Immunity to fungal infections

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Abstract | Fungal diseases represent an important paradigm in immunology, as they can result from either a lack of recognition by the immune system or overactivation of the inflammatory response. Research in this field is entering an exciting period of transition from studying the molecular and cellular bases of fungal virulence to determining the cellular and molecular mechanisms that maintain immune homeostasis with fungi. The fine line between these two research areas is central to our understanding of tissue homeostasis and its possible breakdown in fungal infections and diseases. Recent insights into immune responses to fungi suggest that functionally distinct mechanisms have evolved to achieve optimal host–fungus interactions in mammals.

Yeast
A unicellular form of a fungus, consisting of oval or spherical cells, usually about 3 to 5 μm in diameter, that reproduce asexually by a process termed blastoconidia formation (budding) or by fission.

Spore
An asexual or sexual reproductive element of a fungus.

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Fungi are heterotrophic eukaryotes that are traditionally and morphologically classified into yeast and filamentous forms. The study of these eukaryotes has been motivated by their unique and fascinating biology, their many useful products (including wine, cheese and antibiotics), their use as experimental systems for basic biology and their importance as animal and plant pathogens.

Most fungi are ubiquitous in the environment, and humans are exposed by inhaling spores or small yeast cells. Examples of common fungi include *Aspergillus fumigatus*, *Cryptococcus neoformans* and the thermally dimorphic fungi (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Coccidioides immitis*, *Penicillium marneffei* and *Sporothrix schenckii*) (BOX 1). Fungi are very proficient at sensing their surroundings and responding to cues that promote their survival in changing environments. As a result, they can interact with plants, animals or humans in multiple ways, establishing symbiotic, commensal, latent or pathogenic relationships. Their ability to colonize almost every niche within the human body involves specific reprogramming events that enable them to adapt to environmental conditions, fight for nutrient acquisition and deal with or even exploit 'stresses' generated by host defence mechanisms[1–3]. Genomic and transcriptome-based approaches have revealed a link between fungal metabolism, morphogenesis and the response to stress in adaptation to the host environment[2]. Such adaptations can enhance pathogen virulence but can also provide opportunities for potential therapeutic targets[4].

Fungi are associated with a wide spectrum of diseases in humans and animals, ranging from acute self-limiting pulmonary manifestations and cutaneous lesions in immunocompetent individuals to inflammatory diseases and severe life-threatening infections in immunocompromised patients (BOX 1). As the population of immunosuppressed individuals has increased (secondarily to the increased prevalence of cancer, chemotherapy, organ transplantation and autoimmune diseases), so has the incidence of fungal diseases[5,6]. Furthermore, it has been anticipated that global warming will bring new fungal diseases for mammals[7]. Many fungal species (including *Pneumocystis jiroveci*[8] and commensal fungi, such as *Malassezia* spp. and *Candida albicans*) have co-evolved with their mammalian hosts over millions of years. This suggests the existence of complex mechanisms of immune surveillance in the host and of sophisticated fungal strategies to antagonize immunity.

The immune system does not remain ignorant of commensal or ubiquitous fungi, and so a fine balance between pro- and anti-inflammatory signals is required to maintain a stable host–fungus relationship, the disruption of which can have pathological consequences (BOX 2). In this Review, I explain that the host immune response to fungi comprises two main components — resistance (the ability to limit fungal burden) and tolerance (the ability to limit the host damage caused by the immune response or other mechanisms). Both strategies are evolutionarily conserved in plants and vertebrates[9], and understanding the interplay between them may allow us to define how fungi have adapted to the mammalian immune system and to translate this knowledge into new medical practices.

Recognition of fungi by the innate immune system

PAMPs. Innate immune mechanisms are used by the host to respond to a range of fungal pathogens in a rapid and conserved manner. The constitutive mechanisms of innate defence are present at sites of continuous

Box 1 | **Major fungal pathogens, their habitats and associated diseases**

Respiratory allergy

Asthma is common in the developed world and is increasing in frequency. Studies have linked worsening asthma with exposure to species of *Aspergillus*, *Alternaria*, *Cladosporium* and *Penicillium*. Mould sensitivity has been associated with increased asthma severity, and increased hospital and intensive care admissions and death in adults, and with increased bronchial reactivity in children.

Skin diseases

The skin can be a point of entry for fungal infections when the epithelial barrier is breached, or it can be a site for disseminated, systemic fungal diseases. Although *Malassezia* yeasts are a part of the normal microbiota, they have been associated with a number of diseases affecting the human skin, such as pityriasis versicolor, folliculitis, seborrhoeic dermatitis and dandruff, atopic dermatitis and psoriasis. Chronic mucocutaneous candidiasis, a primary immune deficiency presenting as an inability to clear yeasts, is an intractable manifestation of *Candida albicans* infection.

Recurrent vulvovaginal candidiasis (VVC)

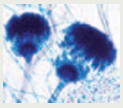
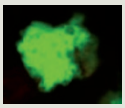
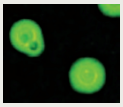
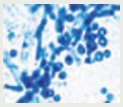
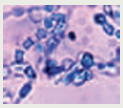
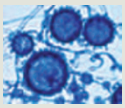
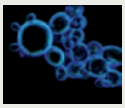
VVC is a widespread mucosal infection, caused by saprophytic and opportunistic yeasts belonging to the *Candida* genus, that can affect up to 75% of women of child-bearing age. There are several predisposing factors, including antibiotic and oral contraceptive usage, hormone replacement therapy, pregnancy and uncontrolled diabetes mellitus. Despite therapeutic advances, VVC remains a common problem worldwide, with a high associated cost and a high concern for drug resistance.

Inflammatory bowel disease (IBD)

The gastrointestinal tract uses a system of tolerance and controlled inflammation to limit the response to dietary or pathogen-derived antigens in the gut. Mucosal homeostasis arises from a highly dynamic balance between host protective immunity and regulatory mechanisms. When this complex system breaks down in a genetically predisposed individual, the resulting immune response may lead to IBD. Antibodies against *Saccharomyces cerevisiae* are present in a subgroup of patients with Crohn's disease and correlate with *C. albicans* colonization. These findings suggest that altered sensing of *C. albicans* colonization could contribute to aberrant immune responses in IBD.

Invasive fungal diseases (IFDs)

IFDs are nosocomial and device-related infections that occur in patients with haematological disorders or following solid organ or haematopoietic stem cell transplantation. It has been suggested that the agricultural use of fungicides may have contributed to drug resistance in people with life-threatening IFDs. IFDs have also been reported in patients who are not at high risk, such as patients with H1N1 influenza virus or *Mycobacterium tuberculosis* infection and those receiving tumour necrosis factor-targeted therapy.

Organism	Habitat	Image*	Disease
Aspergillus spp.	Soil; decaying organic materials; indoor air environments		• Aspergilloma • Acute and chronic pneumonias • Cerebral aspergillosis • Allergy, ABPA, SAFS
Pneumocystis spp.	No known environmental habitat; person-to-person transmission		• Pneumonia • COPD
Cryptococcus spp.	Environment, in association with decaying materials and trees		• Pneumonia • Meningitis • Disseminated disease
Candida spp.	Commensal of human gastrointestinal tract and vagina		• Disseminated infections • Mucocutaneous infections (oropharyngeal, skin and nail infections) • Vaginitis
Malassezia spp.	Commensal of human skin		• Cutaneous infections (pityriasis versicolor, seborrhoeic dermatitis) • Allergic atopic eczema
Blastomyces dermatitidis	Soil, in association with decaying wood		• Acute and chronic pneumonias • Skin lesions • Disseminated disease
Coccidioides immitis	Alkaline soil		• Self-limited influenza-like syndrome • Pneumonia • Disseminated disease
Histoplasma capsulatum	Soil contaminated with bird or bat guano		• Self-limited influenza-like syndrome • Acute and chronic pneumonias • Disseminated disease
Paracoccidioides brasiliensis	Soil and digestive tract of some animals		• Asymptomatic • Acute and chronic pneumonias • Disseminate disease • Cutaneous lesions

ABPA, allergic bronchopulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; SAFS, severe asthma with fungal sensitisation. *Images courtesy of www.doctorfungus.org © (2005).

interaction with fungi and include the barrier function of the skin and the mucosal epithelial cell surfaces of the respiratory, gastrointestinal and genitourinary tracts[10]. Microbial antagonism, defensins, collectins and the complement system also provide constitutive defence mechanisms and opsonic recognition of fungi. For example, complement receptor 3 (CR3; a heterodimer of CD11b and CD18) recognizes complement deposited on β-(1,6)-glucans on the fungus surface (FIG. 1). Moreover, host cells express pattern recognition receptors (PRRs) — such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs) and the galectin family proteins[11–13] — that sense pathogen-associated molecular patterns (PAMPs) in fungi (FIG. 1). PRRs on phagocytes initiate downstream intracellular events that promote the activation of the immune system and the clearance of fungi, with the specific immune response generated depending on the cell type involved. Monocytes, macrophages and neutrophils, as well as some

Box 2 | **Fungal infections and diseases: from immunity to immunopathology**

The bipolar nature of the inflammatory process in fungal infections

Bidirectional influences between infection and immune-related pathology have been known to exist in chronic mucocutaneous candidiasis (CMC) and chronic disseminated candidiasis (CDC). Although occasionally associated with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (a condition of dysfunctional T cell activity), CMC encompasses a variety of clinical disorders, in which the inability to clear *Candida albicans* yeasts results in yeast persistence in recurring lesions of the skin, nails and mucous membranes[125]. Patients with CMC often develop endocrine and inflammatory disorders, which suggests that immune responses are dysregulated. CDC is typically observed during neutrophil recovery in patients with acute leukaemia and requires protracted antifungal therapy. However, the efficacy of adjuvant corticosteroid therapy in these patients supports the pathophysiological hypothesis that CDC is a fungus-related immune reconstitution inflammatory syndrome (IRIS; see below)[135]. These observations highlight the truly bipolar nature of the inflammatory process in infection, at least during infection with specific fungi. Early inflammation is beneficial in containing the infection, but an uncontrolled inflammatory response is detrimental and may eventually oppose disease eradication. This condition is exemplified in mice with chronic granulomatous disease (CGD), in which an intrinsic, genetically determined failure to control inflammation to sterile fungal components determines the animals' inability to resolve an infection with *Aspergillus fumigatus*[136]. One major implication of these findings is that, at least in specific clinical settings, a state of chronic or intractable fungal disease is the result of an exaggerated inflammatory response that probably compromises the host's ability to cope with infecting fungi, and not of an 'intrinsic' susceptibility to infection. Thus, fungal diseases represent an important paradigm in immunology, as they can result from either a lack of recognition or an overactivation of the inflammatory response.

The immune reconstitution inflammatory syndrome

Clinically severe fungal infections occur in patients with IRIS, a disorder that is characterized by local and systemic inflammatory reactions that can result in quiescent or latent infections, which manifest as opportunistic mycoses[137]. IRIS responses are also found in otherwise immunocompetent individuals and are probably associated with disease severity in paracoccidioidomycosis, blastomycosis or *Malassezia* folliculitis. Thus, the conceptual principles of IRIS underscore the adverse effects of an overzealous and dysregulated immune response on the resolution of fungal infections and support a role for immunotherapies that are tailored to augment protective immunity.

Toll-like receptors
(TLRs). A family of membrane-spanning proteins that recognize pathogen-associated molecular patterns (which are shared by various microorganisms), as well as damaged host cell components. TLRs signal to the host that a microbial pathogen is present or that tissue damage has occurred. They are characterized by an ectodomain that has varying numbers of leucine-rich repeat motifs and a cytoplasmic Toll/IL-1 receptor (TIR) domain that recruits adaptors, such as the myeloid differentiation primary response protein 88 (MYD88) and TIR domain-containing adaptor protein inducing IFNβ (TRIF; also known as TICAM1).

C-type lectin receptors
(CLRs). A large family of proteins that have one or more carbohydrate-recognition domains. CLRs exist as transmembrane and soluble proteins, and include the mannose receptor, dectin 1, dectin 2 and DC-SIGN, as well as soluble molecules, such as the complement-activating mannose-binding lectins, which are involved in antifungal immunity.

Inflammasome
A large multiprotein complex that contains certain NOD-like receptors, RIG-I-like receptors and IFI200 proteins, the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC; also known as PYCARD) and pro-caspase 1. Assembly of the inflammasome leads to the activation of caspase 1, which cleaves pro-interleukin-1β (pro-IL-1β) and pro-IL-18 to generate the active cytokines.

cells that are normally non-phagocytic (such as epithelial and endothelial cells)[14], mostly contribute to the antifungal innate immune response through phagocytosis and direct pathogen killing. By contrast, uptake of fungi by dendritic cells (DCs) induces DC maturation and this promotes the differentiation of naive T cells into effector T helper (T_H) cell subtypes. To achieve optimal activation of antigen-specific adaptive immune responses, it is first necessary to activate the pathogen-detection mechanisms of the innate immune system. However, PRR activation is a double-edged sword, as PRRs might, paradoxically, promote some infections and cause tissue damage. Not surprisingly, therefore, fungi exploit PRRs to divert and subvert host immune responses in order to survive and eventually replicate (as discussed later).

The fungal cell wall varies in composition depending on the morphotype, growth stage and environment of the fungal species, and is the main source of PAMPs that are recognized by PRRs on mammalian cells[15]. The three major cell wall components, found in all medically important fungi, are: β-glucans (which are polymers of glucose), especially β-(1,3)-glucans with varying numbers of β-(1,6) branches; chitin (which is a polymer of *N*-acetylglucosamine); and mannans (which are chains of several hundred mannose molecules that are added to fungal proteins via *N*- or *O*-linkages). β-(1,2)-linked oligomannosides are also PAMPs, and these molecules are recognized by galectin 3, which allows phagocytes to discriminate between pathogenic and non-pathogenic yeasts[11] (FIG. 1). During the course of a fungal infection, multiple host PRRs are likely to be stimulated by fungal PAMPs in different combinations depending on the fungal species and on the host cell types. Therefore, the final immune response will depend not only on the relative degree of stimulation of the individual receptors but also on the level of receptor cooperativity and the cellular localization.

CLRs. CLRs are central for fungal recognition and for the induction of the innate and adaptive immune responses, and individuals with genetic deficiencies in CLRs are highly susceptible to fungal infections (TABLE 1). CLR family members include dectin 1 (also known as CLEC7A), dectin 2 (also known as CLEC6A), mincle (also known as CLEC4E), DC-specific ICAM3-grabbing non-integrin (DC-SIGN), the mannose receptor (also known as macrophage mannose receptor 1), langerin (also known as CLEC4K) and mannose-binding lectin[16]. Dectin 1 is the main PRR that recognizes β-glucans and, following ligation, it induces the production of pro- and anti-inflammatory cytokines and chemokines[16] (FIG. 1). This is achieved through the activation of two distinct signalling pathways downstream of dectin 1, the spleen tyrosine kinase (SYK)–caspase recruitment domain-containing protein 9 (CARD9) pathway and the RAF pathway. These pathways act synergistically and, through cross-regulatory mechanisms, induce and fine-tune canonical and non-canonical nuclear factor-κB (NF-κB) activation and cytokine gene expression[17]. The SYK–CARD9 pathway also activates the NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome, which results in proteolytic activation of the pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18 by caspase 1. Both human (TABLE 1) and mouse studies show that genetic deficiencies of dectin 1 (REFS 18–20) and CARD9 (REFS 21,22) are associated with susceptibility to fungal infections.

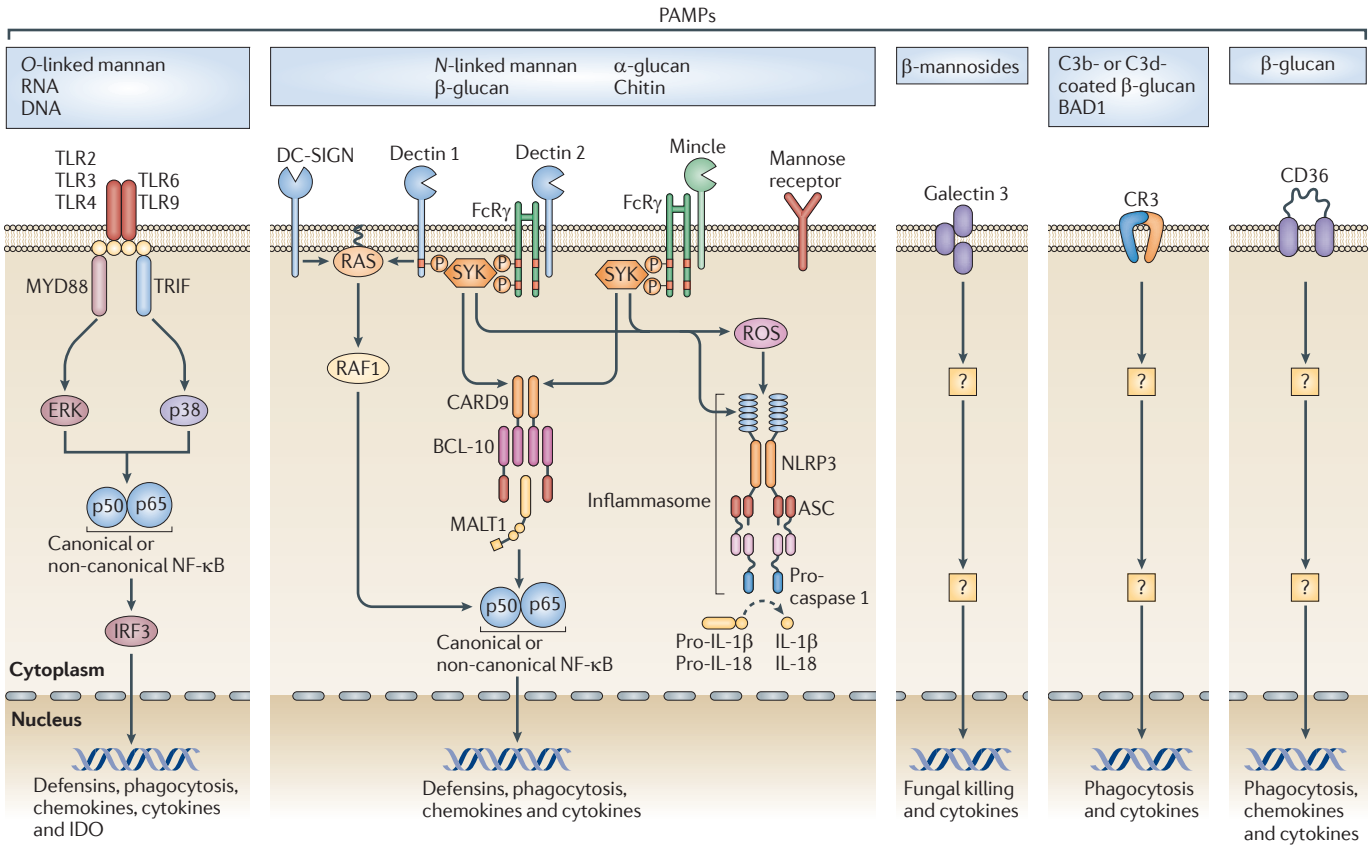
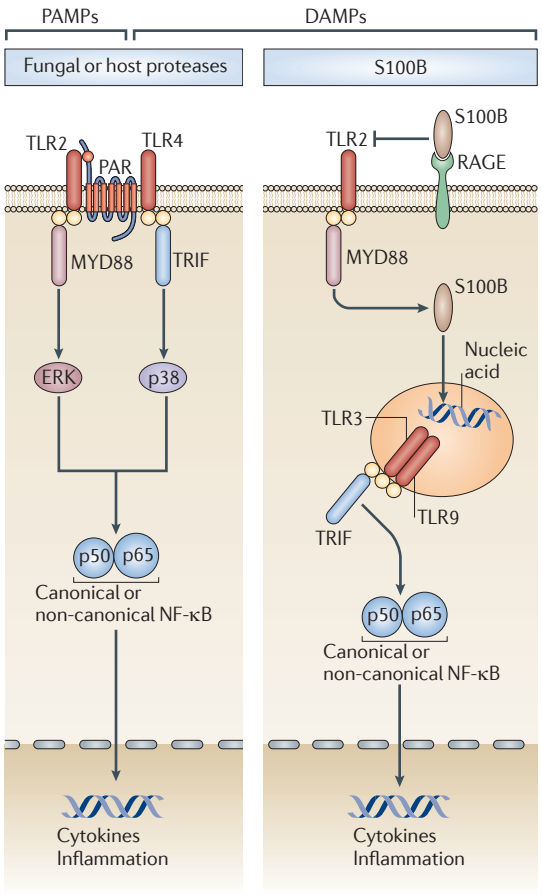


Figure 1 | **Signalling pathways in innate recognition of fungi**. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) that are present during fungal infections are recognized by pattern recognition receptors (PRRs). The major PRRs are Toll-like receptors (TLRs); C-type lectin receptors (CLRs; such as dectin 1 (also known as CLEC7A), dectin 2 (also known as CLEC6A), DC-specific ICAM3-grabbing non-integrin (DC-SIGN), mincle and the mannose receptor); galectin family proteins (such as galectin 3) and receptor for advanced glycation end-products (RAGE). TLRs and CLRs activate multiple intracellular pathways upon binding to specific fungal PAMPs, including β-glucans (especially β-(1,3)-glucans with varying numbers of β-(1,6) branches), chitin, mannans linked to proteins through *N*- or *O*-linkages, β-(1,2)-linked oligomannosides and fungal nucleic acids. These signals activate canonical or non-canonical nuclear factor-κB (NF-κB) and the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome, and this culminates in the production of defensins, chemokines, cytokines, reactive oxygen species (ROS) and indoleamine 2,3-dioxygenase (IDO). Complement receptor 3 (CR3) and members of the scavenger receptor family (such as CD36) mediate recognition of β-glucans and the fungal adhesin BAD1 (*Blastomyces* adhesion 1). After TLR activation, protease-activated receptors (PARs) sense proteolytic virulence factors and tissue injury and contribute to fungal recognition through a dual sensor system. In addition, the alarmin S100B, through the spatio-temporal integration of signals from TLRs and RAGE, allows the immune system to discriminate between pathogen-derived and endogenous danger signals. By forming complexes with various TLR2 ligands, S100B inhibits TLR2 through a paracrine epithelial cell- and neutrophil-mediated regulatory circuit, and this accounts for its anti-inflammatory activity. However, the ability of S100B to bind nucleic acids results in the activation of intracellular TLRs that signal through TIR domain-containing adaptor protein inducing IFNβ (TRIF; also known as TICAM1) and this eventually resolves damage-associated inflammation through transcriptional downregulation of S100B gene expression. ASC; apoptosis-associated speck-like protein containing a CARD; BCL-10, B cell lymphoma 10; CARD9, caspase recruitment domain-containing protein 9; ERK, extracellular signal-regulated kinase; FcRγ, Fc receptor γ-chain; IL, interleukin; IRF3, IFN-regulatory factor 3; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; MYD88, myeloid differentiation primary response protein 88; SYK, spleen tyrosine kinase.



Dectin 2 recognizes high-mannose structures that are common to many fungi and binds hyphal forms with higher affinity than yeast forms. Dectin 2 selectively pairs with the Fc receptor γ-chain (FcRγ) to induce pro-inflammatory cytokine and leukotriene release (FIG. 1). Dectin 2-deficient mice are highly susceptible to infection with *C. albicans* but not with *C. neoformans*[23,24]; however, the underlying reasons for the different susceptibilities are unclear. Mincle, which is mainly expressed by macrophages, is also an FcRγ-associated activating receptor. It senses damaged cells, recognizes *Malassezia* spp.[25] and *C. albicans*[26] and, similarly to dectin 1, induces NF-κB-mediated inflammatory responses through SYK–CARD9 signalling.

The mannose receptor and DC-SIGN recognize branched *N*-linked mannans, and both receptors can direct mannosylated fungal antigens into the DC endocytic pathway[27,28], thereby promoting antigen processing and presentation to T cells. Indeed, the mannose receptor has been shown to be involved in the promotion of antifungal T_H17 cell responses[29]. The mannose receptor also has affinity for α-glucans and chitin, whereas langerin, which is selectively expressed by Langerhans cells, mainly recognizes sulphated and mannosylated glycans[30]. Although the mannose receptor is involved in the phagocytosis of unopsonized *Candida* yeasts[31], deficiency of this receptor does not confer susceptibility to *C. albicans* infection as it does to *C. neoformans* infection[32]. Consistent with the lack of classical signalling motifs within the cytoplasmic tail, the mannose receptor induces the production of inflammatory cytokines in collaboration with TLRs, dectin 1 and peroxisome proliferator activated receptor-γ[33].

TLRs. TLR2, TLR4 and TLR9 are the main TLRs that are involved in sensing fungal components, such as zymosan, phospholipomannan, *O*-linked mannans and fungal DNA[12]. Although studies have shown that mice lacking the TLR signalling adaptor myeloid differentiation primary response protein 88 (MYD88) are highly susceptible to infections with various fungi[13], the physiological roles of individual TLRs in fungal infections are still unclear. In general, the contribution of individual TLRs may vary depending on the fungal species, fungal morphotypes, route of infection and receptor cooperativity. Nevertheless, human studies have shown that a polymorphism in TLR4 (Asp229Gly) is associated with increased susceptibility to pulmonary aspergillosis[34–36] and bloodstream candidiasis[37], and that a polymorphism in the promoter of *TLR9* (T-1237C) is associated with allergic bronchopulmonary aspergillosis (ABPA)[36] (TABLE 1). Similarly to CLRs, such as the mannose receptor and DC-SIGN, TLRs facilitate the presentation of fungal antigens by DCs and tailor T cell responses. This is consistent with the role of TLRs in controlling microbial antigen processing and presentation during the simultaneous phagocytosis of self and non-self components[38].

During inflammation, host and fungal proteases trigger the activation of protease-activated receptors (PARs), a family of G protein-coupled receptors[39]. The stimulation of TLRs by fungi unmasks the divergent roles of PAR1 and PAR2 in downstream signalling and inflammation. After fungal recognition by TLRs, PARs become activated to sense proteolytic virulence factors and tissue injury, to mediate pro-inflammatory (PAR1) or anti-inflammatory (PAR2) responses and to modulate the activity of TLRs (FIG. 1). Thus, TLRs regulate PAR signalling and vice versa[39]. A similar model of dual sensing of fungal PAMPs and virulence factors has been observed in *Drosophila* and plants. In *Drosophila*, a fungal protease used by the entomopathogenic fungus *Beauveria bassiana* to digest the cuticle has been shown to activate the Toll pathway by inducing the maturation of Persephone into an active protease[40]. In plants, an indirect mode of non-self recognition — through the perception of host destruction — has been identified, in which secreted proteins that are produced by biotrophic fungi both trigger and suppress host defence[41].

NLRs. Although cytoplasmic receptors for fungi have yet to be described, the NOD-like receptors (NLRs) are implicated in sensing fungi and, once activated, these receptors induce the production of IL-1β and IL-18 through the formation of inflammasomes[12,42,43]. Mice lacking IL-1 receptor type I (IL-1RI) signalling, IL-18 or caspase 1 have disparate patterns of susceptibility to fungal infections[12]; however, mice lacking NLRP3 consistently show enhanced susceptibility to candidiasis[44,45]. Consistent with an association between the NLRP3 inflammasome and several autoinflammatory conditions, and also with epithelial cell protection in the gut[46], defective NLRP3 activation increases *C. albicans* colonization in the gut and exacerbates inflammation in Crohn's disease[47]. This illustrates how a commensal organism such as *C. albicans* can become pathogenic in certain contexts.

DAMPs. Mammalian PRRs recognize not only PAMPs but also damaged host cell components, such as nucleic acids and alarmins, collectively known as damage-associated molecular patterns (DAMPs)[48]. Despite the identification of specific signalling pathways that negatively regulate responses to either PAMPs or DAMPs[48], the unexpected convergence of the molecular pathways responsible for the recognition of PAMPs and DAMPs raised the question of whether and how the host immune system discriminates between these two types of molecular patterns. The relative contributions of PAMPs and DAMPs to inflammation, immune homeostasis and mechanisms of repair during infection were also unclear. However, a mechanism has recently been described that allows the host to discriminate between PAMP- and DAMP-induced immune responses; the alarmin S100B coordinates this process via the spatiotemporal integration of signals from TLRs and the receptor for advanced glycation end-products (RAGE)[49]. By sequential binding to fungus-derived TLR2 ligands and nucleic acids, S100B first inhibits TLR2-induced inflammation during fungal pneumonia and then subsequently activates intracellular TLR3 and TLR9 to induce its own transcriptional downregulation (FIG. 1). Thus, the cross-talk between RAGE and TLRs represents a regulatory circuit in infection, whereby an endogenous danger signal

Allergic bronchopulmonary aspergillosis
(ABPA). A condition that is characterized by an exaggerated airway inflammation (hypersensitivity response) to *Aspergillus* spp. (most commonly *Aspergillus fumigatus*). It occurs most often in patients with asthma or cystic fibrosis.

Protease-activated receptors
(PARs). A family of four G protein-coupled receptors. Proteolytic cleavage within the extracellular amino terminus exposes a tethered ligand domain, which activates the receptors to initiate multiple signalling cascades. Many proteases that activate PARs are produced during tissue damage, and PARs make important contributions to tissue responses to injury, including haemostasis, repair, cell survival, inflammation and pain.

NOD-like receptors
(NLRs). A family of cytosolic proteins that recognize pathogen-associated molecular patterns and endogenous ligands. The recognition of ligands induces a signalling cascade leading to activation of nuclear factor-κB, or the inflammasome, to produce pro-inflammatory cytokines. NLRs are also involved in signalling for cell death.

Table 1 | **Major single nucleotide polymorphisms associated with susceptibility to fungal infections and diseases**

Gene	SNPs or haplotypes	SNP effect	Disease	Outcome	Refs
CARD9	Q295X	Low numbers of T_H17 cells	Chronic mucocutaneous candidiasis	Susceptibility	21
CXCL10	+11101C/+1642G/ −1101A	Reduced chemokine production by DCs exposed to *Aspergillus fumigatus*	Invasive aspergillosis	Susceptibility	138
DECTIN1	Y223S	Reduced zymosan-binding capacity and IFNγ production	Oropharyngeal candidiasis	Resistance	139
	Y238X	Decreased cell surface expression, β-glucan-binding capacity and impaired cytokine production	Chronic mucocutaneous candidiasis, *Candida albicans* colonization and invasive aspergillosis	Susceptibility	18,140, 141
DEFB1	−44G	Unknown	*C. albicans* carriage	Resistance	142
IFNG	+874TT	Increased levels of IFNγ	ABPA, CCPA	Susceptibility	143
IL1RN *IL1A* *IL1B*	VNTR2/−889C/−511T	Increased levels of C-reactive protein	Invasive aspergillosis	Susceptibility	144
IL4	−1098T/−589C/−33C	Unknown	Chronic disseminated candidiasis	Susceptibility	145
	−589T	Increased levels of vaginal IL-4 and reduced levels of nitric oxide and MBL	Recurrent VVC	Susceptibility	146
	−589T	Reduced levels of IL-4	Paracoccidioidomycosis	Susceptibility	147
IL4R	I75V	Upregulation of CD23 expression	ABPA	Susceptibility	148
IL10	−1082AA −1082A/−819C/−592C	Reduced levels of IL-10	Invasive aspergillosis	Resistance	149,150
	−1082A	Reduced levels of IL-10	CCPA	Susceptibility	143
	−1082GG	Increased levels of serum IL-10	ABPA, *A. fumigatus* colonization	Susceptibility	151
IL15	+13689A	Increased levels of IL-15	ABPA, CCPA	Susceptibility	143
IL23R	R381Q	Impaired production of IL-17A	Invasive aspergillosis	Resistance	152
MASP2	D105G	Impaired MBL function	Invasive aspergillosis	Susceptibility	153
MBL2	O/O, A/O	Impaired MBL activity	Invasive aspergillosis, CCPA, VVC	Susceptibility	153,154
	LXA/O	Reduced levels of circulating MBL	Invasive aspergillosis	Susceptibility	153
	+1011A	Elevated plasma MBL levels and high peripheral blood eosinophilia	ABPA	Susceptibility	155
NLRP3	Length polymorphism (allele 7)	Impaired production of IL-1β	Recurrent VVC	Susceptibility	156
PLG	D472N	Predicted to enhance plasminogen binding to *A. fumigatus*	Invasive aspergillosis	Susceptibility	157
SFTPA2	A91P, R94R	Increased levels of total IgE and eosinophilia	ABPA, CCPA	Susceptibility	158,159
TGFB1	+869C	Decreased levels of TGFβ	CCPA	Susceptibility	143
TLR1	R80T, N248S	Unknown	Invasive aspergillosis	Susceptibility	160
TLR4	D299G/T399I	Predicted to impair the ligand–binding domain	Invasive aspergillosis, *A. fumigatus* colonization, CCPA, *C. albicans* systemic infections	Susceptibility	34–37
TLR6	S249P	Unknown	Invasive aspergillosis	Susceptibility	160
TLR9	T−1237C	Increased NF-κB binding affinity	ABPA	Susceptibility	36
TNF	−308G	Decreased levels of TNF	ABPA, CCPA	Susceptibility	143
TNFR1	+36G, −609T	Decreased levels of *TNFR1* mRNA	Invasive aspergillosis	Susceptibility	161
TNFR2	VNTR at −322	Unknown	Invasive aspergillosis	Susceptibility	162

ABPA, allergic bronchopulmonary aspergillosis; CARD9, caspase-recruitment domain family, member 9; CCPA, chronic cavitary pulmonary aspergillosis; CXCL, CXC-chemokine ligand; DC, dendritic cell; DEFB1, β-defensin 1; IFN, interferon; IL, interleukin; IL1RN, IL-1 receptor antagonist; MASP2, mannan-binding lectin serine protease 2; MBL, mannose-binding lectin; NF-κB, nuclear factor-κB; NLRP3, NOD-, LRR- and pyrin domain-containing 3; PLG, plasminogen; SFTPA2, surfactant protein A2; SNP, single nucleotide polymorphism; TGF, transforming growth factor; TLR, Toll-like receptor; T_H17, T helper 17; TNF, tumour necrosis factor; TNFR, TNF receptor; VNTR, variable-number tandem repeat; VVC, vulvovaginal candidiasis.

protects the host against pathogen-induced inflammation and a nucleic acid-sensing mechanism terminates the inflammation induced by the endogenous danger signal. This raises the intriguing possibility that the host may have developed mechanisms to ameliorate the response to DAMPs via PAMPs.

Fungal evasion of inflammation

Fungi produce several factors that are potent regulators of the host inflammatory response[50,51]. By masking or subverting the host detection systems, fungi may avoid inflammation, and this contributes to fungal adaptation and opportunism[52,53]. As mentioned, the fungal cell wall is a dynamic structure that is continuously changing throughout the fungus cell cycle and during morphological transition. For example, β-(1,3)-glucans are exposed in the bud scar of *C. albicans* yeasts but are masked on hyphae, thus favouring fungal escape from recognition by dectin 1. Similarly, α-(1,3)-glucans, which are associated with virulence in *B. dermatitidis, H. capsulatum* and *P. brasiliensis*, block innate immune recognition of β-glucans by dectin 1 (REF. 54). In addition, *A. fumigatus* conidia are covered by hydrophobins and melanin that prevent immune recognition[55], whereas *P. jiroveci* evades immunosurveillance by changing the expression of major surface glycoproteins[56]. Also, many fungi exploit CR3 to dampen the inflammatory response and allow intracellular fungal parasitism[10].

The most extreme example of evasion of innate immune recognition is mediated by the capsule of *C. neoformans*, which completely covers the fungal cell wall and prevents recognition by PRRs and the induction of inflammation[57]. In addition, *C. neoformans* yeast can escape from macrophages through an expulsive mechanism that does not kill the host cell and avoids inflammation[58]. The so called 'Trojan horse' model suggests that replication within, lateral transfer between and eventual expulsion of yeasts from macrophages might explain how *C. neoformans* establishes latency and spreads in the host without triggering inflammation[59]. By continually activating the PRR system, it is possible that fungi contribute to inflammatory processes and promote autoimmunity. Indeed, dectin 1 and fungal β-glucans have been implicated in the induction of autoimmune arthritis[60] and psoriasis[61], and zymosan has been linked with the induction of experimental autoimmune encephalomyelitis[62].

T cell responses to fungi

In higher organisms, innate sensing mechanisms are hard-wired to activate distinct $CD4^+$ T_H cells that have protective and non-protective functions against fungi (FIG. 2). This suggests that the adaptive immune system has co-evolved with ubiquitous or commensal fungi. DCs are uniquely adept at decoding the fungus-associated information. A whole-genome transcriptional analysis of fungus-stimulated DCs indicated the presence of a specific transcriptional programme that governs the recognition of fungi[63]. The ability of a given DC subset to respond with different activating programmes and to activate distinct intracellular signalling pathways following the ligation of different PRRs[64,65] confers unexpected plasticity to the DC system and contributes to shaping T cell responses in infection[66,67] and following vaccination[68] (FIG. 2). The capacity of DCs to initiate different adaptive antifungal immune responses also depends on specialization and cooperation between DC subsets[66,67]. Inflammatory DCs initiate antifungal T_H17 and T_H2 cell responses *in vivo* through signalling pathways involving the TLR adaptor MYD88, whereas tolerogenic DCs activate T_H1 and regulatory T (T_{Reg}) cell differentiation programmes through mechanisms that involve the signalling adaptor TRIF (TIR domain-containing adaptor protein inducing IFNβ; also known as TICAM1). In addition, signal transducer and activator of transcription 3 (STAT3), which affects the balance between canonical and non-canonical activation of NF-κB and thus the expression of the enzyme indoleamine 2,3-dioxygenase (IDO), has a key contribution to DC plasticity and functional specialization. The multiple, functionally distinct, receptor signalling pathways in DCs ultimately affect the balance between $CD4^+$ effector T cells and T_{Reg} cells and thus are likely to be exploited by fungi to enable them to establish commensalism or infection.

Although epithelial cells are not professional antigen-presenting cells, they may have important immunological roles, as they express PRRs. Following the stimulation of these receptors, epithelial cells can initiate and amplify T_H2 cell responses, via thymic stromal lymphopoietin, IL-25 and IL-33 (REF. 69), and provide the machinery required for the induction of T cell tolerance[70] (FIG. 2).

T_H1 cells. A dominant T_H1 cell response correlates with protective immunity against fungi[10,71–73] and effective fungal vaccines[74]. T_H1 cell activation is determined by the DC response to the combination of TLR and CLR signals provided by fungi (FIG. 2). Through the production of the signature cytokine IFNγ and the provision of help for the production of opsonizing antibodies, T_H1 cells are instrumental in the optimal activation of phagocytes at sites of infection. Therefore, the failure of T cells to deliver activating signals to effector phagocytes may predispose patients to overwhelming infections, limit the therapeutic efficacy of antifungal agents and antibodies and favour the persistence of fungi[10]. Adaptive immune responses to commensal or dimorphic fungi occur in immunocompetent individuals (as indicated by a positive delayed-type hypersensitivity (DTH) response) and correlate with protection and a favourable prognosis. In the case of *C. neoformans* infection, the high prevalence of antibodies to cryptococcal antigens in normal individuals suggests that primary infection is followed by fungal growth restriction and concomitant immunity[10]. Indeed, direct inhibition of T cell proliferation by fungal polysaccharides may underlie the defective cellular immunity of patients with persistent cryptococcal infections[75]. Studies of patients with polar forms of paracoccidioidomycosis have shown an association between T_H1 cell reactivity and asymptomatic and mild forms of the infection, whereas T_H2 cell responses are associated with severe disease and disease relapse. Thus, the finding that oestradiol favours T_H1-type immune responses may explain why paracoccidioidomycosis is at least ten times more frequent in men than in women[76].

Hyphae
In moulds, spores germinate to produce branching filaments called hyphae, which are 2–10 μm in diameter and which may form a mass of intertwining strands called a mycelium.

Hydrophobins
A family of small, moderately hydrophobic proteins that are characterized by the conserved spacing of eight cysteine residues. Hydrophobins are present on the surface of many fungal conidia, and are responsible for the rodlet configuration of the outer conidial layer.

Delayed-type hypersensitivity response
A cellular immune response to antigen that develops over a period of ~24–72 hours. The response is characterized by the infiltration of T cells and monocytes and depends on the production of T helper 1-type cytokines.

Paracoccidioidomycosis
A chronic granulomatous disease involving the lungs, skin, mucous membranes, lymph nodes and internal organs that is caused by *Paracoccidioides brasiliensis*. Symptoms include skin ulcers, adenitis and pain owing to abdominal organ involvement.

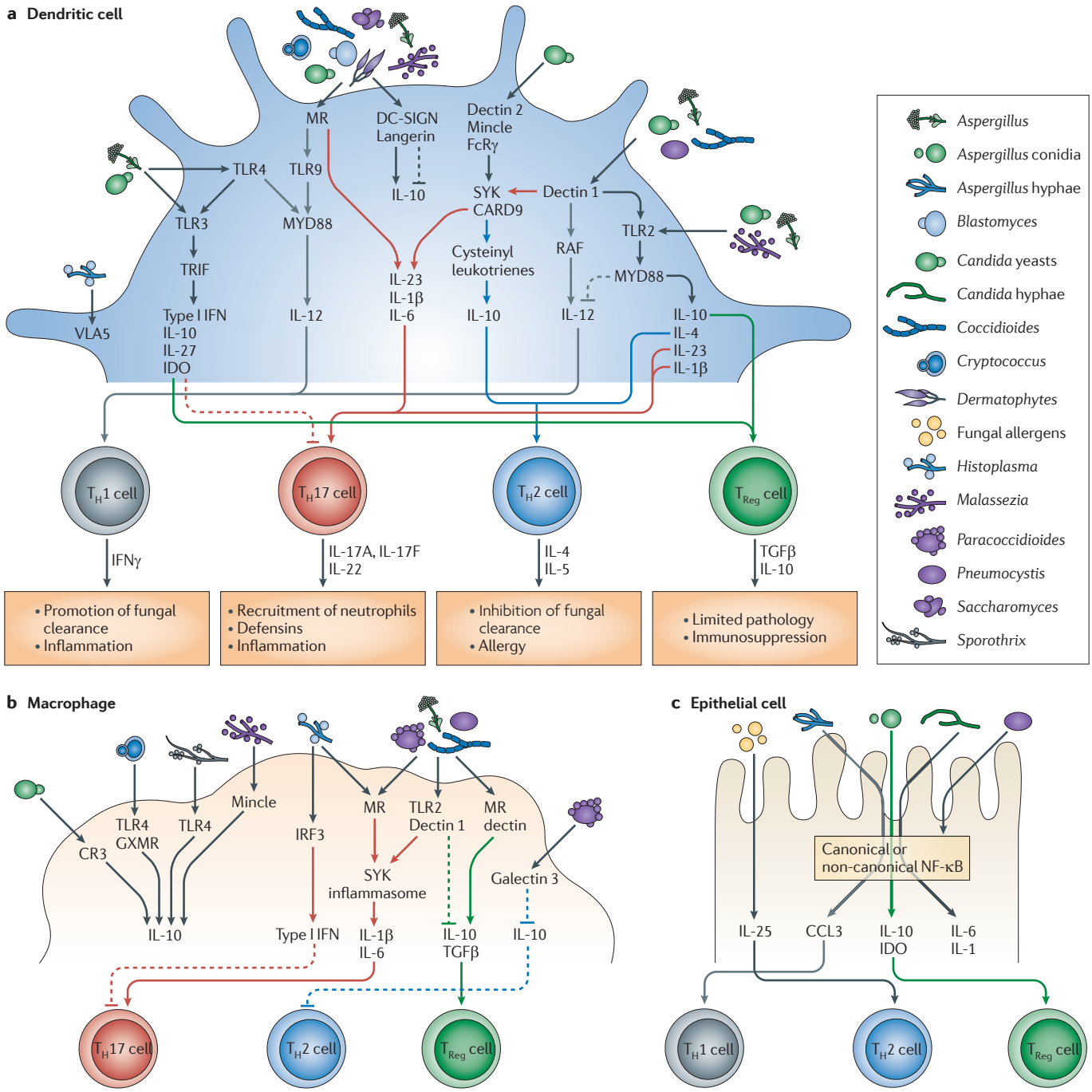


Figure 2 | **CD4⁺ T cell subsets in fungal infections.** The figure shows how different antigen-presenting cells stimulate the differentiation of CD4⁺ T helper (T_H) cells and regulatory T (T_{Reg}) cells in response to fungi, depicting the transcription factors involved, the cytokines produced and the possible effector and regulatory functions induced. Through the production of distinct sets of cytokines and other mediators, T cells can act as immune effectors and as master regulators of the inflammatory and effector responses of innate cells. The ability of dendritic cells (**a**), macrophages (**b**) and epithelial cells (**c**) to respond to fungi with flexible intracellular signalling pathways that reflect the different pattern recognition receptor–pathogen-associated molecular pattern combinations confers unexpected plasticity on the system and contributes to shaping T cell responses. The multiple, functionally distinct signalling pathways in antigen-presenting cells ultimately affect the local T_H cell/T_{Reg} cell balance, and are likely to be exploited by fungi to allow commensalism or opportunism. CARD9, caspase recruitment domain-containing protein 9; CCL3, CC-chemokine ligand 3; CR3, complement receptor 3; DC-SIGN, DC-specific ICAM3-grabbing non-integrin; FcRγ, Fc receptor γ-chain; GXMR, receptor(s) for the *Cryptococcus* capsular component glucuronoxylomannan; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; IRF3, IFN-regulatory factor 3; MR, mannose receptor; MYD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB; SYK, spleen tyrosine kinase; TGFβ, transforming growth factor-β; TLR, Toll-like receptor; TRIF, TIR domain-containing adaptor protein inducing IFNβ (also known as TICAM1); VLA5, very late antigen 5.

T_H2 cells. IL-4 and IL-13 provide the most potent proximal signals for the commitment of naive T cells to the T_H2 cell lineage, which, by dampening protective T_H1 cell responses and promoting the alternative pathway of macrophage activation, favours fungal infections, fungus-associated allergic responses and disease relapse[77–79]. Accordingly, limiting IL-4 production restores antifungal resistance[80]. In atopic subjects and neonates, the suppressed DTH response to fungi is associated with elevated levels of antifungal IgE, IgA and IgG. In patients with cystic fibrosis, heightened T_H2 cell reactivity is associated with ABPA[81]; however, T_H2 cell-dependent humoral immune responses may afford some protection[82], in part by promoting T_H1 cell responses[83,84] and also by altering the intracellular trafficking of fungi within macrophages[85] and fungal gene expression[86]. A mechanism whereby serum IgM with specificity for conserved fungal antigens bridges innate and adaptive immune responses against fungal organisms has also recently been described[87]. The efficacy of certain vaccines that elicit the production of protective antibodies indicates that antibody responses can make a decisive contribution to host defence against medically important fungi[74,88,89].

T_H17 cells. Although T_H1 cell responses are central to host protection against fungi, it is also clear that patients with genetic defects in the IL-12, IL-23 and IFNγ pathways do not have increased susceptibility to most infectious agents, including fungi[22], with few exceptions[90]. Indeed, genetic deficiencies have indicated a role for the dectin 1–CARD9, STAT3 and T_H17 cell pathways in protection against fungal infections[6,22]. T_H17 cells have an important function in the host response against extracellular pathogens, but they are also associated with the pathogenesis of many autoimmune and allergic disorders. T_H17 cell activation occurs in fungal infections[23,44,66,67,70,73,91–101], mainly through the SYK–CARD9, MYD88 and mannose receptor signalling pathways in DCs and macrophages (FIG. 2). It is inhibited by the RAF and TRIF–type I IFN pathways, suggesting that mechanisms of activation and inhibition of T_H17 cells are present downstream of both CLRs and TLRs.

T_H17 cells are present in the fungus-specific T cell memory repertoire in humans[102–104] and mediate vaccine-induced protection in mice[105]. However, host defence against *A. fumigatus* relies on T_H1 cell responses rather than T_H17 cell responses[104], and patients with chronic mucocutaneous candidiasis (with or without autosomal dominant hyper-IgE syndrome) have defective T_H17 and also T_H1 cell responses[106]. This could be explained by the notion that T_H17 cells, although found early during the initiation of an immune response, are involved in a broad range of both T_H1- and T_H2-type responses. Indeed, a role for T_H17 cells in supporting T_H1 cell responses has been shown in experimental mucosal candidiasis[99,107]. In addition, preliminary evidence shows that in experimental aspergillosis, increased T_H2 cell responses and fungal allergy were observed in conditions of defective IL-17A receptor (IL-17RA) signalling (L.R., A. De Luca, T. Zelante and R.G. Iannitti, unpublished observations). These findings point to an important regulatory function for the T_H17 cell pathway in promoting T_H1-type immune responses and restraining T_H2-type responses, and also explain the immunological findings observed in patients with chronic mucocutaneous candidiasis and autosomal dominant hyperIgE syndrome.

In terms of effector functions, although the ability of IL-17A to mobilize neutrophils and induce the production of defensins greatly contributes to the prompt and efficient control of an infection at different body sites, conflicting results have been obtained regarding whether the IL-17A–IL-17RA pathway is essential[24,105,107,108] or not[91,99,109] during infection. This suggests that the activity of this pathway may depend on the stage and site of infection, and is probably influenced by environmental stimuli that induce cells to produce T_H17 cell-associated cytokines, including IL-22 (see below). It is intriguing that T_H17 cell responses are downregulated by *C. albicans*[110], and failure of this downregulation may eventually result in chronic inflammation and impair the resolution of the infection[93,111]. The mechanisms that link inflammation to chronic infection may involve a failure to restrain inflammation following IL-17A-dependent neutrophil recruitment, thereby preventing optimal protection and favouring fungal persistence. Thus, the T_H17 cell pathway could be involved in the immunopathogenesis of chronic fungal diseases, in which persistent fungal antigens may promote immune dysregulation. This may occur in patients with autoimmune polyendocrine syndrome type 1 and in the mouse model of this disorder (autoimmune regulator (AIRE)-deficient mice), in which excessive T_H17-type responses to fungi have been observed[112].

Balancing resistance and tolerance to fungi

The role of T_{Reg} cells. During a fungal infection, the immune response must eliminate the fungus while limiting collateral damage to tissues and restoring a homeostatic environment. Several clinical observations suggest an inverse relationship between IFNγ and IL-10 production in patients with fungal infections[10]. High levels of IL-10, which negatively affect IFNγ production, are detected in chronic candidal diseases, in the severe forms of endemic mycoses and in neutropenic patients with aspergillosis, and thus have been linked to susceptibility to fungal infections[113]. However, given its prominent effect on the resolution of inflammation, IL-10 production may be a consequence, rather than a cause, of the infection[113]. This predicts that, in the case of chronic fungal infections that are dominated by non-resolving inflammation, IL-10 acts as a homeostatic host-driven response to keep inflammation under control. T_{Reg} cells with anti-inflammatory activity have been described in fungal infections of both mice and humans. In experimental fungal infections, both inflammation and immune tolerance in the respiratory or gastrointestinal mucosa were shown to be controlled by the coordinated activation of different T_{Reg} cell subsets. However, as T_{Reg} cell responses may limit the efficacy of protective immune responses, the consequence of T_{Reg} cell activity is reduced damage to the host but also fungal persistence[113] and, eventually,

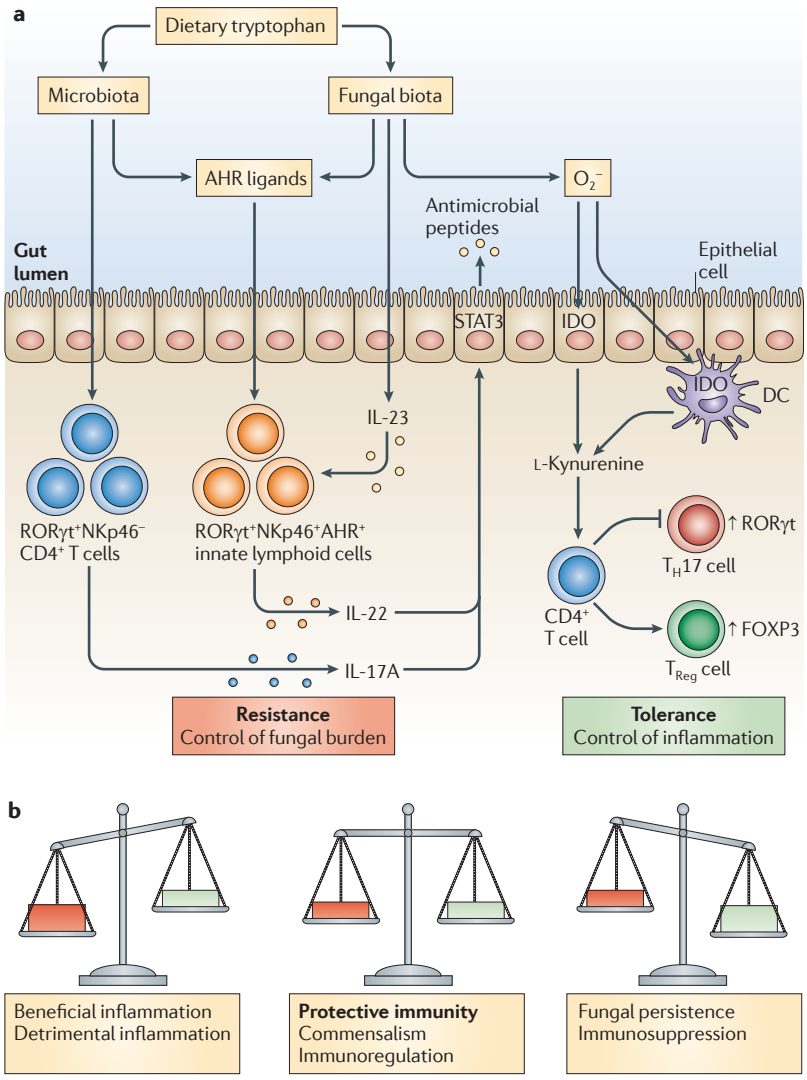


Figure 3 | **Resistance and tolerance to fungi and the regulation of these processes.** **a** | The tryptophan metabolism pathway is exploited by the mammalian host and by commensals to increase fitness in response to fungal infection through the processes of resistance and tolerance. Infection of the gut with *Candida albicans* leads to the production of interleukin-22 (IL-22) by $CD3^-NKp46^+ROR\gamma t^+AHR^+$ innate lymphoid cells, through a mechanism involving aryl hydrocarbon receptor (AHR) ligands and IL-23. IL-22 then acts on epithelial cells, leading to the activation of signal transducer and activator of transcription 3 (STAT3) and, together with IL-17A produced by $NKp46^-ROR\gamma t^+$ T cells, to the production of antimicrobial peptides. Various indole derivatives, which are generated through the conversion of dietary tryptophan by commensal intestinal microorganisms, act as endogenous ligands for AHR and thereby contribute to IL-22 production. Fungus-induced activation of tryptophan catabolism by indoleamine 2,3-dioxygenase (IDO) expressed by dendritic cells (DCs) and epithelial cells leads to the production of immunologically active compounds that induce the transcription of forkhead box P3 (FOXP3) and suppress the transcription of retinoic acid receptor-related orphan receptor-γt (RORγt) in T cells, resulting in the generation of regulatory T (T_{Reg}) cells. **b** | These findings support a model in which the AHR–IL-22 axis, together with the IL-17A–T helper 17 (T_H17) cell pathway, control initial fungal growth (that is, resistance) and epithelial cell homeostasis. By contrast, the exploitation of the interferon-γ–IDO axis for functional specialization of antifungal regulatory mechanisms (that is, tolerance) may have allowed the fungal microbiota to evolve with the mammalian immune system, survive in conditions of inflammation and prevent dysregulated immune responses. The balance between resistance and tolerance to fungi may accommodate the spectrum of host–fungus relationships, ranging from protection and immunopathology to fungal persistence and immunosuppression.

immunosuppression[114] (FIG. 2). Thus, by controlling the quality and magnitude of innate and adaptive effector responses, T_{Reg} cells may be responsible for a spectrum of outcomes, ranging from protective tolerance (defined as a host response that ensures survival of the host through a trade-off between sterilizing immune responses and their negative regulation, which limits pathogen elimination) to overt immunosuppression. Furthermore, this suggests that the interactions between fungi and the host immune system may determine whether a fungus is defined as a commensal or as a pathogen, and this status may change continuously.

The contribution of fungi. It is not surprising that many of the strategies that mammalian hosts have developed to coexist peacefully with their microbiota can be hijacked or manipulated by commensals to ensure their own survival. Manipulation of the regulatory network of the host by the fungal microbiota is one such mechanism to ensure fungal survival[113]. *C. albicans* and the fungal product zymosan have been shown to activate a tolerogenic programme in gut macrophages[115] and DCs[67,98], resulting in the activation of T_{Reg} cell-dependent immune tolerance. In normal skin, *Malassezia* spp. fungi downregulate inflammation by inducing TGFβ1 and IL-10 production, and thus are able to establish themselves as commensals. By contrast, in atopic dermatitis and psoriasis, the interaction of fungi with the defective skin barrier promotes epithelial hyperproliferation, inflammatory cell recruitment and disease exacerbation[116]. In the case of *C. albicans*, besides behaving as a commensal, this fungus can also actively promote tolerance, leading to the amelioration of gut inflammation[67]. Thus, similarly to symbionts, the fungal microbiota may actively contribute to the balance between inflammation and tolerance at mucosal surfaces, as well as at distant sites, to benefit both the host and the fungus. Moreover, host regulatory responses may contribute to the transition of fungi from symbionts to pathobionts. In this scenario, it is clinically important to distinguish between conditions in which yeasts are a cause (that is, required for disease), a trigger (that is, not required, but may favour disease progression) or a sign (that is, pathogenicity is promoted by a host failure) of non-resolving inflammation and associated clinical manifestations.

Tryptophan metabolism. A reciprocal relationship has been described between the development of forkhead box P3 $(FOXP3)^+$ T_{Reg} cells and effector T_H17 cells in fungal infections[96,117]. IDO is a metabolic enzyme that has been shown to affect the T_{Reg}/T_H17 cell balance during fungal infections, resulting in the suppression of inflammation and the promotion of protective tolerance (FIG. 3). Initially identified in infection because of its antimicrobial activity (through tryptophan starvation of intracellular parasites), IDO is now widely recognized as a suppressor of acute inflammatory responses and a regulator of mammalian immune homeostasis[118]. Unsurprisingly therefore, the induction of IDO by microorganisms may be an evasion mechanism that

allows them to establish commensalism or chronic infection. Through their capacity to induce T_{Reg} cells and inhibit T_H17 cell development, IDO-expressing cells and kynurenines (molecules produced by IDO) may have unexpected potential in the control of inflammation and allergy in fungal infections[119].

The AHR–IL-22 pathway. Recent evidence indicates that IL-22, a member of the IL-10 cytokine family, has a crucial role in innate immune defence and mucosal protection from damage[120]. IL-22 is produced by various cell types, including innate lymphoid cells that express natural killer (NK) cell markers (such as NKp46 (also known as NCR1)), NKT cells, lymphoid tissue-inducer cells, T_H1 cells and T_H17 cells. It regulates intestinal homeostasis and wound healing by activating STAT3 in epithelial cells[121]. A recent study has shown that IL-22 is required for the control of *C. albicans* growth at mucosal sites in the absence of T_H1 and T_H17 cells[99]. In this study, IL-22 produced by $NKp46^+$ innate lymphoid cells expressing the aryl hydrocarbon receptor (AHR) was found to directly target intestinal epithelial cells. This resulted in the induction of STAT3 phosphorylation in the epithelial cells and the release of S100A8 and S100A9 peptides, which are known to have antifungal activity and anti-inflammatory effects (FIG. 3). Consistent with this role for IL-22, patients with autosomal dominant hyper-IgE syndrome owing to dominant-negative mutations of STAT3 have a defective T_H17 cell response to *C. albicans*[122], and this is probably amplified by compromised IL-22-induced effects on STAT3-mutant epithelial cells. Vaginal epithelial cells also produce S100A8 and S100A9 following interaction with *C. albicans*[123], suggesting the possible involvement of IL-22 in vaginal candidiasis. In addition, naturally occurring IL-22-producing cells are highly enriched at mucosal sites, where continuous exposure to fungi occurs, and IL-22-expressing $CD4^+$ memory T cells specific for *C. albicans* are present in healthy individuals[124] but are lacking in patients with chronic mucocutaneous candidiasis[125]. So, IL-22 production in the mucosa may be a primitive mechanism of resistance against fungi under conditions of limited inflammation.

Various indole derivatives, which are generated from dietary tryptophan by commensal intestinal microorganisms[126], act as endogenous ligands for AHR and mediate IL-22 production[127,128]. This suggests that the tryptophan metabolism pathway could be exploited by commensals and the host to increase fitness in response to fungi, through the induction of resistance and tolerance. These findings support a model (FIG. 3) in which the AHR–IL-22 axis, in conjunction with the IL-17–T_H17 cell pathway, controls initial fungal growth (that is, host resistance) and epithelial cell homeostasis, through primitive antifungal effector mechanisms, such as the release of defensins and antimicrobial peptides. By contrast, the exploitation of the IFNγ–IDO axis for antifungal regulatory mechanisms (which promote tolerance) may have allowed the fungal microbiota to evolve with the mammalian immune system, survive in conditions of inflammation and prevent dysregulated immune responses[129]. The two pathways, although non-redundant, are reciprocally regulated and compensate for each other in the relative absence of either one[99]. Accordingly, commensal-driven mucosal responses are upregulated in animals that lack IDO[130], and IL-22 responses are upregulated when adaptive immune responses are defective[99].This may have led us to underestimate the role of IL-22 in mucosal candidiasis in IL-22-deficient, but otherwise immunocompetent, mice[107,131]. The model also explains the increased susceptibility to certain fungal infections following antibiotic-induced dysbiosis.

Translating basic research into clinical practices

New antifungal drugs. The past decades have brought important progress to the development of more effective and safe antifungal agents[88]. However, medical treatments that increase host resistance, such as antibiotics, place selective pressures on pathogens. As tolerance mechanisms are not expected to exert the same selective pressure on pathogens, new drugs that target tolerance pathways could provide therapies to which pathogens will not develop resistance.

Immune therapies. Breakthroughs in our understanding of how mucosal homeostasis is established, maintained or disrupted during fungal exposure and/or colonization should help to guide the development of new therapeutics that target specific inflammatory or metabolic end points. For example, limiting inflammation — through PRR agonism or antagonism — to stimulate a protective immune response to fungi should pave the way for the rational design of novel immunomodulatory therapies. Combination therapy with such immunomodulatory agents, including antibody-based immunotherapy[88], will probably maximize antifungal effects and reduce immune-mediated pathology and damage. Tryptophan metabolites are also possible targets for therapy as they simultaneously activate antifungal resistance and limit overzealous inflammatory host responses[117].

Vaccines. With the exception of a killed spherule vaccine against coccidioidomycosis, no fungal vaccine trials have ever been carried out. However, the level of our understanding of fungus–host interactions has progressed to the point at which vaccines against fungi and fungal diseases may become a reality[132,133]. Indeed, the screening of signalling pathways in DCs using a systems biology approach could be exploited for the development of chimeric vaccines that can target resistance and tolerance in fungal infections.

Functional genomics. It is now clear that genetic variants of molecules involved in the innate recognition of fungi may account, in part, for the inherited differences in human susceptibility to fungal infections[35,134]. Although the analysis of the genetic traits that modulate susceptibility to fungal infections is complex, it may allow the identification of genetic markers for fungal diseases that occur in high-risk patients. Understanding which patients are at highest risk of developing a life-threatening infection is at present a major unmet need,

Symbiont
An intestinal microorganism that contributes to host nutrition and fitness through a mutualistic, beneficial interaction.

Pathobiont
A microbial symbiont that can cause diseases as a consequence of the perturbation of intestinal homeostasis.

Dysbiosis
Alteration of the symbiont microbial community.

and genetic markers will probably assist in risk assessment. TABLE 1 summarizes the single nucleotide polymorphisms (SNPs) of human innate immune genes that have been linked with susceptibility to fungal infections and diseases.

Concluding remarks and future directions

There are several challenging issues in the field of medical mycology and infection-related immunological disorders. These include the control of inflammation leading to tolerance, the molecular bases of immune regulation and dysregulation, and the way in which commensal but opportunistic fungi can switch from a 'friendly' relationship with the host to a pathological relationship by evading or subverting host inflammation. If fungi either prevent or trigger excessive and deleterious inflammatory responses, this raises the question of whether collateral damage and inflammatory diseases are provoked only by pathogenic fungi or if commensals can also serve as perpetrators. A related question is how and whether the fungal microbiota contributes to the regulation of inflammation in health and disease. Challenging existing paradigms via a multidisciplinary approach in the fields of fungal pathology and immunopathology, functional genomics, proteomics and bioinformatics will probably lead towards the discovery of 'commensal signatures' for the fungal biota and the development of multi-pronged therapeutic approaches for mucosal and systemic fungal diseases (see the website of the European Project ALLFUN for further information).

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