

Immunity against fungi

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Pathogenic fungi cause a wide range of syndromes in immune-competent and immune-compromised individuals, with life-threatening disease primarily seen in humans with HIV/AIDS and in patients receiving immunosuppressive therapies for cancer, autoimmunity, and end-organ failure. The discovery that specific primary immune deficiencies manifest with fungal infections and the development of animal models of mucosal and invasive mycoses have facilitated insight into fungus-specific recognition, signaling, effector pathways, and adaptive immune responses. Progress in deciphering the molecular and cellular basis of immunity against fungi is guiding preclinical studies into vaccine and immune reconstitution strategies for vulnerable patient groups. Furthermore, recent work has begun to address the role of endogenous fungal communities in human health and disease. In this review, we summarize a contemporary understanding of protective immunity against fungi.

Introduction

Humans are exposed to fungi throughout life via inhalation, digestion, and/or traumatic inoculation of fungal particles. The vast majority of these encounters are asymptomatic, and less than 100 of the estimated 5 million fungi species are associated with human disease (1) (Table 1 and Figure 1). Fungi can either exist as spherical yeast cells (e.g., *Cryptococcus neoformans*) or as molds that form branching tubular hyphae (e.g., *Aspergillus fumigatus*). Dimorphic fungi (e.g., *Histoplasma capsulatum*) grow as molds in the environment and yeasts in human tissue. *Candida albicans* grows as yeast cells and pseudohyphae, a hyphal form with tapered ends, in human tissue; this morphologic switch is essential for virulence (2).

Fungi were recognized to cause disease during investigations into the scalp dermatophyte infection favus, which was widespread in 19th century Europe (3). German physiologist Robert Remak (1815–1865) immersed favus skin samples in acetic acid and observed fungal hyphae and conidia (named *Trichophyton schönleinii* in honor of Johann Schönlein, Remak's mentor). In 1842, Remak injected favus crust-isolated material into his forearm and noted growth in the lesions, thereby establishing causality between the fungus and disease.

Several events, including the advent of myeloablative chemotherapy for neoplasia, glucocorticoids and immune modulators for autoimmunity, transplantation for end-organ failure, and the AIDS pandemic, contributed to the emergence of fungal infections in the second half of the 20th century. Novel pathogenic fungi that pose a threat to humans (e.g., *Cryptococcus gattii*), amphibians (e.g., *Batrachochytrium dendrobatidis*), and bats (e.g., *Pseudogymnoascus destructans*) have also been identified (4). In response, research in fungal pathogenesis and antifungal immunity has intensified to inform vaccine- and therapy-based approaches for mycoses (5). This review focuses on insights gained from animal models and patients with primary immune deficiency disorders (PIDDs), but does not cover allergenic or toxin-mediated fungal disease (6, 7).

Antifungal immunity from the bench: contribution of animal models

This section focuses on antifungal immunity to different yeasts, molds, and dimorphic fungi. Contemporary animal models of fungal infection are reviewed elsewhere (8).

Fungal recognition and immune activation. The fungal cell wall contains polysaccharide and lipid moieties that activate immune responses (9) (Table 2). The cell wall is exterior to the plasma membrane and arranged in layers: the innermost layer typically consists of chitin, an *N*-acetylglucosamine polymer; the adjacent external layer is formed by immunoreactive β -(1,3) and β -(1,6) glucans, which are concealed by

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many fungi. *H. capsulatum* employs an α -glucan layer and the action of a glucanase (9–11). *A. fumigatus* resting conidia utilize a proteinaceous hydrophobin layer (12), while the hyphal cell wall layer contains galactomannan and galactosaminogalactan, the latter of which conceals inflammatory β -glucan (13, 14). The *C. albicans* outer cell wall consists of glycoproteins that incorporate *N*- and *O*-linked mannans and induces inflammatory responses via the mannose receptor and TLR-4 (15). *C. albicans* mannans conceal β -glucans as well; the latter are exposed on bud and birth scars during yeast cell division (9). The *C. neoformans* capsule covers the chitinous and β -glucan-rich cell wall layers and largely consists of glucuronoxylomannan and galactoxylomannan (16). Previously published reviews provide in-depth discussion of fungal cell wall architecture (9, 16–18).

At portals of entry fungal cells encounter and bind to antibodies, complement, and soluble pattern recognition receptors. Collectively, these interactions facilitate signaling responses by membrane-bound receptors and the induction of antifungal effector mechanisms (5, 9). In the lung, the collectin pentraxin-3 (PTX3) binds to *A. fumigatus* conidial galactomannan (19) and facilitates complement deposition and CD32-dependent conidial uptake by neutrophils (20). *Ptx3*^{-/-} mice are susceptible to respiratory *A. fumigatus* challenge (19), and a *PTX3* polymorphism enhances the vulnerability of hematopoietic cell transplant recipients to invasive aspergillosis (21).

The C-type lectin receptor (CLR) dectin-1 (encoded by *Clec7a*) binds β -glucans from a variety of fungi, including those on *C. albicans* bud scars and germinating *A. fumigatus* conidia, and activates signaling responses to *Pneumocystis jirovecii*, *H. capsulatum*, *Coccidioides posadasii*, and *Paracoccidioides brasiliensis* (5, 9, 22–24) (Figure 2). β -Glucan binding displaces regulatory phosphatases CD45 and CD148 (25), induces SRC-dependent phosphorylation of the intracellular ITAM-like motif, and recruits the SHP-2 phosphatase (26). SYK docks to this scaffold and transduces signals via PKC- δ (27) and the VAV family of GEFs (28) to CARD9, which complexes with BCL10 and MALT1 (29) to activate the canonical NF- κ B subunits p65 and c-REL (30). Dectin-1 signaling also modulates the noncanonical NF- κ B subunit RELB through RAF-1-dependent phosphorylation and deacetylation (31). In macrophages and dendritic cells (DCs), the CARD9/BCL10/MALT1 complex directs *Iilb* transcription and caspase-1- and caspase-8-dependent IL-1 β release (32, 33), in part via the activity of NLRP3- and AIM2-containing inflammasomes (34). Rubicon can disrupt signal transduction and NF- κ B activation via the CARD9/BCL10/MALT1 complex (35). Dectin-1/SYK/CARD9-dependent cytokines, such as TNF, CXCL2, IL-6, IL-23, and IL-1 β , promote innate immune activation and Th17 differentiation (36). In addition, dectin-1/SYK signaling in DCs induces IFN- β production via IRF5 (37). The role of type I IFN signaling in defense against candidiasis remains controversial, with both protective (37) and detrimental (38) phenotypes reported.

Dectin-1 signaling regulates ERK (also known as MAP kinase) activity via H-RAS and RAS guanine nucleotide-releasing factor 1 (RASGRF1) (39). This pathway regulates macrophage IL-6, IL-1 β , and TNF, but not IL-12 responses, and is protective during systemic candidiasis (39). c-JUN kinase isoform 1-deficient (JNK1-deficient) mice are resistant to systemic candidiasis (40). Dectin-1-induced JNK1 signaling negatively regulates CD23 (encoded by *Fcer2*) expression via nuclear factor of activated T cells (NFAT) activation. CD23 binds α -mannans and β -glucans and induces the antifungal effector NOS2. Consistent with this model, *Cd23*^{-/-} mice are susceptible to systemic candidiasis (40).

In otherwise nonphagocytic cells, dectin-1 expression promotes phagocytosis of nonopsonized β -glucan particles (5, 9). Bruton's tyrosine kinase (BTK) and VAV-1 interact with dectin-1 in macrophages during *C. albicans* phagocytosis, a process impaired by genetic loss of either protein (41). Dectin-1/SYK/CARD9 signaling in NADPH oxidase activity is controversial, as dectin-1-dependent (24) and -independent (42) control of β 2 integrin (CD18) activation and the respiratory burst have been reported in vitro. Murine *Clec7a*^{-/-} and *Card9*^{-/-} neutrophils display no cell-intrinsic defect in killing *A. fumigatus* conidia, unlike *p47phox*^{-/-} neutrophils (43). These data can be reconciled if the major role of dectin-1/CARD9 is to modulate NADPH oxidase and fungal killing via soluble mediators, rather than by cell-intrinsic activation. β 2 integrins and TLR signaling can collaborate with dectin-1 to mount macrophage inflammatory responses to *H. capsulatum* and other fungi (44, 45).

Dectin-2 (encoded by *Clec4n*) forms a complex with dectin-3 (encoded by *Clec4d*) to bind *Candida* α -mannans (46, 47) or with mincle (encoded by *Clec4e*) to bind *Malassezia* glycolipids (48). *Blastomyces dermatitidis*, *H. capsulatum*, *C. posadasii*, and *A. fumigatus* induce dectin-2 signaling (43, 49). As these CLRs lack a signaling domain, heterodimeric complexes signal via the ITAM-coupled adaptor FcR γ (9).

Table 1. Common human fungal diseases and associated PIDDs

Mycosis Fungal species Most common genera	Morphotype	Clinical Syndromes	Genes (syndromes) linked to enhanced susceptibility ^A
Aspergillosis <i>Aspergillus</i> spp., <i>A. fumigatus</i> , <i>A. flavus</i> , <i>A. niger</i> , <i>A. terreus</i> , <i>A. nidulans</i> (in CGD)	Mold	Pneumonia and systemic disease in immune-compromised hosts; allergic disease (e.g., ABPA) in atopic hosts; cavitary disease in setting of structural lung disease; deep tissue organ disease (e.g., brain abscess, osteomyelitis) in CGD and <i>CARD9</i> -deficient patients	NADPH oxidase (CGD); <i>STAT3</i> (HIES); <i>CARD9</i> (extrapulmonary aspergillosis); <i>GATA2</i> (MonoMAC syndrome); <i>CD18</i> (LAD); <i>ELA2</i> , <i>HAX1</i> (SCN)
Mucormycosis <i>Rhizopus</i> , <i>Mucor</i> and <i>Rhizomucor</i> spp.	Mold	Pneumonia, sinus, and systemic disease in immune-compromised hosts and in diabetic ketoacidosis	
Fusariosis <i>Fusarium oxysporum</i> and <i>F. solani</i>	Mold	Pneumonia, cutaneous, bloodstream, and systemic disease in immune-compromised hosts; fungal keratitis	NADPH oxidase (CGD), <i>STAT1</i> GOF mutations
Dermatophytosis <i>Epidermophyton</i> , <i>Trichophyton</i> , <i>Microsporum</i> spp.	Mold	Skin and nail infections (i.e., keratinized tissues), e.g., tinea pedis (athlete's foot), ringworm	NADPH oxidase (CGD); <i>CARD9</i> (deep tissue infections)
Sporotrichosis <i>Sporothrix schenckii</i>	Dimorph	Lymphocutaneous disease, ascending lymphangitis	NADPH oxidase (CGD)
Blastomycosis <i>Blastomyces dermatitidis</i>	Dimorph	Pneumonia; skin, mucosal, skeletal, and genitourinary disease	<i>GATA2</i> (MonoMAC syndrome)
Histoplasmosis <i>H. capsulatum</i> (North America), <i>H. duboisii</i> (Africa)	Dimorph (intracellular in macrophages)	Pneumonia, mediastinal granuloma and fibrosis, disseminated histoplasmosis	<i>IL12RB1</i> ; <i>IFNGR1</i> ; <i>STAT1</i> GOF mutations; <i>STAT3</i> (HIES); <i>UNC119</i> , <i>MAGT1</i> , <i>RAG1</i> (idiopathic CD4 lymphopenia); <i>DOCK8</i> (HIES); CD40 ligand
Coccidioidomycosis <i>C. immitis</i> , <i>C. posadasii</i>	Dimorph	Pneumonia, skeletal disease, meningitis	<i>IL12RB1</i> ; <i>IFNGR1</i> ; <i>STAT1</i> GOF mutations; <i>STAT3</i> (HIES)
Paracoccidioidomycosis <i>P. brasiliensis</i>	Dimorph	Pneumonia; skin, mucosal, and skeletal disease	<i>IL12RB1</i>
Penicilliosis <i>Talaromyces marneffei</i>	Dimorph	Pulmonary, skin, mucosal, and disseminated disease	
Pneumocystosis <i>P. jirovecii</i>	Trophozoites (asexual) and cysts (sexual)	Pneumonia; common AIDS-defining illness	CD40 ligand, >30 genes that underlie SCID; MHC class II deficiency; <i>NEMO</i> ; <i>DOCK8</i> (HIES); <i>CARD11</i> ; Wiskott-Aldrich syndrome
Candidiasis <i>C. albicans</i> , <i>C. tropicalis</i> , <i>C. glabrata</i> , <i>C. krusei</i> , <i>C. parapsilosis</i> , <i>C. auris</i>	Dimorph Yeast	Thrush, vulvovaginitis; bloodstream and systemic infections in immune-compromised patients; AIDS-defining illness; deep tissue single organ disease (e.g., kidney or brain abscess, osteomyelitis) in CGD and other PIDDs; deep tissue disease uncommon in syndromes associated with CMC with the exception of <i>CARD9</i> deficiency	CMC: <i>IL17F</i> ; <i>IL17RA</i> ; <i>IL17RC</i> ; <i>ACT1</i> ; <i>STK4</i> ; <i>IRF8</i> ; <i>CARD9</i> ; <i>STAT1</i> GOF mutations; <i>STAT3</i> (HIES); <i>RORC</i> ; <i>AIRE</i> ; anti-IL-17 autoantibodies (thymoma) <u>CNS disease</u> : <i>CARD9</i> <u>Invasive and deep tissue disease</u> : <i>ELA2</i> , <i>HAX1</i> (SCN), CGD, complete MPO deficiency
Cryptococcosis <i>C. neoformans</i> , <i>C. gattii</i>	Yeast (pigmented, encapsulated)	Pneumonia, meningitis; AIDS-defining illness	Anti-GM-CSF or -IFN- γ antibodies; CD40 ligand; <i>GATA2</i> ; <i>IL12R</i> ; <i>STAT3</i> (HIES)
Chromoblastomycosis <i>Fonsecaea pedrosii</i> , and others	Yeast (pigmented)	Chronic infection of cutaneous and subcutaneous tissues	
Eumycetoma <i>Scedosporium</i> spp., <i>Madurella</i> spp., and others	Molds (pale or dark grains)	Chronic infection of cutaneous and subcutaneous tissues; <i>Scedosporium</i> spp. associated with bloodstream, pulmonary and CNS disease in immune-compromised hosts	

^AWe did not discuss all listed gene defects associated with mycoses in the text. The reader is referred to references 64 and 65 for a more comprehensive discussion and additional links to the primary literature. ABPA, allergic bronchopulmonary aspergillosis; *CARD9*, caspase recruitment domain-containing protein 9; CMC, chronic mucocutaneous candidiasis; CGD, chronic granulomatous disease; CNS, central nervous system; *DOCK8*, dedicator of cytokinesis 8; GM-CSF, granulocyte-macrophage colony-stimulating factor; *GATA2*, GATA-binding protein 2; GOF, gain of function; HIES, hyper-IgE syndrome; LAD, leukocyte adhesion deficiency; *NEMO*, NF- κ B essential modulator; PIDDs, primary immune deficiency disorders; SCID, severe combined immunodeficiency; SCN; severe combined neutropenia; *STAT*, signal transducer and activator of transcription.

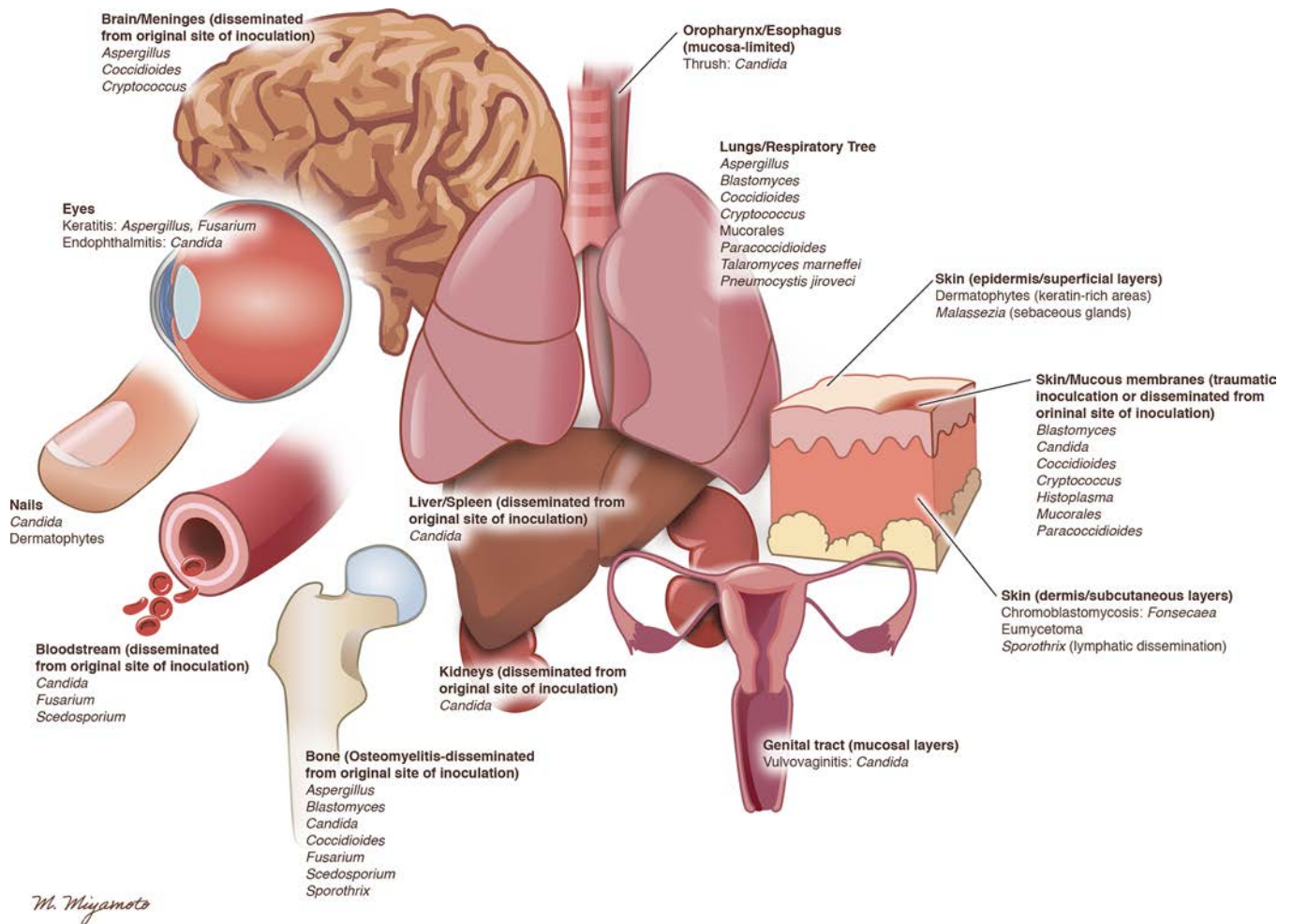


Figure 1. Human fungal diseases. The figure depicts the anatomic sites that are most commonly affected by the fungal genera listed below each organ system. At several sites, fungal disease occurs due to inoculation at the site. For example, humans inhale infectious conidia or desiccated fungal cells of all genera listed under lungs and respiratory tree. For other sites, such as the liver, spleen, and blood stream, disease is the result of dissemination of the indicated fungus from the initial inoculation site. Illustrated by Mao Miyamoto.

Following fungal recognition, the E3 ubiquitin ligase CBLB ubiquitinates dectin-1, dectin-2, and SYK, targeting them for degradation (50–52). In systemic candidiasis, *Cblb*^{-/-} mice exhibit reduced renal fungal burden and improved survival due to decreased inflammation-driven tissue damage (50–52). In contrast, TRIM62-mediated CARD9 ubiquitination is essential for BCL10 interactions, NF- κ B activation, and defense against candidiasis (53).

Mincle/SYK/CARD9 signaling mediates responses to *Fonsecaea pedrosii*, an agent of chromoblastomycosis (54). Mincle-induced cytokines are insufficient to clear this soft tissue infection, and application of TLR-7 agonist imiquinod to fungal lesions can restore sterilizing immunity (55). In DCs, mincle signaling activates the E3 ubiquitin ligase MDM2, in turn suppressing dectin-1- and IRF1-dependent *Ii12a* transcription (56). This MDM2-dependent pathway impairs Th1 responses and may contribute to the chronicity of chromoblastomycosis. During murine pneumocystosis and candidiasis, mincle signaling enhances fungal clearance but is dispensable for survival (57, 58).

Loss of individual CLR results in variable susceptibility to *C. albicans* (22, 23) and *A. fumigatus* (24, 43), in part due to strain-specific differences in CLR activation, as shown for *C. albicans* (59). Consistent with SYK/CARD9 being central for CLR signal integration, mice with hematopoietic or DC-specific *Syk* deletion or with global CARD9 deficiency are highly susceptible to *C. albicans* (29, 60) and *A. fumigatus* (43) challenge. CARD9/SYK-dependent susceptibility maps to defective cytokine responses that control neutrophil, NK, and T cell trafficking or activation. During systemic candidiasis, DCs secrete IL-23 in a SYK-dependent manner, prompting IL-17A-dependent (hereafter referred to as IL-17) NK

Table 2. Mammalian signaling receptors and cognate fungal ligands and species

C-type lectin receptors:	Fungal ligand	Fungal species ^A	References ^B
Dectin-1 (<i>Clec7a</i>)	β -Glucans	AF, CA, CP, ER, HC, PB, PC	(23, 24, 44, 49, 59, 184)
Dectin-2 (<i>Clec4n</i>)	α -Mannans, O-linked mannoproteins	AF, BD, CA, CP, CG	(48, 49, 97, 185)
Dectin-3 (CLECSF8, MCL, <i>Clec4d</i>) ^C	α -Mannans	CA	(47, 186)
Mincle (<i>Clec4e</i>)	α -Mannosyl residues, glyceroglycolipids	CA, FP, MS, PC	(48, 54, 58)
CD209 (DC-SIGN)	Galactomannan, mannans	AF, CA	(187)
Mannose Receptor	N-linked mannans, mannans	CA, PC	(15, 188)
Toll-like receptors:			
TLR-2	α -(1,4)-Glucans	CA	(189)
TLR-1 and TLR-2	Glucuronoxylomannans	CN	(190)
TLR-2-TLR-6	Phospholipomannans, glucuronoxylomannans	CA CN	(191)
TLR-4	O-linked mannans, rhamnomannans	CA, SA	(15, 189, 192)
TLR-9	Unmethylated DNA	AF, CA	(63)
NOD-like receptors:			
NOD1	Unknown	AF	(193)
NOD2	Chitin (?)	CA	(194)
NLRC4	Unknown	CA	(195)
NLRP3	Unknown	AF, CA	(34, 196)
Other receptors:			
CD14	α -(1,4)-Glucans	SA	(197)
CD23 (<i>Fcϵ2a</i>)	α -Mannan, β -glucan	CA	(40)
CD36		CN, CA	(198)
CR3 (integrin α_2/β_M ; CD11b/CD18; Mac-1)	β -Glucan	AF, CA, HC	(42, 44, 45, 72, 73)
Galectin-3	β -Mannosides	CA	(199)
Lactosylceramide (glycosphingolipid)		PC	(200)
Pentraxin-3 (soluble)	Galactomannan	AF	(19, 62)

^ARole in murine survival or fungal clearance. ^BThe references focus on manuscripts that demonstrate in vivo roles for receptors in murine survival or fungal clearance; additional references to the primary literature can be found in references 5 and 9. ^CDectin-3 can form heterodimeric complexes with dectin-2 or with mincle. AF, *Aspergillus fumigatus*; BD, *Blastomyces dermatitidis*; CA, *Candida albicans*; CG, *Candida glabrata*; CN, *Cryptococcus neoformans*; CP, *Coccidioides posadasii*; ER, *Exserohilum rostratum*; FP, *Fonsecaea pedroisii*; HC, *Histoplasma capsulatum*; MS, *Malassezia* spp.; PB, *Paracoccidioides brasiliensis*; PC, *Pneumocystis carinii* from *sp. muris*; SA, *Scedosporium apiospermium*.

cell release of GM-CSF, thereby activating candidacidal neutrophils at infection sites (60, 61).

CLR-independent pathways also mediate fungus-induced inflammation. Fungal ligands activate TLR1–4, TLR-6, TLR-9, and NOD2 signaling in a variety of cell types (5, 9). For example, PTX3-opsonized *A. fumigatus* conidia activate TLR-4/MD-2/TRIF-dependent signaling that mediates IL-10 production (62). Following internalization, *A. fumigatus* conidia trigger macrophage TLR-9-, calcineurin-, and BTK-dependent TNF release (63); however, humans with NLR or TLR/MyD88 signaling defects do not manifest with fungal infections (64, 65). A detailed discussion of Mendelian defects that do manifest with fungal infections follows later in this review.

Fungal killing. Neutrophils rapidly internalize conidia and/or yeast cells and direct the production of ROS to the fungal phagosome (66). In macrophages, NADPH oxidase-dependent LC3-associated phagocytosis represents a potential clearance mechanism for *A. fumigatus* conidia (67, 68). Nutritional immunity, exemplified by zinc and iron sequestration, is critical for macrophage defense against intracellular *H. capsulatum* yeast cells (69), against fungal keratitis (70), and in chronic granulomatous disease (CGD) patients with defects in NADPH oxidase (71–73).

Fungal hyphae (*A. fumigatus*) and pseudohyphae (*C. albicans*) induce NADPH oxidase-dependent neutrophil extracellular trap (NET) formation (74), a form of neutrophil programmed cell death termed NETosis. NETs contain extracellular nucleic acids, histones, and granular proteins, including calprotectin and PTX3 (75, 76), and ensnare fungal organisms that are too large for phagolysosomal killing (74). Neutrophil calprotectin, a major NET component, is important for antihyphal host defense during murine *A. fumigatus* keratitis yet dispensable for anticonidial defense following respiratory *A. fumigatus* challenge (77), illustrating a fungal

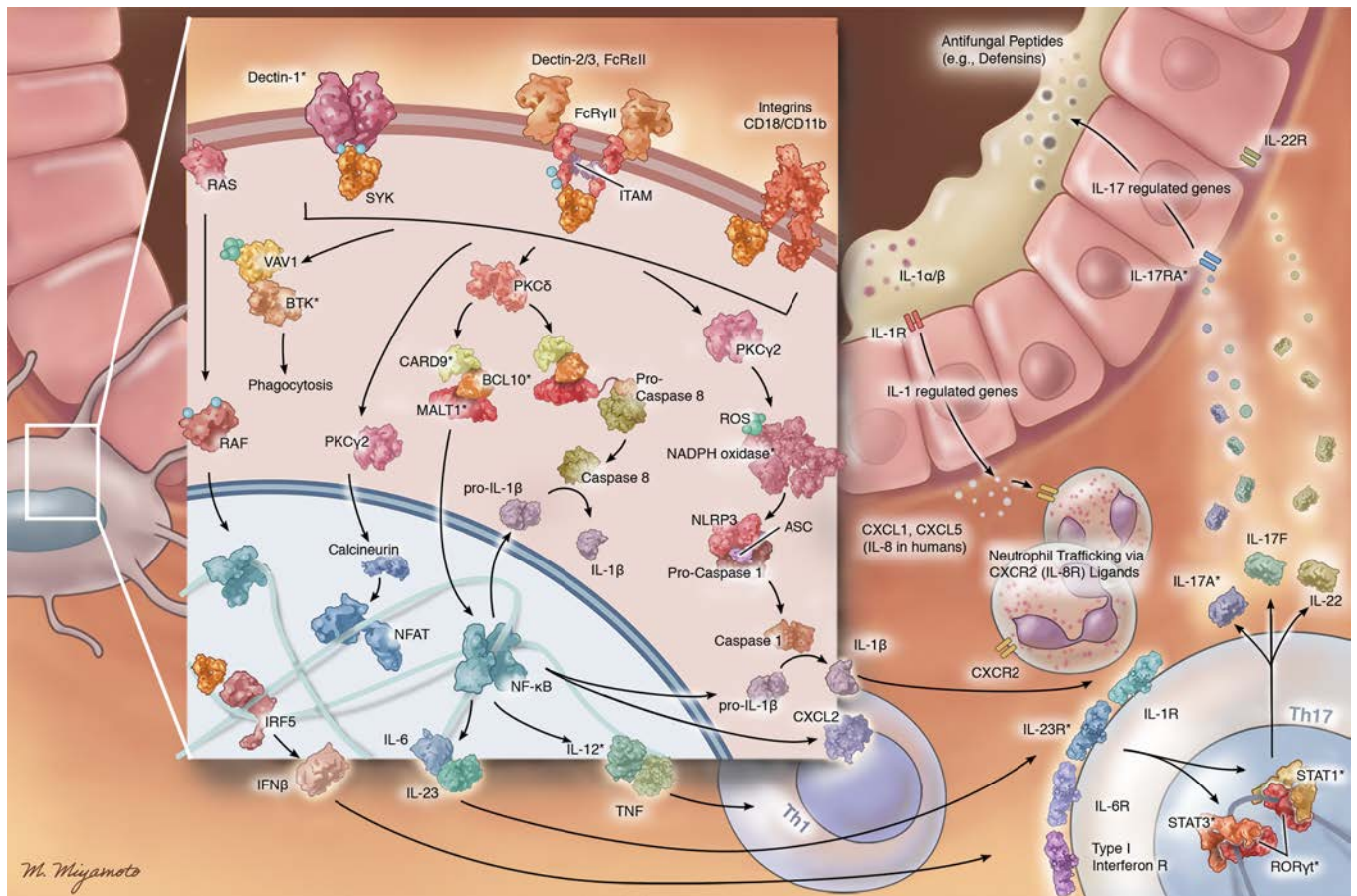


Figure 2. Model of fungus-induced CLR signaling in antifungal defense. At the site of inoculation, particulate fungal polysaccharides bind C-type lectin receptors (CLRs) and Fc receptors (FcRs), resulting in SYK activation via ITAM signaling in the receptor tail, the Fc γ signaling adaptor, or integrin receptor activation. The ensuing PKC δ and CARD9 activation is critical for caspase-1 and caspase-8 activity, MAP kinase signaling (not shown), NF- κ B activation, and cytokine production. SYK-dependent PLC γ 2 activation is linked to NADPH oxidase assembly and calcineurin-dependent NFAT activation. Dectin/SYK signaling controls IRF5-dependent IFN- γ production. VAV1 and BTK can interact with dectin-1 to mediate phagocytosis of *Candida albicans* in macrophages. BTK may also promote calcineurin activation and the production of NFAT-regulated cytokines. The model depicts fungal killing in the phagosome. Myeloid cell-derived cytokines promote the differentiation of both Th1 cells and Th17 cells. Th17 and innately derived IL-17 activate epithelial responses that coordinate clearance of fungal cells at mucosal surfaces. The asterisks indicate genetic or humoral defects that predispose humans to a spectrum of fungal disease. Myeloid and epithelial cells collaborate to regulate CXCR2-dependent neutrophil recruitment to portals of infection. Illustrated by Mao Miyamoto.

morphotype-specific role in host defense. *A. fumigatus* hydrophobins and galactosaminogalactan enhance fungal resistance to NETs (78, 79). The contribution of NETs to fungal clearance *in vivo* remains difficult to quantify, because researchers lack experimental tools that specifically disrupt NETosis in murine models.

Mucosal defense and fungal tissue invasion. At mucosal surfaces, IL-17 is critical for antifungal immunity. Innate lymphoid, Th17, and $\gamma\delta$ T cells produce IL-17 following *C. albicans* challenge in the oropharynx or skin (80, 81). Skin sensory neurons participate in *C. albicans* detection and activate dermal DCs via the neuropeptide calcitonin-related gene product to direct IL-23-dependent $\gamma\delta$ T cell IL-17 release (82). Oral epithelial cells represent an important IL-17 signaling target, as mice lacking IL-17-sensing capacity in these cells display a phenotype similar to that of *Il17ra*^{-/-} mice (83). The IL-17-dependent transcriptional response of oral epithelial cells includes antimicrobial peptides, including β -defensin 3 (DEFB3). Accordingly, *Defb3*^{-/-} mice are susceptible to oropharyngeal candidiasis (83). In *C. albicans*-infected kidneys, IL-17-dependent responses include activation of the kallikrein/kinin system, which prevents apoptosis of tubular cells (84). Neutrophil recruitment to infected oral tissues is complex, with reports of IL-17-dependent and -independent trafficking pathways (85, 86). One IL-17-independent mechanism involves IL-1 α/β -sensing oral keratinocytes that regulate neutrophil influx via CXC-chemokine release and indirect control over G-CSF-dependent granulopoiesis (87). Thus, mucosal infections induce crosstalk between epithelial and hematopoietic cells to regulate innate activation and fungal clearance.

Fungal invasion of epithelial and endothelial cells contributes to tissue damage and disease dissemination. During mucormycosis, the endothelial receptor glucose-regulated protein 78 (GRP78) enables *Rhizopus oryzae* hyphae binding to endothelial cells (88) via spore coat protein surface proteins (CotH), primarily CotH3. Metabolic changes associated with hyperglycemia and diabetic ketoacidosis (DKA) enhance endothelial GRP78 expression, resulting in GRP78-dependent fungal tissue invasion (89). The widespread expression of CotH family members among *Mucorales* and absence from other fungal pathogens may explain the unique susceptibility of patients with DKA to mucormycosis. Consistent with this model, antibodies directed against GRP78 or CotH3 protect mice from mucormycosis (90).

The *C. albicans* adhesin Als3 mediates binding to biotic and abiotic surfaces, including epithelial and endothelial cells, and triggers internalization via E- and N-cadherin (91). The adhesin Hwp1 and the heat-shock protein Ssa1 also contribute to this process (92). An Als3p-based vaccine has emerged as a promising candidate to prevent mucosal and systemic disease (93) (NIH ClinicalTrials.gov identifiers: NCT01926028, NCT02996448). Following epithelial attachment, *C. albicans* pseudohyphae secrete the pore-forming, cytolytic peptide toxin candidalysin that is essential for virulence (94). At the onset of epithelial invasion, candidalysin activates MAPK signaling and c-FOS activation at sublytic concentrations (94). Epithelial activation leads to IL-1 α , IL-6, G-CSF, and GM-CSF release, alerting host cells to the presence of invasive pseudohyphae.

A. fumigatus conidia express the lung mucin-binding lectin FleA that promotes lung macrophages to internalize conidia (95). Mice challenged with Δ fleA conidia have more severe pneumonia than animals challenged with WT conidia. Thus, FleA represents an essential target of the immune system to clear inhaled conidia. *A. fumigatus* hyphae also invade epithelial and endothelial cells, a property mediated in part by the CalA protein (96) and by galactosaminogalactan (14). Although CalA is dispensable for host cell adherence, CalA stimulates integrin α 5 β 1-dependent hyphal endocytosis and is required for virulence in immunosuppressed mice (96).

Trained immunity and fungal infections. Humans maintain sterilizing antifungal immunity in the lung despite daily inhalation of thousands of fungal cells; therefore, single-inoculum animal models are limited in revealing immunologic responses that arise in response to multiple challenges. Repeated exposure to *A. fumigatus* antigens gives rise to ROR γ t⁺IL-17⁺ neutrophils in response to IL-6 and IL-23 production (97). IL-17⁺ neutrophils express IL-17RC and signal in a paracrine manner to boost fungicidal activity following secondary challenge in the eye and lung (97, 98).

Murine Ly6C^{hi} monocytes represent effector cells against *C. albicans* (99), *A. fumigatus* (100), and *B. dermatiditis* (101). During repetitive challenges with β -glucans, murine Ly6C^{hi} monocytes and human CD14⁺ monocytes exhibit attributes reminiscent of immunologic memory, including enhanced responsiveness, based on cytokine responses (102). β -Glucan priming induces epigenetic and metabolic changes in monocytes, the latter of which associates with a shift from oxidative phosphorylation to glycolysis via a dectin-1/AKT/mTOR/HIF-1 α signaling pathway (103) and increased glutaminolysis (104). In macrophages, β -glucan priming partially reverses LPS exposure-associated chromatin modifications, specifically the silencing of proinflammatory genes (105). In humans, a recent study proposes a role for STAT1 signaling in eliciting trained immunity, and by extension, in protection against chronic mucocutaneous candidiasis (CMC) (106).

Adaptive antifungal immunity. Antibody-mediated immunity to fungal pathogens has been extensively reported in the literature (107). For example, natural fungal polysaccharide-targeting IgM antibodies enhance DC-mediated recognition of fungal antigen, the development of Th2 and Th17 responses, and B cell isotype class-switch recombination during murine pneumocystosis (108). In a model of X-linked agammaglobulinemia, pulmonary and CNS cryptococcal disease progressed rapidly, in part due to IgM-dependent defects in macrophage phagocytosis (109). Although there is significant support for the concept that antibody-dependent opsonization and complement activation enhance fungal clearance in animal models (107), loss of antibody-mediated immunity is generally compensated by alternate effector systems, such as myeloid and CD4⁺ T cell-mediated immunity. Additionally, humans with humoral immune defects are generally not susceptible to fungal disease; however, protective fungus-specific antibodies are being researched as an adjunctive therapy in preclinical models (107). Several groups have generated protective antibodies that form the basis for vaccine strategies in murine models of fungal disease and in a phase I trial for recurrent vulvovaginal candidiasis (110–113) (NIH ClinicalTrials.gov identifier: NCT01067131).

In the 1980s and 1990s, the dominant CD4⁺ T cell–dependent protection model involved the dichotomous differentiation of CD4⁺ T cells into Th1 and Th2 subsets. More recent studies have shown that antibody- or cytokine-mediated disruption of Th1 immunity or Th2-favoring interventions correlate with adverse outcomes in murine fungal infection models (5, 9). The discovery of Th17 and regulatory T cells (Tregs), the development of CD4⁺ T cell receptor–transgenic mice (114–116), the identification of fungal epitopes that elicit antigen-specific responses (117–119), and the precise phenotyping of PIDD patients with mycoses have advanced insight into CD4⁺ T cell–driven antifungal immunity (120).

At the site of infection, fungal cells and antigens are internalized by tissue-resident DC subsets and monocyte-derived cells (Mo-DCs). In the lung, Ly6C^{hi} monocytes and derivative Mo-DCs transport *A. fumigatus* conidia and *B. dermatitidis* yeast cells to lung-draining lymph nodes (121, 122). In a *B. dermatitidis* vaccine model, fungal protease–dependent cleavage of CCR2 ligands impedes lung Ly6C^{hi} monocyte trafficking and the development of vaccine protection (123). However, Mo-DCs are not required for direct CD4⁺ T cell priming due to antigen transfer to lymph node–resident DCs (122). Mo-DCs, as well as IRF4-dependent CD11b⁺ DCs, instruct fungal antigen–specific Th17 responses following *A. fumigatus* conidial challenge (124, 125). In the oral mucosa, CCR7-dependent transport of candidal antigens to draining lymph nodes results in antigen presentation by FLT3L-dependent migratory DCs and by Mo-DCs, both of which have the capacity to prime antigen-specific CD4⁺ T cells (116).

In the skin, epidermal Langerhans cells recognize *C. albicans* yeast cell β -glucan via dectin-1, release IL-6, and instruct Th17 cell differentiation. These Th17 cells protect against secondary skin infection, but not against secondary systemic challenge (126). When *C. albicans* pseudophyphae penetrate the epidermis, dermal CD11b–CD103⁺ DCs drive differentiation of Th1 cells (126), which protect against secondary systemic challenge, but not secondary skin challenge (126). Thus, the cellular requirements for CD4⁺ T cell priming and differentiation vary by anatomic site and fungal morphology, and, in most cases, involve antigen transfer from migratory DCs and Mo-DCs to lymph node–resident DCs.

During pulmonary *A. fumigatus* challenge, T helper cell differentiation occurs incrementally. Expression of the transcription factor T-bet, which controls Th1 differentiation, is detectable in antigen-specific CD4⁺ T cells in lung-draining lymph nodes and is enhanced by MyD88-dependent signals. In infected airways, MyD88-independent signals promote further Th1 differentiation and IFN- γ production (114). In this model, dectin-1 signaling counters Th1 differentiation by limiting innate IL-12p35 and IFN- γ production (124). Vaccine immunity to dimorphic fungi relies primarily on pulmonary Th17 cells that likely facilitate mononuclear phagocyte– and neutrophil-dependent killing of these pathogens (127, 128). Recently, researchers identified a fungal calnexin epitope that is widely conserved among ascomycetes (118). Vaccine delivery of fungal calnexin elicited calnexin-specific CD4⁺ T cells that conferred protection against the three North American dimorphic fungal pathogens (118). Calnexin represents the most promising candidate for vaccine design against these mycoses.

Protective Th17 responses at mucosal surfaces can be enhanced by Treg-mediated IL-2 consumption, which enhances IL-17 and IL-22 release by responding Th17 cells and increases resistance to mucosal fungal infection (129). Despite the obligate requirement for IL-17 signaling during systemic candidiasis (61), FOXP3⁺ Treg–mediated potentiation of Th17 responses appears detrimental (130), consistent with the notion that high IL-17 levels lead to immunopathology, as described for type I IFN (38) and CCR1 signaling (131).

During pulmonary cryptococcosis, mammalian chitotriosidase digests fungal chitin, thereby stimulating lung-resident CD11b⁺IRF4⁺ DCs, which in turn promote a Th2-dominant response to virulent serotype A strains (119). Compared with WT mice, *C. neoformans* challenge in chitotriosidase-deficient animals elicited dramatically lower antigen-specific Th2 cell numbers and extended murine survival, despite similar lung fungal burden (119). These data support a model in which antigen-specific Th2 cells exacerbate cryptococcosis by augmenting tissue damage without effecting fungal growth. Consistent with these findings, chitosan-deficient (i.e., deacetylated chitin) cryptococcal strains elicit cytokine mediators that promote a Th1-biased response (132). Similarly, the chitin content of individual *A. fumigatus* strains correlates with the magnitude of Th2 responses and lung eosinophil recruitment (133). The role of eosinophils in fungal clearance remains poorly understood, with several recent reports suggesting these cells help mediate fungal clearance (134–136).

Antifungal immunity: lessons from fungal disease–associated Mendelian disorders

In the 1970s–1980s, characterization of two prototypic PIDDs that result from phagocyte oxidative machinery defects — CGD, caused by mutations in NADPH oxidase subunits and myeloperoxidase (MPO) deficiency

(137, 138) — catalyzed our recognition that phagocyte oxidative cytotoxicity is critical for protection against invasive fungal disease in humans. The spectrum of clinical phenotypes of these disorders highlights the fungus-specific dependence on oxidative versus nonoxidative cytotoxic mechanisms for defense. For example, pulmonary aspergillosis is the signature fungal infection in CGD (137). Yet, only ~40% of CGD patients develop aspergillosis during their lifetime, despite daily inhalation of ubiquitous conidia. This observation indicates that nonoxidative mechanisms compensate in the remainder of the *Aspergillus*-exposed patients; better understanding of these mechanisms is an important future research direction (9, 69, 71, 77, 139). Invasive infections by other molds, such as Mucorales and *Fusarium*, or by commensal *Candida* yeasts are very uncommon (<5%), whereas invasive infections by endemic dimorphic fungi and *Cryptococcus*, or CMC do not develop in CGD (137, 140). In contrast, MPO deficiency is not permissive to infections by inhaled molds, and only a minority (<5%) of MPO-deficient patients develops invasive candidiasis. These clinical observations show that human phagocytes differentially depend on their oxidative capacity to effectively control different fungal pathogens. Importantly, while both CGD and MPO-deficient patients manifest defective hypochlorous acid production within phagocytes (137, 138), they exhibit distinct features in the phenotypic expression of fungal disease. The discrepancy in susceptibility to mold infection in these patients may reflect, at least in part, a potentially significant contribution of superoxide anion-dependent K⁺ influx in activating phagolysosomal granule proteases (141), which is defective with NADPH oxidase, but not MPO, deficiency.

In the 1990s–2000s, the discovery of PIDDs resulting from alterations of IL-12/IFN- γ signaling uncovered the critical role of IL-12/IFN- γ -dependent lymphocyte/macrophage crosstalk in control of intracellular pathogens, including endemic dimorphic fungi, *Cryptococcus*, mycobacteria, and *Salmonella* (65). This pathway is dispensable for control of inhaled molds and mucosal fungal infection in humans. Some of these disorders respond clinically to mechanism-based immunotherapy with IFN- γ or IFN- α (142). Similarly, neutralizing IFN- γ and GM-CSF autoantibodies can underlie adult-onset acquired immunodeficiency characterized by endemic dimorphic fungal (143) and CNS cryptococcal disease (144). Patients with alveolar proteinosis due to impaired GM-CSF signaling develop aspergillosis (145), consistent with murine studies (146).

During the last decade, careful clinical phenotyping combined with next-generation sequencing technologies revealed the critical balance of JAK/STAT signaling in human antifungal immunity (147). Patients with *STAT1* gain-of-function (GOF) mutations and those with hyper-IgE syndrome (Job's syndrome) due to *STAT3* loss-of-function (LOF) mutations develop fungal disease with overlapping and distinct features. *STAT1* GOF mutations lead to disseminated infections by intracellular dimorphic fungi, CMC, and/or infections by inhaled molds in the absence of structural lung disease (65, 148). *STAT3* LOF mutations also result in CMC, but pulmonary infections by inhaled molds occur as a consequence of structural lung disease caused by prior bacterial lung infections. In this cohort, infections by intracellular dimorphic fungi occur very rarely and, when they do, tend to involve the gastrointestinal tract (149). In contrast, LOF *STAT1* mutations or GOF *STAT3* mutations do not cause fungal disease (65).

Mutations in the transcription factor *GATA2* result in a protean PIDD (65, 150) that brings together (a) susceptibility to bacterial, fungal and viral disease, (b) malignancy, and (c) vascular abnormalities. From a fungal disease standpoint, *GATA2* haploinsufficiency leads to infections by endemic dimorphic fungi, *Cryptococcus*, and *Aspergillus*, but not *Candida*. *GATA2*-deficient patients exhibit monocytopenia that, consistent with recent murine models, likely contributes to fungal susceptibility (100, 150).

The discovery of kindreds with CMC that carry mutations in *IL17F*, *IL17RA*, *IL17RC*, and NF- κ B activator 1 (*ACT1*), and complementary studies in IL-17-mutant mice discussed above indicate that IL-17 signaling is indispensable for mucosal, but not systemic, antifungal immunity (64, 65). Patients with *IL17F* or *IL17RC* mutations only develop CMC, whereas those with *IL17RA* or *ACT1* mutations also manifest cutaneous staphylococcal and/or pulmonary bacterial infections, indicating that IL-17E/IL-25 signaling may specifically map to bacterial defense at mucosal surfaces (151, 152). CMC susceptibility has also been linked to mutations in other genes (64, 65), most of which either directly or indirectly interfere with Th17 development and/or responses (Figure 2). These include AIRE deficiency in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) (153), Job's syndrome in which *STAT3* regulates ROR γ t-dependent Th17 development, the various genetic forms of severe combined immunodeficiency disorder (154), and mutations in *STAT1*, *RORC*, *STK4*, *IRF8*, *DOCK8*, *IKBA*, *CLEC7A*, and *CARD9* (64, 65, 155). A *CLEC7A* polymorphism is also associated with susceptibility to invasive aspergillosis in hematopoietic cell transplant recipients (156).

CARD9 deficiency exhibits three distinctive features among Mendelian disorders of antifungal immunity (157). First, a substantial proportion of CARD9-deficient patients exhibit adult-onset fungal disease, in contrast to early childhood onset typical of other PIDDs. It is unclear whether a different threshold of fungal exposure and/or additional genetic, environmental, or other factors accounts for this observation. Second, CARD9 deficiency is the only PIDD in which both mucosal and systemic fungal disease develop, and susceptibility is restricted to fungi without concurrent bacterial or viral infections. Invasive candidiasis, CMC, invasive phaeohyphomycosis, and superficial and deep-seated dermatophytosis have also been reported (157). In contrast to CARD9, MALT1 or BCL-10 deficiency results in a narrower spectrum of fungal susceptibility, with only mucosal infections reported to date (157). Third, CARD9 deficiency strikingly results in infections at anatomical sites that are not typically associated with the specific pathogens. For example, CARD9-deficient patients exhibit a predilection for *Candida* meningoencephalitis, without disease in kidney, liver, or spleen, all of which are commonly affected in CARD9-sufficient patients (157, 158). CARD9 is critical for neutrophil recruitment to the *Candida*-infected CNS but not for neutrophil recruitment to the *Candida*-infected kidney or *Staphylococcus*-infected CNS (159). This tropism is mediated by CARD9-dependent production of CXC chemokines by resident glial cells and neutrophils in the *Candida*-infected CNS, while neutrophil-intrinsic chemotaxis and effector functions are largely intact in CARD9-deficient humans and mice (159–161). Development of CNS and intra-abdominal aspergillosis is another example of altered tissue tropism in CARD9-deficient patients (162) and results from defective CARD9-dependent neutrophil chemoattractant production in and neutrophil mobilization to extrapulmonary infection sites. The absence of pulmonary *Aspergillus* involvement in CARD9 deficiency may be explained by compensatory IL-1R/MyD88-dependent neutrophil lung recruitment (161, 163). Collectively, these human observations have led to our appreciation that CARD9 appears to mediate fungus-, cell type-, and organ-specific neutrophil recruitment during invasive fungal infection.

GM-CSF and G-CSF were reported to improve the outcome of a small number of CARD9-hypomorphic patients with CNS candidiasis (164). In this cohort, mutant CARD9 was impaired in its ability to complex with RASGRF1, but not with BCL10 and MALT1 (165). The mechanism by which these cytokines bypass the CARD9-dependent immune defect in this cohort and the generalizability of this protection in other CARD9-deficient patients remain to be elucidated.

Antifungal immunity and the study of the mycobiome

While commensal fungi have been noted in humans and mice for over five decades, lack of culture-independent methods, delay in developing high-throughput rDNA sequencing methods, and paucity of annotated reference databases to classify fungal rDNA amplicons delayed characterization of endogenous fungal communities, termed the mycobiota (166, 167). Although fungi comprise less than 1% of total microbial rDNA sequences at different anatomic sites, the size of fungal cells (~3–10 μm diameter for most yeast cells, 2–5 μm diameter for typical mold conidia, and 10 to hundreds μm length for hyphae, compared with < 1 μm diameter for bacterial cells) suggests that fungal rDNA quantification underestimates fungal biomass in the microbiota. In the past five years, researchers have analyzed endogenous fungal communities in the oral cavity, gastrointestinal tract, skin, and mucosal sites in healthy and diseased individuals (168–172). In most studies, between 15 and 70 fungal genera have been identified, with *Malassezia* spp. predominant in the skin and *Candida* spp. predominant in the intestine. Recent work has defined mechanisms of *Candida* colonization resistance by intestinal anaerobic bacteria (173).

Our understanding of the reciprocal interplay between endogenous fungal communities and antifungal immunity remains limited. Despite high-quality studies that point to a central role for IL-17 in mucosal antifungal immunity, it remains unclear whether IL-17 controls the composition or diversity of commensal fungi. Administration of secukinumab, an IL-17-neutralizing Ab, in patients with Crohn's disease increased the rate of fungal infections, consistent with IL-17 directing mucosal antifungal immunity (174).

Recent work has examined dectin-1 in shaping endogenous fungal communities and mycobiota-triggered immune responses in the gut. *Clec7a*^{-/-} mice developed intestinal inflammation and *Candida* and *Trichosporon* spp. overgrowth in the gut (168). In turn, *Clec7a*^{-/-} mice were unable to control *Candida* during dextran sulfate sodium-induced colitis and benefited from fluconazole therapy. In the absence of commensal *Candida*, *Clec7a*^{-/-} mice were more resistant to colitis and exhibited a reduction in colonic antimicrobial

peptides that target Gram-positive bacteria, leading to an increase in commensal *Lactobacillus murinus* bacteria, Treg expansion, and resistance to colitis (175). Colonization of *Clec7a*^{-/-} mice with *C. tropicalis* reversed these effects and promoted intestinal inflammation. These findings suggest that dectin-1 signaling indirectly influences the intestinal bacterial microbiota. In humans, a two-marker *CLEC7A* haplotype is associated with treatment-refractory ulcerative colitis (168). Another study identified a negative correlation between a *CLEC7A* single nucleotide polymorphism (SNP) and *Malassezia sympodialis* abundance in the gut of inflammatory bowel disease (IBD) patients, though no additional (positive or negative) correlations with other fungi were reported, likely due to the small cohort size (176). These studies highlight a protective role for dectin-1 in intestinal mycobiota control and antifungal immunity.

Dectin-3 was recently reported to contribute to control of intestinal *Candida* and colitis. Intestinal *C. tropicalis* overgrowth in *Clec4d*^{-/-} mice was accompanied by a decrease in Th17 cells, impaired macrophage fungal phagocytosis, and defective intestinal epithelial cell barrier function (177). Consistent with these findings, antifungal treatment of *Clec4d*^{-/-} mice reduced *C. tropicalis* burden and ameliorated colitis.

CARD9 has also been implicated in IBD pathogenesis, as a nonsynonymous SNP in the *CARD9*-coding region strongly associates with IBD risk (178). In experimental colitis models, CARD9 signaling can be protective against fungi that contact the intestinal mucosa during colitis. Furthermore, antifungal drugs partially ameliorate intestinal inflammation in this context (179). Analysis of the intestinal microbiota of *Card9*^{-/-} mice revealed alteration in fungal and bacterial communities compared with WT animals. The intestinal microbiota in *Card9*^{-/-} mice lacked tryptophan-metabolizing bacteria and did not produce aryl hydrocarbon receptor ligands (180). As a result, *Card9*^{-/-} mice showed defective expression of *Ii22* and antimicrobial peptide-encoding genes *Reg3g* and *Reg3b*. Altogether, these findings suggest CARD9 may dually control fungal and bacterial populations in the gut.

Immunologic effects of intestinal fungi extend beyond the gut. In a house dust mite-induced airway allergy model, disruption of the gut fungal community with antifungal drugs increased disease severity (181). *Aspergillus amstelodami*, *Epicoccum nigrum*, and *Wallemia sebi* increased in abundance during antifungal drug-induced fungal dysbiosis, and intestinal supplementation with these strains replicated the detrimental effects of antifungal drugs on lung allergy (181). Similarly, antibiotic-induced fungal overgrowth exacerbated papain-induced lung allergy by promoting intestinal *Candida* overgrowth (182). This phenomenon, first demonstrated with *C. albicans* (183), is recapitulated by multiple *Candida* species and is mediated in part by eicosanoids (182). Thus, there is a complex interplay between endogenous fungal communities and innate immune tone and responses, both at local and distant sites.

Conclusions and future perspectives

The field of antifungal immunity has rapidly advanced in the past decade, a period marked by the dissection of fungus-specific innate and adaptive immune responses and convergence of human clinical and animal model data. The advances during this era are exemplified by insights into the pivotal role of dectin-1/CARD9 and IL-17 pathways in antifungal immunity. The discovery of β -glucan-induced trained immunity and conserved sterilizing immunity-mediating epitopes lays the foundation for clinical trials to test vaccine protection against multiple fungal genera and species. Important areas of future research include elucidation of the role of epithelial surfaces in fungal virulence and antifungal defense and the intercellular crosstalk underlying innate and adaptive antifungal immunity. It is likely that additional fungal recognition receptors and response pathways remain to be discovered, both in animal models and in human genetic studies. How the composition, diversity, and metabolism of endogenous fungal communities contribute to immune homeostasis and to inflammatory disorders remains largely unexplored, yet are central for deciphering the contribution of fungi to diverse states of human health and disease.

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