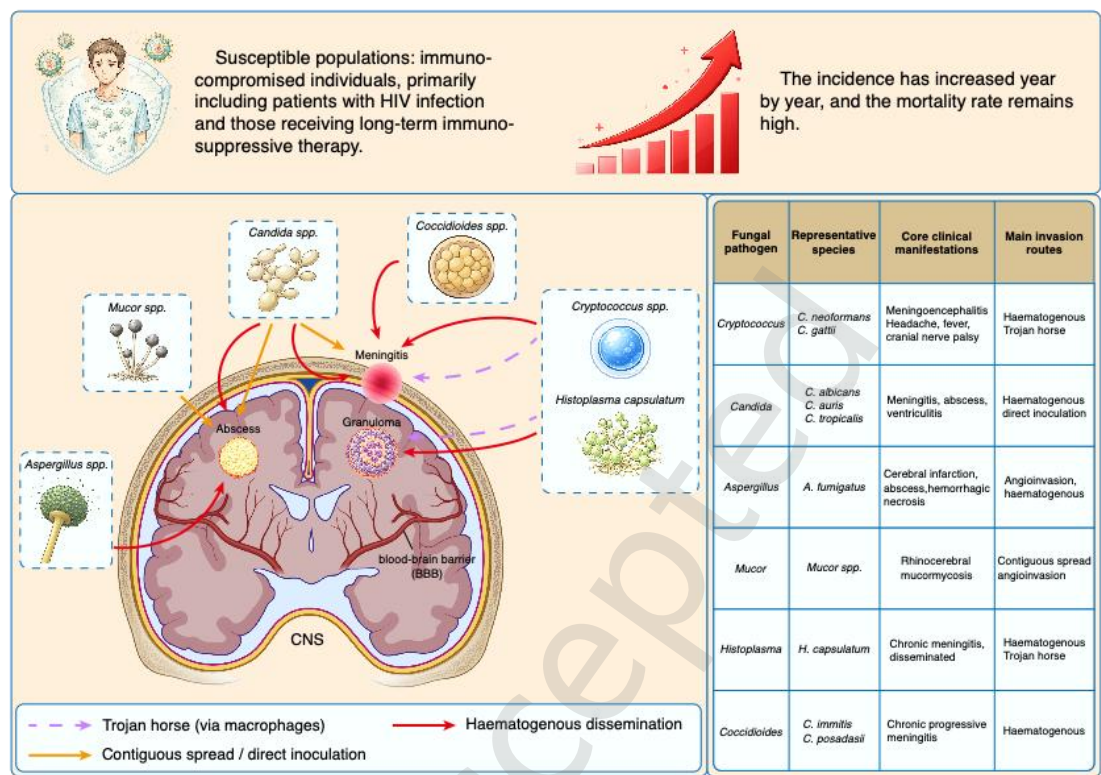


Figure 1 . Major human fungal pathogens associated with CNS invasion and their key clinical characteristics.

Schematic diagram (left) illustrates the six major pathogenic fungal lineages that infect the central nervous system, including *Cryptococcus* spp., *Candida* spp., *Aspergillus* spp., *Mucor* spp., *Histoplasma capsulatum*, and *Coccidioides* spp., together with their primary routes of CNS invasion (haematogenous dissemination, Trojan horse mechanism, contiguous spread, and angioinvasion). The table (right) summarizes representative species, high-risk populations, core clinical manifestations, major invasion routes, and key mortality data for each pathogen.

Other Pathogens

Mucor spp. cause rhinocerebral mucormycosis, with risk factors encompassing diabetic ketoacidosis, stem cell transplantation, iron chelation, AIDS, hypocomplementaemia, and prolonged voriconazole exposure[27]. Dimorphic fungi (*Histoplasma capsulatum*, *Coccidioides* spp., *Blastomyces dermatitidis*), endemic to the Americas, provoke CNS infections—particularly in immunocompromised hosts [1;

28; 29]. *Fusarium* spp (including *F. solani*, *F. oxysporum*, and *F. moliniforme*) cause single or multiple brain abscesses and meningitis[24]. Dematiaceous fungi, *Trichosporon* spp and *Pneumocystis jirovecii* also contribute to CNS pathology[1]. Some dimorphic fungi are also capable of causing CNS infections. *Histoplasma capsulatum* is a classical endocytosed and intracellularly persistent fungal pathogen; CNS involvement most commonly occurs in the setting of disseminated histoplasmosis, but may also present as isolated CNS disease or as chronic meningitis without clear evidence of extracranial involvement, a feature that frequently leads to delayed or missed diagnosis in clinical practice[5]. *Coccidioides* spp. (*C. immitis* and *C. posadasii*) can also disseminate hematogenously, and one of the most severe complications of disseminated coccidioidomycosis is coccidioidal meningitis (CM), which is characteristically a chronic and progressive form of meningitis[6].

2. Invasion Routes and Pathogenic Mechanisms of Fungal CNS Invasion

2.1 Transmission Pathways

Fungi invade the CNS through three principal routes: haematogenous dissemination, direct inoculation, and contiguous spread from adjacent foci, with haematogenous dissemination predominating. In immunocompromised hosts (e.g., AIDS patients), fungi such as *C. albicans* establish disseminated infections that subsequently breach the BBB to access the CNS via the bloodstream[30]. Direct inoculation occurs following trauma or neurosurgical exposure of brain tissue[31], while deep craniofacial fungal infections (e.g., involving sinuses, orbits, or middle ear) may contiguously propagate intracranially[32]. *A. fumigatus* can also disseminate intracranially through the mechanisms described above. Distinct from *C. albicans*, however, *A. fumigatus* possesses the capacity for hyphal angioinvasion, whereby fungal hyphae penetrate vascular walls, triggering thrombosis, tissue ischemic necrosis, and hemorrhage, ultimately resulting in ischemic and hemorrhagic lesions within the CNS[4].

2.2 Molecular Strategies for CNS Invasion

Fungi deploy sophisticated molecular strategies to breach the BBB, including

enzymatic degradation of tight junctions where *C. albicans*-secreted hydrolases (e.g., aspartyl proteases) cleave proteins such as E-cadherin, compromising structural integrity[33]; transcellular transport mediated by Als3 binding gp96 on brain microvascular endothelial cells, inducing endocytosis-dependent entry[34]; Trojan horse evasion where phagocytosed *C. neoformans* hijacks macrophages to traverse the BBB—macrophage-depletion studies validate this mechanism, though intracellular survival machinery remains unresolved[35]; This is also a common mechanism by which *Histoplasma capsulatum* invades the CNS[7]; and paracellular migration initiated by hyaluronic acid-CD44 engagement on endothelia[36]. *In vitro* models demonstrate that *A. fumigatus* hyphae can invade endothelial cells from different surfaces and induce endothelial inflammation and procoagulant responses, including expression of tissue factor, E-selectin, and TNF- α [8]. Emerging evidence further implicates the orogenic-brain axis as a direct neural invasion pathway[37]. As eukaryotes, fungi exhibit multidimensional pathogenic mechanisms that surpass the complexity of bacterial or viral CNS invasion, underpinned by evolutionary adaptations for immune evasion and host tropism (**Figure 2**).

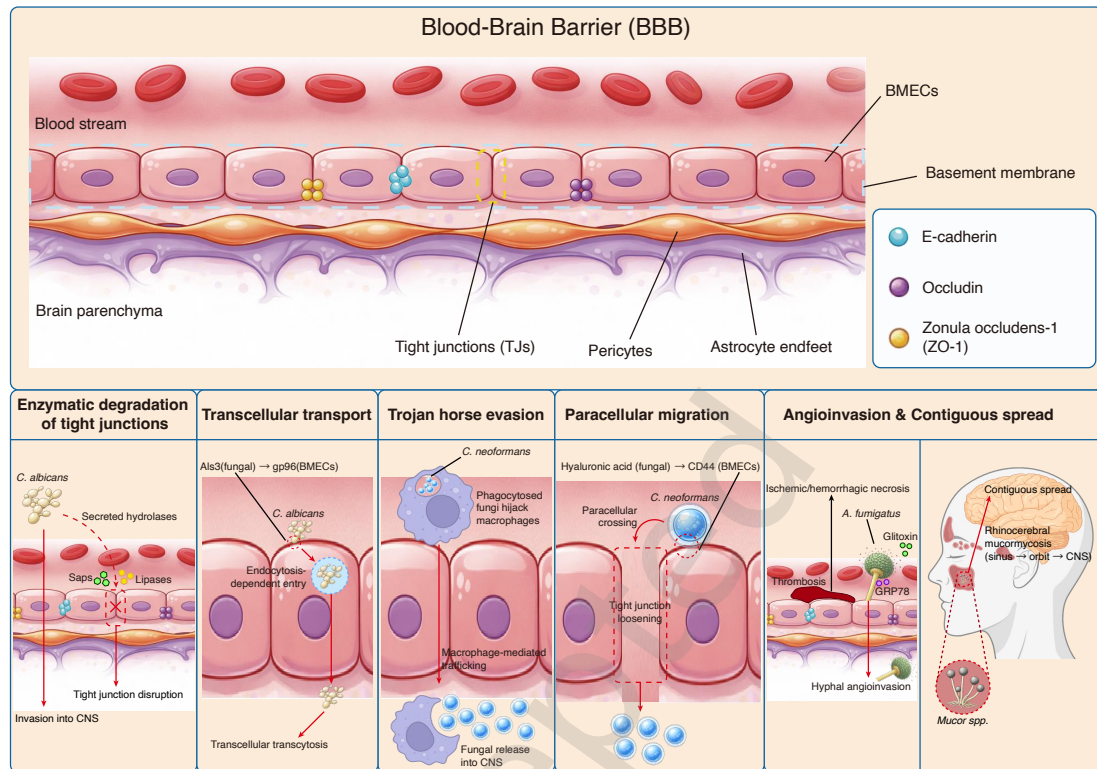


Figure 2. Molecular mechanisms of fungal invasion into the central nervous system by breaching the blood-brain barrier (BBB). The upper panel shows a schematic diagram of the BBB structure, consisting of brain microvascular endothelial cells (BMECs) connected by tight junctions (TJs, with key proteins including E-cadherin, occludin, and ZO-1), basement membrane, pericytes, and astrocyte endfeet, which collectively maintain the structural integrity of the BBB. The lower panel illustrates five major molecular mechanisms of fungal CNS invasion: (1) Enzymatic degradation: *Candida albicans* secretes hydrolases (e.g., aspartyl proteases) to degrade TJ proteins, disrupting BBB integrity; (2) Transcellular transport: *C. albicans* mediates entry into BMECs via the interaction of Als3 (fungal) with gp96 (BMECs), followed by endocytosis-dependent transcytosis; (3) Trojan horse evasion: *Cryptococcus neoformans* and *Histoplasma capsulatum* hijack macrophages to traverse the BBB and release into the brain parenchyma; (4) Paracellular migration: *C. neoformans* initiates TJ loosening through hyaluronic acid-CD44 engagement, facilitating paracellular crossing; (5) Special mechanisms: *Aspergillus fumigatus* invades the CNS via hyphal angioinvasion (involving GRP78 and gliotoxin) that induces thrombosis and tissue necrosis, while *Mucor spp.* spreads intracranially contiguously from adjacent foci (e.g., paranasal sinuses) to cause rhinocerebral mucormycosis.

2.3 Histopathological Responses

Fungal invasion of the central nervous system (CNS) elicits either meningitis—manifesting classical meningeal irritation—or focal parenchymal lesions causing localized neurological deficits[38]. Lesions frequently develop granulomatous structures composed of macrophages, lymphocytes, and multinucleated giant cells that sequester pathogens. Upon colonization, resident microglia and astrocytes, alongside recruited macrophages and neutrophils, rapidly infiltrate infection sites. Stimulated by fungal surface molecules and inflammatory mediators, these cells undergo membrane fusion and reactive gliosis, driving granuloma formation[39]. Angioinvasive fungi (e.g., *A. fumigatus*) penetrate vasculature via hyphal growth, precipitating mycotic thrombosis or haemorrhagic necrosis, which may culminate in cerebral infarction[40].

3. Fungal Immune Evasion: Molecular Tactics for Subverting Host Defenses

Fungal pathogens causing CNS infections evolve complex immune evasion mechanisms to escape immune recognition, phagocytic clearance, and microbicidal activity. These adaptations enable local proliferation at infection sites and systemic dissemination, thereby exacerbating disease severity or precipitating fatal outcomes. Key strategies encompass:

3.1 Molecular Camouflage: Evading Immune Recognition

Fungal cell walls harbour pathogen-associated molecular patterns (PAMPs) recognisable by host pattern recognition receptors (PRRs) [41-44], and a core immune evasion strategy involves concealing these PAMPs with surface components. *C. neoformans* utilises its dense polysaccharide capsule—comprising glucuronoxylomannan (GXM) and galactoxylomannan (GalXM)—to shield underlying cell wall PAMPs, thereby impeding PRR engagement[45; 46]. *C. albicans* employs surface mannans to obscure immunostimulatory β -glucan layers, inhibiting phagocyte uptake, microbicidal activity, and complement pathway activation[42-44] [47-51] [52; 53]. This concealment mechanism is evidenced by enhanced immune recognition in mannan-deficient *C. auris* mutants[54]. Elevated chitin content

similarly obstructs immune cell detection of β -glucan, attenuating cytokine responses[55]. *A. fumigatus* exploits its outer cell wall constituents—galactosaminogalactan (GAG) and the hydrophobin RodA—to mask immunogenic β -glucan, melanin, and α -mannans, dampening host immunity and promoting intracellular persistence[56-58]. *Coccidioides* forms spherules within the host, and interactions between spherule cell wall/external components and host pattern recognition receptors (including CLRs and TLRs) can shape the resultant immune milieu toward Th1/Th17- versus Th2-biased adaptive responses. Adaptive immunity is critical for controlling dissemination (including to the CNS), but host immune responses can also contribute to immunopathology in certain contexts[9][10].

3.2 Construction of Biofilm Barriers and Secretion of Aggressive Effectors

Fungi form biofilms—microbial communities embedded in an extracellular matrix[59]—at infection sites, physically shielding resident fungi from immune cell attack and facilitating persistent infections[60]. These structures resist amphotericin B and caspofungin while exhibiting complete azole resistance (e.g., fluconazole, voriconazole) [61; 62], significantly enhancing host survival. Concurrently, fungi secrete immunosuppressive proteases and virulence determinants to disrupt immune cell function. *C. neoformans* synthesizes phospholipase B (PLB), which augments CNS survival and proliferation[63] while impairing glial function to cause neural damage[64]. Urease secretion promotes haematogenous CNS invasion and cryptococcosis pathogenesis[65; 66]; it facilitates non-lytic exocytosis from macrophages during intracellular transit, enabling dissemination, and accelerates *C. gattii* proliferation and host mortality[67]. In addition, *C. albicans* secretes diverse proteases that directly damage host cells. In addition to soluble virulence factors, fungi actively secrete extracellular vesicles (EVs) as organized delivery platforms for virulence-associated molecules, a mechanism increasingly recognized as critical for CNS invasion[11]. These nanoscale vesicles traverse the fungal cell wall and transport a complex cargo of enzymes, lipids, polysaccharides, and immunomodulatory molecules. In *C. neoformans*, EVs have been shown to contain capsular polysaccharides, phospholipases, urease, and antioxidant enzymes, collectively

enhancing fungal survival, host cell manipulation, and tissue invasion[12]. Simultaneously, EV-associated cargo modulates innate immune responses by altering macrophage and microglial activation states, dampening antifungal cytokine production, and skewing immune polarization. This vesicle-mediated strategy enables fungi to exert coordinated, long-range effects on CNS barriers and immune defenses, complementing biofilm-associated protection and soluble effector activity.

3.3 Active Suppression of Immune Cell Function

Fungi actively subvert immune cell function through multifaceted strategies: inhibition of cellular migration and recruitment, exemplified by *C. albicans* suppressing macrophage trafficking via CLR-mediated modulation of the Spleen tyrosine kinase -B-cell linker protein (Syk-BLNK) pathway[68]; manipulation of the phagosomal microenvironment, demonstrated when *C. neoformans* capsule polysaccharides buffer phagosomal pH to optimize intracellular replication and macrophage lysis[69], while *C. albicans* utilizes the Stp2-Ato5 axis to neutralize phagosomal pH, enabling hyphal morphogenesis and escape[70; 71]; induction of direct cytolysis or non-lytic expulsion, illustrated by *C. albicans* permeabilizing host membranes through candidalysin toxin and NLRP3 inflammasome/gasdermin D activation[72], while both *C. albicans* and *C. neoformans* trigger caspase-1-dependent pyroptosis to achieve non-lytic expulsion preserving pathogen-cell integrity[73-75]; and disruption of intracellular killing via O-mannosylation-mediated interference with GTPase Rab protein activation and phagolysosomal recruitment[76]. *C. neoformans* additionally impedes lymphocyte proliferation[77].

3.4 Shaping an Immunosuppressive Microenvironment and Metabolic Hijacking

Driving the Immunosuppressive Phenotype

A. fumigatus, *C. albicans*, and *C. neoformans* collectively foster immunosuppressive microenvironments to evade host immunity. *C. albicans* polarizes resting and tissue-resident macrophages toward an arginase-1 (Arg1) and transforming growth factor- β (TGF- β)-producing M2 phenotype, reducing nitric oxide

output and impairing antimicrobial functions[78; 79]. Similarly, the *C. neoformans*-secreted effector CPL1 drives M2 polarization in pulmonary infection models, whose production enhances fungal infectivity by initiating TLR4-dependent type 2 immunity through interstitial macrophages[80].

Interfering with Key Cytokine Signaling

C. albicans subverts interleukin-17 (IL-17) and type I interferon (IFN-I) responses through secreted soluble proteins—Cmi1, pH-regulated antigen 1 (Pra1), enolase 1 (Eno1), and Lip2—which disrupt cytokine signaling pathways[81-83]. Lip2 (a *C. albicans*-secreted lipase) catalyzes substrate conversion to palmitic acid, functioning as a TLR 2/4 antagonist that suppresses renal dendritic cell activation. By inactivating these dendritic cells—essential sources of interleukin-23A (IL-23A) for $\gamma\delta$ T cell-derived IL-17a expression—Lip2 compromises IL-17-mediated antifungal immunity and enhances renal colonization[81]. Cmi1 localizes intracellularly, inhibiting TANK-binding kinase 1 (TBK1) to block interferon regulatory factor 3 (IRF3) phosphorylation and subsequent IFN-I transcription[82]. Unlike Lip2 and Cmi1, Pra1 directly binds CD4⁺ T cells zinc-dependently, inhibiting interferon- γ (IFN- γ) and tumour necrosis factor production in vitro[83].

Metabolic Adaptation and Drug Resistance

Fungal pathogens sense host metabolic status and co-opt essential elements to enhance drug resistance. *C. neoformans* evolves enhanced amphotericin B tolerance within the brain via glucan-induced activation of the Mig1–inositol phosphorylceramide pathway, wherein inositol phosphorylceramide competitively binds the drug's target ergosterol, reducing efficacy[84]. Concurrently, copper—essential for antimicrobial immunity and accumulated in macrophages during cryptococcal infection[85]—is exploited through high-level expression of the high-affinity copper transporter CTR4, augmenting virulence during cerebral infection[86]. Iron availability and hypoxia are additional metabolic constraints that critically shape antifungal tolerance and virulence in angioinvasive molds, particularly *Mucorales* (mucormycosis) and *A. fumigatus* (aspergillosis). Mucormycosis is

strongly linked to conditions that increase labile serum iron (e.g., diabetic ketoacidosis) or provide iron via xenosiderophores (e.g., deferoxamine), underscoring that efficient iron acquisition is a prerequisite for rapid tissue invasion and poor clinical outcomes[13]. Mechanistically, *Mucorales* employ high-affinity iron uptake systems (including the iron permease FTR1) and specialized receptors that utilize ferrioxamine-bound iron, and host “nutritional immunity” within macrophages restricts iron to curb fungal growth[14]. In parallel, invasive aspergillosis develops within hypoxic inflammatory foci, where hypoxia adaptation programs are tightly coupled to sterol and iron homeostasis. In *A. fumigatus*, the SREBP pathway (notably SrbA/SrbB) coordinates responses to hypoxia while intersecting with iron regulation and ergosterol biosynthesis, thereby influencing triazole susceptibility and persistence *in vivo*[15].

4. Host Defense Network: Cooperation and Arms Race in Multilayered Immunity

4.1 Innate Immune Defense: Barriers and Resident Sentinels

Mirroring the barrier functions of skin and mucosa, the BBB constitutes the primary defense against CNS-invading fungal pathogens. This structure integrates brain microvascular endothelial cells interconnected by tight junction proteins (e.g., occludin) that establish paracellular impermeability, a basement membrane network of type IV collagen and laminin blocking hyphal penetration (including *A. fumigatus*), pericytes, and astrocytes [87]. Critically, astrocytes generate antimicrobial peptides exerting direct fungicidal activity at the barrier interface, thereby bolstering innate immune protection [88].

Nevertheless, fungal pathogens employ diverse mechanisms to breach the BBB and invade the CNS. Following parenchymal entry, microglia—the resident macrophage-like cells—rapidly initiate innate immunity through surface-expressed CLRs (e.g., Dectin-1, mannose receptor, Mincle) and TLRs (e.g., TLR2/4), with established roles in antifungal defense[89]. Dectin-1 recognizes β -glucans via its

immunoreceptor tyrosine-based activation motif (ITAM)-like domain, triggering Syk/CARD9-dependent signaling that activates NF- κ B and ERK pathways to mediate inflammatory cytokine production (e.g., TNF- α)[90] [91]. Fungal components further induce TLR-mediated upregulation of Mincle—enhancing phagocytosis and NF- κ B activation in macrophages[92]. Additionally, Dectin-3 upregulates Mincle through the CARD9/Bcl10/MALT1-dependent NF- κ B pathway[93], while the understudied receptor Clec2d forms homodimers with TLR2 to modulate interferon regulatory factor 5 (IRF-5) activation[94]. During *C. albicans* challenge, microglia activate CLR-dependent CARD9 signaling and inflammasomes, driving interleukin-1 β release[95]. These cascades collectively underscore the pivotal coordination of CLRs and TLRs in antifungal innate immunity. However, emerging evidence indicates that microglial activation during fungal CNS infections represents a double-edged sword. While these innate immune pathways contribute to fungal containment, sustained or excessive inflammatory signaling can promote a local microenvironment permissive for fungal persistence, for example by altering nutrient availability, metabolic cues, or immune polarization within infected brain regions[16]. Moreover, exaggerated CLR- and TLR-driven cytokine production may precipitate pathological neuroinflammation, leading to collateral neuronal injury and disruption of CNS tissue integrity[17]. Thus, the balance between antifungal immunity and inflammation-induced neuropathology critically shapes disease outcome in fungal CNS infections. Beyond microglia, the CNS contains border-associated macrophages (BAMs) residing in meninges, choroid plexus, and perivascular spaces. The involvement of BAMs in fungal CNS infections remains poorly characterized. Emerging evidence indicates that *C. neoformans* may cross post-capillary venule endothelium via phagocyte-dependent transport to reach perivascular spaces—suggesting BAM participation in cryptococcal neuroinvasion[96]. Functional distinctions further differentiate BAMs from microglia: monocyte-derived BAMs critically activate antifungal CD4⁺ T cell responses in the brain, a capacity absent in microglia, underscoring their unique immunoregulatory role[97]. The precise role of BAMs in fungal neuroinvasion remains poorly defined.

Determining whether they act as early sentinels, facilitate transport, or modulate the perivascular immune response is a crucial frontier.

4.2. Adaptive Immune Modulation and its Dual-Edged Role

The adaptive immune response is crucial for host defense against fungal CNS infections. Gut microbiota-regulated CD4⁺ T cells activated peripherally can migrate into and reside within the CNS[98]. Current understanding of CD4⁺ T cells in antifungal CNS immunity derives primarily from studies of *C. neoformans*—reflecting the capsular polysaccharide-mediated impairment of macrophage/neutrophil fungicidal activity against this pathogen, whereas *C. albicans* and *A. fumigatus* clearance predominantly relies on these innate effectors. Upon CNS invasion by *C. neoformans*, astrocytes produce CXCL10, which recruits CD4⁺ T cells via CXCR3 binding[99]. These T cells drive a Th1-polarized response through interferon- γ (IFN- γ) secretion, enhancing macrophage cryptococcal clearance. However, CD4⁺ T cell-derived IFN- γ exerts a dual function: while promoting pathogen elimination, it simultaneously induces immunopathology that exacerbates meningitis and cerebral edema[100].

Beyond the Th1 axis, Th17 responses participate in host defense against *C. albicans* infection—though current evidence focuses on mucosal contexts. Th17 deficiency increases susceptibility to mucosal *C. albicans* infections, likely due to impaired neutrophil recruitment [101]. While Th17 immunity is essential for mucosal *C. albicans* defense, its role within the CNS parenchyma is virtually unexplored. Its potential synergy or antagonism with Th1 responses in the brain merits investigation. In contrast, Th17 immunity has been extensively investigated in cryptococcal meningoencephalitis and appears to play context-dependent roles in CNS protection and immunopathology. In human HIV-associated cryptococcal meningitis, higher CSF concentrations of Th17-type cytokines (including IL-17) track with a broader intrathecal inflammatory signature and have been associated with enhanced innate effector activation, faster cryptococcal clearance, and improved early survival[18],

suggesting that Th17-related responses can contribute to protective CNS immunity when appropriately balanced with Th1 programs. Mechanistically, *Cryptococcus neoformans* can induce IL-17 production via STAT3-dependent pathways in human immune cells, consistent with an inducible Th17 axis during infection[19]. Moreover, clinical deterioration syndromes such as cryptococcal IRIS highlight that CNS immune activation can become pathogenic; although Th17-associated cytokines can be detected intrathecally, dysregulated inflammatory amplification—often dominated by reconstituted T cell – monocyte signaling — may drive damaging neuroinflammation[20]. Collectively, current evidence supports a nuanced model in which Th17 responses can aid fungal control in cryptococcal meningitis, but their net effect depends on timing, host immune status, and interaction with Th1-driven macrophage activation within the CNS.

4.3. Dynamic Immune Interplay and Coevolution

Fungal pathogens and hosts perpetually adapt through reciprocal evolutionary strategies to gain survival advantages. Long-term coevolution has driven adaptations in both parties: natural selection eliminates individuals harboring deleterious mutations that impair antifungal resistance, thereby enhancing population-level defense capabilities. This principle is exemplified by CARD9 deficiency—first identified in 2009 within a consanguineous family with fatal systemic *C. albicans* infections [102]—where mutations critically compromise antifungal immunity and heighten susceptibility to diverse fungi [103]. Concurrently, fungal pathogens leverage substantially higher mutation rates to evolve enhanced virulence and immune evasion mechanisms, dominating this immunological arms race through sophisticated CNS invasion strategies. Modern clinical practices amplify this dynamic, as widespread immunosuppressant use elevates infection rates in the CNS (creating pathogen adaptation opportunities) while antifungal overuse drives multidrug-resistant strain emergence [104].

As established, fungal neuroinvasion entails breaching the BBB, evading immune surveillance, and manipulating host responses. The spectrum of CNS infection outcomes extends beyond complete pathogen clearance or host fatality to include chronic persistence. Fungi such as *C. neoformans* induce Th2-polarized responses within the CNS, generating an immunosuppressive microenvironment that permits chronic colonization [105]. Although Th2 immunity fails to eradicate pathogens, it conversely mitigates immunopathology and may improve clinical outcomes in the CNS—thereby facilitating fungal persistence [106]. *C. albicans* further evades host defenses through biofilm formation and dormant spore states, conferring resistance to both immune effectors and antimicrobial agents. These ongoing molecular adaptations in the CNS drive coevolutionary trajectories that refine host defenses while enhancing fungal virulence and drug resistance, highlighting pathogenesis complexity and the pressing need for novel therapeutics (Figure 3).

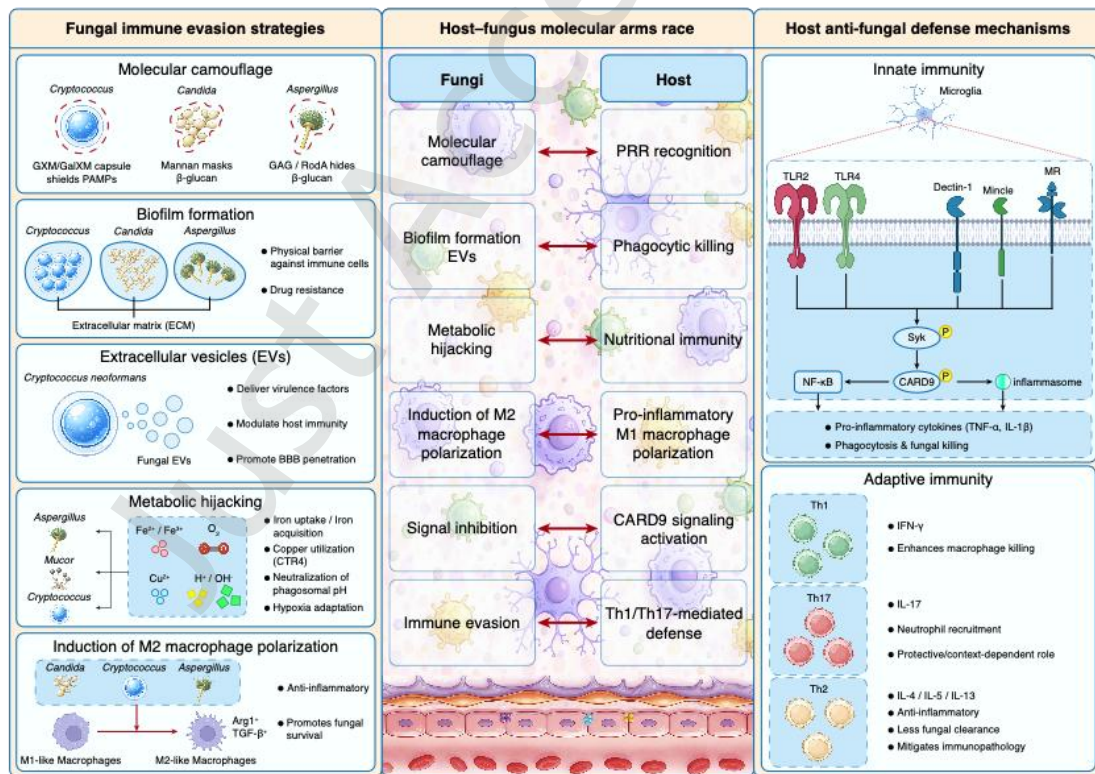


Figure 3. Host–fungal molecular interplay and immune arms race within the CNS microenvironment. Schematic overview of the dynamic host–fungal interaction in the central nervous system. Left: Fungal immune evasion strategies deployed by major CNS-invasive fungi, including (1) molecular camouflage via capsule/mannan/GAG to shield PAMPs; (2) biofilm

formation for physical protection and drug resistance; (3) secretion of extracellular vesicles (EVs) to deliver virulence factors and modulate immunity; (4) metabolic hijacking (iron, copper, hypoxia adaptation, phagosomal pH neutralization); and (5) induction of anti-inflammatory M2 macrophage polarization (Arg1⁺, TGF-β⁺); Right: Host anti-fungal defense network, comprising innate immunity (microglia activation via TLRs and CLRs, followed by Syk/CARD9 signaling, NF-κB activation, and inflammasome-mediated cytokine release) and adaptive immunity (CD4⁺ T cell subsets: Th1/IFN-γ, Th17/IL-17, and Th2 responses); Center: The reciprocal molecular arms race between fungal immune evasion and host defense pathways determines the outcome of CNS fungal infections (clearance, persistence, or immunopathology).

5. Therapeutic Challenges in Central Nervous System Fungal Infections

CNS fungal infections represent acute, high-mortality conditions with complex therapeutic management. Clinical challenges arise from multifactorial interactions between pathogen virulence, host immunity, antifungal pharmacokinetics, and diagnostic delays[107]. A critical obstacle is restricted CNS penetration of antifungals, resulting in subtherapeutic parenchymal concentrations. The BBB—comprising endothelial cells with tight junctions (claudin-5, occludin, zonula occludens-1), pericytes, basement membrane, and astrocytic end-feet—confers protection through three synergistic mechanisms[108]: 1) physical barrier via intercellular tight junctions[109]; 2) metabolic filtration by efflux transporters (P-glycoprotein, multidrug resistance-associated proteins) [110]; and 3) enzymatic detoxification via cytochrome P450[111]. Consequently, most antifungals exhibit minimal BBB penetration (plasma-to-CSF ratios <5%)[112], notably hydrophilic polyenes (e.g., conventional amphotericin B) and echinocandins. Even lipophilic triazoles with moderate CNS bioavailability (e.g., voriconazole) undergo accelerated efflux-mediated clearance, frequently failing to achieve minimum inhibitory concentrations in brain foci, further compounded by *C. neoformans* fluconazole resistance[113]. Recent reports demonstrate that nanocarrier drug delivery enhances the therapeutic efficacy of CNS viral and tuberculosis infections[25][26]. Erythrocyte-membrane-coated liposomal amphotericin B exhibits superior efficacy to

conventional amphotericin B, suggesting that nanocarriers have great potential for the treatment of CNS fungal infections[27], but the clinical efficacy remains elusive. Additionally, the priority in developing improved therapeutic approaches lies in elucidating the mechanistic basis of host-fungal interactions, which will facilitate the rational design of novel and efficacious therapeutic strategies based on these molecular pathways.

6. Conclusion & Future Perspectives

This review has deconstructed the molecular arms race that defines CNS fungal infections, spanning from barrier invasion to deep parenchymal immune conflict. While significant progress has been made, critical voids remain: molecular models of fungal BBB invasion require validation, and immune manipulation networks remain incompletely defined. Beyond acute pathology, Emerging, though controversial, hypotheses suggest chronic CNS fungal colonization may contribute to neuroinflammation and protein aggregation seen in neurodegenerative diseases. Investigating this long-term interplay represents a paradigm-shifting frontier. Moreover, the role of the gut mycobiota as a potential reservoir for CNS-pathogenic fungi and its systemic immunomodulatory effects remain largely unknown. This axis may influence baseline CNS immune readiness and deserves exploration. Importantly, a deeper dive into the metabolic competition within the CNS niche—how fungi scavenge nutrients like glucose, iron, and copper to starve immune cells or fuel drug resistance—is essential for developing metabolic interference strategies. Future research must leverage multi-omics integration and computational modeling to move from studying isolated pathways to understanding the complex, dynamic network of host-fungal interactions. This systems-level approach is key to identifying robust therapeutic nodes.

Deciphering CNS fungal–host interplay necessitates sustained convergence of immunology, microbiology, and neurobiology. Profound understanding of these interaction networks will enable mechanism-based interventions targeting host defense vulnerabilities or fungal virulence factors to improve clinical outcomes.

References

- [1] Nathan, C. L.; Emmert, B. E.; Nelson, E.; Berger, J. R. CNS fungal infections: A review. *J Neurol Sci* **2021**, *422*, 117325. DOI: 10.1016/j.jns.2021.117325.
- [2] Everett, B. A.; Kusske, J. A.; Rush, J. L.; Pribram, H. W. Cryptococcal infection of the central nervous system. *Surg Neurol* **1978**, *9*, 157–163.
- [3] Williamson, P. R.; Jarvis, J. N.; Panackal, A. A.; Fisher, M. C.; Molloy, S. F.; Loyse, A.; Harrison, T. S. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. *Nat Rev Neurol* **2017**, *13*, 13–24. DOI: 10.1038/nrneurol.2016.167.
- [4] Raman Sharma, R. Fungal infections of the nervous system: current perspective and controversies in management. *Int J Surg* **2010**, *8*, 591–601. DOI: 10.1016/j.ijssu.2010.07.293.
- [5] Rajasingham, R.; Govender, N. P.; Jordan, A.; Loyse, A.; Shroufi, A.; Denning, D. W.; Mehta, D. B.; Chiller, T. M.; Boulware, D. R. The global burden of HIV-associated cryptococcal infection in adults in 2020: a modelling analysis. *Lancet Infect Dis* **2022**, *22*, 1748–1755. DOI: 10.1016/s1473-3099(22)00499-6.
- [6] Kunnathu Puthanveedu, N. D.; Lum, J. Central nervous system infections after solid organ transplantation. *Curr Opin Infect Dis* **2021**, *34*, 207–216. DOI: 10.1097/qco.0000000000000722.
- [7] Kanyama, C.; Kouanfack, C.; Nyirenda, S.; Mfinanga, S.; Kivuyo, S. L.; Beaumont, E.; Sturny-Leclère, A.; Phiri, S.; Ngoma, J.; Shimwela, M.; et al. Causes of HIV-related CNS infection in Cameroon, Malawi, and Tanzania: epidemiological findings from the DREAMM HIV-related CNS implementation study. *Lancet Glob Health* **2025**, *13*, e345–e354. DOI: 10.1016/s2214-109x(24)00472-8.
- [8] van den Bogaart, L.; Lang, B. M.; Rossi, S.; Neofytos, D.; Walti, L. N.; Khanna, N.; Mueller, N. J.; Boggian, K.; Garzoni, C.; Mombelli, M.; et al. Central nervous system infections in solid organ transplant recipients: Results from the Swiss Transplant Cohort Study. *J Infect* **2022**, *85*, 1–7. DOI: 10.1016/j.jinf.2022.05.019.
- [9] Tenforde, M. W.; Gertz, A. M.; Lawrence, D. S.; Wills, N. K.; Guthrie, B. L.; Farquhar, C.; Jarvis, J. N. Mortality from HIV-associated meningitis in sub-Saharan Africa: a systematic review and meta-analysis. *J Int AIDS Soc* **2020**, *23*, e25416. DOI: 10.1002/jia2.25416.
- [10] Schmalzle, S. A.; Buchwald, U. K.; Gilliam, B. L.; Riedel, D. J. Cryptococcus neoformans infection in malignancy. *Mycoses* **2016**, *59*, 542–552. DOI: 10.1111/myc.12496.
- [11] Charalambous, L. T.; Premji, A.; Tybout, C.; Hunt, A.; Cutshaw, D.; Elsamadicy, A. A.; Yang, S.; Xie, J.; Giamberardino, C.; Pagadala, P.; et al. Prevalence, healthcare resource utilization and overall burden of fungal meningitis in the United States. *J Med Microbiol* **2018**, *67*, 215–227. DOI: 10.1099/jmm.0.000656.
- [12] Davis, J. A.; Horn, D. L.; Marr, K. A.; Fishman, J. A. Central nervous system involvement in cryptococcal infection in individuals after solid organ transplantation or with AIDS. *Transpl Infect Dis* **2009**, *11*, 432–437. DOI: 10.1111/j.1399-3062.2009.00424.x.
- [13] Neves, N.; Santos, L.; Reis, C.; Sarmiento, A. Candida albicans brain abscesses in an injection drug user patient: a case report. *BMC Res Notes* **2014**, *7*, 837. DOI: 10.1186/1756-0500-7-837.

- [14] G ó ralska, K. ; Blaszkowska, J. ; Dzikowiec, M. Neuroinfections caused by fungi. *Infection* **2018**, *46*, 443–459. DOI: 10.1007/s15010-018-1152-2.
- [15] Rauchway, A. C. ; Husain, S. ; Selhorst, J. B. Neurologic presentations of fungal infections. *Neurol Clin* **2010**, *28*, 293–309. DOI: 10.1016/j.ncl.2009.09.013.
- [16] Murthy, J. M. ; Sundaram, C. Fungal infections of the central nervous system. *Handb Clin Neurol* **2014**, *121*, 1383–1401. DOI: 10.1016/b978-0-7020-4088-7.00095-x.
- [17] Pappas, P. G. ; Kauffman, C. A. ; Andes, D. R. ; Clancy, C. J. ; Marr, K. A. ; Ostrosky-Zeichner, L. ; Reboli, A. C. ; Schuster, M. G. ; Vazquez, J. A. ; Walsh, T. J. ; et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* **2016**, *62*, e1–50. DOI: 10.1093/cid/civ933.
- [18] Mehta, A. ; Yadav, M. ; Gupta, B. K. ; Thapa, B. ; Rai, J. ; Thapa, S. B. ; Yadav, S. K. ; Yadav, D. ; Sharma, M. R. Multiple brain abscesses in a neonate: a rare case report along with review of literature. *Ann Med Surg (Lond)* **2024**, *86*, 4793–4798. DOI: 10.1097/ms9.0000000000002155.
- [19] Santana-Ram í rez, A. ; Esparza-Guti é rrez, S. V. ; Avila-Rodr í guez, P. ; Jim é nez-G ó mez, J. E. ; V é lez-G ó mez, E. ; Bañuelos-Gallo, D. Aspergillosis of the central nervous system in a previously healthy patient that simulated Creutzfeldt–Jakob disease. *Surg Neurol Int* **2016**, *7*, S940–s946. DOI: 10.4103/2152-7806.195230.
- [20] Mattiuzzi, G. ; Giles, F. J. Management of intracranial fungal infections in patients with haematological malignancies. *Br J Haematol* **2005**, *131*, 287–300. DOI: 10.1111/j.1365-2141.2005.05749.x.
- [21] Shamim, M. S. ; Enam, S. A. ; Ali, R. ; Anwar, S. Craniocerebral aspergillosis: a review of advances in diagnosis and management. *J Pak Med Assoc* **2010**, *60*, 573–579.
- [22] Mohammadi, H. ; Sadeghi, S. ; Zandi, S. Central Nervous System Aspergilloma in an Immunocompetent Patient: A Case Report. *Iran J Public Health* **2015**, *44*, 869–872.
- [23] Panda, P. K. ; Mavidi, S. K. ; Wig, N. ; Garg, A. ; Nalwa, A. ; Sharma, M. C. Intracranial Aspergillosis in an Immunocompetent Young Woman. *Mycopathologia* **2017**, *182*, 527–538. DOI: 10.1007/s11046-016-0106-4.
- [24] Athanassiadou, F. ; Tragiannidis, A. ; Papageorgiou, T. ; Velegraki, A. Fungal brain abscesses in leukemia. *Indian Pediatr* **2006**, *43*, 991–994.
- [25] Vergara, G. E. ; Roura, N. ; Del Castillo, M. ; Mora, A. ; Alcorta, S. C. ; Mormandi, R. ; Cervio, A. ; Salvat, J. [Cervical aspergillosis with dissemination to the central nervous system: Case reports and review of the literature]. *Surg Neurol Int* **2015**, *6*, S524–529. DOI: 10.4103/2152-7806.167203.
- [26] Curone, M. ; D'Amico, D. ; Maccagnano, E. ; Bussone, G. Fatal Aspergillus brain abscess in immunocompetent patient. *Neurol Sci* **2009**, *30*, 233–235. DOI: 10.1007/s10072-009-0049-3.
- [27] McCarthy, M. ; Rosengart, A. ; Schuetz, A. N. ; Kontoyiannis, D. P. ; Walsh, T. J. Mold infections of the central nervous system. *N Engl J Med* **2014**, *371*, 150–160. DOI: 10.1056/NEJMr1216008.
- [28] Ara ú z, A. B. ; Papineni, P. Histoplasmosis. *Infect Dis Clin North Am* **2021**, *35*, 471–491. DOI: 10.1016/j.idc.2021.03.011.
- [29] Kirkland, T. N. ; Fierer, J. *Coccidioides immitis* and *posadasii*; A review of their biology,

- genomics, pathogenesis, and host immunity. *Virulence* **2018**, *9*, 1426–1435. DOI: 10.1080/21505594.2018.1509667.
- [30] Sydnor, E. R. M.; Perl, T. M. Hospital Epidemiology and Infection Control in Acute-Care Settings. *Clinical Microbiology Reviews* **2011**, *24*, 141–173. DOI: 10.1128/cmr.00027–10.
- [31] Snarr, B. D.; Drummond, R. A.; Lionakis, M. S. It's all in your head: antifungal immunity in the brain. *Current Opinion in Microbiology* **2020**, *58*, 41–46. DOI: 10.1016/j.mib.2020.07.011.
- [32] Candoni, A.; Klimko, N.; Busca, A.; Di Blasi, R.; Shadrivova, O.; Cesaro, S.; Zannier, M. E.; Verga, L.; Forghieri, F.; Calore, E.; et al. Fungal infections of the central nervous system and paranasal sinuses in onco-haematologic patients. Epidemiological study reporting the diagnostic-therapeutic approach and outcome in 89 cases. *Mycoses* **2019**, *62*, 252–260. DOI: 10.1111/myc.12884.
- [33] Villar, C. C.; Kashleva, H.; Nobile, C. J.; Mitchell, A. P.; Dongari-Bagtzoglou, A. Mucosal Tissue Invasion by *Candida albicans* Is Associated with E-Cadherin Degradation, Mediated by Transcription Factor Rim101p and Protease Sap5p. *Infection and Immunity* **2007**, *75*, 2126–2135. DOI: 10.1128/iai.00054–07.
- [34] Cowen, L. E.; Liu, Y.; Mittal, R.; Solis, N. V.; Prasadarao, N. V.; Filler, S. G. Mechanisms of *Candida albicans* Trafficking to the Brain. *PLoS Pathogens* **2011**, *7*. DOI: 10.1371/journal.ppat.1002305.
- [35] Charlier, C.; Nielsen, K.; Daou, S.; Brigitte, M.; Chretien, F.; Dromer, F. Evidence of a Role for Monocytes in Dissemination and Brain Invasion by *Cryptococcus neoformans*. *Infection and Immunity* **2009**, *77*, 120–127. DOI: 10.1128/iai.01065–08.
- [36] Jong, A.; Wu, C.-H.; Shackelford, G. M.; Kwon-Chung, K. J.; Chang, Y. C.; Chen, H.-M.; Ouyang, Y.; Huang, S.-H. Involvement of human CD44 during *Cryptococcus neoformans* infection of brain microvascular endothelial cells. *Cellular Microbiology* **2008**, *10*, 1313–1326. DOI: 10.1111/j.1462–5822.2008.01128.x.
- [37] Onisiforou, A.; Charalambous, E. G.; Zanos, P. Shattering the Amyloid Illusion: The Microbial Enigma of Alzheimer's Disease Pathogenesis—From Gut Microbiota and Viruses to Brain Biofilms. *Microorganisms* **2025**, *13*. DOI: 10.3390/microorganisms13010090.
- [38] Al-Huthaifi, A. M.; Radman, B. A.; Al-Alawi, A. A.; Mahmood, F.; Liu, T.-B. Mechanisms and Virulence Factors of *Cryptococcus neoformans* Dissemination to the Central Nervous System. *Journal of Fungi* **2024**, *10*. DOI: 10.3390/jof10080586.
- [39] Lyu, J.; Narum, D. E.; Baldwin, S. L.; Larsen, S. E.; Bai, X.; Griffith, D. E.; Dartois, V.; Naidoo, T.; Steyn, A. J. C.; Coler, R. N.; et al. Understanding the development of tuberculous granulomas: insights into host protection and pathogenesis, a review in humans and animals. *Frontiers in Immunology* **2024**, *15*. DOI: 10.3389/fimmu.2024.1427559.
- [40] Economides, M. P.; Ballester, L. Y.; Kumar, V. A.; Jiang, Y.; Tarrand, J.; Prieto, V.; Torres, H. A.; Kontoyiannis, D. P. Invasive mold infections of the central nervous system in patients with hematologic cancer or stem cell transplantation (2000–2016): Uncommon, with improved survival but still deadly often. *Journal of Infection* **2017**, *75*, 572–580. DOI: 10.1016/j.jinf.2017.09.011.
- [41] Latgé, J. P. Immune evasion: Face changing in the fungal opera. *Nat Microbiol* **2017**, *2*, 16266. DOI: 10.1038/nmicrobiol.2016.266.

- [42] Hernández-Chávez, M. J.; Pérez-García, L. A.; Niño-Vega, G. A.; Mora-Montes, H. M. Fungal Strategies to Evade the Host Immune Recognition. *J Fungi (Basel)* **2017**, *3*. DOI: 10.3390/jof3040051.
- [43] Galán-Díez, M.; Arana, D. M.; Serrano-Gómez, D.; Kremer, L.; Casasnovas, J. M.; Ortega, M.; Cuesta-Domínguez, A.; Corbí, A. L.; Pla, J.; Fernández-Ruiz, E. Candida albicans beta-glucan exposure is controlled by the fungal CEK1-mediated mitogen-activated protein kinase pathway that modulates immune responses triggered through dectin-1. *Infect Immun* **2010**, *78*, 1426–1436. DOI: 10.1128/iai.00989-09.
- [44] Bain, J. M.; Louw, J.; Lewis, L. E.; Okai, B.; Walls, C. A.; Ballou, E. R.; Walker, L. A.; Reid, D.; Munro, C. A.; Brown, A. J.; et al. Candida albicans hypha formation and mannan masking of β -glucan inhibit macrophage phagosome maturation. *mBio* **2014**, *5*, e01874. DOI: 10.1128/mBio.01874-14.
- [45] Ueno, K.; Otani, Y.; Yanagihara, N.; Urai, M.; Nagamori, A.; Sato-Fukushima, M.; Shimizu, K.; Saito, N.; Miyazaki, Y. Cryptococcus gattii evades CD11b-mediated fungal recognition by coating itself with capsular polysaccharides. *Eur J Immunol* **2021**, *51*, 2281–2295. DOI: 10.1002/eji.202049042.
- [46] Urai, M.; Kaneko, Y.; Ueno, K.; Okubo, Y.; Aizawa, T.; Fukazawa, H.; Sugita, T.; Ohno, H.; Shibuya, K.; Kinjo, Y.; et al. Evasion of Innate Immune Responses by the Highly Virulent Cryptococcus gattii by Altering Capsule Glucuronoxylomannan Structure. *Front Cell Infect Microbiol* **2015**, *5*, 101. DOI: 10.3389/fcimb.2015.00101.
- [47] Ballou, E. R.; Avelar, G. M.; Childers, D. S.; Mackie, J.; Bain, J. M.; Wagener, J.; Kastora, S. L.; Panea, M. D.; Hardison, S. E.; Walker, L. A.; et al. Lactate signalling regulates fungal β -glucan masking and immune evasion. *Nat Microbiol* **2016**, *2*, 16238. DOI: 10.1038/nmicrobiol.2016.238.
- [48] Pradhan, A.; Avelar, G. M.; Bain, J. M.; Childers, D. S.; Larcombe, D. E.; Netea, M. G.; Shekhova, E.; Munro, C. A.; Brown, G. D.; Erwig, L. P.; et al. Hypoxia Promotes Immune Evasion by Triggering β -Glucan Masking on the Candida albicans Cell Surface via Mitochondrial and cAMP-Protein Kinase A Signaling. *mBio* **2018**, *9*. DOI: 10.1128/mBio.01318-18.
- [49] Ramanan, N.; Wang, Y. A high-affinity iron permease essential for Candida albicans virulence. *Science* **2000**, *288*, 1062–1064. DOI: 10.1126/science.288.5468.1062.
- [50] Pradhan, A.; Avelar, G. M.; Bain, J. M.; Childers, D.; Pelletier, C.; Larcombe, D. E.; Shekhova, E.; Netea, M. G.; Brown, G. D.; Erwig, L.; et al. Non-canonical signalling mediates changes in fungal cell wall PAMPs that drive immune evasion. *Nat Commun* **2019**, *10*, 5315. DOI: 10.1038/s41467-019-13298-9.
- [51] Avelar, G. M.; Pradhan, A.; Ma, Q.; Hickey, E.; Leaves, I.; Liddle, C.; Rodriguez Rondon, A. V.; Kaune, A. K.; Shaw, S.; Maufrais, C.; et al. A CO₂ sensing module modulates β -1,3-glucan exposure in Candida albicans. *mBio* **2024**, *15*, e0189823. DOI: 10.1128/mbio.01898-23.
- [52] Boxx, G. M.; Kozel, T. R.; Nishiya, C. T.; Zhang, M. X. Influence of mannan and glucan on complement activation and C3 binding by Candida albicans. *Infect Immun* **2010**, *78*, 1250–1259. DOI: 10.1128/iai.00744-09.
- [53] Boxx, G. M.; Nishiya, C. T.; Kozel, T. R.; Zhang, M. X. Characteristics of Fc-independent human antimannan antibody-mediated alternative pathway initiation of C3 deposition to

- Candida albicans*. *Mol Immunol* **2009**, *46*, 473–480. DOI: 10.1016/j.molimm.2008.10.008.
- [54] Horton, M. V.; Johnson, C. J.; Zarnowski, R.; Andes, B. D.; Schoen, T. J.; Kernien, J. F.; Lowman, D.; Kruppa, M. D.; Ma, Z.; Williams, D. L.; et al. *Candida auris* Cell Wall Mannosylation Contributes to Neutrophil Evasion through Pathways Divergent from *Candida albicans* and *Candida glabrata*. *mSphere* **2021**, *6*, e0040621. DOI: 10.1128/mSphere.00406–21.
- [55] Mora–Montes, H. M.; Netea, M. G.; Ferwerda, G.; Lenardon, M. D.; Brown, G. D.; Mistry, A. R.; Kullberg, B. J.; O'Callaghan, C. A.; Sheth, C. C.; Odds, F. C.; et al. Recognition and blocking of innate immunity cells by *Candida albicans* chitin. *Infect Immun* **2011**, *79*, 1961–1970. DOI: 10.1128/iai.01282–10.
- [56] Gravelat, F. N.; Beauvais, A.; Liu, H.; Lee, M. J.; Snarr, B. D.; Chen, D.; Xu, W.; Kravtsov, I.; Hoareau, C. M.; Vanier, G.; et al. *Aspergillus galactosaminogalactan* mediates adherence to host constituents and conceals hyphal β –glucan from the immune system. *PLoS Pathog* **2013**, *9*, e1003575. DOI: 10.1371/journal.ppat.1003575.
- [57] Aïmanianda, V.; Bayry, J.; Bozza, S.; Kniemeyer, O.; Perruccio, K.; Elluru, S. R.; Clavaud, C.; Paris, S.; Brakhage, A. A.; Kaveri, S. V.; et al. Surface hydrophobin prevents immune recognition of airborne fungal spores. *Nature* **2009**, *460*, 1117–1121. DOI: 10.1038/nature08264.
- [58] Carrion Sde, J.; Leal, S. M., Jr.; Ghannoum, M. A.; Aïmanianda, V.; Latgé, J. P.; Pearlman, E. The RodA hydrophobin on *Aspergillus fumigatus* spores masks dectin–1– and dectin–2–dependent responses and enhances fungal survival in vivo. *J Immunol* **2013**, *191*, 2581–2588. DOI: 10.4049/jimmunol.1300748.
- [59] Flemming, H. C.; Wingender, J.; Szewzyk, U.; Steinberg, P.; Rice, S. A.; Kjelleberg, S. Biofilms: an emergent form of bacterial life. *Nat Rev Microbiol* **2016**, *14*, 563–575. DOI: 10.1038/nrmicro.2016.94.
- [60] Ciofu, O.; Moser, C.; Jensen, P.; Høiby, N. Tolerance and resistance of microbial biofilms. *Nat Rev Microbiol* **2022**, *20*, 621–635. DOI: 10.1038/s41579–022–00682–4.
- [61] Benaducci, T.; Sardi Jde, C.; Lourencetti, N. M.; Scorzoni, L.; Gullo, F. P.; Rossi, S. A.; Derissi, J. B.; de Azevedo Prata, M. C.; Fusco–Almeida, A. M.; Mendes–Giannini, M. J. Virulence of *Cryptococcus* sp. Biofilms In Vitro and In Vivo using *Galleria mellonella* as an Alternative Model. *Front Microbiol* **2016**, *7*, 290. DOI: 10.3389/fmicb.2016.00290.
- [62] Martinez, L. R.; Casadevall, A. Susceptibility of *Cryptococcus neoformans* biofilms to antifungal agents in vitro. *Antimicrob Agents Chemother* **2006**, *50*, 1021–1033. DOI: 10.1128/aac.50.3.1021–1033.2006.
- [63] Evans, R. J.; Li, Z.; Hughes, W. S.; Djordjevic, J. T.; Nielsen, K.; May, R. C. Cryptococcal phospholipase B1 is required for intracellular proliferation and control of titan cell morphology during macrophage infection. *Infect Immun* **2015**, *83*, 1296–1304. DOI: 10.1128/iai.03104–14.
- [64] Hamed, M. F.; Araújo, G. R. S.; Munzen, M. E.; Reguera–Gomez, M.; Epstein, C.; Lee, H. H.; Frases, S.; Martinez, L. R. Phospholipase B Is Critical for *Cryptococcus neoformans* Survival in the Central Nervous System. *mBio* **2023**, *14*, e0264022. DOI: 10.1128/mbio.02640–22.
- [65] Olszewski, M. A.; Noverr, M. C.; Chen, G. H.; Toews, G. B.; Cox, G. M.; Perfect, J. R.

- J. R. ; Huffnagle, G. B. Urease expression by *Cryptococcus neoformans* promotes microvascular sequestration, thereby enhancing central nervous system invasion. *Am J Pathol* **2004**, *164*, 1761–1771. DOI: 10.1016/s0002-9440(10)63734-0.
- [66] Cox, G. M. ; Mukherjee, J. ; Cole, G. T. ; Casadevall, A. ; Perfect, J. R. Urease as a virulence factor in experimental cryptococcosis. *Infect Immun* **2000**, *68*, 443–448. DOI: 10.1128/iai.68.2.443-448.2000.
- [67] Feder, V. ; Kmetzsch, L. ; Staats, C. C. ; Vidal-Figueiredo, N. ; Ligabue-Braun, R. ; Carlini, C. R. ; Vainstein, M. H. *Cryptococcus gattii* urease as a virulence factor and the relevance of enzymatic activity in cryptococcosis pathogenesis. *Febs j* **2015**, *282*, 1406–1418. DOI: 10.1111/febs.13229.
- [68] Yang, Y. H. ; Xie, K. F. ; Yang, S. ; Wang, H. ; Ma, H. H. ; Zhou, M. ; Wang, Z. W. ; Gu, Y. ; Jia, X. M. BLNK negatively regulates innate antifungal immunity through inhibiting c-Cbl-mediated macrophage migration. *Proc Natl Acad Sci U S A* **2024**, *121*, e2400920121. DOI: 10.1073/pnas.2400920121.
- [69] De Leon-Rodriguez, C. M. ; Fu, M. S. ; Çorbali, M. O. ; Cordero, R. J. B. ; Casadevall, A. The Capsule of *Cryptococcus neoformans* Modulates Phagosomal pH through Its Acid-Base Properties. *mSphere* **2018**, *3*. DOI: 10.1128/mSphere.00437-18.
- [70] Vylkova, S. ; Lorenz, M. C. Modulation of phagosomal pH by *Candida albicans* promotes hyphal morphogenesis and requires Stp2p, a regulator of amino acid transport. *PLoS Pathog* **2014**, *10*, e1003995. DOI: 10.1371/journal.ppat.1003995.
- [71] Danhof, H. A. ; Lorenz, M. C. The *Candida albicans* ATO Gene Family Promotes Neutralization of the Macrophage Phagolysosome. *Infect Immun* **2015**, *83*, 4416–4426. DOI: 10.1128/iai.00984-15.
- [72] Olivier, F. A. B. ; Hilsenstein, V. ; Weerasinghe, H. ; Weir, A. ; Hughes, S. ; Crawford, S. ; Vince, J. E. ; Hickey, M. J. ; Traven, A. The escape of *Candida albicans* from macrophages is enabled by the fungal toxin candidalysin and two host cell death pathways. *Cell Rep* **2022**, *40*, 111374. DOI: 10.1016/j.celrep.2022.111374.
- [73] O'Meara, T. R. ; Veri, A. O. ; Ketela, T. ; Jiang, B. ; Roemer, T. ; Cowen, L. E. Global analysis of fungal morphology exposes mechanisms of host cell escape. *Nat Commun* **2015**, *6*, 6741. DOI: 10.1038/ncomms7741.
- [74] Alvarez, M. ; Casadevall, A. Phagosome extrusion and host-cell survival after *Cryptococcus neoformans* phagocytosis by macrophages. *Curr Biol* **2006**, *16*, 2161–2165. DOI: 10.1016/j.cub.2006.09.061.
- [75] Bain, J. M. ; Lewis, L. E. ; Okai, B. ; Quinn, J. ; Gow, N. A. ; Erwig, L. P. Non-lytic expulsion/exocytosis of *Candida albicans* from macrophages. *Fungal Genet Biol* **2012**, *49*, 677–678. DOI: 10.1016/j.fgb.2012.01.008.
- [76] Erwig, L. P. ; Gow, N. A. Interactions of fungal pathogens with phagocytes. *Nat Rev Microbiol* **2016**, *14*, 163–176. DOI: 10.1038/nrmicro.2015.21.
- [77] Syme, R. M. ; Bruno, T. F. ; Kozel, T. R. ; Mody, C. H. The capsule of *Cryptococcus neoformans* reduces T-lymphocyte proliferation by reducing phagocytosis, which can be restored with anticapsular antibody. *Infect Immun* **1999**, *67*, 4620–4627. DOI: 10.1128/iai.67.9.4620-4627.1999.
- [78] Wagener, J. ; MacCallum, D. M. ; Brown, G. D. ; Gow, N. A. *Candida albicans* Chitin Increases Arginase-1 Activity in Human Macrophages, with an Impact on Macrophage Antimicrobial

- Functions. *mBio* **2017**, *8*. DOI: 10.1128/mBio.01820-16.
- [79] Lin, L.; Wang, M.; Zeng, J.; Mao, Y.; Qin, R.; Deng, J.; Ouyang, X.; Hou, X.; Sun, C.; Wang, Y.; et al. Sequence Variation of *Candida albicans* Sap2 Enhances Fungal Pathogenicity via Complement Evasion and Macrophage M2-Like Phenotype Induction. *Adv Sci (Weinh)* **2023**, *10*, e2206713. DOI: 10.1002/advs.202206713.
- [80] Dang, E. V.; Lei, S.; Radkov, A.; Volk, R. F.; Zaro, B. W.; Madhani, H. D. Secreted fungal virulence effector triggers allergic inflammation via TLR4. *Nature* **2022**, *608*, 161–167. DOI: 10.1038/s41586-022-05005-4.
- [81] Basso, P.; Dang, E. V.; Urisman, A.; Cowen, L. E.; Madhani, H. D.; Noble, S. M. Deep tissue infection by an invasive human fungal pathogen requires lipid-based suppression of the IL-17 response. *Cell Host Microbe* **2022**, *30*, 1589–1601.e1585. DOI: 10.1016/j.chom.2022.10.004.
- [82] Luo, G.; Zhang, J.; Wang, T.; Cui, H.; Bai, Y.; Luo, J.; Zhang, J.; Zhang, M.; Di, L.; Yuan, Y.; et al. A human commensal-pathogenic fungus suppresses host immunity via targeting TBK1. *Cell Host Microbe* **2024**, *32*, 1536–1551.e1536. DOI: 10.1016/j.chom.2024.07.003.
- [83] Bergfeld, A.; Dasari, P.; Werner, S.; Hughes, T. R.; Song, W. C.; Hortschansky, P.; Brakhage, A. A.; Hünig, T.; Zipfel, P. F.; Beyersdorf, N. Direct Binding of the pH-Regulated Protein 1 (Pra1) from *Candida albicans* Inhibits Cytokine Secretion by Mouse CD4(+) T Cells. *Front Microbiol* **2017**, *8*, 844. DOI: 10.3389/fmicb.2017.00844.
- [84] Chen, L.; Tian, X.; Zhang, L.; Wang, W.; Hu, P.; Ma, Z.; Li, Y.; Li, S.; Shen, Z.; Fan, X.; et al. Brain glucose induces tolerance of *Cryptococcus neoformans* to amphotericin B during meningitis. *Nat Microbiol* **2024**, *9*, 346–358. DOI: 10.1038/s41564-023-01561-1.
- [85] Ding, C.; Festa, Richard A.; Chen, Y.-L.; Espart, A.; Palacios, Ò.; Espín, J.; Capdevila, M.; Atrian, S.; Heitman, J.; Thiele, Dennis J. *Cryptococcus neoformans* Copper Detoxification Machinery Is Critical for Fungal Virulence. *Cell Host & Microbe* **2013**, *13*, 265–276. DOI: <https://doi.org/10.1016/j.chom.2013.02.002>.
- [86] Sun, T. S.; Ju, X.; Gao, H. L.; Wang, T.; Thiele, D. J.; Li, J. Y.; Wang, Z. Y.; Ding, C. Reciprocal functions of *Cryptococcus neoformans* copper homeostasis machinery during pulmonary infection and meningoencephalitis. *Nat Commun* **2014**, *5*, 5550. DOI: 10.1038/ncomms6550.
- [87] Reed, M. J.; Damodarasamy, M.; Banks, W. A. The extracellular matrix of the blood-brain barrier: structural and functional roles in health, aging, and Alzheimer's disease. *Tissue Barriers* **2019**, *7*, 1651157. DOI: 10.1080/21688370.2019.1651157.
- [88] Woo, Y. H.; Martinez, L. R. *Cryptococcus neoformans*-astrocyte interactions: effect on fungal blood brain barrier disruption, brain invasion, and meningitis progression. *Crit Rev Microbiol* **2021**, *47*, 206–223. DOI: 10.1080/1040841X.2020.1869178.
- [89] Reyes, E. Y.; Shinohara, M. L. Host immune responses in the central nervous system during fungal infections. *Immunol Rev* **2022**, *311*, 50–74. DOI: 10.1111/imr.13101.
- [90] Goyal, S.; Castrillon-Betancur, J. C.; Klaile, E.; Slevogt, H. The Interaction of Human Pathogenic Fungi With C-Type Lectin Receptors. *Front Immunol* **2018**, *9*, 1261. DOI: 10.3389/fimmu.2018.01261.
- [91] Deerhake, M. E.; Shinohara, M. L. Emerging roles of Dectin-1 in noninfectious settings and

- in the CNS. *Trends Immunol* **2021**, *42*, 891–903. DOI: 10.1016/j.it.2021.08.005.
- [92] Patin, E. C.; Orr, S. J.; Schaible, U. E. Macrophage Inducible C-Type Lectin As a Multifunctional Player in Immunity. *Front Immunol* **2017**, *8*, 861. DOI: 10.3389/fimmu.2017.00861.
- [93] Zhao, X. Q.; Zhu, L. L.; Chang, Q.; Jiang, C.; You, Y.; Luo, T.; Jia, X. M.; Lin, X. C-type lectin receptor dectin-3 mediates trehalose 6,6'-dimycolate (TDM)-induced Mincle expression through CARD9/Bcl10/MALT1-dependent nuclear factor (NF)-kappaB activation. *J Biol Chem* **2014**, *289*, 30052–30062. DOI: 10.1074/jbc.M114.588574.
- [94] Li, F.; Wang, H.; Li, Y.-Q.; Gu, Y.; Jia, X.-M. C-type lectin receptor 2d forms homodimers and heterodimers with TLR2 to negatively regulate IRF5-mediated antifungal immunity. *Nature Communications* **2023**, *14*, 6718. DOI: 10.1038/s41467-023-42216-3.
- [95] Drummond, R. A.; Swamydas, M.; Oikonomou, V.; Zhai, B.; Dambuza, I. M.; Schaefer, B. C.; Bohrer, A. C.; Mayer-Barber, K. D.; Lira, S. A.; Iwakura, Y.; et al. CARD9(+) microglia promote antifungal immunity via IL-1beta- and CXCL1-mediated neutrophil recruitment. *Nat Immunol* **2019**, *20*, 559–570. DOI: 10.1038/s41590-019-0377-2.
- [96] Aguirre, K.; Miller, S. MHC class II-positive perivascular microglial cells mediate resistance to *Cryptococcus neoformans* brain infection. *Glia* **2002**, *39*, 184–188. DOI: 10.1002/glia.10093.
- [97] Kaufman-Francis, K.; Djordjevic, J. T.; Juillard, P. G.; Lev, S.; Desmarini, D.; Grau, G. E. R.; Sorrell, T. C. The Early Innate Immune Response to, and Phagocyte-Dependent Entry of, *Cryptococcus neoformans* Map to the Perivascular Space of Cortical Post-Capillary Venules in Neurocryptococcosis. *Am J Pathol* **2018**, *188*, 1653–1665. DOI: 10.1016/j.ajpath.2018.03.015.
- [98] Pasciuto, E.; Burton, O. T.; Roca, C. P.; Lagou, V.; Rajan, W. D.; Theys, T.; Mancuso, R.; Tito, R. Y.; Kouser, L.; Callaerts-Vegh, Z.; et al. Microglia Require CD4 T Cells to Complete the Fetal-to-Adult Transition. *Cell* **2020**, *182*, 625–640 e624. DOI: 10.1016/j.cell.2020.06.026.
- [99] <[13] Chemokine receptor CXCR3 is required for lethal brain pathology but not pathogen clearance during cryptococcal meningoencephalitis.pdf>.
- [100] Khaw, Y. M.; Aggarwal, N.; Barclay, W. E.; Kang, E.; Inoue, M.; Shinohara, M. L. Th1-Dependent *Cryptococcus*-Associated Immune Reconstitution Inflammatory Syndrome Model With Brain Damage. *Front Immunol* **2020**, *11*, 529219. DOI: 10.3389/fimmu.2020.529219.
- [101] Tangye, S. G.; Puel, A. The Th17/IL-17 Axis and Host Defense Against Fungal Infections. *The Journal of Allergy and Clinical Immunology In Practice* **2023**, *11*, 1624–1634. DOI: 10.1016/j.jaip.2023.04.015.
- [102] Glocker, E.-O.; Hennigs, A.; Nabavi, M.; Schäffer, A. A.; Woellner, C.; Salzer, U.; Pfeifer, D.; Veelken, H.; Warnatz, K.; Tahami, F.; et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. *The New England Journal of Medicine* **2009**, *361*, 1727–1735. DOI: 10.1056/NEJMoa0810719.
- [103] Drummond, R. A.; Lionakis, M. S. Mechanistic Insights into the Role of C-Type Lectin Receptor/CARD9 Signaling in Human Antifungal Immunity. *Front Cell Infect Microbiol* **2016**, *6*, 39. DOI: 10.3389/fcimb.2016.00039.
- [104] Denning, D. W. Global incidence and mortality of severe fungal disease. *Lancet Infect Dis* **2024**,

- 24, e428–e438. DOI: 10.1016/S1473–3099(23)00692–8.
- [105] Yang, C.; Huang, Y.; Zhou, Y.; Zang, X.; Deng, H.; Liu, Y.; Shen, D.; Xue, X. Cryptococcus escapes host immunity: What do we know? *Front Cell Infect Microbiol* **2022**, *12*, 1041036. DOI: 10.3389/fcimb.2022.1041036.
- [106] Antachopoulos, C.; Walsh, T. J. Immunotherapy of Cryptococcus infections. *Clinical Microbiology and Infection : the Official Publication of the European Society of Clinical Microbiology and Infectious Diseases* **2012**, *18*, 126–133. DOI: 10.1111/j.1469–0691.2011.03741.x.
- [107] Kaiser, A. B.; McGee, Z. A. Aminoglycoside therapy of gram-negative bacillary meningitis. *N Engl J Med* **1975**, *293*, 1215–1220. DOI: 10.1056/nejm197512112932401.
- [108] Rubin, L. L.; Staddon, J. M. The cell biology of the blood–brain barrier. *Annu Rev Neurosci* **1999**, *22*, 11–28. DOI: 10.1146/annurev.neuro.22.1.11.
- [109] Luissint, A. C.; Artus, C.; Glacial, F.; Ganeshamoorthy, K.; Couraud, P. O. Tight junctions at the blood brain barrier: physiological architecture and disease-associated dysregulation. *Fluids Barriers CNS* **2012**, *9*, 23. DOI: 10.1186/2045–8118–9–23.
- [110] Yanagida, K.; Liu, C. H.; Faraco, G.; Galvani, S.; Smith, H. K.; Burg, N.; Anrather, J.; Sanchez, T.; Iadecola, C.; Hla, T. Size-selective opening of the blood–brain barrier by targeting endothelial sphingosine 1-phosphate receptor 1. *Proc Natl Acad Sci U S A* **2017**, *114*, 4531–4536. DOI: 10.1073/pnas.1618659114.
- [111] Zlotnik, D.; Rabinski, T.; Halfon, A.; Anzi, S.; Plaschkes, I.; Benyamini, H.; Nevo, Y.; Gershoni, O. Y.; Rosental, B.; HersHKovitz, E.; et al. P450 oxidoreductase regulates barrier maturation by mediating retinoic acid metabolism in a model of the human BBB. *Stem Cell Reports* **2022**, *17*, 2050–2063. DOI: 10.1016/j.stemcr.2022.07.010.
- [112] Ashley, E. D. Antifungal Drugs: Special Problems Treating Central Nervous System Infections. *J Fungi (Basel)* **2019**, *5*. DOI: 10.3390/jof5040097.
- [113] Bongomin, F.; Oladele, R. O.; Gago, S.; Moore, C. B.; Richardson, M. D. A systematic review of fluconazole resistance in clinical isolates of Cryptococcus species. *Mycoses* **2018**, *61*, 290–297. DOI: 10.1111/myc.12747.
- [1] Gow NAR, Latge JP, Munro CA. The Fungal Cell Wall: Structure, Biosynthesis, and Function. *Microbiol Spectr.* **2017** May;5(3):10.1128/microbiolspec.funk–0035–2016. DOI: 10.1128/microbiolspec.FUNK–0035–2016.
- [2] Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. *Sci Transl Med.* **2012** Dec 19;4(165):165rv13. DOI: 10.1126/scitranslmed.3004404.
- [3] Brown AJ, Brown GD, Netea MG, Gow NA. Metabolism impacts upon Candida immunogenicity and pathogenicity at multiple levels. *Trends Microbiol.* **2014** Nov;22(11):614–22. DOI: 10.1016/j.tim.2014.07.001.
- [4] Schwartz S, Thiel E. Cerebral aspergillosis: tissue penetration is the key. *Med Mycol.* **2009**;47 Suppl 1:S387–93. DOI: 10.1080/13693780802537953.
- [5] Ramírez JA, Reyes–Montes MDR, Rodríguez–Arellanes G, Pérez–Torres A, Taylor ML. Central Nervous System Histoplasmosis: An Updated Insight. *Pathogens.* **2023** May 5;12(5):681. DOI: 10.3390/pathogens12050681.
- [6] Jackson KM, Teixeira MdM, Barker BM. From soil to clinic: current advances in

- understanding *Coccidioides* and coccidioidomycosis. *Microbiol Mol Biol Rev.* **2024** Dec 18;88(4):e0016123. DOI: 10.1128/mmbr.00161–23.
- [7] Riddell J 4th, Wheat LJ. Central Nervous System Infection with *Histoplasma capsulatum*. *J Fungi (Basel)*. **2019** Jul 24;5(3):70. DOI: 10.3390/jof5030070.
 - [8] Kamai Y, Lossinsky AS, Liu H, Sheppard DC, Filler SG. Polarized response of endothelial cells to invasion by *Aspergillus fumigatus*. *Cell Microbiol.* **2009** Jan;11(1):170–82. DOI: 10.1111/j.1462–5822.2008.01247.x.
 - [9] Castro–Lopez N, Hung CY. Immune Response to Coccidioidomycosis and the Development of a Vaccine. *Microorganisms.* **2017** Mar 16;5(1):13. DOI: 10.3390/microorganisms5010013.
 - [10] Diep AL, Hoyer KK. Host Response to *Coccidioides* Infection: Fungal Immunity. *Front Cell Infect Microbiol.* **2020** Nov 11;10:581101. DOI: 10.3389/fcimb.2020.581101.
 - [11] Brown Harding H, Kwaku GN, Reardon CM, Khan NS, Zamith–Miranda D, Zarnowski R, Tam JM, Bohaen CK, Richey L, Mosallanejad K, Crossen AJ, Reedy JL, Ward RA, Vargas–Blanco DA, Basham KJ, Bhattacharyya RP, Nett JE, Mansour MK, van de Veerdonk FL, Kumar V, Kagan JC, Andes DR, Nosanchuk JD, Vyas JM. *Candida albicans* extracellular vesicles trigger type I IFN signalling via cGAS and STING. *Nat Microbiol.* **2024** Jan;9(1):95–107. DOI: 10.1038/s41564–023–01546–0.
 - [12] Kwaku GN, Jensen KN, Simaku P, Floyd DJ, Saelens JW, Reardon CM, Ward RA, Basham KJ, Hepworth OW, Vyas TD, Zamith–Miranda D, Nosanchuk JD, Vyas JM, Brown Harding H. Extracellular vesicles from diverse fungal pathogens induce species–specific and endocytosis–dependent immunomodulation. *PLoS Pathog.* **2025** May 30;21(5):e1012879. DOI: 10.1371/journal.ppat.1012879.
 - [13] Andrianaki AM, Kyrnizi I, Thanopoulou K, Baldin C, Drakos E, Soliman SSM, Shetty AC, McCracken C, Akoumianaki T, Stylianou K, Ioannou P, Pontikoglou C, Papadaki HA, Tzardi M, Belle V, Etienne E, Beauvais A, Samonis G, Kontoyiannis DP, Andreacos E, Bruno VM, Ibrahim AS, Chamilos G. Iron restriction inside macrophages regulates pulmonary host defense against *Rhizopus* species. *Nat Commun.* **2018** Aug 20;9(1):3333. DOI: 10.1038/s41467–018–05820–2.
 - [14] Liu M, Lin L, Gebremariam T, Luo G, Skory CD, French SW, Chou TF, Edwards JE Jr, Ibrahim AS. Fob1 and Fob2 Proteins Are Virulence Determinants of *Rhizopus oryzae* via Facilitating Iron Uptake from Ferrioxamine. *PLoS Pathog.* **2015** May 14;11(5):e1004842. DOI: 10.1371/journal.ppat.1004842.
 - [15] Blatzer M, Barker BM, Willger SD, Beckmann N, Blosser SJ, Cornish EJ, Mazurie A, Grahl N, Haas H, Cramer RA. SREBP coordinates iron and ergosterol homeostasis to mediate triazole drug and hypoxia responses in the human fungal pathogen *Aspergillus fumigatus*. *PLoS Genet.* **2011** Dec;7(12):e1002374. doi: 10.1371/journal.pgen.1002374.
 - [16] Mohamed SH, Nyazika TK, Ssebambulidde K, Lionakis MS, Meya DB, Drummond RA. Fungal CNS Infections in Africa: The Neuroimmunology of Cryptococcal Meningitis. *Front Immunol.* **2022** Apr 1;13:804674. DOI: 10.3389/fimmu.2022.804674.
 - [17] Neal LM, Xing E, Xu J, Kolbe JL, Osterholzer JJ, Segal BM, Williamson PR, Olszewski MA. CD4⁺ T Cells Orchestrate Lethal Immune Pathology despite Fungal Clearance during *Cryptococcus neoformans* Meningoencephalitis. *mBio.* **2017** Nov 21;8(6):e01415–17. DOI: 10.1128/mBio.01415–17.
 - [18] Jarvis JN, Meintjes G, Bicanic T, Buffa V, Hogan L, Mo S, Tomlinson G, Kropf P, Noursadeghi

- M, Harrison TS. Cerebrospinal fluid cytokine profiles predict risk of early mortality and immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis. *PLoS Pathog.* **2015** Apr 8;11(4):e1004754. DOI: 10.1371/journal.ppat.1004754.
- [19] Guo X, Mao X, Tian D, Liao Y, Su B, Ye C, Shi D, Liu TF, Ling Y, Hao Y. *Cryptococcus neoformans* Infection Induces IL-17 Production by Promoting STAT3 Phosphorylation in CD4⁺ T Cells. *Front Immunol.* **2022** May 27;13:872286. DOI: 10.3389/fimmu.2022.872286.
- [20] Bowen LN, Smith B, Reich D, Quezado M, Nath A. HIV-associated opportunistic CNS infections: pathophysiology, diagnosis and treatment. *Nat Rev Neurol.* **2016** Oct 27;12(11):662–674. DOI: 10.1038/nrneurol.2016.149.
- [21] O'Brien, D., et al., *Candida infection of the central nervous system following neurosurgery: a 12-year review.* Acta Neurochir (Wien), 2011. **153**(6): p. 1347 – 50.
- [22] Chen, H., et al., *Candida central nervous system infection after neurosurgery: a single-institution case series and literature review.* Ann Palliat Med, 2021. **10**(11): p. 11362 – 11369.
- [23] Huang, C., et al., *Emerging Cryptococcus gattii species complex infections in Guangxi, southern China.* PLoS Negl Trop Dis, 2020. **14**(8): p. e0008493.
- [24] Peterson, A., et al., *Intracranial fusarium fungal abscess in an immunocompetent patient: case report and review of the literature.* J Neurol Surg Rep, 2014. **75**(2): p. e241 – 5.
- [25] Marcianes, P., et al., *Surface-modified gatifloxacin nanoparticles with potential for treating central nervous system tuberculosis.* Int J Nanomedicine, 2017. **12**: p. 1959 – 1968.
- [26] 121. Zhu, S., et al., *Application of Virus Targeting Nanocarrier Drug Delivery System in Virus-Induced Central Nervous System Disease Treatment.* ACS Appl Mater Interfaces, 2019. **11**(21): p. 19006 – 19016.
- [27] 122. Castro, F., et al., *Advances on erythrocyte-mimicking nanovehicles to overcome barriers in biological microenvironments.* Adv Drug Deliv Rev, 2021. **170**: p. 312 – 339.

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Declaration of competing interests

The authors declare no competing financial interests.

Data availability

Not applicable. This review does not generate new raw data.

Author contributions

X.M.J. conceptualized the review topic. X.M.J. and Y.B.G. designed the overall framework. Y.B.G., Y.S.W. and H.Y.W. conducted systematic literature search and analyzed key data from included studies. Y.B.G., Y.S.W. and H.Y.W. drafted the manuscript. All authors discussed the core arguments, revised the content, and approved the final version of the manuscript.

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