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REVIEW

Fungal vaccines and adjuvants: a tool to reveal the interaction between host and fungi

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Abstract

Fungal infections are incurring high risks in a range from superficial mucosal discomforts (such as oropharyngeal candidiasis and vulvovaginal candidiasis) to disseminated life-threatening diseases (such as invasive pulmonary aspergillosis and cryptococcal meningitis) and becoming a global health problem in especially immunodeficient population. The major obstacle to conquer fungal harassment lies in the presence of increasing resistance to conventional antifungal agents used in newly clinically isolated strains. Although recombinant cytokines and mono-/poly-clonal antibodies are added into antifungal armamentarium, more effective antimycotic drugs are exceedingly demanded. It is comforting that the development of fungal vaccines and adjuvants opens up a window to brighten the prospective way in the diagnosis, prevention and treatment of fungal assaults. In this review, we focus on the progression of several major fungal vaccines devised for the control of *Candida* spp., *Aspergillus* spp., *Cryptococcus* spp., *Coccidioides* spp., *Paracoccidioides* spp., *Blastomyces* spp., *Histoplasma* spp., *Pneumocystis* spp. as well as the adjuvants adopted. We then expound the interaction between fungal vaccines/adjuvants and host innate (macrophages, dendritic cells, neutrophils), humoral (IgG, IgM and IgA) and cellular (Th1, Th2, Th17 and Tc17) immune responses which generally experience immune recognition of pattern recognition receptors, activation of immune cells, and clearance of invaded fungi. Furthermore, we anticipate an in-depth understanding of immunomodulatory properties of univalent and multivalent vaccines against diverse opportunistic fungi, providing helpful information in the design of novel fungal vaccines and adjuvants.

Keywords Fungal infection · Immune recognition · *Candida* · Vaccine · Adjuvant

Fungal infections and antifungal therapy

Fungi are the third largest eukaryotic species next to animals and plants and have a globally profound impact on human health. Owning to rising immune dysfunctions caused by such as long-term antibiotic medication, frequent use of immunosuppressants, chemo-/radio-therapy in cancer population and emergence of multidrug resistant fungal strains, the risks induced by fungal infections are tremendously attracting scientific and clinical attentions in recent decades (Fisher et al. 2020). The latest data show that the annual superficial fungal infections involving, for example, skin, hair, nails and eyes, affect about 1 billion people worldwide, the yearly oral and vaginal mucosal fungal infections influence approximate 135 million people around the world, and allergic fungal infections endanger nearly 23.3 million population (Bongomin et al. 2017). At present, the most common opportunistic fungi are *Candida* (~23%) followed by *Aspergillus* (~8.3%) and *Cryptococcus* (~7.7%) which are heavily detrimental to human being in the case of internal colonization, propagation and systemic invasive infections (Bongomin et al. 2017; Suleyman and Alangaden 2021).

At present, the major antifungal drugs consist of polyenes (such as amphotericin B and nystatin), triazoles and imidazole derivatives (such as fluconazole, itraconazole,

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posaconazole, voriconazole and esaconazole), and semi-synthetic echinocandins (such as caspofungin, anidulafungin and micafungin) (Dubey and Singla 2019). However, it is known that these traditional antifungal agents are naturally futile to inhibit several fungi. For example, *C. krusei* and some *C. glabrata* have intrinsic resistance to fluconazole (Hassan et al. 2021). As a result, increasing incidence of antifungal resistance is becoming an obstacle to restrict clinical application of antifungals available due to up-regulation of efflux pumps, metabolic plasticity, impediment of cell wall and extracellular matrix, overexpressed target-encoding genes, presence of persister cells, and biofilm formation (Martinez and Casadevall 2006; Mowat et al. 2008; Johnson et al. 2016; Wu et al. 2017). The side effects caused by traditional antifungal drugs including nephrotoxicity by amphotericin B and hepatotoxicity by azoles are also unhelpful for their clinical application for some patients with severely damaged immunity. Meanwhile, the economic expense is another heavy burden for patients with long-term use of antifungal agents. Besides antifungal agents, there are several biological preparations including recombinant cytokines (e.g. recombinant human IFNα-2b and GM-CSF) and mono-/poly-clonal antibodies (anti-IL-17) that are effective for antifungal purpose in the treatment of, for example, vulvovaginal candidiasis, refractory oropharyngeal candidiasis and candidiasis (Vazquez et al. 1998; Li et al. 2019; Yamanaka-Takaichi et al. 2022). There are also growing evidence to support the connection of fungal dysbiosis with the aggravation of inflammatory bowel diseases, systemic lupus erythematosus, Alzheimer's disease, colorectal cancer, and psoriasis with obscure mechanisms (Ling et al. 2020; Bruno et al. 2022; Li et al. 2022; Zhang et al. 2022; Yang et al. 2023). In the face of increased fungal or fungus-related infections, existing antifungal approaches are still limited and new antifungal approaches are desperately required. Due to specialized target recognition and relatively low toxicity, vaccines aim to protect host from invaded fungi by stimulating antibody-mediated humoral immune response and acquire growing interest.

Fungal vaccines and adjuvants

Fungal vaccines are considered an effective way to prevent acute and recurrent invasive infections caused by aggressive fungi, and usually composed of either killed/weakened fungal cells or purified fungal components. During the past decades, the development of fungal vaccines is being emphasized due to increasing challenges posed by, for example, *Candida* spp., *Aspergillus* spp., *Cryptococcus* spp., and *Coccidioides* spp.. To gain strong immune response, adjuvants are concomitantly administered with vaccines.

Fungal vaccines

Candida spp. are a group of well-studied dimorphic opportunistic fungi that can cause from superficial skin/mucosal disturbs to systemic invasive/deep-seated infections with high morbidity and mortality. The cell wall components (e.g. glucans and adhesins) and live/attenuated strains can be proper candidates in the design of *Candida* vaccines, some of which have been tested in pre-clinical trials (Table 1). *Aspergillus* spp. can cause systemic invasive aspergillosis through spores and usually involves bronchus, lung, gastrointestinal tract, eye, nose, mucosa, and skin. *Aspergillus* spp. were previously known to affect only severely immunocompromised patients, making vaccination difficult. However, extra studies have shown that immunocompetent subjects can also be affected by *Aspergillus*, some of them can gain positive effects after vaccination (Table 1). Cryptococcosis is a type of disseminated infectious diseases caused by *Cryptococcus* spp. which frequently induces pneumonia and meningitis, and occasionally involves skin, bone and visceral organ. Patients with cryptococcosis are usually asymptomatic when initially infected with this genus, but the immune-deficient or suppressed patients may suffer from burrowing abscess and granuloma after *Cryptococcus* spp. change from a latent state to an active state (Brunet et al. 2018). Similarly, *Cryptococcus* vaccines also need to work in patients with severe T-cell deficiency, e.g. HIV/AIDS patients (Caballero Van Dyke and Wormley 2018). A number of *Cryptococcus* vaccines have been designed, and their mechanisms of action are elucidated in Table 1. Besides, there are also several reported vaccines against other endemic fungi including *Coccidioides* spp., *Paracidioides* spp., *Blastomyces* spp., *Histoplasma* spp., *Pneumocystis* spp. which are also reviewed in Table 1.

Adjuvants for fungal vaccines

Adjuvants are non-specific immune enhancers that can prime the immune response to an antigen or alter the type of immune response when injected with or pre-injected with a vaccine. Adjuvants can enlarge or lengthen the response and improve the memory response, thus reducing vaccine dosage required (Di Pasquale et al. 2015).

Conventional adjuvants

Conventional adjuvants consists of Freund's adjuvant and toxin adjuvant. The former consists of complete and incomplete Freund's adjuvants. The complete Freund's adjuvant can bind to the recombinant N terminal of Als1p and Als3p of *C. albicans*. The incomplete Freund's adjuvant can bind to

Table 1 Fungal vaccines and adjuvants

Fungi	Type	Composition		Vaccine efficacy	Reference
		Vaccine	Adjuvants		
Candida	Live attenuated vaccine	Defective *C. albicans* strain PCA-2	Nd	A protective effect against highly virulent strains of *C. albicans* CA-6, *Staphylococcus aureus*, and *Aspergillus fumigatus* in CD2F1 mice by inducing high levels of GM-CSF, TNF-α, IL-2, and IFN-γ	(Vecchiarelli et al. 1989)
		MAP kinase Hog1 gene knock-out *C. albicans* CNC13	Nd	Increasing the survival rate of BALB/c mice to 60–70% via synergistic effects of cellular and humoral immunity	(Fernández-Arenas et al. 2004)
		C. albicans RML2U with Cell wall deficient in ecm33	Nd	Inducing strong phagocytosis of BALB/c mouse macrophages with weak toxicity and enhanced adaptive immunity	(Martínez-López et al. 2008)
		C. albicans SSY50-B constructs tet-NRG1	Nd	Improving T-cell immunity in BALB/c mice, protecting B-cell deficient mice and DBA/2N mouse strains from secondary CAF-2 infection with 100% survival rate	(Saville et al. 2009)
		C. albicans HLC54 (cph1Δ/Δefg1Δ/Δ)	Nd	Partially protecting the mice from systemic infection with deadly wild-type *C. albicans*	(Yang et al. 2009)
	Heat-inactivated vaccine	Polyvalent bacterial preparation (PBP) of whole heat-inactivated bacteria-MV140	Nd	Inducing an effective systemic Th1/Th17 and IL-10 response to significantly improve the survival rate of BALB/c mice	(Benito-Villalvilla et al. 2017)
		Polyvalent bacterial preparation of whole heat-inactivated bacteria-MV140, *C. albicans* V132	Nd	Enhancing splenic T-cell responses and inducing specific antibodies in immunized BALB/c mice with significantly increased mouse survival	(Martín-Cruz et al. 2022)
	Polysaccharide vaccine	β-mannan triose, Hwp1 of *C. albicans*	Nd	Producing targeted antibodies to improve mouse survival and reduce renal fungal burden	(Xin et al. 2008)
		β- (1,2) mannan trisugars of *C. albicans*, Fba peptide	TT	Inducing protective response against disseminated candidiasis in BALB/c mice and significantly improved survival time of the mice	(Xin and Cutler 2011; Xin et al. 2012)

Table 1 (continued)

Fungi	Type	Composition		Vaccine efficacy	Reference
		Vaccine	Adjuvants		
		β- (1,2) mannan, β- glucan of *C. albicans*	TT	Improved immune response manifested by high titers of antibody recognizing *C. albicans* β-mannan antigen	(Lipinski et al. 2013)
		Mannan derivative heptamannoside of *C. albicans* (M7)	BSA conjugate protein	Significantly promoting humoral immune response intensity and specificity of antibody production against *C. albicans* in BALB/c mice	(Paulovičová et al. 2012)
		β-glucan of *C. albicans*	MF59	Significant protection on mice which is related to the production of serum and vaginal anti-glucan IgG antibody	(Bromuro et al. 2002; Pietrella et al. 2010)
		β-(1,3) glucan and β-(1,6) branch chain of *C. albicans*	Diphtheria toxin CRM197	Triggering and regulating host immune response to reduce fungal load	(Bromuro et al. 2010)
		Polysaccharide capsular of *Enterobacter basiformis*, β-glucan preparation of *C. albicans*	CRM197	Eliciting a Dectin-1 dependent innate immune response to prevent systemic and mucosal (vaginal) *C. albicans* infection in BALB/c mice	(Torosantucci et al. 2005)
		β-glucan oligosaccharide of *C. albicans*	carrier protein KLH	Inducing a protective immune response with high titers of antigen-specific total and IgG antibodies against *C. albicans* infection in a murine systemic challenge model	(Liao et al. 2015)
	Protein vaccine	rAls1p-N of *C. albicans*	CFA	A moderate enhancement in the survival rate of mice with disseminated candidiasis	(Spellberg et al. 2005; Ibrahim et al. 2006)
		rAls3p-N of *C. albicans*	CFA/aluminum hydroxide adjuvant	Inducing antibody IgG and IgA in C57BL/6 mice and enhancing Th1/Th17 immune response	(Spellberg et al. 2006; Lin et al. 2009)
		Sap2 of *C. albicans*	Cholera toxin (CT)	Inducing protective antibodies and T-helper type 1 cytokines and reducing fungal colonization in a rat vaginitis model caused by *C. albicans*	(De Bernardis et al. 2002)

Table 1 (continued)

Fungi	Type	Composition		Vaccine efficacy	Reference
		Vaccine	Adjuvants		
		A Sap2p truncated version of *C. albicans* PEV7	Nd	Producing a potent serum antibody response following induction of B-cell-mediated immune responses in mice and rats. It has now entered human clinical trials	(De Bernardis et al. 2012)
		Recombinant *C. albicans* Hsp90p	*Astragalus* root low molecular weight polysaccharide (LMW-ASP)	Significantly promoting specific antibody titers IgG, IgG1, IgG2b, and IL-2, IL-4, IL-10, IL-12 in sera of C57BL/6 mice	(Yang et al. 2016)
		rP-Hsp90C of *C. albicans*	chitosan hydrogel (CH-HG)	Improved survival and reduced kidney fungal load of infected BALB/c mice with systemic candidiasis by augmenting Th1, Th2, and Th17 responses and inducing long-lasting specific IgG	(Li et al. 2021)
		rHsp90 of *C. albicans*	NorAbuMDP pyrogen adjuvant associated nickel chelate liposomes	Increased serum specific antibody IgG, IgG2, and IgG2b titers in mice	(Mašek et al. 2011)
		DNA vaccine pD-Hsp90C containing *C. albicans* Hsp90 epitope C (LKVIRK) recombinant plasmid	PPSB	Enhanced specific antibody IgG, IgG1, IgG2b titers, and IL-2 and IL-4 concentrations in mice sera	(Yang et al. 2014)
		rHyr1p-N of *C. albicans*	Alum	Improved survival and reduced fungal burden in mice with disseminated candidiasis	(Luo et al. 2010, 2011)
		β-glucan and Hyr1p of *C. albicans*	Nd	Highly immunogenic and protective in C57BL/6 mice	(Cassone et al. 2010)
		Eno1p of *C. albicans*	IFA	Extending mice survival with an increase of antibody IgG titer	(Shibasaki et al. 2013)
		rFba1 of *C. albicans*	Filamentous phage	Apparently inducing humoral and cellular immune responses, reducing fungal burden, relieving kidney damage, significantly lengthening survival rate in infected BALB/c mice	(Shi et al. 2018)

Table 1 (continued)

Fungi	Type	Composition		Vaccine efficacy	Reference
		Vaccine	Adjuvants		
	Bacterial vaccine	Bacille Calmette-Guérin (BCG)	Nd	Inducing T- and B-lymphocyte-independent protection in severe combined immunodeficiency SCID mice with 100% survival from disseminated candidiasis compared with 30% in control mice	(Kleinnijenhuis et al. 2012)
	Nanoparticle vaccine	Hsp90-CTD	PEI	Promoting the differentiation of B cells into long-lived plasma cells, maintaining the long-term existence of antibodies which protect the mice from *C. albicans* infection	(Jin et al. 2022)
		AuNPs and photosensitizer	Nd	Enhanced photodynamic therapy, disrupting the membrane stability of *C. glabrata*, effectively reducing *C. albicans* cell viability. No animal experiments are available	(Khan et al. 2012; Sherwani et al. 2015; Maliszewska et al. 2017)
		AmB, nystatin and Magnetic NPs	Nd	Maintaining immunomodulatory properties and significantly improving the survival rate of mice	(Niemirowicz et al. 2016, 2017)
		AmB and PLGA-PEG	Nd	Increased permeability by forming microporous channels in a *C. albicans* infected mouse model	(Radwan et al. 2017; Ludwig et al. 2018)
		AmB/FLZ and Solid lipid NPs	Nd	Enhanced solubility of AmB and reduced toxicity	(Moazeni et al. 2016; Jansook et al. 2018)
		FLZ and AgNPs	Nd	Interfering with ergosterol biosynthesis, increasing membrane permeability, destroying fungal cell wall integrity, but in vivo efficacy is unknown	(Monteiro et al. 2011; Lara et al. 2015)
		AgNPs and Ethanol propolis extract PE	Nd	Inhibited oral *Candida* biofilm formation and fungal load in organs, increased BALB/c mice survival rate	(Kischkel et al. 2020)
		Chitin NPs, farnesol and miconazole	Nd	Effective inhibition on fungal proliferation	(Fernandes Costa et al. 2019)

Table 1 (continued)

Fungi	Type	Composition		Vaccine efficacy	Reference
		Vaccine	Adjuvants		
Aspergillus	Whole-cell vaccines (live attenuated or killed cells)	Knockout of steroidal glucosidase coding gene in *A. fumigatus* sglA	Nd	Recruitment of CD4 and/or CD8 T cells, atypical γδ T cells, and neutrophils to the lungs to clear pulmonary fungi in corticosteroid-induced immunosuppressed mice and cyclophosphamide induced leukopenia mice	(Fernandes et al. 2022)
		Live or heat-killed *Aspergillus* strain lacking chitin deacetylase activity (Cda123)	Nd	Robust protective immunity to lethal challenge with a virulent wild-type *C. neoformans* strain	(Upadhya et al. 2016)
		Aspergillus strain overexpressing transcription factor Znf2 (Znf2OE)	Nd	Offering 100% protection to the mice from a subsequent challenge with the lethal clinical strain H99	(Zhai et al. 2015)
		A heat-inactivated *S. cerevisiae*	Nd	Effectively extended the survival time of mice, but did not depend on antibody action	(Clemons et al. 2014a, 2014b)
		A. fumigatus crude culture filtrate AGs	Nd	Inducing Th1 and Th2 type responses during infection in BALB/c mice	(Cenci et al. 2000)
		Live spores of *A. fumigatus*	Nd	Improved survival in mice with CF-1 invasive pulmonary aspergillosis through adoptive transfer of antigen-specific CD2 T cells to produce IFN-γ and IL-4	(Ito and Lyons 2002)
	Recombinant /subunit vaccines	Asp f3 of *A. fumigatus*	Nd	Protecting cortisone acetate immunosuppressed mice from experimentally induced pulmonary aspergillosis by activating $CD4^+$T cells	(Diaz-Arevalo et al. 2011)
		Aspf3 of *A. fumigatus*	TiterMax	Enhanced and/or restored function of corticosteroid-suppressed macrophages to clear fungal elements	(Ito et al. 2006)
		Aspf16 of *A. fumigatus*	Unmethylated CpG oligodeoxynucleotides (ODNs)	Induced activation of $CD4^+$ Th1 cells capable of conferring resistance to the infection in a murine model of invasive pulmonary aspergillosis	(Bozza et al. 2002)

Table 1 (continued)

Fungi	Type	Composition		Vaccine efficacy	Reference
		Vaccine	Adjuvants		
		A. fumigatus Cell wall glucanase (Crfl) epitope p41	CpG	Induced memory $CD4^{+}$Th1 cells to trigger cross protection against fatal infections of *C. albicans* and *A. fumigatus* in BALB/c mice	(Stuehler et al. 2011)
		Mannoglycoprotein AFMP2	TT	Effectively activating antigen-specific $CD8^{+}$T cell response, and significantly improving mice survival rate	(Chong et al. 2004; Gu et al. 2021)
Cryptococcus	Whole-cell vaccines (live attenuated or killed cells)	*C. neoformans* H99γ	Nd	Stimulating the production of Th1 cytokine IFN-γ to induce a protective immune response against *Cryptococcus* in mice	(Caballero Van Dyke and Wormley 2018; Wozniak et al. 2011)
		Heat-killed *Cryptococcus* Fbp1Δ-yeast(HK-Fbp1)	Nd	Inducing excellent protective Th1 host immunity in A/Jcr, BALB/c, C57BL/6, CBA/J, and IFN-γ-R mouse lungs	(Wang et al. 2019)
		Cryptococcus sgl1Δ-yeast	Nd	Protecting mice against cryptococcosis following infections with *C. neoformans* or *C. gattii*	(Rella et al. 2015)
		GXM of *Cryptococcus*	CFA	Inducing a high titer IgG response	(Kuttel et al. 2020)
	Recombinant /subunit vaccines	GalXM of *Cryptococcus*	BSA	Eliciting high-titer IgG responses in mice	(Oscarson et al. 2005)
		P13 (peptide analog of GXM) of *Cryptococcus*	TT/DT	Increased anti-GXM antibody responses (IgG2 and IgG4), eliciting an antibody response in human immunoglobulin transgenic mice	(Maitta et al. 2004; Datta et al. 2008; Chow and Casadevall 2011)
		Glucan particles packaged with *C. neoformans* alkaline extracts	Nd	Eliciting robust T cell immune responses and protecting mice from lethal challenges with virulent *C. neoformans* and *C. gattii* strains	(Beenhouwer et al. 2002; Specht et al. 2017)
		CneF (culture filtrate Ags) of *Cryptococcus*	Mannoglycoprotein	Stimulating the production of Th1 cells and antibodies to improve the survival time of BALB/c mice	(Specht et al. 2015)

Table 1 (continued)

Fungi	Type	Composition		Vaccine efficacy	Reference
		Vaccine	Adjuvants		
		Anti-β-glucan monoclonal antibody of *Cryptococcus* (MAb 2G8) (immunoglobulin G2b)	Nd	A reduction in fungal burden in the brains and livers of mice systemically infected with a highly virulent, encapsulated *C. neoformans* strain	(Rachini et al. 2007)
Coccidioides	Whole-cell vaccines (live attenuated or killed cells)	Live *coccidioides* (Silveira, ATCC 24) strain deleted of Cps1	Nd	A slight but statistically insignificant reduction in the incidence of coccidioidomycosis	(Pappagianis 1993; Narra et al. 2016)
		Attenuated *coccidioides* (C735) strain Δcts2/Δard1/Δcts3	Nd	Promoting the activation of Th1 and Th17 cells, reducing the visceral fungal load, and improving the survival rate of C57BL/6 mice	(Mead et al. 2020)
	Recombinant /subunit vaccines	Proline-rich antigen on cell surface of *Coccidioides*	CpG	Unknown	(Hung et al. 2012) (Johannesson et al. 2004)
		pBK-CMV phagemid vector of *Coccidioides*	Nd	Promoting $CD4^+$ and $CD8^+$T responses	(Ivey et al. 2003)
		T-cell epitopes Antigen 2/proline rich Ag (Ag2/PRA)/Chimeric polyprotein	CpG	Inducing Th1, Th2, and Th17 responses and protecting mice from *C. posadasii* infection	(Tarcha et al. 2006)
		Immunodominant T cell epitopes	CpG	Early pulmonary infiltration of activated T helper cells 1 (Th1), Th2, and Th17, increased production of interferon gamma (IFN-γ) and interleukin-17, a significant reduction in fungal burden, and prolonged survival	(Shubitz et al. 2006; Hurtgen et al. 2012)
		C. posadasii Gel-1 (β-1,3-glucosyltransferase)	CpG ODN	A protective efficacy against a lethal challenge of *C. posadasii* in BALB/c or C57BL/6 mice	(Delgado et al. 2003)
		Spherule phase of *C. posadasii* peroxisomal matrix protein (Pmp1)	Monophosphoryl lipid A-stable emulsion (MPL-SE) adjuvant	Evoking protection in two murine models of infection with *C. posadasii*	(Orsborn et al. 2006)
		Urease, Plasmid vector:pSecTag2A	CpG ODN	82% immunized animals with over 40 days of survival compared to 10% of the control mice	(Li et al. 2001)

Table 1 (continued)

Fungi	Type	Composition		Vaccine efficacy	Reference
		Vaccine	Adjuvants		
		A 15-mer peptide from the major diagnostic antigen gp43 (P10) of *Coccidioides* and plasmid vector	Nd	Restoring normal lung structure and eradicating fungi in mice infected one month before treatment	(Rittner et al. 2012)
		A 15-mer peptide from the major diagnostic antigen gp43 (P10) and *S. cerevisiae* expressing gp43	Nd	Reduced fungal burden in the lung and spleen of immunized mice with higher levels of IL-12 and IFN-γ	(Assis-Marques et al. 2015)
Paraccidioides	DNA vaccines	*Mycobacterium leprae* Hsp65 and Vector pVAX1	Nd	An increase of Th1 cytokines and a reduction of fungal burden resulting in a marked reduction of collagen and lung remodeling in BALB/c mice	(Ribeiro et al. 2009)
		Sequence recombinant protein Hsp60	Adjuvant containing monophosphoryl lipid A, synthetic trehalose dicorynomycolate and cell wall skeleton	Proliferated splenocytes in immunized mice, increased interleukin-12 and gamma interferon (IFN-gamma), and reduced fungal burden in mice	(de Bastos Ascenço Soares et al. 2008)
	Recombinant /subunit vaccines	P10- FliC fusion protein of *Paracidioides*	CFA	Reduced *P. brasiliensis* growth and mice lung damages	(Braga et al. 2009)
Blastomyces	Subunit vaccine	C-type lectin receptors (CLRs)-MCL(Dectin-3) of *Blastomyces*	Nd	Regulating the development of vaccine-induced Th17 cells and protective immunity against lethal infection with *B. dermatitidis*	(Wang et al. 2015)
Histoplasma	Subunit vaccine	Sec31of *Histoplasma* homologue, Monophosphoryl lipid A, trehalose dicorynomycolate	cell wall skeleton	Reduced fungal burden and improved survival in mice	(Scheckelhoff and Deepe 2006)
Pneumocystis	DNA vaccine	Antigenic epitopes of the gene encoding the 55 kDa antigen fragment of *Pneumocystis* (p55) p55-TAG	Nd	Significantly reduced pathogen burden and lung-weight to body-weight ratios, eliciting both cell-mediated and humoral immunity	(Fan et al. 2016)

Nd no data, *KLH* Keyhole hemocyanin, *TT* Tetanus toxoid, *MF59* oil-in-water emulsion, *FAB* Fragment antigen-binding (T cell peptide in the cell wall protein of *C. albicans*), *ALS* Lectin like sequence protein, *CFA* Complete Freund's adjuvant, *IFA* Incomplete Freund's adjuvant, *SAP* Aspartic protease, *Hsp90* Heat shock protein 90, *Hyr1* Mycelium regulatory protein, *BSA* Bovine serum albumin, *MAP* Mitogen activating protein, *AuNP* Au nanoparticles, *AgNP* Ag nanoparticles, *AmB* Amphotericin B, *PLGA* Polylactic acid glycolic acid, *PEG* Polyethylene glycol, *FLZ* Fluconazole, *PEI* polyvinylimide, *CpG* cytidine-phosphatte-guanonine, *CpGODN* cytidine-phosphatte-guanonine oligodeoXynucleotides, *GXM* glucuronoxylomannan

the antigen protein Eno1p (Spellberg et al. 2005; Shibasaki et al. 2013). Toxin adjuvants mainly contains cholera toxin (CT), tetanus toxoid (TT) and diphtheria toxin (CRM197). These adjuvants can present β-mannan and some Sap antigen proteins to adaptive cells, effectively promoting antigen-specific immune responses (Wu et al. 2007; Bromuro et al. 2010; Sandini et al. 2011; De Bernardis et al. 2012). MF59 is the commonly used milk adjuvant and composed of squalene, span 85 and tween 80 which are dissolved in citrate buffer. MF59 can induce significantly higher humoral immunity than aluminum salt adjuvant and certain cellular immune responses (Pietrella et al. 2010).

Delivery adjuvants

Delivery adjuvants is primarily comprised of nanoparticle adjuvants and glucan particles. The advantages of nanoparticle adjuvants involve their interactions with antigen-presenting cells (APC) to promote cross-presentation and cross-protection against fungal antigens. Biocompatible materials possess good absorption and low degradation, making nanoparticle adjuvants safer than conventional adjuvants (Ahmed et al. 2018). Nanoparticle adjuvants can deliver traditional antifungal drugs, e.g. amphotericin B, fluconazole, itraconazole, to the designated locus, displaying potent anti-mycotic effects (Grego et al. 2021). Glucan particles, derived from *Saccharomyces cerevisiae* cell wall, own spherical complex internal cavities to load diverse antifungal drugs. Since Dectin-1 are widely distributed in myeloid cells, most innate cells like macrophages and dendritic cells (DC) can recognize the major fungal cell wall component β-glucan through Dectin-1, thereby activating innate immune response to invaded fungi. As a result, glucan particles can not only deliver antifungal cargos to inflammatory foci, but also trigger intrinsic immune-stimulatory property of innate immunity (Mirza et al. 2017).

Toll-like receptor (TLR) adjuvants

TLR adjuvants for fungal vaccines mainly contain alum and combined adjuvant. Alum can help *C. albicans* Als and Hyr1 antigens induce antibody response and $CD4^+$T helper cell response (Baquir et al. 2010; Luo et al. 2011; De Bernardis et al. 2012). Alum can also rapidly recruit neutrophils and other immune cells, and enhance adaptive immunity by inducing tissue damages and activating inflammatory DCs (Oleszycka and Lavelle 2014). Combined adjuvants are prepared by formulating the fungal recombinant protein Bl-Eng2 (*Blastomyces* endoglucanase 2) which contains an immunodominant antigen and Dectin-2 agonist/adjuvant with δ inulin (Advax) containing TLR agonists. Several of these combined adjuvants, i.e. Bl-Eng4 formulated with Advax3 containing TLR2 agonists or Advax8 containing TLR9 agonists, could provide better protection against pulmonary infection with *Blastomyces dermatitidis* than Freund's adjuvant (Wüthrich et al. 2021).

Chinese herbal polysaccharide adjuvant

Since polysaccharides are potent activators of immune response, a variety of polysaccharides are extracted from Chinese herbal medicines and purified as adjuvants for fungal vaccines. These polysaccharide preparations include *Rehmannia glutinosa* polysaccharide (RGP), *Radix isatidis* polysaccharide (RIPS), *Ganoderma lucidum* polysaccharide (GLP) and *Astragalus* polysaccharide (APS) and their derivatives (Hagan et al. 2015). It was found that RGP liposome controlled release preparation was effective to improve the immune response and increase the number of central memory cells and efficient memory cells through enhancing the phagocytosis activity of macrophages and the production of IL-6, IL-12, IL-1β and TNF-α (Wang et al. 2018). Similarly, nano self-assembled lipid RGP adjuvant could also significantly promote macrophage proliferation, pro-inflammatory cytokine production, and cellular uptake through macroendocytosis-dependent and radioimmunotherapy-mediated endocytosis (Huang et al. 2019). RIPS has been demonstrated to enhance spleen cell antigen-specific cellular immune responses, T cell activation, and cytokine production (Wang et al. 2021). GLP-2, a novel β-glucan extracted from *Ganoderma lucidum*, is a potent TLR4 agonist for adaptive immune response. Studies have shown that GLP-carrying liposome drug delivery system could significantly improve the activity of GLP in promoting splenocyte proliferation and peritoneal macrophage activation (Liu et al. 2015). In another study, GLP and ovalbumin (OVA) were encapsulated into liposome as a vaccine and inoculated into mice. The results showed that GLP-OVA-loaded liposomes (GLPL/OVA) could induce more powerful antigen-specific immune responses, higher antigen-specific IgG antibodies, better splenocyte proliferation, stronger cytokine secretion by splenocytes and activation of $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells than each single-component formulation (Liu et al. 2016). Polysaccharides extracted from the fruits of Physalis alkekengi L. are used as an adjuvant of a DNA vaccine (pD-HSP90C) which is composed of the recombinant plasmid of epitope C (LKVIRK) from heat shock protein 90 (HSP90) of *C. albicans* (Yang et al. 2014). The low molecular weight polysaccharides (LMW-ASP) isolated from the root of *Astragalus membranaceus* (Fisch) Bge. could enhance immune response of a recombinant protein (rP-HSP90C) vaccine containing epitope C (LKVIRK) of Hsp90. Studies have further shown that LMW-ASP promoted the levels of antibodies IgG, IgG1 and IgG2b and cytokines IL-2, IL-4, IL-10 and IL-12 in mice immunized with rP-HSP90C (Yang et al. 2016).

Immune response to *fungi*

Most opportunistic fungi are symbiotic with and tolerated by host when immunocompetent (Cassone and Cauda 2012). Once the host immune defense is compromised or suppressed, these commensal fungi have great opportunity to transform into aggressive pathogens attacking host organs and tissues (Del Poeta and Casadevall 2012). In-depth understanding of potential mechanisms by which the immune response to fungal infections is performed contributes to the design and application of specific fungal vaccine, and vice versa. Multiple factors including the recognition of immune cells, the site of infected tissues or organs, the morphology of fungi (yeast/mycelial state), the generation of fungal virulence factors, and the structural changes of cell wall affect the initiation, duration and strength of host immune reaction to fungi (Gross et al. 2006; Brunke et al. 2016). Mostly, innate immunity has to work together with adaptive immunity to remove invaded or overgrown fungi (Fig. 1).

Candida

The cell wall components of *Candida* spp., such as β-glucans, α-mannan, N-mannan, O-mannan, β-mannosides, can be recognized by a set of pattern recognition receptors (PRRs) including toll-like receptors (TLRs), C-type lectin receptors (CLRs), RIG I-like receptors (RLRs), NOD-like receptors (NLRs), complement receptors (CRs) and galectins (Zheng et al. 2015). One of the most well-studied CLRs Dectin-1 can recognize β-glucan which is a key constituent of *Candida* cell wall, followed by activation of multiple innate cells (macrophages, DCs, neutrophils) and clearance of fungi through oxidative stress, apoptosis, phagocytosis, extracellular traps, and antimicrobial peptides (Nikolakopoulou et al. 2020). During this process, Dectin-1 can cooperate with TLR2 and TLR4 to coordinate antifungal immune responses via spleen tyrosine kinase (Syk) dependent (Syk-CARD9/NLRP3) or independent (Raf-1) pathways and myeloid differentiation factor 88 (MyD88) associated NF-κB pathway (Jia et al. 2014; Luisa Gil et al. 2016). As the most powerful antigen presenting cell (APC), DC connects innate immunity with adaptive immunity, and efficiently presents the recognized antigen constituents of *Candida* to T cells. The stimulated IL-12 drives differentiation of naive T cells into $CD4^+$Th1 subpopulation which further produce IFN-γ to upregulate the expression of IL-12Rβ2. The upregulated IL-12Rβ2 conversely increase IL-12 sensitivity to promote Th1 cell differentiation, facilitating Th1 protective response to *Candida* infections (Tong and Tang 2017). Th17 cell is another crucial adaptive cells in the protection from *Candida* infections. The differentiation of Th17 is influenced by cytokines IL-17, IL-21, and IL-22. Individuals with dysfunctional Th17 cells are inclined to increased susceptibility to chronic mucocutaneous candidiasis (Huppler et al. 2012).

Aspergillus

The first line of host immunity against *Aspergillus* is the airway epithelium of upper respiratory tract containing mucus secreting cells and ciliated cells. The former generate mucus to capture inhaled conidia. The latter drive trapped conidia to the oropharyngeal junction. The airway epithelium of upper respiratory tract can also produce chitinase to destroy the cell wall chitin of *A. fumigatus* (van de Veerdonk et al. 2017; Garth et al. 2018). Alveolar macrophages (AMs) and neutrophils are the primary phagocytes to clear *Aspergillus*. AMs can produce pentraxin 3 and surface protein-D which immediately combine with inhaled conidia of *A. fumigatus* to trigger phagocytosis (Smole et al. 2020). AMs can also recognize and swallow conidia via TLR2/4 and Dectin-1 to elicit inflammatory cytokines and chemokines through NF-κB (Anthoney et al. 2018). Captured conidia by AMs can also recruit neutrophils by TNF-α and CXCL2 to the site of infection, enabling the formation of neutrophils extracellular trap (NET) and the production of lactoferrin which can inactivate conidia and mycelium in germination state (Guo et al. 2020). Immature DCs can also recognize and engulf conidia and mycelia via PRRs and present processed antigens to T cells, ultimately activating adaptive immune response to *Aspergillus* (Wang et al. 2017a).

Cryptococcus

Cryptococcosis is the most common cause of meningitis in HIV positive patients. The innate immunity to *Cryptococcus* mainly depends on phagocytic cells including macrophages, DCs and neutrophils (Voigt et al. 2014; Wang et al. 2022b). When *Cryptococcus* spp. are inhaled into the lung, they encounter diverse phagocytic effector cells and are engulfed through the recognitions of complement receptors (CRs, e.g. CR1, CR3, and CR4) and Fc receptors (Guerra et al. 2014; Sun and Shi 2016). The adaptive immune response to *Cryptococcus* mainly relies on T and B lymphocytes. $CD4^+$T cells play a dominant role in pulmonary *Cryptococcus* infections by releasing IL-17 (Guo et al. 2022). $CD8^+$T cells can kill *Cryptococcus* by granulysin (Ma et al. 2002). γδT cells (mostly $CD4^-CD8^-$T) secrete anti-inflammatory Th2 cytokines to balance the exaggerated Th1 response, thereby regulating the Th1-Th2 response to *Cryptococcus*. However, depletion of γδT cells can boost IFN-γ synthesis and *Cryptococcus* clearance

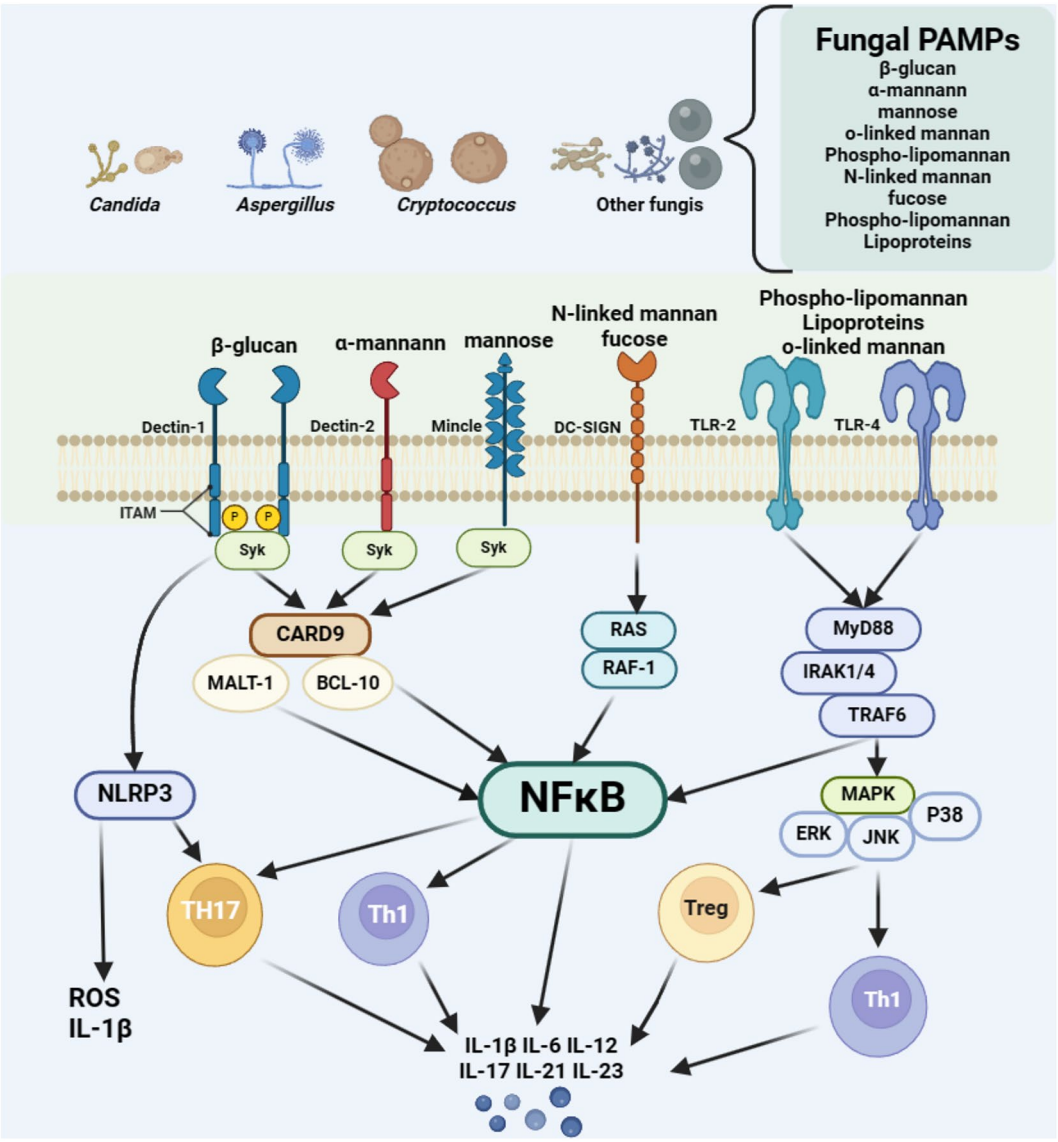

Fig. 1 Immune defense to Fungi. Fungal cell walls contain several pathogen-associated molecular patterns (PAMPs) that can be recognized by a group of pattern recognition receptors (PRRs). Activation of PRR induces a series of downstream events that contribute to the formation of antigen-specific adaptive immune responses. After identifying the fungal component, TLR (TLR-2, TLR2/6, TLR-4) activates the TIR domain, leading to stimulation of MyD88 or TRIF and downstream complexes (IRAK, TRAF, IKK) followed by translocation of NF-κB, IRF-3, MAPK and other transcription factors. CLRs such as Dectin-1, 2, and Mincle stimulate T cell lineage-specific tyrosine kinases (Syk) and downstream complexes (CARD9-BCL10-MALT1), and initiate the NF-κB signaling. DC-specific intracellular adhesion molecules grab non-integrin (DC-SIGN) receptors modulate NF-κB translocations through RAS and Raf1 activation pathways. These transcription factors drive the expression of various cytokines and regulate T cell differentiations. TLR: Toll like receptor; MyD88: Myeloid differentiation factor 88; IRAK1: Interleukin 1 receptor associated kinase 1; TRAF: Tumor necrosis factor receptor-associated factor; CLR: C-lectin receptor; Mincle: macrophage inducible Ca2+-dependent lectin receptor; SYK: Spleen tyrosine kinase; CARD9: caspase recruitment domain-containing protein 9; Malt1: mucosa-associated lymphoid tissue lymphoma translocation 1; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; MAPK: mitogen-activated protein kinase; ERK: Extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinase; NLRP3: NLR family pyrin domain containing 3

through Th1-mediated lung response (Uezu et al. 2004). Cryptococcal infections are lethal in mice deficient of B cells compared with those with normal B cells, which can be partly due to B-cell secreted IgM that can bind to *Cryptococcus*. Depletion of IgM secreted B cells ends up with declined AM phagocytosis and high-risk fungal transmission to brain (Rohatgi and Pirofski 2012). Moreover, B-cell defects are closely tied up with pulmonary immunopathology and inflammation in company with cryptococcal infections (Feldmesser et al. 2002).

Coccidioides

Coccidioidosis is characterized by primary respiratory infections. Occasional dissemination of *Coccidioides* spores can cause lesions in skin, lung, skeleton, liver, brain and lymph nodes. T-cell-mediated immunity is the most critical part of the immune response to *Coccidioides* (Cox and Magee 2004). It is reported that neutrophils are more effective in inhibiting arthroconidia than mature spherules, and pretreatment of macrophages with IFN-γ or TNF-α enhances the killing of arthroconidia in vitro (Castro-Lopez and Hung 2017). When the inhaled arthroconidia reach alveoli, they interact with DCs which migrate to local lymph nodes where the antigenic information is presented to and activate Naive T lymphocytes. Activated T cells migrate back to the lung infection loci, differentiate into antigen-specific $CD4^{+}$Th or $CD8^{+}$T cells and perform antifungal activity through secreting inflammatory cytokines and triggering granulomatous responses (Castro-Lopez and Hung 2017). It should be noted that Th1 and Th17 can synergistically enhance the recruitment of phagocytic cells to alveoli, ultimately promoting early reduction of *Coccidioides* load and inhibiting inflammatory pathology at the site of infection (Wüthrich et al. 2011b; Wang et al. 2014). It is believed that MyD88 and Card9 are the two pivotal intracellular immune adaptors for activating the protective Th17 response to *Coccidioides* infections (Hung et al. 2011, 2016).

Other *fungi*

There are several other opportunistic fungi that can cause diverse endemic fungal diseases. Paracocccidioidomycosis is a systemic fungal disease caused by the fungi *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii* (Santos et al. 2020). Blastomycosis, an endemic fungal infection by *Blastomyces*, can cause chronic pneumonia as the primary clinical manifestation, and occasionally trigger extrapulmonary infections involving skins and subcutaneous tissues, bones and joints, prostates and central nervous system (Mazi et al. 2021). *Histoplasmosis*, another common endemic fungal disease induced by *Histoplasma*, can cause severe acute pulmonary infections in immunocompromised patients (Azar and Hage 2017). Th1 and Th17-mediated immune responses are regarded as major effectors to protect the host from infections caused by these fungal pathogens (Wu et al. 2013b; Ketelut-Carneiro et al. 2019). In non-immunized host, Th17/IL-17 axis confers protection to primary infections through recruiting and activating neutrophils and macrophages to the site of infection in the company of producing a group of chemokines and pro-inflammatory cytokines. During this process, a cluster of well-known PRRs including Dectin-1, Dectin-2, TLR, mannose receptor (MR) and galactin-3 are responsible to recognize the pathogen associated molecular patterns (PAMPs) on the fungal cell wall (Wüthrich et al. 2011a; Ketelut-Carneiro et al. 2019), thereby stimulating a series of downstream events. Other than T cells, multiple effects of neutrophils include phagocytosis, oxidative and non-oxidative cytotoxicity mechanisms that kill intracellular and extracellular pathogens, the production of pro-inflammatory cytokines and chemokines, as well as the elicited neutrophil extracellular traps (NET) are also involved in the combat against these endemic fungal infections (Puerta-Arias et al. 2020).

Fungal vaccine/adjuvant-host interaction

The antigen used for fungal vaccine preparation is usually univalent. Although multivalent fungal vaccines which contain more than one unrelated antigen are of better choice to prevent fungal infections, the immune responses elicited by fungal vaccines are largely different from those by whole fungal cells. In addition, adjuvants can also trigger intense and distinctive immune responses (Fig. 2).

Innate immune response to fungal vaccine and adjuvant

During vaccination, the innate immune cells including macrophages, DCs, neutrophils are extensively activated to elicit multiple downstream events. A recent study showed that chitosan hydrogel (CH-HG) can act as an adjuvant to enhance the protection of a recombinant protein vaccine containing epitope C from *C. albicans* HSP90 (rP-HSP90C) against systemic candidiasis. The study found that CH-HG was not only effective to cross-present and internalize rP-HSP90C in BMDCs, but also recruit considerable macrophages and DCs in vivo post vaccination for 15 and 5 days (Li et al. 2021). Another study revealed that immunization of a recombinant protein mannosyltransferase 4 (rPmt4p) of *C. albicans* could generate IgG antibodies to reduce the fungal burden, alleviate kidney inflammation, and prolong the survival rate in a murine model of systemic candidiasis. The protective mechanisms of rPmt4p vaccine could be ascribed to the activation of macrophage opsonization and neutrophil killing of *C. albicans* (Wang et al. 2022a). It was believed that tyrosine phosphatase SHP-2 renders macrophages and neutrophils contributory to the early control of *C. albicans* infection via regulating CLR-induced activation of Syk (Deng et al. 2015). The mice vaccinated by a recombinant Pb27 protein (rPb27) from *P. brasiliensis* with CPG oligodeoxynucleotide motif as an adjuvant were spared from

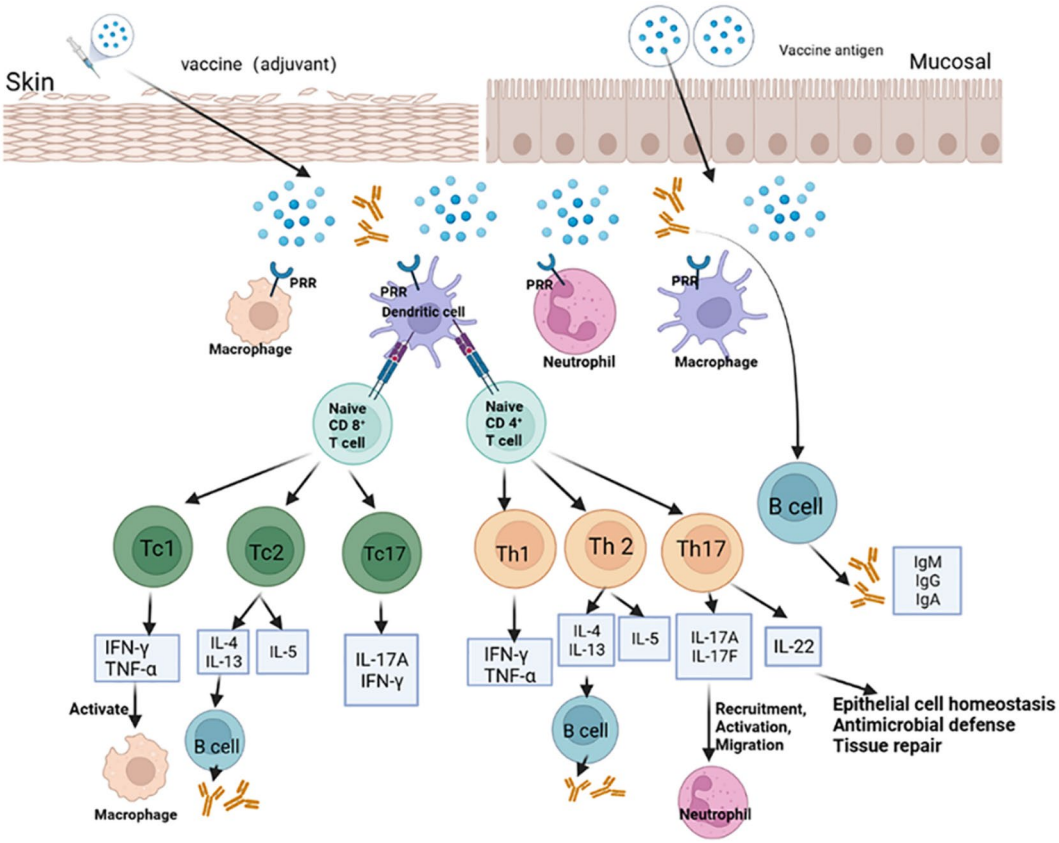

Fig. 2 Interactions between fungal vaccines (adjuvants) and host immune system. Fungal vaccines and adjuvants orally and subcutaneously enter into host and encounter at first the innate immune cells including macrophages, dendritic cells (DCs) and neutrophils. Recognizing vaccine epitopes by pattern recognition receptors (PRRs), the innate cells can be widely primed with the help of adjuvants. The antigen processing cells (APCs) like DC gain antigenic information and present to naïve $CD4^+$ and $CD8^+$ T cells. Subsequently, naïve $CD4^+$ T cells are activated and evolve into Th1, Th2 and Th17 cells, whereas $CD8^+$ T cells are stimulated and differentiate into Tc1, Tc2 and Tc17 subtypes. These responsive T cells trigger a variety of inflammatory cytokine release. For example, IL-4 and IL-13 produced by Th1 and Th2 cells facilitate B cells to produce IgM, IgG and IgA subtypes in the serum and mucosa. Th17 cell-produced IL-17A/F and IL-22 recruit and activate neutrophils and macrophages to the site of infection, thereby promoting epithelial homeostasis, tissue repair and fungal eradication. Tc1, Tc2 and Tc17 cells produce IFN-γ TNF-α, IL-4, IL-5, IL-13, IL-17A and IL23 to promote phagocytosis of macrophages, maturation of B cells and antibody release, as well as apoptosis, thereby enhancing fungal clearance

Paracoccidioidomycosis through a mechanism dependent on TLR-9 associated phagocytosis and microbicidal activity of macrophages (Morais et al. 2016). An avirulent vaccine *Coccidioides* strain NR-166 (Δcts2/Δard1/Δcts3) could influence the activation and polarization of macrophages and DCs in response to *C. posadasii* infection (Diep et al. 2021). Similar to immune memory established by adaptive immunity, the heat killed *C. neoformans* strain H99γ elicited an innate memory-like phenotype in macrophages that was maintained for at least 70 days, providing a pathogen-specific protection against secondary challenge of wild-type *C. neoformans* strain H99 in the absence of adaptive immune cells after immunization in mice. This study revealed that the secondary challenge triggered a rapid up-regulation of IFN-γ and STAT1 signaling pathways (Leopold Wager et al. 2018). Similarly, a sublingual vaccine V132 prepared from heat-inactivated *C. albicans* was able to induce innate trained immunity in combination with a polyvalent bacterial vaccine MV140 by promoting metabolic and epigenetic reprogramming in human DCs through activating mitogen-activated protein kinases (MAPK), nuclear factor-κB (NF-κB) and mammalian target of rapamycin (mTOR)-mediated signaling pathways in the prevention of recurrent urinary tract infections (RUTIs) (Martin-Cruz et al. 2020). As a main force in antifungal immunity, different DC subsets are considered to be target candidates in fungal vaccine design (Roy and Klein 2012). Intranasal immunization of a DC-vaccine (Ag2-DC) prepared by transfecting the primary BMDCs with a plasmid DNA encoding a protective epitope of *Coccidioides* called Antigen-2 or proline rich antigen (Ag2/PRA) contributes to significant retention of DCs and IFN-γ, IL-4 and IL-17 cytokine-secreting T cells in lungs (Awasthi et al. 2019).

Humoral immune response to fungal vaccine and adjuvant

When fungal vaccines in combination with adjuvants come into contact with antigen-reactive B cells, the humoral immune response will commence (Cyster and Allen 2019). Compared with complement system, collectins and antimicrobial peptides, B-mediated antibodies confer principal and indispensable protections to invasive candidiasis (Xin and Cutler 2011). The responses of antibody to diverse pathogenic fungi comprise neutralization of antigen, inhibition of pathogen adherence to host cells, opsonization, antibody-dependent cellular cytotoxicity (ADCC), complement activation, blockage of filament and biofilm formations, and immune regulation (Torosantucci et al. 2005; Shukla et al. 2021). Among the five antibody isotypes, IgG, IgM and IgA are the major protectors upon the stimulation of fungal vaccines. It is known that antibodies are useful in bloodstream infections, but fungal hematogenous dissemination seldom occurs in, for example, AIDS patients unless neutropenia is confronted. A recombinant DNA vaccine containing epitope C (LKVIRK) from HSP90 of *C. albicans* (pD-HSP90C) enhanced specific antibody titers IgG, IgG1, IgG2b assisted by a polysaccharide adjuvant isolated from the fruits of *Physalis alkekengi* L., significantly elongating the survival rate in a systemic candidiasis murine model (Yang et al. 2016). A study observed that vaccination with secreted aspartyl proteinase 2 protein (Sap2) from *C. parapsilosis* increased titers of Sap2-specific IgG and IgM antibodies, inhibited *C. tropicalis* biofilm formation, and enhanced neutrophil-mediated fungal killing in *C. tropicalis*-associated systemic candidiasis (Shukla and Rohatgi 2020). Recently, with a multi-kingdom antibody profiling (multiKAP) approach, a mechanism by which gut mycobiota modulates the human B cell expansion and CARD9-dependent induction of host-protective antifungal IgG was expounded (Doron et al. 2021). Although B cell-mediated antibody generation provides potent antifungal protection during vaccination, vaccine-induced antibodies are pivotal drivers to initiate and promote cellular response. For example, post immunization with *Pneumocystis*, the responses of IgG, IgM and IgA to *Pneumocystis* protein, β-glucan and chitosan/chitin are heavily dependent on $CD4^+$T cells (Rapaka et al. 2019). Due to a challenging fact that most individuals with high-risk of fungal infections are usually immunocompromised, normal vaccination is unable to elicit effective and lasting humoral immune response. As a result, direct injection/gavage of antibody is becoming a well-recognized passive immunotherapy for antifungal purpose. Monoclonal antibodies (MAbs) C7 (against *C. albicans* cell wall mannoprotein), A9 (against *A. fumigatus* cell wall glycoprotein), 18B7 (against *cryptococcal* capsular polysaccharide) and Mycograb (against *Candida* Hsp90 protein) were exploited to prevent and treat fungal infections (Chaturvedi et al. 2005; Larsen et al. 2005; Sevilla et al. 2006; Bugli et al. 2013). Recently, an antibody-like Dectin1-Fc(IgG)(s) from distinct subclasses (IgG2a and IgG2b) was devised and demonstrated to have a dose-dependent protections against fungal infections by *C. albicans* SC5314, *H. capsulatum* G217B and *C. neoformans* H99 (Ruiz Mendoza et al. 2022).

Cellular immune response to fungal vaccine and adjuvant

Vaccine/adjuvant-mediated $CD4^+$T responses

Of note, the pathogen-specific $CD4^+$T cells primarily induce Th1, Th2 and Th17 immune responses which become the major cellular defense during vaccination (Becattini et al. 2015). The three T subtypes have disparate cytokine profiles. It is known that IFN-γ and TNF-α are the signature cytokines for Th1, while IL-4, IL-5 and IL13 are characteristic factors for Th2, IL-17A, IL-17F and IL-22 are classical Th17 associated cytokines (Annunziato et al. 2015). It is well-accepted that Th1 cells can help B lymphocytes produce IgG2a isotype in mice and IgM, IgG, and IgA, but not IgE, in human. Both IL-4 and IL-13 can facilitate B cells to produce IgG1 and IgE in mice and the five classes of immunoglobulin in human. IL-17A and IL-17F can target either immune or nonimmune cell types and play a key role in the recruitment, activation, and migration of neutrophils, while IL-22 can promote epithelial cell homeostasis, antimicrobial defense and tissue repair (Annunziato et al. 2015). Multiple types of fungal vaccines are competent to arouse Th1, Th2 and Th17 responses and alter Th1/Th2 and Th1/Th17 ratios in the treatment of systemic candidiasis (Spellberg et al. 2006; Li et al. 2021), invasive cryptococcosis (Masso-Silva et al. 2018), and aspergillosis (Clemons et al. 2014a). It is noteworthy that the cellular immune response to these vaccines is usually characterized by increased Th1 and Th17 responses together with diminished Th2 reaction (Masso-Silva et al. 2018). An immunoproteomic study further indicated that Th2-related antigens represent hopeful candidates for the design of immunotherapy regimens, whereas Th1-related antigens may serve as alterative option for vaccine device (Firacative et al. 2018). The vaccine-motivated Th1/Th2 differentiation might partly attribute to oxidized/reduced mannan derived from fungal cell walls which could activate DCs to stimulate the polarization of Th1 and Th2. It appeared that oxidized mannan could stimulate Th1 responses via phosphorylated p38 dependent IL-12p70 production, while reduced mannan instructed a Th2 bias via phosphorylated ERK dependent IL-10 and

IL-4 (Tong et al. 2016). It is well-recognized that Th17 responses provide protection against cutaneous fungal infections, while Th1 responses offer protection against systemic fungal infections (Kashem et al. 2015; Shukla and Rohatgi 2020). The protective features of Th1 and Th17 are corroborated in vaccinations against diverse pathogenic fungi (Specht et al. 2015; Ueno et al. 2019; Li et al. 2021; Wang et al. 2023). Consistently, the fungal vaccines/adjuvants also skew Th1/Th2/Th17 polarization against diverse endemic fungi. For example, a subunit vaccine by encapsulating a recombinant coccidioidal antigen (rCpa1) in *Rhodotorula mucilaginosa* yeast-derived glucan-chitin particles (GCPs) could stimulate a robust Th17 immunity to confer protection against pulmonary coccidioidomycosis in mice caused by *Coccidioides posadasii* through a mechanism requiring activation of CARD9-associated Dectin-1 and Dectin-2 signal pathways (Campuzano et al. 2020). The mice vaccine made from *Sporothrix schenckii* cell wall proteins (ssCWP) and the adjuvant Montanide™ Pet Gel A (PGA) stimulated a preferential Th1/Th2 profile, promoting *S. schenckii* yeast to be phagocytosed (Portuondo et al. 2017). The combined use of a pan-fungal vaccine calnexin and the conjugates of glycoprotein *Blastomyces* Eng2 (Bl-Eng2) and Dectin-2 as the adjuvant could augment activation of immune effectors to kill fungi and safeguard mice from lethal fungal challenge by *B. dermatitidis* (Wang et al. 2017b).

Vaccine/adjuvant-mediated CD8$^+$T responses

CD8$^+$T cells are mostly referred to cytotoxic T or Tc cells which mainly consist of three subtypes, i.e. Tc1, Tc2 and Tc17 (Annunziato et al. 2015). The representative cytokines produced by Tc1 cells are IFN-γ and TNF-α, while those by Tc2 include IL-4, IL-5, IL-13 without IFN-γ (Annunziato et al. 2015). Although CD8$^+$T cells target intracellular pathogens and provide protections in diverse inflammations and autoimmune diseases (allergy and asthma), several fungal vaccines/adjuvants can evoke a skewed CD8$^+$T responses. A previous study showed that co-immunization with rP-HSP90C and CH-HG provoked a stronger CD8$^+$T responses than rP-HSP90C alone in a systemic candidiasis (Li et al. 2021). Although depletion of CD8$^+$T or CD4$^+$T cells did not affect the protection from a *C. neoformans* mutant (Δsgl1) vaccine, the immune protection was completely lost once both CD8$^+$T and CD4$^+$T cells were exhausted (Normile et al. 2021). It appears that CD4$^+$T cells can help elicit CD8$^+$T-cell responses upon viral and bacterial infections. However, there may have distinct intracellular pathways for the priming of CD4$^+$ and CD8$^+$T responses to *A. fumigatus* (De Luca et al. 2012). It was assumed that TLR3 was an essential receptor to sense fungal RNA by cross-presenting DCs, promoting antifungal memory CD8$^+$T responses to aspergillosis in high-risk patients (Carvalho et al. 2012). Tc17 cells, a unique subgroup of IL-17-producing CD8$^+$T cells, are found to be an essential player in systemic autoimmune pathology, such as experimental autoimmune encephalomyelitis (EAE), due to its in vivo plasticity (Liang et al. 2015). Several documents demonstrated the protective role of Tc17 cells elicited by HBV DNA vaccination (pcD-S2) and *Mycobacterium* vaccine therapy (Wu et al. 2013a; Kannan et al. 2020). Recently, a study revealed that vaccine-induced Tc17 cells could persist and confer resistance against *B. dermatitidis* and *H. capsulatum*, and are indispensable in vaccine immunity against lethal fungal pneumonia in CD4$^+$T cell-deficient hosts (Nanjappa et al. 2012). In contrast to largely normal IFN-γ$^+$ CD8$^+$T cell (Tc1) responses, sustaining the proliferation of Tc17 cells requires the activation of intrinsic MyD88-Akt1-mTOR signaling during vaccine immunity against fungal pneumonia caused by *B. dermatitidis* (Nanjappa et al. 2015). Due to high levels of basal homeostatic proliferation and low levels of anti-apoptotic molecules Bcl-2 and Bcl-xL, vaccine-induced antifungal Tc17 cells are durable and stable with long-lasting memory without plasticity towards IFNγ-producing Tc1 cells (Nanjappa et al. 2017). Intriguingly, vaccine-induced GM-CSF$^+$ Tc17 cells, a lineage more like Tc17 cells than IFN-γ-producing Tc1 cells, are instrumental to prevent pulmonary fungal infection caused by *B. dermatitidis* without inflamed pathology. During the vaccination, IL-23 is dispensable for memory GM-CSF$^+$ Tc17 cell maintenance and recall responses (Mudalagiriyappa et al. 2022). Given that evidence available focuses on the functionality of CD8$^+$T responses to a limited fungal vaccines mainly from *Aspergillus* and *Blastomyces*, extra efforts are warranted to decipher the underlying mechanisms of CD8$^+$T responses to other commonly encountered fungal vaccines.

Perspective

Over the past few decades, we have achieved a great progression toward understanding of host immune responses to opportunistic fungi in multiple context of fungal infections, providing useful thoughts for design of novel fungal vaccines and associated adjuvants. Yet, there is no successful fungal vaccines approved for clinically purposes. Considering extremely low immune-competence of at-risk patients with fungal infections, it is a challenging task for fungal vaccines and adjuvants available to induce safe and sufficient immune reactions to eradicate overgrown fungi at no expense of immune system breakdown by such as cytokine release syndrome (CRS). It is important to notice that most antibody vaccines may be useful in mouse intravenous infection models. However, in patients with AIDS there may be a lot of fungi attached to the mucosal surface, but if the patient is not neutropenic, it is difficult for antibody

vaccines to encounter the spread fungus via bloodstream. Although a promising approach to combining the vaccine with a cytokine or cytokines known to enhance the immune system can enhance the safety and efficacy of fungal vaccines, a thorough understanding of the interaction between fungi and host immune defense is a prerequisite which still require more efforts in animal and even pre-clinical tests. Nevertheless, it is still worth looking forward to several emerging potential technologies and platforms for designing fungal vaccines and adjuvants. These promising candidates include adoptive T-cell therapy, chimeric antigen receptor (CAR) T-cell therapy, fungal extracellular vesicles-mediated vaccines, as well as mRNA vaccines (Tso et al. 2018; Rivera et al. 2022; Loh and Lam 2023). Of note, consistent with long-lasting protective memory responses by adaptive immune cells, innate immune memory known as "trained immunity" can also be strongly elicited by non-fungal components, such as Bacillus Calmette-Guerin (BCG), offering a possibility to be used for the design of fungal vaccines and adjuvants to generate cross-species protection (Yang et al. 2016). As a result, in-depth exploration of the interaction between fungal vaccines (adjuvants) and host immune system will benefit for understanding the host immune response to opportunistic fungi, which in reverse, accelerates the development of universal and effective fungal vaccines and adjuvants with trans-species protections.

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