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Fungal infections: Immune defense, immunotherapies and vaccines

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ABSTRACT

Invasive fungal infection is an under recognized and emerging global health threat. Recently, the World Health Organization (WHO) released the first ever list of health-threatening fungi to guide research and public health interventions to strengthen global response to fungi infections and antifungal resistance. Currently, antifungal drugs only demonstrate partial success in improving prognosis of infected patients, and this is compounded by the rapid evolution of drug resistance among fungi species. The increased prevalence of fungal infections in individuals with underlying immunological deficiencies reflects the importance of an intact host immune system in controlling mycoses, and further highlights immunomodulation as a potential new avenue for the treatment of disseminated fungal diseases. In this review, we will summarize how host innate immune cells sense invading fungi through their pattern recognition receptors, and subsequently initiate a series of effector mechanisms and adaptive immune responses to mediate fungal clearance. In addition, we will discuss emerging preclinical and clinical data on antifungal immunotherapies and fungal vaccines which can potentially expand our antifungal armamentarium in future.

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1. Introduction

The global incidence of invasive fungal infections has risen exponentially over the last 50 years due to burgeoning population of susceptible individuals, such as the immunocompromised patients undergoing chemotherapy and organ transplantation, those treated with broad-spectrum antibiotics or invasive medical procedures, as well as a newly identified group of COVID-19 patients who had received corticosteroids or tocilizumab treatments [1]. Although effective antifungal drugs (five major classes – azoles, echinocandins, polyenes, allylamines and antimetabolites) are currently available in the clinics, there is a growing concern that they may become inadequate for treatment due to the rapid emergence of drug resistance [2]. Every year, at least 150 million severe fungal infections and 1.5 million deaths are reported [3–5], and this is grossly underestimated due to the lack of surveillance and diagnostics. Despite the imminent threat of fungal infection to public health, there is a paucity of mycology research and antifungal therapeutics development worldwide.

In such context, the World Health Organization (WHO) released an unprecedented list of fungal priority pathogens (FPPL) in late 2022, with the aim of driving global research efforts and investment towards fungal infections and antifungal resistance [6]. In this list, fungal pathogens associated with invasive infections were prioritized into three groups – critical, high, and medium priority – based on integration of criteria such as mortality rate, incidence over the last 10 years, geographical distribution, availability of diagnostics and treatments, transmissibility, drug resistance and complications of disease. *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Candida auris* and *Candida albicans* are regarded as critical fungi, while *Nakaseomyces glabrata*, *Fusarium* spp., *Candida parapsilosis*, *Histoplasma* spp., Mucorales, *Candida tropicalis* and Eumycetoma causative agents belong to the high priority group. These were followed by the medium priority Scedosporium spp., *Lomentospora prolificans*, *Coccidioides* spp., *Pichia kudriavzeveii*, *Cryptococcus gattii*, *Talaromyces marneffei*, *Pneumocystis jirovecii* and *Paracoccidioides* spp (Table 1). As highlighted in the WHO FPPL, lack of quality data on the distribution of the abovementioned fungi makes it impossible to estimate the exact burden of fungal infections globally. In that regard, WHO called for three key actions, namely (1) improved surveillance, (2) support for research, development and innovation, and (3) public health interventions, to be taken to recognize and tackle this neglected public health issue associated with devastating outcomes.

In this review, we will outline current knowledge on host immune recognition of fungi pathogen, and further highlight various innate and adaptive mechanisms which are activated to clear the invading fungi. Finally, we will address recent developments in the field of antifungal immunotherapies and fungal vaccines, and the hurdles which must be overcome for advancement in mycology medicine.

2. Innate recognition of fungi by pattern recognition receptors

The first step in mounting an immune response towards invading fungal pathogens is their recognition by host pattern recognition receptors (PRRs). The fungal cell wall, composed of a highly conserved β-1,3-glucan, β-1,6-glucan and chitin core structure surrounded by an outer network of O- and N-linked mannoproteins, constitutes a number of pathogen associated molecular patterns (PAMPs) which can be recognized by distinct PRRs, including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs) and retinoic acid-inducible gene-I (RIG-I)-like receptors (RIRs) (Fig. 1). These PRRs are widely expressed on a variety of innate immune cells such as circulating and tissue-resident neutrophils, monocytes, macrophages and dendritic cells (DCs), which provide the first line of defense against invading microbes. The recognition of conserved fungal PAMPs by distinct PRR families has been comprehensively reviewed by others [7–9]. In this section, we will highlight the innate signaling mechanisms initiated upon engagement of PRRs during fungal infection. Depending on the site of infection, as well as the combination of PRRs and innate immune cells triggered, a tailored immune response specific to the fungal species and morphotype will be mounted [9,10].

Table 1
Summary of fungal pathogens on WHO FPPL. Data adapted from: WHO fungal priority pathogens list to guide research, development and public health action.

Fungus	Mortality rate of invasive infection (%)	Trends over last 10 years	Major risk factors	Current treatment options
Critical Priority Group				
Cryptococcus neoformans	41–61	Consistent	HIV infection, iatrogenic immunosuppression, autoimmune disease and decompensated liver cirrhosis	Fluconazole, amphotericin B in combination with flucytosine
Candida auris	29–53	Increasing	Hospital outbreaks, immunocompromised patients, previous use of antifungals especially triazoles	Echinocandins, azoles
Aspergillus fumigatus	47–88	Could not be established	Haematological malignancy, chronic lung disease, transplantation, corticosteroid therapy, neutropenia, chronic liver disease	Azoles, liposomal amphotericin B
Candida albicans	20–50	Consistent	Critically ill and immunocompromised patients	Echinocandins, azoles
High Priority Group				
Nakaseomyces glabrata	20–50	Increasing	Altered host immunity	Echinocandins, azoles
Histoplasma spp.	21–53	Consistent	Critically ill and immunocompromised patients	Amphotericin B, itraconazole
Eumycetoma causative agents	Low, but amputation rates as high as 39%	Consistent	Famer, male and young (11–30 years old)	Long-term antifungals
Mucorales	23–80 (adults) up to 72.7 (pediatrics)	Increasing	Neutropenia, diabetes mellitus, trauma	Amphotericin B
Fusarium spp.	43–67	Increasing	Acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation, cytomegalovirus reactivation, presence of skin lesions positive for *Fusarium* spp.	Inherently resistant to most antifungals
Candida tropicalis	55–60 (adults) 26–40 (pediatrics)	Increasing	Critical illness, decreased host immunity, neonatal ICUs	Echinocandins
Candida parapsilosis	20–45	Increasing	Critically ill and immunocompromised, neonatal ICUs	Echinocandins, azoles
Medium Priority Group				
Scedosporium spp.	42–46	Consistent	Malignancy, HSCT, severe infection	Voriconazole
Lomentospora prolificans	50–71 (adults) 50 (immuno-compromised pediatrics)	Could not be established	Critically ill and immunocompromised patients	Voriconazole, terbinafine
Coccidioides spp.	2–13	Increasing	Immunocompromised patients, African descent, increasing age (>40–60 years old), occupation, environmental dust and soil exposure	Fluconazole, itraconazole, amphotericin B
Pichia kudriavzeveii	44–67	Consistent	Critically ill and immunocompromised patients	Echinocandins, azoles
Cryptococcus gattii	10–25	Could not be established	Critically ill, immunocompromised, old age, pre-existing immunosuppression	Liposomal amphotericin B in combination with flucytosine, fluconazole
Talaromyces marneffei	12–21	Increasing	Critically ill and immunocompromised patients	Amphotericin B, itraconazole, voriconazole
Pneumocystis jirovecii	0–100	Consistent	AIDS, cancer, iatrogenic immunosuppression with organ transplantation, autoimmune and inflammatory disease, nephrotic syndrome	Cotrimoxazole
Paracoccidiodes spp.	3–23	Consistent	Age (>40 years old), male	Itraconazole, amphotericin B, cotrimoxazole

2.1. Fungal recognition by TLRs

TLRs are an important family of receptors with a common structural architecture characterized by a leucine-rich repeat (LRR) ectodomain involved in the recognition of PAMPs, a transmembrane domain, and an intracellular Toll-IL-1 receptor (TIR) domain for transmission of downstream signaling [11]. Upon sensing of fungi via their ectodomain, TLRs recruit TIR domain-containing adaptor protein myeloid differentiation primary response 88 (MyD88) to initiate a series of downstream signaling cascade which culminate in the activation of nuclear factor-kB (NF-kB) and mitogen-activated protein kinases (MAPKs) for the induction of antifungal effector responses. Even though the importance of MyD88 can be clearly exemplified by the enhanced susceptibility of its knockout mice to numerous fungal diseases [12,13], it surprisingly, was found to be dispensable in humans for fighting spontaneous mycotic infections [14]. This reveals the presence of an alternative and compensatory TRIF-dependent pathway, which utilizes TRAF6 and TRAF3, downstream of TLR4 and TLR3, for the activation of NF-kb and MAPK signaling, as well as the nuclear translocation of IRF3 for the induction of type I interferon (IFN), respectively [11] (Fig. 1).

2.2. Fungal recognition by CLRs

CLRs including Dectin-1, Dectin-2, macrophage-inducible C-type lectin (Mincle) and dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) play a central role in the recognition and initiation of antifungal immunity. These receptors contain the characteristic C-type lectin-like domain (CTLD) involved in the recognition of fungal carbohydrate structures such as β-glucan, mannan and chitin. Following engagement of PAMPs, CLRs signal through Syk kinase, either directly (Dectin-1) or indirectly via immunoreceptor tyrosine-based activation motif (ITAM)-containing adaptor Fc receptor common γ-chain (FcRγ) (Dectin-2 and Mincle), to activate the Card9/Bcl10/Malt1 (CBM) signalosome and its downstream canonical NF-kB signaling pathway [15,16] (Fig. 1). CBM complex represents the key signaling platform which governs antifungal defense in mammalian cells, and individuals with deficiency or loss-of-function mutations in

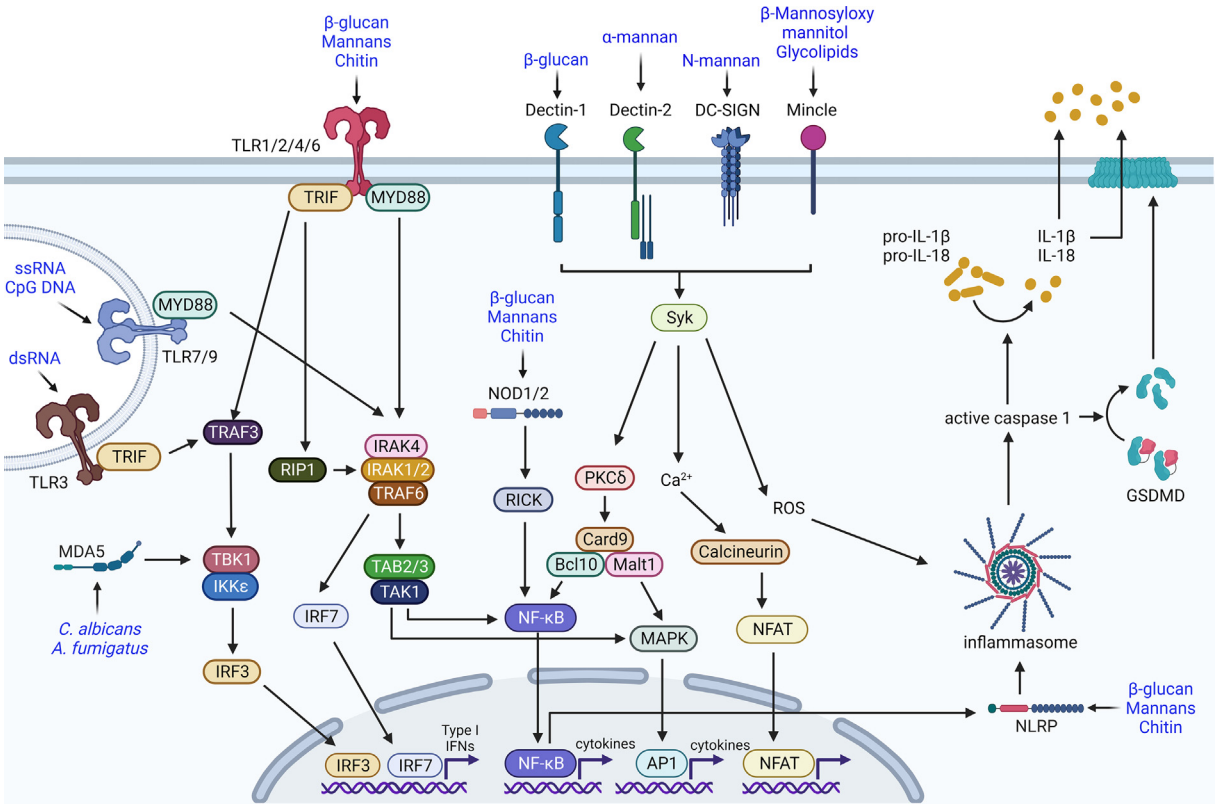

Fig. 1. Major signaling pathways induced upon fungal recognition by innate immune cells. Upon sensing of fungal PAMPs, TLRs signal through MyD88 to mediate downstream activation of NF-kB and MAPKs for the induction of antifungal effector activities. TLRs can also utilize a TRIF-dependent pathway to turn on type I IFN production. NOD1 and NOD2 oligomerize upon recognition of PAMPs, and this turns on downstream effector RICK, which subsequently promotes NF-kB activation. On the other hand, CLRs (Dectin-1, dectin-2, DC-SIGN, Mincle) recruit Syk to activate CBM signalosome, calcineurin-NFAT signaling pathway, as well as ROS production. These signaling events culminate in the assembly and activation of inflammasome, leading to the maturation of caspase 1 and the subsequent cleavage of pro-IL-1β and pro-IL-18 into their active forms for release. Caspase 1 is also involved in the cleavage of gasdermin D (GSDMD), which results in membrane pore formation and cell death by pyroptosis.

Card9 have been reported for their predisposition towards recurrent and severe invasive fungal infections [17–19]. Concurrently, Dectin-1 can also activate non-canonical NF-kB through Raf-1 in a Syk-independent manner, and this pathway plays a key role in modulating the crosstalk between TLR and Dectin-1 during fungal infection to enhance cytokine production [20].

2.3. Fungal recognition by NLRs

Cytosolic NLRs can be broadly classified into two main subfamilies— the nucleotide-binding oligomerization domain (NOD) 1 or 2 receptors and the inflammasome-forming NLRs which include nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing proteins (NLRP) 1 to 14. In general, NLRs consist of a N-terminal caspase activation and recruitment domain (CARD) or pyrin domain (PYD) for protein–protein interaction, a central NACHT domain with ATPase activity for self-oligomerization, and a C-terminal domain with multiple LRR for ligand sensing [21].

Upon PAMP sensing, NOD1 and NOD2 will oligomerize through their CARD-CARD domain interactions, and this facilitates the recruitment of CARD-containing adaptor Receptor-interacting protein kinase 2 (RIPK2), leading to the assembly of a multi-protein signaling complex called Nodosome, which facilitates downstream signal transduction for NF-kB and MAPK activation [21]. Although NOD1 and NOD2 have been shown to be involved in fungal sensing and activation of antifungal immune responses [22,23], their deficiencies and mutations do not seem to affect the susceptibility of both mice and humans towards fungal infection [24,25].

On the other hand, NLRPs, together with apoptosis-associated speck like protein (ASC) and inflammatory protease caspase-1, will assemble into macromolecular multi-protein complex termed inflammasome. Inflammasomes have been proposed to play a key role in discriminating between commensal and invasive fungi through the recognition of filamentous fungal hyphae structures associated with tissue invasion and diseases. Among them, NLRP3 is most widely studied and characterized, and hence is labelled as the prototypic inflammasome. Activation of NLRP3 inflammasome is a two-stage process involving: (1) a priming step by TLRs or cytokine receptors ligands to induce NF-kB signaling for the increased expression of NLRP3 and pro-IL-1β, and (2) an activation step mediated by NLRP3 agonists for assembly and activation of the inflammasome. Following these two steps, NLRP3 will undergo self-oligomerization to promote ASC recruitment via PYD domain interaction. The resultant ASC speck will subsequently associate with pro-caspase-1 through homotypic CARD domain binding, thereby culminating in the assembly of NLRP3 inflammasome. Once the inflammasome is activated, pro-caspase-1 will undergo auto-catalytic self-cleavage to form the active caspase-1, thus facilitating the maturation of proinflammatory cytokines interleukin (IL)-1β and IL-18. Moreover, active caspase-1 can also cleave gasdermin D (GSDMD) to induce pore formation in cell membrane and pyroptosis, hence promoting the release of IL-1β and IL-18 [26] (Fig. 1). The importance of inflammasome in antifungal defense can be demonstrated by the susceptibility of NLPR3, ASC

and Caspase-1 knock-out mice to *A. fumigatus*, *C. albicans* and *C. neoformans* infections [27–29].

2.4. Fungal recognition by RLRs

RLRs, including retinoic acid-inducible gene (RIG)-I, melanoma differentiation factor 5 (MDA5) and laboratory of genetics and physiology 2 (LGP2), are a family of cytosolic RNA sensors involved in the activation of type I IFN responses during antiviral immunity. Interestingly, emerging studies revealed that MDA5 can also recognize fungi like *C. albicans* and *A. fumigatus* [30,31], although the role of other RLR members during fungal infection remains to be determined.

2.5. Crosstalk among the PRRs

While the PRRs appear to demonstrate redundancy and overlapping functions, it is increasingly apparent that fungal recognition does not only rely on the engagement of a particular PRR, but instead, is an integrated process involving the co-stimulation of a mosaic of receptors recognizing multiple PAMPs on the fungal pathogen. Such molecular crosstalk among the PRRs serves as a key immune regulatory mechanism by directing the activation of distinct intracellular signaling pathways, which ultimately dictates the sensitivity and specificity of host immune responses. For instance, Dectin-1 and complement receptor 3 (CR3) work synergistically, by colocalizing on macrophages lipid rafts, to promote the release of tumour necrosis factor (TNF) α and IL-6 through the Syk-JNK-AP-1 pathway in response to *Histoplasma capsulatum* infection[32]. In addition, Dectin-1 signaling can induce TLR9 trafficking to phagosomes upon stimulation with β-1,3 glucan, *C. albicans*, and *A. fumigatus* [33]. TLR2 can also upregulate NOD2 expression to enhance IL-6, IL-8 and TNFα production during *A. fumigatus* infection [34]. Together, we can envisage a dynamic clustering of and interaction among PRRs at the host-pathogen interface to facilitate efficient fungal recognition. Such extensive and complex crosstalk among the different PRRs will exert a synergistic effect to generate a specific and potent antifungal immune response for effective fungal clearance from the host.

2.6. Fungi evasion of immune recognition

Although a multitude of host PRRs have evolved to recognize the highly conserved polysaccharide cell wall components of fungi for surveillance and defense, these pathogens possess mechanisms to actively evade host immune recognition and elimination. For instance, fungi are highly morphogenetic species which can transit rapidly from yeast to hyphal form, in the process changing their cell wall composition to avoid detection by the host immune system. Unlike the yeast form of *C. albicans* which frequently exposes their surface β-glucan on bud scars, β-glucans on filamentous hyphae are shielded by their surface mannoproteins, thus blocking Dectin-1 recognition and making them less immunogenic through disruption of the Dectin-1-TLR crosstalk [10,35]. On the other hand, fungi like *A. fumigatus* conidia make use of an immunologically inert hydrophobin rodlet layer to mask their underlying immunogenic cell wall components [36], whereas *H. capsulatum* is coated with an outer α-1,3 glucan layer to block host recognition of the underlying β-glucans [37]. In addition, *Aspergillus* has also been reported to subvert host detection through secretion of proteases which degrade complements and their receptor CR3 [38].

While these evasive strategies are usually insufficient for fungi to escape from an intact immune system, they represent key events integral to the establishment of infection in an immunocompromised host. As such, a comprehensive understanding of the strategies employed by fungi to avoid host recognition and capture is paramount to the successful development of novel antifungal therapeutic approaches for the highly susceptible individuals. For instance, preclinical studies demonstrated that pharmacological inhibition of exoglucanase Xog1, a glucosidase responsible for cleavage and masking of β-glucan, enhances immunogenicity and thereby reduces virulence of *C. albicans* [39]. Moreover, disruption of genes like *Cek1* involved in cell wall remodeling can promote unmasking of β-glucan on *C. albicans* [40]. By blocking the ability of fungal pathogens to evade immune defenses, we can potentially develop more effective therapeutics for management of fungal infections.

3. Innate antifungal immune mechanisms

Following recognition of fungal PAMPs by their respective PRRs, a series of oxidative and non-oxidative effector mechanisms will be initiated in the innate immune cells to promote fungal clearance (Fig. 2).

3.1. Phagocytosis

Phagocytosis serves as the primary mode of defense against invading fungal pathogens, and it is initiated upon recognition of fungal pathogens by PRRs on phagocytic cells including macrophages which are constantly patrolling the tissues, and neutrophils which are rapid responders present in abundance in the bloodstream. In response to such trigger, phagocytes will accumulate in large numbers at the infected site through chemokine-mediated recruitment. They will subsequently engulf the fungi into phagosomes via extension of their ruffle-like pseudopods or protrusion of phagocytic cups, before fusing them with a series of lysosomal vesicles to mediate fungi killing [41]. However, fungi possess several inherent mechanisms which can interfere with phagocytosis and hence promote their survival after internalization. One of the major limiting factors for phagocytosis is cell size, and to circumvent this, fungi can switch from yeast to hyphal growth in order to physically challenge the phagocytes. On the other hand, some fungi can survive in the phagolysosome by activating mechanisms to mitigate the hostile acidic and oxidative environment which acts to kill the fungal pathogens. Engulfed *H. capsulatum* and *C. glabrata* can prevent acidification of the host phagolysosome to inactivate various antimicrobial and lysosomal enzymes [42,43], while *C. albicans* can activate the glutathione system to maintain redox homeostasis to evade oxidative killing within the phagolysosome [44]. Alternatively, fungi can escape from the phagocytes following uptake by inducing invasive hyphal growth to directly rupture the host cells [45,46]. At the same time, these hyphae structures can drive NLRP3-dependent pyroptosis, further contributing to cell lysis [47,48].

3.2. Oxidative killing

In response to fungal infection, innate immune cells such as macrophages and neutrophils will assemble and activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex on cellular membranes to generate a strong oxidative burst and large amounts of reactive oxygen species (ROS) for fungal killing through induction of protein cross-linking and fragmentation, DNA break and lipid peroxidation [49]. As such, patients with inherited X-link chronic granulomatous disease characterized by a partial or complete loss of NADPH oxidase suffer from increased susceptibility to *aspergillus* infection [50]. In addition, loss of myeloperoxidase (MPO), an enzyme required for the generation of hydrogen peroxide in neutrophils, also enhances the susceptibil-

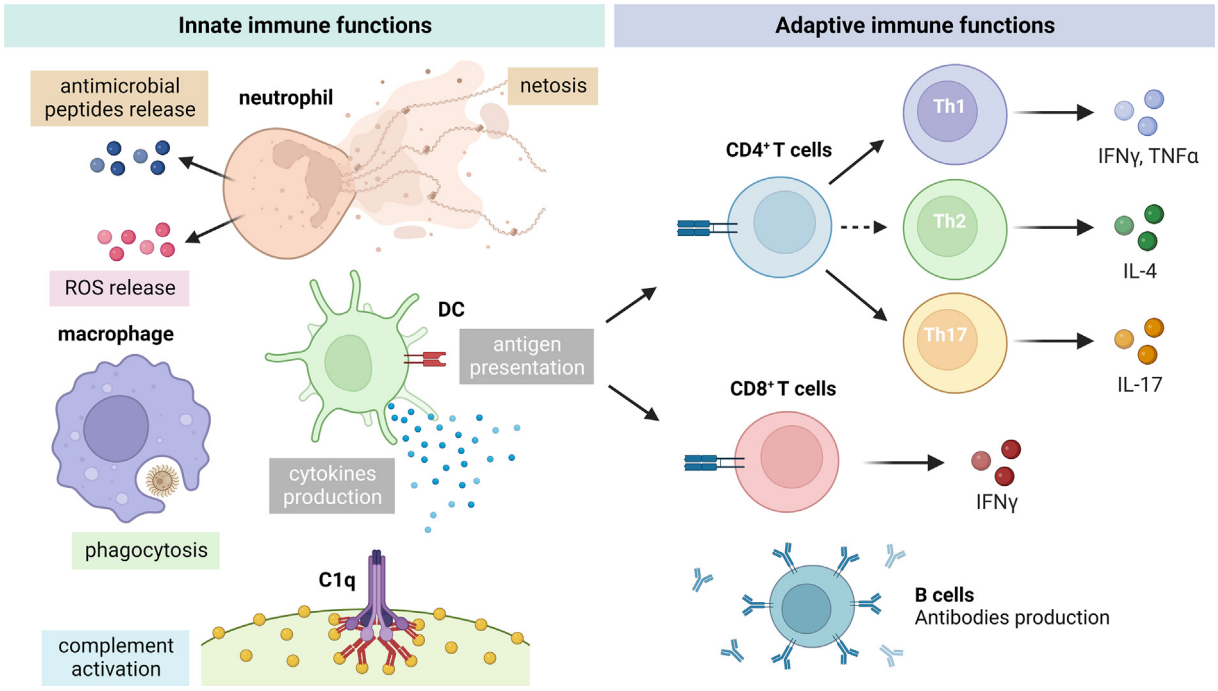

Fig. 2. Effector functions involved in the clearance of invading fungi. Upon sensing of fungal pathogens, innate immune cells such as neutrophils, DCs and macrophages are activated to trigger a series of effector mechanisms for fungal clearance. Killing of fungi can occur intracellularly through phagocytosis (green), or extracellularly through oxidative (pink) and non-oxidative means (yellow). Complements deposited on fungal surfaces can mediate their killing directly and at the same time activate other immune cells (blue). DCs are also involved in the processing and presentation or cross-presentation of fungal antigens to $CD4^+$ and $CD8^+$ T cells respectively, as well as the secretion of cytokines to shape T cell responses (grey). Th1, Th17 and $CD8^+$ T cells can protect against fungal infections, while Th2 cells are considered detrimental during antifungal defense. B cells antibodies production also contribute to anti-fungal immunity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ity of mice to *C. albicans*, *A. fumigatus* and *C. neoformans* infection [51,52]. However, fungi have evolved several anti-oxidative mechanisms, including the scavenging of superoxide by melanin, mannitol and superoxide dismutase (SODs), as well as the removal of hydrogen peroxide by catalases, to interfere with such host oxidative killing [53–55].

3.3. Non-oxidative killing

Apart from oxidative killing, the innate immune cells also utilize a multitude of non-oxidative mechanisms to destroy the invading fungal pathogens. Antimicrobial peptides (AMPs) including cathelicidin LL-37, histatins (Hst) and defensins, are small soluble effectors that can directly destroy or inhibit growth of fungi. For instance, LL-37 exerts its fungicidal activity by associating with and disrupting the membrane integrity, subsequently leading to the leakage of nucleotides, ATP and proteins from *C. albicans* [56]. On the other hand, Hst5 is taken up by *C. albicans* through the polyamine transporters Dur3 and Dur31, and accumulates intracellularly to induce ROS generation and non-lytic efflux of ATP from mitochondria, thereby triggering cell death [57,58]. Similarly, defensin 1 induces cytotoxicity by depleting the intracellular ATP levels in fungi [59]. The granules and lysosomes of phagocytes also contain various antimicrobial enzymes including cathepsin G, proteinase 3 and neutrophil elastase which exert fungicidal effects against *A. fumigatus* and *C. albicans* [60,61]. Neutrophils can release net-like structures called neutrophil extracellular traps (NETs), which are composed of decondensed chromatin and antimicrobial molecules, to mediate killing of fungal hyphae which are too large to be phagocytosed. To overcome such host antifungal responses, fungi have co-evolved by secreting glycosylphosphatidylinositol (GPI)-anchored proteases like Sap9 and Sap10 to degrade AMPs [62], or expressing polyamine efflux transporter Flu1 to facilitate efflux of Hst5 [63].

3.4. Complement-mediated killing

The complement system represents another arm of the host innate immunity, and it can be activated by fungal pathogens via three main pathways, namely the classical, lectin and alternative pathways. The classical pathway is initiated upon binding of C1q, a component of C1 complex, to the Fc region of IgM and IgG clusters attached to the fungi, while the lectin pathway can be triggered upon recognition of foreign carbohydrate patterns on fungal surfaces by mannose-binding lectin (MBL) and ficolins. On the other hand, the alternative pathway involves the deposition of C3b released during spontaneous hydrolysis of C3 on fungal surfaces. These three pathways converge toward the assembly of C3 and C5 convertases for the generation of anaphylatoxins C3a and C5a, which mediate immune activation and chemoattraction, and C3b for opsonization and phagocytosis. Even though the thick cell wall of fungi may prohibit lysis by membrane-inserted C5b-9 (membrane attack complex), the soluble form of C5b-9 termed terminal complement complex can still exert an activating effect on immune cells [64,65]. However, fungi have co-evolved various mechanisms to evade complement attack. For instance, *C. albicans* are shielded by a layer of mannan to mask the underlying β-glucan to prevent activation of the alternative pathway [66]. In addition, *C. albicans* and *C. parapsilosis* have also been reported to secrete various aspartyl proteases (Sap proteins) to degrade complements [67,68].

3.5. Antigen presentation

In addition to promoting direct fungal killing, innate immune cells, specifically the DCs, also function as professional antigen presenting cells (APCs) to facilitate activation of the adaptive immune system for further destruction of fungal pathogens and generation of long-lived immune memory to protect against subsequent re-infection (Fig. 2). In general, DCs can (1) process and present fungal antigens on MHC class I or II molecules, (2) provide the costimulatory signals and (3) secrete specific cytokines and chemokines to regulate lymphocyte functions essential for the control of fungal infection. DCs can discriminate between the avirulent and virulent forms of fungi differentially depending on their morphotypes (yeast vs hyphae), and this results in the activation of distinct T cell subsets and immune responses. Specifically, uptake of *Candida* yeasts by DCs occur through coiling phagocytosis upon engagement of mannose receptor, and this promotes the upregulation of co-stimulatory molecules and production of pro-inflammatory cytokine IL-12 to activate a protective T helper (Th)1 response. On the other hand, internalization of *Candida* hyphae relies on a zipper-type mechanism involving FcγR and CR3, and this favors the production of IL-4 and IL-10, leading to the induction of non-protective Th2 and tolerogenic Treg responses [69]. As such, the nature of ligand-receptor interaction between fungi and DCs can dictate the type of adaptive immune response induced. Moreover, there exists a plethora of DC subsets with specialized functions. Plasmacytoid DCs (pDCs) have been shown to confer protection of mice against *A. fumigatus* infection via secretion of type I interferon (IFNα) and TNFα [70], while monocyte-derived inflammatory DCs are involved in the transport of *Blastomyces dermatitidis* antigen to the lymph nodes (LN) for subsequent priming of $CD4^+$ T cells by LN-resident DCs [71]. In response to gut mycobiota, $CD11b^+$ $CD103^+$ $RALDH^+$ DCs in the lamina propria migrate to the peripheral lymph nodes to direct homing of lymphocytes for formation and maintenance of gut-associated lymphoid tissues [72]. As such, the functional plasticity and specialization of DCs serve to shape and modulate downstream T cell responses to achieve a balance between tolerance and inflammation.

4. Adaptive antifungal immunity

4.1. Th1 cells

Th1 cells which secrete IFNγ and TNFα have long been implicated in the eradication of fungal pathogens. IFNγ promotes MHC I expression and enhances the antigen processing and presentation capacity, as well as phagocytosis and superoxide production by innate cells such as macrophages during *B. dermatitidis*, *Paracoccidioides brasiliensis*, *C. albicans* and *H. capsulatum* infection [73–77]. Notably, IFNγ-knockout mice are highly susceptible to mucosal and systemic candidiasis [78], and adjunctive treatment with IFNγ has been shown to increase immune production of pro-inflammatory cytokines IL-1β, TNFα, IL-17 and IL-22, thereby leading to improved clinical outcomes of patients with invasive candidiasis or aspergillosis [79]. HIV-infected patients also demonstrated faster clearance of *C. neoformans* from their cerebrospinal fluid upon adjunctive IFNγ immunotherapy [80]. Furthermore, humans with genetic deficiency or mutations in IFNγ receptor 1 are predisposed to severe coccidioidomycosis and histoplasmosis [81,82]. In addition, TNFα can promote ROS production and immune cells infiltration while suppressing regulatory T cells expansion to limit *H. capsulatum* and *aspergillus* growth [83–85].

4.2. Th2 cells

Th2 responses are generally considered to be detrimental during antifungal defense. Transgenic mice overexpressing Th2 cytokine IL-4 were significantly impaired in *H. capsulatum* clearance [86], and conversely, IL-4-deficient mice were more resistant to invasive pulmonary aspergillosis as compared to wild-type mice [87]. Moreover, overexpression of GATA-3, the master transcription factor for Th2 differentiation, is associated with a reduction in IFNγ level, and hence increased susceptibility to systemic candidiasis [88].

4.3. Th17 cells

More recently, Th17 cells have been shown to play a critical role against mucocutaneous fungal infection through their secretion of IL-17. Th17-deficient and IL-17A receptor knockout mice exhibited impaired neutrophil responses, heightened fungal burden, and reduced survival in response to oropharyngeal (OPC) candidiasis [89]. Indeed, adoptive transfer of Th17 cells into Rag1-deficient mice confers protection against OPC [90]. Moreover, Th17 cells can promote intestinal immunoglobulin (Ig) A production for protection against mucosal fungi [91,92]. In humans, chronic mucocutaneous candidiasis disease has been reported in individuals with complete or partial deficiency in IL-17 receptor and IL-17F cytokine respectively, further supporting the importance of Th17 cells in antifungal defense [93]. In addition, psoriatic patients treated with various inhibitors of the IL-17 signaling pathway have been reported to be at a higher risk of developing mucocutaneous candidiasis [94]. However, conflicting studies have implicated Th17 in the suppression of Th1-mediated response, thereby enhancing susceptibility to *C. albicans* and *A. fumigatus* infection [95]. Furthermore, loss of Toll IL-1R8 (TIR8), a negative regulator of Th17, enhances susceptibility of mice to mucosal and disseminated candidiasis [96]. As such, the role of Th17 in antifungal immunity remains controversial.

4.4. $CD8^+$ T cells

Although the role of $CD8^+$ T cells towards antifungal defense is not as well-documented as $CD4^+$ Th cells, various line of evidence suggests that they can restrict fungal growth. $CD8^+$ T cells produce IFNγ to limit *C. neoformans* survival in macrophages [97], and further promote the killing of *pneumocystis carinii* [98]. $CD4^+$ T cells-depleted mice were able to generate antifungal memory IL-17A-producing $CD8^+$T cells following immunization with attenuated *B. dermatitidis*, thereby protecting them from pulmonary lethal rechallenge [99]. In addition, low $CD8^+$ T cell count was found to be associated with higher risk and worse outcome in critically ill and immunocompromised patients with invasive pulmonary aspergillosis [100,101].

4.5. B cells

As compared to cellular immune responses, the role of humoral immunity against fungal infections remains less clear. Although various independent studies demonstrated the redundancy of B cells during candidiasis [102–105], adoptive transfer of B cells have been shown to confer protection of rat against vaginal candidiasis [106]. Moreover, depletion of B cells in peripheral blood mononuclear cells (PBMCs) with rituximab results in reduced Th17-mediated antifungal responses [107]. At the same time, the role of antibody responses during fungal infection remains controversial. Natural immunoglobulin (Ig) M antibodies targeting the con-

served carbohydrates on fungal cell wall can promote trafficking of APCs to the draining lymph nodes to mediate Th2 and Th17 differentiation during *P. murina* infection [108], and secretory IgA from human breast milk have been shown to block binding of *C. albicans* to human oral epithelial cells [109]. Yet, no difference in IgA levels was detected between healthy controls and patients with recurrent vulvovaginal candidiasis [110].

5. Antifungal immunotherapy

Currently, antifungal agents such as polyenes, azoles, flucytosine and echinocandins which primarily target fungi pathogen remain the first line of therapy for infected patients, although their application is frequently hampered by their limited efficacy, off-target toxicity, and emerging resistance among fungi species. While efforts have been made to identify and develop new antifungal compounds, the financial incentive for pharmaceutical companies to bring these drugs to the clinics remain low. More recently, immuno-modulating agents have been explored as an adjunctive therapy to conventional antifungal drugs. This is based on the rationale that such two-pronged approach may help boost immune responses of patients, particularly the immunocompromised, to successfully eradicate the fungal infection. However, it is often clinically challenging to establish the added value of such adjunctive immunotherapy, given that conventional antifungal drugs already provide a certain level of efficacy in the infected patients. In this section, we will outline preclinical and clinically approved immune-based strategies adopted as adjunctive treatments for fungal infections (Fig. 3 and Table 2).

5.1. Cytokine-based therapy

Administration of cytokines which stimulate proliferation, differentiation and activation of immune cells can restore or enhance the function of immune system to fight fungal infections.

5.1.1. Colony-Stimulating factors (CSFs)

CSFs, including macrophage CSF (M−CSF), granulocyte CSF (G-CSF) and granulocyte–macrophage CSF (GM-CSF), are secreted glycoproteins which act as master regulators of myeloid cells by enhancing myelopoiesis and augmenting their functional activities.

G-CSF stimulates proliferation, survival, and function of neutrophils, and hence can be applied to restore neutrophil numbers and activity in neutropenic patients such as those undergoing cancer chemotherapy or organ transplantation. Since the risk of fungal infection is directly correlated to the duration and extent of neutropenia, G-CSF may be adopted in adjunction with conventional antifungal drugs to improve clinical outcomes of these patients. Indeed, a study by Grigull et al. revealed that such combinatorial therapy effectively treated fungal infection in three children with hematological malignancies [111]. Moreover, G-CSF administration in conjunction with fluconazole or amphotericin B has been demonstrated to improve clinical outcomes of leukemia and neutropenic patients with refractory mucormycosis [112].

On the other hand, GM-CSF acts on a wider range of myeloid cells including DCs, macrophages, neutrophils, monocytes, megakaryocytes and eosinophils, and thus is proposed to have an advantage over G-CSF during host defense against fungal pathogens. It was reported back in 1998 by Giles that prophylactic treatment of acute myeloid leukemia (AML) patients with recombinant GM-CSF led to significant protection from deadly fungal infection (1.9%) in comparison with the placebo group (19%) [113]. Moreover, immunotherapy with GM-CSF, in combination with antifungal drugs voriconazole and caspofungin, successfully treated a life-threatening central nervous system infection with *A. ventriculitis* in a post-chemotherapy patient [114]. Adjunctive GM-CSF therapy has also been shown to improve clinical outcomes in a small number of patients with OPC and systemic *Blastoschizomyces capitatus* infection [115,116]. Despite the promising results GM-CSF demonstrated during antifungal treatment, concerns have been raised over its safety, predominantly due to the pro-inflammatory nature of the cytokine. Capillary leak syndrome, as well as a rare and fatal haemoptysis complication, were reported in patients treated with GM-CSF and amphotericin B for disseminated fungal infection [117,118].

Even though M−CSF, unlike G-GSF and GM-CSF, is not clinically approved by U.S. Food and Drug Administration (FDA), various clinical trials have explored its utility as an adjunctive therapy for fungal infection. M−CSF can specifically promote proliferation and activity of macrophages, and bone marrow transplant patients with invasive fungal infection demonstrated improved survival upon treatment with M−CSF [119]. Yet, given the direct involvement of macrophages in cancer progression, the clinical use of M−CSF as an adjunctive antifungal therapy, especially when administered to immunosuppressed cancer patients, should be investigated in greater details.

5.1.2. IFNγ

Recombinant IFNγ has also been explored as an adjunctive antifungal treatment, and the results of these studies are promising and encouraging. Short-course administration of IFNγ in addition to amphotericin B treatment can enhance clearance of *C. neoformans* from the cerebrospinal fluid of infected HIV patients [80]. Beyond *Cryptococcus* infection, IFNγ immunotherapy has also demonstrated efficacy in controlling disseminated infection with *Candida* [120] and *aspergillus* [121,122].

5.1.3. TNFα

Several preclinical studies revealed that TNFα treatment exerts a protective effect against systemic and pulmonary *A. fumigatus* infection in both wild-type and neutropenic mice [123,124], suggesting their potential application as an adjunctive immunotherapy clinically.

5.1.4. IL-12

IL-12 is a Th1-polarizing cytokine, and hence has been implicated in promoting a protective antifungal immune response. Indeed, recombinant IL-12 can act synergistically with fluconazole in neutropenic mice to protect against invasive candidiasis [125]. Furthermore, IL-12 alone, or when given in conjunction with fluconazole, can improve outcomes of mice infected systemically with *C. neoformans* [126]. However, the role of IL-12 in antifungal defense remains controversial. Since IL-12 can induce the production of anti-inflammatory cytokine IL-10, there exists a possibility that IL-12 treatment may instead predispose individuals to fungal infection [127].

5.2. Cell-based therapy

5.2.1. Adoptive T-cell therapy

Adoptive T-cell therapy, which involves the purification and *in vitro* stimulation and expansion of donor- or patient-derived T cells before re-infusing back into the patient, can be adopted in the context of fungal infection. This usually follows an allogeneic hematopoietic stem cell transplantation since the patients are likely to harbor a long-lasting impaired cellular immunity. The remarkable clinical benefit of such therapy was first demonstrated by Perruccio et al., who reported that nine out of ten transplant patients diagnosed with invasive aspergillosis had their infection cleared within 7.8 ± 3.4 weeks upon anti-*Aspergillus* adoptive T-

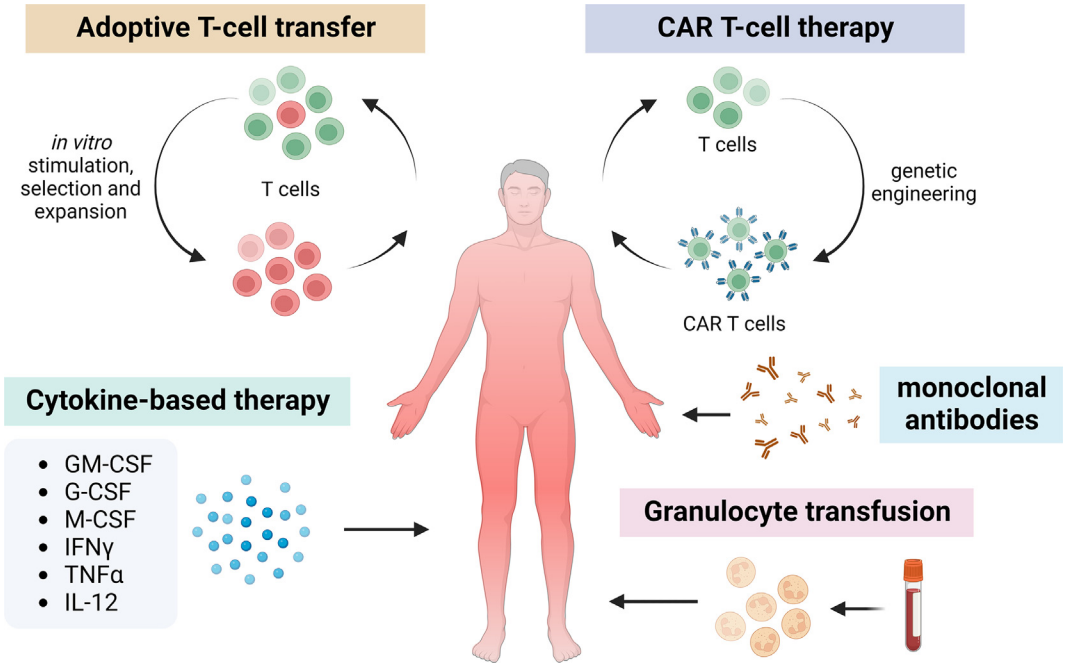

Fig. 3. Adjunctive immunotherapies for prevention and treatment of fungal infections.

Table 2
Summary of preclinical and clinical immunotherapies and vaccines available for fungi listed under critical group on WHO FPPL.

Critical fungus	Antifungal drug resistance	Preclinical & clinical immunotherapy	Preclinical & clinical vaccine	Ref
Cryptococcus neoformans	Under-reported, with reduced susceptibility to fluconazole reported	IFNγ, IL-12, 18B7	NA	[80,126,136–138]
Candida auris	Fluconazole-resistance (87–100%) Amphotericin B-resistance (8–35%) Echinocandins-resistance (0–8%)	PD-1/PD-L1 inhibition, anti-CR3-RP polyclonal antibody	NDV-3A	[164–166]
Aspergillus fumigatus	Azole-resistance on the rise	IFNγ, TNFα, adoptive T-cell therapy, CAR T-cell therapy	Lam-CRM conjugate	[121,123,124,128,130,153]
Candida albicans	Relatively uncommon, with some azole-resistance and echinocandins-resistance reported	IFNγ, IL-12, GM-CSF, G-CSF, Mycograb	NDV-3, PEV7, Lam-CRM conjugate	[115,125,134,153,167–170]

cell transfer [128]. However, this approach is technically challenging because the low frequencies of fungi-specific T cells make their large-scale expansion difficult. Moreover, the feasibility of this therapy is questioned by the possible development of graft versus host disease (GvHD), and immunosuppressants given as an anti-GvHD prophylaxis may end up impairing the function of the infused T cells [129].

5.2.2. Chimeric antigen receptor (CAR) T-cell therapy

Beyond its use in cancer, CAR T-cell therapy has also been explored to fight fungal infections through the engineering of a CLR Dectin-1-specific CAR (D-CAR). Such D-CAR$^+$ T cells were able to secrete IFNγ upon activation by β-glucan, hence suppressing the growth of *A. fumigatus* in a preclinical immunodeficient mouse model [130]. While CAR T-cell therapy is one of the most promising immunotherapeutic tools, it frequently can elicit serious and potentially fatal adverse side effects including cytokine release syndrome (CRS) and neurologic toxicity [131]. Moreover, the timeline associated with the manufacturing of autologous CAR T-cell may be too long in the context of an acute fungal infection. In addition, the cost of CAR T-cell therapy is prohibitive, ruling it out as a mainstream standard of care. As such, these limitations must be circumvented before CAR T-cell therapy can be introduced as an immunotherapy for invasive fungal infection.

5.2.3. Granulocyte transfusion

Since neutropenia and neutrophil dysfunction are long known to increase the risk of invasive fungal infection, granulocyte transfusion may be used as an adjunctive treatment to reduce mortality and morbidity in this group of high-risk patients. Diaz et al. reported that 80% of neutropenic children receiving granulocyte transfusion experienced complete or partial resolution of invasive fungal infection [132]. In addition, granulocyte transfusion for pediatric stem cell transplantation patients reduced the overall incidence of invasive fungal infection [133].

5.3. Monoclonal antibodies (mAbs)

MAb has long been adopted for the treatment of various infectious diseases on the basis that it can eliminate pathogens directly through neutralization, antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), or indirectly by enhancing immune responses in patients. However, our lack of understanding on the role of humoral immunity during antifungal defense has significantly hampered the development of such antibody-based therapy for fungal infections. Moreover, manufacturing of mAbs remains costly and laborious. Currently, only two antifungal mAbs have advanced into the clinical trial stage, although their further development for clinical use were halted due to various hurdles.

5.3.1. Mycograb

Mycograb, also known as Efungumab, is a human recombinant single-chain fragment variable (scFv) antibody targeting the fungal heat shock protein 90 (HSP90), and it demonstrates broad spectrum activity against a wide range of *Candida* species including *C. albicans*, *C. krusei*, *C. tropicalis* and *C. parapsilosis*. In a clinical trial conducted by Pachl et al., combinatorial treatment with amphotericin B and Mycograb significantly improved the clinical outcome of patients with invasive candidiasis (84%) as compared to treatment with amphotericin B alone (48%), and the overall mortality was reduced by more than four-fold [134]. Despite the positive results, Mycograb was not granted marketing authorization due to issue with quality control during manufacturing [135].

5.3.2. 18B7

18B7 is a murine mAb directed against the polysaccharide capsule of *C. neoformans* [136]. It was found to be well-tolerated in a phase I clinical trial conducted on human immunodeficiency virus (HIV)-infected patients with a history of cryptococcal meningitis, and could also transiently reduce serum cryptococcal antigen at high doses [137]. In addition, radioactively-labelled 18B7 was able to reduce susceptibility of mice to *C. neoformans* with minimal off-target effects [138]. However, further clinical development of 18B7 was unfortunately halted due to lack of industrial support [139].

5.4. Future of antifungal immunotherapy

It is increasingly recognized that malignancies and infectious agents such as fungi utilize parallel pathogenic mechanisms to evade host immune surveillance. With the remarkable success of immunotherapies in cancer treatment over the past decade, it has led us to postulate that these immunotherapeutic agents can also be adopted in the context of fungal diseases. Just like cancer cells, fungi pathogens can exploit various immune checkpoint molecules to trigger immune suppression and exhaustion, thereby escaping immune clearance. For instance, *A. fumigatus* has been reported to induce checkpoint inhibitor PD-L1 expression on DCs, thereby promoting tolerance through Treg polarization [140]. Immune checkpoint molecules such as PD-1, LAG-3 and TIM-3 were also found to be elevated on PBMCs from patients with invasive candidiasis, among which PD-1 expression was found to correlate strongly with poor survival outcomes in these patients [141]. Together, these warrant the investigation of immune checkpoint blockade as a potential avenue to re-invigorate the immune cells to fight fungal infections. Apart from immune checkpoint inhibitors, Bi- and Tri-specific T cell engagers (BiTE or TriTE), which are originally developed for cancer immunotherapy, are also unexplored tools which may be used to physically link and activate T cells to fungi pathogens for their killing. However, as mentioned above, T-cell-retargeting therapies are frequently associated with toxic and adverse events like CRS. Since the innate immune system plays a crucial role in antifungal defense, it may be of interest to design DC as well as neutrophil engagers to exploit their effector functions for fungal clearance.

Notably, patients with inherited mutations and deficiency in Card9 are uniquely predisposed to various superficial and invasive fungal infections, highlighting that restoration or augmentation of Card9 signaling may be a promising immune-based strategy to enhance antifungal immune responses. We have previously identified Dok3 as a novel inhibitor of Card9 signaling in neutrophils, and mice deficient in Dok3 were protected from systemic infection with *C. albicans* [142]. As such, small molecules which can specifically disrupt the interaction between Dok3 and Card9 can promote a "primed" Card9 signaling state and thus have the potential to enhance host immune responses for improved prognosis during candidiasis. As opposed to biologics, these small-molecule drugs have the advantages of lower manufacturing cost, ease of administration and easier patient access, and hence are more likely to be translated and licensed for human use.

Even though remarkable progress has been made in the field of antifungal immunotherapy, there are major challenges to be overcome for its successful clinical translation and application. Firstly, one of the key lessons learnt from cancer immunotherapy is the variability in clinical response of treated patients. Due to the complex nature of our immune system, myriad of genetic alterations present in each individual, as well as the evolving nature of fungi pathogens, the outcome of immunotherapy will be heterogeneous. To improve our confidence in selecting the right immunotherapeutic approach and to identify patients who are likely to show favorable response to treatment, we will need to search for composite biomarkers which can predict treatment outcome. Omics-based approaches may guide development of a predictive model to maximize clinical benefits of immunotherapy, although this is still a challenging, complex, and on-going process.

Another major hurdle in the clinical application of immunotherapy is the potential development of toxic and adverse events associated with hyperactivation of the immune system. While the success of immunotherapy hinges on the activation of host immune cells, a delicate balance needs to be achieved to avoid exuberant responses leading to immunopathology. For instance, up to one-third of the patients receiving cancer immunotherapies have reported life-threatening immune-mediated toxicities such as CRS and neurotoxicity syndrome [143]. While CRS can usually be managed with immunosuppressants such as tocilizumab and corticosteroids, such treatment can limit the efficacy of the antifungal immunotherapy. Currently, efforts have been made to understand the underlying mechanism of CRS so as to develop targeted therapies which do not compromise the intended action of the immunotherapy, thereby making it a safer option for clinical application.

6. Fungal vaccines

Vaccines are hailed as one of the most cost-effective and successful ways to eradicate infectious diseases. Yet, no clinically approved fungal vaccine is available to date, and this neglect on fungal diseases has been extensively discussed by Rodrigues and Nosanchuk [144].Given the rapid emergence of drug resistance towards current arsenal of antifungals, as well as the high mortality rate associated with invasive fungal infection, there is an urgent and unmet clinical need for the development of an effective fungal vaccine for the high-risk population. However, there are various challenges to be overcome during vaccine development. Firstly, the impaired immune responses of immunocompromised patients, who are the main target group for vaccination, would imply that a delicate balance needs to be maintained between safety and efficacy. While the high immunogenicity of live vaccines may be ideal to generate a protective immune response, the immunological status of these patients may put them at risk of infection from the vaccine itself. On the other hand, inactivated and subunit vaccines which are comparatively safer may not elicit sufficient response from these patients to confer them protection against subsequent infection. In addition, from the investors' and pharmaceutical industries' point of view, it is not cost-effective to develop a vaccine which will be used to vaccinate only a small population of high-risk individuals. On average, the cost of vaccine development from conceptualization to market stage has been estimated to be approximately $200 to $500 million dollars, spanning a period of more than 10 years [145]. Despite these obstacles, it is encouraging to see that three fungal vaccines have made it to the clinical trial stage, and it is not a formidable goal to see a fungal vaccine approved for human use in future.

6.1. Candida vaccines

Candida species is the most common cause of invasive fungal infections, and it is associated with a mortality rate exceeding 50%. Moreover, it is also responsible for mucosal infections such as vulvovaginal candidiasis (VVC), which affects 50–70% of women at least once in their lifetime [146]. PEV7 is a subunit vaccine consisting of recombinant truncated Sap2 protein assembled on virosomes which can generate specific IgG and IgA antibodies for protection against vaginal candidiasis in rats [106]. It was subsequently tested in a Phase I clinical trial on 48 healthy female volunteers, and promising results were obtained with regards to the safety profile as well as efficacy of the vaccine [147].

A second vaccine, NDV-3, composed of the *C. albicans* agglutinin-like sequence 3 protein (Als3p), was first shown to confer protection of mice against *C. albicans* infection. A phase I clinical trial revealed that NDV-3 is well tolerated among the 40 healthy volunteers, and it increased the titers of IgG and IgA1, as well as production of IFNγ and IL-17A by T cells, as compared to the placebo [148]. Based on these results, a phase 1b/2a clinical trial was conducted for NDV-3A (NDV-3 without 6-His tag and linker sequences) on 188 women with recurrent VVC, and the fungal vaccine demonstrated favorable safety and immunogenicity profile [149].

Both vaccines have been licensed to NovaDigm Therapeutics Inc, and the aim of the company is to develop a multivalent fungal vaccine to protect patients against recurrent and multi-drug resistant *C. albicans* infection [147]. However, given that *C. albicans* exists as a commensal in the human gut, concerns have been raised regarding the unknown effect of such vaccines on the gut microbiome.

6.2. Coccidioides vaccine

Coccidioides immitis is a fungi endemic in southwestern United States and northwestern Mexico, and it can cause coccidioidomycosis (valley fever) even in immunocompetent individuals. A vaccine containing formaldehyde-killed spherules of *C. immitis* was tested in a phase III clinical trial involving 2867 healthy volunteers, but the results were disappointing, with no reduction in the incidence and severity of coccidiomycosis in the vaccinated group [150]. Subsequent research efforts hence focused on development of recombinant antigen vaccines based on antigen 2/PRA (Ag2/PRA) and Coccidioides-specific antigen (CSA). When given in combination, these two antigens can improve the survival of mice with coccidioidomycosis [151]. The use of Ag2/$PRA_{1\text{-}106}$ as a vaccine antigen candidate was patented in 2006, but vaccine development has since been slow due to technical and funding issue [139].

6.3. Pan-fungal vaccines

While the vaccines discussed above are specific for individual fungi species, an ideal vaccine will be one with broad spectrum activity targeting numerous clinically relevant fungi. Although none of these vaccine candidates have progressed to the clinical trial stage, promising results from preclinical studies have established the feasibility of such pan-fungal vaccines. Recently, a recombinant peptide vaccine NXT-2, based on a conserved KEX1 sequence present on multiple pathogenic fungi, has been shown to be efficacious in protecting both murine and nonhuman primate models against invasive aspergillosis, systemic candidiasis and pneumocystosis [152]. In addition, a β-glucan-based vaccine CRM197 was able to elicit protective responses in mice challenged with *C. albicans* and *A. fumigatus* [153,154]. It is noteworthy that β-glucans are potent inducers of trained immunity, and as such raises the possibility that these vaccines may further confer nonspecific beneficial protection against other infectious agents such as *Mycobacterium tuberculosis* [155]. Such pan-fungal vaccine would significantly benefit public health, and hence are more likely to attract industry interest.

6.4. DCs-targeted antifungal vaccines

DC is a key immune cell type driving the activation of T cell responses, and as such, various DC-targeting strategies have been explored during the rational design of vaccines. Fungal carbohydrates such as mannose and β-glucan have been demonstrated to selectively promote uptake of OVA antigen by DCs through CLR, thereby enhancing Th1, Th17, as well as antibody responses in mice following immunization [156,157]. Additionally, nanoparticles specifically targeting DC-SIGN are able to deliver TLR ligands to human DCs for priming of $CD8^+$ T cell responses [158]. By exploiting these DC-targeting strategies, it may be possible to load DCs with fungal antigens necessary for the induction of cellular immune responses. Even though DC-targeted vaccine holds great promise with the potential to elicit a robust and long-lasting T cell response, the fact that DCs exist in distinct subsets which can orchestrate disparate T cell responses remains an issue to be addressed during *in vivo* DC targeting.

6.5. Future of fungal vaccines

Since the outbreak and rapid transmission of SARS-CoV-2 in December 2019, massive efforts and resources have been devoted to the field of vaccine development. The first COVID-19 vaccination was developed at revolutionary speed and approved for clinical use in less than a year. Yet, not a single vaccine is clinically available for protection against fungal pathogens. This has clearly illustrated the lack of research and funding for this imminent public health threat. Hence, we should draw valuable lessons from the COVID-19 pandemic and extrapolate the success of such mRNA-based vaccines for the prevention of human fungal diseases. Theoretically, with the need to modify only the encoded RNA sequence, RNA-based vaccines hold the advantages of a simple, rapid, versatile, scalable, and low-cost manufacturing process. Moreover, mRNA is non-infectious and hence relatively safe for use in immunocompromised individuals, and at the same time, it has the potential to self-amplify within the host to achieve high immunogenicity required to generate immunological memory [159]. However, as with other vaccine development, significant hurdles exist in the identification of ideal candidate antigens. Given that the fungi cell wall is highly complex and immunogenic, it will be extremely challenging to search for antigens of interest for vaccine development. Reverse vaccinology is a top-down bioinformatics-based approach which makes use of whole genome sequencing data and *in silico* prediction for the discovery of potential vaccine candidates, and this pipeline has been deployed successfully to identify functional antigens in pathogens such as *Mycobacterium tuberculosis*, *Bordetella pertussis* and *Staphylococcus aureus* [160,161]. Recently, studies have further complemented reverse vaccinology approach with the ability to interrogate surface-exposed proteins on bacterial pathogens. Such technique combines mass spectrometry-based identification of surface proteins released through sequential proteolytic digestion of bacteria with bioinformatics analyses to select potential vaccine antigens for testing [162,163]. By implementing the unprecedented advances in vaccine technologies and exploiting the established mRNA vaccine platforms, we will be able to accelerate the identification of novel and immunogenic fungal vaccine candidates, thus offering hope for a new fungal vaccine breakthrough in the near future.

7. Conclusions and outlook

Over the last few decades, we have made remarkable progress towards understanding of host immune mechanisms against fungi infection. Despite that, development of new antifungal therapeutics has been substantially slow as compared to other communicable diseases. Fungi and mammalian cells are closely related evolutionarily, resulting in high toxicity of antifungal drugs and the limited numbers of fungi-specific targets available for novel drug development. In this regard, advances have been made in the field of adjunctive immunomodulating therapies, which have the benefits of better safety profile, decreased risk of resistance and broad-spectrum activity. However, the use of immunotherapy to combat fungal infections is still in its infancy, with most studies being preclinical or in early clinical trial stages. Nevertheless, the results have been encouraging, and future research may lead to seminal discoveries which can revolutionize the field of medical mycology. By expanding our antifungal armamentarium with a combination of prophylactic vaccines, antifungal agents and immune-base adjunctive therapies, we are optimistic to win the battle against fungal infections in the near future.

8. Data availability

No data was used for the research described in the article.

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Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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