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Neglected mycobiome in HIV infection: Alterations, common fungal diseases and antifungal immunity

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Human immunodeficiency virus (HIV) infection might have effects on both the human bacteriome and mycobiome. Although many studies have focused on alteration of the bacteriome in HIV infection, only a handful of studies have also characterized the composition of the mycobiome in HIV-infected individuals. Studies have shown that compromised immunity in HIV infection might contribute to the development of opportunistic fungal infections. Despite effective antiretroviral therapy (ART), opportunistic fungal infections continue to be a major cause of HIV-related mortality. Human immune responses are known to play a critical role in controlling fungal infections. However, the effect of HIV infection on innate and adaptive antifungal immunity remains unclear. Here, we review recent advances in understanding of the fungal microbiota composition and common fungal diseases in the setting of HIV. Moreover, we discuss innate and adaptive antifungal immunity in HIV infection.

KEYWORDS

mycobiome, fungal diseases, fungal microbiota, antifungal immunity, HIV

Introduction

The human mycobiome inhabits the skin, respiratory tract, gastrointestinal tract, genitourinary tract, and other mucosal surfaces of the host. It has been shown that over 600 different fungi can cause disease in humans (1). In addition, over 300 million people are affected by serious fungal diseases, causing over 1.6 million deaths each year (2). The

increased incidence of global epidemic mycoses might be attributed to changes in the environment, population growth in endemic areas, and increased human immunodeficiency virus (HIV)-related immunosuppressive status (3).

In HIV infection, differences in bacterial population composition, including the oral microbiome (4, 5), lung microbiome (6, 7) and gut microbiome (8, 9), have been reported in HIV-infected compared to uninfected individuals. In addition, immunity compromised by HIV infection may lead to altered fungal composition, promoting the development of opportunistic fungal infections in HIV-infected individuals (10). It has been shown that opportunistic fungal infections have an unacceptably high toll on people living with HIV (PLWH) and are a major driver of HIV-related death (11). Although ART might decrease the mortality rate, the substantial burden of fungal disease remains high for HIV-infected individuals who are undiagnosed, untreated or fail ART (12). Fungal diseases in HIV infection have also not received sufficient attention from the global community (11).

It has been shown that host innate and adaptive immune responses play an important role in controlling fungal infections (13). Innate antifungal immune responses are triggered when fungal antigens, such as α- and β-glucans, O- and N-linked mannans, and chitin, stimulate pattern recognition receptors (PRRs) expressed on host cells, including C-lectin receptors (CLRs), NOD (nucleotide-binding and oligomerization domain)-like receptors (NLRs), and Toll-like receptors (TLRs), to initiate signal transduction cascades, which promote the production of chemokines and cytokines to eliminate fungal pathogens and activate adaptive responses (14). However, the substantial loss of $CD4^+$ T cells in HIV infection might lead to deficiencies in antifungal immunity, contributing to an increased risk of opportunistic fungal infections. Furthermore, depletion of interleukin (IL)-17 and IL-22-producing T helper (Th) 17 cells might result in impaired integrity of mucosal epithelial barriers, leading to fungal translocation from the gut lumen into the systemic circulation (15, 16). Microbial translocation might contribute to HIV-associated immune activation and inflammation, as well as the development of non-AIDS events (15, 16).

Because appropriate culture conditions remain unclear, most of the human mycobiome is nonculturable by culture-dependent methods (17). However, with the advent of new techniques, next-generation sequencing has been widely used for mycobiome detection in recent years (18). Internal transcribed spacer (ITS) sequencing and 18S rRNA are the most applied techniques to detect the mycobiome (19). In this review, we discuss alterations in the mycobiome and common fungal diseases in HIV infection, as well as the effects of HIV infection on innate and adaptive antifungal immunity.

Alterations of the mycobiome in HIV infection

The oral mycobiome in HIV infection

Alterations in oral bacterial communities and virome in HIV-infected individuals have been reported in many studies (4, 5, 20–22). The possible reasons for oral microbiome dysbiosis might be the disrupted oral immunity caused by HIV infection, including changes in secretory components in saliva, deficiency of innate immune responses and adaptive immune responses (5).

In addition to oral bacterial and virus communities, the oral mycobiome might contribute to understanding host–pathogen interactions that occur in HIV infection (23). For example, Ghannoum et al. characterized the oral mycobiome in healthy individuals using ITS sequencing (24), detecting 74 culturable and 11 nonculturable fungal genera (24). *Candida* species were the most frequent of the oral mycobiome (isolated from 75% of participants), followed by *Cladosporium* (65%), *Aureobasidium* and *Saccharomycetales* (50%, respectively) (24). Previous studies have demonstrated that oral fungal colonization is altered in HIV infection (25–28) (Table 1). In HIV-infected individuals, *Candida* (92%), *Epicoccum* (33%), and *Alternaria* (25%) are the most common genera in the oral mycobiome, whereas the most abundant oral mycobiome genera in HIV-uninfected controls are *Candida*, *Pichia*, and *Fusarium*, present in 58%, 33%, and 33%, respectively (25, 26). A recent study also compared the oral mycobiome between 30 HIV-infected individuals and 30 healthy controls and explored the effect of ART on the oral mycobiome in HIV infection. They found *Candida*, *Mortierella*, *Malassezia*, *Simplicillium*, and *Penicillium* to be significantly increased in HIV-infected individuals and dramatically decreased after ART. In contrast, the abundances of *Verticillium*, *Issatchenkia*, and *Alternaria* were significantly increased in PLWH after ART (27). They found that the composition of the oral mycobiome in the HIV-infected subjects after 6 months of ART was similar to that in the HIV-uninfected individuals. Moreover, *Mortierella*, *Malassezia*, *Simplicillium*, and *Chaetomium* were positively associated with viral load (VL), and *Verticillium*, *Thyrostroma* and *Archaeorhizomyces* were negatively associated with VL and positively correlated with $CD4^+$ T-cell counts. In addition, *Saccharomyces* was positively correlated with VL and negatively associated with $CD4^+$ T-cell counts (27). Therefore, HIV infection and ART administration might impact on the composition of the oral mycobiome, and the dysbiosis of oral mycobiome in HIV infection could be partially restored after ART. Furthermore, some oral fungi were sensitive to the changes in $CD4^+$ T-cell counts and VL in the blood of HIV-infected individuals, thus changes in the oral mycobiome in HIV infection after ART may reflect the immune status of patients.

The respiratory tract mycobiome in HIV infection

Due to incomplete restoration of pulmonary immunity with ART, HIV-infected individuals continue to have high burdens of pulmonary comorbidities, including chronic obstructive pulmonary disease (COPD) (34, 35), lung cancer (36–38), pulmonary fibrosis (39) and pulmonary emphysema (39–41). Overall, the complex respiratory tract microbiome, including the lung mycobiome, may play an important role in lung disease (42).

Previous studies have indicated that the diversity and composition of the lung microbiome in HIV-infected patients are altered compared with HIV-uninfected individuals (43–45) (Table 1). In addition, studies have also reported alterations in the respiratory tract mycobiome in HIV-infected individuals. Bittinger et al. analyzed bronchoalveolar lavage (BAL) samples from 42 lung transplant patients, 19 HIV-positive patients, 13 patients with various pulmonary diseases and 12 healthy controls; only low levels of fungal reads were detected in the healthy individuals, and the fungi detected comprised taxa with little clinical significance, except for *Aspergillus*. Conversely, clinical pathogens such as *Pneumocystis*, *Cryptococcus*, and *Aspergillus* were found in BAL of HIV-infected subjects (30). Another study published by Cui et al. compared fungal communities in the respiratory tract from 24 healthy subjects and 32 HIV-infected subjects: 9 species were overrepresented in the BAL of HIV-infected subjects, including *Pneumocystis jirovecii*, *Junghuhnia nitida*, *Phlebia tremellosa*, *Oxyporus latemarginatus*, *Sebacina incrustans*, *Ceriporia lacerata*, *Pezizella discrete*, *Trametes hirsute*, and *Daedaleopsis confragosa* (29). Of these species, *Pneumocystis jirovecii* and *Ceriporia lacerata* are known to be pulmonary pathogens associated with immunosuppression. In addition, *Pneumocystis jirovecii* pneumonia (PCP) is one of the most common opportunistic infections in PLWH. These data reveal that alterations in the respiratory tract mycobiome might be an important driver of opportunistic infection in HIV-infected individuals.

The gut mycobiome in HIV infection

The gut microbiome is being progressively recognized as playing an important role in promoting immune activation and inflammation in HIV infection. Dysbiosis of the gut microbiome

TABLE 1 The mycobiome in HIV infection.

References	Study cohort	Samples	Design	Mycobiome alterations
The oral mycobiome in HIV infection				
Chang et al. (27)	30 HIV$^+$ subjects prior to and after 6 months of ART and 30 healthy controls	Saliva	Cross-sectional and longitudinal	• Increased *Candida*, *Mortierella*, *Malassezia*, *Simplicillium*, and *Penicillium* in the HIV group, decreasing after ART. • Increased *Verticillium*, *Issatchenkia*, and *Alternaria* in HIV$^+$ subjects after ART.
Fidel et al. (28)	149 HIV$^+$ subjects and 88 HIV$^-$ subjects	Oral rinse	Cross-sectional	• Predominated by four major clusters: *Candida albicans*, *Candida dubliniensis*, *Malassezia restricta*, and *Saccharomyces cerevisiae*. • Several clinical variables affect the oral mycobiome, including HIV positivity and ART.
Mukherjee et al. (25)	12 HIV-infected and 12 uninfected individuals	Oral rinse	Cross-sectional	• Enrichment of *Candida*, *Epicoccum*, and *Alternaria* in HIV-infected individuals (present in 92%, 33%, and 25%, respectively) and *Candida*, *Pichia*, and *Fusarium* in uninfected individuals (58%, 33%, and 33%, respectively).
The respiratory tract mycobiome in HIV infection				
Cui et al. (29)	32 HIV-infected and 24 HIV-uninfected individuals	Oral washes, induced sputa, and BAL	Cross-sectional	• Increased *Pneumocystis jirovecii*, *Junghuhnia nitida*, *Phlebia tremellosa*, *Oxyporus latemarginatus*, *Sebacina incrustans*, *Ceriporia lacerata*, *Pezizella discrete*, *Trametes hirsute*, and *Daedaleopsis confragosa* in HIV-infected individuals.
Bittinger et al. (30)	19 HIV$^+$ subjects and 12 healthy controls	Oropharyngeal wash and BAL	Cross-sectional	• Increased clinical pathogens *Pneumocystis*, *Cryptococcus*, and *Aspergillus* in HIV-infected individuals.
The gut mycobiome in HIV infection				
Hamad et al. (31)	31 HIV-infected individuals and 12 uninfected-HIV individuals	Fecal	Cross-sectional	• Enriched *Ascomycota*, *Pichia*, *Penicillium brevicompactum* and *Penicillium* in healthy controls and enriched *Candida albicans* and *Candida tropicalis* in HIV-infected individuals.
Wu et al. (32)	75 HIV-infected patients and 55 HIV-uninfected participants	Fecal	Cross-sectional	• Nectriaceae, Hypocreales, and Sordariomycetes were the top 3 fungal taxa in HIV-infected individuals. While Basidiomycota, Phallaceae, and Phallales were particularly enriched in HIV-uninfected controls.
Yin et al. (33)	18 HIV-infected patients and 22 healthy controls	Fecal	Cross-sectional	• *Aspergillus* was the most abundant genus (49.92%) in the HIV-infected group, while the most abundant fungal genus was *Candida* (38.31%) in the healthy controls. • Unclassified_Aspergillaceae and Dirkmeia were enriched in the high-CD4$^+$ T-cell group, while *Candida*, Sordariales, Saccharomycetaceae, and *Neocosmospora* were enriched in the low-CD4$^+$ T-cell group.

HIV, human immunodeficiency virus; ART, antiretroviral therapy; BAL, bronchoalveolar lavage.

has been demonstrated in many studies (9, 46, 47), and such alterations of the gut microbiome composition in HIV infection might be attributed to the loss of appropriate innate and adaptive immune responses (48).

In the human gut, the diversity of the fungal community is much lower than that of the bacterial microbiota (49). Fungi in the gastrointestinal tract are often ignored, as fungi comprise a tiny fraction of the gut microbes and most are unculturable. Previous studies have been shown that *Candida*, *Saccharomyces*, *Aspergillus*, *Cryptococcus*, *Malassezia*, *Cladosporium*, *Galactomyces* and *Trichosporon* can grow at 37°C and therefore have the potential to permanently colonize in the gut (50). In addition, although *Histoplasma* spp., *Coccidioides* spp. and *Blastomyces* spp. cannot colonize the mucosal surfaces, they can cause severe lung infections (51) (Figure 1). A recent study investigated the gut mycobiome of the Human Microbiome Project (HMP) cohort and revealed *Saccharomyces*, *Malassezia*, and *Candida* to be the most abundant genera present in this cohort (49). In a study of 96 healthy individuals, the most common genera in fecal samples were *Saccharomyces*, *Candida* and *Cladosporium* (present in 89%, 57% and 42%, respectively) (52). Another study showed that the most prevalent genus in healthy individuals is *Penicillium* (present in 73% of samples), followed by *Candida* and *Saccharomyces* (55% for both), *Mucor* (38%) and *Aspergillus* (35%) (53). Additionally, gut mycobiome alterations in HIV infection have been reported (Table 1). Gouba et al. found decreased fungal species diversity in HIV-infected individuals (54), showing significantly more abundance of *Candida* spp. in HIV-infected patients than in healthy individuals. *Candida albicans* in the gut can affect many processes, such as digestion and immunity (55). *Candida* spp. are more prevalent in HIV-infected individuals with diarrhea and

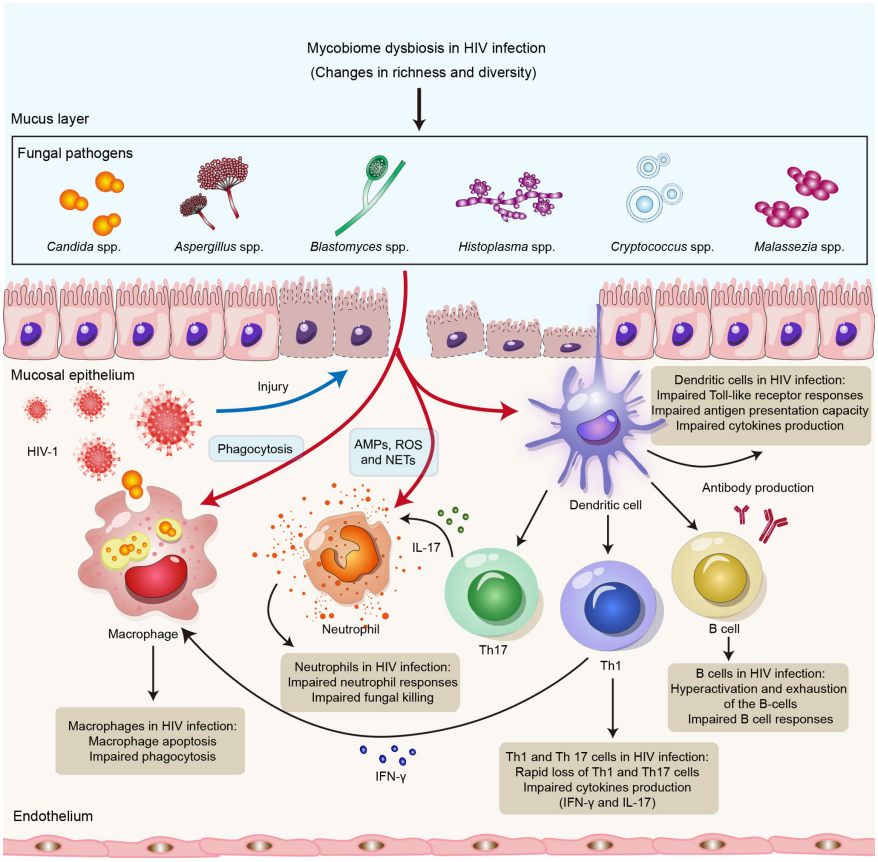

FIGURE 1
Impact of HIV infection on innate and adaptive immune responses to opportunistic fungal pathogens. HIV infection might lead to impairment of the innate and adaptive arms of the immune system, resulting in susceptibility to opportunistic fungal infections. Neutrophils control fungal infections through multiple mechanisms, including AMPs, ROS and NETs. Macrophages directly kill invading fungi through phagocytosis. DCs recognize fungal antigens by PRRs and also promote Th1 and Th17 immunity, as well as antibody production, to clear fungal infections. HIV can not only lead to impairment of neutrophil responses, phagocytosis of macrophages and the antigen presentation capacity of DCs but also cause defects in Th1, Th12 and B-cell responses. Abbreviations: AMPs, antimicrobial peptides; ROS, reactive oxygen species; NETs, neutrophil extracellular traps; DCs, dendritic cells; Th1, T helper 1 cell; Th17, T helper 1 cell; PRR, pattern recognition receptor.

recent antibiotic treatment than in healthy controls (54). Yin et al. showed that *Aspergillus* was the most abundant genus (49.92%) in the HIV-infected group, while the most abundant fungal genus was *Candida* (38.31%) in the healthy controls (33). Wu et al. found that 4 taxa from Ascomycota and 16 taxa from Basidiomycota were differentiated between HIV-infected individuals and HIV-uninfected controls in the fungal linear discriminant analysis (LDA) analysis. *Nectriaceae*, *Hypocreales*, and *Sordariomycetes* were the top 3 fungal taxa in HIV-infected individuals. While *Basidiomycota*, *Phallaceae*, and *Phallales* were particularly enriched in HIV-uninfected controls (32). Another study also compared the fungal populations of fecal samples from HIV-infected individuals and healthy controls; *Ascomycota*, *Pichia*, *Penicillium brevicompactum* and *Penicillium* were more abundant in healthy controls, whereas the abundances of *Candida albicans* and *Candida tropicalis* were enriched in HIV-infected individuals (31). In addition, Yin et al. demonstrated the relationship between $CD4^+$ T-cell counts and the gut mycobiome in the HIV-infected participants (33). They found that patients with low $CD4^+$ T-cell counts and patients with high $CD4^+$ T-cell counts have different fungal community characteristics. *Eurotiomycetes* was significantly decreased and *Saccharomycetes* was significantly increased in the low $CD4^+$ T-cell group compared to the high $CD4^+$ T-cell group. At the genus level, *Candida* was significantly increased in the low $CD4^+$ T-cell group, indicating a high risk of opportunistic infection. Moreover, unclassified *Aspergillaceae* and *Dirkmeia* were enriched in the high $CD4^+$ T-cell group, while *Sordariales*, *Saccharomycetaceae*, and *Neocosmospora* were enriched in the low $CD4^+$ T-cell group. It has been shown that members of the genus *Neocosmospora* can lead to lung infections in liver transplant patients (56) and contain highly prevalent and aggressive fungal pathogens (57), suggesting that the immune T-cell reduction might expose patients to a state of high-risk infection.

Common fungal diseases in HIV infection

Oropharyngeal candidiasis

OPC is the most common opportunistic fungal infection in the early stages of HIV infection (58–60). OPC is caused by various *Candida* species, with *Candida albicans* being the most prevalent species isolated from HIV-infected patients (58, 59, 61, 62). In patients with a new diagnosis of HIV, the prevalence of OPC is reportedly 27% (63). It has also been found that OPC occurs in approximately 80%-90% of HIV-infected individuals in different phases of the disease (64). Although the occurrence of OPC in HIV infection has significantly decreased after the introduction of ART, it remains a common opportunistic infection in HIV (65, 66).

The incidence of OPC in HIV infection is influenced by a multitude of factors (67), including immune status (68), bacteriome–mycobiome interaction (69), anti-fungal therapy and ART (70). Several studies have shown that a lower $CD4^+$ T-cell count, especially below 200 cells/μl, is strongly associated with increased occurrence of OPCs (71–74). A reduction in $CD4^+$ T cells, especially IL-17-producing cells, in the oral mucosa may be associated with susceptibility to OPC (75). In addition, impairment of oral immunity by the reduction of salivary components such as salivary IgA, defensins, and some cytokines might lead to the onset of OPC (76). However, host defense mechanisms executed by keratinocytes, calprotectin, $CD8^+$ T cells, and phagocytes partly compensate for these defects, which may play a key role in controlling *C. albicans* proliferation and preventing systemic dissemination in HIV infection (68).

Pneumocystis jirovecii pneumonia

PCP is one of the most common opportunistic fungal infections in immunocompromised individuals and HIV-infected individuals (77, 78). In the late 1980s, PCP occurred in approximately 75% of HIV-infected individuals (79), though the incidence of HIV-associated PCP has decreased dramatically with the implementation of ART and chemoprophylaxis (80). Nonetheless, PCP continues to be a serious problem in HIV-infected patients who are undiagnosed and untreated or in those with ART failure (81). It is speculated that there are more than 400,000 cases of PCP worldwide each year (82, 83).

As mentioned above, PCP tends to occur most frequently when the $CD4^+$ T-cell count is below 200 cells/μl (84–86), and $CD4^+$ T cells, $CD8^+$ T cells, neutrophils, alveolar macrophages and soluble mediators have been implicated in clearance of PCP (87). Carmona et al. demonstrated that *Pneumocystis*-derived β-glucans activate dendritic cells (DCs) through the Fas ligand (FasL) mechanism and the Dectin-1 receptor, leading to increased expression of costimulatory molecules and T helper 1 (Th1) cell activation (88). Another study found that DCs stimulated by cell-surface β-glucan components of *Pneumocystis* interact with lymphocytes to produce IL-17 and IL-22 (89). Th1, Th2 and Th17 responses are essential in *Pneumocystis* clearance and contribute to host protection against this pathogen (90). However, Th2 and Th17 responses also play a role in *Pneumocystis*-driven pathology (90). In addition, the cytokines produced by $CD4^+$ T cells, such as IFN-γ, also are important for the control of PCP (87, 90).

Cryptococcal meningitis

Cryptococcal meningitis (CM) is one of the most common opportunistic infections in the late stage of AIDS (91), and

Cryptococcus neoformans is the most common cause of death in HIV-infected individuals. An estimated 223,100 cases of CM occur globally each year, resulting in 181,100 deaths; 135,900 occur in sub-Saharan Africa, and CM accounts for 15% of all AIDS-related deaths (91). Despite effective ART and antifungal drugs, the mortality rate of CM in AIDS patients is still as high as 30%-50%, especially in patients in resource-poor areas (92–94).

Evidence suggests that host immune responses to cryptococcosis play a critical role in disease progression (95–97). CM can occur following primary lung infection or by reactivation and dissemination of latent pulmonary infection in the setting of cell-mediated immunodeficiency when $CD4^+$ T-cell counts are <100 cells/μl in the late-stages of HIV-infection (98). Previous studies have shown that $CD4^+$ T cells possibly mediate protective host immunity against cryptococcal *via* production of Th1-type cytokine responses, including IL-2, IL-12, tumor necrosis factor alpha (TNF-α), and IFN-γ, which play an essential role in recruitment of lymphocytes and phagocytes to clear the infection (99, 100). Higher levels of IFN-γ in cerebrospinal fluid (CSF) are associated with a faster rate of fungal clearance and lower fungal burdens (101, 102). Moreover, higher pre-ART levels of IL-4 and IL-17 and lower TNF-α, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and vascular endothelial growth factor (VEGF) might predict future immune reconstitution inflammatory syndrome (IRIS) (103).

Talaromyces marneffei infection

Talaromycosis is an invasive fungal disease caused by the opportunistic fungus *Talaromyces marneffei* (TM) and is prevalent mainly in Southeast Asia. Since the HIV pandemic, the prevalence of talaromycosis has rapidly increased, especially in areas of Southeast Asia, including Thailand, Vietnam and Myanmar, and East Asia, including South China, Hong Kong, Taiwan, and northeastern India (104). A recent study showed that the prevalence of TM infection in Asia was 3.6% in HIV-infected individuals (105). The prevalence of TM infection in HIV-infected individuals has been reported to be 6.4% in Vietnam, 3.9% in Thailand, 3.3% in China, 3.2% in India, and 2.1% in Malaysia (105). Furthermore, mortality rate of TM infection is reportedly higher than that of most HIV-related complications in PLWH (106). Although ART has led to a decline in the incidence of TM infection, it remains a major problem in undiagnosed and untreated HIV-infected individuals (81).

Innate and acquired immune responses play a crucial role in controlling TM infection (107). Innate immune cells, including monocytes (108), macrophages (109, 110), polymorphonuclear neutrophils (PMNs) (111), and DCs (112) have been shown to play an essential role in combating TM. These innate immune cells promote clearance of TM infection by producing proinflammatory cytokines such as IL-1β, TNF-α, and IFN-γ and anti-inflammatory cytokines such as IL-10 (107). A recent study also demonstrated that single-nucleotide polymorphisms (SNPs) in TLR2 might contribute to increased susceptibility and severity of TM in Han Chinese populations (113). Moreover, another study found that severe TM infection in Southeast Asia may be related to the high prevalence of anti-IFN-γ autoantibody-associated HLA-DRB1*16:02 and HLA-DQB1*05:02 alleles (114). A previous study found that HIV-infected individuals with $CD4^+$ T-cell counts below 200 cells/μl had a higher risk of TM infection (105). In general, immune deficiencies that reduce $CD4^+$ T cells and IFN-γ, IL-12, and IL-17 functions may be predisposing factors for TM infection, as evidenced by the high infection burden in advanced HIV-infected individuals, highlighting the important roles of Th1 and Th17 responses in host resistance to TM infection (115).

Histoplasmosis

Histoplasmosis is caused by *Histoplasma capsulatum*, which is a common endemic mycosis in PLWH (116). Globally, epidemic distribution of histoplasmosis mainly in regions of the Americas (81). In addition, histoplasmosis is also endemic in many Asia areas, including Southeast Asia, India, and China along the Yangtze River (117, 118). With the spread of HIV, the case-fatality rates of disseminated histoplasmosis increased among culture-positive cases, ranging from 10% to 53% (119). Disseminated histoplasmosis has been neglected due to its nonspecific symptoms, frequent misdiagnosis as tuberculosis, and insensitive diagnostic methods (120).

HIV-infected individuals are at greatly increased risk of developing histoplasmosis, especially those with $CD4^+$ T-cell counts <200 cells/μl (121). *Histoplasma capsulatum* yeasts can infect macrophages and survive within phagocytic cells (122). The strategies of *Histoplasma capsulatum* against macrophages might include immune response evasion on entry, inactivation of nitrogen and oxygen reactive species, hindrance of lysosomal pH reduction, production of siderophore, prevention of phagolysosomal fusion, and induction of apoptosis (123). In addition to the control of *Histoplasma capsulatum* infection by cellular immune response, the roles of antibodies in the serodiagnosis of histoplasmosis have also been proposed. Almeida et al. characterized *Histoplasma capsulatum* proteins specifically recognized by antibodies in serum samples from histoplasmosis patients by an immunoproteomic approach (123).

Aspergillosis

Aspergillosis is a life-threatening fungal disease in immunocompromised individuals, including PLWH. Previous study has been shown that the incidence of aspergillosis was 3.5

cases per 1000 person-years among 35,252 HIV-infected individuals (124). Although aspergillosis occurs uncommonly in HIV-infected individuals, it is associated with a short lifespan after diagnosis.

It has been shown that older people, people with severe immunosuppression or advanced HIV disease, and people with leukopenia and neutropenia are at increased risk of developing aspergillosis (124). Before the advent of ART, invasive aspergillosis in HIV-infected individuals tended to occur when CD4 T-cell counts <100 cells/μl, especially in patients with prior or concomitant opportunistic infections (125). Therefore, modulation of host immunity plays a critical role in the control of aspergillosis. Animal studies in aspergillosis have also demonstrated beneficial effects of G-CSF, GM-CSF, IFN-γ, and monoclonal antibodies (126).

Antifungal immunity in HIV infection

Innate antifungal immunity in HIV infection

The innate immune response is the first line of defense against fungal infections (127). Innate immune cells, such as neutrophils, monocytes, macrophages, and dendritic cells, are known to have a crucial function in recognizing and clearing fungi, inducing protective immune responses, and initiating adaptive immune responses during fungal infections (127, 128). Neutrophils control fungal infections through multiple mechanisms, including production of granule proteins, antimicrobial peptides (AMPs) and reactive oxygen species (ROS) and formation of neutrophil extracellular traps (129, 130). Indeed, neutrophils are critical cells against *Candida* spp. and *Aspergillus* spp (131). Macrophages not only directly kill invading fungi through phagocytosis but also initiate and regulate downstream immune responses to clear fungal infections by releasing cytokines, presenting antigens, and recruiting other immune cells (132). Fungal antigens are also recognized by DCs mediated by CLRs, including dectin-1, dectin-2 and DC-SIGN, as well as TLRs, including TLR2, TLR4 and TLR9 (133). DCs might also collaborate with other immune cells, such as Group 2 innate lymphoid cells (ILC2s), to promote innate antifungal immune responses and regulate adaptive immune responses (130). Nevertheless, the effect of HIV infection on innate antifungal immunity remains unclear.

HIV does not directly infect neutrophils but can cause impaired neutrophil responses, leading to impaired bacterial and fungal killing, which might result in increased susceptibility to bacterial infections and mycoses (134). Enomoto et al. found that anti-cryptococcal activity in HIV-infected patients is enhanced by administration of granulocyte colony stimulating factor (G-CSF) to enhance neutrophil defense (135). Moreover, Kalem et al. showed that HIV-1 infection of THP-1 macrophages increases the rate of *Cryptococcus neoformans* cell phagocytosis (136); these authors revealed that macrophages infected with HIV-1 alone might upregulate production of TNF-α and activate NF-κB signaling but that *Cryptococcus neoformans* coinfection rapidly represses this proinflammatory response (136). In addition, HIV-infected macrophages might contribute to increased susceptibility to opportunistic fungal infections (137). Studies have indicated that HIV infection of macrophages impairs the phagocytosis and killing of *Pneumocystis jirovecii* (138), *Candida albicans* (139) and *Aspergillus fumigatus* (140). A possible reason is that the HIV-1 accessory proteins Nef and Tat downregulate the mannose receptor expressed on the surface of macrophages. It has also been shown that HIV-1 reduces the number of DCs and disrupt their function. In HIV infection, DCs have a reduced ability to present antigens and stimulate T-cell proliferation and show a partially activated phenotype and impaired TLR responses (141, 142). T-cell proliferation in HIV-infected individuals might be inhibited by plasmacytoid DCs (pDCs) *via* induction of indoleamine-2,3-dioxygenase (IDO) (143). IDO expression by pDCs also blocks T-cell differentiation into Th17 cells, which might have a negative effect in adaptive antifungal immunity and predispose patients toward opportunistic infections, such as fungal infections with *C. albicans* and *C. neoformans* (141). Overall, HIV infection might lead to quantitative and qualitative deficiencies in innate antifungal immunity (Figure 1).

Adaptive antifungal immunity in HIV infection

$CD4^+$ T cells are generally considered to play an important role in defense against fungal infections. The importance of Th1 and Th17 responses in antifungal defense mechanisms has been described (144). It is well known that the Th1 response provides protective immunity mainly through production of proinflammatory cytokines, such as IFN-γ, IL-2, IL-12, and TNF-α (144). The IFN-γ produced by Th1 cells activates phagocytes, such as macrophages, and promotes phagocytosis, MHC-II molecule upregulation and antigen presentation by APCs (145). Enhanced protection against *Aspergillosis*, *Cryptococcosis*, and coccidioidomycosis has been demonstrated in patients receiving IFN-γ immunotherapy (146). Th17 cells produce cytokines, including IL-17A, IL-17F, and IL-22, which promote neutrophil recruitment and fungicidal activity and induce production of AMPs from epithelial cells and keratinocytes to prevent fungal overgrowth (145). The Th17 response has been shown to play an essential role in promoting clearance of fungi, such as *Candida albicans* and *Malassezia* spp (147). In addition, antibodies are important in limiting the fungal burden and its clearance (148). Antibodies can defend against fungal pathogens through direct mechanisms, including

inhibition of fungal pathogen growth or fungicidal activity, and indirect mechanisms, including opsonization, complement pathway activation and antibody-directed cell toxicity (ADCC) (146). Antibody responses to *Cryptococcus neoformans* (149) and *Candida albicans* (150) have been reported.

HIV infection leads to a rapid and massive reduction in $CD4^+$ T cells. One recent study showed that levels of Th1 cytokines in CSF, including IL-12 and TNF-α, correlate positively with HIV-associated cryptococcal meningitis (151). Moreover, in HIV-infected individuals, IFN-γ produced by Th1 cells plays an important function in improving the antifungal immune response to cryptococcal infection (102) and oral candidiasis (152). Jarvis et al. found that the Th1 responses of *Cryptococcus*-specific $CD4^+$ T cells play a key role in promoting circulating lymphocyte and monocyte recruitment to the central nervous system (CNS), CNS macrophage and microglial activation and organism clearance (153). In addition to the Th1 response, Th17 cells are critical in defense against bacterial and fungal infections at mucosal sites (154, 155). However, Liu et al. found that Th17-associated functions (IL-22, IL-17 and IL-2) of *Candida albicans*-specific CD4 T cells are disrupted in early HIV infection (156). Early massive loss of Th17 cells in HIV infection has also been shown to be a likely cause of the high prevalence of chronic mucocutaneous candidiasis in people with early HIV infection (157). Therefore, mucosal candidiasis susceptibility in HIV infection may be attributed to Th17-cell depletion.

HIV-1 replication might lead to abnormalities in all major lymphocyte populations as well as hyperactivation and exhaustion of the B-cell compartment (158). Studies have found that impaired B-cell responses due to HIV infection might affect B-cell responses in cryptococcal coinfection (159, 160). Moreover, levels of antibodies, such as plasma IgM, laminarin (Lam)-binding IgM and IgG, are significantly lower in HIV-infected individuals who develop *Cryptococcus*-associated IRIS than in those who do not, supporting the role for antibody immunity in cryptococcosis (161). Immune status is also important in antibody responses to *Pneumocystis jirovecii* (162). A previous study showed that IgM antibody responses to *Pneumocystis jirovecii* major surface glycoprotein (Msg), including MsgC1 (carboxyl terminus), MsgC3, MsgC8 and MsgC9, were significantly lower in HIV-infected individuals than in HIV-uninfected controls (163). Taken together, these findings suggest that competent adaptive immune responses are crucial for defense against fungal infections and that HIV infection might lead to impaired antifungal immunity (Figure 1).

Conclusion

Our review discusses recent findings on alterations in the mycobiome in the setting of HIV infection. The mycobiome contributes greatly to opportunistic infections in individuals with advanced HIV infection. Despite widespread use of ART, fungal opportunistic infections are the leading cause of HIV-related death globally. It is evident that human immune responses play a critical role in defense against fungal infection. We review the impact of HIV infection on host innate and adaptive antifungal immunity, contributing to a better understanding of the underlying immunopathogenesis of fungal infections in HIV infection. In addition, further efforts to develop new diagnostics and global access to antifungal drugs and other effective therapies are needed to enable early diagnosis and treatment of fungal infections.

Author contributions

BS and TZ conceptualized and supervised the whole study, SL, XY, HW, BS, and TZ searched the literature, contributed to the analysis and provided important scientific input. SL, CM and BS wrote the first draft and revised version of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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