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Cryptococcus neoformans-Host Interactions Determine Disease Outcomes

Jintao Xu, Peter R. Williamson and Michal A. Olszewski

Abstract

The fungal pathogen *Cryptococcus neoformans* can infect the central nervous system (CNS) and cause fatal meningoencephalitis, which accounts for an estimated 180,000 deaths per year. Cryptococcal meningoencephalitis (CM) occurs mainly in the individuals with compromised immune systems. Thus, cryptococcal disease in the CNS has been predominantly attributed to insufficient immune responses and subsequent uncontrolled fungal growth. However, evidence has emerged that an inappropriate immune response, as much as an insufficient response, may promote clinical deterioration and pathogenesis. In this chapter, we will review the different types of immune responses to *C. neoformans* and their contribution to tissue damage and diseases.

Keywords: *Cryptococcus neoformans*, pathogenesis, immune pathology

1. Introduction

The human fungal pathogen *Cryptococcus neoformans* causes substantial morbidity and mortality worldwide, with an estimated 1 million infections and 180,000 deaths per year [1–3]. Although the primary route of infection is through inhalation of yeast into the lungs, fungal dissemination to the central nervous system (CNS) leads to severe meningoencephalitis that can cause death or long-lasting neurological sequelae, including memory loss, vision deficiencies, hearing and speech impairments, and motor deficits [4–6]. Treatment options for cryptococcal meningoencephalitis (CM) are limited and often unsuccessful due to the increasing development of drug resistance, the high toxicity of the antifungal drugs and the poor permeability of the blood brain barrier [7–9]. Unsuccessful treatments are often accompanied with high mortality rates up to 15% and relapse rates of 30–50% [10–12]. Thus, there is a pressing need for understanding the pathogenesis of *C. neoformans* infection to develop more effective therapeutic strategies.

Cryptococcal infections usually manifest in patients who are immunocompromised secondary to HIV infection, cancer therapies, or organ transplantation [3]. This has led to the characterization of *C. neoformans* as an “opportunistic pathogen” that causes disease only when the immune system cannot control its growth. Prior studies have established a central role for T cell mediated immunity in fungal clearance from the lungs and suggested that T-cell mediated immunity is also beneficial in the CNS [13–25]. These studies also support a paradigm that clinical failures are predominantly due to a deficiency in microbiological control. However, attempts

to develop immunotherapies that enhance the immune responses in CM have been largely unsuccessful, indicating other factors may also participate in the disease pathology [26]. Furthermore, clinical and experimental studies increasingly show that an exaggerated host immune response can promote cryptococcal pathogenesis. For example, a common complication of CM in HIV/AIDS patients is the immune reconstitution inflammatory syndrome (cIRIS) that develops after initiation of anti-retroviral therapy [27, 28]. A parallel syndrome occurs among non-HIV patients with severe cryptococcal CNS infection, termed post infectious immune inflammatory syndrome (PIIRS) [29–31]. These patients develop severe neurological sequelae and morbidity with persisting inflammatory responses, often despite fungal eradication [28, 32–36]. A detrimental role of host inflammation is further supported by the therapeutic effects of corticosteroids in ameliorating IRIS and PIIRS symptoms and by observations that premature or abrupt steroid-weaning may result in the recurrence of CNS lesions and clinical relapse [29, 30, 37].

This evidence challenges the view that cryptococcal disease is a consequence of a compromised immune system. Instead, the outcomes of cryptococcal disease can be better understood as a balance of *C. neoformans*-host interactions. The effect of *C. neoformans* on host disease can be explained by the damage-response framework (DRF), a theory for microbial pathogenesis proposed in 1999 [38]. The DRF theory incorporates the contributions of host-microbe interaction, rather than presenting microbial pathogenesis as a singular outcome of either microbial factors or host factors. The results of host-microbe interaction can be visualized with a single parabola depicting host damage as a function of the strength of the immune response [26]. Weak host immune responses due to HIV infection or immunosuppressive therapies fail to control fungal growth, which results in fungus-mediated host damage. However, strong immune responses elicited by *C. neoformans* can also lead to host damages and diseases. In this chapter, we will review recent human clinical and experimental animal studies that have enhanced our understanding of the complex mechanisms involved in immunopathogenesis during *C. neoformans* infection. Uncovering the mechanisms that are involved in anticryptococcal host defense or in immunopathogenesis will facilitate the discovery of new intervention strategies to treat cryptococcal infections.

2. Cryptococcal immune reconstitution inflammatory syndrome

C. neoformans can cause infection in both the meninges and the Virchow-Robin channels surrounding the penetrating vessels within the brain parenchyma [39]. Although the exact mechanism by which this encapsulated pathogen migrates into the CNS is currently unclear, studies have found that circulating *C. neoformans* was trapped in the brain capillary and can actively transmigrate the microvasculature with contributions from urease and metalloprotease [40–42]. After migration, *C. neoformans* causes fatal meningoencephalitis which accounts for 15–20% of AIDS-related deaths [1, 43, 44]. The high fungal burdens during CM in AIDS are associated with mortality, suggesting a prominent role of the fungal pathogen for host damage [45]. Thus, in HIV infection/AIDS, susceptibility to CM is thought to occur due to lack of T cell-mediated fungal clearance. Indeed, studies have shown that presence of CSF cytokine and chemokine responses consisting primarily of IL-6, IFN- γ , IL-8, IL-10, IL-17, CCL5 and TNF- α , are associated with increased macrophage activation, more rapid fungal clearance from the CSF, and patient survival [45]. The overall low levels of cytokine production in AIDS patients and insufficient activation of resident or recruited macrophages in the absence of T cells producing IFN- γ /TNF- α lead to uncontrolled fungal growth [45, 46].

Antiretroviral therapy (ART) in AIDS patients rapidly restores host T cell responses. However, in a portion of patients it leads to a highly lethal complication, cIRIS, which is defined as a paradoxical clinical deterioration after initiation of ART, despite efficient control of fungal infection [28]. cIRIS occurs in 15–30% of HIV-infected individuals with cryptococcosis [28, 47]. Similarly, patients who undergo immune suppressive regimens during bone marrow transplantation or autoimmune diseases can develop cIRIS like syndromes once the host immune response is restored when immunosuppressive therapy is tapered [48]. Previous studies have found that paucity of initial CSF inflammation, low IFN- γ levels, and high fungal loads are risk factors for the development of IRIS [27, 45]. During cIRIS, the immune response in the brain is characterized by excessive activation of Th1 CD4⁺ subsets with elevated production of cytokines including IFN- γ and TNF- α [27, 33, 49].

While the exact pathogenic mechanisms of IRIS have not been unraveled, the lymphopenic environment during HIV infection may result in abnormal function of residual CD4 T cells, rendering them more pathogenic as the population expands after ART [50]. Furthermore, it has also been proposed that there exists a decoupling of innate and adaptive immune responses in AIDS patients prior to ART due to deficient T cell responses, which sets the stage for excessive inflammation after T cell reconstitution. Indeed, several lines of evidence show that mononuclear immune cells are implicated in cIRIS. Predisposition to cIRIS has been shown to be associated with higher CCL2/MCP-1, CCL3/MIP-1 α , and GM-CSF production in the CSF, which promotes trafficking and activation of macrophages in the infection sites [45]. Patients with cIRIS had increased numbers of proinflammatory intermediate monocytes (CD14^{high}CD16⁺) which produce reactive oxygen species [51, 52]. Although macrophages can be primed by fungal pathogens in AIDS patients prior to ART, they never become fully activated in the absence of T cell help to exert their effector functions in fungal clearance. This results in high levels of pathogen replication as the disease progresses. Nevertheless, increasing numbers of primed macrophages accumulate and create a state of immunological hyperresponsiveness to the subsequently CD4⁺ T cell help. ART rapidly restores Th1 type response in the host with high level of IFN- γ production. Large numbers of primed macrophages then become fully activated to produce an acute spike in proinflammatory mediators, which may drive immunopathology during cIRIS. Thus, macrophage activation in cIRIS may act in concert with T-cell responses resulting in tissue-destructive inflammatory responses.

The mechanisms of tissue damage by host inflammation during fungal infections are still under active research. Macrophage or T cell production of TNF- α , IL-1 β , reactive oxygen species (ROS) and nitrogen species (RNS), may contribute to irreversible tissue damage and/or lead to neuronal apoptosis [53–55]. *C. neoformans* infection also induces cerebral edema and raised CSF pressure that are associated with symptoms including headache, nausea, and mental status deterioration.

3. Postinfectious inflammatory response syndrome

Another example showing that strong host immune responses during *C. neoformans* infection can induce immunopathology is post-infectious inflammatory response syndrome (PIIRS). It is characterized in non-HIV patients during initial therapy by severe mental deficits despite antifungal therapy and their apparent immunocompetent state. Reports showed that up to 25% of cases in the United States and 60% in the Far East occur in apparently immune competent patients [56, 57]. Despite antifungal therapy and negative CSF-*C. neoformans* cultures, PIIRS patients

many times require ventricle-peritoneal shunts to relieve the high CSF pressure caused by inflammation. Recent studies have shown that patients with PIIRS exhibit strong intrathecal Th1 responses with high levels of IFN- γ production and a relatively lack of Th2 responses [30]. Importantly, elevated levels of CSF neurofilament light chain (NFL), a marker of axonal injury, indicate ongoing immunological host neuron damage. Interestingly, macrophages recruited to the CNS infection site are often alternatively activated (M2) and exhibit poor phagocytic effect during PIIRS [30]. This apparent Th1-M2 discrepancy suggests that PIIRS patients may have downstream defects in monocyte activation. New therapies that consider immune-mediated host injury may decrease mortality in these severe or refractory clinical cases [43].

4. Animal models of IRIS and PIIRS

Detrimental roles for immune responses in the pathogenesis of cryptococcus-associated IRIS or PIIRS have also been recently demonstrated in experimental mouse models. A recent study in our lab established a reproducible mouse model of CM using C57BL/6 mice infected intravenously with 10^6 CFU of *C. neoformans* strain 52D [58]. Using this model, we found that infected mice displayed overt and severe symptoms similar to that of human patients, including increased cranial pressure, ataxia, and limb paralysis after 21 days post infection (dpi). Importantly, over 50% of animals succumbed to infection between 21 and 35 dpi, despite apparent fungal control in the CNS (**Figure 1**). Thus, we showed that the magnitude of CNS fungal burden does not directly correlate with the intensity of disease symptoms or mortality during CM.

Brain cellular inflammation, marked by leukocyte accumulation after 21 dpi and dominated by CD4+ T cell infiltration, plays an important role in the pathology of the CNS in cryptococcal-infected mice. Similar to human patients with IRIS and PIIRS, infiltrating CD4+ T cells in brains of cryptococcal-infected mice exhibit a Th1-type bias and produce high levels of IFN- γ . Critically, the influx of immune cells into the CNS after 21 dpi was synchronized with the onset of fungal clearance, development of neurological symptoms, and mortality. The depletion of CD4 + T cells leads to a reduction in mortality and inflammatory pathology, providing conceptual evidence that CD4 + T cells are a principal mediator of inflammation and pathology in this model. Notably, over the course of the study, the survival of CD4+

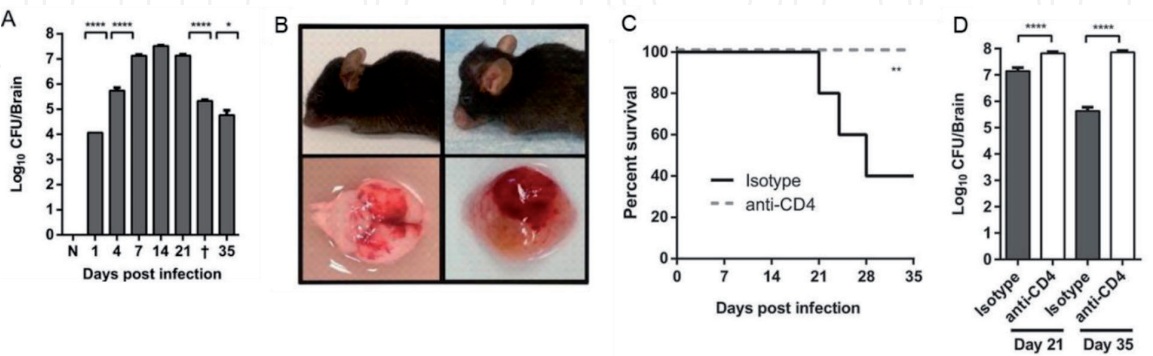


Figure 1. Depletion of CD4+ T cells resulted in improved survival despite higher fungal burden during CM. C57BL/6 mice were infected with 10^6 CFU of *C. neoformans* 52D via retro-orbital intravenous inoculation. (A) Fungal burdens were measured in whole-brain homogenates at the indicated time points. Naive mice and animals that succumbed to infection (†) are indicated. (B) Representative images of severe cranial swelling and CNS tissue injury in infected mice. (C) Survival of infected CD4-depleted (broken line) and isotype-treated mice through 35 dpi. (D) Brain fungal burdens were calculated on day 21 and 35 dpi. *, $P < 0.05$; **, $P < 0.01$; ****, $P < 0.0001$. Reproduced from Neal et al., [58].

T cell depleted mice significantly improved despite having higher fungal loads in the CNS compared to mice with sufficient CD4⁺ T cells (**Figure 1**). Depletion of CD4⁺ T cells during CM also broadly inhibited all other aspects of the CNS inflammatory response, including accumulation of CD8⁺ T cells and CD11b⁺ + Ly6C⁺ myeloid effector cells. Taken together, these data strongly support the idea that CD4⁺ T cells exert dual but opposing roles during CM: promoting the elimination of the fungal pathogen in the CNS but simultaneously driving tissue damage, neurological deterioration, and death.

Another animal model has also demonstrated the pathological role of CD4⁺ T cells in cIRIS. Eschke and colleagues reconstituted RAG^{-/-} mice, which are deficient in T and B cells, with WT CD4⁺ T cells after infection with *C. neoformans* [59]. They found that mice receiving CD4⁺ T cells displayed high levels of Th1-type cytokines such as TNF- α and IFN- γ compared to mice not receiving CD4⁺ T cells. These results suggested that CD4⁺ T cell reconstitution in mice infected with *C. neoformans* may lead to syndromes similar to IRIS in HIV-infected patients [59]. These animal models provide important tools for further investigating the mechanism of cryptococcal pathology.

5. Host immunity to *C. neoformans* infection: protective or non-protective, the yin and yang

Protective immunity is conferred by a fine balance between immune responses that eliminate the pathogen and those that limit host damages. However, an immune response induced by the pathogen may be non-protective for any one or combination of the following reasons: (1) it could occur in the wrong location or timeframe, promoting inflammatory injury without effective clearance of pathogens; (2) it could be too strong and cause immunopathology despite control of pathogen burden; 3) regulatory mechanisms meant to maintain host tissue integrity may lead to microbial survival and persistence and thus result in chronic inflammation. Below, we describe cellular and molecular mechanisms by which dysregulation of immune responses contribute to host disease during infection with *C. neoformans*.

5.1 Host immune responses contribute to fungal clearance but also tissue damage

Upon infection, *C. neoformans* is sensed by a variety of innate receptors including Toll-like receptors [60–62], mannose receptors [60], and β -glucan receptors [63–65]. Macrophages [66, 67], DCs [68], natural killer cells [69–72] and neutrophils [73] have been shown to mediate killing *C. neoformans*, however, the development of the adaptive immune response is required for controlling the fungal growth in the host [74–76]. Specifically, the development of Th1 and Th17 responses that are associated with classical activation of macrophages (M1) promotes fungal clearance in both humans and experimental mouse models [14, 77]. DCs and macrophages function as the potential sensors for infection through PRRs or inflammasomes, and produce cytokines such as IL-12, IL-23, IL-6, IL-18, TNF- α and IL-1 β , which have been shown to promote the Th1/Th17 response during *C. neoformans* infection [78–84]. During this response, Th1 and Th17 cells produce cytokines such as IFN- γ , IL-17 and IL-22, which act on macrophages, neutrophils or epithelial cells and induce robust antimicrobial and phagocytic responses, including the production of reactive oxygen and nitrogen species [16, 85–90]. As a result, resident and/or recruited macrophages and DCs can become highly activated and function as the main effector cells for controlling fungal infection [91, 92].

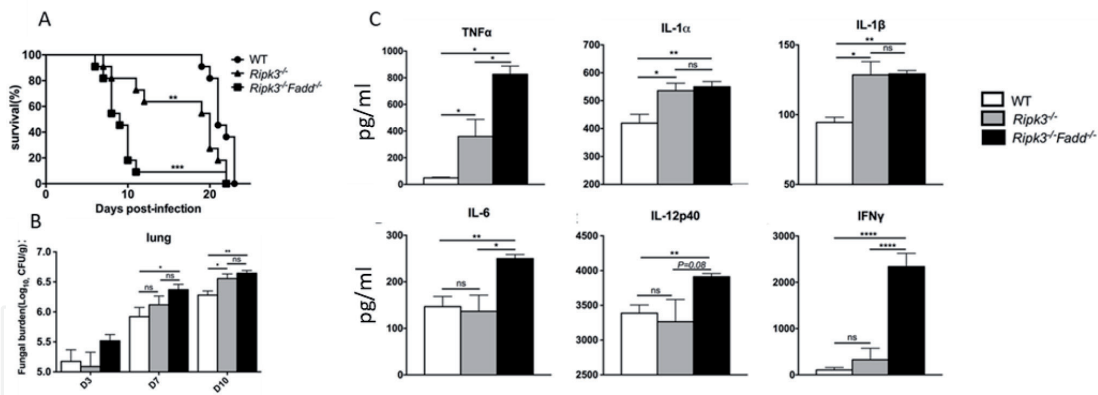


Figure 2.

*RIPK3 and FADD modulate host responses against C. neoformans infection. (A) Ripk3^{-/-} and Ripk3^{-/-}Fadd^{-/-} mice were more susceptible to C. neoformans infection. (B) Diminished fungal clearance in lungs of Ripk3^{-/-} and Ripk3^{-/-}Fadd^{-/-} mice. (C) RIPK3 or FADD deletions altered Th-polarizing and pro-inflammatory cytokine profiles in pulmonary response to cryptococcal infection. *, P < 0.05; **, P < 0.01; ****, P < 0.0001. Reproduced from Fa et al., [93].*

Although generation of the Th1/Th17 response and subsequent M1 activation play a critical role in controlling fungal growth, excessive immune responses can become destructive and cause lung immunopathology following fungal infection. Recent studies demonstrated that FADD and RIPK3 proteins, which are mediators of death receptor-triggered extrinsic apoptosis, play a crucial immune regulatory role in preventing excessive inflammation during *C. neoformans* infection [93]. Deletion of RIPK3 and FADD led to a robust Th1-biased response with M1-biased macrophage activation, which is accompanied by marked upregulation of cytokines like TNF- α , IL-1 α , IL-1 β , IL6, and IFN- γ (**Figure 2**). Rather than being protective, this robust host response was deleterious and is associated with paradoxical fungal growth and rapid clinical deterioration (**Figure 2**). These findings showed that excessive inflammation can mediate tissue damage and host disease during cryptococcal infection [93]. Furthermore, the balance between Th1 and Th17 immune responses plays important roles in optimizing clearance and minimizing inflammatory damage to the host tissues during fungal infections. For example, it has been shown that IL-23 and Th17 pathway act as a negative regulator of Th1 response and thus contribute to fungal growth during *C. albicans* and *A. fumigatus* infection [94]. Recent studies show that the Th1, Th2, Th17 responses and cytokines co-exist and evolve during different time points in a chronic fungal infection [13], while fungus adapts to and exploit the dysregulation of this immune balance. Thus, therapeutic cytokines and vaccines may create a new therapeutic mean to restore protective host responses and fungal control, but would need to be introduced with extreme caution not to induce an excessive immune bias.

DCs play a critical role in modulating host antifungal responses. Distinct PRRs and intracellular signaling pathways in DCs help to define the immune response to fungal pathogens [95]. Studies from Bonifazi *et al.* showed that *C. albicans* exploits multiple, functionally distinct, receptor-signaling pathways in DCs ultimately affecting the local inflammatory/anti-inflammatory state in the gut [96]. Furthermore, depletion of DC through administration of diphtheria toxin to transgenic mice resulted in rapid clinical deterioration and death of mice infected with *C. neoformans* [97]. Early mortality in DC-depleted mice was related to increased neutrophil accumulation accompanied with histopathologic evidence of alveolar damage, including hemorrhagic and proteinaceous exudates [97]. Similar changes mediated by neutrophils were associated with respiratory failure and death [98]. Collectively, these data define an important role for DC in regulating the initial innate and adaptive response following fungal infections.

5.2 Host immune responses normally associated with homeostasis can contribute to fungal persistence

Cryptococcal virulence includes evasion of immune recognition, interference with phagocytosis, and modulation of host immune responses [56, 99]. Many fungal factors have been shown to promote allergic Th2 or Treg responses. These types of responses are characterized by alternatively activated macrophages and may promote uncontrolled fungal growth [56]. However, the regulatory immune response is also crucial for maintaining host tissue homeostasis and limiting the inflammatory responses that can cause tissue damage.

Th2: In murine models, *C. neoformans* exhibits a remarkable ability to induce Th2 response, which is associated with fungal growth, fungus-associated allergic responses and disease relapse. Although rare for *C. neoformans* infection, other fungal pathogens such as *Aspergillus fumigatus* can induce devastating allergic bronchopulmonary mycosis in human patients that is accompanied by a Th2 response [100, 101]. Additionally, enhancing the Th2 response in a mouse model has been shown to exacerbate pulmonary disease during cryptococcal infection, supporting a causal role of Th2 response in pathology [102].

IL-4 and IL-13 provide the most potent proximal signals for Th2 cell polarization [13, 17, 103]. The epithelial-derived cytokines thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 have been shown to regulate the development of Th2 response during asthma [104, 105]. A time-dependent increase in IL-33 expression in the lungs has been found during *C. neoformans* infection, and IL-33 signaling can promote Th2 response and facilitates cryptococcal growth in the lungs [106]. In addition, chitin recognition via host chitotriosidase promotes harmful Th2 cell differentiation by CD11b⁺ conventional DCs in response to pulmonary fungal infection [102]. However, Th2 polarization may play beneficial roles at certain stage of infection. IL-4Ra has been shown to afford protection early upon infection associated with increased IFN- γ and nitric oxide production. More importantly, Th2 response plays important roles in wound healing to tissue destructive pathogens [107] and down regulating inflammatory responses [108]. Many of the proteins produced in response to IL-4 and IL-13, such as arginase, MMP12, and TREM-2, are associated with injury [109]. Th2-activated macrophages also produce TGF- β which can suppress pro-inflammatory responses while at the same time serving as a potent pro-fibrotic mediator [110].

Treg: CD4⁺ CD25⁺ Treg cells expressing the transcription factor forkhead box protein 3 (FoxP3) play critical roles in down-regulating immune responses and promoting homeostasis [111, 112]. Accumulation of antigen specific Treg has been shown during infection with fungal pathogens [113–116]. Multiple studies have shown that Treg can suppress effector cells and lead to fungal persistence. For example, Treg in mice infected with *C. albicans* were shown to be capable of inhibiting Th1 activity, thereby limiting protective responses. However, the roles of Treg in modulating Th17 activity are still controversial, with both positive and negative effects reported [117, 118]. Similar enhancement of effector function in the absence of Treg can be found in multiple other models of viral, bacterial, and parasitic infection [119].

While Treg may lead to pathogen persistence, they can actually be beneficial in protecting against immune-mediated damage to the host. This has been demonstrated in diseases caused by *Pneumocystis pneumonia*, HSV, *Schistosoma mansoni* where depletion of Treg leads to enhanced pathology [120–123]. It has been shown that depletion of Tregs enhanced Th2 response during pulmonary cryptococcal infection as evidenced by increased mucus production, enhanced eosinophilia, and increased IgE production [113]. Interestingly, Treg-depleted mice exhibited elevated fungal burden compared to control mice, suggesting that Treg mediated enhanced fungal control by inhibiting non-protective Th2

responses [113]. Confirming these observations, therapeutic expansion of Tregs during pulmonary cryptococcal infection has been shown to limit allergic airway inflammation, as demonstrated by reduced production of IgE and Th2 cytokines [116, 124]. Since laboratory mice show a strong tendency to develop a detrimental Th2 response during *C. neoformans* infection, Tregs may be protective in this context by inhibiting the tissue-damaging Th2 response. Furthermore, Tregs have also been demonstrated to be required for resistance to reinfection with *C. albicans* [120].

IL-10 is a critical effector molecule involved in the immunoregulatory functions of Treg cells [125]. IL-10 has been reported to inhibit production of cytokines such as IL-1, IL-6, IL-23, IFN- γ , TNF- α and chemokines including CCL2(MCP-1), CCL12(MCP-5), CCL5(RANTES), IL-8, CXCL10(IP-10), and CXCL2(MIP-2) [126]. During *C. neoformans* infection, IL-10-deficient mice display reduced expression of IL-4, IL-5, and IL-13, but enhanced TNF- α and IL-12 expression [127]. Studies have further shown that IL-10 signaling blockade can promote fungal control even if administered after persistent infection has been established [128]. IL-10 expression also occurs and dampens fungal control in response to other fungal pathogens such as *C. albicans*, *H. capsulatum* and *A. fumigatus* [129–131]. These studies suggest that IL-10 production plays an essential role in the development of persistent fungal infections. Deficiency or blockade of IL-10 may result in better fungal control, however, it comes at the cost of excessive inflammation that may cause greater tissue damage [127, 132, 133].

The roles of Tregs in the CNS during fungal infection, however, remain less studied. One report shows an increase in the abundance of Treg cells within cIRIS patients [134]. Further clinical and animal studies are needed to investigate the functions of Tregs during fungal CNS infections.

6. Conclusions and future directions

A tightly-regulated balance between inflammatory and regulatory mechanisms is required to control fungal infection, maintain host homeostasis, and ultimately develop protective immunity (**Figure 3**). Recent studies have demonstrated that disease and mortality in cryptococcal infection can result from either uncontrolled fungal growth due to defective host immunity, or excessive host inflammation. As the spectrum of hosts with cryptococcal disease expands, it is critical to understand and distinguish pathology caused by the pathogen or host responses. For example, additional suppression of weak immunity by steroid therapy in patients with uncontrolled fungal growth may lead to enhanced fungus-mediated damage and mortality in HIV-associated cryptococcal patients [135]. Instead, adjunctive IFN- γ therapy to bolstering immunity in these patients has the potential to ameliorate fungus-mediated damage and mortality [136]. However, in cIRIS patients, who experience inflammation-mediated tissue damage and mortality, corticosteroids can be effective to control disease-related deterioration [30]. Furthermore, mounting evidence implies that the top priority for cIRIS and PIIRS is to control the devastating immunopathology. Thus, comprehensive therapeutic strategies that take fungus- and host mediated damage into account could have the potential to significantly improve therapeutic outcomes.

Recent studies have identified the involvement of a number of immunopathogenic mechanisms including CD4⁺ T cells. However, the function of CD4 T cells overlaps with the mechanisms required for fungal clearance. Little is known about whether it is possible to uncouple the anti-fungal host defense mechanisms from the host immune responses that mediate deleterious immunopathology. One of

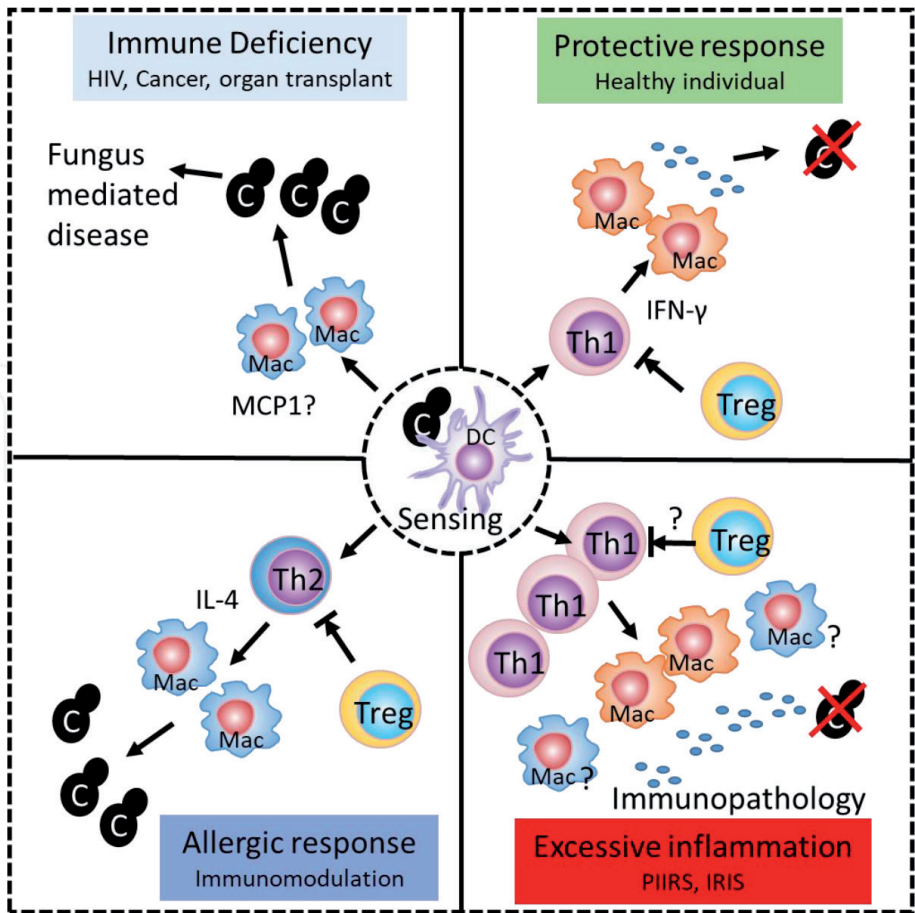


Figure 3.
C. neoformans and host interactions determine disease outcomes. In the center, innate immune cells such as DCs recognize *C. neoformans* using multiple pattern recognition receptors. A weak immune response due to HIV, cancer, or organ transplant can result in fungal-mediated tissue damage. Macrophages recruited into the infected tissue without T cell stimulation fail to control fungal growth. In healthy individuals, the DC-initiated Th1 response, which completely activated macrophages to efficiently control *C. neoformans* infection. Cytokines such as TNF- α and IFN- γ , as well as iNOS, are critical for fungal control. Tregs play important roles in limiting inflammation and maintaining homeostasis of the host. During IRIS and PIIRS, however, excessive inflammation can cause tissue damage despite fungal control. Whether Tregs are functional under this state is not clear. Macrophages may not be activated in PIIRS patients even with strong Th1 and IFN- γ production. Overproduction of cytokines and iNOS may promote tissue damage and cause disease. For certain host genetic backgrounds or highly virulent strains, an allergic Th2 response is developed and control of fungal growth fails. Host tissue damage in this circumstance may stem from both the pathogen and the detrimental Th2 responses.

the future directions in this research field is to identify mechanisms that are not required for fungal clearance but are major culprits in immunopathology which could be promising targets for future immunotherapies.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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