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Review article

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Immune responses to human fungal pathogens and therapeutic prospects

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Abstract

Pathogenic fungi have emerged as significant causes of infectious morbidity and death in patients with acquired immunodeficiency conditions such as HIV/AIDS and following receipt of chemotherapy, immunosuppressive agents or targeted biologics for neoplastic or autoimmune diseases, or transplants for end organ failure. Furthermore, in recent years, the spread of multidrug-resistant *Candida auris* has caused life-threatening outbreaks in health-care facilities worldwide and raised serious concerns for global public health. Rapid progress in the discovery and functional characterization of inborn errors of immunity that predispose to fungal disease and the development of clinically relevant animal models have enhanced our understanding of fungal recognition and effector pathways and adaptive immune responses. In this Review, we synthesize our current understanding of the cellular and molecular determinants of mammalian antifungal immunity, focusing on observations that show promise for informing risk stratification, prognosis, prophylaxis and therapies to combat life-threatening fungal infections in vulnerable patient populations.

Sections

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Introduction

Of the approximately five million fungal species, only a few regularly infect humans. However, in recent decades, the AIDS pandemic and the increasing number of patients who have received myeloablative chemotherapy and/or solid organ or haematopoietic stem cell transplantation (HSCT) have led to a marked increase in the global burden of fungal disease in these immunocompromised individuals (Table 1 and Supplementary Table 1). Furthermore, new at-risk populations have emerged, including patients with severe respiratory virus-associated mould disease and individuals being treated with novel, precision immune-targeted biologics (monoclonal antibodies or small-molecule kinase inhibitors) for autoimmune, inflammatory and/or neoplastic disorders[1–3]. Emerging fungi such as multidrug-resistant *Candida auris* present new threats to public health[4] (Box 1). Fungi exhibit distinct morphotypes (such as yeast and hyphae) and can cause superficial and life-threatening invasive infections, primarily in immunocompetent individuals and immunocompromised individuals, respectively (Table 1 and Supplementary Table 1).

Thus, interest in fungal immunology research has increased in recent years, catalysed by our growing understanding of the biology and functions of C-type lectin receptors (CLRs)[5,6], which are the main class of fungal-sensing pattern recognition receptors (reviewed in ref. 5). Notably, humans with inherited deficiency of the CLR adaptor protein CARD9 are susceptible to severe mucocutaneous and invasive fungal disease, without developing other infectious or non-infectious complications; this selective susceptibility to fungal infection is a unique feature among the more than 450 known inborn errors of immunity (see later)[7]. In this Review, we synthesize immunological insights from the expanding number of inborn errors of immunity that predispose to fungal infection (Table 2 and Supplementary Table 2) and from fungal infection-promoting, immune-targeted biologics (Table 3 and Supplementary Table 3), together with mechanistic insights from animal models of fungal disease. We focus on observations that have translational implications for informing risk stratification, prognosis, treatment and vaccination of fungus-infected individuals. The text is structured according to the clinical disease phenotypes that are caused by various pathogenic yeasts, moulds and dimorphic endemic fungi.

Mucocutaneous candidiasis

Candida species (primarily *Candida albicans*) are commensal yeasts of the gastrointestinal and reproductive tracts in most humans. When disruptions to the immune system and/or the resident microbiota occur, *Candida* can cause opportunistic infections at mucocutaneous or deep-seated anatomical sites, which have different requirements for immune defence[8] (Table 1). Specifically, whereas innate and adaptive lymphocytes mediate protection against mucocutaneous candidiasis, myeloid phagocytes are crucial for protection against invasive candidiasis[9]. Indeed, patients with HIV/AIDS, having low $CD4^+$ T cell counts, are at risk of developing mucocutaneous candidiasis, whereas patients with neutropenia are susceptible to invasive candidiasis, but not vice versa[8].

Mucocutaneous candidiasis presents clinically as oropharyngeal candidiasis (OPC), oesophageal candidiasis or vulvovaginal candidiasis

Table 1 | Clinical features of the most prevalent human fungal infections

Infection (most common fungal genera or species)	Fungal morphotype	Clinical presentation	Commonly affected patient population[a]	Annual global incidence; all-cause mortality	Current principles of treatment
Mucocutaneous candidiasis[b] (*Candida albicans, Candida dubliniensis, Candida glabrata*)	Yeast (with pseudohyphae and hyphae depending on the species)	Oropharyngeal or oesophageal candidiasis	HIV/AIDS, corticosteroid use	~3.3 million (HIV/AIDS only); NA	Topical or oral azoles; echinocandins (for azole-resistant *Candida* strains)
		Vaginal candidiasis	Healthy women, antibiotic use	~138 million; NA	
Invasive candidiasis (*C. albicans, C. glabrata, Candida tropicalis, Candida parapsilosis, Candida auris*)	Yeast (with pseudohyphae and hyphae depending on the species)	Candidaemia	Critical illness (ICU), after COVID-19	~750,000; ~30–40%	Echinocandins; removal of central venous catheter
		Intra-abdominal candidiasis	Abdominal surgery		
		Disseminated candidiasis	Neutropenia, corticosteroid use, SOT, low birthweight premature neonates		
Invasive aspergillosis (*Aspergillus fumigatus, Aspergillus flavus, Aspergillus terreus, Aspergillus niger*)	Filamentous mould	Pulmonary or disseminated aspergillosis	Neutropenia, corticosteroid use, HSCT, SOT, after influenza or COVID-19, ibrutinib therapy	~300,000; ~30–50%	Voriconazole (first line), isavuconazole or posaconazole; reduction of immunosuppression
		Allergic bronchopulmonary aspergillosis	Atopic individuals	~5 million[c]; NA	Itraconazole and corticosteroids
Cryptococcosis[b] (*Cryptococcus neoformans, C. gattii*)	Yeast	Pneumonia	HIV/AIDS, corticosteroid use	~223,000 (HIV/AIDS only); ~20–70%	Amphotericin B (+ 5-flucytosine for CNS disease) followed by fluconazole; reduction of immunosuppression
		CNS or disseminated cryptococcosis	HIV/AIDS, HSCT, ibrutinib therapy		
Pneumocystosis[b] (*Pneumocystis jirovecii*)	Cysts and trophozoites	Pneumonia	HIV/AIDS, corticosteroid use	~500,000; ~20–80%	Trimethoprim–sulfamethoxazole; reduction of immunosuppression
		Disseminated infection	HIV/AIDS		

An expanded version of Table 1 is presented in Supplementary Table 1. CNS, central nervous system; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; NA, not applicable; SOT, solid organ transplantation. [a]At-risk conditions caused by inborn errors of immunity or administration of immune pathway-targeted biologics are presented separately in Tables 2 and 3. [b]AIDS-defining illness. [c]Global burden of infection.

(VVC). A major breakthrough in the field of fungal immunology has been the discovery that IL-17 receptor (IL-17R) signalling is a crucial defence pathway against mucocutaneous candidiasis[10] (Fig. 1a). Mice and humans with complete genetic deficiencies in IL-17RA, IL-17RC or their adaptor protein ACT1 (also known as TRAF3IP2) are highly susceptible to fully penetrant chronic mucocutaneous candidiasis (CMC)[10–16]. Several other CMC-manifesting inborn errors of immunity exhibit varying degrees of impaired IL-17 cellular responses and/or decreased frequencies of circulating T helper 17 (T_H17) cells[9,17] (Table 2 and Supplementary Table 2). Moreover, administration of IL-17 pathway-targeting biologics for the treatment of psoriasis has been associated with mild, treatment-responsive OPC, with a mean frequency of ~2–12%, depending on the biologic agent[18,19] (Table 3). The relatively low frequency of OPC and the lack of CMC in these patients likely reflect that mucosal IL-17 responses are not completely inhibited by these biologics and are consistent with the notion that profound and sustained inhibition of the IL-17 pathway is required for the development of mucosal fungal disease[18].

At the cellular level, IL-17A and IL-17F are produced by αβ T cells, γδ T cells and type 3 innate lymphoid cells during OPC[14,15] (Fig. 1a). The *C. albicans* toxin candidalysin, Langerin-expressing dendritic cells (DCs) and microbiota-derived retinoic acid prime natural T_H17 cell responses initially, followed by *Candida*-specific T_H17 cell generation that is facilitated by antigen presentation by $CCR2^+$ monocyte-derived DCs[10,20–22]. By contrast, the *C. albicans* lipase Lip2 was recently shown to suppress IL-17 responses by γδ T cells indirectly through inhibition of IL-23 production by tissue-resident DCs[23]. Notably, mucosal $CD8^+$ T cells, γδ T cells and type 3 innate lymphoid cells can compensate for IL-17 production when T_H17 cells are absent, as *Cd4*$^{-/-}$ mice are not susceptible to OPC in primary or recall models and patients with loss-of-expression *CD4* mutations or idiopathic CD4 lymphocytopenia who lack $CD4^+$ T cells are resistant to CMC[18,24–26]. Thus, decreased levels of circulating T_H17 cells may not in isolation be a reliable immunological biomarker for risk assessment of human CMC, and the direct evaluation of global mucosal IL-17 responses may be needed to determine the mechanisms of CMC.

Following IL-17RA–IL-17RC engagement on epithelial cells by IL-17A and/or IL-17F, the generation of antimicrobial peptides restricts local *Candida* growth and epithelial invasion[10,13,20]. Furthermore, the epithelial cell pattern recognition receptor EPHA2 recognizes fungal β-glucan, activates STAT3 and epidermal growth factor receptor 2 (EGFR2) signalling, and boosts mucosal IL-17 responses likely through priming the production of IL-1α/IL-1β during mucosal infection, which facilitates natural T_H17 cell proliferation[20,22,27]. IL-22, another type 17 cytokine produced by lymphocytes, binds to IL-22RA1–IL-10RB on epithelial cells, activates STAT3 and promotes epithelial cell proliferation and repair, thereby replenishing IL-17R-expressing epithelial cells and enabling their responsiveness to IL-17A and IL-17F[28] (Fig. 1a).

Whereas IL-17 is protective during OPC, in certain settings — such as the autoimmune syndrome of AIRE deficiency, which features an incompletely penetrant association between CMC and IL-17-neutralizing autoantibodies[18,29,30] — excessive interferon-γ (IFNγ) production by mucosal αβ T cells can promote OPC susceptibility by driving epithelial barrier disruption, which is ameliorated by IFNγ inhibition or inhibition of JAK–STAT signalling downstream of the IFNγ receptor[31] (Fig. 1b). This finding suggests that OPC susceptibility could be classified across a spectrum that encompasses impaired type 17 mucosal defences and/or immunopathology-promoting type 1 mucosal inflammation. Indeed, the recent discovery of CMC-manifesting inborn errors of immunity with intact or enhanced IL-17 responses in the setting of autoinflammation or autoimmunity (Supplementary Table 2) may uncover additional conditions in which OPC may be driven by mucosal immunopathology rather than by impaired host resistance. Notably, in patients with *STAT1* gain-of-function mutations, who universally develop CMC associated with decreased circulating T_H17 cells and increased IFNγ cellular responses, pharmacological JAK–STAT inhibition ameliorates CMC, pointing to a beneficial immunotherapeutic strategy in this setting[32].

VVC occurs at least once in ~75% of healthy women during their reproductive years. An estimated 6–9% of these women have more than three recurrent episodes of VVC per year, a pervasive condition termed 'recurrent VVC'. As opposed to OPC, VVC is characterized by maladaptive, fungus-driven, neutrophil-associated inflammation with excessive local production of alarmins and pro-inflammatory cytokines[33]. Correspondingly, genetic polymorphisms in *NLRP3, SIGLEC15, IDO1* and other genes that augment the vaginal inflammatory milieu are associated with a greater risk of recurrent VVC[33,34]. Interestingly, whereas patients with HIV/AIDS and patients receiving IL-17 pathway-targeted biologics

Box 1

Candida auris

Since 2009, when it was initially identified in Japan, *Candida auris* has rapidly spread across six continents, causing multiple outbreaks of skin colonization and subsequent life-threatening bloodstream infections in vulnerable patients; *C. auris* accounts for up to 30% of cases of candidaemia in certain health care settings[4,185,186]. *C. auris* is a major threat to public health owing to its unique propensity for long-term skin colonization, antimicrobial resistance and high person-to-person transmissibility within health care facilities, leading the US Centers for Disease Control and Prevention to designate it as an urgent threat in 2019 (ref. 187). The predilection of *C. auris* to colonize the skin, which distinguishes it from *Candida albicans* and other *Candida* species that reside within the gastrointestinal tract, has been verified both ex vivo in human and pig skin models and in vivo in mouse skin, where it establishes long-term residence within deep skin tissue and hair follicles[188,189]. *C. auris* has structurally unique mannoproteins compared with other *Candida* species, and its immune recognition by human circulating mononuclear cells and their induction of cytokine production is primarily mediated by complement receptor 3 and the mannose receptor, not dectin 1 (ref. 190). In a mouse model of skin colonization, IL-17A and IL-17F, but not IL-22, produced by innate and adaptive lymphocytes were crucial for curtailing *C. auris* skin colonization[189], and chlorhexidine application ameliorated fungal burden[189], which is in keeping with a similar finding in human patients[185]. In invasive candidiasis in mice, *C. auris* is less lethal than *Candida albicans*[189–191], yet neutrophils have been shown to be poorly recruited to sites of *C. auris* infection and to ineffectively produce neutrophil extracellular traps and kill *C. auris* relative to *C. albicans*, which suggests that *C. auris* has specific immune-evading properties that are driven by its unique mannoprotein structure[191]. A better understanding of the fungal and host determinants of the unique skin tropism of *C. auris* may help to develop improved preventive and therapeutic strategies against this pathogen.

Table 2 | Key human inborn errors of immunity that predispose to fungal infection

Gene [protein name] (chromosome arm)	Predominant cellular expression	OMIM no. (clinical syndrome)	Mode of inheritance	Fungal infection susceptibility	Other clinical phenotypes	Antifungal immunological defects
CARD9 (9q)	Myeloid phagocytes and to a lesser extent epithelial cells	212050	AR (LOF)	CMC, CNS candidiasis, phaeohyphomycosis, aspergillosis, skin mucormycosis, onychomycosis, deep dermatophytosis	None	Decreased number of blood T_H17 cells, impaired cytokine responses by PBMCs and microglia, impaired neutrophil recruitment to the CNS and killing of unopsonized *Candida* yeasts
STAT1 (2q)	Broadly expressed	614162	AD (GOF)	Invasive candidiasis, CMC, aspergillosis, mucormycosis, PJP, cryptococcosis, histoplasmosis, coccidioidomycosis	Bacterial, NTM and viral infections, autoimmunity, aneurysms, carcinomas	Decreased number of blood T_H17 cells and decreased IL-17 production by PBMCs associated with increased cellular responses to IFNα/β, IFNγ and IL-27
STAT3 (17q)	Broadly expressed	147060 (AD HIES, Job syndrome)	AD (DN)	CMC, dermatophytosis, aspergillosis, cryptococcosis, histoplasmosis, gastrointestinal tract coccidioidomycosis, skin fusariosis, PJP	Skin staphylococcal infections, bacterial pneumonias, eczema, pneumatoceles, aneurysms, skeletal abnormalities, increased IgE	Decreased number of blood T_H17 cells
IL12RB1 (19p)	Lymphoid and myeloid cells	614891 (MSMD)	AR (LOF)	CMC, cryptococcosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis	*Salmonella* and NTM infections	Impaired T_H17 cell differentiation, impaired IL-12-dependent and IL-23-dependent IFNγ production
IL17RA (22q)	Myeloid cells and epithelial cells	613953	AR (LOF)	CMC	Skin staphylococcal infections, bacterial pneumonias, eczema	Abolished IL-17 cellular responses
IL17RC (3p)	Epithelial cells	616445			None	
AIRE (21q)	mTECs and eTACs	240300 (APECED)	AR (LOF) or AD (DN)	CMC	Multiorgan autoimmunity, ectodermal dystrophy, severe COVID-19	Neutralizing serum autoantibodies to IL-17A, IL-17F and IL-22, epithelial barrier disruption caused by IFNγ produced by mucosal T cells
CYBB [gp91^{phox}] (Xp)	Myeloid phagocytes	306400 (X-linked CGD)	X-linked (LOF)	Aspergillosis, invasive candidiasis	Invasive infections with *Nocardia*, *Staphylococcus*, *Serratia* and *Burkholderia*, IBD	Impaired generation of superoxide
NCF2 [p67^{phox}] (1q)		233710 (AR CGD)	AR (LOF)			
CYBA [p22^{phox}] (16q)		233690 (AR CGD)				
NCF1 [p47^{phox}] (7q)		233700 (AR CGD)				
IFNGR1 (6q)	Broadly expressed	209950 (AR MSMD)	AR (LOF)	Histoplasmosis, coccidioidomycosis	*Salmonella* and NTM infections	Impaired IFNγ cellular responses
		615978 (AD MSMD)	AD (DN)			
GATA2 (3q)	Neutrophils, and to a lesser extent mononuclear phagocytes and T cells	614172 (MonoMAC syndrome, Emberger syndrome)	AD (HI)	Aspergillosis, cryptococcosis, histoplasmosis, coccidioidomycosis, blastomycosis, PJP	Viral and NTM infections, PAP, MDS, leukaemia, lymphedema	Decreased monocyte and DC counts, neutrophil granule abnormalities

An expanded version of Table 2 is presented in Supplementary Table 2. AD, autosomal dominant; APECED, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy; AR, autosomal recessive; CGD, chronic granulomatous disease; CMC, chronic mucocutaneous candidiasis; CNS, central nervous system; DC, dendritic cell; DN, dominant negative; eTAC, extrathymic AIRE-expressing cell; GOF, gain of function; HI, haploinsufficiency; HIES, hyper-IgE syndrome; IBD, inflammatory bowel disease; IFN, interferon; LOF, loss of function; MDS, myelodysplastic syndrome; MSMD, Mendelian susceptibility to mycobacterial disease; mTEC, medullary thymic epithelial cell; NTM, non-tuberculous mycobacteria; OMIM, Online Mendelian Inheritance in Man; PAP, pulmonary alveolar proteinosis; PBMC, peripheral blood mononuclear cell; PJP, *Pneumocystis jirovecii* pneumonia; T_H17, T helper 17.

are at increased risk of developing OPC, they are not at risk of developing VVC, in agreement with the finding that IL-17R deficiency does not impair fungal control during mouse VVC[35]. By contrast, antibiotics predispose women to VVC, but not OPC, which indicates that the vaginal microbiota has a role in restricting local growth of *Candida* through poorly defined mechanisms that require further investigation[36].

Thus, the oral and vaginal mucosal immune responses to *C. albicans* are distinct. Importantly, VVC has been a target disease for protection with the *C. albicans* agglutinin-like sequence 3 (Als3)-based vaccine, which was shown to be immunogenic and efficacious in mouse models of VVC and in women with recurrent VVC[37,38]. The Als3-based vaccine is the only fungal vaccine that has thus far exhibited clinical protection in humans[37] (Box 2).

C. albicans is effectively controlled at the cutaneous barrier by an IL-17-enforced neuroimmune axis and rarely causes clinical skin disease in humans[39]. Specifically, cutaneous *C. albicans* infection in mice promotes the activation of TRPV1$^+$ sensory neurons expressing the neuropeptide calcitonin gene-related peptide, which is both necessary and sufficient to drive protective IL-17 responses[39,40]. These neuroimmune findings paved the way for the recent demonstration that gut fungi drive IL-17-dependent neuroimmune modulation of mouse behaviour[41], further expanding our knowledge of the essential roles of neuroimmune circuits in tissue homeostasis and immunity (reviewed in ref. 42).

Invasive candidiasis

Invasive candidiasis is a leading cause of nosocomial bloodstream infection in higher-income countries, with mortality that can exceed 40% despite treatment[8]. It typically occurs in patients who are critically ill in whom *Candida* transitions from a commensal pathogen to

Table 3 | Key FDA-approved immune-targeted biologics associated with the development of human fungal infections

Molecular target	Name (and type) of biologic	Approved indications	Fungal infection susceptibility	Risk of fungal infection (mean frequency)	Non-fungal infection susceptibility	Antifungal immunological defects (when known)
TNF	Infliximab (mouse–human chimeric IgG1κ mAb)	RA, AS, psoriasis, IBD	Histoplasmosis, coccidioidomycosis, blastomycosis, PJP	Moderate/high	Mycobacterial infections (including disseminated TB)	Impaired IFNγ production and granuloma formation; impaired phagocyte trafficking and function
	Etanercept (p75 TNF soluble receptor fused to the Fc portion of IgG1)					
	Adalimumab (humanized IgG1κ mAb)		Mucosal candidiasis, invasive candidiasis, aspergillosis, phaeohyphomycosis	Low (<5%)		
	Golimumab (humanized IgG1κ mAb)					
CD52	Alemtuzumab (humanized IgG1κ mAb)	MS, CLL	Cryptococcosis, PJP, mucosal candidiasis	Moderate/high	Herpetic infections, CMV infection, toxoplasmosis, nocardiosis, pneumonias	Prolonged and profound T lymphocytopenia
IL-17A	Ixekizumab (humanized IgG4 mAb)	Psoriasis, AS, IBD	Mucosal candidiasis	Low/moderate (~2–12% depending on the biologic)	None	Impaired IL-17 cellular responses
	Secukinumab (humanized IgG1κ mAb)					
IL-17RA	Brodalumab (humanized IgG2 mAb)					
IL-12p40	Ustekinumab (humanized IgG1κ mAb)					
IL-23p19	Risankizumab (humanized IgG1κ mAb)					
	Guselkumab (humanized IgG1λ mAb)					
	Tildrakizumab (humanized IgG1κ mAb)					
JAK1/2/3	Ruxolitinib, tofacitinib, baricitinib, upadacitinib, fedratinib (kinase inhibitors)	MF, PV, GvHD, RA, IBD	Histoplasmosis, coccidioidomycosis, cryptococcosis, talaromycosis, PJP, aspergillosis	Moderate/high	Herpetic infections, CMV infection, mycobacterial infections	Impaired IFNγ and IFNλ responses, impaired lymphocyte and macrophage activation, lymphopenia
BTK	Ibrutinib, acalabrutinib, zanubrutinib (kinase inhibitors)	CLL, MZL, MCL, WM, GvHD	Aspergillosis (with CNS involvement), mucormycosis, cryptococcosis, blastomycosis, PJP	Moderate/high	Viral and bacterial infections	Impaired myeloid phagocyte activation and function
PI3K (p110δ)	Idelalisib (kinase inhibitor)	CLL, lymphomas	PJP	Moderate (~5–10%)	CMV infection, pneumonias	Impaired T cell activation

An expanded version of Table 3 is presented in Supplementary Table 3. AS, ankylosing spondylitis; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; CNS, central nervous system; GvHD, graft-versus-host disease; IBD, inflammatory bowel disease; IFN, interferon; mAb, monoclonal antibody; MCL, mantle-cell lymphoma; MF, myelofibrosis; MS, multiple sclerosis; MZL, marginal zone lymphoma; PJP, *Pneumocystis jirovecii* pneumonia; PV, polycythaemia vera; RA, rheumatoid arthritis; TB, tuberculosis; TNF, tumour necrosis factor; WM, Waldenström macroglobulinaemia.

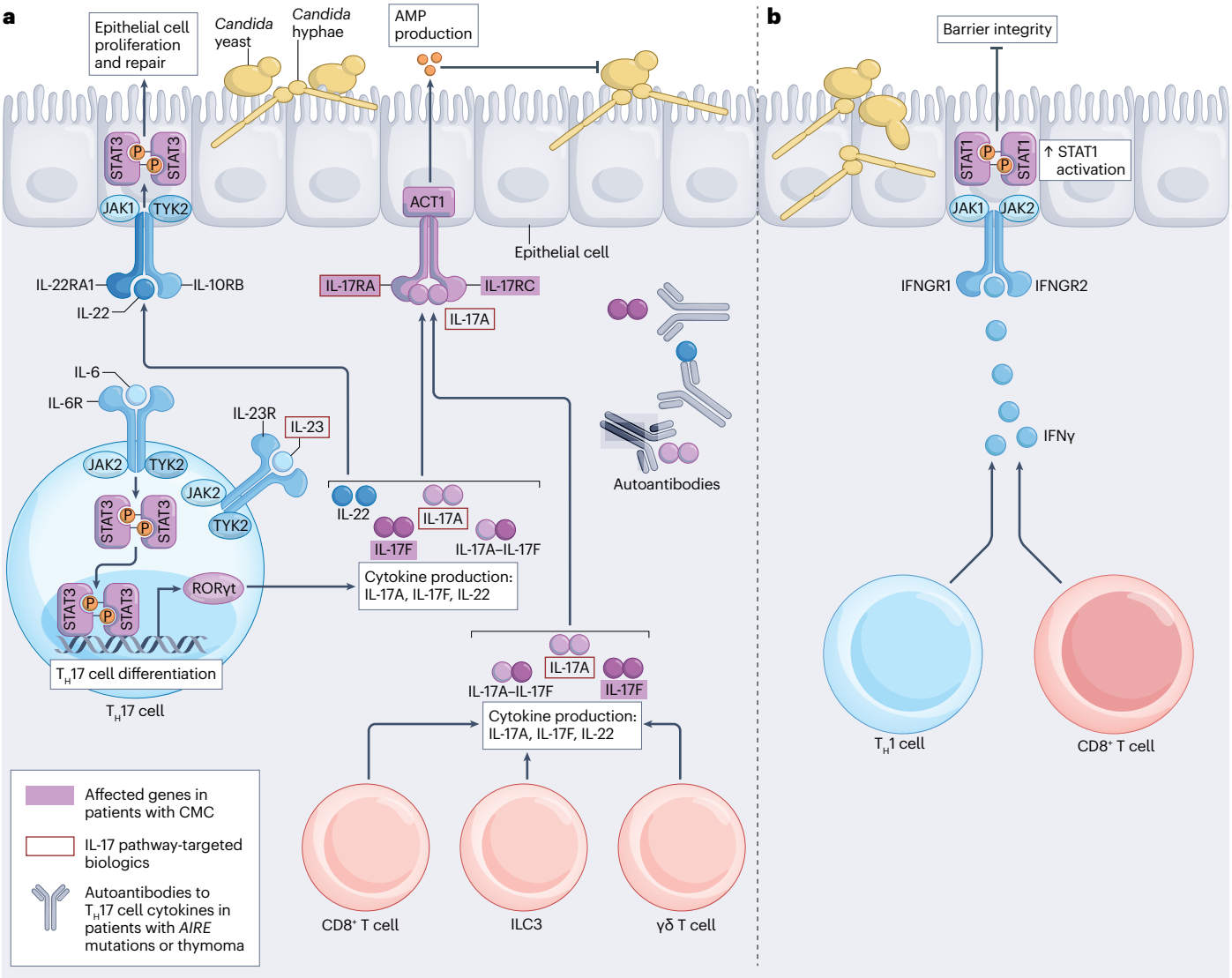


Fig. 1 | Host defence against *Candida* at the oral mucosal interface. **a**, Protective responses to *Candida* at mucosal surfaces are mediated by IL-17 and IL-22 produced by T helper 17 (T_H17) cells, $CD8^+$ T cells, type 3 innate lymphoid cells (ILC3s) and γδ T cells. T_H17 cell differentiation depends on signal transducer and activator of transcription 3 (STAT3)-mediated retinoic acid receptor-related orphan receptor-γt (RORγt) induction downstream of signalling through IL-6 receptor (IL-6R) and IL-23R, which is defective in individuals with mutations in *RORC* (which encodes RORγt), *STAT3* or *ZNF341* (which regulates STAT3 expression and function), making them highly susceptible to chronic mucocutaneous candidiasis (CMC). T_H17 cells produce IL-17A, IL-17F and IL-22. IL-17A, IL-17F and IL-17A–IL-17F bind to IL-17R, consisting of IL-17RA and IL-17RC, on suprabasal epithelial cells, which leads to the activation of ACT1 and induces the production of antimicrobial peptides (AMPs; such as β-defensin 3 and S100A8/S100A9) that restrict *Candida* growth. CMC also develops in patients with mutations in *IL17F*, *IL17RA*, *IL17RC* or *TRAF3IP2* (which encodes ACT1), and in patients with thymoma or *AIRE* mutations, both of which are associated with autoantibodies to IL-17 and/or IL-22. Furthermore, mild oral thrush can develop in a subset of patients receiving IL-17 pathway-targeted biologics such as those inhibiting IL-17A, IL-17RA, IL-12p40 (not shown) or IL-23 (Table 3). IL-22 produced by T_H17 cells, $CD8^+$ T cells, ILC3s and γδ T cells binds to the IL-22 receptor consisting of IL-22RA1 and IL-10RB on basal epithelial cells, which activates STAT3 and facilitates epithelial cell proliferation and repair, thereby enabling the replenishment and responsiveness of the IL-17R-expressing suprabasal epithelial cell layer. **b**, Mucosal type II interferonopathy. In the setting of autoimmunity caused by autoimmune regulator (AIRE) deficiency, mucosal $CD4^+$ T_H1 cells and $CD8^+$ T cells locally produce increased levels of interferon-γ (IFNγ), which binds to the IFNγ receptor consisting of IFNGR1 and IFNGR2 on epithelial cells, activates STAT1 and impairs oral epithelial barrier integrity. This leads to increased susceptibility to oropharyngeal candidiasis. JAK, Janus kinase; TYK2, tyrosine kinase 2.

an opportunistic pathogen by translocating into the bloodstream and seeding deep-seated organs such as liver, spleen and kidney[8]. Although *C. albicans* is most often responsible for invasive candidiasis, *Candida glabrata*, *Candida tropicalis* and *Candida parapsilosis* also cause disease with increasing frequency, and the multidrug-resistant *Candida auris* has spread rapidly worldwide in recent years[8] (Box 1).

Certain iatrogenic factors are typically associated with the development of invasive candidiasis in humans[8]. Broad-spectrum antibiotics induce gut dysbiosis, impair lymphocyte-mediated IL-17A-dependent and granulocyte–macrophage colony-stimulating factor (GM-CSF)-dependent intestinal immune responses and inhibit the local generation of antimicrobial peptides, thereby enhancing *Candida* gut colonization and invasion[43,44]; this antibiotic-induced susceptibility was ameliorated by IL-17A or GM-CSF immunotherapy in a mouse model of invasive candidiasis[44]. Central venous catheters or chemotherapy-induced mucositis and surgery, which breach the integrity of the cutaneous barrier or the intestinal barrier, respectively, can allow *Candida* to translocate into the bloodstream[8]. Iatrogenic immunosuppression (for example, chemotherapy-induced neutropenia or use of corticosteroids), which impairs protective myeloid phagocyte-dependent antifungal responses, facilitates the invasion of deep-seated organs by *Candida*[8]. Rapid neutrophil influx and activation in *Candida*-infected tissues are crucial for effective host defence in mice, in agreement with the profound susceptibility of humans with neutropenia to invasive candidiasis[8].

The CLRs dectin 1 (also known as CLEC7A), dectin 2 (also known as CLEC6A) and dectin 3 (also known as CLEC4D) recognize *Candida* β-glucans and α-mannans and signal through the kinase SYK and the CARD9–MALT1–BCL-10 signalling complex to activate NF-κB, collectively promoting T_H17 cell development and pro-inflammatory cytokine production[5,8]. CARD9 deficiency is so far the only known inborn error of immunity that predisposes to both mucosal candidiasis and invasive candidiasis, with a unique tropism for the central nervous system (CNS)[45] (Table 2). Mechanistically, in response to fungal candidalysin, CNS-resident microglia produce IL-1β in a CARD9-dependent manner, which mediates protective neutrophil recruitment to the CNS through CXCL1–CXCR2-dependent chemotaxis[46]. In line with this, pharmacological blockade of the CLR–SYK–CARD9 signalling axis with the SYK inhibitor fostamatinib has been associated with opportunistic fungal infections (Supplementary Table 3).

Invasive candidiasis also occurs in a small proportion of patients with severe congenital neutropenia syndromes or inborn errors of immunity that affect the phagocyte oxidative burst, such as complete myeloperoxidase deficiency or chronic granulomatous disease (caused by mutations in NADPH oxidase complex subunits)[9] (Table 2 and Supplementary Table 2). Although invasive candidiasis is not a recognized phenotype of inherited deficiency of complement component C5 (ref. 9), acute pharmacological inhibition of C5a with eculizumab increases susceptibility to *Candida* infection, which suggests a crucial role of complement activation in mounting innate antifungal responses in vulnerable patients[47] (Supplementary Table 3).

Within *Candida*-infected tissues, an intricate intercellular crosstalk orchestrates the candidacidal activity of neutrophils. Specifically, $Ly6C^+$ inflammatory monocytes and monocyte-derived DCs produce IL-15 and IL-23, respectively, which in turn activate natural killer cells to release GM-CSF, which primes neutrophils to kill *Candida*[48,49]. Consistent with these results, a phase IV clinical trial showed that GM-CSF administration in allogeneic HSCT recipients decreased the incidence of invasive candidiasis and associated mortality[50]. Neutrophil reactive oxygen species (ROS)-dependent killing of *Candida* involves dectin 1-dependent metabolic rewiring of neutrophils and dectin 1-mediated activation of the calcineurin–NFAT and MAC1 (CD11B–CD18)–VAV–PKCδ pathways[8,51]. Uraemia, which is another

Box 2

Fungal vaccines

Despite the substantial global burden, cost, morbidity and mortality associated with opportunistic fungal infections, no human fungal vaccine has been licensed to date. Major challenges in developing human fungal vaccines include concerns about their safety and efficacy in the immunocompromised patients who are typically at risk of serious fungal disease and difficulties in attracting pharmaceutical industry interest. Promising results have been obtained with various vaccine formulations (for example, killed or live attenuated fungi, crude fungal extracts, recombinant fungal subunits and nucleic acids encoding fungal antigens) in animal models of candidiasis, aspergillosis, cryptococcosis, coccidioidomycosis, histoplasmosis and blastomycosis (reviewed elsewhere[192,193]). Among these, only three have reached human clinical trials. The first-in-human fungal vaccine was a formalin-killed spherule vaccine for coccidioidomycosis, which showed no efficacy and caused topical and systemic adverse reactions in a phase III trial in the 1980s[194]. The other two are recombinant *Candida* vaccines. The first vaccine, termed 'PEV7', was based on recombinant *C. albicans* secreted aspartic protease 2 (Sap2) formulated with influenza virosomes. It protected rats from vulvovaginal candidiasis, and a phase I clinical trial found it to be safe and immunogenic, but no further clinical development has occurred since 2012 (ref. 195). The second vaccine, termed 'NDV-3', is based on recombinant amino terminus of *C. albicans* agglutinin-like sequence 3 (Als3) formulated with alum adjuvant. NDV-3 protected mice against mucosal and invasive candidiasis caused by several *Candida* species, including *C. auris*, cross-protected against *Staphylococcus aureus* owing to structural homology between Als3 and an *S. aureus* clumping factor, and stimulated T helper 1 (T_H1) cell, T_H17 cell and B cell responses[38,196–198]. In a phase I clinical trial, NDV-3 was safe and immunogenic, eliciting antigen-specific IgA and IgG and T_H1 cell- and T_H17 cell-associated cytokine responses[199]. In a recent double-blind, placebo-controlled phase Ib/IIa trial involving 188 women with recurrent vulvovaginal candidiasis, the vaccine was safe and immunogenic, and it decreased the frequency of vulvovaginal candidiasis in women older than 40 years[37]. A forthcoming goal is to test the efficacy of the vaccine in preventing candidaemia in high-risk patients in intensive care. Moving forward, harnessing fungal cell wall constituents as adjuvants and exploiting conserved fungal epitopes to induce cross-protection against multiple fungi are exciting strategies towards pan-fungal vaccine development[192]. For example, vaccine delivery of the conserved *Blastomyces*-derived chaperone calnexin in glucan particles protected mice against endemic dimorphic fungi, aspergillosis, chromoblastomycosis and *Pseudogymnoascus destructans*, which causes the life-threatening white-nose syndrome in bats[146,200,201].

known risk factor for human invasive candidiasis, impairs neutrophil ROS production and *Candida* killing by reducing GLUT1-dependent glucose uptake through hyperactivation of glycogen synthase kinase-3β (GSK3β)[52]. Pharmacological inhibition of GSK3β restores neutrophil candidacidal activity in mice and humans with uraemia, pointing to a potential therapeutic intervention in this setting[52].

Although neutrophils are protective during invasive candidiasis, their excessive accumulation and activation may also have detrimental effects, as seen in patients with neutropenia upon neutrophil recovery. Corticosteroids ameliorate inflammation and clinical symptoms in this setting, but certain immunopathogenic factors have been delineated in mice and humans — for example, the chemokine receptor CCR1, the CLR DNGR1, the endoribonuclease MCPIP1, the secreted growth factor progranulin and IFNγ — that show promise for eventually developing more selective therapeutic approaches[9,53–57]. Moreover, immunopathology during renal candidiasis can be ameliorated through activation of the IL-17-dependent kallikrein–kinin system, which prevents renal tubular cell apoptosis and preserves kidney function[58]. Administration of bradykinin combined with antifungal therapy provided a synergistic survival benefit during mouse kidney infection with *Candida*[58], raising the possibility that the antihypertensive class of angiotensin-converting enzyme inhibitors, which increase bradykinin levels, might have protective effects in this context.

In mouse invasive candidiasis, in addition to neutrophils, $CCR2^+$ infiltrating monocytes and $CX3CR1^+$ tissue-resident macrophages also contribute to protective immunity in the kidney and CNS by promoting *Candida* uptake and killing[59,60]. Importantly, beyond acute experimental candidiasis, monocytes and macrophages also protect against systemic *C. albicans* reinfection through a process termed 'trained immunity'. Mechanistically, protection in this setting is conferred through activation of dectin 1, RAF1, AKT, mTOR and hypoxia-inducible factor 1α (HIF1α) signalling that drives epigenetic reprogramming and cellular metabolic rewiring of monocytes and macrophages, with a switch to aerobic glycolysis[9,61]. By contrast, activation of macrophage JNK1 increases mortality during invasive candidiasis by downregulating expression of the CLR CD23 (also known as FcεRII) and impairing macrophage production of nitric oxide[62]. Thus, whereas JNK1 deficiency predisposes to CMC in humans (Supplementary Table 2), it may protect against invasive candidiasis[62,63]. Interestingly, although patients with humoral defects are not considered at risk of bloodstream candidiasis, mouse gut-educated IgA^+ meningeal plasma cells located near dural venous sinuses were recently shown to entrap *C. albicans* and restrict its spread in the CNS, uncovering a potential role for humoral immunity in protection against invasive candidiasis at this anatomical site[64].

Population studies in patients who are critically ill have shown that genetic polymorphisms in genes including *TLR1*, *CXCR1*, *CX3CR1*, *STAT1* and *TAGAP*, many of which have shown corroborating protective effects in mouse models of invasive candidiasis, are associated with greater risk of invasive candidiasis and/or worse outcome after infection. Notably, the combined presence of certain polymorphisms can increase susceptibility to invasive candidiasis by up to ~20-fold[8,65]. Collectively, these findings may provide a foundation for the eventual development of immunogenomic approaches for personalized risk stratification, prophylaxis and prognostication in high-risk patients.

Aspergillosis

Aspergillosis is an opportunistic, life-threatening fungal infection that develops following inhalation of ubiquitous *Aspergillus* moulds (primarily *Aspergillus fumigatus*) in humans with numeric or functional deficits in myeloid phagocytes, such as individuals with neutropenia, who receive corticosteroids or who are HSCT recipients, and, recently, in patients with severe influenza or COVID-19 pneumonia[1,3,66] (Table 1). Humans continuously inhale *Aspergillus* conidia (2–3 μm in diameter in the case of *A. fumigatus*), and an important immunological checkpoint involves preventing the formation of tissue-invasive filamentous hyphae in the respiratory tree. Myeloid phagocytes are necessary and sufficient to maintain this checkpoint as *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice that lack innate and adaptive lymphocytes clear conidia without developing invasive disease[67], similarly to humans with defects in lymphoid function or numbers[9]. Although lymphocytes seem to be redundant for protection against aspergillosis in hosts with intact myeloid cells, it is possible that adoptively transferred lymphocytes may provide benefit in hosts with an injured myeloid compartment[68,69]. *Aspergillus* also causes allergic disease and chronic cavitation in individuals with atopy and structural lung damage, respectively (reviewed in refs. 70,71).

A central theme of defence against inhaled *Aspergillus* is molecular and cellular redundancy in achieving sterilizing immunity and an essential role of intercellular crosstalk to regulate leukocyte infiltration and effector functions within the lung (Fig. 2). In immunocompetent individuals, conidia are engulfed by alveolar macrophages[72] and conidial germination within phagosomes triggers a pro-inflammatory cascade through dectin 1-dependent recognition of β-1,3-glucan[73], which is exposed on the surface of the germinating conidia[74]. Moreover, exposure of fungal mannans engages soluble pentraxin 2 (ref. 75) and pentraxin 3 (ref. 76) and the CLRs dectin 2 and dectin 3, sequentially activating SYK, CARD9–MALT1–BCL-10, NF-κB and the NLRP3 inflammasome, and thereby resulting in pro-inflammatory cytokine production[9]. CLR-dependent activation of phospholipase-γ induces Ca^{2+}–calcineurin phosphatase activity and nuclear translocation of the transcription factor NFAT[9]. In addition to these immunostimulatory *Aspergillus* polysaccharides, conidial dihydroxynaphthalene melanin activates the CLR MelLec (also known as CLEC1A) and induces downstream signalling through an unknown pathway[77]. The *Aspergillus* thaumatin-like protein CalA binds to epithelial and endothelial cells through α5β1 integrin to promote its internalization and spread, and antibody-mediated blockade of CalA ameliorates mortality in *Aspergillus*-infected mice[78].

Among the inborn errors of immunity, aspergillosis is a signature infection of chronic granulomatous disease[9], which highlights the importance of ROS generation in maintaining sterilizing lung immunity (Table 2). *Aspergillus* hyphae induce neutrophil production of ROS through β2 integrin and SYK[79], which triggers a regulated cell death process in *Aspergillus* that is opposed by the fungal anti-cell-death gene *Afbir1* (ref. 80). On the basis of the fact that IFNγ stimulates phagocyte ROS production, recombinant IFNγ has been approved for use as an immunotherapy to prevent invasive (including fungal) infections in patients with chronic granulomatous disease[81]. In addition to licensing neutrophil fungicidal activity, ROS also regulate LC3-associated phagocytosis, an adjunctive mechanism of fungal clearance[82]. *Aspergillus* conidial melanin hinders dectin 1-dependent and SYK-dependent activation of LC3-associated phagocytosis in macrophages, and phagosomal removal of melanin enhances macrophage antifungal activity by increasing calcium flux through glycolysis[83].

In pulmonary aspergillosis in mice, infiltrating neutrophils, $Ly6C^+$ inflammatory monocytes and $CXCR3^+$ plasmacytoid DCs are essential cellular effectors[67,84] (Fig. 2). Rapid neutrophil influx depends on sequential IL-1R–MYD88 signalling-dependent release of CXCL1 and CXCL5 by the lung epithelium, including club cells[85,86]. Thereafter,

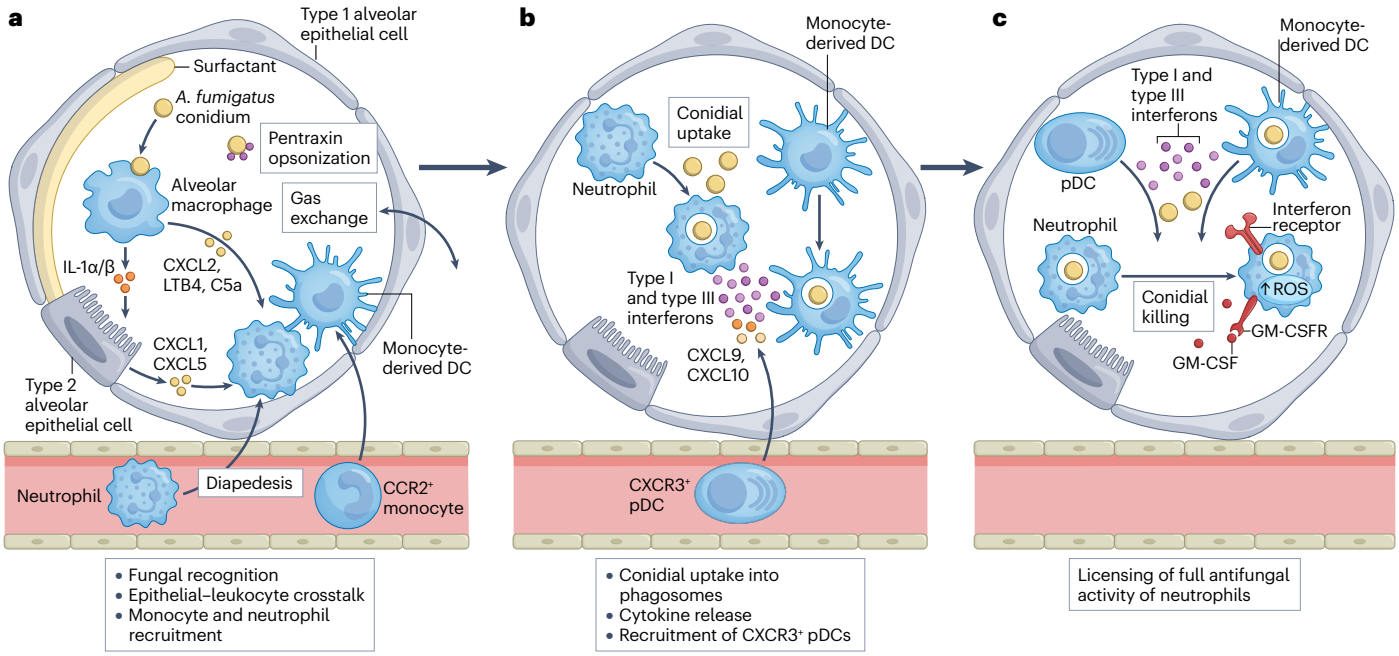


Fig. 2 | Cellular crosstalk regulates antifungal innate immunity in the lung. **a**, Fungal recognition and epithelial cell–leukocyte crosstalk coordinate the recruitment of neutrophils and monocytes to the alveoli. Alveolar macrophages and lung-resident dendritic cells (DCs; not shown) engulf *Aspergillus fumigatus* conidia that reach the terminal airways, which are the site of gas exchange. Rapid release of IL-1α/β by macrophages and DCs stimulates the IL-1 receptor (IL-1R)–MYD88-dependent production of the neutrophil-recruiting chemokines CXCL1 and CXCL5 by lung epithelial cells. The release of CXCL2 by haematopoietic cells, including macrophages, through C-type lectin receptor (CLR)–CARD9 activation, and the rapid production of leukotriene B_4 (LTB4) and complement component C5a also contribute to sustained neutrophil recruitment. In addition, $CCR2^+$ circulating monocytes enter the lung parenchyma and differentiate into monocyte-derived DCs. Opsonization of *A. fumigatus* conidia by pentraxins enables their efficient uptake and killing by neutrophils. **b**, The recruited neutrophils and monocyte-derived DCs engulf conidia into phagolysosomes, which are the site of intracellular conidial killing. Both resident myeloid cells and infiltrating $CCR2^+$ monocytes produce type I interferon early in the response and regulate ensuing type III interferon release. Fungus-engaged neutrophils and monocyte-derived DCs secrete CXCL9 and CXCL10 (through CLR–CARD9–SYK and type I interferon-dependent pathways, respectively), which recruit $CXCR3^+$ plasmacytoid DCs (pDCs) to the lung. **c**, Innate crosstalk licenses the full spectrum of neutrophil antifungal activity. Conidial killing by neutrophils and monocyte-derived DCs is enhanced by the entry of $CXCR3^+$ pDCs and by type I and type III interferons that converge on signal transducer and activator of transcription 1 (STAT1) signalling in neutrophils. Fungus-induced release of granulocyte–macrophage colony-stimulating factor (GM-CSF) also potentiates neutrophil antifungal properties by enhancing NADPH oxidase activity and the production of reactive oxygen species (ROS). In the context of blastomycosis, $CCR6^+$ innate lymphocytes and natural T helper 17 cells contribute to GM-CSF production during acute pulmonary infection.

CLR–CARD9-dependent signalling in haematopoietic cells, including macrophages, sustains pulmonary neutrophil influx through CXCL2 production, which is consistent with a model of sequential and compartment-specific regulation of pulmonary neutrophil recruitment in this context. In CARD9-deficient humans, aspergillosis is typically extrapulmonary, which supports the idea that CARD9-dependent and CARD9-independent pathways of neutrophil recruitment collaborate in the lung, but that CARD9 predominantly controls neutrophil recruitment to extrapulmonary sites of *Aspergillus* infection[87]. In addition to IL-1R–MYD88-dependent and CLR–CARD9-dependent leukocyte recruitment to the *Aspergillus*-infected lung, signalling through the RNA sensor MDA5–MAVS[88] and leukotriene B_4 biosynthesis[89] also contribute. Within the *Aspergillus*-infected lung, the lectin family member galectin 3 increases neutrophil motility and facilitates neutrophil extravasation into bronchoalveolar air spaces[90].

In addition to neutrophils, mononuclear phagocytes also promote pulmonary defences against *Aspergillus* both directly and indirectly by priming neutrophil effector functions. $CCR2^+$ lung-infiltrating monocytes differentiate into monocyte-derived DCs that engulf, inactivate and transport conidia to lung-draining lymph nodes[67,91]. $CCR2^+$ monocyte-derived DCs also produce type I interferons, which in turn control type III interferon production within the fungus-infected lung. Type I and type III interferon receptor engagement and STAT1 signalling are essential for host defence by enhancing neutrophil ROS production and fungicidal activity, and JAK–STAT inhibitors have been reported to promote aspergillosis in humans[92] (Table 3). In addition, STAT1 signalling in $CCR2^+$ monocytes facilitates the formation of monocyte-derived DCs and enhances their fungicidal activity; this process is supported by reciprocal interferon–STAT1 crosstalk with neutrophils[93]. Fungus-induced release of GM-CSF also stimulates neutrophil ROS production and promotes fungal clearance[94]. Concordantly, humans with mutations in GM-CSF receptor signalling develop pulmonary alveolar proteinosis, a condition that is associated with opportunistic pulmonary infections, including aspergillosis[95] (Supplementary Table 2).

Upon conidial engulfment, lung-infiltrating neutrophils and monocytes produce CXCR3-targeted chemokines (CXCL9 and CXCL10) to recruit circulating $CXCR3^+$ plasmacytoid DCs into the lung, where they boost neutrophil ROS production, neutrophil extracellular trap

formation and fungicidal activity[84]. Thus, both epithelial cell-derived chemokines and haematopoietic cell-derived chemokines coordinate early neutrophil influx to the *Aspergillus*-infected lung, and tissue-infiltrating mononuclear phagocytes license neutrophil functions to achieve sterilizing immunity. Nutrient limitation via metal chelators (for example, lactoferrin or calprotectin) also contributes to tissue-specific control of *Aspergillus*, with a role shown for calprotectin in protecting against *Aspergillus* keratitis but not pulmonary infection in mice[96,97]. Corroborating these mechanistic studies of protective immunity in mice, human population studies have identified genetic polymorphisms in *APCS* (encoding pentraxin 2), *PTX3*, *CLEC7A* (encoding dectin 1), *CLEC1A* and *CXCL10* that predispose to aspergillosis following allogeneic HSCT[75,77,98,99].

Moreover, pharmacological susceptibility to aspergillosis has provided additional insights into host defence pathways (Table 3 and Supplementary Table 3). Chief among these is the observation that ibrutinib-induced inhibition of Bruton's tyrosine kinase (BTK) promotes aspergillosis in patients with lymphoma[100,101], which is recapitulated in *Btk*$^{-/-}$ mice, consistent with BTK having an evolutionarily conserved role in defence against *Aspergillus*[100]. In macrophages, phagocytosis of *Aspergillus* conidia triggers dectin 1-dependent and Toll-like receptor 9 (TLR9)-dependent activation of BTK, which regulates calcineurin–NFAT activity and synergizes with NF-κB to promote the production of tumour necrosis factor (TNF)[102]. The mechanisms by which BTK mediates neutrophil anti-*Aspergillus* defence remain poorly defined and require further study.

Mucormycosis

Mucormycosis is a life-threatening infection caused by ubiquitous inhaled moulds of the order Mucorales (primarily *Rhizopus* species)[103]. As is the case for aspergillosis, mucormycosis typically occurs in patients with quantitative and/or qualitative phagocyte defects, such as individuals with neutropenia, who receive corticosteroids or who are HSCT recipients[103]. However, Mucorales members are unique among the human mould pathogens in terms of their predilection to cause disease in the settings of diabetic ketoacidosis or iron overload[103] (Supplementary Table 1). Moreover, mucormycosis has emerged as a devastating complication of COVID-19, particularly in India (where it had a prevalence of 0.27% among hospitalized patients with COVID-19), associated with corticosteroid use and uncontrolled hyperglycaemia[1]. Strikingly, mucormycosis has distinct infection patterns in patients with different risk factors. Specifically, diabetic ketoacidosis typically predisposes to the rhino-orbital–cerebral form of the disease, whereas patients with neutropenia or who are HSCT recipients typically develop sinopulmonary mucormycosis[103].

During infection in mice, Mucorales members produce mucoricin, a plant ricin-like toxin that promotes cellular necrosis, vascular permeability and death[104]. Recent work has uncovered tissue-specific mechanisms by which hyperglycaemia and iron overload increase susceptibility to mucormycosis. Specifically, increased levels of glucose, iron and ketone bodies, all of which occur during diabetic ketoacidosis, attenuate neutrophil-mediated damage to *Rhizopus* and induce expression of the glucose-regulated receptor GRP78 on the surface of endothelial cells and nasal epithelial cells and of the Mucorales invasin CotH3 (refs. 105–108). The CotH3–GRP78 interaction enables fungal invasion and damage of the nasal epithelium, and can be targeted with therapeutic benefit in *Rhizopus*-infected mice with diabetic ketoacidosis[105–107]. Because *Aspergillus* does not encode CotH3, this functional attribute of Mucorales may underlie the selective predisposition of patients with diabetes to mucormycosis. By contrast, in the setting of pulmonary mucormycosis, *Rhizopus* CotH7 interacts with β1 integrin, not GRP78, on the surface of alveolar epithelial cells to promote fungal invasion, EGFR activation and cellular damage[108,109]. Pharmacological inhibition of β1 integrin or EGFR with the FDA-approved inhibitors cetuximab or gefitinib blocks fungal invasion of alveolar epithelial cells and prolongs mouse survival during pulmonary mucormycosis[108,109]. Thus, *Rhizopus* interacts with different tissue-specific mammalian receptors depending on the underlying predisposing factor to instigate opportunistic disease. Furthermore, during pulmonary mucormycosis in mice, alveolar macrophages contribute to fungal clearance and host survival by stimulating an intracellular iron restriction programme that curbs *Rhizopus* growth within phagosomes, underscoring the importance of protective nutritional immunity in this setting[110].

Chromoblastomycosis and phaeohyphomycosis

Chromoblastomycosis is a disfiguring, tumour-like, progressive and often treatment-unresponsive infection in tropical areas, which has been designated as a neglected tropical disease by the World Health Organization. It is primarily caused by the pigmented fungus *Fonsecaea pedrosoi*, which typically enters the skin via traumatic inoculation (Supplementary Table 1). In *F. pedrosoi*-infected mice, CD4$^+$ T cells are essential for fungal clearance, primarily involving T_H1 cell and T_H17 cell responses[111,112]. Unlike *Candida* and *Aspergillus* species, *F. pedrosoi* stimulates modest CLR responses through the dectin 2-dependent and Mincle-dependent SYK–CARD9 axis and fails to effectively activate TLRs, resulting in inadequate local inflammatory responses in infected mice and humans[111,113]. Topical administration of the TLR7 agonist imiquimod combined with antifungal therapy markedly improved clinical outcomes in patients with refractory chromoblastomycosis[114], demonstrating a key adjunctive role for this immunotherapeutic intervention.

Phaeohyphomycosis is another mycosis caused by melanin-bearing, pigmented fungi that typically enter the skin via traumatic inoculation. Although infection is self-limited in most healthy individuals, it can cause severe subcutaneous or disseminated disease in patients who are HSCT recipients or who have CARD9 deficiency[7,115] (Supplementary Table 1). *Exserohilum rostratum*, one of the agents of phaeohyphomycosis, caused a meningitis outbreak following epidural injections of contaminated methylprednisolone in the USA in 2012 (ref. 116). CARD9-dependent defence against phaeohyphomycosis in mice was recently shown to rely on macrophages, whereas neutrophil recruitment to the infected skin was CARD9 independent[117]. Specifically, CARD9 primes macrophages to produce IL-1β and TNF, which promote macrophage killing of fungi in an interdependent manner[117]. Consistent with this finding, phaeohyphomycosis has been reported following treatment with TNF-targeted biologics such as infliximab[118] (Table 3). Upstream of CARD9, dectin 1 is also crucial for macrophage-mediated defence against phaeohyphomycosis in mice, and deleterious mutations in the gene encoding dectin 1 (*CLEC7A*) that impair fungal sensing and TNF production were found in ~70% of putatively immunocompetent patients with severe forms of phaeohyphomycosis[117]. These findings suggest that human dectin 1 deficiency may contribute to susceptibility to severe phaeohyphomycosis in the setting of traumatic inoculation.

Cryptococcosis

Cryptococcosis is caused by the encapsulated yeasts *Cryptococcus neoformans* and *Cryptococcus gattii*, which have distinct infection patterns in humans[119]. *C. neoformans* is more common, and typically

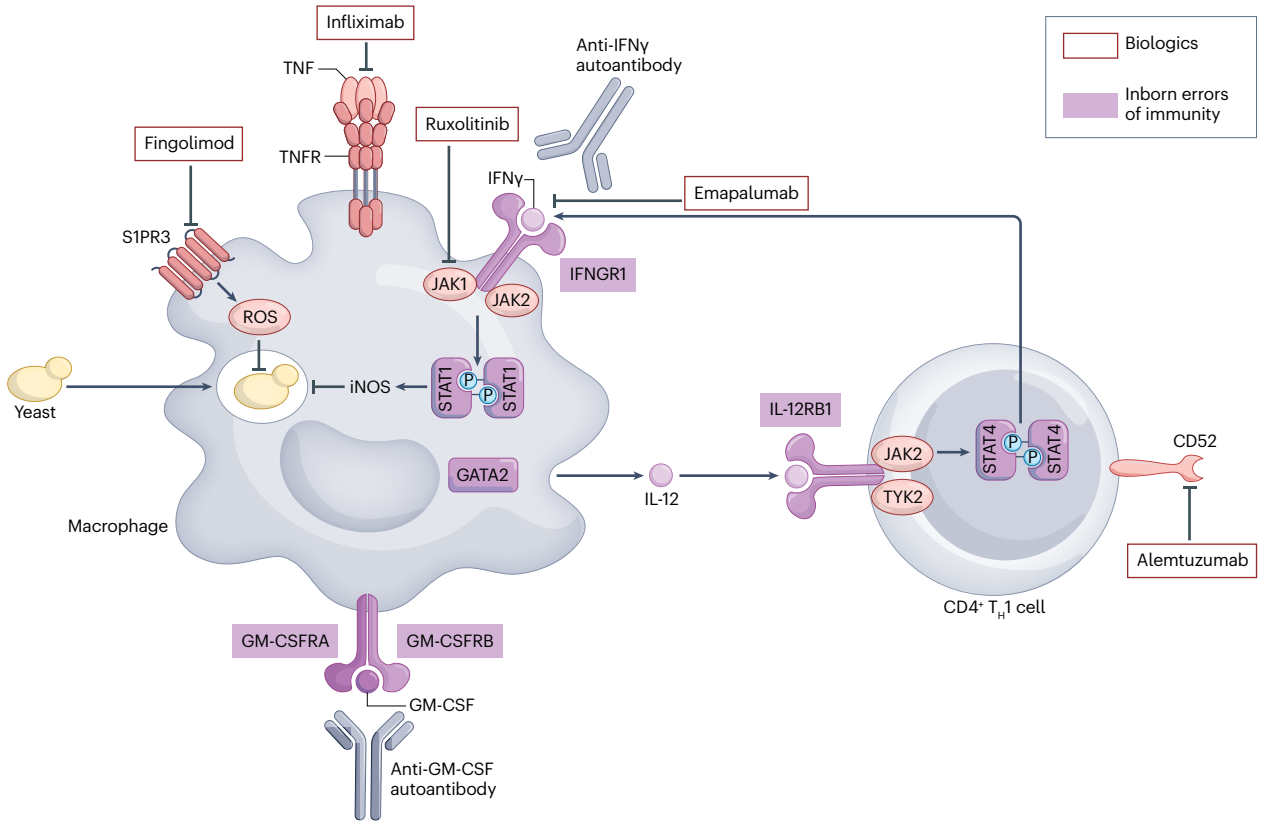


Fig. 3 | Crosstalk between macrophages and T cells during infection with intracellular fungi. Type 1 immune responses, characterized by interferon-γ (IFNγ)-producing T cells and macrophages, are crucial for protection against intramacrophagic fungi (such as *Cryptococcus* and *Histoplasma*). Infected macrophages produce IL-12, which drives T helper 1 (T_H1) cell polarization of $CD4^+$ T cells through Janus kinase 2 (JAK2)–signal transducer and activator of transcription 4 (STAT4) signalling. T_H1 cells produce IFNγ, which binds to the IFNγ receptor, comprising IFNGR1 and IFNGR2, on macrophages and activates JAK1/JAK2–STAT1-dependent signalling to induce expression of inducible nitric oxide synthase (iNOS). In turn, iNOS mediates fungal killing together with the production of reactive oxygen species (ROS), which is partly controlled by sphingosine 1-phosphate receptor 3 (S1PR3) in the setting of cryptococcal infection. Tumour necrosis factor (TNF) activates macrophages for fungal killing and promotes the formation of granulomas and IFNγ production by lymphocytes. Granulocyte–macrophage colony-stimulating factor (GM-CSF) also primes macrophages to effectively kill fungi intracellularly. The transcription factor GATA2 regulates fungal uptake by macrophages[184]. Disruption of these protective antifungal immune pathways by biologics, inborn errors of immunity or anti-cytokine autoantibodies enhances susceptibility to infections with intracellular fungi in humans.

causes meningoencephalitis in immunocompromised patients with $CD4^+$ T cell depletion and/or dysfunction (Table 1). Cryptococcal meningoencephalitis is an AIDS-defining illness and remains a significant cause of death in resource-limited areas (for example, some parts of Africa) that are associated with limited availability of antiretroviral therapy and first-line antifungal drugs. The incidence of cryptococcal meningoencephalitis is increasing in non-HIV-infected individuals in the Western hemisphere. By contrast, *C. gattii* primarily causes pulmonary disease in putatively immunocompetent individuals and rarely affects individuals with HIV/AIDS.

Human exposure to inhaled *Cryptococcus* is widespread by early childhood. The crucial immunological checkpoint for preventing local proliferation of yeast in the lung and extrapulmonary dissemination is the containment and killing of inhaled *Cryptococcus* by lung-resident macrophages, which is enabled by their crosstalk with IFNγ-producing $CD4^+$ T cells[119] (Fig. 3). Notably, *Cryptococcus* yeasts secrete a capsule containing glucuronoxylomannan and galactoxylomannan that shields its pathogen-associated molecular patterns from immune recognition[119,120]. Unsurprisingly, therefore, defective TLR-mediated and CLR-mediated responses in the setting of human MYD88 deficiency and CARD9 deficiency, respectively, do not predispose to cryptococcosis[9]. By contrast, a few inborn errors of immunity primarily affecting numbers of lymphocytes and/or monocytes and macrophages, and/or their activation, underlie human cryptococcosis (Table 2 and Supplementary Table 2), which supports the crucial role of effective crosstalk between lymphocytes and mononuclear phagocytes in cryptococcal clearance[9,119].

Loss-of-function mutations in *IL12RB1* are associated with cryptococcosis, which is explained by impaired IL-12-driven IFNγ production by T cells and the resulting inability of macrophages to promote intracellular killing of fungi[9] (Fig. 3). Consistent with this notion, cryptococcosis develops in adult patients with neutralizing autoantibodies to IFNγ[121], which may be amenable to anti-CD20 or anti-CD38 targeted biologics that deplete B cells and plasma cells, respectively[122,123]. The higher prevalence of autoantibodies to IFNγ in individuals of Asian ancestry who were born in Asia but not elsewhere suggests that both

environmental and genetic factors are involved[121]. Moreover, impaired T cell responses promote cryptococcosis in the setting of CD40L deficiency[124]. GATA2 deficiency predisposes to infection with various intramacrophagic pathogens, including mycobacteria and *Cryptococcus*, associated with profound monocytopenia[125]. GM-CSF is a key factor that promotes anticryptococcal immunity by activating macrophages to a functional state that is associated with efficient fungal killing[126]. Inherited deficiency of GM-CSF receptor signalling or neutralizing autoantibodies to GM-CSF can underlie cryptococcosis, with an enrichment for *C. gattii* infections in particular[121,127]. A genome-wide association study in individuals with HIV/AIDS of African descent uncovered a correlation between *CSF1* genetic variation and cryptococcosis[128]. *CSF1* encodes macrophage colony-stimulating factor (M-CSF), another growth factor that is crucial for macrophage activation and survival, particularly for CNS-resident microglia[129].

Pharmacological susceptibility to cryptococcosis has provided additional evidence for the importance of crosstalk between T_H1 cells and macrophages (Table 3 and Supplementary Table 3). For example, JAK–STAT inhibitors (which block IFNγ receptor signalling), TNF inhibitors (which impair IFNγ production and granuloma formation) and BTK inhibitors (which impair macrophage activation) all increase the risk of cryptococcosis[9]. Alemtuzumab (which targets CD52 on lymphocytes) and natalizumab (which targets α4β1 integrin on lymphocytes) promote cryptococcosis through profound and prolonged T cell depletion and through impaired integrin-mediated T cell trafficking to *Cryptococcus*-infected tissues, respectively[9]. The sphingosine 1-phosphate receptor (S1PR) inhibitor fingolimod was recently reported to promote cryptococcosis. In a mouse model of cryptococcosis, fingolimod enhanced susceptibility by impairing S1PR3-dependent macrophage phagocytosis and granuloma formation and by driving a macrophage phenotype with poor oxidative killing capacity, not by affecting S1PR1-mediated T cell trafficking[130].

Defective IFNγ signalling in macrophages impairs the activity of inducible nitric oxide synthase (iNOS) and hence macrophage oxidative killing pathways, which enables *Cryptococcus* to survive within phagosomes, where it can be shielded from immune recognition, as has been shown in infected brain tissue of patients with HIV/AIDS[131]. Intracellular growth in macrophages is promoted by fungal-derived urease and modification of the phagosome microenvironment[132,133]. In patients with HIV/AIDS, a lack of $CD4^+$ T cells and paucity of pro-inflammatory cytokines (IFNγ and TNF) in the cerebrospinal fluid were the strongest predictors of cryptococcosis severity in the CNS, and T cell responses producing IFNγ and TNF were associated with increased survival[134–136]. Consistent with the idea that IFNγ may boost macrophage antifungal activity in patients with HIV/AIDS in the absence of T cell help, a clinical trial showed that adjunctive IFNγ immunotherapy rapidly reduced fungal burden in the cerebrospinal fluid, the level of which is a known surrogate of patient survival[137].

Although they are crucial for fungal control, T_H1 cells may also promote pathogenic effects in the settings of non-HIV cryptococcosis and HIV-associated immune reconstitution inflammatory syndrome (IRIS), a condition characterized by the development of life-threatening immunopathology upon initiation of antiretroviral therapy. In these patients, corticosteroids ameliorate inflammatory sequelae and neurological symptoms[138]. In patients without HIV infection with cryptococcosis, significant infiltration of $CXCR3^+$ T_H1 cells into the CNS is observed, associated with high levels of CXCL10 in cerebrospinal fluid, poor colocalization of macrophages and fungus, and neuronal damage[139]. Correspondingly, in a mouse model of non-HIV cryptococcosis, CXCR3 inhibition abrogated the recruitment of T_H1 cells into the CNS by glial-derived CXCL10 and increased survival[140]. Furthermore, patients with AIDS without IRIS have increased numbers of T_H1 cells and increased serum levels of IFNγ relative to patients without IRIS[141]. In a mouse model of cryptococcus-associated IRIS, IFNγ-producing $CD4^+$ T cells were sufficient to mediate CNS damage associated with upregulation of aquaporin 4, which modulates water influx and swelling within the brain[142]. Better understanding of the molecular underpinnings of pathogenic inflammation during cryptococcus-associated IRIS may help to identify targeted, corticosteroid-sparing immunomodulatory strategies for affected patients.

Other endemic fungal infections

Histoplasma, *Coccidioides*, *Paracoccidioides, Talaromyces* and *Blastomyces* species are geographically restricted dimorphic fungi that typically cause self-limited pneumonia in healthy individuals but that can lead to progressive pulmonary and/or extrapulmonary disease in immunocompromised patients with HIV/AIDS, corticosteroid use or transplantation (Table 1 and Supplementary Table 1). Race, ethnicity and hormonal factors can influence the risk and severity of these infections, through mechanisms that remain poorly understood. For example, African American, Native American and Asian ancestries are associated with increased risk of blastomycosis and disseminated coccidioidomycosis, pregnancy increases the risk of severe coccidioidomycosis, and chronic paracoccidioidomycosis more commonly affects males[9].

As for cryptococcosis, defence against histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, talaromycosis and blastomycosis depends on the coordinated crosstalk between IFNγ-producing T cells and fungicidal macrophages (Fig. 3). In line with this crucial role of granulomatous inflammation, inborn errors of immunity affecting type 1 immune responses caused by mutations in the genes encoding IL-12RB1, IFNγR1, STAT1, STAT3, CD40L or GATA2 (Table 2 and Supplementary Table 2) predispose to severe, disseminated infections by these fungi, as do neutralizing autoantibodies to IFNγ[121] and receipt of TNF inhibitors, JAK–STAT inhibitors or the IFNγ-targeted biologic emapalumab[9] (Table 3 and Supplementary Table 3). In *Coccidioides*-infected patients, genetic variants in β-glucan sensing and response genes (for example, *CLEC7A* and *PLCG2*) that impair TNF production were recently shown to underlie disseminated disease in ~50% of evaluated patients[143]. By contrast, type 2 immune responses are detrimental for pathogen control by dampening type 1 responses and skewing macrophages towards a phenotype that is permissive for intracellular fungal persistence[144]. Macrophage-mediated nutritional immunity to *Histoplasma* is also mediated by T_H1 cell responses, particularly GM-CSF, which promotes metallothionein-mediated zinc sequestration that starves the pathogen. By contrast, the T_H2 cell cytokine IL-4 promotes zinc acquisition by yeast, which enables its intracellular survival[145]. The *Blastomyces* adhesin BAD1 inhibits $CD4^+$ T cell-derived IFNγ release, and *Blastomyces* uses additional immune-evasion strategies, including cleavage and inactivation of GM-CSF and of monocyte-recruiting CC chemokines[146].

Immunomodulatory restoration of the T_H1 cell–T_H2 cell balance during endemic mycoses can be exploited with therapeutic benefit. Specifically, a child with no known inborn error of immunity and refractory disseminated coccidioidomycosis who had increased levels of IL-4 and decreased levels of IFNγ achieved rapid symptom resolution and infection remission after adjunctive administration of recombinant IFNγ and the IL-4/IL-13 receptor inhibitor dupilumab[147].

Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii pneumonia (PJP) is an AIDS-defining illness that develops with declining $CD4^+$ T cell counts and carries a high global disease burden and mortality. In HIV-negative individuals, PJP is most often seen following corticosteroid administration (Table 1). Epidemiological data indicate that inhalational exposure to *P. jirovecii* is universal during infancy without causing severe clinical disease, which is indicative of potent, protective host responses to *Pneumocystis*[148]. In mice infected with *Pneumocystis murina*, the mouse-specific *Pneumocystis* species, $CD4^+$ T cells are crucial for defence as CD4-deficient animals are highly susceptible, which is consistent with the increased risk of PJP in individuals with HIV/AIDS or patients treated with the T cell-depleting biologic alemtuzumab (Table 3). Although T_H1 cells, T_H2 cells and T_H17 cells are all induced during mouse infection, none of them has been shown individually to promote disease resolution using corresponding gene-deficient mouse strains[149]. Recently, $CD4^+$ T cell-intrinsic signalling through IL-21R and STAT3 was found to be crucial for defence in *Pneumocystis*-infected mice, by priming T cell effector functions and protective class-switched antibody responses[150]. These findings recapitulate the susceptibility to PJP that is seen in patients with *STAT3* and *IL21R* mutations (Table 2 and Supplementary Table 2). In addition to T cells, B cells are also crucial for anti-*Pneumocystis* defence through antigen presentation to and priming of $CD4^+$ T cell responses in the lung, by facilitating opsonic phagocytosis by alveolar macrophages, and through secreted IgM[151–153]. In agreement with this role for B cells, recipients of CD20-targeted B cell-depleting antibodies are at risk of developing PJP (Supplementary Table 3). Among myeloid phagocytes, alveolar macrophages and eosinophils, but not neutrophils, contribute to *Pneumocystis* clearance during mouse infection[154,155]. Other PJP-manifesting inborn errors of immunity that involve impaired T cell and/or B cell responses include severe combined immunodeficiency, anhidrotic ectodermal dysplasia with immune deficiency due to IKBA deficiency, and mutations in *CD40L*, *IKZF1* or *IKZF3* (ref. 149) (Supplementary Table 2). Biologics that predispose humans to PJP include TNF, PI3K and JAK–STAT inhibitors, which impair the responses of T cells and macrophages to *Pneumocystis*[149] (Table 3).

Endogenous fungi: protection and pathology

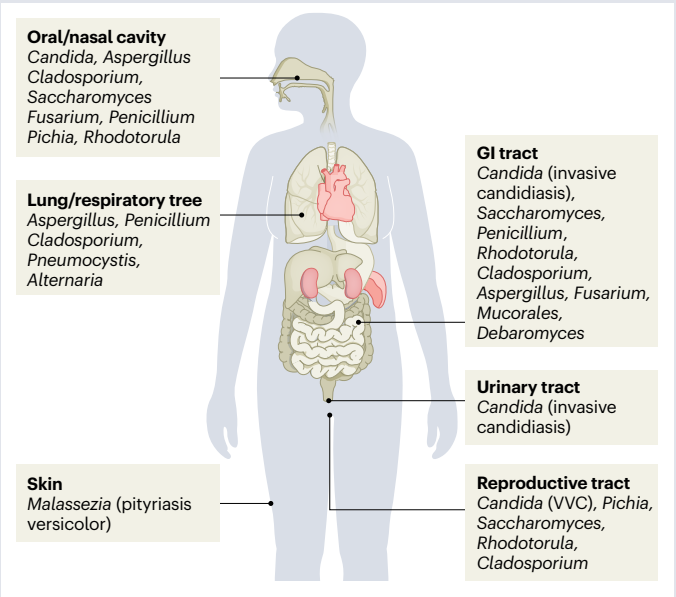
Fungi are core constituents of endogenous microbial communities at several human barrier sites (Box 3). Recent studies have advanced the concept that tissue-resident fungi shape immune homeostasis and development, function as reservoirs for invasive fungal infections and

Box 3

The human mycobiota: localization, species and biomass

Fungi are core constituents of microbial communities in human tissues, including the skin, mouth and respiratory, intestinal and genitourinary tracts[160], although they typically account for less than 1% of total microbial amplicon sequences, with 50–100 fungal genera being reliably identified[202]. A core fungal signature at different tissue sites has been challenging to define, as humans inhale and ingest fungi daily, blurring the distinction between passenger and colonizer species. Longitudinally collected faecal samples show high intra-individual and interindividual variability of fungal taxa, and low day-to-day stability of intestinal fungi, which is in contrast to the relative intra-individual stability of bacterial communities[170,203]. Frequent tooth brushing reduced *Candida* levels in dental plaque, saliva and stool, which is consistent with the oral reservoir contributing to intestinal flux[204]. *Saccharomyces* stool levels dropped precipitously when human volunteers consumed *Saccharomyces*-free diets, only to increase again when the volunteers ate a single bite of bread[204]. Notwithstanding this variability, certain genera predominate at distinct sites: *Saccharomyces*, *Candida*, *Debaromyces* and *Pichia* are commonly found in the digestive and genital tracts, *Malassezia* is commonly found in the skin, and *Aspergillus*, *Fusarium*, *Alternaria* and *Cladosporium* moulds are commonly found in the airways, albeit at lower densities. The figure depicts commensal fungal communities that are adapted to specific tissue niches of humans. Common taxa found under homeostatic conditions are indicated, as are common diseases associated with some of these taxa, such as invasive candidiasis, vulvovaginal candidiasis (VVC) and pityriasis versicolor.

Nucleic acid-based methods underestimate fungal biomass given the size difference of bacteria (~0.5–2-μm diameter) and fungi (~3–5-μm diameter for yeasts and ~10 to >100 μm and greater diameter for hyphae) and metagenomic sequencing has not been widely applied to analyse fungal communities, owing to large and complex fungal genomes (typically more than 20 Mb in size, with both haploid and diploid genomes), low fungal reads compared with bacteria and incomplete, poorly annotated reference libraries[202]. Thus, the true size and composition of the mycobiome in humans remain incompletely understood.



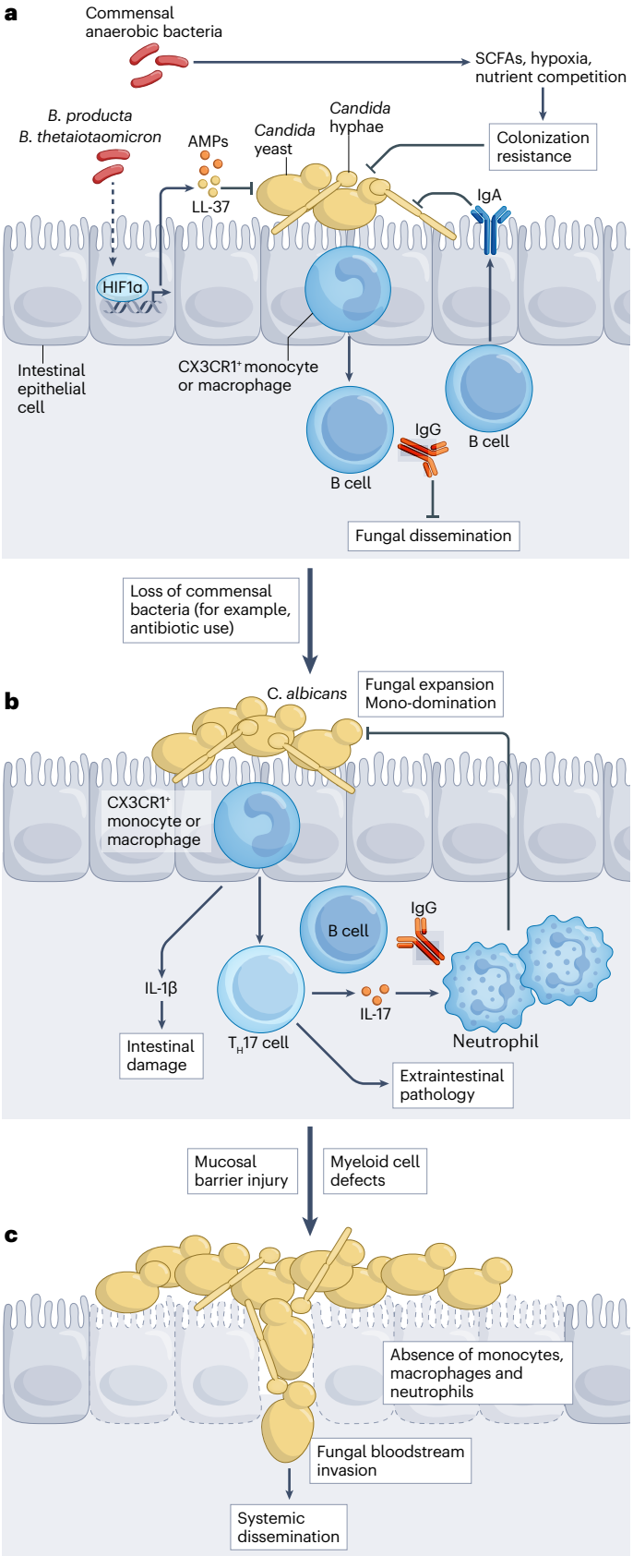


Fig. 4 | Endogenous fungal communities and their relationship to invasive fungal disease. a, Mucosal and intestinal bacterial communities outnumber and compete with site-specific endogenous fungi. In the intestine, commensal anaerobic bacteria, exemplified by *Blautia producta* and *Bacteroides thetaiotaomicron*, provide colonization resistance against *Candida* species by activating the transcription factor hypoxia-inducible factor 1α (HIF1α) in intestinal epithelial cells to regulate the release of LL-37, an antimicrobial peptide (AMP) that restricts *Candida albicans* growth. Bacterial products of fermentation, specifically short-chain fatty acids (SCFAs), and metabolites likely also contribute to fungal colonization resistance and inhibition of *Candida* filamentation. Nutrient competition and regulation of tissue oxygen levels contribute to the balance between endogenous bacteria and competing fungal species in the gastrointestinal and reproductive tracts. CX3CR1^{+} mononuclear phagocytes recognize intestinal fungi through C-type lectin receptor (CLR)–CARD9 signalling and regulate the production of IgA and IgG antibodies to *Candida* by B cells. IgA antibodies recognize and target *C. albicans* adhesins (such as agglutinin-like sequence 3 (Als3)) that are primarily expressed by pseudohyphae and thus promote maintenance of the commensal yeast cell morphology. *Candida*-targeted IgG antibodies can protect against bloodstream invasion and disseminated candidiasis. **b**, In the intestinal and reproductive tracts, antibiotic-induced loss of predominantly anaerobic bacterial taxa reduces *Candida* colonization resistance and facilitates domination by individual fungal taxa. *C. albicans* strains from patients with inflammatory bowel disease with fungal dysbiosis can aggravate tissue damage, correlating with fungal strain-specific induction of IL-1β production by immune cells. The induction of T helper 17 (T_H17) cells and IL-17 production can promote neutrophil recruitment to inhibit fungal tissue invasion and dissemination. However, *Candida*-specific T_H17 cells can also promote extraintestinal inflammation. For example, mould aeroallergens can stimulate *C. albicans*-primed T_H17 cells and aggravate fungus-associated asthma. **c**, Systemic bloodstream infections can arise from intestinal fungal dysbiosis with concomitant epithelial cell damage (for example, following chemotherapy) and with defects in the number or function of circulating myeloid phagocytes.

contribute to the pathogenesis of autoimmune, inflammatory and neoplastic diseases (Fig. 4). Here we focus primarily on human studies of the mycobiota, with mouse work having been reviewed elsewhere[156,157].

In early human life, fungal–bacterial interactions shape the orderly assembly of the microbiota[158]. For example, ecological modelling in preterm neonates in an intensive care unit predicted that high abundance of intestinal *Candida* inhibited the expansion of Enterobacteriaceae, which facilitate the ensuing transition to commensal bacterial anaerobes[159]. This prediction was validated in interkingdom co-culture experiments with infant-derived *Candida* strains and in sequential intestinal colonization studies in mice, which showed that gut-resident *Candida* decreased the load of sequentially introduced Enterobacteriaceae. A recent review provides an excellent summary of numerous studies on the functional interactions between commensal, probiotic and potentially pathogenic bacteria and fungi[160].

In addition to the role of fungi in microbiota assembly, the density of intestinal fungi and, in particular, the abundance of *Pichia kudriavzevii* (the sexual state of *Candida krusei*) have been linked to subsequent atopy in independent birth cohorts[161]. Transient *P. kudriavzevii* colonization exacerbated house dust mite-induced allergic airway disease in neonatal specific pathogen-free mice[161]. In human adults, circulating fungus-reactive memory T_H17 cells preferentially target *C. albicans*-derived antigens, consistent with the idea that intestinal colonization with *C. albicans* induces T_H17 cell differentiation[162]. Circulating *C. albicans*-induced T_H17 cells cross-react with other fungi and can exacerbate the pathology of *A. fumigatus*-triggered allergic lung disease.

Glossary

Agglutinin-like sequence 3
(Als3). A *Candida albicans* hyphal protein that facilitates adhesion and invasion in host epithelial and endothelial cells through binding to E-cadherin and N-cadherin, respectively, and that has formed the basis for developing the investigational vaccine NDV-3.

Candidalysin
A pore-forming, cytolytic peptide toxin produced by *Candida albicans* hyphae that promotes damage to oral epithelial cells and is required for virulence during mucosal candidiasis.

Chronic mucocutaneous candidiasis
(CMC). A clinical condition characterized by severe, recurrent and treatment-refractory episodes of candidiasis of mucosal surfaces, skin and/or nails.

Diabetic ketoacidosis
A life-threatening complication of uncontrolled diabetes that is characterized by insulin deficiency driving excessive accumulation of ketone bodies in the blood, which leads to acidosis.

Hyphae
Long filamentous branching structures of certain fungi (for example, *Aspergillus*) that grow by apical extension.

Inborn errors of immunity
Conditions caused by deleterious germ line mutations in single immune-related genes that manifest themselves with various infectious complications with or without other accompanying clinical manifestations, such as autoimmunity, autoinflammation, atopy and/or malignancy.

Kallikrein–kinin system
A family of serine proteases (kallikreins) that cleave kininogens to generate the kinin peptides bradykinin and kallidin, which as a collective system have important roles in renal homeostasis and blood pressure regulation, with additional roles now emerging during inflammation, immunity and tissue repair.

LC3-associated phagocytosis
A non-canonical autophagy pathway activated downstream of pattern recognition receptors which promotes phagosome maturation and intracellular killing of pathogens within phagocytes and regulates other mononuclear phagocyte functions, such as antigen presentation, efferocytosis and anti-inflammatory cytokine responses.

Natural T_H17 cell
A type 17 cell subpopulation that develops in the thymus, expresses CD4, TCRαβ, RORγt, CCR6 and IL-23R and, in contrast to inducible T_H17 cells, is characterized by an intrinsic capacity for rapid activation in response to T cell receptor-independent stimulation in naive hosts.

Trained immunity
The ability of the innate immune system, through epigenetic and metabolic reprogramming, to develop a form of immunological memory that can provide protection against a subsequent challenge with homologous or even heterologous pathogens.

Uraemia
A clinical syndrome characterized by increased concentrations of urea in the blood and electrolyte, volume and metabolic abnormalities that are collectively caused by deteriorating kidney function.

Yeast
A eukaryotic, unicellular fungal organism that reproduces by budding (for example, *Candida*).

Malassezia, the major fungal commensal of human skin[163], can cause pityriasis versicolor, characterized by hyperpigmented or hypopigmented flaky skin lesions. In a mouse epicutaneous infection model, *Malassezia* induced T_H17 cell differentiation and elicited IL-23-dependent IL-17 release by γδ T cells and type 3 innate lymphoid cells[164]. These sources of IL-17 restrict fungal growth in intact skin but can exacerbate *Malassezia*-driven inflammation in injured skin. Local IL-17 recall responses to *Malassezia* and *Candida* also aggravated psoriasiform skin inflammation in mice, which recapitulates transcriptional features of human psoriatic skin lesions[165].

In the gut, the humoral immune response can shape mutualism between intestinal *Candida* and its human host by preferentially targeting adhesins expressed by *C. albicans* hyphae but not the yeast form. This IgA-dependent selection favours the growth of yeast rather than hyphal morphotypes in the intestine and enhances the competitive fitness of yeast in antibiotic-treated mice[166,167]. Furthermore, the human repertoire of antibodies to *C. albicans* includes IgG antibodies, which depend on $CARD9^+$ intestinal macrophages to promote their production and are protective in mice infected systemically with *C. albicans* and *C. auris*[168].

Commensal anaerobic bacteria can regulate intestinal fungal density, partly by inducing the production of antimicrobial peptides, by producing short-chain fatty acids through fermenting dietary fibre and by maintaining a low-oxygen environment. *Bacteroides* and *Blautia* bacteria activate intestinal epithelial cell signalling through HIF1α, which regulates enterocyte release of the antimicrobial peptide LL-37 and *C. albicans* colonization resistance[43] (Fig. 4a). Antibiotics that promote the loss of anaerobic bacterial taxa drive intestinal fungal expansion. For example, antibiotic-induced injury to the bacterial microbiota facilitates intestinal expansion and domination by pathogenic *Candida* (Fig. 4b), which in the context of chemotherapy-induced mucosal injury can translocate across the intestinal barrier to cause life-threatening bloodstream infections in HSCT recipients[169] (Fig. 4c). Intestinal fungal dysbiosis during the peri-HSCT period is also linked to reduced long-term survival and increased non-relapse mortality[170,171].

In human cohorts, fungal gut dysbiosis characterized by *Malassezia*, *Debaromyces* or *Candida* expansion is associated with inflammatory bowel disease (IBD) phenotypes. In mice, during intestinal wound healing and dextran sodium sulfate (DSS)-induced colitis, the introduction of representative clinical strains from individual fungal genera (*Malassezia*, *Debaromyces* or *Candida*) caused exuberant tissue pathology, whereas laboratory-passaged strains did not[172–175]. Genetic variation in *CLEC7A* (Y238*) and *CARD9* (S12N) is associated

with increased risk and severity of IBD[157,176,177]. Responsiveness to faecal microbiota transplantation in patients with IBD is associated with high levels of *Candida* before faecal microbiota transplantation, and disease amelioration is associated with low levels of *Candida* after faecal microbiota transplantation, which is consistent with the idea that faecal microbiota transplantation may reduce the contribution of fungus-associated inflammation to IBD severity[178].

A recent study explored how fungal strain-specific attributes affect functional interactions with host cells to affect IBD severity. A collection of *C. albicans* strains cultured from colonic lavages of patients with IBD and non-disease controls was classified on the basis of filamentation properties and ability to induce IL-1β production by macrophages as a measure of strain-dependent aggravation of intestinal inflammation[179] (Fig. 4b). High damage-inducing strains induced IL-1β-dependent tissue damage and instructed T_H17 cell differentiation through recognition of candidalysin. These strain attributes were linked to IBD severity in humans and were recapitulated in a mouse DSS-induced colitis model, in which IL-1 blockade ameliorated inflammation.

In the pancreas, tissue-resident fungi (particularly *Malassezia*) are markedly enriched in pancreatic ductal adenocarcinoma compared with non-cancerous tissue[180]. In a mouse model of pancreatic ductal adenocarcinoma, antifungal drugs ameliorated tumour progression and the reintroduction of *Malassezia* accelerated tumour growth. Mechanistically, mannose-binding lectin bound to *Malassezia* glycans and activated the C3 complement cascade, which enhanced the growth of tumour cells expressing C3a receptor[180]. Depletion of commensal fungi was recently shown to enhance responsiveness to radiotherapy in a mouse model of breast cancer, and intratumoural dectin 1 expression negatively correlated with survival of patients with breast cancer[181]. The recent comprehensive characterization of the composition of the tumour-associated mycobiota across multiple human cancers has revealed the low-level, yet ubiquitous, presence of fungal DNA and cells in a tumour type-specific manner, often in close spatial association with macrophages and malignant cells[182,183]. Clinically, certain plasma or tumour-associated mycobiota subtypes were associated with differential response to immunotherapy, disease severity and/or survival, which indicates that cell-free or tumour-associated fungal DNA may be a potentially promising diagnostic and prognostic biomarker in patients with cancer[182,183].

Conclusions and future perspectives

Opportunistic fungal infections cause a substantial disease burden globally and are a major threat to the well-being of vulnerable patients. The past decade of research on fungal immunology has moved at a remarkable pace and has yielded exciting advances in our basic understanding of the cellular and molecular determinants of antifungal defences. In this Review, we have delineated promising immunogenomic factors that may enable personalized risk assessment and prognosis of patients at risk of fungal disease, and adjunctive immunotherapeutic strategies that may protect fungus-infected patients by modulating antifungal responses. We have highlighted the expanding universe of inherited and iatrogenic immunodeficiency conditions that predispose to opportunistic fungal disease, as well as the conceptual advances in our understanding of protective and pathogenic antifungal immune pathways that have been derived from studying these conditions. We have also discussed how the endogenous mycobiota shape immune homeostasis and regulate responses to neoplasia, infections, autoimmunity and other exogenous insults. Moving forward, further increasing our understanding of tissue-specific mechanisms of antifungal defence should help to improve the management of life-threatening fungal infections and curtail their detrimental impact on human health.

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Competing interests
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