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# It's all in your head: antifungal immunity in the brain

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As the incidence rate of invasive fungal infections has increased with the use of modern medical interventions, so too has the occurrence of fungi invading the brain. Fungi such as *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* often infect immunocompromised individuals, and can use several strategies to invade the central nervous system (CNS) by penetrating the blood–brain barrier. Once in the brain parenchyma the specialized resident immune cells need to effectively recognize the fungus and mount an appropriate immune response to clear the infection, without causing debilitating immune-mediated toxicity and neuronal damage. Here we review the current knowledge pertaining to the antifungal response of the CNS and highlight areas where future research is required.

## Addresses

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## Introduction

In recent decades, invasive fungal infections (IFIs) have increased due to expanded immunosuppressed populations and invasive medical interventions [1]. *Candida albicans* infects critically ill and immunocompromised patients and is the most common cause of hospital-acquired fungemia [2]. *Cryptococcus neoformans* causes invasive central nervous system (CNS) infections in HIV/AIDS patients, while the related *Cryptococcus gattii* typically infects the lungs of putatively immunocompetent individuals [3]. *Aspergillus fumigatus* is responsible for invasive infections in patients with neutropenia or allogeneic hematopoietic stem cell transplantation (HSCT).

Current treatments for IFIs remain insufficient, with mortalities >50% [4].

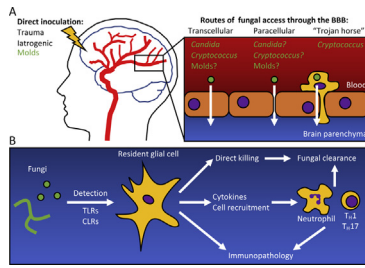
As IFIs disseminate, a common target tissue is the CNS. Additionally, fungi can gain direct access to the CNS following traumatic inoculation or neurosurgical procedures [5]. Within the CNS, fungi come in contact with the brain's specialized resident immune system, comprising barrier-associated macrophages, microglia and astrocytes [6]. This review summarizes our current understanding of the most common CNS-associated IFIs in terms of at-risk populations, mechanisms of fungal CNS entry, and host immune responses (Figure 1). Gaps in our knowledge and opportunities for future research are highlighted.

## CNS candidiasis

*Candida* is the most common human fungal pathogen. Mucosal infections and candidemia are more common [7], whereas CNS infections are relatively rare [8]. *C. albicans* enters the CNS through bloodstream dissemination, causing encephalitis as a result of an ineffective antifungal immune response. Populations at-risk for *Candida* encephalitis include premature infants and severely immunocompromised patients with prolonged neutropenia, HSCT, and specific genetic deficiencies [8].

The mechanism by which *C. albicans* crosses the blood–brain barrier (BBB) and invades the CNS remains poorly understood. Evidence exists of *C. albicans* crossing between endothelial cells (paracellular route) and being taken up by endothelial cells and exiting the basal surface (transcellular route) [9]. The importance of the paracellular route for accessing the BBB remains unclear. *C. albicans* can degrade the tight junction protein E-cadherin through secreted aspartyl proteases [10] and E-cadherin is expressed by bovine brain endothelial cells [11]. However, expression of E-cadherin by human or mouse brain endothelial cells has not been reported. In contrast, greater evidence exists implicating the transcellular route for *C. albicans* accessing the brain. *C. albicans* interacts with the heat-shock protein gp96 on brain microvascular endothelial cells via its invasin Als3 [12]. Gp96 is uniquely expressed on brain endothelial cells, and its interaction with Als3 induces fungal endocytosis. Less is known about how the fungus exits the endothelial cell to gain access into the CNS; whether it is through active exocytosis, or a fungus-induced lytic process causing endothelial cell death remains unknown. Magnetic

Figure 1



(a) Fungi enter the brain through either direct inoculation, or by crossing the blood–brain barrier (BBB). Direct inoculation can be the result of a traumatic event, or iatrogenically through neurosurgery. Fungi can cross the BBB by being taken up by endothelial cells (transcellular), degrading the tight junctions between the cells (paracellular), or carried across the BBB in a phagocyte ('Trojan horse'). Brain Image adapted from <https://www.health.harvard.edu/heart-health/the-crucial-controversial-carotid-artery-part-i-the-artery-in-health-and-disease>. (b) Fungi are detected in the brain by resident glial cells (microglia, astrocytes) through Toll-like receptors (TLR) and C-type lectin receptors (CLR). Glial cells can then directly engage the fungi, clearing them from the brain, or recruit immune cells through the release of cytokines and chemoattractants. Innate immune cells such as neutrophils, and adaptive immune cells such as T<sub>H</sub>1 and T<sub>H</sub>17 lymphocytes are effective at clearing the infection. However, excessive inflammation and immunotoxicity can lead to irreversible neurological damage.

resonance imaging suggested the latter scenario, as *C. albicans*-infected mice display loss of BBB integrity [13]. However, it is unclear whether loss of BBB integrity is due to endothelial cell lysis as a result of the fungus exiting them, or due to damage from the ensuing CNS infection. While *C. albicans* deep-tissue invasion is often assumed to require hyphal differentiation, it is important to note that this is not necessary for CNS invasion, as heterologous expression of Als3 in *Saccharomyces cerevisiae* resulted in their uptake by brain endothelial cells [12], and a yeast-locked strain of *C. albicans* establishes CNS invasion in mice [14]. Intravital microscopy studies are required to further clarify how *C. albicans* establishes CNS infection.

Microglia play a central role in anti-*Candida* CNS host responses. In a low-dose candidemia model, self-limited fungal granulomas develop in infected brains surrounded by microglia and astrocytes [15]. While limited cellular recruitment was noted, amyloid- $\beta$  peptides bound to *C. albicans* and enhanced microglial phagocytosis and killing [15]. Accordingly, amyloid-deficient mice had larger fungal lesions and impaired fungal-clearing ability [15].

*Candida* encephalitis stemming from high-dose candidemia requires neutrophil recruitment to avoid uncontrolled CNS invasion [16]. Human and animal studies have identified a role for Caspase Recruitment Domain 9

(CARD9), encoding a signal adaptor downstream of fungal-sensing C-type lectin receptors (CLRs), in recruiting neutrophils to the *Candida*-infected CNS [14,16]. Brain-resident microglia are pivotal in orchestrating the Card9-dependent release of neutrophil-recruiting CXCL1 [14]. Microglia respond to the fungal toxin candidalysin, upregulating c-Fos in a Card9-dependent manner [14,17] and releasing interleukin (IL)-1 $\beta$  into their surroundings via Card9-dependent effects on *I11b* transcription and inflammasome activation [14]. IL-1 $\beta$  is required for the subsequent production of microglial CXCL1, with contribution from astrocytes acting *in trans* [14]. The molecular basis of microglial-astrocyte cross-talk however, remains incompletely defined.

### Cryptococcosis

The two *Cryptococcus* human pathogens are *C. neoformans* and *C. gattii* [18]. *C. neoformans* causes life-threatening pulmonary and CNS infections in immunocompromised individuals like those living with HIV/AIDS or undergoing immunosuppressive therapy [19]. *C. gattii* mostly causes lung infections, and can affect putatively immunocompetent individuals [3]. A recently described risk factor for *C. gattii* CNS infections is the presence of neutralizing anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies, which were detected in 7 of 9 putatively immunocompetent patients with *C. gattii* CNS infections [20]. Anti-GM-CSF autoantibodies may also contribute to susceptibility to non-*gattii* CNS cryptococcosis, as recently shown in a patient with *C. neoformans* var. *grubii* CNS vasculitis [21]. Both fungi are initially inhaled as desiccated yeasts from their environmental niches (i.e. trees, bird guano) [18]. Inhalation establishes a pulmonary infection, before dissemination to the blood and CNS. Cryptococci possess an array of infection-enabling virulence factors including a carbohydrate-rich capsule shielding pathogen-associated molecular patterns (PAMPs) from immune detection, and melanin production that protects from reactive oxygen species (ROS) [19].

*Cryptococcus* traverses the BBB and gains CNS entry through multiple mechanisms. *In vitro* experiments demonstrated the ability of phagocytes containing engulfed viable *C. neoformans* to cross a brain endothelial cell layer, suggesting that *Cryptococcus* can utilize a 'Trojan horse' strategy for brain invasion, albeit with a lesser efficiency than free yeast cells [22]. This observation is supported by the demonstration that mouse intravenous administration of monocytes containing phagocytosed *C. neoformans* develop cryptococcal encephalitis with greater fungal burden than mice inoculated with free yeast cells [23]. Intravital imaging observed Ly6C<sup>low</sup> monocytes being recruited to the CNS microvasculature in a TNFR-dependent manner, engulfing cryptococcal cells and carrying them across the endothelium into the CNS [24]. Phagocyte depletion of

mice using chlodronate liposomes reduced fungal burden in the spleen, lungs and brains [23], further underscoring the importance of this entry mechanism. These data were partially corroborated using inflammatory-monocyte-depleted CCR2-DTR mice, which were more resistant to cryptococcosis with lower lung and lymph node fungal burden, yet similar brain fungal burden [25]. This discrepancy may suggest that CCR2-negative phagocytes are sufficient to deliver *Cryptococcus* to the CNS, or that phagocyte-independent mechanisms are operational. Indeed, as mentioned above, *Cryptococcus* can traverse the BBB in the absence of a 'Trojan horse' cell. Intravital microscopy experiments visualizing *C. neoformans* within the brain vasculature observed the abrupt arrest of yeasts as they reached capillaries of similar diameter, followed by their transmigration across the microvasculature into the brain [26]. While fungal arrest in the microcapillaries was independent of endothelial adherence, expression of urease by *C. neoformans* was required for BBB crossing, in keeping with a urease-deficient strain being impaired at establishing CNS infection [26]. While it remains unclear how urease enhances cryptococcal brain invasion, it is speculated that urease-dependent localized production of toxic ammonia levels might increase BBB permeability [26]. *C. neoformans* hyaluronic acid interacts with CD44 on brain endothelial cells *in vitro*, inducing yeast phagocytosis and initiating transcellular migration [27,28\*]. This method of transcellular migration occurs via CD44-dependent phosphorylation of the tyrosine kinase receptor EphA2, which orchestrates the GTPase-mediated cytoskeletal actin reorganization necessary for transcytosis [28\*]. Accordingly, CD44-deficient mice are resistant to cryptococcosis, exhibiting prolonged survival and reduced brain fungal burden [29]. Additionally, prolonged cytoskeletal rearrangement through EphA2 engagement causes degradation of the tight junctions of brain endothelial cells that are critical for maintaining BBB integrity [28\*]. Supporting this notion, extended exposure of endothelial cells to *C. neoformans in vitro* results in degradation of the tight junction-stabilizing protein occludin [30].

Following CNS entry, the two cryptococcal species exhibit different pathologies, likely reflective of the patient populations they infect and their differential interactions with the immune system. While *C. gattii* primarily features large cryptococcomas in the mouse brain, these were rare in *C. neoformans*-infected mice [31]. *C. neoformans* elicits a relatively weak immune response, driven by the combination of PAMP concealment via its capsule and infection of immunocompromised hosts. Conversely, *C. gattii* infection manifests a robust inflammatory response. When stimulated *in vitro* with several strains from both *Cryptococcus* species, human monocytes produced greater quantities of TNF $\alpha$ , IL-1 $\beta$ , IL-6, IL-17 and IL-22 in response to *C. gattii* strains than

*C. neoformans* [32]. However, a mouse model of pulmonary infection found reduced inflammation in response to *C. gattii* strain JP02 compared to *C. neoformans* strain H99, and *in vitro* stimulation of the mouse dendritic cell (DC) line JAWSII with the two strains exhibited IL-6 release in response to H99, but not JP02 [33]. The PAMP responsible for this pro-inflammatory response is acetylated glucuronoxylomannan, which resides in the capsule of *C. neoformans*, but not *C. gattii* [33]. Consequently, *C. gattii* induced attenuated adaptive T<sub>H1</sub> and T<sub>H17</sub> responses compared to *C. neoformans*, both via DC-mediated stimulation *in vitro*, and during pulmonary infection *in vivo* [34]. Further studies are required to determine whether this discrepancy of the immune activation potential of *C. gattii* is due to fundamental differences between humans and mice, or other factors.

Interestingly, while CARD9-deficiency renders patients susceptible to cerebral candidiasis, it appears dispensable for CNS cryptococcosis. In agreement, a Card9-deficient mouse model of pulmonary cryptococcosis found no increased brain fungal burden [35\*]. Instead, Card9 drives lung macrophage killing of *C. neoformans* by promoting a protective M1-like phenotype [35\*]. A possible explanation for the limited role of Card9 in defense against cerebral cryptococcosis is that cryptococcal recognition is less dependent on Card9-mediated CLR signaling due to masking of CLR ligands by the cryptococcal capsule [36]. Instead, microglia rely on Toll-like receptors for *Cryptococcus* recognition and phagocytosis, and pro-inflammatory cytokine production (e.g. TNF $\alpha$ , IL-1 $\beta$ , IL-6) [37,38]. The resulting inflammatory milieu attracts neutrophils and initiates an effective adaptive immune response [39]. During cryptococcosis, microglia upregulate MHCII [40], enhancing their ability for antigen presentation.

As shown by the susceptibility of HIV/AIDS patients to cryptococcosis, CD4<sup>+</sup> T-cells are essential for fungal clearance. CD4<sup>+</sup> T-cells are recruited to the brain in experimental cryptococcosis via increased TNF $\alpha$ , CCL2 and CCL5 [40]. Interestingly, treating *C. neoformans*-infected mice with poly-ICLC resulted in heightened T<sub>H1</sub>/T<sub>H17</sub> responses and reduced mortality and lowered lung and brain fungal burden in a IFN $\alpha$ R1-dependent and MDA5-dependent, but TLR3-independent manner [41]. While poly-ICLC increased survival and decreased pulmonary fungal burden in *C. gattii*-infected mice, it had no effect of brain fungal burden [41]. While the T-cell response is effective at fungal clearance, the ensuing inflammation can cause irreversible and fatal CNS damage [40], a phenomenon mirrored clinically by immune reconstitution inflammatory syndrome and post-infectious inflammatory response syndrome. Better understanding of the pathogenic T-cell mechanisms in these conditions could help developing targeted immunotherapies.

### Mold infections

*Aspergillus*, Mucorales, *Scedosporium* and *Cladophialophora* molds can infrequently cause CNS infections in susceptible hosts, associated with mortality rates between 50–100% [5,8]. These infections occur secondary to dissemination of pulmonary disease in immunocompromised patients (*Aspergillus*), direct extension from sinoorbital disease in diabetic hosts (mucormycosis) or inoculation during trauma or neurosurgical procedures, independent of the host immune status [5]. Notably, *Scedosporium* causes CNS infections following near-drownings [5], and *Cladophialophora* infects putatively immunocompetent individuals in tropical areas [42].

Little is known about how molds cross the BBB and invade the CNS. It is thought that *Aspergillus* invades through hyphal expansion that causes endothelial destruction [9]. Additionally, *Aspergillus* toxins were shown to affect the barrier integrity of human brain microvascular endothelial cells *in vitro*. Indeed, aflatoxin caused endothelial cell death [43], while gliotoxin reduced barrier integrity without disrupting tight junctions [44]. *Rhizopus oryzae*, the most common cause of mucormycosis, disseminates throughout the body by angioinvasion via the interaction between endothelial cell GRP78 and fungal CotH3 [45,46]. GRP78 is expressed by brain endothelial cells [45], and blocking CotH3 resulted in reduced brain fungal burden [46], suggesting this protein–protein interaction is involved in *R. oryzae* CNS invasion.

Similar to *Candida*, CARD9 is critical in mounting effective anti-*Aspergillus* CNS responses [47]. A CARD9-deficient patient was described with CNS aspergillosis, associated with impaired neutrophil accumulation [47]. Pulmonary aspergillosis was not observed in that patient [47], despite mouse studies showing a partial role for Card9 mediating pulmonary neutrophil recruitment [48]. CNS aspergillosis also develops in hematological malignancy patients receiving the BTK inhibitor Ibrutinib, with up to 40–50% of cases involving the CNS [49]. While the underlying mechanisms remain unclear, Ibrutinib affects TLR-dependent macrophage activation, and thus could have a similar effect on microglia [49].

Invasive pulmonary aspergillosis has recently been associated with severe influenza infection, and on at least one occasion a patient had developed fungal brain abscesses [50]. Recently, invasive pulmonary aspergillosis has also been observed in association with SARS-CoV-2 infection [51], and thus it will be important to determine whether cerebral aspergillosis may also manifest under these circumstances in patients receiving corticosteroids.

Little is known about host-*Cladophialophora* interactions in the CNS. A key feature of *Cladophialophora* is that in

addition to conidia, its hyphae are also melanized, which may promote resistance from ROS [42]. The ability of molds to resist the CNS immune response leads to granuloma formation as seen with *Cladophialophora* [52], *Aspergillus* [53] and *Scedosporium* [54], which may contain the fungus from further spreading, but is not permissive for disease eradication.

### Conclusions

CNS fungal infections typically affect patients with iatrogenic or inherited immunosuppressive conditions with high mortality despite treatment. Recent work has begun outlining the mechanisms by which different fungi invade into the CNS. The host immune responses that promote protection or immunopathology in the fungal-infected CNS are also now emerging (Figure 1). A better understanding of the cellular and molecular basis of host–fungal interactions in the CNS could help devise strategies to enhance immunity and neuroprotection, block fungal CNS entry and improve patient outcomes.

### Conflict of interest statement

Nothing declared.

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