Immune defence against *Candida* fungal infections

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Abstract | The immune response to *Candida* species is shaped by the commensal character of the fungus. There is a crucial role for discerning between colonization and invasion at mucosal surfaces, with the antifungal host defence mechanisms used during mucosal or systemic infection with *Candida* species differing substantially. Here, we describe how innate sensing of fungi by pattern recognition receptors and the interplay of immune cells (both myeloid and lymphoid) with non-immune cells, including platelets and epithelial cells, shapes host immunity to *Candida* species. Furthermore, we discuss emerging data suggesting that both the innate and adaptive immune systems display memory characteristics after encountering *Candida* species.

Candida species are fungi that have a major role in human pathology. In healthy individuals, *Candida* species are commensal in nature and colonize mucous membranes and the skin[1]. However, they can cause severe invasive disease when tissue homeostasis is disrupted — for example, in patients with neutropenia, pancreatitis or renal insufficiency — or following treatment with glucocorticosteroids, systemic antibiotics, indwelling medical devices, total parenteral nutrition or major abdominal surgery[1–3]. In patients with invasive candidiasis, treatment with antifungal drugs has shown only partial success in improving prognosis, and it is believed that only adjunctive immunotherapy could further improve the outcome of these infections.

In this Review, we provide a detailed account of the interaction of *Candida* species with the immune system. We describe the various pattern recognition receptors (PRRs) that are involved in sensing *Candida* species and explain how both innate and adaptive immune cells, as well as non-immune cells, contribute to the antifungal response. In addition, we discuss the emerging data suggesting that the host may develop innate (or 'trained') memory in addition to the well-known adaptive memory responses to *Candida* species.

Most studies to date have investigated host defences against *Candida albicans*, which is the most abundant *Candida* species in humans; for this reason, we focus on *C. albicans* here. Finally, we explain the consequences of the *Candida*–host immune system interaction and discuss the future challenges for the field.

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Innate sensing of *Candida* species

The first step in the development of an immune response to *Candida* species is the recognition of invading fungi via PRRs. Although there are differences in the ways in which innate immune cell populations recognize *Candida* species, the general framework is identical and involves the recognition of conserved pathogen-associated molecular patterns (PAMPs) by several families of PRRs, including the Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs) (FIG. 1).

In the *C. albicans* cell wall, two layers can be distinguished: the outer layer is mainly composed of *O*- and *N*-linked glycoproteins that consist of 80–90% mannose, whereas the inner cell wall contains the skeletal polysaccharides chitin, β-1,3-glucan and β-1,6-glucan, which confer strength and shape to the cells. These polysaccharide structures, which have been reported to differ between yeasts and hyphae[4,5,6], represent the main PAMPs recognized by host PRRs during an encounter with the fungus[7], as we discuss below.

Fungal sensing by CLRs

Sensing of β-glucans. CLRs are the most important family of innate receptors for the recognition of *Candida* species. Crucial components of the *Candida* cell wall recognized by CLRs are the β-1,3- and β-1,6-glucans. Interestingly, structural differences between the β-glucans found in yeasts and those found in hyphae have been reported — with hyphal β-glucans reported to have a 'closed shape' structure — leading to differences in

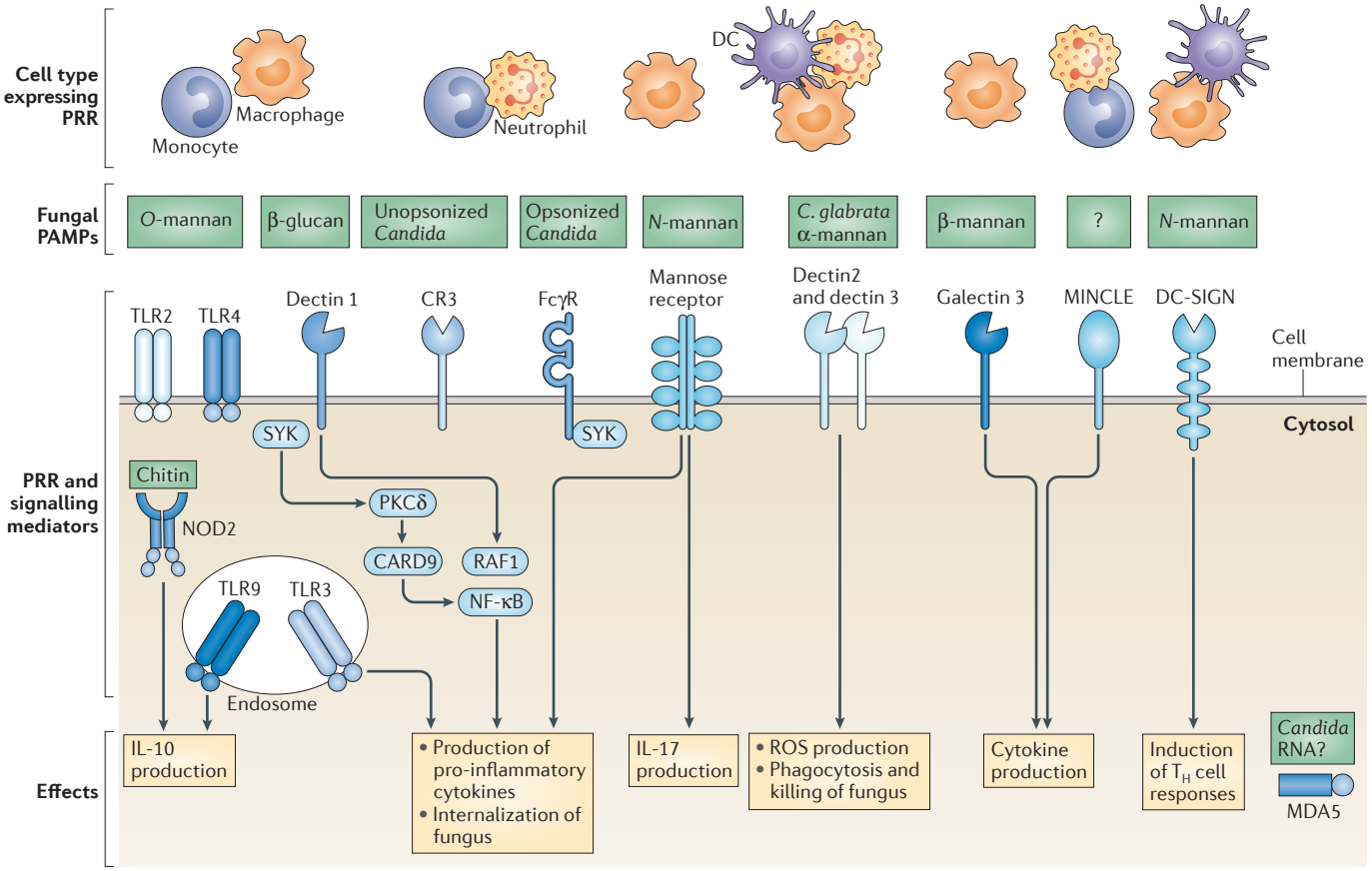


Figure 1 | **Recognition of *Candida* species by innate immune cells.** Ligand binding to extracellular Toll-like receptors (TLRs), such as TLR2 and TLR4, leads to the production of pro-inflammatory cytokines during *Candida* infections. The intracellular TLRs that recognize nucleic acids — namely, TLR3 and TLR9 — might also have a role in anti-*Candida* host responses. Chitin from *Candida albicans* has been proposed to induce the production of interleukin-10 (IL-10) via a nucleotide-binding oligomerization domain-containing protein 2 (NOD2)-dependent mechanism and in this way may contribute to dampening pro-inflammatory host responses during fungal infection. The pattern recognition receptors (PRRs) dectin 1, dectin 2 and dectin 3, and Fc receptors for IgG (FcγRs), induce responses in a spleen tyrosine kinase (SYK)-dependent manner, whereas the signalling pathways engaged by the mannose receptor remain unknown. Dectin 1 can interact with TLR2 and can induce intracellular signalling via SYK- and RAF1-dependent pathways. Complement receptor 3 (CR3) is important for the recognition of unopsonized *Candida*, whereas FcγRs are important for recognition of opsonized *Candida* by neutrophils. Dendritic cell (DC)-specific -ICAM3-grabbing non-integrin (DC-SIGN) recognizes *N*-linked mannans of *Candida* and has a role in inducing T helper (T_H) cell responses. There is no known *Candida*-derived ligand that triggers the C-type lectin receptor MINCLE, whereas β-mannans from *Candida* are recognized by galectin 3. Although a role for melanoma differentiation-associated protein 5 (MDA5) in anti-*Candida* host responses has been described, it remains to be determined what ligand induces MDA5 activation. Together, these signalling pathways induce the secretion of cytokines and chemokines and initiate phagocytosis to clear *Candida* infections. CARD9, caspase activation and recruitment domain-containing 9; *C. glabrata*, *Candida glabrata*; NF-κB, nuclear factor-κB; PAMP, pathogen-associated molecular pattern; PKCδ, protein kinase Cδ; ROS, reactive oxygen species.

their immunological properties[5]. β-glucans are shielded from immune recognition by the mannoproteins in *C. albicans* yeast but become exposed on the budding yeast and in *Candida* hyphae[8]. The most well-studied β-glucan receptor is dectin 1 (also known as CLEC7A), a CLR expressed mainly on monocytes and macrophages that induces cytokine production, as well as internalization of the fungus by formation of a 'phagocytic synapse' (REFS 9–11). Dectin 1 induces intracellular signals through a pathway mediated by spleen tyrosine kinase (SYK), caspase activation and recruitment domain-containing 9 (CARD9) and protein kinase Cδ[12–16], as well as through the RAF1 kinase signalling pathway[17]. In addition to inducing direct cellular activation, engagement of dectin 1 amplifies responses to TLR2 and TLR4 ligation; these TLRs recognize mannan-containing structures of *C. albicans* cell wall, as discussed below[18–20]. Recently, another important biological function of dectin 1 has been described. Signalling via dectin 1 is reported to prevent the uncontrolled release of neutrophil extracellular traps (NETs) during fungal infection. Importantly, this prevents extensive tissue damage from occurring during immune responses to fungi[21]. Interestingly though, not all *C. albicans* strains are recognized by dectin 1, most likely

owing to subtle strain-related differences in the structure of the β-glucan components of the cell wall, which may explain the different susceptibility of dectin 1-deficient hosts to different *Candida* strains[22].

Polymorphisms in dectin 1 are associated with colonization of the genitourinary tract by *Candida* species, recurrent vulvovaginal candidiasis in humans and other human fungal infections such as aspergillosis[23–26]. However, one study found that they are not associated with candidemia (that is, systemic fungal infections) in humans, although more studies are needed[24]. By contrast, the downstream adaptor molecule CARD9 is essential for systemic antifungal host defence. CARD9-deficient mice are more susceptible than wild-type mice to invasive candidiasis[14], and patients with loss-of-function mutations in *CARD9* also show increased susceptibility to invasive candidiasis, particularly candidal meningitis[15,27]. The association of CARD9 deficiency with a much more severe phenotype than dectin 1 deficiency is probably due to the fact that CARD9 also mediates signalling downstream of CLRs other than dectin 1 (REF. 28).

β-glucans are also recognized by complement receptor 3 (CR3); this receptor is mainly involved in the recognition of β-glucans by neutrophils[29]. CR3 is used by neutrophils to phagocytose and kill unopsonized *C. albicans*, whereas Fc receptors for IgG (FcγRs) facilitate the killing of opsonized fungi[30]. Although both of these pathways of *Candida* killing by neutrophils require SYK activation, they are independent of dectin 1, although CARD9 is essential for neutrophil killing of unopsonized fungi[30]. Interestingly, the expression of interleukin-1 (IL-1) receptor antagonist (IL-1RA), which is an anti-inflammatory member of the IL-1 cytokine family, by β-glucans is independent of both dectin 1 and CR3; an unidentified pathway or receptor that specifically activates AKT kinase is expected to be involved[31].

Recognition of mannans and mannoproteins by CLRs. Mannans and mannoproteins are important components of the *Candida* cell wall. Virulence and immune recognition of *C. albicans* are dependent on modulation of the mannoprotein fibril length by the mannosyltransferase MNN2, and hence, deficiencies of this enzyme have an impact on virulence[32]. Mannans and mannoproteins are recognized by several CLRs, including mannose receptor, dectin 2 (also known as CLEC6A), dendritic cell (DC)-specific ICAM3-grabbing non-integrin (DC-SIGN; also known as CD209) and MINCLE (also known as CLEC4E)[33–36]. The mannose receptor is primarily expressed on macrophages and recognizes *Candida* *N*-mannan[37]; signalling via this pathway has an important role in the expression of pro-inflammatory cytokines, especially IL-17 (REF. 35). Dectin 2, which is mainly expressed on dendritic cells (DCs), macrophages and neutrophils, recognizes *Candida* α-mannan[34]. In addition to its role in modulating T helper 17 (T_H17) cell responses, dectin 2 has been associated with the production of reactive oxygen species (ROS), and with phagocytosis and killing of *Candida glabrata*, which is the second most common strain of *Candida*[38]. Dectin 2 has been reported to form heterodimers with dectin 3, leading to pro-inflammatory responses, such as the production of tumour necrosis factor (TNF), IL-1β and IL-6, during *C. albicans* infection[39]. Galectin 3 on macrophages recognizes β-mannans[40] and induces a protective antifungal response in mouse macrophages through secretion of TNF. Hence, mice deficient in galectin 3 are more susceptible to disseminated candidiasis[41]. MINCLE is a CLR expressed on both monocytes and neutrophils, and it is responsible for inducing protective responses against *C. albicans*, mainly by initiating TNF production[42]. DC-SIGN is present on DCs as well as macrophages and recognizes *Candid*a *N*-linked mannan[33]; activation of DC-SIGN promotes adaptive immune responses by inducing the expression of cytokines that drive the activation and differentiation of T_H cells. Finally, mannose-binding lectin (MBL; also known as MBPC) is a soluble CLR that also binds mannan and modulates the recruitment of phagocytes and pro-inflammatory responses against *Candida* species[43]. The scavenger receptors CD36 (also known as platelet glycoprotein 4) and SCARF1 have also been reported to recognize *Candida* species[44].

Fungal recognition by TLRs and RLRs

TLRs have been extensively studied in the context of fungal infection. In addition to membrane-bound TLRs such as TLR2, TLR4 and TLR6, which mainly recognize mannoprotein constituents of the fungal cell wall[37], it has become apparent that the intracellular receptors that recognize cytoplasmic nucleic acids — namely, TLR3 and TLR9 — may also have a role in anti-*Candida* host defence. TLR3 has a protective role against *Candida* species, as expression of the mutated L412F variant of TLR3 leads to reduced activation of nuclear factor-κB (NF-κB) and decreased levels of interferon-γ (IFNγ), resulting in increased susceptibility to cutaneous candidiasis in humans[45]. Furthermore, chitin is recognized by TLR9 resulting in the anti-inflammatory cytokine production that is needed to maintain a balanced immune response[46].

RLRs are another family of PRRs that recognize cytoplasmic nucleic acids, and they are important for viral recognition[47]. A recent study has described the involvement of the RLR melanoma differentiation-associated protein 5 (MDA5; also known as IFIH1), an intracellular RNA sensor, in the recognition of *C. albicans*, with polymorphisms in this receptor influencing susceptibility to disseminated candidiasis in humans[48].

Fungal sensing by NLRs

The role of NLRs in pattern recognition. NLRs are cytoplasmic receptors that fulfil several important biological functions, including the recognition of bacterial peptidoglycans, antigen processing and presentation, and activation of the inflammasomes. The main recognition function of NLRs in the context of *Candida* infection is represented by the recognition and mediation of chitin-mediated responses, especially the production of IL-10 in the context of interaction between nucleotide-binding oligomerization domain-containing protein 2 (NOD2), mannose receptor and TLR9 (REF. 46).

The role of NLRs in inflammasome activation and IL-1β processing. Another important biological effect of NLRs is their function as components of the inflammasome. The best-characterized inflammasome is the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome, which activates caspase 1 and processes pro-IL-1β and pro-IL-18 into their biologically active forms[49]. Activation of the NLRP3 inflammasome by *Candida* hyphae, but not yeasts, has been reported in several studies[50–52], and this has been proposed to be important for enabling the host to discriminate between *Candida* colonization and invasion[53]. The unmasking of β-glucan in hyphae due to ineffective mannan fibril formation leads to the dectin 1-dependent activation of the inflammasome[54] (FIG. 2). Other possible activators of the inflammasome are the secreted aspartic proteases Sap2 and Sap6 (REF. 55). Mice deficient in NLRP3 are unable to activate caspase 1, and hence their macrophages release less bioactive IL-1β; these mice are therefore more susceptible to *Candida* infections[50,51,56]. Recent studies have reported that in addition to caspase 1, a non-canonical caspase 8 inflammasome is important for the processing of pro-IL-1β in response to *C. albicans*[57]. Another study reported that caspase 8 activation is in turn important for the NLRP3-dependent maturation of IL-1β maturation following recognition of *Candida* species[58]. In addition, activation of the NLRP3 inflammasome by *C. albicans* has been described to trigger pyroptosis in macrophages[59,60]. This represents a second mechanism of macrophage damage by the fungus, in addition to hyphae-induced mechanical disruption of membrane integrity. Finally, it was recently proposed that the NOD-, LRR- and CARD-containing 4 (NLRC4) inflammasome has a role in mucosal defence against *C. albicans* through its induction of pro-inflammatory cytokines and antimicrobial peptides[61].

However, it is important to note that inflammasome activation is not the only mechanism through which pro-IL-1β can be processed and activated (FIG. 2). Primary human monocytes express constitutively active caspase 1 (REF. 62), and hence inflammasome activation in these cells is not needed to process pro-IL-1β[63]. Neutrophil-derived serine proteases such as proteinase 3 can also cleave pro-IL-1β[64,65]. As neutrophils are the main cellular component in inflammatory infiltrates in the tissues during disseminated candidiasis[66], these enzymes may account for the generation of active IL-1β during the initial stages of *Candida* infection[67]. Indeed, neutrophil-derived proteinase 3, rather than caspase 1, is likely to have an important role in protecting mice against disseminated candidiasis[68]. Finally, during infection with *C. albicans*, a fungus-derived protease can lead to the processing and activation of host-derived pro-IL-1β and thus can activate of the immune system[69] (FIG. 2).

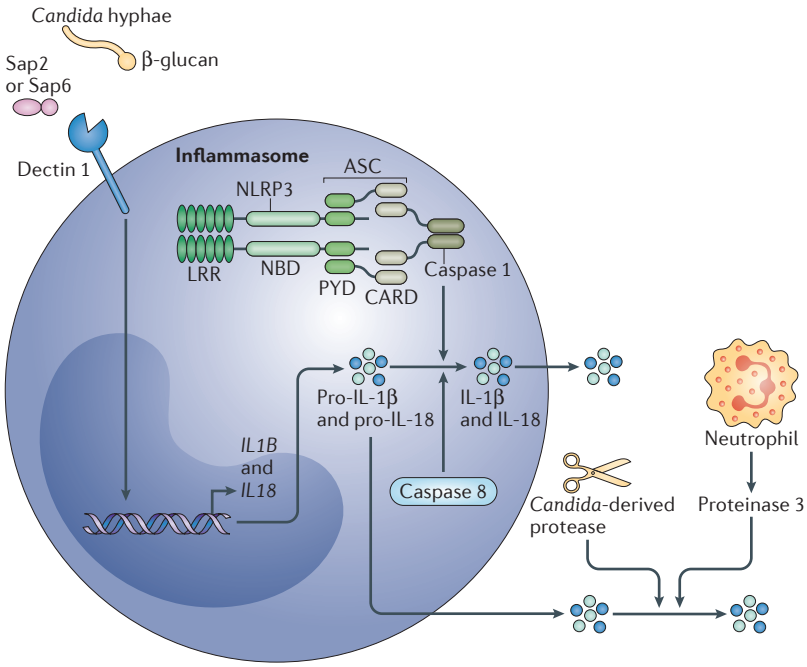


Figure 2 | **Interleukin-1β processing during *Candida* infection.** Activation of NOD-, LRR- and pyrin domain (PYD)-containing protein 3 (NLRP3) by *Candida* hyphae or secreted aspartic protease (Sap) proteins triggers the assembly of the inflammasome with subsequent activation of caspase 1, which cleaves pro-interleukin-1β (pro-IL-1β) and pro-IL-18 into bioactive cytokines. In addition, caspase 8 has also been demonstrated to cleave pro-IL-1β into active IL-1β in response to *Candida*. When pro-IL-1β is released in the inflammatory environment where neutrophils are present, it can also be cleaved into bioactive IL-1β by neutrophil-derived serine proteases, such as proteinase 3. *Candida* itself can also contribute to IL-1β activity as it can release proteases that cleave pro-IL-1β. CARD, caspase activation and recruitment domain; NBD, nucleotide-binding domain.

Recognition of yeasts versus hyphae

The capacity to undergo reversible yeast to hyphae morphogenesis is linked to the virulence of *C. albicans*[53,70]. Studies of differences in the stimulation of cytokines by yeasts and hyphae have shown that hyphae are incapable of inducing IL-12 expression in DCs, resulting in a tolerant phenotype[71], and this was attributed to the lack of TLR4-mediated recognition of the hyphae[72]. In addition, the differential exposure of β-glucans on the surface of yeasts and hyphae has been proposed to account for differences in stimulation of cytokines, with β-glucans being exposed on the bud scars of yeasts but not on hyphae[73]. However, other studies suggest that recognition of hyphal β-glucans can still be mediated by dectin 1, perhaps due to the shorter and less abundant mannan fibrils on the surface of hyphae[54]. The loss of shielding by mannans and thus the exposure of other immunostimulatory PAMPs could account for the difference in inflammasome activation by hyphae and yeast in tissue macrophages. Strikingly, inflammasome activation is induced by *Candida* hyphae but not yeasts. This reflects an important mechanism of discrimination between colonization and invasion[53]. Finally, differential recognition of mannans from hyphae and yeasts by dectin 2 has been proposed[34], but not fully confirmed, in additional studies[33]. Newer data suggest that the chemistry of cell wall polysaccharides differs significantly between *C. albicans* yeasts and hyphae, and this may add an additional mode of discrimination[5].

When considering the importance of the dimorphism between yeast and hyphae for the virulence of *Candida* species, it should be mentioned that *C. glabrata* is an exception, as it does not germinate into hyphae but

yet is virulent. Much remains to be learned about the particularities of the infection by *C. glabrata* and about the immune response to this pathogen (for a review of this topic see REF. 74).

Effector mechanisms of defence

After the initial recognition of fungal PAMPs by the various families of PRRs, a chain of effector mechanisms is initiated that ultimately leads to the clearance of the invading fungi (FIG. 3). Below, we summarize the immune and non-immune cell populations that contribute to the antifungal response.

Epithelial cells. An intact epithelium and endothelium constitute important mechanical barriers against tissue invasion by fungi. Tissue invasion is associated with morphological changes from yeast into hyphae, with *Candida* hyphae penetrating the epithelial cells through two distinct mechanisms: induced endocytosis and active penetration. Epithelial cells respond to *Candida* species colonization through a TLR4-dependent mechanism[75]. This leads to the activation of NF-κB and JUN (also known as AP-1), and this response is independent of fungal morphology. By contrast, when *Candida* germinates and forms hyphae it also activates mitogen-activated protein kinase 1 (MAPK1) and FOS signalling in epithelial cells, a mechanism that permits sensing of tissue invasion[76,77]. It remains to be determined which *Candida* cell wall components and which host receptors are important for mediating these different epithelial cell responses to yeasts and hyphae. Activation of the second phase of the response is accompanied by the release of pro-inflammatory cytokines and initiation of a host response. In addition, epithelial cells contribute to controlling the commensal state of *Candida* by producing β-defensins, which have potent antifungal activity, in response to the IL-22 that is released by T_H17 cells or innate lymphoid cells (ILCs)[78,79].

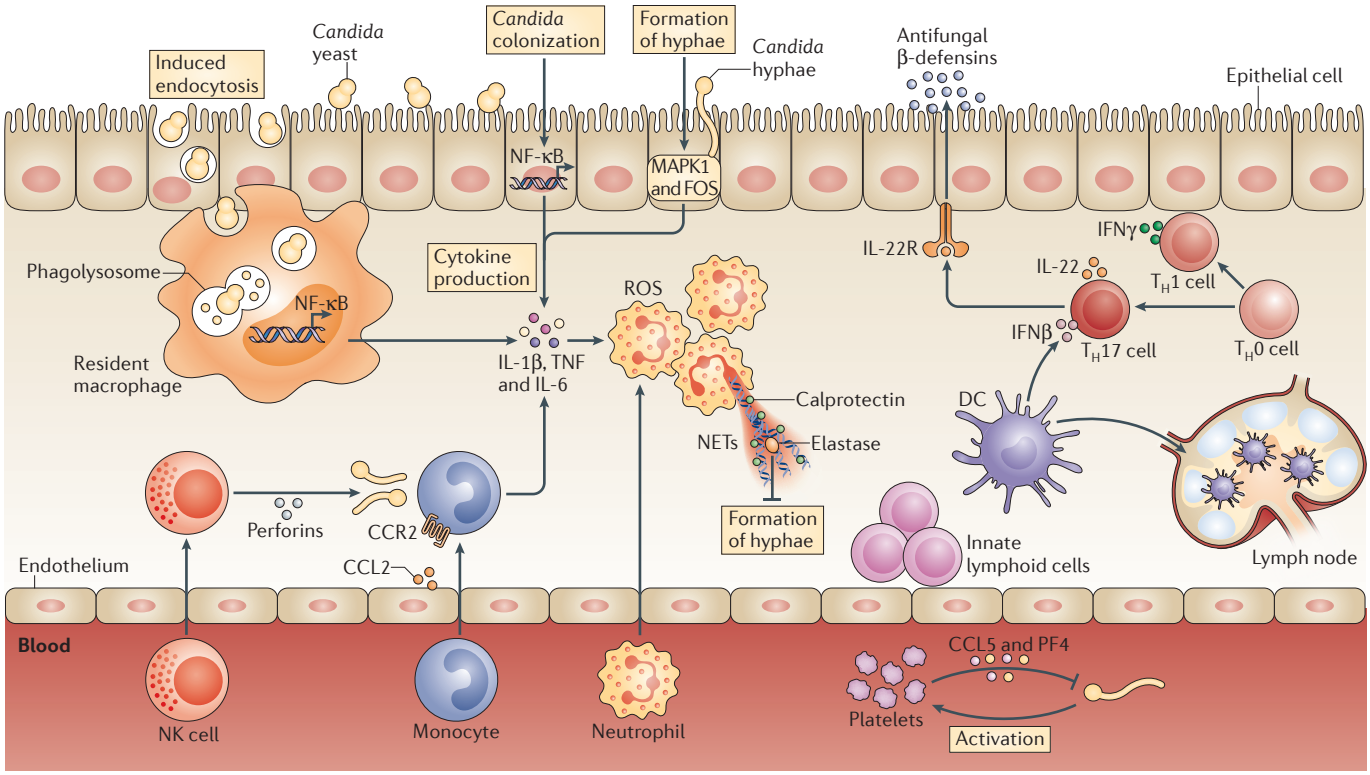


Figure 3 | **Effector mechanisms for the clearance of *Candida*.** The epithelium provides a mechanical barrier against invading *Candida*. However, *Candida* can invade the tissue by inducing endocytosis or actively penetrating the epithelial cells. Epithelial cells produce cytokines via a mitogen-activated protein kinase 1 (MAPK1)- and FOS-dependent pathway when *Candida* hyphae are present, which leads to the recruitment of phagocytic immune cells. Epithelial cells can also respond by producing β-defensins that have direct anti-*Candida* activity. After *Candida* has penetrated the tissue, it will first encounter the tissue resident-macrophages, which will phagocytose and clear *Candida*. Upon invasion, neutrophils are recruited by pro-inflammatory cytokines produced by macrophages and epithelial cells. In addition to their capacity to kill *Candida* by phagocytosis and the production of reactive oxygen species (ROS), neutrophils can also release neutrophil extracellular traps (NETs) that capture *Candida* conidia and hyphae and contain antimicrobial proteins such as calprotectin that inhibit fungal growth. Inflammatory monocytes are also recruited to the site of infection via CC-chemokine ligand 2 (CCL2) and will contribute to clearing *Candida*. Dendritic cells (DCs) can migrate to the lymph nodes and contribute by shaping adaptive T helper (T_H) cell responses. T_H17 cell responses have an important role in mucosal host defences against *Candida* by producing interleukin-17 (IL-17) that recruits and activates neutrophils, and IL-22 that induces the secretion of β-defensins. T_H1 cell-derived interferon-γ (IFNγ) strongly activates phagocytic cells. Innate lymphoid cells also have the capacity to produce pro-inflammatory cytokines and contribute to mucosal antifungal defence. The last step of *Candida* invasion is breach of the endothelium, allowing access to the bloodstream. In addition to neutrophils, systemic *Candida* can activate platelets that can produce CCL5 and platelet factor 4 (PF4), which both have anti-*Candida* activity. CCR2, CC-chemokine receptor 2; IL-22R, IL-22 receptor; NF-κB, nuclear factor-κB; NK, natural killer; TNF, tumour necrosis factor.

Monocytes and macrophages. Tissue-resident macrophages are key effector cells that function in antifungal defence. These macrophages produce inflammatory cytokines and chemokines that recruit and activate other immune cells at the site of infection (FIG. 3). The relevance of the macrophage lineage for anti-*Candida* host defence was demonstrated by early *in vivo* studies in macrophage-depleted mice; these animals showed accelerated fungal proliferation in tissues and increased mortality[80]. By contrast, neutrophil depletion in the blood did not reverse inhibition of *Candida* growth in the blood[81], despite the important role that neutrophils have in the elimination of the fungus in organs (see below). Therefore, tissue-resident macrophages exert potent candidacidal activity[81,82].

Blood monocytes are also recruited to the infected tissue where they differentiate into inflammatory macrophages. In mice deficient in CX_3C-chemokine receptor 1 (CX_3CR1), impaired accumulation of monocyte-derived macrophages in the kidney leads to renal failure and death[82]. Moreover, patients with a polymorphism leading to a decreased CX_3CR1 function are more susceptible to disseminated candidiasis[82], whereas their susceptibility to mucosal *Candida* infections is not affected[83]. Furthermore, both human blood classical $CD14^{hi}CD16^{-}$ monocytes and non-classical $CD14^{+}CD16^{low}$ monocytes have candidacidal activity[84], and deficiency of CC-chemokine receptor 2 (CCR2; which is essential for monocyte recruitment to inflamed tissues) leads to increased susceptibility to disseminated candidiasis[81]. These data highlight the essential role of monocytes and macrophages in controlling disseminated fungal infection.

Neutrophils. Neutrophils are of major importance in host defence against *Candida* infections. Activated epithelial cells and tissue-resident macrophages release chemokines that recruit neutrophils to the site of fungal infection[37]. Neutrophil activation is essential for clearance of *Candida*, with neutropenia being a major risk factor for invasive fungal infections[85,86]. Neutrophils are the most potent killers of *Candida* and are the only host cells that are capable of successfully inhibiting the germination of *Candida* yeasts into hyphae[87]. Neutropenic mouse models have clearly demonstrated the crucial role of neutrophils in disseminated fungal infection[66].

Neutrophils use both oxidative and non-oxidative effector mechanisms to kill *Candida*[88]. Although both mouse and human granulocytes that are deficient in either NADPH oxidase or myeloperoxidase (MPO) are incapable of efficient *Candida* killing *in vitro*[89,90], NADPH oxidase deficiency in patients with chronic granulomatous disease is associated with significantly increased susceptibility to invasive mould infection, but it has little effect on susceptibility to *Candida* infection. This suggests that alternative mechanisms *in vivo* can compensate for a defect in NADPH oxidase-dependent killing mechanisms. Similarly, MPO deficiency in humans does not predispose to *Candida* infection, unless there are concomitant risk factors (such as diabetes)[91].

In addition to ROS, neutrophils also use non-oxidative mechanisms to kill *Candida*; they produce antimicrobial factors such as lysozyme, lactoferrin, elastase, β-defensins, gelatinases and cathepsin G[92]. Neutrophil elastase and cathepsin B have been described to have antifungal activity, and elastase was found to contribute to the release of NETs that form large DNA-containing fibril structures[93]. These fibrils bind and neutralize pathogens, providing a mechanism to combat hyphae that are too big to be phagocytosed[94]. Calprotectin was also identified as an important component of NETs[95], and NET formation induces the release of antimicrobial substances (for example, MPO, lactoferrin, azurocidin and cathelicidin) from the granules of the neutrophils. Proteinase 3 derived from these cells cleaves cathelicidin into the antimicrobial peptide LL-37 (also known as CAMP)[96], which has a number of antimicrobial effects: it promotes disruption of the fungal cell membrane[97,98], inhibition of biofilm formation and fungal adhesion[99], enhanced chemotaxis, production of ROS and inhibition of neutrophil apoptosis[100,101]. Very recently, it has been shown that simultaneous exposure of *Candida* to oxidative and cationic stresses synergizes with the fungicidal capacity of human neutrophils[102]. With regard to the role of autophagy, a process by which cells can clear unwanted cytosolic content, there is some controversy. Although an initial study reported that mice deficient in autophagy are more susceptible to *Candida* infection[103], recent studies have shown that autophagy is most likely to be redundant in host defence against *Candida*[104,105].

The receptor pathways that lead to *Candida* killing by neutrophils have recently been elucidated. The ROS-dependent mechanisms that are needed for clearance of opsonized *Candida* depend on FcγRs and protein kinase C, whereas the ROS-independent pathway— which is important for killing unopsonized *Candida* — relies on CR3 ligation and CARD9 recruitment[30]. Interestingly, dectin 1 is dispensable for both of these mechanisms. A recent study demonstrated that glycosylation of proteins is important for the fungicidal function of neutrophils: defects in the Jagunal homologue 1 protein result in impaired responses to *C. albicans* and an increased susceptibility to infection[106].

Natural killer cells. In addition to neutrophils, monocytes and macrophages, natural killer (NK) cells contribute to the rapid innate immune response against invading pathogens. Depletion of NK cells had variable results in mouse models of *Candida*, with either a lack of effect[107] or an increase in susceptibility to disseminated candidiasis[12]. The additional depletion of NK cells in lymphocyte-deficient severe combined immunodeficiency (SCID) mice increased the susceptibility to systemic candidiasis, whereas such depletion had no effect in immunocompetent mice[108]. Although NK cells do not inhibit hyphal growth of *Candida*, perforin-dependent antifungal activity by NK cells has been reported[109].

Activation of a potent innate immune response by epithelial cells and phagocytic cells, possibly aided by NK cells, is in most cases enough to counteract displacement of *Candida* species from surface colonization to tissue invasion and to prevent a disseminated infection. However, for situations in which the infection is not promptly controlled by the innate immune mechanisms, adaptive immunity is activated to establish an additional layer of defence.

DCs and activation of T cells. DCs have been shown to be essential for the host response against *Candida* species through their production of IFNβ via a SYK- and IFN-regulatory factor 5 (IRF5)-dependent pathway[110–112]. Although DCs can also ingest and kill *Candida* species, they are less efficient than macrophages at fungal killing[113]. Instead, DCs are important for processing and presenting fungal antigens for the activation of T_H cell responses.

Candida-specific T_H cells in humans were found to produce a combination of IL-17 and IFNγ[114]. The importance of T_H1 cell responses and IFNγ production for the fungicidal activities of both neutrophils[115] and macrophages[116] is well established. IFNγ-deficient mice are more susceptible to disseminated candidiasis, as are mice defective in the pro-inflammatory cytokine IL-18, which induces T_H1 cell responses[117]. Treatment of mice with either recombinant IFNγ[118] or IL-18 (REF. 119) protects them against systemic candidiasis. In line with this, a recent proof-of-principle trial in patients with systemic candidiasis demonstrated improvement of immunological parameters after treatment with recombinant IFNγ[120].

T_H17 cell production of IL-17 and IL-22 is also important for host defence against *Candida* species. These cytokines induce neutrophil recruitment and activation, and are responsible for the activation of epithelial cells and the release of antifungal β-defensins[78], often in a cooperative manner[121]. Several studies have shown that mice deficient in IL-17 signalling are more susceptible to both systemic candidiasis[122,123] and mucosal infections[124]. However, patients with a deficiency of IL-17 production or signalling owing to mutations in *IL-17F*, *IL17RA* (which encodes IL-17 receptor A), *DECTIN1*, *STAT1* (which encodes signal transducer and activator of transcription 1) or *STAT3* suffer from mucosal candidiasis but not invasive candidiasis. This suggests that in humans, T_H17 cell responses are mainly necessary for mucosal antifungal responses[25,125–128]. T_H17 cells also seem to be less important for the control of vaginal candidiasis than for the control of other forms of mucosal infection. In mice, the recruitment of neutrophils in response to vaginal epithelial cell-mediated production of S100 alarmins was found to be independent of IL-17 production[129], and patients with defects in T_H17 cell responses do not suffer from recurrent vulvovaginal candidiasis[126,130]. Moreover, the importance of IL-17 for the host defence against *Candida* infections has been underlined by the increased number of infectious complications seen in patients with psoriasis who have been treated with IL-17A-targeted antibodies[131].

In contrast to these T_H1- and T_H17-type immune responses that are important for a protective host response to *Candida* species, cytokines associated with T_H2-type immunity have been shown to have conflicting roles. On the one hand, therapeutic ablation of IL-4 or IL-10 signalling in wild-type mice increased their resistance to systemic candidiasis[132], and IL-10-deficient mice showed greater resistance to candidiasis, suggesting a detrimental role for these cytokines[133,134]. On the other hand, other studies showed that IL-4 is necessary for the development of a protective host response to *Candida* infection[135] and that early IL-10 production contributes to the development of protective T_H1 cell responses in IL-12-deficient mice[136].

Antifungal roles for ILCs. In addition to the classical T_H cell subsets, the recently described group of ILCs may also contribute to immunity to *Candida* species (FIG. 3). Three groups of ILCs have been proposed: ILC1s that express T-bet and produce IFNγ; ILC2s that express GATA-binding protein 3 (GATA3) and produce IL-5 and IL-13; and ILC3s that express nuclear receptor RORγt and produce IL-17 and IL-22 (REF. 136). Evidence that ILCs may help to control fungal infection and colonization came from experimental mouse models of mucosal infections, in which fungal control of oral candidiasis was found to be mediated by IL-17-secreting ILCs. Both ILC-depleted *Rag1*$^{-/-}$ mice (which lack expression of recombination activating gene 1) and *Rorc*$^{-/-}$ ILC-deficient mice failed to control mucosal *Candida* infection[137]. However, it is still unclear how ILCs contribute to the immune response during invasive fungal infections. In addition to the ILCs, other 'innate-like' lymphocyte subpopulations may have a role in host defence against *Candida* species, especially at the level of skin and mucosa; γδ T cells are one such cell type that releases protective IL-17 (REF. 138).

Humoral antifungal mechanisms. Humoral immune mechanisms have also been suggested to be involved for host defence against *Candida* infections, although their contribution to antifungal defence is likely to be more modest than the cellular mechanisms discussed above. Although activated complement cannot kill *Candida* hyphae during infection, it can contribute to the induction of a proper cytokine response[139]. Mice with a deficiency of either complement factor C3 or C5 exhibit increased mortality as a consequence of impaired anti-*Candida* resistance or excessive exuberant infection-driven immunopathology, respectively[140,141]. The impact of B cells and antibodies on host defence against *Candida* species is less clear. Although patients with agammaglobulinaemia or hypogammaglobulinaemia do not suffer from an increased susceptibility to fungal infection, eliciting protective antibodies through vaccination has been proposed as a viable strategy for improving resistance to infection[142–145].

Platelets. Less well-appreciated players in antifungal host defence are platelets. When *C. albicans* are injected into mice, the fungi bind and activate platelets in the bloodstream[146]. Platelets produce immune mediators

such as CC-chemokine ligand 5 (CCL5; also known as RANTES) and platelet factor 4, which have antimicrobial activity against *Candida* species, and platelet-rich plasma inhibits the growth of *Candida*[147]. More studies are needed to fully decipher the role of platelets in antifungal host defence.

Compartmentalized response to Candida species. In summary, the host defence response against *Candida* infections is complex and involves a cascade of mechanisms. The initial recognition of fungi by epithelial cells and tissue macrophages promotes inflammation and innate immune cell activation, and breach of epithelial barriers leads to antigen presentation and the induction of specific antifungal lymphocyte responses. Innate immune mechanisms are crucial for host defence against both mucosal and systemic candidiasis, whereas adaptive host defences are mainly involved in mucosal anti-*Candida* responses. However, one has to be aware of the often compartmentalized nature of the immune responses: whereas adaptive T cell responses are crucial for anti-*Candida* defence at the level of the intestinal mucosa, these cells have a much more restricted role in host defence in the vaginal mucosa[148]. Although the vast majority of the studies have been performed with *C. albicans*, similar mechanisms have also been described for other *Candida* species: although this is not the focus of this Review, other very good recent papers have described these mechanisms in detail (for reviews, see REFS 149,150).

Evasion of host defences by *Candida*

Although the host immune system is generally very efficient in keeping fungal infections at bay, *Candida* species have developed strategies to escape clearance by the immune system. One mechanism involves the shielding of PAMPs that are capable of eliciting an immune response. *C. albicans* hyphae are less inflammatory than the yeast forms, and this is thought to be due to the shielding of β-glucans from the surface of hyphae by mannans[73]. These findings also demonstrate how morphogenetic changes that occur in *Candida* species may modulate the immune response to the advantage of the fungus[72].

Candida species are also capable of inhibiting phagolysosome maturation and the production of nitric oxide by macrophages[151], although the precise molecular mechanisms underlying these effects still need to be investigated. Furthermore, *C. albicans* can enhance its survival by inducing macrophages to switch from a more inflammatory M1 phenotype to a less inflammatory M2 macrophage phenotype[152]. Interestingly, *Candida* species can also hijack certain PRR pathways. For example, *Candida*-mediated activation of TLR2 can induce immunomodulatory signals that promote a tolerogenic DC profile[153] and the proliferation of regulatory T cells[154]. Understanding these evasion strategies that interfere with successful clearance of the fungus could guide the way for the development of novel therapeutic approaches.

Insights from functional genomics

In the past decade, novel technologies such as genomics, proteomics, metabolomics and transcriptomics, as well as advances in computational analyses, have led to a better understanding of the host immune response to *Candida* infections[155].

Comparisons of RNA profiles in the blood of mice infected with *C. albicans* have shown that certain inflammatory pathways (TLR4–MYD88, inflammasome and STAT3 pathways) are activated throughout all phases of infection, whereas other pathways characterize specific phases of the infection, such as caspase 3-dependent apoptosis in the late phase[156]. Assessment of transcriptional profiles induced by *C. albicans* in bone marrow-derived macrophages identified host–pathogen modules, such as *MTA2–Hap3*, that drive host IL-2 and IL-4 production[157]. Using an elegant combination of transcriptome and functional validation experiments, the same study also identified pentraxin-related protein PTX3 as an important modulator of antifungal host defence[157]. In humans, assessment of the transcriptome profile in vascular endothelial cells after stimulation with *C. albicans* revealed that chemotaxis, angiogenesis and inhibition of apoptosis were among the main processes induced[158]. By contrast, the interaction between *C. albicans* and human granulocytes induced genes involved in cell–cell signalling, cell signal transduction and cell growth[159]. A recent study compared the transcriptome induced by stimulation with *C. albicans* and different bacterial stimuli in human blood mononuclear cells: surprisingly, a strong type I IFN signature was identified to be specific for *Candida* stimulation[160]. This relatively unexpected finding was validated by genetic and functional studies and supported by independent studies in mouse models[111,161]. Finally, transcriptome studies have also been performed in epithelial cells stimulated with *Candida albicans*: these studies reported early expression in epithelial cells of genes that are involved in immune pathways. These genes included components of immune signalling pathways, such as the NF-κB, MAPK and phosphoinositide 3-kinase (PI3K)–AKT pathways[162], as well as chemokines and adhesion molecules[163].

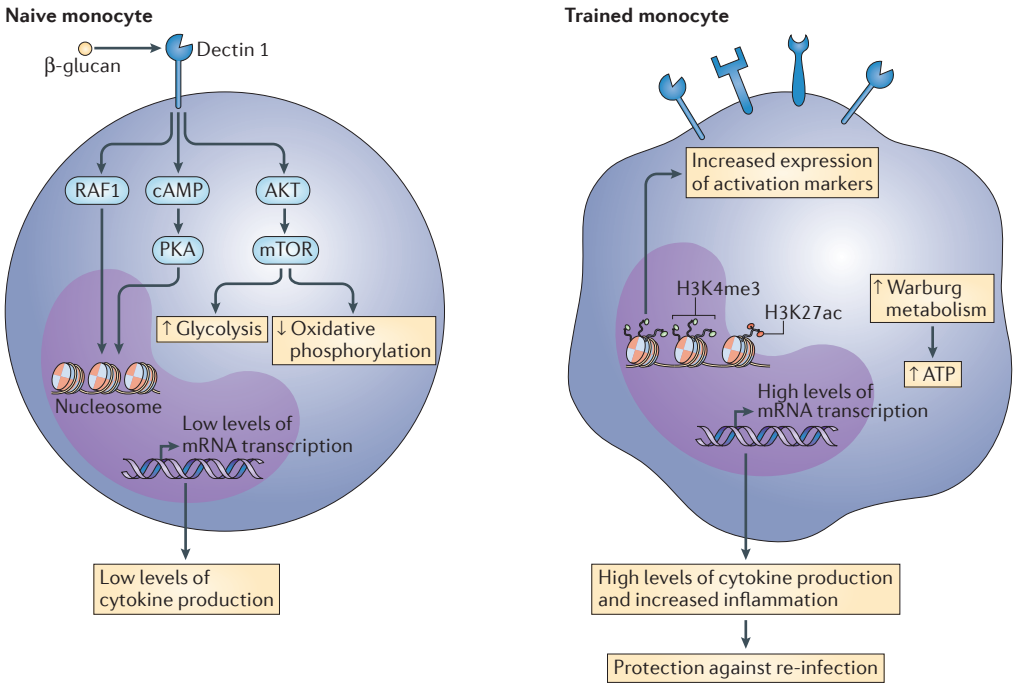
Although genome-wide association studies (GWASs) have been a part of mainstream genetic research for almost a decade, comprehensive genetic studies in individuals with *Candida* infections have been notoriously scarce. Recently, the first GWAS on a fungal infection has been published. This study of patients with candidemia reports an association with three genes that were not previously known to be involved in antifungal defence: *CD58*, *TAGAP* (which encodes T cell activation RHO-GTPase-activating protein) and *LCE4A* (which encodes late cornified envelope 4A)[164]. CD58 has been shown to be involved in the inhibition of *Candida* germination, whereas TAGAP influences cytokine production induced by the fungus. In the same cohort of patients, genetic variation in *MDA5* was subsequently demonstrated to also influence susceptibility to candidiasis[48].

The microbiome–immune response interaction

It is becoming clear that other components of the host microbiota also affect fungal colonization and the antifungal immune response. Metagenomic analysis showed that the human microbiome contains bacterial, fungal and viral communities that vary significantly by body site and across individuals[165]. A first insight into this complex interaction is highlighted by the skin microbiome of patients with primary immunodeficiencies. The microbiome of patients with chronic mucocutaneous candidiasis showed a significant reduction in the prevalence of species that normally colonize the skin (such as *Corynebacterium* species) and an increased prevalence of Gram-negative bacteria (such as *Acinetobacter* species); these changes were associated with a suppressed cytokine response to *C. albicans*[166]. By contrast, *Pseudomonas aeruginosa* and *Enterococcus faecalis* inhibit hyphal growth of *C. albicans*[167], whereas H_2O_2 and bacteriocin-like compounds released by lactobacilli inhibit fungal adhesion and growth[168]. In addition, the interaction between *C. albicans* and streptococci has been suggested to contribute to the colonization of the oral cavity by *C. albicans*[169]. Fungi themselves belong to the 'rare biosphere' (REF. 170), which functions as a reservoir for potentially pathogenic microorganisms and can expand when the environment is disturbed or when the host is immunocompromised[171]. In the setting of dectin 1 deficiency, the mycobiome of the gut in mice is significantly altered, and this was associated with increased susceptibility to experimental colitis[172]. The microbiota can also influence the immune

Box 1 | **The relevance of trained immunity for host defence and human pathology**

The biological relevance of trained immunity as a fundamental process of immune responses is multifold. First, this concept shows that the dichotomy between innate immunity and adaptive immunity is too simple, and that during evolution the innate component of the immune system has developed characteristics that are more typically associated with adaptive immunity. Indeed, innate immune memory probably evolved before adaptive immunity and remained functional despite the development of the latter. Second, the concept is most likely fundamental for a comprehensive understanding of host defence on the one hand, and immunopathology of inflammatory diseases on the other hand[186,187]. Third, the trained immunity concept may be relevant for vaccine development. Epidemiological studies have shown that bacille Calmette–Guérin (BCG) vaccine displays important protective nonspecific vaccine effects[188]. The relevance of trained immunity effects induced by β-glucan can be also discerned in its use as an immunotherapeutic agent against cancer[189], and this effect could be potentially used to revert other forms of 'immunoparalysis' such as that in severe sepsis. Conversely, inhibition of trained immunity may be relevant for therapy of atherogenesis and other inflammatory disorders. In the depiction of trained immunity, naive monocytes produce moderate amounts of cytokines, and before stimulation, they rely mainly on oxidative phosphorylation for the metabolism of glucose. The recognition of *Candida albicans* by dectin 1 induces both immunological signals through RAF1 and cAMP that lead to epigenetic reprogramming, and metabolic stimulation through AKT and mammalian target of rapamycin (mTOR). As a result, the *Candida*-trained cells shift their metabolism towards aerobic glycolysis (a process known as the Warburg effect), with increased ATP synthesis and a stronger inflammatory phenotype.



H3K4me3, histone 3 lysine 4 trimethylation; H3K27ac, histone 3 lysine 27 acetylation; PKA, protein kinase A.

system through the release of metabolites. Tryptophan metabolites produced by lactobacilli in the gut induce IL-22 production from NKp46^{+}NK1.1^{low} cells via the aryl hydrocarbon receptor (AHR)[173]. IL-22 provides resistance to *C. albicans* colonization at mucosal surfaces. In addition, lactobacilli can produce short-chain fatty acids that can inhibit fungal growth[174] and — via G protein-coupled receptors such as GPR41 and GPR43 — modulate host immune responses[175,176]. Therefore, changes in the microbiome might have a dramatic impact on *Candida*-induced host immune responses and disease severity[177–179].

Trained immunity in the response to *Candida*

Studies performed more than two decades ago reported that infection of mice with an attenuated *C. albicans* strain provided protection against lethal invasive candidiasis in a T cell-independent but macrophage-dependent manner[180,181]. This unexpected 'innate memory' response has been referred to as 'trained immunity', and it has recently been demonstrated to be mediated by epigenetic reprogramming in innate immune cells (see the figure in BOX 1)[182].

C. albicans and β-glucans induce trained immunity through ligation of dectin 1 and activation of the non-canonical RAF1 signalling pathway, which leads to stable changes in histone methylation and acetylation[183]. In this way, the capacity of monocytes and macrophages to produce pro-inflammatory cytokines is enhanced[183]. The induction of trained immunity by β-glucans is dependent on a pathway mediated by AKT, mammalian target of rapamycin (mTOR) and hypoxia-inducible factor 1α (HIF1α), and on a switch of glucose metabolism from oxidative phosphorylation to aerobic glycolysis[184]. The clinical relevance of trained immunity for antifungal host defence has recently been suggested by the report of defective trained immunity in patients with chronic mucocutaneous candidiasis who are deficient for STAT1 (REF. 185).

Conclusions and future perspectives

In conclusion, the past decade has witnessed a marked improvement in our understanding of the molecular and immunological mechanisms that lead to the induction of an efficient antifungal immune response. The discovery of PRRs has greatly increased our knowledge of the innate immune response, and the specific roles of T_H cell subsets for systemic or mucosal immunity to *Candida* have become apparent. Moreover, the recent descriptions of patients with dectin 1 or CARD9 deficiency and those with defective T_H17-type immune responses have underlined the crucial role of these responses for mucosal immunity to fungal pathogens.

In which areas will the main discoveries occur in the coming years? First of all, additional efforts are being made to characterize the genetic mutations that are responsible for the development of severe forms of *Candida* infection in patients for which no genetic defects have yet been identified. Second, the ongoing recruitment of large cohorts of patients with both invasive candidiasis and recurrent vulvovaginal candidiasis is expected to lead to a much more detailed and precise understanding of how common genetic variability in PRRs affects susceptibility to disseminated disease. Third, an increased understanding of the immunological, cellular and molecular pathways responsible for activation of host defence will be obtained both by refining our molecular research armamentarium and by improving analyses of 'omics' data through systems biology. With regard to metagenomics, we are only at the very beginning of understanding the complex interplay between bacteria, fungi and the human host, and understanding the implications of this interplay for health and disease. Another exciting area of new research is that of epigenomics. The concept of trained immunity, which is epigenetically determined, will enable us to learn how to modulate the immune response to greater benefit of patients. We should thus expect that further research in the field may lead to novel discoveries and new therapies that will have an important impact on the treatment of fungal infections.

1. Brown, G. D., Denning, D. W. & Levitz, S. M. Tackling human fungal infections. *Science* **336**, 647 (2012).
2. Gudlaugsson, O. *et al.* Attributable mortality of nosocomial candidemia, revisited. *Clin. Infect. Dis.* **37**, 1172–1177 (2003).
3. Wisplinghoff, H. *et al.* Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin. Infect. Dis.* **39**, 309–317 (2004).
4. Shibata, N., Suzuki, A., Kobayashi, H. & Okawa, Y. Chemical structure of the cell-wall mannan of *Candida albicans* serotype A and its difference in yeast and hyphal forms. *Biochem. J.* **404**, 365–372 (2007).
5. Lowman, D. W. *et al.* Novel structural features in *Candida albicans* hyphal glucan provide a basis for differential innate immune recognition of hyphae versus yeast. *J. Biol. Chem.* **289**, 3432–3443 (2014).
6. Munro, C. A., Schofield, D. A., Gooday, G. W. & Gow, N. A. Regulation of chitin synthesis during dimorphic growth of *Candida albicans*. *Microbiol.* **144**, 391–401 (1998).
7. Naglik, J. *Candida* immunity. *New J. Sci.* **1**, 1–27 (2014).
8. Davis, S. E. *et al.* Masking of β(1-3)-glucan in the cell wall of *Candida albicans* from detection by innate immune cells depends on phosphatidylserine. *Infect. Immun.* **82**, 4405–4413 (2014).
9. Brown, G. D. & Gordon, S. Immune recognition. A new receptor for β-glucans. *Nature* **413**, 36–37 (2001). **This study was the first to describe a specific CLR for the recognition of fungal β-glucans, which are a crucial component of the *C. albicans* cell wall.**
10. Goodridge, H. S. *et al.* Activation of the innate immune receptor Dectin-1 upon formation of a 'phagocytic synapse'. *Nature* **472**, 471–475 (2011).
11. Brown, G. D. *et al.* Dectin-1 is a major β-glucan receptor on macrophages. *J. Exp. Med.***196**, 407–412 (2002).
12. Whitney, P. G. *et al.* Syk signaling in dendritic cells orchestrates innate resistance to systemic fungal infection. *PLoS Pathog.* **10**, e1004276 (2014).
13. Bishu, S. *et al.* The adaptor CARD9 is required for adaptive but not innate immunity to oral mucosal *Candida albicans* infections. *Infect. Immun.* **82**, 1173–1180 (2014).
14. Gross, O. *et al.* Card9 controls a non-TLR signalling pathway for innate anti-fungal immunity. *Nature* **442**, 651–656 (2006).
15. Glocker, E. O. *et al.* A homozygous *CARD9* mutation in a family with susceptibility to fungal infections. *N. Engl. J. Med.***361**, 1727–1735 (2009). **References 13–15 describe the function of CARD9, the main adaptor molecule for several important CLRs, and reported the CARD9 primary immunodeficiency, which leads to very severe disseminated *Candida* infections.**
16. Strasser, D. *et al.* Syk kinase-coupled C-type lectin receptors engage protein kinase C-σ to elicit Card9 adaptor-mediated innate immunity. *Immunity* **36**, 32–42 (2012).
17. Gringhuis, S. I. *et al.* Dectin-1 directs T helper cell differentiation by controlling noncanonical NF-κB activation through Raf-1 and Syk. *Nat. Immunol.* **10**, 203–213 (2009).
18. Brown, G. D. *et al.* Dectin-1 mediates the biological effects of β-glucans. *J. Exp. Med.* **197**, 1119–1124 (2003).
19. Ferwerda, G., Meyer-Wentrup, F., Kullberg, B. J., Netea, M. G. & Adema, G. J. Dectin-1 synergizes with TLR2 and TLR4 for cytokine production in human primary monocytes and macrophages. *Cell. Microbiol.* **10**, 2058–2066 (2008).
20. Gantner, B. N., Simmons, R. M., Canavera, S. J., Akira, S. & Underhill, D. M. Collaborative induction of inflammatory responses by dectin-1 and Toll-like receptor 2. *J. Exp. Med.* **197**, 1107–1117 (2003).
21. Branzk, N. *et al.* Neutrophils sense microbe size and selectively release neutrophil extracellular traps in response to large pathogens. *Nat. Immunol.* **5**, 1017–1025 (2014).
22. Marakalala, M. J. *et al.* Differential adaptation of *Candida albicans in vivo* modulates immune recognition by dectin-1. *PLoS Pathog.* **9**, e1003315 (2013).

23. Cunha, C., Aversa, F., Romani, L. & Carvalho, A. Human genetic susceptibility to invasive aspergillosis. *PLoS Pathog.* **9**, e1003434 (2013).
24. Smeekens, S. P., van de Veerdonk, F. L., Kullberg, B. J. & Netea, M. G. Genetic susceptibility to *Candida* infections. *EMBO Mol. Med.* **5**, 805–813 (2013).
25. Ferwerda, B. *et al.* Human dectin-1 deficiency and mucocutaneous fungal infections. *N. Engl. J. Med.* **361**, 1760–1767 (2009).
26. De Luca, A. *et al.* IL-22 and IDO1 affect immunity and tolerance to murine and human vaginal candidiasis. *PLoS Pathog.* **9**, e1003486 (2013).
27. Drewniak, A. *et al.* Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency. *Blood* **121**, 2385–2392 (2013).
28. Drummond, R. A., Saijo, S., Iwakura, Y. & Brown, G. D. The role of Syk/CARD9 coupled C-type lectins in antifungal immunity. *Eur. J. Immunol.* **41**, 276–281 (2011).
29. van Bruggen, R. *et al.* Complement receptor 3, not Dectin-1, is the major receptor on human neutrophils for β-glucan-bearing particles. *Mol. Immunol.* **47**, 575–581 (2009).
30. Gazendam, R. P. *et al.* Two independent killing mechanisms of *Candida albicans* by human neutrophils: evidence from innate immunity defects. *Blood* **124**, 590–597 (2014).
31. Smeekens, S. P. *et al.* An anti-inflammatory property of *Candida albicans* β-glucan: Induction of high levels of interleukin-1 receptor antagonist via a Dectin-1/CR3 independent mechanism. *Cytokine* **71**, 215–222 (2015).
32. Hall, R. A. *et al.* The Mnn2 mannosyltransferase family modulates mannoprotein fibril length, immune recognition and virulence of *Candida albicans*. *PLoS Pathogens* **9**, e1003276 (2013).
33. Cambi, A. *et al.* Dendritic cell interaction with *Candida albicans* critically depends on *N*-linked mannan. *J. Biol. Chem.* **283**, 20590–20599 (2008).
34. Saijo, S. *et al.* Dectin-2 recognition of α-mannans and induction of Th17 cell differentiation is essential for host defense against *Candida albicans*. *Immunity* **32**, 681–691 (2010).
35. van de Veerdonk, F. L. *et al.* The macrophage mannose receptor induces IL-17 in response to *Candida albicans*. *Cell Host Microbe* **5**, 329–340 (2009).
This study described mannose receptor as an important receptor for *C. albicans* mannans that has a key role in the induction of protective T_H17 cell responses.
36. Yamasaki, S. *et al.* C-type lectin Mincle is an activating receptor for pathogenic fungus, *Malassezia*. *Proc. Natl Acad. Sci. USA* **106**, 1897–1902 (2009).
37. Netea, M. G., Brown, G. D., Kullberg, B. J. & Gow, N. A. An integrated model of the recognition of *Candida albicans* by the innate immune system. *Nat. Rev. Microbiol.* **6**, 67–78 (2008).
38. Ifrim, D. C. *et al.* Role of Dectin-2 for host defense against systemic infection with *Candida glabrata*. *Infect. Immun.* **82**, 1064–1073 (2014).
39. Zhu, L. L. *et al.* C-type lectin receptors Dectin-3 and Dectin-2 form a heterodimeric pattern-recognition receptor for host defense against fungal infection. *Immunity* **39**, 324–334 (2013).
40. Jouault, T. *et al.* Specific recognition of *Candida albicans* by macrophages requires galectin-3 to discriminate *Saccharomyces cerevisiae* and needs association with TLR2 for signaling. *J. Immunol.* **177**, 4679–4687 (2006).
41. Linden, J. R., De Paepe, M. E., Laforce-Nesbitt, S. S. & Bliss, J. M. Galectin-3 plays an important role in protection against disseminated candidiasis. *Med. Mycol.* **51**, 641–651 (2013).
42. Wells, C. A. *et al.* The macrophage-inducible C-type lectin, mincle, is an essential component of the innate immune response to *Candida albicans*. *J. Immunol.* **180**, 7404–7413 (2008).
43. Saevarsdottir, S., Vikingsdottir, T. & Valdimarsson, H. The potential role of mannan-binding lectin in the clearance of self-components including immune complexes. *Scand. J. Immunol.* **60**, 23–29 (2004).
44. Means, T. K. *et al.* Evolutionarily conserved recognition and innate immunity to fungal pathogens by the scavenger receptors SCARF1 and CD36. *J. Exp. Med.* **206**, 637–653 (2009).
45. Nahum, A., Dadi, H., Bates, A. & Roifman, C. M. The L412F variant of Toll-like receptor 3 (*TLR3*) is associated with cutaneous candidiasis, increased susceptibility to cytomegalovirus, and autoimmunity. *J. Allergy Clin. Immunol.* **127**, 528–531 (2011).
46. Wagener, J. *et al.* Fungal chitin dampens inflammation through IL-10 induction mediated by NOD2 and TLR9 activation. *PLoS Pathog.* **10**, e1004050 (2014).
47. Kato, H. *et al.* Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. *Nature* **441**, 101–105 (2006).
48. Jaeger, M. *et al.* The RIG-I-like helicase receptor MDA5 (*IFIH1*) is involved in the host defense against *Candida* infections. *Eur. J. Clin. Immunol. Infect. Dis.* **34**, 963–974 (2015).
49. Agostini, L. *et al.* NALP3 forms an IL-1β-processing inflammasome with increased activity in Muckle–Wells autoinflammatory disorder. *Immunity* **20**, 319–325 (2004).
50. Gross, O. *et al.* Syk kinase signalling couples to the Nlrp3 inflammasome for anti-fungal host defence. *Nature* **459**, 433–436 (2009).
This study is the first to describe the role of the inflammasome in antifungal host defence.
51. Hise, A. G. *et al.* An essential role for the NLRP3 inflammasome in host defense against the human fungal pathogen *Candida albicans*. *Cell Host Microbe* **5**, 487–497 (2009).
52. Joly, S. *et al.* Cutting edge: *Candida albicans* hyphae formation triggers activation of the Nlrp3 inflammasome. *J. Immunol.* **183**, 3578–3581 (2009).
53. Gow, N. A., van de Veerdonk, F. L., Brown, A. J. & Netea, M. G. *Candida albicans* morphogenesis and host defence: discriminating invasion from colonization. *Nat. Rev. Microbiol.* **10**, 112–122 (2012).
54. Cheng, S. C. *et al.* The dectin-1/inflammasome pathway is responsible for the induction of protective T-helper 17 responses that discriminate between yeasts and hyphae of *Candida albicans*. *J. Leuk. Biol.* **90**, 357–366 (2011).
This study proposes differential recognition of yeasts and hyphae by the inflammasome as an important mechanism for discrimination between colonization and invasion of mucosae.
55. Pietrella, D. *et al.* Secreted aspartic proteases of *Candida albicans* activate the NLRP3 inflammasome. *Eur. J. Immunol.* **43**, 679–692 (2013).
56. Robinson, M. J. *et al.* Dectin-2 is a Syk-coupled pattern recognition receptor crucial for Th17 responses to fungal infection. *J. Exp. Med.* **206**, 2037–2051 (2009).
57. Gringhuis, S. I. *et al.* Dectin-1 is an extracellular pathogen sensor for the induction and processing of IL-1β via a noncanonical caspase-8 inflammasome. *Nat. Immunol.* **13**, 246–254 (2012).
58. Ganesan, S. *et al.* Caspase-8 modulates dectin-1 and complement receptor 3-driven IL-1β production in response to β-glucans and the fungal pathogen, *Candida albicans*. *J. Immunol.* **193**, 2519–2530 (2014).
59. Wellington, M., Koselny, K., Sutterwala, F. S. & Krysan, D. J. *Candida albicans* triggers NLRP3-mediated pyroptosis in macrophages. *Eukar. Cell.* **13**, 329–340 (2014).
60. Uwamahoro, N. *et al.* The pathogen *Candida albicans* hijacks pyroptosis for escape from macrophages. *mBio* **5**, e00003–e00014 (2014).
61. Tomalka, J. *et al.* A novel role for the NLRC4 inflammasome in mucosal defenses against the fungal pathogen *Candida albicans*. *PLoS Pathogens* **7**, e1002379 (2011).
62. Netea, M. G. *et al.* Differential requirement for the activation of the inflammasome for processing and release of IL-1β in monocytes and macrophages. *Blood* **113**, 2324–2335 (2009).
63. van de Veerdonk, F. L. *et al.* Bypassing pathogen-induced inflammasome activation for the regulation of interleukin-1β production by the fungal pathogen *Candida albicans*. *J. Infect. Dis.* **199**, 1087–1096 (2009).
64. Dinarello, C. A. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood* **117**, 3720–3732 (2011).
65. Netea, M. G., van de Veerdonk, F. L., van der Meer, J. W., Dinarello, C. A. & Joosten, L. A. Inflammasome-independent regulation of IL-1-family cytokines. *Annu. Rev. Immunol.* **33**, 49–77 (2014).
66. Kullberg, B. J., van 't Wout, J. W. & van Furth, R. Role of granulocytes in increased host resistance to *Candida albicans* induced by recombinant interleukin-1. *Infect. Immun.* **58**, 3319–3324 (1990).
67. Vonk, A. G., Netea, M. G., van der Meer, J. W. & Kullberg, B. J. Host defence against disseminated *Candida albicans* infection and implications for antifungal immunotherapy. *Exp. Opin. Biol. Ther.* **6**, 891–903 (2006).
68. Mencacci, A. *et al.* Interleukin 18 restores defective Th1 immunity to *Candida albicans* in caspase 1-deficient mice. *Infect. Immun.* **68**, 5126–5131 (2000).
69. Beausejour, A., Grenier, D., Goulet, J. P. & Deslauriers, N. Proteolytic activation of the interleukin-1β precursor by *Candida albicans*. *Infect. Immun.* **66**, 676–681 (1998).
70. Gow, N. A., Brown, A. J. & Odds, F. C. Fungal morphogenesis and host invasion. *Curr. Opin. Microbiol.* **5**, 366–371 (2002).
71. d'Ostiani, C. F. *et al.* Dendritic cells discriminate between yeasts and hyphae of the fungus *Candida albicans*. Implications for initiation of T helper cell immunity *in vitro* and *in vivo*. *J. Exp. Med.* **191**, 1661–1674 (2000).
72. van der Graaf, C. A., Netea, M. G., Verschueren, I., van der Meer, J. W. & Kullberg, B. J. Differential cytokine production and Toll-like receptor signaling pathways by *Candida albicans* blastoconidia and hyphae. *Infec. Immun.* **73**, 7458–7464 (2005).
73. Gantner, B. N., Simmons, R. M. & Underhill, D. M. Dectin-1 mediates macrophage recognition of *Candida albicans* yeast but not filaments. *EMBO J.* **24**, 1277–1286 (2005).
74. Brunke, S. & Hube, B. Two unlike cousins: *Candida albicans* and *C. glabrata* infection strategies. *Cell. Microbiol.* **15**, 701–708 (2013).
75. Weindl, G. *et al.* Human epithelial cells establish direct antifungal defense through TLR4-mediated signaling. *J. Clin. Invest.* **117**, 3664–3672 (2007).
76. Moyes, D. L. *et al.* A biphasic innate immune MAPK response discriminates between the yeast and hyphal forms of *Candida albicans* in epithelial cells. *Cell Host Microbe* **8**, 225–235 (2010).
This study describes the recognition of yeasts and hyphae by epithelial cells and the mechanisms of discrimination between these two morphological forms.
77. Moyes, D. L. *et al. Candida albicans* yeast and hyphae are discriminated by MAPK signaling in vaginal epithelial cells. *PLoS ONE* **6**, e26580 (2011).
78. Eyerich, S. *et al.* IL-22 and TNF-α represent a key cytokine combination for epidermal integrity during infection with *Candida albicans*. *Eur. J. Immunol.* **41**, 1894–1901 (2011).
79. Tomalka, J. *et al.* β-defensin 1 plays a role in acute mucosal defense against *Candida albicans*. *J. Immunol.* **194**, 1788–1795 (2015).
80. Qian, Q., Jutila, M. A., van Rooijen & N. & Cutler, J. E. Elimination of mouse splenic macrophages correlates with increased susceptibility to experimental disseminated candidiasis. *J. Immunol.* **152**, 5000–5008 (1994).
81. Ngo, L. Y. *et al.* Inflammatory monocytes mediate early and organ-specific innate defense during systemic candidiasis. *J. Infect. Dis.* **209**, 109–119 (2014).
82. Lionakis, M. S. *et al.* CX_3CR1-dependent renal macrophage survival promotes *Candida* control and host survival. *J. Cin. Invest.* **123**, 5035–5051 (2013).
This is the first study to describe the crucial role of chemokine receptors in host defence against *C. albicans*.
83. Break, T. J. *et al.* CX_3CR1 is dispensable for control of mucosal *Candida albicans* infections in mice and humans. *Infect. Immun.* **83**, 958–965 (2015).
84. Smeekens, S. P. *et al.* The classical $CD14^{++}$ $CD16^{-}$ monocytes, but not the patrolling $CD14^{+}$ $CD16^{+}$ monocytes, promote Th17 responses to *Candida albicans*. *Eur. J. Immunol.* **41**, 2915–2924 (2011).
85. Horn, D. L. *et al.* Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin. Infect. Dis.* **48**, 1695–1703 (2009).
86. Uzun, O., Ascioglu, S., Anaissie, E. J. & Rex, J. H. Risk factors and predictors of outcome in patients with cancer and breakthrough candidemia. *Clin. Infect. Dis.* **32**, 1713–1707 (2001).
87. Brown, G. D. Innate antifungal immunity: the key role of phagocytes. *Annu. Rev. Immunol.* **29**, 1 (2011).
88. Aratani, Y. *et al.* Critical role of myeloperoxidase and nicotinamide adenine dinucleotide phosphate-oxidase in high-burden systemic infection of mice with *Candida albicans*. *J. Infect. Dis.* **185**, 1833–1837 (2002).
89. Lehrer, R. I. Measurement of candidacidal activity of specific leukocyte types in mixed cell populations I. Normal, myeloperoxidase-deficient, and chronic granulomatous disease neutrophils. *Infect. Immun.* **2**, 42–47 (1970).

90. Lehrer, R. I. & Cline, M. J. Leukocyte myeloperoxidase deficiency and disseminated candidiasis: the role of myeloperoxidase in resistance to *Candida* infection. *J. Cin. Invest.* **48**, 1478–1488 (1969).
91. Lanza, F. Clinical manifestation of myeloperoxidase deficiency. *J. Mol. Med.* **76**, 676–681 (1998).
92. Amulic, B., Cazalet, C., Hayes, G. L., Metzler, K. D. & Zychlinsky, A. Neutrophil function: from mechanisms to disease. *Annu. Rev. Immunol.* **30**, 459–489 (2012).
93. McCormick, A. *et al.* NETs formed by human neutrophils inhibit growth of the pathogenic mold *Aspergillus fumigatus*. *Microbes Infect.* **12**, 928–936 (2010).
94. Menegazzi, R., Decleva, E. & Dri, P. Killing by neutrophil extracellular traps: fact or folklore? *Blood* **119**, 1214–1216 (2012).
95. Urban, C. F. *et al.* Neutrophil extracellular traps contain calprotectin, a cytosolic protein complex involved in host defense against *Candida albicans*. *PLoS Pathogens* **5**, e1000639 (2009).
96. Sorensen, O. E. *et al.* Human cathelicidin, hCAP-18, is processed to the antimicrobial peptide LL-37 by extracellular cleavage with proteinase 3. *Blood* **97**, 3951–3959 (2001).
97. Kahlenberg, J. M. & Kaplan, M. J. Little peptide, big effects: the role of LL-37 in inflammation and autoimmune disease. *J. Immunol.* **191**, 4895–4901 (2013).
98. Zhang, X. *et al.* Dual functions of the human antimicrobial peptide LL-37-target membrane perturbation and host cell cargo delivery. *Biochim. Biophys. Acta* **1798**, 2201–2208 (2010).
99. Tsai, P. W., Yang, C. Y., Chang, H. T. & Lan, C. Y. Human antimicrobial peptide LL-37 inhibits adhesion of *Candida albicans* by interacting with yeast cell-wall carbohydrates. *PLoS ONE* **6**, e17755 (2011).
100. Alalwani, S. M. *et al.* The antimicrobial peptide LL-37 modulates the inflammatory and host defense response of human neutrophils. *Eur. J. Immunol.* **40**, 1118–1126 (2010).
101. Nagaoka, I., Tamura, H. & Hirata, M. An antimicrobial cathelicidin peptide, human CAP18/LL-37, suppresses neutrophil apoptosis via the activation of formyl-peptide receptor-like 1 and $P2X_7$. *J. Immunol.* **176**, 3044–3052 (2006).
102. Kaloriti, D. *et al.* Mechanisms underlying the exquisite sensitivity of *Candida albicans* to combinatorial cationic and oxidative stress that enhances the potent fungicidal activity of phagocytes. *mBio* **5**, e01334 (2014).
103. Nicola, A. M. *et al.* Macrophage autophagy in immunity to *Cryptococcus neoformans* and *Candida albicans*. *Infect. Immun.* **80**, 3065–3076 (2012).
104. Rosentul, D. C. *et al.* Role of autophagy genetic variants for the risk of *Candida* infections. *Med. Mycol.* **52**, 333–341 (2014).
105. Smeekens, S. P. *et al.* Autophagy is redundant for the host defense against systemic *Candida albicans* infections. *Eur. J. Clin. Microbiol. Infect. Dis.* **33**, 711–722 (2014).
106. Wirnsberger, G. *et al.* Jagunal homolog 1 is a critical regulator of neutrophil function in fungal host defense. *Nat. Genet.* **46**, 1028–1033 (2014).
107. Romani, L. *et al.* Natural killer cells do not play a dominant role in $CD4^+$ subset differentiation in *Candida albicans*-infected mice. *Infect. Immun.* **61**, 3769–3774 (1993).
108. Quintin, J. *et al.* Differential role of NK cells against *Candida albicans* infection in immunocompetent or immunocompromised mice. *Eur. J. Immunol.* **44**, 2405–2414 (2014).
109. Voigt, J. *et al.* Human natural killer cells acting as phagocytes against *Candida albicans* and mounting an inflammatory response that modulates neutrophil antifungal activity. *J. Infect. Dis.* **209**, 616–626 (2014).
110. Biondo, C. *et al.* Recognition of yeast nucleic acids triggers a host-protective type I interferon response. *Eur. J. Immunol.* **41**, 1969–1979 (2011).
111. del Fresno, C. *et al.* Interferon-β production via Dectin-1–Syk– IRF5 signaling in dendritic cells is crucial for immunity to *C. albicans*. *Immunity* **38**, 1176–1186 (2013).
112. Bourgeois, C. *et al.* Conventional dendritic cells mount a type I IFN response against *Candida* spp. requiring novel phagosomal TLR7-mediated IFN-β signaling. *J. Immunol.* < /**vs** > **186**, 3104–3112 (2011).
113. Netea, M. G. *et al.* Human dendritic cells are less potent at killing *Candida albicans* than both monocytes and macrophages. *Microb. Infect.* **6**, 985–989 (2004).
114. Zielinski, C. E. *et al.* Pathogen-induced human T_H17 cells produce IFN-γ or IL-10 and are regulated by IL-β. *Nature* **484**, 514–518 (2012).
This study demonstrates the presence of pathogen-specific T_H17 cells that differentially produce either IFNγ or IL-10.
115. Shalaby, M. R. *et al.* Activation of human polymorphonuclear neutrophil functions by interferon-gamma and tumor necrosis factors. *J. Immunol.* **135**, 2069–2073 (1985).
116. Nathan, C. F., Murray, H. W., Wiebe, M. E. & Rubin, B. Y. Identification of interferon-γ as the lymphokine that activates human macrophage oxidative metabolism and antimicrobial activity. *J. Exp. Med.* **158**, 670–689 (1983).
117. Netea, M. G. *et al.* Differential role of IL-18 and IL-12 in the host defense against disseminated *Candida albicans* infection. *Eur. J. Immunol.* **33**, 3409–3417 (2003).
118. Kullberg, B. J., van 't Wout, J. W., Hoogstraten, C. & van Furth, R. Recombinant interferon-γ enhances resistance to acute disseminated *Candida albicans* infection in mice. *J. Infect. Dis.* **168**, 436–443 (1993).
119. Stuyt, R. J., Netea, M. G., van Krieken, J. H., van der Meer, J. W. & Kullberg, B. J. Recombinant interleukin-18 protects against disseminated *Candida albicans* infection in mice. *J. Infect. Dis.* **189**, 1524–1527 (2004).
120. Delsing, C. E. *et al.* Interferon-gamma as adjunctive immunotherapy for invasive fungal infections: a case series. *BMC Infect. Dis.* **14**, 166 (2014).
This is a proof-of-principle clinical trial demonstrating the ability of recombinant IFNγ to restore immune defects during fungal sepsis.
121. Liang, S. C. *et al.* Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J. Exp. Med.* **203**, 2271–2279 (2006).
122. Huang, W., Na, L., Fidel, P. L. & Schwarzenberger, P. Requirement of interleukin-17A for systemic anti-*Candida albicans* host defense in mice. *J. Infect. Dis.* **190**, 624–631 (2004).
123. van de Veerdonk, F. L. *et al.* Differential effects of IL-17 pathway in disseminated candidiasis and zymosan-induced multiple organ failure. *Shock* **34**, 407–411 (2010).
124. Conti, H. R. *et al.* Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. *J. Exp. Med.* **206**, 299–311 (2009).
125. Milner, J. D. *et al.* Impaired T_H17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature* **452**, 773–776 (2008).
126. van de Veerdonk, F. L. *et al. STAT1* mutations in autosomal dominant chronic mucocutaneous candidiasis. *N. Engl. J. Med.***365**, 54–61 (2011).
127. Liu, L. *et al.* Gain-of-function human *STAT1* mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J. Exp. Med.***208**, 1635–1648 (2011).
References 125–127 report that mutations in *STAT3* and *STAT1* are associated with chronic mucocutaneous candidiasis.
128. Puel, A. *et al.* Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science* **332**, 65–68 (2011).
129. Yano, J. *et al.* The acute neutrophil response mediated by S100 alarmins during vaginal *Candida* infections is independent of the Th17-pathway. *PLoS ONE* **7**, e46311 (2012).
130. Holland, S. M. *et al. STAT3* mutations in the hyper-IgE syndrome. *N. Engl. J. Med.* **357**, 1608–1619 (2007).
131. Langley, R. G. *et al.* Secukinumab in plaque psoriasis — results of two phase 3 trials. *N. Engl. J. Med.* **371**, 326–338 (2014).
132. Mencacci, A. *et al.* Defective antifungal T-helper 1 (T_H1) immunity in a murine model of allogeneic T-cell-depleted bone marrow transplantation and its restoration by treatment with T_H2 cytokine antagonists. *Blood* **97**, 1483–1490 (2001).
133. Tavares, D., Ferreira, P. & Arala-Chaves, M. Increased resistance to systemic candidiasis in athymic or interleukin-10-depleted mice. *J. Infect. Dis.* **182**, 266–273 (2000).
134. Vazquez-Torres, A., Jones-Carson, J., Wagner, R. D., Warner, T. & Balish, E. Early resistance of interleukin-10 knockout mice to acute systemic candidiasis. *Infect. Immun.* **67**, 670–674 (1999).
135. Mencacci, A. *et al.* Endogenous interleukin 4 is required for development of protective $CD4^+$ T helper type 1 cell responses to *Candida albicans*. *J. Exp. Med.* **187**, 307–317 (1998).
136. Spits, H. *et al.* Innate lymphoid cells — a proposal for uniform nomenclature. *Nat. Rev. Immunol.* **13**, 145–149 (2013).
137. Gladiator, A., Wangler, N., Trautwein-Weidner, K. & LeibundGut-Landmann, S. Cutting edge: IL-17-secreting innate lymphoid cells are essential for host defense against fungal infection. *J. Immunol.* **190**, 521–525 (2013).
This study is the first to report a role for ILCs in antifungal host defence.
138. Conti, H. R. *et al.* Oral-resident natural Th17 cells and γδ T cells control opportunistic *Candida albicans* infections. *J. Exp. Med.* **211**, 2075–2084 (2014).
139. Cheng, S. C. *et al.* Complement plays a central role in *Candida albicans*-induced cytokine production by human PBMCs. *Eur. J. Immunol.* **42**, 993–1004 (2012).
140. Tsoni, S. V. *et al.* Complement C3 plays an essential role in the control of opportunistic fungal infections. *Infect. Immun.* **77**, 3679–3685 (2009).
141. Mullick, A. *et al.* Dysregulated inflammatory response to *Candida albicans* in a C5-deficient mouse strain. *Infect. Immun.* **72**, 5868–5876 (2004).
142. Magliani, W. *et al.* Therapeutic potential of antiidiotypic single chain antibodies with yeast killer toxin activity. *Nat. Biotechnol.* **15**, 155–158 (1997).
143. Polonelli, L. *et al.* Idiotypic intravaginal vaccination to protect against candidal vaginitis by secretory, yeast killer toxin-like anti-idiotypic antibodies. *J. Immunol.* **152**, 3175–3182 (1994).
144. Sandini, S. *et al.* A highly immunogenic recombinant and truncated protein of the secreted aspartic proteases family (rSap2t) of *Candida albicans* as a mucosal anticandidal vaccine. *FEMS Immunol. Med. Microbiol.* **62**, 215–224 (2011).
145. Torosantucci, A. *et al.* Protection by anti-β-glucan antibodies is associated with restricted β-1,3 glucan binding specificity and inhibition of fungal growth and adherence. *PLoS ONE* **4**, e5392 (2009).
146. Robert, R. *et al.* Adherence of platelets to *Candida* species *in vivo*. *Infect. Immun.* **68**, 570–576 (2000).
147. Drago, L., Bortolin, M., Vassena, C., Taschieri, S. & Del Fabbro, M. Antimicrobial activity of pure platelet-rich plasma against microorganisms isolated from oral cavity. *BMC Microbiol.* **13**, 47 (2013).
148. Peters, B. M., Yano, J., Noverr, M. C. & Fidel, P. L. Jr. *Candida* vaginitis: when opportunism knocks, the host responds. *PLoS Pathog.* **10**, e1003965 (2014).
149. Miramon, P., Kasper, L. & Hube, B. Thriving within the host: *Candida* spp. interactions with phagocytic cells. *Med. Microbiol. Immunol.* **202**, 183–195 (2013).
150. Toth, R. *et al.* Kinetic studies of *Candida parapsilosis* phagocytosis by macrophages and detection of intracellular survival mechanisms. *Front. Microbiol.* **5**, 633 (2014).
151. Slesiona, S. *et al.* Persistence versus escape: *Aspergillus terreus* and *Aspergillus fumigatus* employ different strategies during interactions with macrophages. *PLoS ONE* **7**, e31223 (2012).
152. Reales-Calderōn, J. A., Aguilera-Montilla, N., Corbí, A. L., Molero, G. & Gil, C. Proteomic characterization of human proinflammatory M1 and anti-inflammatory M2 macrophages and their response to *Candida albicans*. *Proteomics* **14**, 1503–1518 (2014).
153. Dillon, S. *et al.* Yeast zymosan, a stimulus for TLR2 and dectin-1, induces regulatory antigen-presenting cells and immunological tolerance. *J. Cin. Invest.***116**, 916–928 (2006).
This study reports that fungal stimulation of a TLR2–dectin 1 pathway can induce immunological tolerance.
154. Sutmuller, R. P. *et al.* Toll-like receptor 2 controls expansion and function of regulatory T cells. *J. Clin. Invest.* **116**, 485–494 (2006).
155. Tierney, L., Kuchler, K., Rizzetto, L. & Cavalieri, D. Systems biology of host–fungus interactions: turning complexity into simplicity. *Cur. Opin. Microbiol.* **15**, 440–446 (2012).
156. Zaas, A. K., Aziz, H., Lucas, J., Perfect, J. R. & Ginsburg, G. S. Blood gene expression signatures predict invasive candidiasis. *Sci. Transl. Med.* **2**, 21ra17 (2010).
157. Tierney, L. *et al.* An interspecies regulatory network inferred from simultaneous RNA-seq of *Candida albicans* invading innate immune cells. *Front. Microbiol.* **3**, 85 (2012).
158. Barker, K. S. *et al.* Transcriptome profile of the vascular endothelial cell response to *Candida albicans*. *J. Infect. Dis.* **198**, 193–202 (2008).

159. Fradin, C. *et al.* The early transcriptional response of human granulocytes to infection with *Candida albicans* is not essential for killing but reflects cellular communications. *Infect. Immun.* **75**, 1493–1501 (2007).
160. Smeekens, S. P. *et al.* Functional genomics identifies type I interferon pathway as central for host defense against *Candida albicans*. *Nat. Commun*. **4**, 1342 (2013).
161. Majer, O. *et al.* Type I interferons promote fatal immunopathology by regulating inflammatory monocytes and neutrophils during *Candida* infections. *PLoS Pathog.* **8**, e1002811 (2012).
162. Moyes, D. L. *et al.* Protection against epithelial damage during *Candida albicans* infection is mediated by PI3K/Akt and mammalian target of rapamycin signaling. *J. Infect. Dis.* **209**, 1816–1826 (2014).
163. Ikuta, T. *et al.* Identification by DNA microarray of genes involved in *Candida albicans*-treated gingival epithelial cells. *J. Oral Pathol. Med.* **41**, 769–778 (2012).
164. Kumar, V. *et al.* Immunochip SNP array identifies novel genetic variants conferring susceptibility to candidaemia. *Nat. Commun*.**5**, 4675 (2014).
This first GWAS of a fungal infection identifies new pathways involved in host defence against systemic *Candida* infections.
165. Oh, J. *et al.* Biogeography and individuality shape function in the human skin metagenome. *Nature* **514**, 59–64 (2014).
166. Smeekens, S. P. *et al.* Skin microbiome imbalance in patients with STAT1/STAT3 defects impairs innate host defense responses. *J. Innate Immun.* **6**, 253–262 (2014).
167. Hogan, D. A., Vik, A. & Kolter, R. A *Pseudomonas aeruginosa* quorum-sensing molecule influences *Candida albicans* morphology. *Mol. Microbiol.* **54**, 1212–1223 (2004).
168. Kennedy, M. J. & Volz, P. A. Ecology of *Candida albicans* gut colonization: inhibition of *Candida* adhesion, colonization, and dissemination from the gastrointestinal tract by bacterial antagonism. *Infect. Immun.* **49**, 654–663 (1985).
169. Jenkinson, H. F., Lala, H. C. & Shepherd, M. G. Coaggregation of *Streptococcus sanguis* and other streptococci with *Candida albicans*. *Infect. Immun.* **58**, 1429–1436 (1990).
170. Findley, K. *et al.* Topographic diversity of fungal and bacterial communities in human skin. *Nature* **498**, 367–370 (2013).
This is a first description of human skin mycobiome and bacteriome.
171. Huffnagle, G. B. & Noverr, M. C. The emerging world of the fungal microbiome. *Trends Microbiol.* **21**, 334–341 (2013).
172. Iliev, I. D. *et al.* Interactions between commensal fungi and the C-type lectin receptor Dectin-1 influence colitis. *Science* **336**, 1314–1317 (2012).
This study demonstrates the importance of fungal colonization in a chronic inflammatory process.
173. Zelante, T. *et al.* Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity* **39**, 372–385 (2013).
174. Noverr, M. C. & Huffnagle, G. B. Regulation of *Candida albicans* morphogenesis by fatty acid metabolites. *Infect. Immun.* **72**, 6206–6210 (2004).
175. Maslowski, K. M. *et al.* Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* **461**, 1282–1286 (2009).
176. Trompette, A. *et al.* Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat. Med.* **20**, 159–166 (2014).
177. Romani, L. *et al.* The cross-talk between opportunistic fungi and the mammalian host via microbiota's metabolism. *Sem. Immunopathol.* **37**, 163–171 (2015).
178. Oever, J. T. & Netea, M. G. The bacteriome–mycobiome interaction and antifungal host defense. *Eur. J. Immunol.* **44**, 3182–3191 (2014).
179. Kolwijck, E. & van de Veerdonk, F. L. The potential impact of the pulmonary microbiome on immunopathogenesis of *Aspergillus*-related lung disease. *Eur. J. Immunol.* **44**, 3156–3165 (2014).
180. Bistoni, F. *et al.* Evidence for macrophage-mediated protection against lethal *Candida albicans* infection. *Infect. Immun.* **51**, 668–674 (1986).
181. Bistoni, F. *et al.* Immunomodulation by a low-virulence, agerminative variant of *Candida albicans*. Further evidence for macrophage activation as one of the effector mechanisms of nonspecific anti-infectious protection. *J. Med. Vet. Mycol.* **26**, 285–299 (1988).
References 180 and 181 demonstrate lymphocyte-independent, macrophage-dependent protection in a vaccination model against invasive candidiasis that represents *de facto* innate immune memory.
182. Netea, M. G., Quintin, J. & van der Meer, J. W. Trained immunity: a memory for innate host defense. *Cell Host Microbe* **9**, 355–361 (2011).
183. Saeed, S. *et al.* Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. *Science* **345**, 1251086 (2014).
184. Cheng, S. C. *et al.* mTOR- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity. *Science* **345**, 1250684 (2014).
These studies report the epigenetic and metabolic substrates of innate immune memory (trained immunity).
185. Ifrim, D. C. *et al.* Defective trained immunity in patients with STAT1-dependent chronic mucocutaneaous candidiasis. *Clin. Exp. Immunol.* **181**, 434–440 (2015).
186. Bekkering, S. *et al.* Oxidized low-density lipoprotein induces long-term proinflammatory cytokine production and foam cell formation via epigenetic reprogramming of monocytes. *Arterioscler. Thromb. Vasc. Biol.* **34**, 1731–1738 (2014).
187. Bekkering, S., Joosten, L., Netea, M. G. & Riksen, N. P. Trained innate immunity as a mechanistic link between sepsis and atherosclerosis. *Crit. Care* **18**, 645 (2014).
188. Benn, C. S., Netea, M. G., Selin, L. K. & Aaby, P. A small jab — a big effect: nonspecific immunomodulation by vaccines. *Trends Immunol.* **34**, 431–439 (2013).
189. Aleem, E. β-Glucans and their applications in cancer therapy: focus on human studies. *Anticancer Agents Med. Chem.* **13**, 709–719 (2013).

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