Review article

The pathobiology of human fungal infections

Gordon D. Brown ✉, Elizabeth R. Ballou, Steven Bates, Elaine M. Bignell, Andrew M. Borman, Alexandra C. Brand, Alistair J. P. Brown, Carolina Coelho, Peter C. Cook, Rhys A. Farrer, Nelesh P. Govender, Neil A. R. Gow, William Hope, J. Claire Hoving, Rachael Dangarembizi, Thomas S. Harrison, Elizabeth M. Johnson, Liliane Mukaremera, Mark Ramsdale, Christopher R. Thornton, Jane Usher, Adilia Warris & Duncan Wilson

Abstract

Human fungal infections are a historically neglected area of disease research, yet they cause more than 1.5 million deaths every year. Our understanding of the pathophysiology of these infections has increased considerably over the past decade, through major insights into both the host and pathogen factors that contribute to the phenotype and severity of these diseases. Recent studies are revealing multiple mechanisms by which fungi modify and manipulate the host, escape immune surveillance and generate complex comorbidities. Although the emergence of fungal strains that are less susceptible to antifungal drugs or that rapidly evolve drug resistance is posing new threats, greater understanding of immune mechanisms and host susceptibility factors is beginning to offer novel immunotherapeutic options for the future. In this Review, we provide a broad and comprehensive overview of the pathobiology of human fungal infections, focusing specifically on pathogens that can cause invasive life-threatening infections, highlighting recent discoveries from the pathogen, host and clinical perspectives. We conclude by discussing key future challenges including antifungal drug resistance, the emergence of new pathogens and new developments in modern medicine that are promoting susceptibility to infection.

Sections

Medical Research Council Centre for Medical Mycology, University of Exeter, Exeter, UK. ✉e-mail: gordon.brown@exeter.ac.uk

Review article

Introduction

Of all classes of microorganisms that can infect humans, fungi are among the least studied and understood. Yet, their cumulative impact on human health is staggering, as fungal infections affect billions of people and result in more than 2 million deaths every year[1]. The publication of the fungal pathogen priority list by the WHO in 2022 (ref. [2]) was a major acknowledgement of the importance of these pathogens to human health (Fig. 1 and Supplementary Table 1) and the difficulties we face in tackling the diseases they cause, including the limited diagnostic and therapeutic options currently available (Table 1). Over the past decade, there have been considerable increases in our knowledge and understanding of the pathogenesis of fungal infections. New discoveries have revealed startling and unexpected insights into the underlying mechanisms of fungal virulence and host immunity and their impact on human health. In this Review, we integrate these exciting recent advances into a comprehensive overview of fungal pathobiology from the pathogen, host and clinical perspectives. Although superficial fungal infections of the nails, hair and skin and allergic fungal diseases can have a huge impact on human morbidity, the primary focus of this Review is on fungi that can cause invasive life-threatening infections.

Fungal virulence

The evolution of virulence

Only a small proportion of fungal species (about 600) have been reported to cause infections in humans[3]. The ability of fungi to infect humans has emerged numerous times, independently across the kingdom[4], spanning millions of years of evolution. Indeed, nearly half of the fungal phyla include species able to infect humans. Increasing numbers of fungi are emerging as aetiological agents of disease in humans as a result of increased human exposure to the pathogens, larger populations with host immune impairments, as well as fungi exhibiting increased pathogenicity and/or by colonizing new ecological niches (geographically or zoonotically)[4] (Box 1). For example, the recent emergence of *Candida auris* is causing concern in health-care facilities worldwide[5].

Despite their evolutionary diversity, fungal pathogens of humans display common phenotypic properties that reflect the biotic and abiotic challenges imposed by mammalian host tissues. These common phenotypes include thermotolerance, which is an important prerequisite to be able to cause infections in humans. Whether they are principally saprobic (such as *Aspergillus*, *Histoplasma* or *Talaromyces* species), form part of the commensal microbiota (such as *Candida* species and other related yeast genera) or are obligately associated with their human host (for example, *Pneumocystis jirovecii*), fungi that are capable of causing human infections must be able to tolerate the ambient temperature of the site or sites they infect[4]. This is of importance, as the global climate crisis may select for adaptive thermotolerance, which might lead to the emergence of new fungal pathogens, as well as increasing the geographical spread of extant fungal pathogens.

The role of fungal morphology in virulence

Fungi display a wide variety of morphological forms, and their ability to switch forms can have a key role in virulence (Fig. 2). For example, *Candida albicans* is polymorphic and forms yeast, pseudohyphae, hyphae and chlamydospores, as well as yeast-like morphologies, opaque and grey[6]. This organism is a common human commensal and is found in more than 80% of individuals[7] but can also cause mucosal as well as life-threatening invasive infections in certain situations. The yeast–hypha transition has received widespread attention, with earlier work

demonstrating its importance in disseminated disease, as well as roles in tissue invasion and destruction, and biofilm formation. *C. albicans* hyphae have direct roles in virulence through induced endocytosis[8], thigmotropism[9] and active penetration driving invasion[9,10], the formation of transcellular tunnels[11] and escape from macrophages[12]. In addition, genes co-regulated with hyphal development have a key role in virulence, encoding factors such as adhesins (for example, Als3 (ref. 13) and Hwp1 (ref. 14)), hydrolytic enzymes (for example, Sap4–6 (ref. 15) and Sod5 (refs. 16,17)) and the hypha-specific cytolytic peptide toxin (candidalysin (derived from Ece1)), which might be involved in nutrient acquisition from the host[18]. Nonetheless, the close association between the yeast–hypha transition and virulence has been brought into question, with recent work demonstrating that metabolic flexibility and cell wall remodelling can overcome the impact of filamentation defects[19,20]. However, the ability to undergo transitions between yeast and hyphal forms is key to its success as a commensal and pathogen[21–23]. The yeast-like morphologies, opaque and grey, may also have a more specific role in virulence in certain microenvironments, as these cells seem to be better adapted to colonize the skin, tongue and gastrointestinal tract[24].

In contrast to *C. albicans*, thermally dimorphic fungi, such as *Paracoccidioides* spp., *Talaromyces marneffei*, *Histoplasma* spp. and *Coccidioides* spp., switch from their environmental hyphal form to the pathogenic yeast form or, for *Coccidioides* spp., a spherule tissue form, in the host, mainly driven by temperature. These thermo-dimorphic switches are generally co-regulated with cell wall remodelling and the expression of secreted factors that have a role in virulence: such as *Blastomyces* virulence adhesin-1 (BAD1 (ref. 25)) and *Coccidioides* spherule outer wall fraction glycoprotein (SOWgp)[26], which promote adhesion, and *Histoplasma capsulatum* calcium-binding protein 1 (CBP1) that promotes phagocyte cell death[27]. In the host, *Cryptococcus* species become encapsulated yeasts and have the capacity to form large polyploid cells, termed 'titan' cells[28–30]. The balance between yeast and titan cells in the lung is key to virulence[31] and is discussed in more detail subsequently. Filamentous fungal pathogens such as *Aspergillus*, *Fusarium* and *Mucorales* spp. also undergo morphological changes linked to cell wall remodelling and protein secretion during host colonization. However, unlike the aforementioned examples of inducible morphogenesis, the spore-to-hypha germination in filamentous fungi is an obligatory feature of proliferation and tissue invasion.

The role of secretory products in virulence

The secretion of molecules into the extracellular environment is a fundamental property of the fungal kingdom required for the enzymatic degradation of large molecules for nutrient acquisition. For human fungal pathogens, many secreted factors can drive the infection process and contribute to immune evasion (Fig. 2). Fungal genomes often carry genes that encode secreted factors in higher copy numbers and greater diversity compared with their non-pathogenic relatives. One of the best characterized examples is the family of secreted aspartic proteases of *C. albicans*, several of which are released into the extracellular environment[15]. As well as processing proteins to function as a nutrient source (predominantly nitrogen), many secreted aspartic proteases also modulate host immunity, for example, by degrading antimicrobial peptides and components of the complement cascade. Similarly, *Aspergillus fumigatus* Mep1 and *Cryptococcus neoformans* App1 cleave complement components[32]. *C. neoformans* secretes an M36 metalloproteinase, Mpr1, which mediates fungal traversal of the blood–brain barrier[33]. Although such proteases are not unique to pathogens, these species often have larger protease gene families, which
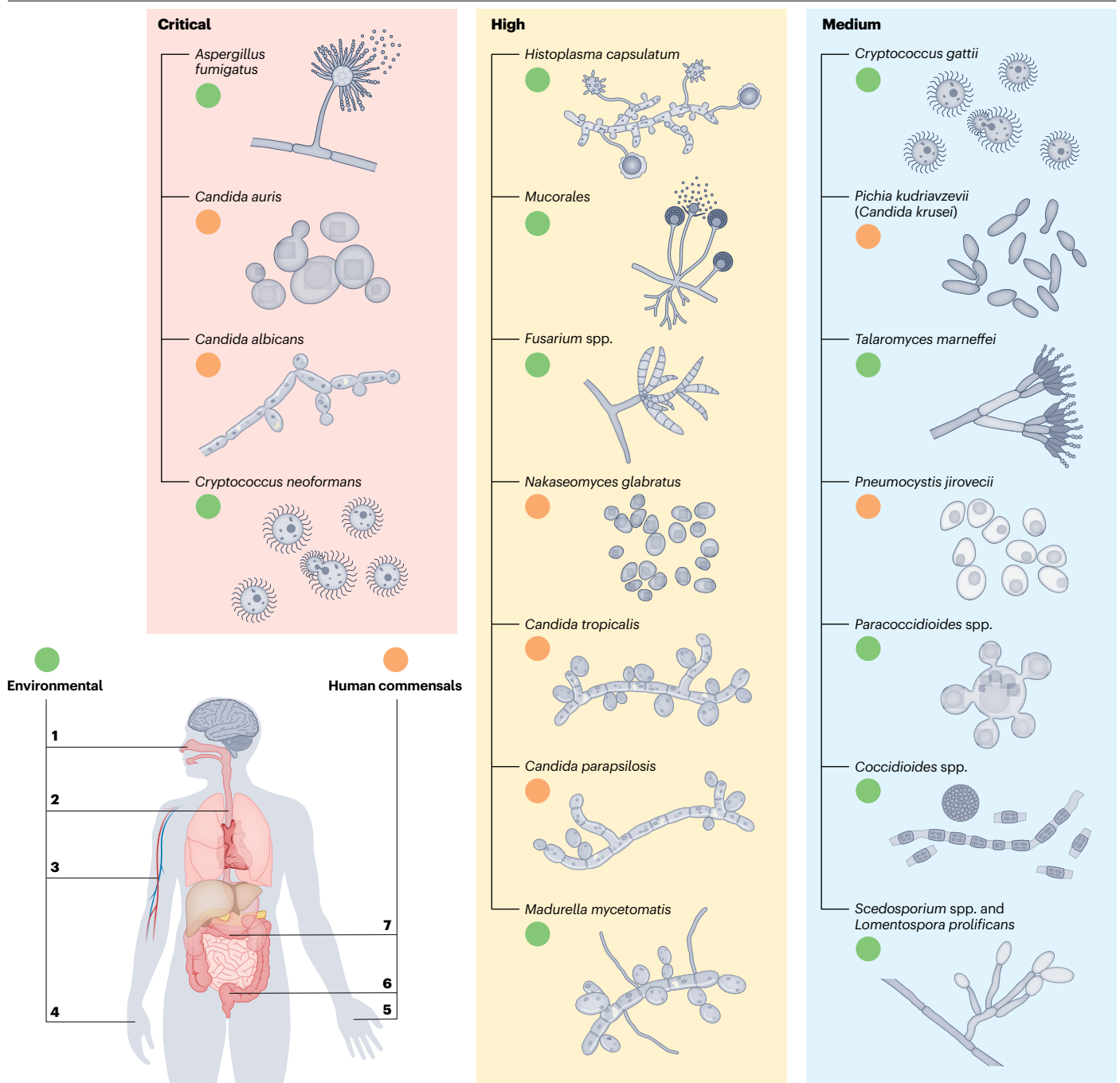
Fig. 1 | Human pathogenic fungi designated as critical, high and medium risk by the WHO. Shown are 18 fungal pathogens that have been categorized as critical, high or medium risk to human health by the WHO during compilation of the first Fungal Pathogens Priority List[2]. The Fungal Pathogens Priority List was generated via multicriteria decision analysis to achieve a systematic prioritization of fungal pathogens causing acute or subacute invasive disease, with a view to identifying urgent unmet research and development needs, areas for sustainable investment and to inform and enable policymakers. Ten assessment criteria were used for ranking including incidence, case fatality rates, global distribution, antifungal resistance and access to diagnostics and treatments. Primary niches of the fungi are designated as green circles for pathogens of environmental origin (for example, soil or airborne fungi) or orange circles for pathogens derived from human commensal mycobiota. Fungal pathogens acquired from environmental sources may enter the human body (bottom left) to cause disease via inhalation (1 and 2) or traumatic implantation (3 and 4), including during surgery. Human commensals may translocate from the skin (5) and/or mucosa (6 and 7) to cause disease or via traumatic implantation (7) including during surgery. At-risk populations, routes of acquisition and corresponding fungal diseases are documented in Supplementary Table 1. Drawings are indicative of fungal morphologies and are not to scale.

Table 1 | Diagnostic considerations and antifungal resistance

Fungal disease	Diagnostic							Resistance					
	Microscopy and culture	Biomarker: BDG	Biomarker: GM	Molecular test: Sp-sp PCR	Molecular test: Panfungal PCR[a]	Antigen	Antibody	Fluconazole	Amphotericin B	Mould-active azoles	Echinocandins	Flucytosine	Terbinafine
Aspergillosis	BALF, T, SBF, Sp	B, CSF	B, BALF, CSF	B, BALf, T, SBF	B, T, SBF	GM only; B, BALF, CSF	B[b]	IR	Very rare (H, IR, AR), Aspergillus terreus (IR)	AR (environment, l-Th)	Rare (IR, AR)	IR[c]	NR
Candidosis	B, T, CSF, SBF	B, CSF	ND	B, T, SBF	B, T, SBF	B, CSF	B, CSF	Sp-sp (IR), l-Th (AR)	Sp-sp (IR)	Sp-sp (IR), l-Th (AR)	Sp-sp (IR), l-Th (AR; rare)	Sp-sp (IR), l-Th (AR)	NR
Cryptococcosis	CSF, B	ND	ND	X	CSF, B	CSF, B	X	H, AR	Rare	H, AR (both not common)	IR	H, AR	NR
Other yeast species	B, T, CSF, SBF	B, CSF	ND	X	B, T, SBF	X	X	Sp-sp (IR), l-Th (AR)	Sp-sp (IR)	Sp-sp (IR), l-Th (AR)	Sp-sp (IR), l-Th (AR; rare)	Sp-sp (IR), l-Th (AR)	NR
Pneumocystis	BALF, Sp (microscopy only)	B, BALF	ND	BALF, B	BALF, B	X	X		IR	IR	RS (active against cyst form)	IR	NR
Mucoromycosis	BALF, T, SBF	ND	ND	B, T	B, T	X	X	IR	Very rare	IR (exception posa and isa for some species)	IR	IR	NR
Hyalohyphomycosis													
Fusarium	T, CSF, SBF, Sp	B, CSF	B, BALF, CSF	X	B, T, SBF	X	X	IR	IR (common)	IR encountered (vori treatment of choice)	IR	IR[c]	NR
Scedosporium	T, CSF, SBF, Sp	B, CSF	ND	X	B, T, SBF	X	X	IR	IR (common)	Rare	IR	IR	NR
Lomentospora	T, CSF, SBF, Sp	B, CSF	ND	X	B, T, SBF	X	X	IR	IR	IR	IR	IR	NR
Phaeohyphomycosis													
Cladophialophora	T, CSF, SBF, Sp	B, CSF	ND	X	B, T, SBF	X	X	IR	Rare	Rare	IR	IR[c]	NR
Exophiala	T, CSF, SBF, Sp	B, CSF	ND	X	B, T, SBF	X	X	IR	Rare	AR (rare)	IR	IR[c]	NR
Rhinocladiella	T, CSF, SBF, Sp	B, CSF	ND	X	B, T, SBF	X	X	IR	IR[d]	Rare	IR	IR[c]	NR
Endemic dimorphic mycoses													
Blastomycosis	T, CSF, SBF, Sp	ND	ND	X	B, T, SBF, BALF	X	B	IR	Rare	Rare	RS, IR	NR	NR
Coccidioidomycosis	T, CSF, SBF, Sp	P	CR[d]	X	B, T, SsBF, BALF	X	B	Rare	Rare	Rare	RS, IR	NR	NR
Emergomycosis	T, CSF, SBF, Sp	P	CR[d]	X	B, T, SBF, BALF	X	B	IR	Rare	Rare	RS, IR	NR	NR

Table 1 (continued) | Diagnostic considerations and antifungal resistance

Fungal disease	Diagnostic							Resistance					
	Microscopy and culture	Biomarker: BDG	Biomarker: GM	Molecular test: Sp-sp PCR	Molecular test: Panfungal PCR[a]	Antigen	Antibody	Fluconazole	Amphotericin B	Mould-active azoles	Echinocandins	Flucytosine	Terbinafine
Endemic dimorphic mycoses (continued)													
Histoplasmosis	B, T, CSF, SBF (BM), Sp	P	CR[d]	X	B, T, SBF, BALF	B, U	B	Rare	Rare	Rare	RS, IR	NR	NR
Paracoccidioido-mycosis	T, CSF, SBF, Sp	P	CR[d]	X	B, T, SBF, BALF	X	B	Rare	Rare	Rare	RS, IR	NR	NR
Talaromycosis	T, CSF, SBF, Sp	P	CR[d]	X	B, T, SBF, BALF	X	B	IR	Rare	Rare	RS, IR	NR	NR
Superficial and subcutaneous													
Alternaria	T	ND	ND	X	T	X	X	IR	Rare	IR (voriconazole)	RS, IR	IR[c]	NR
Candida	Swab, T	ND	ND	T	T	X	X	Sp-sp (IR), l-Th (AR)	Sp-sp (IR)	Sp-sp (IR), l-Th (AR)	Sp-sp (IR), l-Th (AR; rare)	Sp-sp (IR), l-Th (AR)	NR
Chromoblasto-mycosis	T	ND	ND	X	T	X	X	IR	Rare	Uncommon	RS, IR	IR[c]	NR
Dermatophytosis	T	ND	ND	T	T	X	X	Sp-sp (IR), l-Th (AR)	Rare	Sp-sp (IR), l-Th (AR)	RS, IR	IR	Rare (IR and AR) except *Trichophyton indotineae*, *Microsporum canis* (AR)
Eumycetoma	T	ND	ND	X	T	X	X	IR	Rare	Uncommon	RS, IR	IR[c]	NR
Sporotrichosis	T	ND	CR[d]	X	T	X	X	IR	IR common	IR common	IR	IR[c]	NR

AR, acquired resistance; B, blood; BALF, bronchoalveolar lavage fluid; BDG, β-D-glucan; BM, bone marrow; CR, cross-reactivity; CSF, cerebrospinal fluid; GM, galactomannan; H, heterogenous; IR, intrinsic resistance; isa, isavuconazole; l-Th, long-term therapy; ND, not detected or only at very low levels; NR, not relevant; P, present in most strains; posa, posaconazole; RS, reduced susceptibility; SBF, sterile body fluid; Sp, sputum; Sp-sp, species-specific; T, tissue; U, urine; vori, voriconazole; X, unavailable commercially, although in-house methods may be available. [a]Panfungal PCR can be used on BALF but it is likely to detect only the predominant organism and commensal yeasts are often detected. It is most helpful on BALF for *Pneumocystis* or the endemic dimorphic mycoses. [b]In immunocompetent patients (for example, aspergilloma and endocarditis). [c]May be helpful in combination. [d]May have clinical utility.

Review article

Box 1 | Emergence of fungal antimicrobial resistance and new pathogens

It is critical to make a concerted effort to understand the life cycle and reservoirs of human fungal pathogens and to complement this with strict antimicrobial resistance (AMR) surveillance and improved diagnosis. The high incidence of fungal diseases in susceptible individuals indicates that humans are frequently exposed to fungal pathogens. Moreover, the worldwide dissemination of previously endemic pathogens, including multidrug resistant *Candida auris*[5], suggests that fungal diseases are spreading and the incidence of drug resistance is rising.

Overuse of pharmaceuticals drives AMR in fungi

In 2006, to prevent AMR in bacterial diseases, the EU restricted agricultural and farm use of antibiotics, with further restrictions enacted in 2022 (ref. [207]). Unfortunately, these regulations do not apply to antifungals. Thus, the extensive use of azoles in agriculture has already been linked to the rise in infections by azole-resistant *Aspergillus fumigatus*[208]. Another example is *Trichophyton indontineae* which is intrinsically resistant to terbinafine and its emergence has been attributed to misuse and overuse of topical antifungals and corticosteroids[209].

Anthropogenic activity driving the emergence of new pathogens

Fungi typically thrive in moderate temperatures, with only a fraction of fungi tolerating 37 °C. High basal internal temperature of mammals provides a key innate resistance to fungi. These fungal–mammal interactions may have contributed to the evolution of thermotolerance of mammals[196,210]. A key example is white nose syndrome, a fungal infection in hibernating bats that occurs when their body temperature drops, resulting in substantially reduced bat populations. Worldwide global warming reduces this thermal barrier and may be driving the adaptation of 'thermosensitive' fungi to mammalian body temperatures. Indeed, an entomopathogenic fungus, *Metarhizium anisopliae*, was rapidly adapted to higher temperatures by laboratory thermal selection[211]. Urban heat traps may compound this risk: fungal species in cities may become more thermotolerant than their rural counterparts.

Human travel and globalization also facilitate the dissemination of pathogens. White nose syndrome, as an example, is thought to have spread to the USA from endemic populations in Europe, possibly on equipment of cavers. Moreover, the global spread of chytrids, causing dozens of extinctions in amphibians, is attributed to global trade in amphibians[212].

---

indicate positive selection in human (and other animal) pathogens[34]. *C. albicans* also secretes a lipase, Lip2, that alters host tissue lipids, which results in suppression of T_H17 responses[35]. In addition to secreted proteins, many fungi produce and secrete small-molecule secondary metabolites, which have a wide range of activities: penicillin is a well-known example of a secondary metabolite antibiotic. Others function in micronutrient scavenging (siderophores, discussed subsequently) and immune modulation[36]. *Aspergillus* and *Fusarium* species also produce small-molecule toxins including gliotoxin, aflatoxin and fumonisins[37].

To proliferate in the infected host, fungi must secure micronutrients such as iron and zinc. Indeed, infections with *Mucorales* spp. are strongly associated with iron overload[38,39]. Fungal acquisition of these micronutrients is particularly challenging because the immunocompetent host actively restricts access to these trace minerals via nutritional immunity. To capture iron from the host, *A. fumigatus* relies upon intracellular (ferricrocin and hydroxyferricrocin) and extracellular (fusarinine C and triacetylfusarinine C) siderophores[40], whereas *C. albicans* cannot produce its own siderophores, instead utilizing host iron-binding protein scavengers including a ferritin receptor and a multimember family of haem-binding proteins[38,41,42]. Most other pathogenic fungi, including *H. capsulatum*, also compete with the host for zinc[43,44].

Beyond classic secreted proteins, many human fungal pathogens release extracellular vesicles (EVs). First identified in *C. neoformans*, EVs are proposed to act as 'virulence-bags', by trafficking proteins and other biomolecules[45]. EVs are likely to play a key role in fungal pathogenicity in humans. Indeed, *C. albicans* EVs were recently shown to induce type I interferon signalling through the cGAS–STING pathway[46]. However, the exact role of EVs in fungal cell surface remodelling, nutrient acquisition and export of virulence factors is still under investigation. As well as being released by fungi into their environments, EVs can traverse the cell wall in the opposite direction and be taken up by fungal cells. In

this context, EVs may play key roles in intercellular communication[47,48]. *C. albicans* EVs have recently been shown to contribute towards the extracellular matrix production of biofilms. Indeed, endosomal sorting complexes required for transport mutants, which are defective in EV production, display highly reduced resistance to antifungals (a clinically important property of biofilms). Intriguingly, the addition of exogenous EVs to these defective biofilms reverses this effect, strongly suggesting that EVs directly contribute towards biofilm-mediated drug resistance[49].

Fungal fitness

Fungal pathogenicity is also dependent on 'fitness attributes' that enhance adaptation to, and thereby physiological robustness within, host niches. In addition to micronutrient scavenging and thermotolerance, described earlier, fitness attributes include metabolic adaptation; adaptation to local pH, oxygen and carbon dioxide levels; and the activation of robust responses to local environmental stresses such as hypoxia[50] and reactive chemical species delivered by local innate immune defences. For example, pathogens that evolved in environmental niches have developed metabolic flexibility and environmental stress resistance to pivot between periods of starvation and active recycling of environmental detritus, when available. Indeed, fatty acid metabolism and thermotolerance have become tightly linked in *A. fumigatus* through functionality of the heat shock transcription factor[51]. Similarly, pH-dependent expression of germination-specific and virulence-specific genes is implicated in a metabolic shift that enables survival of *Mucor circinelloides* within macrophages[39]. Meanwhile, fungal pathogens that have co-adapted with their host seem to have tuned their metabolic flexibility accordingly. For example, in contrast to biotechnological strains of *Saccharomyces cerevisiae*, which assimilate simple sugars before switching to less-efficient carbon sources, clinical isolates of *S. cerevisiae* and *C. albicans* have the capacity to

assimilate sugars and alternate carbon sources simultaneously, thereby enhancing their pathogenicity[52]. Conversely, *P. jirovecii* has become so dependent on its human host that it has lost biosynthetic pathways and corresponding regulatory transcription factors required for the synthesis of most amino acids as well as certain lipids, cofactors and vitamins[53].
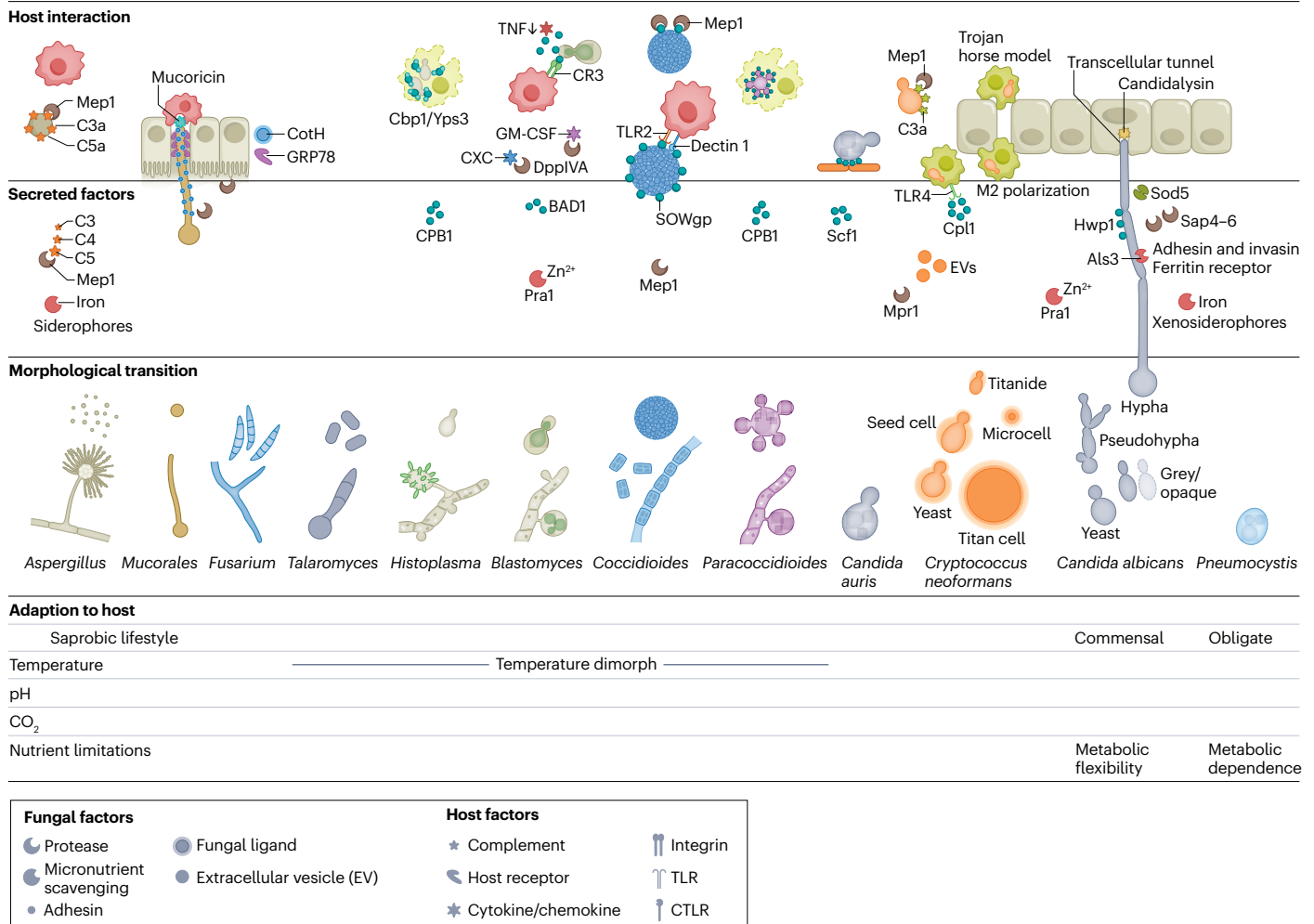

Fig. 2 | Fungal virulence factors and virulence attributes. Pathogen potential in diverse fungi emerges through common phenotypic traits that enable growth in mammalian host tissues. Pathogenesis has emerged repeatedly and independently across the fungal kingdom. Representative species and their key traits are shown. Pathogen potential in mammals is underpinned by adaptation to host environment conditions, including temperature, pH, CO_2 and nutrient acquisition. Close association with humans can occur either as commensal (*Candida* spp. with *C. albicans* shown as a representative member) or obligate (*Pneumocystis*) interactions, with metabolic rewiring enabling (*Candida*) or restricting (*Pneumocystis*) host niche adaptation. Drivers of pathogenesis include morphological changes, secreted factors and host-specific strategies. Morphogenesis: the germination of spores and the switch to invasive specific growth forms characterize pathogenesis of *Aspergillus*, *Fusarium* and *Mucorales* species. Thermal dimorphism across a wide range of species supports morphological switches that enable dissemination or tissue penetration and are associated with cell wall changes (Fig. 3) relevant to stress resistance and immune evasion. Pleomorphic growth forms (*Cryptococcus*; *Candida*) enable dissemination, translocation across tissue barriers and tissue invasion. Secreted factors: the expression of cell surface adhesins is a major driver of environmental spread (*Candida auris* Scf1) and adhesion to host cells (*Rhizopus* CotH via Gpr78; *Blastomyces* BAD1 via CR3; *Coccidioides* spherule outer wall fraction glycoprotein via TLR2 and Dectin 1; *Candida* Als3 via E-cadherin or N-cadherin; *Candida* Hwp1 via transglutaminase), and these can additionally be degraded by fungal enzymes to enable masking (*Coccidioides* Mep1). Secreted proteins can additionally modulate host immune factors (*Blastomyces* BAD1 and *Cryptococcus* Cpl1) or detoxify host responses (*Candida* Sod5 and ROS). In addition, micronutrient acquisition is mediated via secreted factors including siderophores or zincophores (Pra1), iron-binding receptors (Als3) or scavenging via xenosiderophores. Secreted factors can also directly modulate host interaction including *Aspergillus fumigatus* Mep1 and *Cryptococcus* App1 that cleave complement components (C3, C4 and C5) to block phagocyte recruitment, *Blastomyces* DppIVA that targets host cytokines and chemokines (CXC) and calcium-binding protein 1 (CBP1) that promotes phagocyte cell death in *Histoplasma capsulatum* and *Paracoccidiodes* spp. Proteases (*Cryptococcus* Mpr1), hydrolytic enzymes (*Candida* Sap4–6) and toxins (*Rhizopus* mucoricin; *Candida*; candidalysin) can directly impact tissue barriers. Translocation across tissue barriers can be mediated by host cells (Trojan horse model) or via the formation of transcellular tunnels. Sizes of the fungal pathogens drawn are not to scale. GM-CSF, granulocyte–macrophage colony-stimulating factor; TLR, toll-like receptor; TNF, tumour necrosis factor.
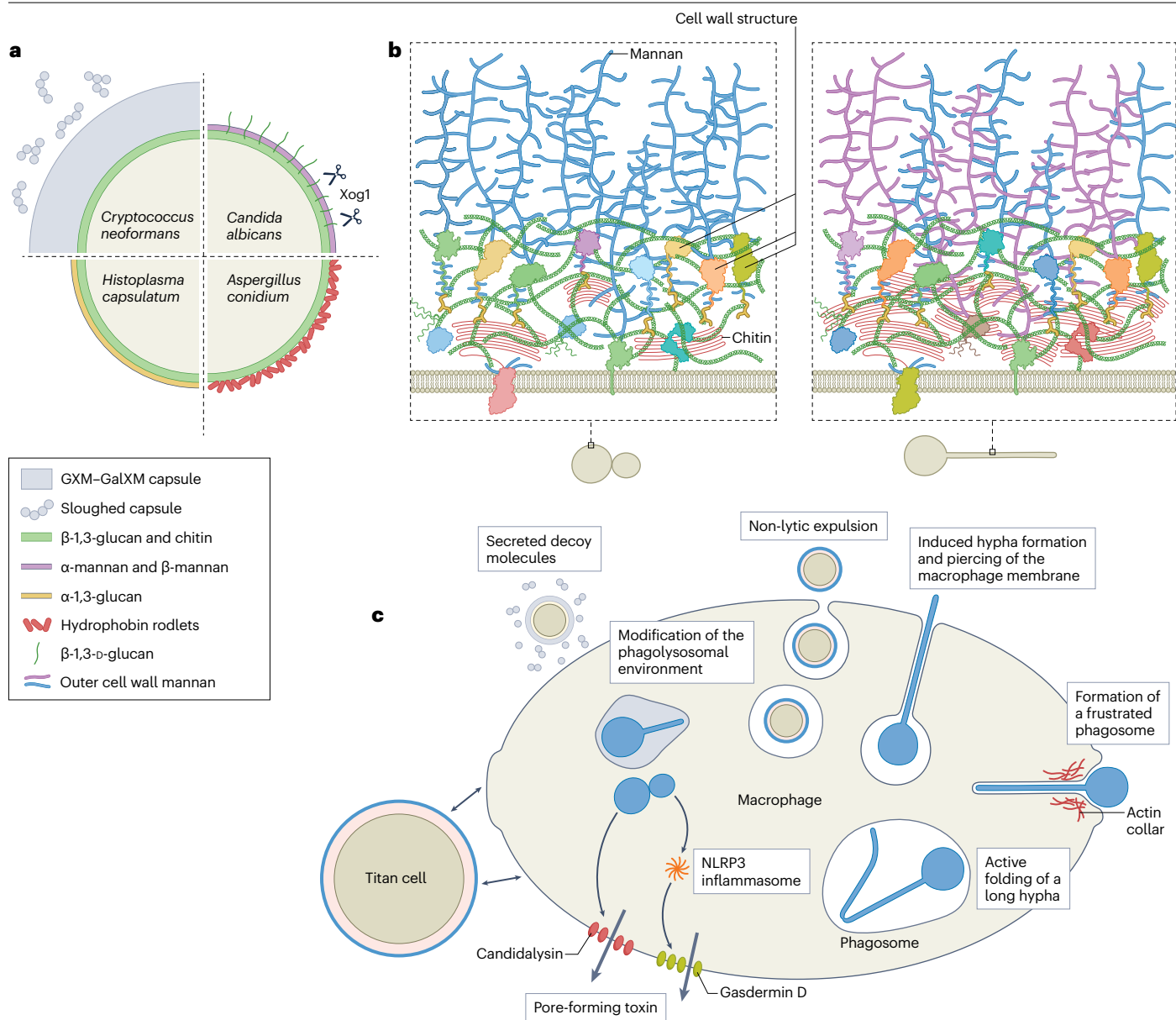
Fungal pathogens also display a wide range of stress sensitivities. Host defences include the generation of reactive oxygen species (ROS), which promote apoptosis-like programmed cell death in *C. albicans* and *A. fumigatus*[54,55]. The clinical significance of ROS-mediated fungal killing is exemplified by the sensitivity of individuals with reduced ROS-generating capacity (for example, with defective NADPH oxidase 2) to fungal infections[56]. Not surprisingly, therefore, most fungal pathogens are resistant to host-derived ROS. *Nakaseomyces glabratus* (formerly *Candida glabrata*), in particular, is extremely resistant to oxidative stresses even relative to other fungal pathogens, which is thought to be due to the evolutionary assimilation of novel stress-protective proteins[57]. At the other extreme, *P. jirovecii* has lost key transcription factors that, in other fungi, promote resistance to environmental stresses[53], and this is likely to contribute to the difficulties in culturing the organism in vitro.

Genetic variation

Fungal pathogens can infect diverse hosts and ecological niches, which are facilitated by the rapid responses of their genomes to natural selection[58]. Many examples of this have been described, including horizontal transfer of whole chromosomes (for example, *Fusarium oxysporum*, although the impact of horizontal transfer has only been shown in plants)[59], repeat-driven genome expansions[60] and structural variation[61], all of which are associated with host adaptation and changes in virulence across lineages and species. Maintaining sufficient genetic diversity to respond to selection is facilitated by the ability of fungi to use multiple reproductive modes, including cryptic recombination that enables inbreeding, outcrossing, hybridization and the generation of diversity via parasexual mechanisms[62].

Mechanisms increasingly recognized as driving dynamic genome structure in pathogenic fungi of humans include chromosomal

Review article

Fig. 3 | Fungal immune evasion mechanisms. Fungal immune evasion strategies include differing chemistries of the outer cell wall (part **a**); modification of the cell wall associated with the yeast–hypha transition of *Candida albicans* (part **b**) and a range of encounters and interactions with phagocytes (part **c**). **a**, The inner cell wall of these fungi (green) contains β-1,3-glucan (which is a strong immune agonist) and various other polysaccharides in different fungi, which are not represented in this diagram. Immune recognition of components of the inner cell wall can be blocked or shielded by the presence of a gelatinous capsule of *Cryptococcus neoformans* that also generates sloughed decoy capsule fragments; the shaving of superficial β-1,3-glucan by the *C. albicans* glucanase Xog1; the presence of an immunologically inert outer layer of rodlets of the *Aspergillus conidium*; or α-1,3-glucan in the outer wall of *Histoplasma capsulatum* and *Blastomyces dermatitidis* that shields the underlying β-1,3-glucan from detection. **b**, Model of the cell wall of *C. albicans* of the yeast and hyphal form showing greatly increased chitin content of hyphae and differences in the outer cell wall mannan chemistry (indicated by the purple structures). These lead, for example, to increased recognition of hyphae by the mannose receptor immune receptor. **c**, Interactions of *C. neoformans* or *C. albicans* with macrophages, exemplifying strategies used by a wider range of fungal pathogens. Cellular gigantism is illustrated by a Titan cell of *C. neoformans* (or Goliath cells of *C. albicans* or spherule formation by *Coccidioides immitis*) that are too large to be easily engulfed. The use of secreted decoy molecules such as capsule fragments of *C. neoformans* that block macrophage function or Bad1 production by *B. dermatitidis*, which interferes with macrophage and neutrophil function. Non-lytic expulsion (vomocytosis) of a yeast cell of *Cryptococcus neoformans* and other unicellular pathogens. Induced hypha formation and piecing of the macrophage membrane by a *C. albicans* hypha and the induction of pyroptosis-mediated macrophage cell death. Formation of a 'frustrated' phagosome with a collar of formin-dependent actin enabling the partial engulfment and inhibition of long hyphae that cannot be completely phagocytosed. The active folding of a long hypha of *C. albicans* within the phagosome of a macrophage to enable its destruction. The modification of the toxic phagolysosomal environment by *C. albicans* by affecting RAB GTPase localization and restricting phagosome acidification, oxidative or nitrosative damage. The induction of the pore forming toxin candidalysin or the fungus activates the NLRP3 inflammasome and the release of gasdermin D, which leads to phagocyte membrane leakage. GXM, glucuronoxylomannan. Part **b** adapted from ref. 206, Springer Nature Limited.

copy-number variation (also known as aneuploidy)[63] and the duplication of chromosome arms (isochromosomes). The mechanism or mechanisms that generate chromosomal copy-number variation in fungi remain unclear, but exposure to environmental and host stresses enhances genome instability and thereby evolutionary adaptability[64]. A change in ploidy or chromosome number can change how a cell senses and responds to its environment. Ploidy changes in fungi not only result in changes in cell size, growth rates, gene expression, adaptation to host niches and antifungal resistance but also have long-term effects on genetic changes and potentially the evolution of novel traits. Although demonstrated in many fungi, aneuploidy has been best studied in *C. albicans*, where metabolism-induced oxidative stress[65] or exposure to the model host, *Caenorhabditis elegans*[66], promoted changes in ploidy and loss of heterozygosity. The high frequency of chromosome mis-segregation in *C. albicans*, and hence the high level of adaptability of this fungal pathogen, seems to be related to the expression of a particular histone H2A variant, combined with the depletion of the centromeric histone CENP-A[67]. Of the resultant *C. albicans* aneuploids, most display reduced fitness under experimental conditions in vitro[68]. However, a subset of aneuploids display enhanced fitness under certain selective conditions, thereby promoting the emergence of drug resistance to azoles during prolonged antifungal therapy in patients with candidiasis[69]. In *Cryptococcus* species, large-scale, reversible changes in ploidy are inducible by the host environment, which are also associated with aneuploidy. These changes underpin heterogeneity in virulence, morphotypes and drug resistance, although research in this field is still in its infancy.

Recent investigations have also revealed a role for hypermutating strains belonging to several important fungal pathogens that harbour an enhanced ability to rapidly evolve resistance to both biotic (for example, host) and abiotic (for example, antifungal drug) stresses, thereby providing enhanced pathogenicity and resistance, respectively[70,71]. Hypermutating phenotypes have thus far primarily been attributed to loss of regulatory control via RNAi[70] and defects in DNA repair[71]. Further undiscovered genetic and epigenetic factors are likely to be responsible for variable rates of selection and resistance among populations of fungal pathogens.

Fungal immune evasion and manipulation
Variation in the cell wall

The fungal cell wall has a major role in immune recognition. Fungal cell walls are mainly composed of polysaccharides, some of which are not present in mammalian and other animal cells and, as such, are a rich source of pathogen-associated molecular pattern molecules that are recognized by immune pattern recognition receptors (PRRs). These fungal polysaccharides include α-glucans and β-glucans, mannans, chitin and its deacetylated form, chitosan, as well as other non-polysaccharide components such as melanin, lipids and proteins[72] (Fig. 3). The amounts and types of different polysaccharides as well as their arrangement vary in different fungal genera and species. For example, α-1,3-glucans are present in *Aspergillus, Histoplasma* and *Cryptococcus* species but absent in *Candida* species[73]. The *Cryptococcal* cell wall has some considerable differences from that of most other major human fungal pathogens. For example, it contains high levels of chitosan and more β-1,6-glucans than are found in most other fungal pathogens[74]. In addition to a cell wall, *Cryptococcus* species possess an outer polysaccharide capsule (composed primarily of glucuronoxylomannan (GXM) and glucuronoxylomannogalactan) that contributes to immune evasion and masking. Additionally, many fungi produce a complex, mixed morphology biofilm via the production of extracellular matrix that includes cell-wall-associated components such as β-glucan.

The cell wall changes continuously in response to growth rate, cellular morphogenesis, nutrient availability and imposed stress, including immunological stress and exposure to antifungal drugs. In response to specific environmental signals associated with host niches, such as ambient pH, lactate, iron depletion or hypoxia, *C. albicans* alters the exposure of β-1,3-glucan and chitin at the cell surface[75,76]. This might represent a form of 'adaptive prediction', whereby *C. albicans* exploits host signals to activate an anticipatory response that protects against impending recognition by innate immune cells and subsequent fungal clearance[75–77], which would be consistent with coevolution of the fungus with its host. These behaviours emerge when microorganisms 'learn' to exploit one specific environmental challenge to trigger an anticipatory protective response against a second stress that is likely to follow the first. In evolutionary terms, such behaviours can be rapidly gained and lost owing to their additional fitness costs[55], which explains why

Review article

even closely related fungal pathogens can display different forms of adaptive prediction[78,79].

Older *C. albicans* cells have a thicker cell wall with changes in the amounts of chitin, chitooligomers, glucans and mannans and alterations in the cell wall proteome and the way in which wall components are crosslinked[80]. In addition to the known differences between fungal hyphae and yeast or conidia[81], recent studies reported cell wall and capsule differences between *Cryptococcus species* yeast and titan cells[82] and a range of other fungal pathogen cell types[83]. Some cell wall and capsule components (for example, *Cryptococcal* GXM and *Aspergillus* galactomannan) can also be released into the extracellular milieu. This phenotypic plasticity and heterogeneity make the cell wall a moving target for immune recognition, contributing to immune evasion and also, presumably, to the commensal lifestyles of relevant organisms[84].

PRRs have been identified for almost all carbohydrate components of fungal walls[38]. β-1,3-glucan, which resides in the inner cell wall layer, is a common element in the cell wall of most fungal pathogens and is recognized by several host PRRs, including dectin-1 (ref. [85]), complement receptor 3 (refs. [86,87]), CD23 (ref. [88]) and EphA2 (ref. [89]). The other conserved element of the inner wall of most fungi is chitin, and although the exact mechanism of chitin recognition is still unclear, several receptors including toll-like receptor 2 (TLR2), dectin-1, LysMD3, NOD2 and TLR9 have been implicated[90–92]. The outer layer of fungal cell walls is more chemically diverse, and numerous PRRs have been shown to recognize outer wall mannans, galactomannans, galactosaminoga-lactan, glucuronoxylo-mannans, phospholipo-mannans, α-1,4-glucan, melanin and other components. Mannans, in particular, are the ligands for several PRRs including the mannose receptor, DC-SIGN, dectin-2, MINCLE, TLR4 and galectin-3 (ref. [38]). Interestingly, galactosaminoga-lactan can activate the NLRP3 inflammasome by binding to ribosomal proteins and by inhibiting host-cell translation[93]. Site-specific PRRs also drive fungal invasion: *Mucorales* CotH3 interacts with host nasal epithelial GRP78, whereas CotH7 specifically targets alveolar epithelial β1 integrin, triggering epidermal growth factor receptor and damage[38]. Fungi are thought to mask immune-stimulatory cell wall components to evade immune recognition. For example, β-1,3-glucan is thought to be masked by outer cell wall layers in several fungal pathogens, thereby evading recognition by dectin-1 (ref. [77]). However, masking may only be effective against specific immune cell types as some immune cells, such as monocytes, have multiple receptors for outer cell wall layers (see ref. [94] for an example). Active masking has been demonstrated in several fungi, including *H. capsulatum* and *C. albicans*, which shave extraneous superficial β-1,3-glucan from their surface using glucanases (Eng1 and Xog1, respectively) to dampen immune recognition[95,96]. In other organisms, such as *Cryptococcus gattii*, much of the chitin is deacetylated, attenuating immune recognition, which is further blocked by the presence of the outer capsule[97]. Release of the capsule polysaccharide, GXM, by *Cryptococcus* spp. can function as a protective decoy, and the presence of biofilms can physically impede the access of immune cells to the fungal cell wall[98,99].

Impact of fungal morphology on immunity

Fungal morphology shapes immunity and commensalism, and the size of the infectious propagule influences the site of infection. For example, spores of *Cryptococcus* and *Aspergillus* species (2–3 µm) can penetrate deep into airways before germinating to proliferate as yeast or via invasive hyphae[100]. By contrast, *Mucorales* species spores are substantially larger (6 µm to >10 µm), which limits their penetration of the lower airways, leading to rhinosinusitis more frequently than pulmonary infection[101]. Yeast-phase growth of organisms such as *Candida* and *Cryptococcus* spp. is key to their haematogenous dissemination in susceptible hosts[19]. There has also been a rise of invasive and bloodstream yeast infections with non-*albicans* species, *N. glabratus* (*C. glabrata*) as well as other species that do not form hyphae. Conversely, yeast-like grey and opaque forms of *C. albicans* are associated with a gut commensal, rather than pathogenic, lifestyle[6]. Variation in the ability of clinical isolates of *C. albicans* to filament has also been linked to the ability of these strains to induce inflammation in the context of ulcerative colitis[102].

In *Candida* species, zinc limitation induces the formation of large 'goliath' cells, which is accompanied by hyper-adherence and increased chitin exposure[103]. *Cryptococcus* species also differentiate into large titan cells, which can be as large as 100 µm, and thus cannot easily be cleared by phagocytes[104]. The switch to titan cells is associated with production of an altered capsule and inhibition of phagocytosis of smaller fungal cells and thought to promote proliferation in the host lung. Titan cells are also associated with inducing a non-protective Th$_2$-tilted immune response, which is induced through the expression of a secreted factor, Cpl1, that functions through TLR4 (ref. [105]). *Pneumocystis* species also induce M2 polarization of phagocytes, although the specific mechanisms driving this remain unclear[106].

Fungal evasion and modulation of phagocytic cells and their responses

Phagocyte-mediated uptake and intracellular killing of pathogens represent a major antimicrobial host mechanism, for which many fungi have developed evasion strategies (Fig. 3). In addition to pathogen-associated molecular pattern masking, detailed earlier, changes to morphology, such as titan cell formation or the generation of hyphae, can prevent uptake or allow the fungus to escape from the phagocyte through physical penetration of host-cell membranes following engulfment and escape from phagosomes[12]. *C. albicans* and *N. glabratus* (*C. glabrata*) can rupture macrophages. For *C. albicans*, hypha formation can physically rupture phagocytes, whereas for *N. glabratus* rupture is driven by the multiplication of yeasts to high levels within the phagosome[107]. Fungal hyphae can also induce host-cell death, through pyroptosis and other cell-death mechanisms, without penetrating the host-cell membranes[108]. However, hyphal growth does not always guarantee evasion, as phagocytes have the capacity to physically fold hyphae, mediating fungal clearance[109]. Phagocytes can also function as 'Trojan horses' facilitating systemic dissemination of fungi[110]. In fact, *C. neoformans* was recently shown to differentiate into 'seed cells', which are similar to the yeast form but with an altered surface, which enhances their uptake by macrophages and promotes extrapulmonary dissemination[111].

Other phagocytes, such as neutrophils, also have a key role through the phagocytosis and killing of fungi. Moreover, neutrophils can undergo a programmed cell-death response to form neutrophil extracellular traps (NETs) that can entangle, immobilize and kill fungi. Notably, the formation of NETs is tightly regulated by pathogen size and primarily induced following encounter with non-ingestible fungal forms, such as hyphae[112]. However, fungi have developed mechanisms to evade NETosis through, for example, the formation of biofilms, changes in fungal cell wall components and the secretion of NET-degrading enzymes such as DNAse[113]. Many fungi have also developed mechanisms that enable them to survive within host cells, using strategies including inhibition of phagosome maturation, resisting degradation within the phagolysosome,

Review article

escape from the phagosome or modulation of host metabolism. Following uptake, *C. neoformans*, for example, can prevent acidification, calcium flux and protease activity within the phagosome and limit phagolysosome maturation[114]. *C. neoformans* can also induce non-lytic expulsion (vomocytosis) to escape the host cell[115,116]. This process has also been described for other fungal pathogens including *Candida* spp.[117] and been linked to fungal cell transfer between phagocytes[118]. Another example of an intracellular survival mechanism is the secreted HscA protein of *A. fumigatus*, which diverts the phagosomal sorting process in epithelial cells to facilitate fungal persistence and expulsion via the endosomal recycling pathway[119]. Other pathogens also secrete virulence factors that modulate host-cell function, such as *H. capsulatum* Cbp1, which enables escape by killing the host cell[27]. By contrast, *C. auris* kills host macrophages by inducing immunometabolic reprogramming, resulting in host-cell metabolic stress induced through glucose starvation[120].

Perhaps uniquely among human fungal pathogens, *P. jirovecii* survives in close proximity to host cells. These pathogens exist as extracellular, obligate biotroph organisms that bind type I and type II pneumocytes in the lung and avoid immune detection in this niche[121]. Although not completely understood, in part due to the inability to culture this organism in vitro, there is evidence that indicates that the trophic form (a very simple life stage form with no cell wall, β-glucan or chitin) alters dendritic cell function and their ability to induce adaptive immunity, thereby enabling fungal survival[122].

Some pathogenic fungi, such as *Cryptococcus* species, may be sequestered by the host within tissue granulomas that are formed by the host to control infection and prevent dissemination. However, if the immune system becomes weakened, the fungi can escape to cause disease. For example, patients with multiple sclerosis who undergo long-term treatment with FTY720 (a sphingosine-1-phosphate receptor antagonist that affects immune cell function) are prone to develop *C. neoformans* infections[123]. In mouse models, FTY720 treatment led to disorganization of granulomas and resurgence of cryptococcosis[124].

Many fungi secrete factors including polysaccharides, toxins, small metabolites and secreted proteins that prevent phagocyte uptake, dampen immune cell activation and/or alter immune responses. For example, swollen *Mucorales* spores can evade uptake by secreting antiphagocytic factors of fungal origin, such as mucoricin, or factors derived from bacterial endosymbionts such as rhizoxin-producing *Mycetohabitans rhizoxinica*[125,126]. In addition to Cpl1, described earlier, *C. neoformans* sheds capsular polysaccharides (including GXM) that possess considerable immunoregulatory activities, including suppression of inflammatory cell recruitment and the development of adaptive immunity[127]. *C. neoformans* also secretes small metabolites, such as DL-p-hydroxyphenyllactic acid and DL-indole-3-lactic acid (ILA) that inhibit secretion of key cytokines, such as IL-1β (ref. [36]). Another example of a secreted immunomodulatory fungal factor is Pra1, which is involved in zinc acquisition in *C. albicans*[128]. Pra1, which is induced by low levels of zinc, interacts with multiple components of the complement pathway, facilitating immune evasion[129], and binds to CD4⁺ T cells, which affects their proliferation and cytokine production[130]. The *A. fumigatus* orthologue of Pra1 (named AspF2) has a similar impact on immunity, which suggests conservation of the immunomodulating function of this protein across different pathogenic fungal species[131]. Intriguingly, zinc-regulated *C. albicans* Pra1 is also a potent neutrophil chemoattractant, which promotes fungal clearance during systemic infection[132] but exacerbates inflammation in vulvovaginal candidiasis (VVC)[133]. Zinc supplementation, to downregulate the levels of Pra1, offers therapeutic benefit to women suffering from recurrent VVC[133].

The host and clinical perspective
Host immunity
Rapid advances in knowledge of antifungal immune mechanisms (reviewed elsewhere[38]) have contributed considerably to our understanding of fungal pathobiology. Discoveries of the importance and underlying components of innate and adaptive T_H1 (required for the control of systemic infections) and T_H17 (required for the control of mucosal infections) immunities have not only provided insights into the susceptibility of specific patient groups to fungal infection but also offered therapeutic prospects (detailed subsequently). For example, chronic mucocutaneous candidiasis is a common consequence of numerous inborn errors of the immune system (such as autosomal dominant hyper-IgE syndrome) that involve alterations in the T_H17 immunity[134]. However, the functions of T_H1 versus T_H17 immunity are likely to be oversimplified as susceptibility to at least one chronic mucocutaneous candidiasis-related disease (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy) was also linked to aberrant T_H1 immunity[135]. Far less is understood about the contributions of other key adaptive immune components, including T_{reg} and T_H2 responses, with the former thought to have a role in limiting pathology and the latter linked to non-protective and allergic responses[136].

Substantial advances have also been made in understanding the contributions of individual PRRs, intracellular signalling pathways, specific immune cell populations, immune modulators (such as cytokines and chemokines) and host-cell metabolism during fungal infections, as well as their roles in shaping tissue-specific immunity (for reviews, see, for example, refs. [38],[137],[138]). For example, in the kidney, fungal sensing by dectin-1 causes neutrophils to undergo a metabolic shift by upregulating glucose uptake through glucose transporter-1, which enhances their fungicidal functions, including the production of ROS and NET formation[139]. Recent discoveries have also started to reveal how the immune system can influence the balance of pathogenicity versus commensalism in relevant species. For example, in the gastrointestinal tract, a Paneth cell antimicrobial peptide (peptide YY) and hyphal-specific IgA supress the formation of the tissue damaging *C. albicans* hyphal morphotype, favouring the yeast form and commensalism[140–142].

Optimal activation of the host immune response is essential for controlling fungal infections, but balance is essential to avoid excessive or prolonged inflammation, which can have severe pathological consequences and may be a cause of mortality. This is exemplified by immune reconstitution inflammatory syndrome (IRIS), a paradoxical hyper-inflammatory response that occurs in immunosuppressed patients with a pre-existing fungal infection when their immune function is restored. Immunosuppressed individuals living with HIV/AIDS are at risk of developing cryptococcal IRIS following initiation of antiretroviral therapy, and IRIS can occur with other fungal diseases including histoplasmosis[143] and *P. jirovecii* pneumonia[144]. In the context of mouse oropharyngeal candidiasis, fungal secretion of candidalysin and activation of the epithelium (via epidermal growth factor receptor-mediated pathways) are essential for driving host damage responses and orchestrating sterilizing immunity[145]. This is not just limited to the oral barrier, as candidalysin also forms a key signal for microglial-mediated clearance of *C. albicans* cerebral mycosis in mice[146]. Fungi can also modify human macrophage function via boosting arginase expression[147], which in other disease settings is linked to wound repair[148]. However, how fungi modify host repair mechanisms is still poorly understood.

Review article

Fungal exacerbation and regulation of disease

It is becoming increasingly clear that fungi have an enormous influence on human physiology, although the underlying mechanisms are still largely unknown. Although commensal fungi can have homeostatic roles in promoting beneficial immune responses[149], recent discoveries have also begun to reveal the impact of both commensal fungi (see, for example, ref. 150) and pathogenic fungi on the immune pathology of cancer as well as inflammatory and autoimmune diseases such as inflammatory bowel disease and alcoholic liver disease (reviewed elsewhere[151,152]). Indeed, changes to the mycobiome can have a considerable impact on clinical outcomes. For example, in patients who undergo allogeneic haematopoietic stem cell transplantation, pre-engraftment dominance of *C. parapsilosis* (which accounts for >90% of fungi detected by *ITS1* sequencing in stool samples and an associated loss in bacterial diversity in this study) correlated with reduced overall survival and increased transplant-associated mortality[153].

Fungi are thought to be major drivers of allergic disease with estimates that over half of the individuals with asthma (~150 million sufferers globally) display sensitivity to fungi[154]. Moreover, individuals with chronic lung diseases, including patients with asthma, bronchiectasis, cystic fibrosis and chronic obstructive pulmonary disease,

---

Box 2 | Impact of fungal–bacterial interactions on virulence

Fungal pathogens exist in the wider context of the microbiota exhibiting both antagonistic and agonistic interactions with bacteria that impact fungal virulence across important host sites. The presence or absence of a particular fungal species can influence the abundance of bacterial taxa, and bacteria can in turn influence fungal growth, morphogenesis and virulence (reviewed elsewhere[213–215]). Interactions can be species-specific, mediated by the expression of secreted factors or surface-expressed molecules[216–219], via cross-utilization of metabolic biproducts, secondary metabolites or micronutrient depletion[220–223] or via interactions between fungal and bacterial microorganism-associated molecular patterns such as cell wall sugars, which can influence fungal morphology, growth and virulence[30,224–228]. Various bacterial effectors can also directly inhibit fungal growth via type VI secretion systems[229]. Factors shed or secreted by bacteria can also indirectly affect fungal morphologies in agonistic and antagonistic ways[218,219,226,228,230]. Understanding the impact of cross-kingdom interactions on fungal virulence requires a holistic examination of both microbial partners and the host response. For example, siderophores secreted by *Pseudomonas aeruginosa* that enhance bacterial growth and block neutrophil function also inhibit the germination and growth of *Aspergillus fumigatus* and *Rhizopus* and *Mucor* species and can even enhance the fungicidal activity of fluconazole against *Candida albicans*[231,232]. Bacteria can also enhance fungal pathogenesis through the establishment of endosymbiotic or endofungal relationships. For example, *Ralstonia pickettii* can reside within *Rhizopus microsporus*, enhancing cell-wall-mediated stress resistance and producing a secondary metabolite that blocks phagocytosis of the fungus[125]. Endofungal bacteria are well established in microbial soil communities[233], but we only have a limited understanding of their impact on human disease.

---

show increased fungal airway colonization and infection associated with increased disease severity[155–157]. Fungi are likely to exacerbate allergy partly via multiple secreted factors including proteases and toxins. For example, *Alternaria* spp. proteases damage the lung epithelial cell lining to release IL-33, which results in innate lymphoid cells coordinated allergic inflammation[158], whereas *Aspergillus* spp. proteases can activate calcium channels (TRPV4) on epithelial club cells triggering CD4^{+} T cell-dependent recruitment of eosinophils[159]. By contrast, the fungal toxin candidalysin activates platelets to exacerbate allergic inflammatory CD4^{+} T cells[160]. The precise mechanisms through which T cells are activated are likely to be a critical determinant of allergic diseases, and functionally distinct populations of effector Th cells targeting different *A. fumigatus* proteins were recently detected in patients with cystic fibrosis[161].

Fungi also exacerbate the pathology of viral and bacterial infections, including tuberculosis[162,163]. In fact, interactions between bacteria and fungi can directly influence fungal virulence (Box 2). For respiratory viral infections, in particular, there is now considerable evidence that fungal co-infections are associated with higher mortality rates (excess mortality of 50% compared with those without fungal co-infection). For example, influenza-associated pulmonary aspergillosis during the 2009 H1N1 pandemic[164] and COVID-19-associated pulmonary aspergillosis during the COVID-19 pandemic[165] have revealed the susceptibility of patients with severe viral pneumonia to develop invasive pulmonary fungal disease. Although the pathophysiology of viral–fungal co-infections is unclear, disruption of the respiratory barrier and impaired antifungal immune responses resulting from viral infection have been proposed to have a role (reviewed elsewhere[166]).

Invasive fungal diseases

Diagnosis of patients who are at risk of developing invasive fungal disease (IFD) is paramount as clinical signs and symptoms are often nonspecific and can be comparable with those seen in invasive bacterial disease[167] (Table 1 and Supplementary Table 1). Except for endemic dimorphic fungi, invasive fungal pathogens are opportunistic in nature, causing disease in those with a compromised immune system (including primary immune deficiencies), severely ill patients admitted to an intensive care unit, among patients with invasive medical interventions such as abdominal surgery and those with predisposing conditions including chronic lung diseases and diabetes mellitus. Endemic dimorphic mycoses affect both immunocompetent and immunocompromised patients, but those with underlying immunosuppression usually display more severe disease phenotypes[168]. IFD caused by moulds, such as *Aspergillus* spp. and the *Mucorales*, is mainly localized in the sinus or lungs (but can disseminate)[169,170], *P. jirovecii* infection is primarily pulmonary[171], whereas IFD caused by yeasts, for example, *Candida* spp., and moulds in the genus *Fusarium* predominantly result in a bloodstream infection, with or without dissemination to other organs[172,173]. *C. neoformans* has a predilection for the central nervous system (neurotropic) and infection will result in cryptococcal meningoencephalitis in most cases, in particular in HIV-infected individuals with advanced defects in cellular immunity[174].

The case fatality of IFD in immunocompromised patients is high (ranging from 30% to 80%), especially if there is no recovery of the underlying immunocompromised state and if there is disseminated disease. The high case: fatality ratio is one of the reasons that empiric antifungal therapy is frequently started when an IFD is suspected, based on the underlying condition and risk factors (for example, prolonged febrile neutropenia) with no response to antibacterial therapy. Fungal biomarkers and PCR assays to detect *Aspergillus*, *Candida*, *Cryptococcus*

Review article

Table 2 | Unmet clinical needs for systemic fungal infections[a]

Needs of progress and/or promising leads	Continued need and/or stage of development	
Fungal vaccines	*Candida albicans* vaccine (NDV-3) in phase I clinical trial, showing modest benefit in rVVC	As yet no licensed fungal vaccine for humans
Candida auris infection control in ICU	Guidelines have been developed[202]; examples of best practice have been published[203–205]	Wider surveillance and implementation are required
Global surveillance	The WHO Global Antimicrobial Resistance Surveillance System (GLASS) now includes *Candida* spp.	Much more work is needed in regard to the optimization and harmonization of fungal surveillance
Better rapid, point-of-care diagnostics, enabling earlier, targeted treatment	Cryptococcal Ag LFA (in use) *Histoplasma* Ag EIA and LFA format (in use) *Talaromyces* Ag detection (not yet commercialized) (in development) *Mucorales* Ag LFA format (preclinical)	Further improvement in diagnostics for invasive aspergillosis, invasive mould infection and candidiasis (with sensitivity data and species identification) is needed to enable a shift from empiric towards targeted therapy *Pneumocystis* diagnostics suitable for LMIC are needed General accessibility to antifungals and fungal diagnostics are a continued need in LMIC
Improved antifungal stewardship	Programmes and guidelines have been developed	Implementation studies to drive uptake and measure impact Better diagnostics
New antifungals, new classes Selected for efficacy, safety, spectrum (including against resistant isolates), cidal (compromised hosts), oral and intravenous formulation, high barrier to resistance development, long-acting, synergistic potential with existing agents and ideally with related compounds not developed for agricultural use	Ibrexafungerp (activity: *Candida* spp.) oral β-glucan synthase inhibitor	Licensed for rVVC
	Rezafungin, long-acting, once-weekly echinocandin	Licensed for candidaemia, invasive candidiasis
	Olorofim (activity: *Aspergillus* spp., rare moulds, *Coccidioides* spp.) inhibits pyrimidine synthesis	In phase III for IA, vs L-AmB
	Fosmanogepix APX001 (activity: *Candida* spp., *Aspergillus* spp.) inhibits GPI-anchored wall transfer protein 1 (Gwt1)	Small phase II candidaemia trials completed
	APX-2039 enhanced activity against *Cryptococcus*	Preclinical stage
	Sfunga-001, AmB derivative, based on concept of sterol sponge mechanism of action	Preclinical stage
	Nebulized opelconazole (PC945) (Pulmocide)	In phase III trial for invasive aspergillosis in addition to systemic SOC
Optimized or extended use of existing antifungals Combinations (synergy and/or resistance protection) and optimized PK/PD	Dectin-2-coated AmB liposomes	Preclinical
	Cryptococcal meningitis induction regimens	Phase II/III clinical trials
	Azole echinocandin combination trial for invasive aspergillosis	Phase III clinical trials Ibrexafungerp in phase II trial in combination with voriconazole vs voriconazole alone in invasive aspergillosis Rezafungin in combination with 7 days co-trimoxazole versus co-trimoxazole alone in phase II trial in PCP
Global antifungal drug access	5FC, two new manufacturers, cost has halved since 2018; 5FC and L-AmB provision through Global Fund for cryptococcal meningitis; generic voriconazole, echinocandins	Only one main manufacturer of L-AmB
Anti-virulence agents	Targeting filamentation in *C. albicans*, for example, filastatin, compound 61894700	Preclinical
	MAb against mucoricin, CotH3, for mucormycosis	Preclinical
Host-directed approaches, immune-diagnostics to enable patient-specific targeting	MAbs targeting IgE, IL-5, IL-4 for allergic fungal diseases	Evidence for immunotherapies based mainly on small case series
	Cytokines (IFNγ, GM-CSF)	There is a need for more randomized controlled trials and rapid diagnostics for identifying immune defects
	Engineered β-glucan-specific CAR-T cells	
Novel Clinical Trial Strategies and Designs	Adaptive designs, coordinated funding and implementation and streamlined approval processes delivered rapid large trials in COVID-19	Novel, cooperative approaches are needed to facilitate trials in systemic fungal infection

CAR, chimeric antigen receptor; EIA, enzyme immune assay; GM-CSF, granulocyte–macrophage colony-stimulating factor; ICU, intensive care unit; IFNγ, interferon-γ; L-AmB, liposomal amphotericin B; LFA, lateral flow assay; LMIC, low-income and middle-income country; MAb, monoclonal antibody; PCP, pneumocystis pneumonia; PK/PD, pharmacokinetics/pharmacodynamics; rVVC, recurrent vulvovaginal candidiasis; SOC, standard of care; 5FC, 5-flucytosine. [a]This is broad overview of priorities and not exhaustive. Many aspects are not highlighted, including the unmet needs associated with non-invasive fungal diseases.

species, mucoraceous moulds and *P. jirovecii* can guide the decision-making process to start or stop antifungal therapy, but positive cultures from otherwise sterile material and/or direct microscopy or histopathology on tissue samples are required to make a definitive diagnosis. Over the past decade, a number of international management guidelines addressing specific IFD have been developed, providing a useful tool in guiding management decisions at the bedside[173,175–177]. Nevertheless, patient care is substantially compromised by difficulties in diagnosis, a limited arsenal of antifungal agents and the rapid rise of antifungal drug resistance (described subsequently) (Table 2).

Review article

Host-directed therapy

Our increased understanding of the complex interplay between fungi and host immune responses, and their contributions to disease pathology and the specific pathways involved, underpins the increasing clinical use of host-directed therapies. In the setting of overactive or dysfunctional immune responses, adjunctive corticosteroids, for example, are used to treat allergic fungal diseases, severe *Pneumocystis* pneumonia and HIV-associated and non-HIV-associated immune reconstitution reactions in the setting of fungal infection[178]. The more specific agents for fungal allergy, omalizumab, mepolizumab and dupilumab, which target IgE, IL-5 and IL-4, respectively, show promise in allergic bronchopulmonary aspergillosis[179–181]. Cytokines, notably interferon-γ and GM-CSF, have been successfully used to promote T_H1 immunity and activate neutrophils and mononuclear phagocytes in several infectious settings, including aspergillosis in patients with chronic granulomatous disease and HIV-associated cryptococcal meningitis, and to prevent and manage fungal infections in allogeneic bone marrow transplant recipients[182]. A randomized trial of adjunctive interferon-γ in candidaemia has recently started (NCT04979052). Selection and transfer of donor *Aspergillus*-specific T cells to haploidentical transplant recipients reduced *Aspergillus*-related deaths[183], and protocols for generating fungal-specific T cells have subsequently been improved[184].

Our growing knowledge of the function of fungal PRRs is also offering new therapeutic avenues. For example, topical administration of a TLR agonist, imiquimod, markedly improves chromoblastomycosis lesions[185] (a chronic fungal infection of the skin), whereas coating amphotericin B liposomes with the binding domain of dectin-2 substantially increased antifungal efficacy in a mouse model of pulmonary aspergillosis[186]. PRRs are also being considered for chimeric antigen receptor T cell therapies, such as chimeric antigen receptor T cells expressing dectin-1 fused to CD28 and CD3ζ signalling domains, which inhibited *Aspergillus* growth in vitro and in vivo[187].

Disappointingly, there is still no vaccine in clinical use for any human fungal disease. However, a few are in development, including an agglutinin-like sequence 3-based *C. albicans* vaccine (NDV-3), which showed benefit in a randomized trial in women with recurrent VVC[188]. Other strategies, including delivery of antigens within glucan or glucan/chitin particles, have potential for the future (reviewed elsewhere[189]).

Conclusions

The number of humans succumbing to fungal infections is projected to increase, owing to a rapid rise in resistance to antifungal drugs, developments in modern medicine that alter protective immunity and the emergence of new pathogens, including zoonoses. Until recently, fungal AMR has received much less attention than the threat of drug resistance in other pathogens. However, highly drug-resistant species such as *C. auris*, environmentally (predominantly agricultural) driven increases in resistance to azoles in *A. fumigatus*[190] and the occurrence of fungal infections in newly recognized patient populations with SARS-CoV-2 and influenza infections have heightened concerns about the increasing difficulties in treating natural or acquired resistance in fungal species[190,191]. Several fungi, including azole-resistant *A. fumigatus*, *N. glabratus*, *Pichia kudriavzevii*, *C. auris*, *Lomentospora prolificans* and the Mucorales, now present major clinical challenges to the effectiveness of currently available antifungals[190].

Clinically, the consequences of fungal AMR are made worse by inadequate and late diagnosis and by the lack of availability and accessibility of antifungal options in impoverished regions of the world that have high burdens of IFDs. Improved agents, formulations and novel classes of antifungals, such as rezafungin, encochleated amphotericin B, opelconazole, ibrexafungerp, olorofim and fosmanogepix, offer new clinical opportunities[192]. In addition, an exploration of the benefits of combination therapy[193] and careful antifungal drug stewardship[194] is critical to extend the durability and efficacy of the antifungal pipeline in the context of growing levels of fungal AMR.

The incidence and burden of fungal infections are also increasing and evolving because of medical advances. In addition to rising numbers of immunosuppressed patients, particularly those undergoing therapy for cancer or transplantation, increasing use of monoclonal antibodies and kinase inhibitors with specific immunological targets for a wide range of autoimmune and inflammatory diseases is resulting in new patient groups at heightened risk of fungal infections (reviewed elsewhere[38]). In addition, international travel and trade, pollution and population expansion within areas endemic for geographically restricted dimorphic fungi have further increased the numbers of persons at risk.

The emergence of new pathogens, driven by, or coinciding with, climate change, poses considerable challenges for the future. Genomic studies suggest a near-simultaneous emergence of *C. auris* on multiple continents[195,196]. Another example is *Emergomyces africanus* (previously *Emmonsia* species), the first new thermally dimorphic fungal pathogen identified in nearly 60 years, found originally in South Africa with closely related species identified in four continents[197,198]. Furthermore, sporotrichosis caused by *Sporothrix brasiliensis*, which is transmitted by cats, represents the first reported invasive fungal zoonotic disease. Originally considered endemic to Brazil, cat-transmitted sporotrichosis is now spreading throughout South America and cases are now being reported across the world[199].

In conclusion, our knowledge of human fungal infections has advanced considerably. Tackling the extant and emerging threats posed by these pathogens will require continued and greater awareness and more investment from governments, funding agencies and industry. Increased capacity in this field is essential to tackle the huge burden of human fungal diseases, including the billions of people suffering from non-life-threatening infections by dermatophytes (including drug-resistant pandemic species such as *Trichophyton indotineae*[200]), which were not covered in this Review. As we highlighted over a decade ago[201], we must continue to gain a better understanding of fungal pathobiology to aid the development of safer and more effective antifungal management strategies in the future.

References

1. Denning, D. W. Global incidence and mortality of severe fungal disease. *Lancet Infect. Dis.* https://doi.org/10.1016/S1473-3099(23)00692-8 (2024).
2. WHO. WHO fungal priority pathogens list to guide research, development and public health action. https://www.who.int/publications/i/item/9789240060241 (2022).
3. Fisher, M. C. et al. Emerging fungal threats to animal, plant and ecosystem health. *Nature* **484**, 186–194 (2012).
4. Rokas, A. Evolution of the human pathogenic lifestyle in fungi. *Nat. Microbiol.* **7**, 607–619 (2022).
5. Chybowska, A. D., Childers, D. S. & Farrer, R. A. Nine things genomics can tell us about *Candida auris*. *Front. Genet.* **11**, 351 (2020).
6. Tao, L. et al. Discovery of a 'white-gray-opaque' tristable phenotypic switching system in *Candida albicans*: roles of non-genetic diversity in host adaptation. *PLoS Biol.* **12**, e1001830 (2014).
7. Delavy, M. et al. Unveiling *Candida albicans* intestinal carriage in healthy volunteers: the role of micro- and mycobiota, diet, host genetics and immune response. *Gut Microbes* **15**, 2287618 (2023).
8. Phan, Q. T. et al. Als3 is a *Candida albicans* invasin that binds to cadherins and induces endocytosis by host cells. *PLoS Biol.* **5**, e64 (2007).
9. Thomson, D. D. et al. Contact-induced apical asymmetry drives the thigmotropic responses of *Candida albicans* hyphae. *Cell Microbiol.* **17**, 342–354 (2015).

Review article

10. Dalle, F. et al. Cellular interactions of *Candida albicans* with human oral epithelial cells and enterocytes. *Cell Microbiol.* **12**, 248–271 (2010).

11. Lachat, J. et al. Trans-cellular tunnels induced by the fungal pathogen *Candida albicans* facilitate invasion through successive epithelial cells without host damage. *Nat. Commun.* **13**, 3781 (2022).

12. Westman, J., Moran, G., Mogavero, S., Hube, B. & Grinstein, S. *Candida albicans* hyphal expansion causes phagosomal membrane damage and luminal alkalinization. *mBio* **9**, e01226-18 (2018).

13. Hoyer, L. L., Payne, T. L., Bell, M., Myers, A. M. & Scherer, S. *Candida albicans* ALS3 and insights into the nature of the ALS gene family. *Curr. Genet.* **33**, 451–459 (1998).

14. Staab, J. F., Bradway, S. D., Fidel, P. L. & Sundstrom, P. Adhesive and mammalian transglutaminase substrate properties of *Candida albicans* Hwp1. *Science* **283**, 1535–1538 (1999).

15. Naglik, J. R., Challacombe, S. J. & Hube, B. *Candida albicans* secreted aspartyl proteinases in virulence and pathogenesis. *Microbiol. Mol. Biol. Rev.* **67**, 400–428 (2003).

16. Martchenko, M., Alarco, A. M., Harcus, D. & Whiteway, M. Superoxide dismutases in *Candida albicans*: transcriptional regulation and functional characterization of the hyphal-induced SOD5 gene. *Mol. Biol. Cell* **15**, 456–467 (2004).

17. Fradin, C. et al. Granulocytes govern the transcriptional response, morphology and proliferation of *Candida albicans* in human blood. *Mol. Microbiol.* **56**, 397–415 (2005).

18. Moyes, D. L. et al. Candidalysin is a fungal peptide toxin critical for mucosal infection. *Nature* **532**, 64–68 (2016).

19. Dunker, C. et al. Rapid proliferation due to better metabolic adaptation results in full virulence of a filament-deficient *Candida albicans* strain. *Nat. Commun.* **12**, 3899 (2021).

20. O'Meara, T. R. et al. High-throughput screening identifies genes required for *Candida albicans* induction of macrophage pyroptosis. *mBio* **9**, e01581-18 (2018).

21. Lemberg, C. et al. *Candida albicans* commensalism in the oral mucosa is favoured by limited virulence and metabolic adaptation. *PLoS Pathog.* **18**, e1010012 (2022).

22. Witchley, J. N. et al. *Candida albicans* morphogenesis programs control the balance between gut commensalism and invasive infection. *Cell Host Microbe* **25**, 432–443.e6 (2019).

23. Liang, S. H. et al. The hyphal-specific toxin candidalysin promotes fungal gut commensalism. *Nature* **627**, 620–627 (2024).

24. Prieto, D., Roman, E., Alonso-Monge, R. & Pla, J. Overexpression of the transcriptional regulator WOR1 increases susceptibility to bile salts and adhesion to the mouse gut mucosa in *Candida albicans*. *Front. Cell. Infect. Microbiol.* **7**, 389 (2017).

25. Beaussart, A., Brandhorst, T., Dufrene, Y. F. & Klein, B. S. Blastomyces virulence adhesin-1 protein binding to glycosaminoglycans is enhanced by protein disulfide isomerase. *mBio* **6**, e01403–e01415 (2015).

26. Hung, C. Y., Yu, J. J., Seshan, K. R., Reichard, U. & Cole, G. T. A parasitic phase-specific adhesin of *Coccidioides immitis* contributes to the virulence of this respiratory fungal pathogen. *Infect. Immun.* **70**, 3443–3456 (2002).

27. Azimova, D. et al. Cbp1, a fungal virulence factor under positive selection, forms an effector complex that drives macrophage lysis. *PLoS Pathog.* **18**, e1010417 (2022).

28. Hommel, B. et al. Titan cells formation in *Cryptococcus neoformans* is finely tuned by environmental conditions and modulated by positive and negative genetic regulators. *PLoS Pathog.* **14**, e1006982 (2018).

29. Trevijano-Contador, N. et al. *Cryptococcus neoformans* can form titan-like cells in vitro in response to multiple signals. *PLoS Pathog.* **14**, e1007007 (2018).

30. Dambuza, I. M. et al. The *Cryptococcus neoformans* titan cell is an inducible and regulated morphotype underlying pathogenesis. *PLoS Pathog.* **14**, e1006978 (2018).

31. Reuwsaat, J. C. V. et al. The transcription factor Pdr802 regulates titan cell formation and pathogenicity of *Cryptococcus neoformans*. *mBio* **12**, e03457-20 (2021).

32. Shende, R. et al. *Aspergillus fumigatus* conidial metalloprotease Mep1p cleaves host complement proteins. *J. Biol. Chem.* **293**, 15538–15555 (2018).

33. Vu, K. et al. Invasion of the central nervous system by *Cryptococcus neoformans* requires a secreted fungal metalloprotease. *mBio* **5**, e01101–e01114 (2014).

34. Butler, G. et al. Evolution of pathogenicity and sexual reproduction in eight *Candida* genomes. *Nature* **459**, 657–662 (2009).

35. Basso, P. et al. Deep tissue infection by an invasive human fungal pathogen requires lipid-based suppression of the IL-17 response. *Cell Host Microbe* **30**, 1589–1601.e5 (2022).

36. Burgel, P. H. et al. *Cryptococcus neoformans* secretes small molecules that inhibit IL-1beta inflammasome-dependent secretion. *Mediators Inflamm.* **2020**, 3412763 (2020).

37. Scharf, D. H., Heinekamp, T. & Brakhage, A. A. Human and plant fungal pathogens: the role of secondary metabolites. *PLoS Pathog.* **10**, e1003859 (2014).

38. Lionakis, M. S., Drummond, R. A. & Hohl, T. M. Immune responses to human fungal pathogens and therapeutic prospects. *Nat. Rev. Immunol.* **23**, 433–452 (2023).

39. Garre, V. Recent advances and future directions in the understanding of mucormycosis. *Front. Cell. Infect. Microbiol.* **12**, 850581 (2022).

40. Misslinger, M., Hortschansky, P., Brakhage, A. A. & Haas, H. Fungal iron homeostasis with a focus on *Aspergillus fumigatus*. *Biochim. Biophys. Acta Mol. Cell Res.* **1868**, 118885 (2021).

41. Almeida, R. S. et al. The hyphal-associated adhesin and invasin Als3 of *Candida albicans* mediates iron acquisition from host ferritin. *PLoS Pathog.* **4**, e1000217 (2008).

42. Kuznets, G. et al. A relay network of extracellular heme-binding proteins drives *C. albicans* iron acquisition from hemoglobin. *PLoS Pathog.* **10**, e1004407 (2014).

43. Dade, J. et al. HcZrt2, a zinc responsive gene, is indispensable for the survival of *Histoplasma capsulatum* in vivo. *Med. Mycol.* **54**, 865–875 (2016).

44. Subramanian Vignesh, K., Landero Figueroa, J. A., Porollo, A., Caruso, J. A. & Deepe, G. S. Jr. Granulocyte macrophage-colony stimulating factor induced Zn sequestration enhances macrophage superoxide and limits intracellular pathogen survival. *Immunity* **39**, 697–710 (2013).

45. Rodrigues, M. L. et al. Extracellular vesicles produced by *Cryptococcus neoformans* contain protein components associated with virulence. *Eukaryot. Cell* **7**, 58–67 (2008).

46. Brown Harding, H. et al. *Candida albicans* extracellular vesicles trigger type I IFN signalling via cGAS and STING. *Nat. Microbiol.* **9**, 95–107 (2024).

47. de Oliveira, H. C. et al. Biogenesis of fungal extracellular vesicles: what do we know? *Curr. Top. Microbiol. Immunol.* **432**, 1–11 (2021).

48. Coelho, C. & Casadevall, A. Answers to naysayers regarding microbial extracellular vesicles. *Biochem. Soc. Trans.* **47**, 1005–1012 (2019).

49. Zarnowski, R. et al. *Candida albicans* biofilm-induced vesicles confer drug resistance through matrix biogenesis. *PLoS Biol.* **16**, e2006872 (2018).

50. Puerner, C., Vellanki, S., Strauch, J. L. & Cramer, R. A. Recent advances in understanding the human fungal pathogen hypoxia response in disease progression. *Annu. Rev. Microbiol.* **77**, 403–425 (2023).

51. Fabri, J. et al. The heat shock transcription factor HsfA plays a role in membrane lipids biosynthesis connecting thermotolerance and unsaturated fatty acid metabolism in *Aspergillus fumigatus*. *Microbiol. Spectr.* **11**, e0162723 (2023).

52. Childers, D. S. et al. The rewiring of ubiquitination targets in a pathogenic yeast promotes metabolic flexibility, host colonization and virulence. *PLoS Pathog.* **12**, e1005566 (2016).

53. Ames, R., Brown, A. J. P., Gudelj, I. & Nev, O. A. Analysis of pneumocystis transcription factor evolution and implications for biology and lifestyle. *mBio* **14**, e0271122 (2023).

54. Phillips, A. J., Sudbery, I. & Ramsdale, M. Apoptosis induced by environmental stresses and amphotericin B in *Candida albicans*. *Proc. Natl Acad. Sci. USA* **100**, 14327–14332 (2003).

55. Shlezinger, N. et al. Sterilizing immunity in the lung relies on targeting fungal apoptosis-like programmed cell death. *Science* **357**, 1037–1041 (2017).

56. Holland, S. M. Chronic granulomatous disease. *Clin. Rev. Allergy Immunol.* **38**, 3–10 (2010).

57. Usher, J., Chaudhari, Y., Attah, V., Ho, H. L. & Haynes, K. Functional characterization of a novel oxidative stress protection protein in the pathogenic yeast *Candida glabrata*. *Front. Genet.* **11**, 530915 (2020).

58. Farrer, R. A. & Fisher, M. C. Describing genomic and epigenomic traits underpinning emerging fungal pathogens. *Adv. Genet.* **100**, 73–140 (2017).

59. Ma, L. J. et al. Comparative genomics reveals mobile pathogenicity chromosomes in *Fusarium*. *Nature* **464**, 367–373 (2010).

60. Wacker, T. et al. Two-speed genome evolution drives pathogenicity in fungal pathogens of animals. *Proc. Natl Acad. Sci. USA* **120**, e2212633120 (2023).

61. Farrer, R. A. et al. Genome evolution and innovation across the four major lineages of *Cryptococcus gattii*. *mBio* **6**, e00868-15 (2015).

62. Hirakawa, M. P., Chyou, D. E., Huang, D., Slan, A. R. & Bennett, R. J. Parasex generates phenotypic diversity de novo and impacts drug resistance and virulence in *Candida albicans*. *Genetics* **207**, 1195–1211 (2017).

63. Ene, I. V. et al. Global analysis of mutations driving microevolution of a heterozygous diploid fungal pathogen. *Proc. Natl Acad. Sci. USA* **115**, E8688–E8697 (2018).

64. Chen, Y. et al. Microevolution of serial clinical isolates of *Cryptococcus neoformans* var. *grubii* and *C. gattii*. *mBio* **8**, e00166-17 (2017).

65. Thomson, G. J. et al. Metabolism-induced oxidative stress and DNA damage selectively trigger genome instability in polyploid fungal cells. *EMBO J.* **38**, e101597 (2019).

66. Smith, A. C. & Hickman, M. A. Host-induced genome instability rapidly generates phenotypic variation across *Candida albicans* strains and ploidy states. *mSphere* **5**, e00433-20 (2020).

67. Brimacombe, C. A. et al. A natural histone H2A variant lacking the Bub1 phosphorylation site and regulated depletion of centromeric histone CENP-A foster evolvability in *Candida albicans*. *PLoS Biol.* **17**, e3000331 (2019).

68. Yang, F. et al. The fitness costs and benefits of trisomy of each *Candida albicans* chromosome. *Genetics* **218**, iyab056 (2021).

69. Todd, R. T. & Selmecki, A. Expandable and reversible copy number amplification drives rapid adaptation to antifungal drugs. *eLife* **9**, e58349 (2020).

70. Priest, S. J. et al. Uncontrolled transposition following RNAi loss causes hypermutation and antifungal drug resistance in clinical isolates of *Cryptococcus neoformans*. *Nat. Microbiol.* **7**, 1239–1251 (2022).

71. Gambhir, N., Harris, S. D. & Everhart, S. E. Evolutionary significance of fungal hypermutators: lessons learned from clinical strains and implications for fungal plant pathogens. *mSphere* **7**, e0008722 (2022).

72. Gow, N. A. R., Latge, J. P. & Munro, C. A. The fungal cell wall: structure, biosynthesis, and function. *Microbiol. Spectr.* https://doi.org/10.1128/microbiolspec.FUNK-0035-2016 (2017).

73. Erwig, L. P. & Gow, N. A. Interactions of fungal pathogens with phagocytes. *Nat. Rev. Microbiol.* **14**, 163–176 (2016).

74. Mukaremera, L. The *Cryptococcus* wall: a different wall for a unique lifestyle. *PLoS Pathog.* **19**, e1011141 (2023).

75. Pradhan, A. et al. Non-canonical signalling mediates changes in fungal cell wall PAMPs that drive immune evasion. *Nat. Commun.* **10**, 5315 (2019).

76. Cottier, F. et al. Remasking of *Candida albicans* beta-glucan in response to environmental pH is regulated by quorum sensing. *mBio* **10**, e02347-19 (2019).

Review article

77. Lopes, J. P. et al. Evasion of immune surveillance in low oxygen environments enhances *Candida albicans* virulence. *mBio* **9**, e02120-18 (2018).

78. Larcombe, D. E. et al. Glucose-enhanced oxidative stress resistance — a protective anticipatory response that enhances the fitness of *Candida albicans* during systemic infection. *PLoS Pathog.* **19**, e1011505 (2023).

79. Pradhan, A. et al. Hypoxia promotes immune evasion by triggering beta-glucan masking on the *Candida albicans* cell surface via mitochondrial and cAMP-protein kinase a signaling. *mBio* **9**, e01318-18 (2018).

80. Silva, V. K. A. et al. Replicative aging remodels the cell wall and is associated with increased intracellular trafficking in human pathogenic yeasts. *mBio* **13**, e0019022 (2021).

81. Garcia-Rubio, R., de Oliveira, H. C., Rivera, J. & Trevijano-Contador, N. The fungal cell wall: Candida, Cryptococcus, and Aspergillus species. *Front. Microbiol.* **10**, 2993 (2019).

82. Mukaremera, L. et al. Titan cell production in *Cryptococcus neoformans* reshapes the cell wall and capsule composition during infection. *Cell Surf.* **1**, 15–24 (2018).

83. Bain, J., Gow, N. A. & Erwig, L. P. Novel insights into host–fungal pathogen interactions derived from live-cell imaging. *Semin. Immunopathol.* **37**, 131–139 (2015).

84. Avelar, G. M. et al. Impact of changes at the *Candida albicans* cell surface upon immunogenicity and colonisation in the gastrointestinal tract. *Cell Surf.* **8**, 100084 (2022).

85. Brown, G. D. & Gordon, S. Immune recognition. A new receptor for beta-glucans. *Nature* **413**, 36–37 (2001).

86. Ross, G. D., Cain, J. A., Myones, B. L., Newman, S. L. & Lachmann, P. J. Specificity of membrane complement receptor type three (CR3) for beta-glucans. *Complement* **4**, 61–74 (1987).

87. Mata-Martinez, P., Bergon-Gutierrez, M. & Del Fresno, C. Dectin-1 signaling update: new perspectives for trained immunity. *Front. Immunol.* **13**, 812148 (2022).

88. Guo, Y. et al. C-type lectin receptor CD23 is required for host defense against *Candida albicans* and *Aspergillus fumigatus* infection. *J. Immunol.* **201**, 2427–2440 (2018).

89. Swidergall, M. et al. EphA2 is a neutrophil receptor for *Candida albicans* that stimulates antifungal activity during oropharyngeal infection. *Cell Rep.* **28**, 423–433.e5 (2019).

90. He, X. et al. LYSMD3: a mammalian pattern recognition receptor for chitin. *Cell Rep.* **36**, 109392 (2021).

91. Elieh Ali Komi, D., Sharma, L. & Dela Cruz, C. S. Chitin and its effects on inflammatory and immune responses. *Clin. Rev. Allergy Immunol.* **54**, 213–223 (2018).

92. Yokoyama, C. C. et al. LysMD3 is a type II membrane protein without an in vivo role in the response to a range of pathogens. *J. Biol. Chem.* **293**, 6022–6038 (2018).

93. Briard, B. et al. Galactosaminogalactan activates the inflammasome to provide host protection. *Nature* **588**, 688–692 (2020).

94. Yadav, B. et al. Differences in fungal immune recognition by monocytes and macrophages: N-mannan can be a shield or activator of immune recognition. *Cell Surf.* **6**, 100042 (2020).

95. Childers, D. S. et al. Epitope shaving promotes fungal immune evasion. *mBio* **11**, e00984-20 (2020).

96. Garfoot, A. L., Shen, Q., Wuthrich, M., Klein, B. S. & Rappleye, C. A. The Eng1 beta-glucanase enhances histoplasma virulence by reducing beta-glucan exposure. *mBio* **7**, e01388-15 (2016).

97. Hole, C. R., Lam, W. C., Upadhya, R. & Lodge, J. K. *Cryptococcus neoformans* chitin synthase 3 plays a critical role in dampening host inflammatory responses. *mBio* **11**, e03373-19 (2020).

98. Casadevall, A. et al. The capsule of *Cryptococcus neoformans*. *Virulence* **10**, 822–831 (2019).

99. Yang, C. et al. *Cryptococcus* escapes host immunity: what do we know? *Front. Cell. Infect. Microbiol.* **12**, 1041036 (2022).

100. Kwon-Chung, K. J. & Sugui, J. A. *Aspergillus fumigatus* — what makes the species a ubiquitous human fungal pathogen? *PLoS Pathog.* **9**, e1003743 (2013).

101. Li, C. H. et al. Sporangiospore size dimorphism is linked to virulence of *Mucor circinelloides*. *PLoS Pathog.* **7**, e1002086 (2011).

102. Li, X. V. et al. Immune regulation by fungal strain diversity in inflammatory bowel disease. *Nature* **603**, 672–678 (2022).

103. Malavia, D. et al. Zinc limitation induces a hyper-adherent goliath phenotype in *Candida albicans*. *Front. Microbiol.* **8**, 2238 (2017).

104. Okagaki, L. H. & Nielsen, K. Titan cells confer protection from phagocytosis in *Cryptococcus neoformans* infections. *Eukaryot. Cell* **11**, 820–826 (2012).

105. Dang, E. V. et al. Secreted fungal virulence effector triggers allergic inflammation via TLR4. *Nature* **608**, 161–167 (2022).

106. Deckman, J. M. et al. *Pneumocystis* infection alters the activation state of pulmonary macrophages. *Immunobiology* **222**, 188–197 (2017).

107. Wilson, D., Naglik, J. R. & Hube, B. The missing link between *Candida albicans* hyphal morphogenesis and host cell damage. *PLoS Pathog.* **12**, e1005867 (2016).

108. Krysan, D. J., Sutterwala, F. S. & Wellington, M. Catching fire: *Candida albicans*, macrophages, and pyroptosis. *PLoS Pathog.* **10**, e1004139 (2014).

109. Bain, J. M. et al. Immune cells fold and damage fungal hyphae. *Proc. Natl Acad. Sci. USA* **118**, e202084118 (2021).

110. Scherer, A. K. et al. Redundant Trojan horse and endothelial-circulatory mechanisms for host-mediated spread of *Candida albicans* yeast. *PLoS Pathog.* **16**, e1008414 (2020).

111. Denham, S. T. et al. A dissemination-prone morphotype enhances extrapulmonary organ entry by *Cryptococcus neoformans*. *Cell Host Microbe* **30**, 1382–1400.e8 (2022).

112. Branzk, N. et al. Neutrophils sense microbe size and selectively release neutrophil extracellular traps in response to large pathogens. *Nat. Immunol.* **15**, 1017–1025 (2014).

113. Liang, C., Lian, N. & Li, M. The emerging role of neutrophil extracellular traps in fungal infection. *Front. Cell. Infect. Microbiol.* **12**, 900895 (2022).

114. Fu, M. S. et al. *Cryptococcus neoformans* urease affects the outcome of intracellular pathogenesis by modulating phagolysosomal pH. *PLoS Pathog.* **14**, e1007144 (2018).

115. Alvarez, M. & Casadevall, A. Phagosome extrusion and host-cell survival after *Cryptococcus neoformans* phagocytosis by macrophages. *Curr. Biol.* **16**, 2161–2165 (2006).

116. Ma, H., Croudace, J. E., Lammas, D. A. & May, R. C. Expulsion of live pathogenic yeast by macrophages. *Curr. Biol.* **16**, 2156–2160 (2006).

117. Bojarczuk, A. et al. *Cryptococcus neoformans* intracellular proliferation and capsule size determines early macrophage control of infection. *Sci. Rep.* **6**, 21489 (2016).

118. Pazhakh, V. et al. Beta-glucan-dependent shuttling of conidia from neutrophils to macrophages occurs during fungal infection establishment. *PLoS Biol.* **17**, e3000113 (2019).

119. Jia, L. J. et al. *Aspergillus fumigatus* hijacks human p11 to redirect fungal-containing phagosomes to non-degradable pathway. *Cell Host Microbe* **31**, 373–388.e10 (2023).

120. Weerasinghe, H. et al. *Candida auris* uses metabolic strategies to escape and kill macrophages while avoiding robust activation of the NLRP3 inflammasome response. *Cell Rep.* **42**, 112522 (2023).

121. Liu, Y. et al. MUC1 mediates *Pneumocystis murina* binding to airway epithelial cells. *Cell Microbiol.* **22**, e13182 (2020).

122. Evans, H. M. & Garvy, B. A. The trophic life cycle stage of *Pneumocystis* species induces protective adaptive responses without inflammation-mediated progression to pneumonia. *Med. Mycol.* **56**, 994–1005 (2018).

123. Grebenciucova, E., Reder, A. T. & Bernard, J. T. Immunologic mechanisms of fingolimod and the role of immunosenescence in the risk of cryptococcal infection: a case report and review of literature. *Mult. Scler. Relat. Disord.* **9**, 158–162 (2016).

124. Bryan, A. M. et al. FTY720 reactivates cryptococcal granulomas in mice through S1P receptor 3 on macrophages. *J. Clin. Invest.* **130**, 4546–4560 (2020).

125. Itabangi, H. et al. A bacterial endosymbiont of the fungus Rhizopus microsporus drives phagocyte evasion and opportunistic virulence. *Curr. Biol.* **32**, 1115–1130.e6 (2022).

126. Soliman, S. S. M. et al. Mucoricin is a ricin-like toxin that is critical for the pathogenesis of mucormycosis. *Nat. Microbiol.* **6**, 313–326 (2021).

127. Decote-Ricardo, D. et al. Immunomodulatory role of capsular polysaccharides constituents of *Cryptococcus neoformans*. *Front. Med.* **6**, 129 (2019).

128. Citiulo, F. et al. *Candida albicans* scavenges host zinc via Pra1 during endothelial invasion. *PLoS Pathog.* **8**, e1002777 (2012).

129. Zipfel, P. F., Skerka, C., Kupka, D. & Luo, S. Immune escape of the human facultative pathogenic yeast *Candida albicans*: the many faces of the *Candida* Pra1 protein. *Int. J. Med. Microbiol.* **301**, 423–430 (2011).

130. Bergfeld, A. et al. Direct binding of the pH-regulated protein 1 (Pra1) from *Candida albicans* inhibits cytokine secretion by mouse CD4(+) T cells. *Front. Microbiol.* **8**, 844 (2017).

131. Dasari, P. et al. Aspf2 from Aspergillus fumigatus recruits human immune regulators for immune evasion and cell damage. *Front. Immunol.* **9**, 1635 (2018).

132. Soloviev, D. A. et al. Identification of pH-regulated antigen 1 released from *Candida albicans* as the major ligand for leukocyte integrin alphaMbeta2. *J. Immunol.* **178**, 2038–2046 (2007).

133. Roselletti, E. et al. Zinc prevents vaginal candidiasis by inhibiting expression of an inflammatory fungal protein. *Sci. Transl. Med.* **15**, eadi3363 (2023).

134. Tangye, S. G. & Puel, A. The Th17/IL-17 axis and host defense against fungal infections. *J. Allergy Clin. Immunol. Pract.* **11**, 1624–1634 (2023).

135. Break, T. J. et al. Aberrant type 1 immunity drives susceptibility to mucosal fungal infections. *Science* **371**, eaay5731 (2021).

136. Woodring, T., Deepe, G. S., Levitz, S. M., Wuethrich, M. & Klein, B. S. They shall not grow mold: soldiers of innate and adaptive immunity to fungi. *Semin. Immunol.* **65**, 101673 (2023).

137. Drummond, R. A. & Lionakis, M. S. Organ-specific mechanisms linking innate and adaptive antifungal immunity. *Semin. Cell Dev. Biol.* **89**, 78–90 (2019).

138. Heung, L. J., Wiesner, D. L., Wang, K., Rivera, A. & Hohl, T. M. Immunity to fungi in the lung. *Semin. Immunol.* **66**, 101728 (2023).

139. Li, D. D. et al. Fungal sensing enhances neutrophil metabolic fitness by regulating antifungal Glut1 activity. *Cell Host Microbe* **30**, 530–544.e6 (2022).

140. Doron, I. et al. Mycobiota-induced IgA antibodies regulate fungal commensalism in the gut and are dysregulated in Crohn's disease. *Nat. Microbiol.* **6**, 1493–1504 (2021).

141. Ost, K. S. et al. Adaptive immunity induces mutualism between commensal eukaryotes. *Nature* **596**, 114–118 (2021).

142. Pierre, J. F. et al. Peptide YY: a paneth cell antimicrobial peptide that maintains *Candida* gut commensalism. *Science* **381**, 502–508 (2023).

143. Myint, T., Leedy, N., Villacorta Cari, E. & Wheat, L. J. HIV-associated histoplasmosis: current perspectives. *HIV AIDS* **12**, 113–125 (2020).

144. Wen, Y. et al. Immune reconstitution inflammatory syndrome associated with *Pneumocystis* pneumonia in a patient with AIDS. *J. Int. Med. Res.* **48**, 300060520946544 (2020).

145. Ho, J. et al. Candidalysin activates innate epithelial immune responses via epidermal growth factor receptor. *Nat. Commun.* **10**, 2297 (2019).

Review article

146. Wu, Y. et al. Toll-like receptor 4 and CD11b expressed on microglia coordinate eradication of *Candida albicans* cerebral mycosis. *Cell Rep.* **42**, 113240 (2023).

147. Wagener, J., MacCallum, D. M., Brown, G. D. & Gow, N. A. *Candida albicans* chitin increases arginase-1 activity in human macrophages, with an impact on macrophage antimicrobial functions. *mBio* **8**, e01820-16 (2017).

148. Allen, J. E. IL-4 and IL-13: regulators and effectors of wound repair. *Annu. Rev. Immunol.* **41**, 229–254 (2023).

149. Shao, T. Y. et al. Commensal *Candida albicans* positively calibrates systemic Th17 immunological responses. *Cell Host Microbe* **25**, 404–417.e6 (2019).

150. Bacher, P. et al. Human anti-fungal Th17 immunity and pathology rely on cross-reactivity against *Candida albicans*. *Cell* **176**, 1340–1355.e15 (2019).

151. Ost, K. S. & Round, J. L. Commensal fungi in intestinal health and disease. *Nat. Rev. Gastroenterol. Hepatol.* https://doi.org/10.1038/s41575-023-00816-w (2023).

152. Fan, Y., Wu, L. & Zhai, B. The mycobiome: interactions with host and implications in diseases. *Curr. Opin. Microbiol.* **75**, 102361 (2023).

153. Rolling, T. et al. Haematopoietic cell transplantation outcomes are linked to intestinal mycobiota dynamics and an expansion of *Candida parapsilosis* complex species. *Nat. Microbiol.* **6**, 1505–1515 (2021).

154. Knutsen, A. P. et al. Fungi and allergic lower respiratory tract diseases. *J. Allergy Clin. Immunol.* **129**, 280–291 (2012).

155. Mirhakkak, M. H. et al. Genome-scale metabolic modeling of *Aspergillus fumigatus* strains reveals growth dependencies on the lung microbiome. *Nat. Commun.* **14**, 4369 (2023).

156. Lin, L. et al. The airway microbiome mediates the interaction between environmental exposure and respiratory health in humans. *Nat. Med.* **29**, 1750–1759 (2023).

157. Mac Aogain, M. et al. Integrative microbiomics in bronchiectasis exacerbations. *Nat. Med.* **27**, 688–699 (2021).

158. Cayrol, C. et al. Environmental allergens induce allergic inflammation through proteolytic maturation of IL-33. *Nat. Immunol.* **19**, 375–385 (2018).

159. Wiesner, D. L. et al. Club cell TRPV4 serves as a damage sensor driving lung allergic inflammation. *Cell Host Microbe* **27**, 614–628.e6 (2020).

160. Wu, Y. et al. *Candida albicans* elicits protective allergic responses via platelet mediated T helper 2 and T helper 17 cell polarization. *Immunity* **54**, 2595–2610.e7 (2021).

161. Schwarz, C. et al. Antigen specificity and cross-reactivity drive functionally diverse anti-*Aspergillus fumigatus* T cell responses in cystic fibrosis. *J. Clin. Invest.* **133**, e161593 (2023).

162. Hosseini, M., Shakerimoghaddam, A., Ghazalibina, M. & Khaledi, A. *Aspergillus* coinfection among patients with pulmonary tuberculosis in Asia and Africa countries; a systematic review and meta-analysis of cross-sectional studies. *Microb. Pathog.* **141**, 104018 (2020).

163. Page, I. D. et al. Chronic pulmonary aspergillosis commonly complicates treated pulmonary tuberculosis with residual cavitation. *Eur. Respir. J.* **53**, 1801184 (2019).

164. Chong, W. H., Saha, B. K. & Tan, C. K. Clinical characteristics and outcomes of influenza-associated pulmonary aspergillosis among critically ill patients: a systematic review and meta-analysis. *J. Hosp. Infect.* **120**, 98–109 (2022).

165. Feys, S. et al. A visual and comprehensive review on COVID-19-associated pulmonary aspergillosis (CAPA). *J. Fungi* **7**, 1067 (2021).

166. Salazar, F., Bignell, E., Brown, G. D., Cook, P. C. & Warris, A. Pathogenesis of respiratory viral and fungal coinfections. *Clin. Microbiol. Rev.* **35**, e0009421 (2022).

167. Donnelly, J. P. et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for research and treatment of cancer and the Mycoses Study Group Education and Research Consortium. *Clin. Infect. Dis.* **71**, 1367–1376 (2020).

168. Thompson, G. R. III et al. Global guideline for the diagnosis and management of the endemic mycoses: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology. *Lancet Infect. Dis.* **21**, e364–e374 (2021).

169. Gupta, I., Baranwal, P., Singh, G. & Gupta, V. Mucormycosis, past and present: a comprehensive review. *Future Microbiol.* **18**, 217–234 (2023).

170. Latge, J. P. & Chamilos, G. *Aspergillus fumigatus* and aspergillosis in 2019. *Clin. Microbiol. Rev.* **33**, e00140-18 (2019).

171. Salzer, H. J. F. et al. Clinical, diagnostic, and treatment disparities between HIV-infected and non-HIV-infected immunocompromised patients with *Pneumocystis jirovecii* pneumonia. *Respiration* **96**, 52–65 (2018).

172. Nucci, M., Barreiros, G., Akiti, T., Anaissie, E. & Nouer, S. A. Invasive fusariosis in patients with hematologic diseases. *J. Fungi* **7**, 815 (2021).

173. Pappas, P. G., Lionakis, M. S., Arendrup, M. C., Ostrosky-Zeichner, L. & Kullberg, B. J. Invasive candidiasis. *Nat. Rev. Dis. Prim.* **4**, 18026 (2018).

174. Williamson, P. R. et al. *Cryptococcal meningitis*: epidemiology, immunology, diagnosis and therapy. *Nat. Rev. Neurol.* **13**, 13–24 (2017).

175. Chen, S. C. et al. Global guideline for the diagnosis and management of rare yeast infections: an initiative of the ECMM in cooperation with ISHAM and ASM. *Lancet Infect. Dis.* **21**, e375–e386 (2021).

176. Hoenigl, M. et al. Global guideline for the diagnosis and management of rare mould infections: an initiative of the European Confederation of Medical Mycology in cooperation with the International Society for Human and Animal Mycology and the American Society for Microbiology. *Lancet Infect. Dis.* **21**, e246–e257 (2021).

177. Cornely, O. A. et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect. Dis.* **19**, e405–e421 (2019).

178. Ssebambulidde, K. et al. Treatment recommendations for non-HIV associated cryptococcal meningoencephalitis including management of post-infectious inflammatory response syndrome. *Front. Neurol.* **13**, 994396 (2022).

179. Tolebeyan, A., Mohammadi, O., Vaezi, Z. & Amini, A. Mepolizumab as possible treatment for allergic bronchopulmonary aspergillosis: a review of eight cases. *Cureus* **12**, e9684 (2020).

180. Ramonell, R. P., Lee, F. E., Swenson, C. & Kuruvilla, M. Dupilumab treatment for allergic bronchopulmonary aspergillosis: a case series. *J. Allergy Clin. Immunol. Pract.* **8**, 742–743 (2020).

181. Koutsokera, A. et al. Omalizumab for asthma and allergic bronchopulmonary aspergillosis in adults with cystic fibrosis. *J. Cyst. Fibros.* **19**, 119–124 (2020).

182. Wan, L. et al. Effect of granulocyte-macrophage colony-stimulating factor on prevention and treatment of invasive fungal disease in recipients of allogeneic stem-cell transplantation: a prospective multicenter randomized phase IV trial. *J. Clin. Oncol.* **33**, 3999–4006 (2015).

183. Perruccio, K. et al. Transferring functional immune responses to pathogens after haploidentical hematopoietic transplantation. *Blood* **106**, 4397–4406 (2005).

184. Papadopoulou, A. et al. Clinical-scale production of *Aspergillus*-specific T cells for the treatment of invasive aspergillosis in the immunocompromised host. *Bone Marrow Transpl.* **54**, 1963–1972 (2019).

185. de Sousa Mda, G. et al. Topical application of imiquimod as a treatment for chromoblastomycosis. *Clin. Infect. Dis.* **58**, 1734–1737 (2014).

186. Ambati, S. et al. Antifungal liposomes directed by dectin-2 offer a promising therapeutic option for pulmonary aspergillosis. *mBio* **12**, e00030-21 (2021).

187. Kumaresan, P. R. et al. Bioengineering T cells to target carbohydrate to treat opportunistic fungal infection. *Proc. Natl Acad. Sci. USA* **111**, 10660–10665 (2014).

188. Edwards, J. E. Jr et al. A fungal immunotherapeutic vaccine (NDV-3A) for treatment of recurrent vulvovaginal candidiasis — a phase 2 randomized, double-blind, placebo-controlled trial. *Clin. Infect. Dis.* **66**, 1928–1936 (2018).

189. Oliveira, L. V. N., Wang, R., Specht, C. A. & Levitz, S. M. Vaccines for human fungal diseases: close but still a long way to go. *NPJ Vaccines* **6**, 33 (2021).

190. Fisher, M. C. et al. Tackling the emerging threat of antifungal resistance to human health. *Nat. Rev. Microbiol.* **20**, 557–571 (2022).

191. Gow, N. A. R. et al. The importance of antimicrobial resistance in medical mycology. *Nat. Commun.* **13**, 5352 (2022).

192. Hoenigl, M. et al. The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. *Drugs* **81**, 1703–1729 (2021).

193. Molloy, S. F. et al. Antifungal combinations for treatment of *Cryptococcal meningitis* in Africa. *N. Engl. J. Med.* **378**, 1004–1017 (2018).

194. Hart, E., Nguyen, M., Allen, M., Clark, C. M. & Jacobs, D. M. A systematic review of the impact of antifungal stewardship interventions in the United States. *Ann. Clin. Microbiol. Antimicrob.* **18**, 24 (2019).

195. Chow, N. A. et al. Tracing the evolutionary history and global expansion of *Candida auris* using population genomic analyses. *mBio* **11**, e03364-19 (2020).

196. Casadevall, A., Kontoyiannis, D. P. & Robert, V. On the emergence of *Candida auris*: climate change, azoles, swamps, and birds. *mBio* **10**, e01397-19 (2019).

197. Schwartz, I. S. et al. Emergomyces: the global rise of new dimorphic fungal pathogens. *PLoS Pathog.* **15**, e1007977 (2019).

198. Kenyon, C. et al. A dimorphic fungus causing disseminated infection in South Africa. *N. Engl. J. Med.* **369**, 1416–1424 (2013).

199. Morgado, D. S. et al. Global distribution of animal sporotrichosis: a systematic review of *Sporothrix* sp. identified using molecular tools. *Curr. Res. Microb. Sci.* **3**, 100140 (2022).

200. Lockhart, S. R., Chowdhary, A. & Gold, J. A. W. The rapid emergence of antifungal-resistant human-pathogenic fungi. *Nat. Rev. Microbiol.* **21**, 818–832 (2023).

201. Brown, G. D. et al. Hidden killers: human fungal infections. *Sci. Transl. Med.* **4**, 165rv113 (2012).

202. CDC. Infection control guidance: *Candida auris*. *CDC* https://www.cdc.gov/fungal/candida-auris/c-auris-infection-control.html (2024).

203. Kenters, N. et al. Control of *Candida auris* in healthcare institutions: outcome of an International Society for Antimicrobial Chemotherapy expert meeting. *Int. J. Antimicrob. Agents* **54**, 400–406 (2019).

204. Caceres, D. H. et al. *Candida auris*: a review of recommendations for detection and control in healthcare settings. *J. Fungi* **5**, 111 (2019).

205. Borman, A. M. & Johnson, E. M. *Candida auris* in the UK: introduction, dissemination, and control. *PLoS Pathog.* **16**, e1008563 (2020).

206. Gow, N. A. R. & Lenardon, M. D. Architecture of the dynamic fungal cell wall. *Nat. Rev. Microbiol.* **21**, 248–259 (2023).

207. European Commission. EU action on antimicrobial resistance. *European Commission* https://health.ec.europa.eu/antimicrobial-resistance/eu-action-antimicrobial-resistance_en#stepping-up-eu-actions (2024).

208. Rhodes, J. et al. Population genomics confirms acquisition of drug-resistant *Aspergillus fumigatus* infection by humans from the environment. *Nat. Microbiol.* **7**, 663–674 (2022).

209. Verma, S. B. Emergence of recalcitrant dermatophytosis in India. *Lancet Infect. Dis.* **18**, 718–719 (2018).

210. Casadevall, A. Fungal virulence, vertebrate endothermy, and dinosaur extinction: is there a connection? *Fungal Genet. Biol.* **42**, 98–106 (2005).

211. de Crecy, E., Jaronski, S., Lyons, B., Lyons, T. J. & Keyhani, N. O. Directed evolution of a filamentous fungus for thermotolerance. *BMC Biotechnol.* **9**, 74 (2009).

Review article

212. O'Hanlon, S. J. et al. Recent Asian origin of chytrid fungi causing global amphibian declines. *Science* **360**, 621–627 (2018).

213. Forster, T. M. et al. Enemies and brothers in arms: *Candida albicans* and Gram-positive bacteria. *Cell Microbiol.* **18**, 1709–1715 (2016).

214. Santus, W., Devlin, J. R. & Behnsen, J. Crossing kingdoms: how the mycobiota and fungal–bacterial interactions impact host health and disease. *Infect. Immun.* **89**, e00468-20 (2021).

215. Snelders, N. C., Rovenich, H. & Thomma, B. Microbiota manipulation through the secretion of effector proteins is fundamental to the wealth of lifestyles in the fungal kingdom. *FEMS Microbiol. Rev.* **46**, fuac022 (2022).

216. Graham, C. E., Cruz, M. R., Garsin, D. A. & Lorenz, M. C. *Enterococcus faecalis* bacteriocin EntV inhibits hyphal morphogenesis, biofilm formation, and virulence of *Candida albicans*. *Proc. Natl Acad. Sci. USA* **114**, 4507–4512 (2017).

217. Hwang, G. et al. *Candida albicans* mannans mediate *Streptococcus mutans* exoenzyme GtfB binding to modulate cross-kingdom biofilm development in vivo. *PLoS Pathog.* **13**, e1006407 (2017).

218. MacAlpine, J. et al. A small molecule produced by *Lactobacillus* species blocks *Candida albicans* filamentation by inhibiting a DYRK1-family kinase. *Nat. Commun.* **12**, 6151 (2021).

219. Montelongo-Jauregui, D., Saville, S. P. & Lopez-Ribot, J. L. Contributions of *Candida albicans* dimorphism, adhesive interactions, and extracellular matrix to the formation of dual-species biofilms with *Streptococcus gordonii*. *mBio* **10**, e01179-19 (2019).

220. Alonso-Roman, R. et al. *Lactobacillus rhamnosus* colonisation antagonizes *Candida albicans* by forcing metabolic adaptations that compromise pathogenicity. *Nat. Commun.* **13**, 3192 (2022).

221. Ballou, E. R. et al. Lactate signalling regulates fungal beta-glucan masking and immune evasion. *Nat. Microbiol.* **2**, 16238 (2016).

222. Pedro, N. A., Fontebasso, G., Pinto, S. N., Alves, M. & Mira, N. P. Acetate modulates the inhibitory effect of *Lactobacillus gasseri* against the pathogenic yeasts *Candida albicans* and *Candida glabrata*. *Microb. Cell* **10**, 88–102 (2023).

223. Bastos, R. W. et al. Secondary metabolites produced during *Aspergillus fumigatus* and *Pseudomonas aeruginosa* biofilm formation. *mBio* **13**, e0185022 (2022).

224. Naseem, S. & Konopka, J. B. *N*-acetylglucosamine regulates virulence properties in microbial pathogens. *PLoS Pathog.* **11**, e1004947 (2015).

225. Naseem, S., Min, K., Spitzer, D., Gardin, J. & Konopka, J. B. Regulation of hyphal growth and *N*-acetylglucosamine catabolism by two transcription factors in *Candida albicans*. *Genetics* **206**, 299–314 (2017).

226. Tan, C. T., Xu, X., Qiao, Y. & Wang, Y. A peptidoglycan storm caused by beta-lactam antibiotic's action on host microbiota drives *Candida albicans* infection. *Nat. Commun.* **12**, 2560 (2021).

227. Ye, L. et al. Functional characterization of the GlcNAc catabolic pathway in *Cryptococcus neoformans*. *Appl. Environ. Microbiol.* **88**, e0043722 (2022).

228. Briard, B. et al. Dirhamnolipids secreted from *Pseudomonas aeruginosa* modify anjpegungal susceptibility of *Aspergillus fumigatus* by inhibiting β1,3 glucan synthase activity. *ISME J.* **11**, 1578–1591 (2017).

229. Storey, D. et al. *Klebsiella pneumoniae* type VI secretion system-mediated microbial competition is PhoPQ controlled and reactive oxygen species dependent. *PLoS Pathog.* **16**, e1007969 (2020).

230. Allonsius, C. N. et al. Inhibition of *Candida albicans* morphogenesis by chitinase from *Lactobacillus rhamnosus* GG. *Sci. Rep.* **9**, 2900 (2019).

231. Kousser, C., Clark, C., Sherrington, S., Voelz, K. & Hall, R. A. *Pseudomonas aeruginosa* inhibits *Rhizopus microsporus* germination through sequestration of free environmental iron. *Sci. Rep.* **9**, 5714 (2019).

232. Hattab, S., Dagher, A. M. & Wheeler, R. T. *Pseudomonas* synergizes with fluconazole against *Candida* during treatment of polymicrobial infection. *Infect. Immun.* **90**, e0062621 (2022).

233. Bonfante, P. & Desiro, A. Who lives in a fungus? The diversity, origins and functions of fungal endobacteria living in Mucoromycota. *ISME J.* **11**, 1727–1735 (2017).

Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

W.H. has received research funding from the FDA; research funding and personal fees from F2G and Pfizer; and personal fees from GSK, Mundipharma and Pulmocide. T.S.H. has received an investigator award to institution from Gilead Sciences and speaker fees from Gilead and Pfizer and serves on Advisory or Data Monitoring Boards for F2G and Mundipharma. A.W. has received consultancy fees from Gilead and Mundipharma and payment for educational events from Gilead and F2G. The other authors declare no conflicts of interest.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41579-024-01062-w.

Peer review information *Nature Reviews Microbiology* thanks Tobias Hohl, who co-reviewed with Mariano Aufiero; Bernhard Hube; and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.