Published in final edited form as:

Curr Opin Immunol. 2012 August ; 24(4): 449–458. doi:10.1016/j.coi.2012.04.007.

Immunity to Fungi

Salomé LeibundGut-Landmann^{1,4}, Marcel Wüthrich^{2,4}, and Tobias M. Hohl³

¹Institute for Microbiology, Swiss Federal Institute of Technology, CH-8093 Zürich, Switzerland

²Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI, 53711, USA ³Vaccine and Infectious Disease Division, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, 98109, USA

Abstract

The global increase in fungal disease burden, the emergence of novel pathogenic fungi, and the lack of fungal vaccines have focused intense interest in elucidating immune defense mechanisms against fungi. Recent studies in animal models and in humans identify an integrated role for C-type lectin and Toll-like receptor signaling in activating innate and adaptive responses that control medically relevant fungi. Beyond the critical role of phagocytes in host defense, the generation and balance of specific T helper subsets contributes to sterilizing immunity. These advances form a basis for the development of fungal vaccines and immune-based therapeutic adjuncts.

Introduction

Humans encounter, ingest, and inhale fungi daily. Although only several hundred of the estimated 10^5 fungal species cause human disease, the incidence of clinically relevant fungal infections has risen substantially in the past 3–4 decades. This increase is largely due to the AIDS pandemic and the advent of transplantation, chemotherapy, immunosuppression, and vascular access in modern medicine. In sub-Saharan Africa, cryptococcal meningitis exceeds well-known infections such as tuberculosis as a cause of HIV-associated deaths [1]. The Pacific Northwest *Cryptococcus gattii* outbreak [2], and the worldwide amphibian (chytridiomycosis; *Batrachochytrium dendrobatidis*) and North American bat extinction (white nose syndrome; *Geomyces destructans*) highlight emerging fungal pathogens as agents of human and animal disease [3,4].

Fungi are eukaryotic, saprophytic organisms with a rigid cell wall. Yeasts form round, oval, or spherical cells that usually divide asexually by budding. Molds form asexual spores (conidia) that are dispersed in the environment and germinate into tubular filaments, termed hyphae. Dimorphic fungi (e.g. *Blastomyces dermatitidis*, *Coccidioides posadasii*, *Histoplasma capsulatum*, and *Paracoccidioides brasiliensis*) can exist as yeast cells (in human tissues) or as hyphae (in soil) with environmental conditions (e.g. temperature) guiding the transition between morphologic states.

© 2012 Elsevier Ltd. All rights reserved.

Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, D3-100, Seattle, WA 98109. Tel.: +206-667-2995; fax: +206-667-4411, thohl@fhcrc.org.

⁴these authors contributed equally to the manuscript

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Fungi cause a broad range of diseases with syndromes that involve superficial, tissue-invasive, and allergenic manifestations (Fig. 1). Route of acquisition, tissue tropism, and nutritional requirements all contribute to fungal pathogenesis. Deep-seated mycoses develop from inhalation of infectious propagules into the airways of susceptible hosts (e.g. *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Pneumocystis jiroveci*) or penetration of mucosal breaches by commensal organisms such as *Candida albicans*. Disruption of host microbial communities (e.g. vulvovaginal candidiasis ensuing antibiotic therapy) or metabolic disorders (e.g. mucormycosis in diabetic ketoacidosis; [5••]) can predispose to superficial and invasive disease.

This review focuses on emerging concepts in fungal recognition and effector mechanisms, the generation of protective T cell responses, and current efforts to develop vaccine-based therapies for vulnerable patient groups. A more in-depth analysis of innate and adaptive immunity to human fungal pathogens and host evasion strategies is discussed elsewhere [6–8].

Fungal innate immune activation

Fungi bind antibodies, complement, surfactant, and soluble pattern recognition receptors at portals of entry. For example, the soluble collectin pentraxin-3 binds to inhaled *A. fumigatus* conidia, triggering complement deposition and CD32-dependent uptake by neutrophils [9]. Opsonization by these mechanisms promotes fungal uptake and innate immune activation by a wide range of phagocytic and signaling receptors [6].

Highly conserved fungal cell wall components and nucleic acids trigger innate immune activation in macrophages, dendritic cells, and neutrophils, as well as in epithelial cells [6]. The latter is exemplified by a MAP kinase response that discriminates between *C. albicans* yeast cell and filamentous growth [10•]. Deciphering the role of specific pattern recognition receptors in these interactions is complex since fungal cell wall composition changes during yeast cell and filamentous growth as well as after cell division (e.g. *C. albicans* bud scars), morphotype switching, and antifungal drug exposure [11]. In some fungi immune-activating polysaccharides are concealed beneath immunologically inert polymers such α -glucan (*H. capsulatum*) and hydrophobins (*A. fumigatus*) [6].

Toll-like receptors

The ligation of fungal cell wall polysaccharides and nucleic acids [12–14] activates murine Toll-like receptor (TLR; TLR1-4, 6, 7, and 9) signaling (Fig. 2). Although deficiency of the TLR adaptor protein MyD88 renders mice susceptible to *C. neoformans* and *C. albicans* and delays *A. fumigatus* clearance [6], fungal infections are not a prominent clinical phenotype in humans with MyD88 deficiency [15], suggesting that MyD88-dependent signals are not essential to prevent the development of symptomatic fungal infections in pediatric patients. However, TLR1 polymorphisms predispose to candidemia [16] and TLR4 polymorphisms to invasive aspergillosis in allogeneic hematopoietic stem cell transplant (HCT) patients [17], consistent with the notion that TLR-dependent signals contribute to optimal host defense against fungal pathogens in humans. The biological role of other receptors, such as the mannose receptor, DC-SIGN, CD36, complement receptor 3, and Galectin-3, implicated in fungal recognition and immune activation is discussed in detail elsewhere [6–8].

C-type lectin receptors

Three immunoreceptor tyrosine-based activation motif (ITAM)-dependent C-type lectin receptors (CLRs; Dectin-1, Dectin-2, and Mincle) activate innate and adaptive antifungal responses (Fig. 2). Dectin-2 and Mincle lack an intracellular ITAM motif but pair with FcR γ , an ITAM-containing adaptor protein. Particulate β -(1,3)-glucan activates Dectin-1

signaling through a mechanism that excludes the phosphatases CD45 and CD148 from the phagocytic cup, facilitating phosphorylation of its intracellular ITAM-like motif and activation of spleen tyrosine kinase (Syk) [18••]. Dectin-1/Syk signaling induces the assembly of the CARD9/BCL10/MALT1 (Caspase recruitment domain-containing protein 9/ B cell leukemia/lymphoma 10/Mucosa-associated lymphoid tissue lymphoma translocation protein 1) complex via PKC δ [19] and subsequent activation of the canonical NK- κ B pathway via the kinase TAK1, resulting in TNF, IL-6, IL-23, and IL-1 β synthesis. *C. albicans* and particulate β -(1,3)-glucans can trigger Syk- and phospholipase C γ 2 (PLC γ 2)-dependent nuclear factor of activated T cells (NFAT) activation via Dectin-1 or Dectin-2, resulting in the production of IL-2, IL-10, lipid mediators, and Egr transcription factors [6]. Dectin-1-dependent phagocytosis by macrophages and non-canonical NK- κ B activation via Raf-1 [20] illustrate Syk-independent functions of the receptor.

Dectin-1, Dectin-2, and Mincle contribute to murine host defense against systemic candidiasis [21–23], aspergillosis [24] and pneumocystosis [25]. While individual CLRs are dispensable, deficiencies in PKC δ [19] PLC γ 2 [26], and CARD9 [27] result in rapid lethality in systemic candidiasis. The association of mucosal candidiasis and aspergillosis (in the context of allogeneic HCT) and defined allelic variations in Dectin-1 and CARD9 (Table I) further illustrates the critical role of the CLR/Syk/CARD9 pathway in antifungal defense.

Simultaneous CLR and TLR activation by fungal antigens augments NF- κ B responses in macrophages and dendritic cells [6]. *Fonsecaea pedrosoi*, the most common cause of chromoblastomycosis, triggers Mincle/FcR γ /Syk-dependent cytokine production that is inadequate to eradicate the organism, resulting in chronic infection [28••]. Administration of the TLR7 agonist imiquinod enhances cytokine production by *F. pedrosoi*-stimulated dendritic cells *in vitro* and enhances fungal clearance in a TNF-dependent manner *in vivo*, providing a novel therapeutic strategy for this disfiguring soft tissue infection.

Inflammasome function during fungal infection

Production of IL-1 β is critical for host defense in murine models of candidiasis [6]. The production and release of IL-1 β requires two independent signals: one regulating the transcription and translation of pro-IL-1 β , the other inducing its proteolytic cleavage into active IL-1 β . Fungi trigger both steps of IL-1 β synthesis by CLR-dependent caspase activation via the assembly of inflammasomes with distinct subunit composition. The NOD-like receptor NLRP3 (Nucleotide oligomerization domain-like receptor family, pyrin domain containing 3) and the adaptor protein ASC (Apoptosis-associated speck-like protein containing a CARD) form the scaffold of the NLRP3 inflammasome for caspase-1-activation. NLRP3- and ASC-deficient mice lack caspase-1 activation and IL-1 β secretion and display increased mortality in response to *C. albicans* infection [29–32]. In humans, allelic variations in NLRP3 have been associated with recurrent vulvovaginal candidiasis [33].

The NLRC4 (NLR family CARD domain-containing protein 4) inflammasome is protective in systemic candidiasis and its function may be particularly important in the stromal compartment [34]. However, alternative IL-1 β processing mechanisms have been reported. Caspase-1 may exist in an active form in circulating monocytes and induce IL-1 β maturation independent of additional activation signals [35]. In neutrophils, caspase-1-independent IL-1 β maturation is also mediated by serine proteinases, including proteinase 3, elastase and cathepsin G. Finally, *C. albicans* or *A. fumigatus*-induced Dectin-1/Syk signaling can recruit caspase-8 into a complex with CARD9, BCL10, and MALT1 to generate IL-1 β [36•].

Innate Fungal Killing Mechanisms

Beyond the established roles of mononuclear phagocytes, neutrophils, and NK cells in antifungal defense [6], recent studies identify a role for plasmacytoid dendritic cells in aspergillosis [37] and invariant NKT (iNKT) cells in cryptococcosis [38] and aspergillosis [39]. iNKT cells accumulate and produce interferon- γ (IFN- γ) in fungus-infected airways [39]. *In vitro*, a wide range of fungi stimulate dendritic cells to activate iNKTs in a Dectin-1- and CD1d-dependent fashion, with no apparent requirement for fungal lipid antigen presentation [39].

NADPH oxidase is a conserved antifungal effector mechanism that underlies Dectin-1-dependent [24] and -independent activation, as demonstrated by β 2-integrin (CD18)-, phosphoinositide-3-kinase- β - and - δ -, and Syk-dependent ROS activation by killed *A. fumigatus* hyphae [40]. Control of neutrophil NADPH oxidase activity by Vav guanine nucleotide exchange factors appears to be a critical defense mechanism against systemic candidiasis [41]. Loss of NADPH oxidase activity results in chronic granulomatous disease (CGD) in humans and GCD patients have a 25–40% lifetime risk of developing aspergillosis (Table I). Beyond the production of fungicidal ROS, loss of NADPH oxidase-dependent indoleamine-2,3-dioxygenase activity results in dysregulated IL-17 production and lethal immunopathology in a murine model of CGD [42]. Restoration of NADPH oxidase activity by gene therapy can resolve treatment-refractory aspergillosis [43] and correlates with the ability of neutrophils to form extracellular traps by releasing decondensed chromatin fibers decorated with antifungal proteins, e.g. calprotectin. These neutrophil extracellular traps ensnare *C. albicans* [44] and *A. fumigatus* hyphae [45], though their role in fungal killing remains controversial [46].

The phosphatase calcineurin B, the target of cyclosporine A and FK506, controls neutrophil killing of *C. albicans* without perturbing phagocytosis or ROS production [47•]. Neutrophil serine protease activity plays a protective role in murine systemic candidiasis [48], but appears to be dispensable for host defense following pulmonary *A. fumigatus* challenge [49]. Iron sequestration exerts fungistatic effects, exemplified by CGD neutrophil lactoferrin release to limit *A. fumigatus* hyphal growth [6]. *H. capsulatum* exerts control over macrophage phagolysosomal fusion to create an obligate intracellular niche for survival. In turn, macrophages sequester zinc, however the precise mechanism of this antifungal strategy has not been elucidated [50].

Induction of Adaptive Immunity

TLR and CLR signaling induces MHC class II, co-stimulatory molecule, and cytokine expression by antigen-presenting cells that dictate T cell differentiation (Fig. 2). In the lung, inflammatory monocytes and CCR2⁺Ly6C^{hi} monocyte-derived DCs are essential for fungal antigen transport to draining lymph nodes and facilitate *Aspergillus*-, *Histoplasma*-, and *Blastomyces*-specific CD4⁺ T cell priming and expansion [51,52•]. Following subcutaneous administration, multiple skin-resident and lymph node dendritic cell subsets cooperate to transport vaccine yeast and to prime antigen-specific CD4 T cell responses [53].

Th1 and Th17 cells are the principal T helper subsets that contribute to protective immunity to several pathogenic fungi. Below, we discuss the signaling pathways and other factors that influence T cell differentiation and mechanisms of protection. The recent development of *A. fumigatus*- and *B. dermatitidis*-specific T cell receptor (TCR) transgenic mice facilitates studies on antigen-specific CD4 T cell differentiation and memory development during fungal infections [54,55]. Interestingly, *B. dermatitidis*-specific 1807 TCR transgenic cells recognize a protective antigen that is shared among the major systemic dimorphic fungi including *H. capsulatum*, *Coccidioides posadasii* and *Paracoccidioides brasiliensis* [54].

IL-17 contributes to host resistance in oropharyngeal, cutaneous, and systemic infection with *C. albicans* [23,56,57], and pulmonary infection with *H. capsulatum* [58], *A. fumigatus* [24], and *P. carinii* [59]. In fungal infection models, IL-17 can arise from myeloid sources [60], $\gamma\delta$ T cells [42] [61], or CD4 T cells that have differentiated into Th17 effector cells [62•]. Thus, the role of IL-17 and Th17 cells in antifungal host defense are not synonymous in all instances. The recent discovery of human polymorphisms in genes that regulate Th17 differentiation (*IL-12R β 1*, *STAT3*, *STAT1*) and IL-17 function (*IL-17F*, *IL-17RA*, *AIRE*) in individuals suffering from mucocutaneous candidiasis underlines the importance of IL-17-dependent immunity (Table I).

In contrast to the studies cited above, IL-17 and Th17 cells have been suggested to be pathogenic in a model of gastric candidiasis and in pulmonary *A. fumigatus* infection [63]. In other experimental systems, deleterious effects of Th17 cells are kept in check by regulatory T (Treg) cells. In a murine model of pulmonary *P. brasiliensis* infection, TLR2 promoted the induction of Treg cells that limited Th17 cell development and tissue pathology [64]. Similarly, the chemokine receptor CCR5 regulates the balance between Tregs and Th17 cells in *H. capsulatum* infection [65]. In contrast, Tregs enhance Th17 responses and fungal clearance in a murine model of oral candidiasis [66].

TLR signaling mediates the development of antifungal Th1 cells. MyD88-dependent signals are dispensable for CD4⁺ T cell priming and trafficking to infected airways during respiratory fungal infection, but mediate the stepwise differentiation of *A. fumigatus*-specific CD4 T cells into IFN- γ -producing airway effector cells [55]. Vaccine-induced Th17 cells mediate resistance to *B. dermatitidis*, *H. capsulatum* and *C. posadasii* [62•,67]. *C. albicans*, *A. fumigatus* and curdlan, a β -(1,3)-glucan agonist, can induce the development of Th17 cells via Dectin-1/Syk/CARD9-dependent signals [68,69]. In *A. fumigatus*-infected mice, Dectin-1 enhances Th17 differentiation by decreasing IL-12 and IFN- γ production in innate cells and T-bet expression in *A. fumigatus*-specific CD4⁺ T cells [69]. In contrast, development of vaccine-induced *Blastomyces*-specific Th17 cells depends on MyD88, but not Dectin-1 [62•], while Dectin-2 is also implicated in Th17 cell development during candidiasis [23,70].

Fungal vaccination strategies

Despite a growing medical need, no fungal vaccines are commercially available. Virulence-attenuated mutants represent one of the best ways to induce sterilizing immunity and achieve maximal protection, as evidenced in experimental models of blastomycosis, histoplasmosis and coccidioidomycosis [54,71,72]. In addition, vaccination with attenuated mutants induces antifungal memory CD8⁺ T cells that are maintained without numeric or functional loss for at least 6 months [73]. Although these vaccine strains are not likely to be safe in immunocompromised individuals, the knowledge gained from experimental vaccine models is crucial for the rational design of human vaccine candidates. Experimental vaccines against candidiasis, aspergillosis, and the endemic mycosis [62,67,74,75] owe their protection chiefly to Th17 and Th1 cells, a novel paradigm for human vaccines.

Two subunit vaccines designed to protect against *C. albicans* infections are in Phase 1 clinical trials. The rAls3p-N vaccine (NovaDigm Therapeutics, USA) contains the N terminal portion of the adhesin agglutinin-like sequence (Als) 3 and stimulates protective immunity to *C. albicans* and *S. aureus* infection by eliciting Th17 and Th1 T cells that enhance microbial killing independent of B cell function [74]. The antigen specificity of the protective Als3p-N-specific T cells may reside within a naturally processed and presented epitope that is reactive to multiple, clinically relevant *Candida* species [76•]. Another T cell

epitope from the *A. fumigatus* cell wall glucanase Crf1 cross-protects against infection with *A. fumigatus* and *C. albicans* [77].

Naturally acquired infections with fungi and virulence-attenuated live vaccines do not induce protective isotype-switched antibodies, but conserved natural IgM antibodies are beneficial during pneumocystosis [78]. Protective monoclonal antibodies (mAbs) recognize the cryptococcal capsule, β -glucan on *C. albicans* and *A. fumigatus*, and the secreted virulence factor aspartyl proteinase 2 (Sap2) from *C. albicans*. Neutralizing antibodies to Sap2 provide the functional basis of the second fungal vaccine currently in a Phase 1 clinical trial. The virosome-formulated vaccine induces Sap-neutralizing antibodies (PEV7 by Pevion Biotech, Switzerland) that confer protection against candidal vaginitis [79]. A conjugate vaccine that elicits β -glucan antibodies protects in experimental models of aspergillosis, candidiasis, and cryptococcosis is in preclinical development [80,81].

In summary, fungal vaccines confer protection by T cells and antibodies. T cell based vaccines mediate acquired resistance by the production of inflammatory cytokines (e.g. IFN- γ , TNF, IL-17 and IL-22) that regulate the influx and killing by phagocytes and the synthesis of epithelial-cell derived antimicrobial proteins (e.g. cathelicidins and histatins) [8,82]. Antibodies contribute to protection by neutralizing virulence factors (e.g. adhesins), inhibiting fungal growth, and by stimulating direct killing, opsonophagocytosis, and complement activation. Thus, strategies that harness both arms of the adaptive antifungal immune response may yield the most rational and successful vaccine candidates [80,81,83,84].

Conclusions

In the past several years, researchers have made significant progress in understanding innate and adaptive immunity to medically important fungi. Important milestones include the dissection of fungal recognition and killing pathways in animal models and the discovery of the genetic causes of human syndromes characterized by fungal disease. These lines of investigation identify a key role for CLR signaling and genes related to IL-17-mediated immunity in regulating tissue inflammation and fungal clearance. Integrated CLR/TLR signals underlie host control of chromoblastomycosis and can be elicited by administering a TLR agonist, establishing a novel treatment paradigm for fungal disease. The identification of new vaccine antigens and their underlying mechanisms of protection in preclinical models of disease are essential steps in the development of candidate human vaccines. Greater understanding of the molecular and cellular basis of antifungal immunity will undoubtedly provide opportunities for novel therapeutic strategies and applications.

Acknowledgments

We thank Kyoko Kurosawa (Fig. 1) and Robert Gordon (Fig. 2) for graphical support. T.M.H. acknowledges the Robert Sinskey Foundation, the American Heart Association, and NIH grant RO1 AI093808 for support. S.L.-L. is funded by the Swiss National Science Foundation (grant number PP00P3_123342), the Swiss Life Anniversary Foundation and by ETH Zürich. M.W. is supported by NIH grant R01 AI093553 and AI40996. We apologize to our many colleagues whose important contributions to fungal immunity we were not able to cite owing to space constraints.

References

1. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS*. 2009; 23:525–530. [PubMed: 19182676]
2. Byrnes EJ 3rd, Bartlett KH, Perfect JR, Heitman J. *Cryptococcus gattii*: an emerging fungal pathogen infecting humans and animals. *Microbes Infect*. 2011; 13:895–907. [PubMed: 21684347]

3. Fisher MC, Garner TW, Walker SF. Global emergence of Batrachochytrium dendrobatidis and amphibian chytridiomycosis in space, time, and host. *Annu Rev Microbiol.* 2009; 63:291–310. [PubMed: 19575560]
4. Frick WF, Pollock JF, Hicks AC, Langwig KE, Reynolds DS, Turner GG, Butchkoski CM, Kunz TH. An emerging disease causes regional population collapse of a common North American bat species. *Science.* 2010; 329:679–682. [PubMed: 20689016]
5. Liu M, Spellberg B, Phan QT, Fu Y, Fu Y, Lee AS, Edwards JE Jr, Filler SG, Ibrahim AS. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. *J Clin Invest.* 2010; 120:1914–1924. [PubMed: 20484814] Mucormycosis, commonly caused by *Rhizopus oryzae*, is a feared complication of diabetic ketoacidosis (DKA) and is associated with angioinvasion, thrombosis, and tissue infarction. The authors demonstrate that *Rhizopus oryzae* binds to an endothelial receptor, GRP78, that is upregulated during hyperglycemia. Antibody-mediated blockade of GRP78 improves the outcomes of mucormycosis in DKA mice, thereby identifying a host target for therapeutic manipulation.
6. Brown GD. Innate antifungal immunity: the key role of phagocytes. *Annu Rev Immunol.* 2011; 29:1–21. [PubMed: 20936972]
7. Wüthrich M, Deepe G, Klein B. Adaptive Immunity to Fungi. *Annu Rev Immunol.* 2011
8. Romani L. Immunity to fungal infections. *Nat Rev Immunol.* 2011; 11:275–288. [PubMed: 21394104]
9. Moalli F, Doni A, Deban L, Zelante T, Zagarella S, Bottazzi B, Romani L, Mantovani A, Garlanda C. Role of complement and Fc{gamma} receptors in the protective activity of the long pentraxin PTX3 against *Aspergillus fumigatus*. *Blood.* 2010; 116:5170–5180. [PubMed: 20829368]
10. Moyes DL, Runglall M, Murciano C, Shen C, Nayar D, Thavaraj S, Kohli A, Islam A, Mora-Montes H, Challacombe SJ, et al. A biphasic innate immune MAPK response discriminates between the yeast and hyphal forms of *Candida albicans* in epithelial cells. *Cell Host Microbe.* 2010; 8:225–235. [PubMed: 20833374] This paper demonstrates that epithelial cells can discriminate between colonizing (yeast cell) and invading (filamentous) morphotypes of *C. albicans*, thereby calibrating innate immune activation to the invasive potential of the prevalent fungal morphotype.
11. Hohl TM, Feldmesser M, Perlin DS, Pamer EG. Caspofungin modulates inflammatory responses to *Aspergillus fumigatus* through stage-specific effects on fungal beta-glucan exposure. *J Infect Dis.* 2008; 198:176–185. [PubMed: 18500928]
12. Biondo C, Signorino G, Costa A, Midiri A, Gerace E, Galbo R, Bellantoni A, Malara A, Beninati C, Teti G, et al. Recognition of yeast nucleic acids triggers a host-protective type I interferon response. *Eur J Immunol.* 2011; 41:1969–1979. [PubMed: 21480215]
13. Bourgeois C, Majer O, Frohner IE, Lesiak-Markowicz I, Hildering KS, Glaser W, Stockinger S, Decker T, Akira S, Muller M, et al. Conventional dendritic cells mount a type I IFN response against *Candida* spp. requiring novel phagosomal TLR7-mediated IFN-beta signaling. *J Immunol.* 2011; 186:3104–3112. [PubMed: 21282509]
14. Kasperkovitz PV, Cardenas ML, Vyas JM. TLR9 is actively recruited to *Aspergillus fumigatus* phagosomes and requires the N-terminal proteolytic cleavage domain for proper intracellular trafficking. *J Immunol.* 2010; 185:7614–7622. [PubMed: 21059889]
15. von Bernuth H, Picard C, Jin Z, Pankla R, Xiao H, Ku CL, Chrabieh M, Mustapha IB, Ghandil P, Camcioglu Y, et al. Pyogenic bacterial infections in humans with MyD88 deficiency. *Science.* 2008; 321:691–696. [PubMed: 18669862]
16. Plantinga TS, Johnson MD, Scott WK, van de Vosse E, Velez Edwards DR, Smith PB, Alexander BD, Yang JC, Kremer D, Laird GM, et al. Toll-like Receptor 1 Polymorphisms Increase Susceptibility to Candidemia. *J Infect Dis.* 2012; 205:934–943. [PubMed: 22301633]
17. Bochud PY, Chien JW, Marr KA, Leisenring WM, Upton A, Janer M, Rodrigues SD, Li S, Hansen JA, Zhao LP, et al. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. *N Engl J Med.* 2008; 359:1766–1777. [PubMed: 18946062]
18. Goodridge HS, Reyes CN, Becker CA, Katsumoto TR, Ma J, Wolf AJ, Bose N, Chan AS, Magee AS, Danielson ME, et al. Activation of the innate immune receptor Dectin-1 upon formation of a 'phagocytic synapse'. *Nature.* 2011; 472:471–475. [PubMed: 21525931] The authors provide an important insight into the initiation of Dectin-1-mediated signaling events by demonstrating that

particulate ligands cluster and activate Dectin-1, displacing two phosphatases from the phagocytic cup. This mechanism permits macrophage to focus immune responses upon direct pathogen engagement.

19. Strasser D, Neumann K, Bergmann H, Marakalala MJ, Guler R, Rojowska A, Hopfner KP, Brombacher F, Urlaub H, Baier G, et al. Syk kinase-coupled C-type lectin receptors engage protein kinase C-sigma to elicit Card9 adaptor-mediated innate immunity. *Immunity*. 2012; 36:32–42. [PubMed: 22265677]
20. Gringhuis SI, den Dunnen J, Litjens M, van der Vlist M, Wevers B, Bruijns SC, Geijtenbeek TB. Dectin-1 directs T helper cell differentiation by controlling noncanonical NF-kappaB activation through Raf-1 and Syk. *Nat Immunol*. 2009; 10:203–213. [PubMed: 19122653]
21. Taylor PR, Tsoni SV, Willment JA, Dennehy KM, Rosas M, Findon H, Haynes K, Steele C, Botto M, Gordon S, et al. Dectin-1 is required for beta-glucan recognition and control of fungal infection. *Nat Immunol*. 2007; 8:31–38. [PubMed: 17159984]
22. Wells CA, Salvage-Jones JA, Li X, Hitchens K, Butcher S, Murray RZ, Beckhouse AG, Lo YL, Manzanero S, Cobbold C, et al. The macrophage-inducible C-type lectin, mincle, is an essential component of the innate immune response to *Candida albicans*. *J Immunol*. 2008; 180:7404–7413. [PubMed: 18490740]
23. Saijo S, Ikeda S, Yamabe K, Kakuta S, Ishigame H, Akitsu A, Fujikado N, Kusaka T, Kubo S, Chung SH, et al. Dectin-2 recognition of alpha-mannans and induction of Th17 cell differentiation is essential for host defense against *Candida albicans*. *Immunity*. 2010; 32:681–691. [PubMed: 20493731]
24. Werner JL, Metz AE, Horn D, Schoeb TR, Hewitt MM, Schwiebert LM, Faro-Trindade I, Brown GD, Steele C. Requisite role for the dectin-1 beta-glucan receptor in pulmonary defense against *Aspergillus fumigatus*. *J Immunol*. 2009; 182:4938–4946. [PubMed: 19342673]
25. Saijo S, Fujikado N, Furuta T, Chung SH, Kotaki H, Seki K, Sudo K, Akira S, Adachi Y, Ohno N, et al. Dectin-1 is required for host defense against *Pneumocystis carinii* but not against *Candida albicans*. *Nat Immunol*. 2007; 8:39–46. [PubMed: 17159982]
26. Gorjestani S, Yu M, Tang B, Zhang D, Wang D, Lin X. Phospholipase Cgamma2 (PLCgamma2) is key component in Dectin-2 signaling pathway, mediating anti-fungal innate immune responses. *J Biol Chem*. 2011; 286:43651–43659. [PubMed: 22041900]
27. Gross O, Gewies A, Finger K, Schafer M, Sparwasser T, Peschel C, Forster I, Ruland J. Card9 controls a non-TLR signalling pathway for innate anti-fungal immunity. *Nature*. 2006; 442:651–656. [PubMed: 16862125]
28. Sousa Mda G, Reid DM, Schweighoffer E, Tybulewicz V, Ruland J, Langhorne J, Yamasaki S, Taylor PR, Almeida SR, Brown GD. Restoration of pattern recognition receptor costimulation to treat chromoblastomycosis, a chronic fungal infection of the skin. *Cell Host Microbe*. 2011; 9:436–443. [PubMed: 21575914] This study demonstrates that inadequate innate immune activation can lead to chronic fungal infection. Innate immune augmentation via TLR agonism resolves murine chromoblastomycosis and provides a proof of concept to advance into a clinical trial.
29. Gross O, Poeck H, Bscheider M, Dostert C, Hanneschlager N, Endres S, Hartmann G, Tardivel A, Schweighoffer E, Tybulewicz V, et al. Syk kinase signalling couples to the Nlrp3 inflammasome for anti-fungal host defence. *Nature*. 2009; 459:433–436. [PubMed: 19339971]
30. Hise AG, Tomalka J, Ganesan S, Patel K, Hall BA, Brown GD, Fitzgerald KA. An essential role for the NLRP3 inflammasome in host defense against the human fungal pathogen *Candida albicans*. *Cell Host Microbe*. 2009; 5:487–497. [PubMed: 19454352]
31. Joly S, Ma N, Sadler JJ, Soll DR, Cassel SL, Sutterwala FS. Cutting edge: *Candida albicans* hyphae formation triggers activation of the Nlrp3 inflammasome. *J Immunol*. 2009; 183:3578–3581. [PubMed: 19684085]
32. Kumar H, Kumagai Y, Tsuchida T, Koenig PA, Satoh T, Guo Z, Jang MH, Saitoh T, Akira S, Kawai T. Involvement of the NLRP3 inflammasome in innate and humoral adaptive immune responses to fungal beta-glucan. *J Immunol*. 2009; 183:8061–8067. [PubMed: 20007575]
33. Lev-Sagie A, Prus D, Linhares IM, Lavy Y, Ledger WJ, Witkin SS. Polymorphism in a gene coding for the inflammasome component NALP3 and recurrent vulvovaginal candidiasis in

- women with vulvar vestibulitis syndrome. *Am J Obstet Gynecol.* 2009; 200:303, e301–e306. [PubMed: 19254587]
34. Tomalka J, Ganesan S, Azodi E, Patel K, Majmudar P, Hall BA, Fitzgerald KA, Hise AG. A novel role for the NLRC4 inflammasome in mucosal defenses against the fungal pathogen *Candida albicans*. *PLoS Pathog.* 2011; 7 e1002379.
 35. van de Veerdonk FL, Joosten LA, Devesa I, Mora-Montes HM, Kanneganti TD, Dinarello CA, van der Meer JW, Gow NA, Kullberg BJ, Netea MG. Bypassing pathogen-induced inflammasome activation for the regulation of interleukin-1 β production by the fungal pathogen *Candida albicans*. *J Infect Dis.* 2009; 199:1087–1096. [PubMed: 19222370]
 36. Gringhuis SI, Kaptein TM, Wevers BA, Theelen B, van der Vlist M, Boekhout T, Geijtenbeek TB. Dectin-1 is an extracellular pathogen sensor for the induction and processing of IL-1 β via a noncanonical caspase-8 inflammasome. *Nat Immunol.* 2012; 13:246–254. [PubMed: 22267217]
This paper shows that the apoptosis-related caspase-8 has the capacity to process pro-IL-1 β into mature IL-1 β when recruited into a complex with Card9 and Bcl10 in response to Dectin-1/Syk signaling.
 37. Ramirez-Ortiz ZG, Lee CK, Wang JP, Boon L, Specht CA, Levitz SM. A nonredundant role for plasmacytoid dendritic cells in host defense against the human fungal pathogen *Aspergillus fumigatus*. *Cell Host Microbe.* 2011; 9:415–424. [PubMed: 21575912]
 38. Kawakami K, Kinjo Y, Yara S, Koguchi Y, Uezu K, Nakayama T, Taniguchi M, Saito A. Activation of Valpha14(+) natural killer T cells by alpha-galactosylceramide results in development of Th1 response and local host resistance in mice infected with *Cryptococcus neoformans*. *Infect Immun.* 2001; 69:213–220. [PubMed: 11119508]
 39. Cohen NR, Tatituri RV, Rivera A, Watts GF, Kim EY, Chiba A, Fuchs BB, Mylonakis E, Besra GS, Levitz SM, et al. Innate recognition of cell wall beta-glucans drives invariant natural killer T cell responses against fungi. *Cell Host Microbe.* 2011; 10:437–450. [PubMed: 22100160]
 40. Boyle KB, Gyori D, Sindrilaru A, Scharffetter-Kochanek K, Taylor PR, Mocsai A, Stephens LR, Hawkins PT. Class IA phosphoinositide 3-kinase beta and delta regulate neutrophil oxidase activation in response to *Aspergillus fumigatus* hyphae. *J Immunol.* 2011; 186:2978–2989. [PubMed: 21257963]
 41. Li X, Utomo A, Cullere X, Choi MM, Milner DA Jr, Venkatesh D, Yun SH, Mayadas TN. The beta-glucan receptor Dectin-1 activates the integrin Mac-1 in neutrophils via Vav protein signaling to promote *Candida albicans* clearance. *Cell Host Microbe.* 2011; 10:603–615. [PubMed: 22177564]
 42. Romani L, Fallarino F, De Luca A, Montagnoli C, D'Angelo C, Zelante T, Vacca C, Bistoni F, Fioretti MC, Grohmann U, et al. Defective tryptophan catabolism underlies inflammation in mouse chronic granulomatous disease. *Nature.* 2008; 451:211–215. [PubMed: 18185592]
 43. Bianchi M, Hakkin A, Brinkmann V, Siler U, Seger RA, Zychlinsky A, Reichenbach J. Restoration of NET formation by gene therapy in CGD controls aspergillosis. *Blood.* 2009; 114:2619–2622. [PubMed: 19541821]
 44. Urban CF, Ermert D, Schmid M, Abu-Abad U, Goosmann C, Nacken W, Brinkmann V, Jungblut PR, Zychlinsky A. Neutrophil extracellular traps contain calprotectin, a cytosolic protein complex involved in host defense against *Candida albicans*. *PLoS Pathog.* 2009; 5 e1000639.
 45. Bruns S, Kniemeyer O, Hasenberg M, Aimaniananda V, Nietzsche S, Thywissen A, Jeron A, Latge JP, Brakhage AA, Gunzer M. Production of extracellular traps against *Aspergillus fumigatus* in vitro and in infected lung tissue is dependent on invading neutrophils and influenced by hydrophobin RodA. *PLoS Pathog.* 2010; 6 e1000873.
 46. Menegazzi R, Decleva E, Dri P. Killing by neutrophil extracellular traps: fact or folklore? *Blood.* 2012; 119:1214–1216. [PubMed: 22210873]
 47. Greenblatt MB, Aliprantis A, Hu B, Glimcher LH. Calcineurin regulates innate antifungal immunity in neutrophils. *J Exp Med.* 2010; 207:923–931. [PubMed: 20421389] The authors demonstrate that neutrophil calcineurin expression regulates *C. albicans* killing *in vitro* and *in vivo*. Thus, beyond the well-known effects on T cell function, targeting calcineurin therapeutically during transplantation may lower phagocyte defenses against opportunistic fungi.

48. Reeves EP, Lu H, Jacobs HL, Messina CG, Bolsover S, Gabella G, Potma EO, Warley A, Roes J, Segal AW. Killing activity of neutrophils is mediated through activation of proteases by K⁺ flux. *Nature*. 2002; 416:291–297. [PubMed: 11907569]
49. Vethanayagam RR, Almyroudis NG, Grimm MJ, Lewandowski DC, Pham CT, Blackwell TS, Petraitiene R, Petraitis V, Walsh TJ, Urban CF, et al. Role of NADPH oxidase versus neutrophil proteases in antimicrobial host defense. *PLoS One*. 2011; 6:e28149. [PubMed: 22163282]
50. Winters MS, Chan Q, Caruso JA, Deepe GS Jr. Metallomic analysis of macrophages infected with *Histoplasma capsulatum* reveals a fundamental role for zinc in host defenses. *J Infect Dis*. 2010; 202:1136–1145. [PubMed: 20731582]
51. Hohl TM, Rivera A, Lipuma L, Gallegos A, Shi C, Mack M, Pamer EG. Inflammatory monocytes facilitate adaptive CD4 T cell responses during respiratory fungal infection. *Cell Host Microbe*. 2009; 6:470–481. [PubMed: 19917501]
52. Wüthrich M, Ersland K, Galles KJ, Sullivan TD, Klein BS. Fungi subvert vaccine T cell priming at the respiratory mucosa by preventing chemokine-induced influx of inflammatory monocytes. *Immunity*. 2012 **in press**. This article, together with [51] and [53], highlight the role of inflammatory monocytes and monocyte-derived dendritic cells for the induction of *Aspergillus*-, *Blastomyces*-, and *Histoplasma*-specific CD4 T cells in the lung.
53. Ersland K, Wüthrich M, Klein BS. Dynamic interplay among monocyte-derived, dermal, and resident lymph node dendritic cells during the generation of vaccine immunity to fungi. *Cell Host Microbe*. 2010; 7:474–487. [PubMed: 20542251]
54. Wüthrich M, Hung CY, Gern BH, Pick-Jacobs JC, Galles KJ, Filutowicz HI, Cole GT, Klein BS. A TCR transgenic mouse reactive with multiple systemic dimorphic fungi. *J Immunol*. 2011; 187:1421–1431. [PubMed: 21705621]
55. Rivera A, Ro G, Van Epps HL, Simpson T, Leiner I, Sant'Angelo DB, Pamer EG. Innate immune activation and CD4⁺ T cell priming during respiratory fungal infection. *Immunity*. 2006; 25:665–675. [PubMed: 17027299]
56. Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, Ho AW, Hai JH, Yu JJ, Jung JW, et al. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. *J Exp Med*. 2009; 206:299–311. [PubMed: 19204111]
57. Kagami S, Rizzo HL, Kurtz SE, Miller LS, Blauvelt A. IL-23 and IL-17A, but not IL-12 and IL-22, are required for optimal skin host defense against *Candida albicans*. *J Immunol*. 2010; 185:5453–5462. [PubMed: 20921529]
58. Deepe GS Jr, Gibbons RS. Interleukins 17 and 23 influence the host response to *Histoplasma capsulatum*. *J Infect Dis*. 2009; 200:142–151. [PubMed: 19469707]
59. Rudner XL, Happel KI, Young EA, Shellito JE. Interleukin-23 (IL-23)-IL-17 cytokine axis in murine *Pneumocystis carinii* infection. *Infect Immun*. 2007; 75:3055–3061. [PubMed: 17403873]
60. Werner JL, Gessner MA, Lilly LM, Nelson MP, Metz AE, Horn D, Dunaway CW, Deshane J, Chaplin DD, Weaver CT, et al. Neutrophils produce interleukin 17A (IL-17A) in a dectin-1- and IL-23-dependent manner during invasive fungal infection. *Infect Immun*. 2011; 79:3966–3977. [PubMed: 21807912]
61. Martin B, Hirota K, Cua DJ, Stockinger B, Veldhoen M. Interleukin-17-producing gammadelta T cells selectively expand in response to pathogen products and environmental signals. *Immunity*. 2009; 31:321–330. [PubMed: 19682928]
62. Wüthrich M, Gern B, Hung CY, Ersland K, Rocco N, Pick-Jacobs J, Galles K, Filutowicz H, Warner T, Evans M, et al. Vaccine-induced protection against 3 systemic mycoses endemic to North America requires Th17 cells in mice. *J Clin Invest*. 2011; 121:554–568. [PubMed: 21206087] This article demonstrates the obligate and sufficient role for Th17 cells in vaccine-induced immunity to three systemic endemic fungi.
63. Zelante T, De Luca A, Bonifazi P, Montagnoli C, Bozza S, Moretti S, Belladonna ML, Vacca C, Conte C, Mosci P, et al. IL-23 and the Th17 pathway promote inflammation and impair antifungal immune resistance. *Eur J Immunol*. 2007; 37:2695–2706. [PubMed: 17899546]
64. Loures FV, Pina A, Felonato M, Calich VL. TLR2 is a negative regulator of Th17 cells and tissue pathology in a pulmonary model of fungal infection. *J Immunol*. 2009; 183:1279–1290. [PubMed: 19553529]

65. Kroetz DN, Deepe GS Jr. CCR5 dictates the equilibrium of proinflammatory IL-17+ and regulatory Foxp3+ T cells in fungal infection. *J Immunol.* 2010; 184:5224–5231. [PubMed: 20335531]
66. Pandiyan P, Conti HR, Zheng L, Peterson AC, Mathern DR, Hernandez-Santos N, Edgerton M, Gaffen SL, Lenardo MJ. CD4(+)CD25(+)Foxp3(+) regulatory T cells promote Th17 cells in vitro and enhance host resistance in mouse *Candida albicans* Th17 cell infection model. *Immunity.* 2011; 34:422–434. [PubMed: 21435589]
67. Hung CY, Gonzalez A, Wüthrich M, Klein BS, Cole GT. Vaccine immunity to coccidioidomycosis occurs by early activation of three signal pathways of T helper cell response (Th1, Th2, and Th17). *Infect Immun.* 2011; 79:4511–4522. [PubMed: 21859851]
68. LeibundGut-Landmann S, Gross O, Robinson MJ, Osorio F, Slack EC, Tsoni SV, Schweighoffer E, Tybulewicz V, Brown GD, Ruland J, et al. Syk- and CARD9-dependent coupling of innate immunity to the induction of T helper cells that produce interleukin 17. *Nat Immunol.* 2007; 8:630–638. [PubMed: 17450144]
69. Rivera A, Hohl TM, Collins N, Leiner I, Gallegos A, Saijo S, Coward JW, Iwakura Y, Pamer EG. Dectin-1 diversifies *Aspergillus fumigatus*-specific T cell responses by inhibiting T helper type 1 CD4 T cell differentiation. *J Exp Med.* 2011; 208:369–381. [PubMed: 21242294]
70. Robinson MJ, Osorio F, Rosas M, Freitas RP, Schweighoffer E, Gross O, Verbeek JS, Ruland J, Tybulewicz V, Brown GD, et al. Dectin-2 is a Syk-coupled pattern recognition receptor crucial for Th17 responses to fungal infection. *J Exp Med.* 2009; 206:2037–2051. [PubMed: 19703985]
71. Wüthrich M, Filutowicz HI, Warner T, Deepe GS Jr, Klein BS. Vaccine immunity to pathogenic fungi overcomes the requirement for CD4 help in exogenous antigen presentation to CD8+ T cells: implications for vaccine development in immune-deficient hosts. *J Exp Med.* 2003; 197:1405–1416. [PubMed: 12782709]
72. Xue J, Chen X, Selby D, Hung CY, Yu JJ, Cole GT. A genetically engineered live attenuated vaccine of *Coccidioides posadasii* protects BALB/c mice against coccidioidomycosis. *Infect Immun.* 2009; 77:3196–3208. [PubMed: 19487479]
73. Nanjappa SG, Heninger E, Wüthrich M, Sullivan T, Klein B. Protective antifungal memory CD8+ T cells are maintained in the absence of CD4+ T cell help and cognate antigen in mice. *J Clin Invest.* 2012; 122:987–999. [PubMed: 22354169]
74. Lin L, Ibrahim AS, Xu X, Farber JM, Avanesian V, Baquir B, Fu Y, French SW, Edwards JE Jr, Spellberg B. Th1–Th17 cells mediate protective adaptive immunity against *Staphylococcus aureus* and *Candida albicans* infection in mice. *PLoS Pathog.* 2009; 5 e1000703.
75. Diaz-Arevalo D, Bagramyan K, Hong TB, Ito JI, Kalkum M. CD4+ T cells mediate the protective effect of the recombinant Asp f3-based anti-aspergillosis vaccine. *Infect Immun.* 2011; 79:2257–2266. [PubMed: 21422177]
76. Bär E, Gladiator A, Bastidas S, Roschitzki B, Acha-Orbea H, Oxenius A, LeibundGut-Landmann S. A Novel T Helper Cell Epitope of *Candida albicans* Mediates Protection from Fungal Infection. *J Immunol.* 2012 (**In press**). This study describes a naturally processed and presented fungal CD4⁺ T cell epitope that is conserved in multiple clinically relevant *Candida* species. In vaccine formulations, the epitope elicits a protective response in murine models of systemic candidiasis.
77. Stuehler C, Khanna N, Bozza S, Zelante T, Moretti S, Kruhm M, Lurati S, Conrad B, Worschech E, Stevanovic S, et al. Cross-protective TH1 immunity against *Aspergillus fumigatus* and *Candida albicans*. *Blood.* 2011; 117:5881–5891. [PubMed: 21441461]
78. Rapaka RR, Ricks DM, Alcorn JF, Chen K, Khader SA, Zheng M, Plevy S, Bengten E, Kolls JK. Conserved natural IgM antibodies mediate innate and adaptive immunity against the opportunistic fungus *Pneumocystis murina*. *J Exp Med.* 2010; 207:2907–2919. [PubMed: 21149550]
79. Sandini S, La Valle R, Deaglio S, Malavasi F, Cassone A, De Bernardis F. A highly immunogenic recombinant and truncated protein of the secreted aspartic proteases family (rSap2t) of *Candida albicans* as a mucosal anticandidal vaccine. *FEMS Immunol Med Microbiol.* 2011; 62:215–224. [PubMed: 21535228]
80. Bromuro C, Romano M, Chiani P, Berti F, Tontini M, Proietti D, Mori E, Torosantucci A, Costantino P, Rappuoli R, et al. Beta-glucan-CRM197 conjugates as candidates antifungal vaccines. *Vaccine.* 2010; 28:2615–2623. [PubMed: 20096763]

81. Xin H, Dziadek S, Bundle DR, Cutler JE. Synthetic glycopeptide vaccines combining beta-mannan and peptide epitopes induce protection against candidiasis. *Proc Natl Acad Sci U S A*. 2008; 105:13526–13531. [PubMed: 18725625]
82. Conti HR, Baker O, Freeman AF, Jang WS, Holland SM, Li RA, Edgerton M, Gaffen SL. New mechanism of oral immunity to mucosal candidiasis in hyper-IgE syndrome. *Mucosal Immunol*. 2011; 4:448–455. [PubMed: 21346738]
83. Avci FY, Li X, Tsuji M, Kasper DL. A mechanism for glycoconjugate vaccine activation of the adaptive immune system and its implications for vaccine design. *Nat Med*. 2011; 17:1602–1609. [PubMed: 22101769]
84. Huang H, Ostroff GR, Lee CK, Specht CA, Levitz SM. Robust stimulation of humoral and cellular immune responses following vaccination with antigen-loaded beta-glucan particles. *MBio*. 2010; 1
85. Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Sriel AB, Venselaar H, Elbers CC, Johnson MD, Cambi A, Huysamen C, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. *N Engl J Med*. 2009; 361:1760–1767. [PubMed: 19864674]
86. Plantinga TS, van der Velden WJ, Ferwerda B, van Sriel AB, Adema G, Feuth T, Donnelly JP, Brown GD, Kullberg BJ, Blijlevens NM, et al. Early stop polymorphism in human DECTIN-1 is associated with increased candida colonization in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2009; 49:724–732. [PubMed: 19614557]
87. Cunha C, Di Ianni M, Bozza S, Giovannini G, Zagarella S, Zelante T, D'Angelo C, Pierini A, Pitzurra L, Falzetti F, et al. Dectin-1 Y238X polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. *Blood*. 2010; 116:5394–5402. [PubMed: 20807886]
88. Chai LY, de Boer MG, van der Velden WJ, Plantinga TS, van Sriel AB, Jacobs C, Halkes CJ, Vonk AG, Blijlevens NM, van Dissel JT, et al. The Y238X stop codon polymorphism in the human beta-glucan receptor dectin-1 and susceptibility to invasive aspergillosis. *J Infect Dis*. 2011; 203:736–743. [PubMed: 21242599]
89. Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, Pfeifer D, Veelken H, Warnatz K, Tahami F, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. *N Engl J Med*. 2009; 361:1727–1735. [PubMed: 19864672]
90. Holland SM. Chronic granulomatous disease. *Clin Rev Allergy Immunol*. 2010; 38:3–10. [PubMed: 19504359]
91. de Beaucoudrey L, Samarina A, Bustamante J, Cobat A, Boisson-Dupuis S, Feinberg J, Al-Muhsen S, Janniere L, Rose Y, de Suremain M, et al. Revisiting human IL-12Rbeta1 deficiency: a survey of 141 patients from 30 countries. *Medicine (Baltimore)*. 2010; 89:381–402. [PubMed: 21057261]
92. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, Freeman AF, Demidowich A, Davis J, Turner ML, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 2007; 357:1608–1619. [PubMed: 17881745]
93. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, Kawamura N, Ariga T, Pasic S, Stojkovic O, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature*. 2007; 448:1058–1062. [PubMed: 17676033]
94. Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A, Toubiana J, Itan Y, Audry M, Nitschke P, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med*. 2011
95. van de Veerdonk FL, Plantinga TS, Hoischen A, Smeekens SP, Joosten LA, Gilissen C, Arts P, Rosentul DC, Carmichael AJ, Smits-van der Graaf CA, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med*. 2011; 365:54–61. [PubMed: 21714643]
96. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, Migaud M, Israel L, Chrabieh M, Audry M, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science*. 2011; 332:65–68. [PubMed: 21350122]
97. Kisand K, Boe Wolff AS, Podkrajsek KT, Tserel L, Link M, Kisand KV, Ersvaer E, Perheentupa J, Erichsen MM, Bratanic N, et al. Chronic mucocutaneous candidiasis in APECED or thymoma

- patients correlates with autoimmunity to Th17-associated cytokines. *J Exp Med.* 2010; 207:299–308. [PubMed: 20123959]
98. Puel A, Doffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, Cobat A, Ouachee-Chardin M, Toulon A, Bustamante J, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med.* 2010; 207:291–297. [PubMed: 20123958]

\$watermark-text

\$watermark-text

\$watermark-text

Highlights

Genetic defects predispose to fungal infections and illustrate key defense mechanisms

C type lectin receptor signaling pathways play a central role in immunity to fungi

Toll-like receptor agonism can resolve fungal infections

IL-17 is a key mediator of antifungal immunity, particularly at mucosal surfaces

Experimental fungal vaccines elicit protective immunity by Th1 and Th17 cells

\$watermark-text

\$watermark-text

\$watermark-text

Figure 1.

Medically relevant fungi, syndromes, and common sites of disease.

The asterisks (*) indicate examples of organ involvement following fungal dissemination from the primary site of infection. Disseminated fungal disease occurs typically in severely immune compromised patients, e.g. disseminated cryptococcosis in patients with CD4 T cell dysfunction.

Figure 2.

Pattern recognition receptors and signaling pathways contributing to innate and adaptive antifungal responses. The recognition of fungal cell wall components by CLRs induces Syk-dependent and -independent signaling events that converge in the activation of NFAT, NF-κB and processing enzymes and result in the production of cytokines including those that drive T cell differentiation. The depicted signaling pathways are all induced by Dectin-1, but whether in particular the inflammasome and RAF signaling are also activated by Dectin-2 and Mincle, and whether Mincle can trigger antifungal T cell differentiation remains to be demonstrated. Phospholipomannans and O-linked mannans are recognized by TLRs at the plasma membrane, whereas fungal nucleic acids are sensed by endosomal TLRs and induce

NF- κ B-, MAPK- and IRF-dependent cytokine production. Numbers refer to human genetic polymorphisms listed in Table I. Th17 activation in response to CLR signaling is drawn out of scale to illustrate the polymorphisms that affect Th17 differentiation and function.

\$watermark-text

\$watermark-text

\$watermark-text

Table I**Genetic Polymorphisms associated with Spontaneous Fungal Disease Development**

	Gene	Mutation ¹	Associated Disease	Ref.
1	<i>Dectin-1</i> ²	<ul style="list-style-type: none"> Y238X (AR) biological activity 	<ul style="list-style-type: none"> mild CMC³ (vaginal candidiasis, onychomycosis) susceptibility to aspergillosis (2 of 3 studies) and <i>Candida</i> colonization in HCT recipients 	[85] [86–88]
2	<i>CARD9</i>	<ul style="list-style-type: none"> Q295X (AR) lack of protein expression 	<ul style="list-style-type: none"> CMC³ (thrush, vaginal candidiasis), dermatophytosis 	[89]
3	<i>gp91^{phox}</i> <i>p22^{phox}</i> <i>p67^{phox}</i> <i>p47^{phox}</i>	<ul style="list-style-type: none"> X-linked (<i>gp91^{phox}</i>) or AR (other subunits) mutations NADPH oxidase function 	<ul style="list-style-type: none"> CGD bacterial and fungal infections, particularly aspergillosis (<i>A. nidulans</i> is a significant pathogen) 	[90]
4	<i>IL-12Rβ1</i>	<ul style="list-style-type: none"> various mutations (AR) 	<ul style="list-style-type: none"> mild CMC (thrush, in 25% of cases) 	[91]
5	<i>STAT3</i>	<ul style="list-style-type: none"> mutations in DNA-binding or SH2 domain (AD); DNA binding activity (DN) 	<ul style="list-style-type: none"> Hyper IgE syndrome (HIES) CMC (thrush, vaginal candidiasis, onychomycosis, dermatophytosis), aspergillosis, recurrent <i>Staphylococcus aureus</i> infections 	[92,93]
6	<i>STAT1</i>	<ul style="list-style-type: none"> mutations in coiled-coil domain⁴ (AD) gain of function mutation 	<ul style="list-style-type: none"> CMC 	[94,95]
7	<i>IL-17F</i>	<ul style="list-style-type: none"> S65L (AD with incomplete penetrance) deficient receptor binding 	<ul style="list-style-type: none"> CMC 	[96]
8	<i>IL-17RA</i>	<ul style="list-style-type: none"> Q284X (AR) lack of protein expression 	<ul style="list-style-type: none"> <i>C. albicans</i> dermatitis, <i>S. aureus</i> dermatitis 	[96]
9	<i>AIRE</i>	<ul style="list-style-type: none"> various (~ 60 known, AR) IL-17A, IL-17F, and IL-22 autoantibodies 	<ul style="list-style-type: none"> APS-I / APECED⁵: autoimmune APS-I / APECED⁵: autoimmune endocrinopathies, hypoparathyroidism, adrenal insufficiency, CMC 	[97,98]

¹ first line: mutation (AR = autosomal recessive, AD = autosomal dominant); second line: effect on protein function

² The Dectin-1 Y238X allele is a common polymorphism in specific European and African populations.

³ CMC = chronic mucocutaneous candidiasis

⁴ the coiled-coil domain plays a key role in unphosphorylated STAT1 dimerization and STAT1 nuclear dephosphorylation

⁵ APS-I = autoimmune polyendocrine syndrome type I; APECED = autoimmune polyendocrinopathy candidiasis ectodermal dystrophy