



ELSEVIER

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in
Microbiology

Importance of the *Candida albicans* cell wall during commensalism and infection

Neil AR Gow¹ and Bernhard Hube^{2,3,4}

An imbalance of the normal microbial flora, breakage of epithelial barriers or dysfunction of the immune system favour the transition of the human pathogenic yeast *Candida albicans* from a commensal to a pathogen. *C. albicans* has evolved to be adapted as a commensal on mucosal surfaces. As a commensal it has also acquired attributes, which are necessary to avoid or overcome the host defence mechanisms. The human host has also co-evolved to recognize and eliminate potential fungal invaders. Many of the fungal genes that have been the focus of this co-evolutionary process encode cell wall components. In this review, we will discuss the transition from commensalism to pathogenesis, the key players of the fungal cell surface that are important for this transition, the role of the morphology and the mechanisms of host recognition and response.

Addresses

¹ School of Medical Sciences, Institute of Medical Sciences, Foresterhill University of Aberdeen, Aberdeen AB25 2ZD, UK

² Department of Microbial Pathogenicity Mechanisms, Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute Jena (HKI), D-07745 Jena, Germany

³ Friedrich Schiller University, Jena, Germany

⁴ Center for Sepsis Control and Care, Jena, Germany

Corresponding authors: Gow, Neil AR (n.gow@abdn.ac.uk) and Hube, Bernhard (bernhard.hube@hki-jena.de)

Current Opinion in Microbiology 2012, 15:406–412

This review comes from a themed issue on **Host–microbe interactions: Fungi**

Edited by **Mihai G Netea** and **Gordon D Brown**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 18th May 2012

1369-5274 © 2012 Elsevier Ltd. Open access under [CC BY license](#).

<http://dx.doi.org/10.1016/j.mib.2012.04.005>

Introduction

The yeast *Candida albicans* is by far the most common human pathogenic *Candida* species and can cause a broad spectrum of diseases including skin, mucosal and systemic infections (candidiasis) [1]. *C. albicans* infections of mucosal surfaces are extremely common and occur in otherwise healthy individuals. However, *Candida* species can cause life threatening infections in immunocompromised individuals or when natural barriers are damaged. During these infections, the fungus is able to colonize and multiply within almost all organs of the human body. Under normal circumstances, *C. albicans* is a mucosal commensal, predominantly in the gastrointestinal tract,

of the majority of the human population. Here, the fungus is controlled by: (1) the normal microbial flora, (2) epithelial barriers and (3) the innate immune system. This is reflected by the fact that antibiotic treatments, or surgery, polytrauma and catheters and neutropenia are all considered as major risk factors for invasive candidiasis. Human polymorphisms that affect mucosal recognition mechanisms have also been recognized as underlying a range of superficial forms of candidiasis in specific patient groups [2]. Although the commensal stage is frequently described as ‘harmless’ to the host, it is likely that this stage is highly regulated and the fungus is continuously or transiently interacting with the host immune system [3]. Therefore, it may be that the adaptation to warm-blooded animals includes not only an adaptation to a life on mucosal surfaces, but also selection of attributes, which are necessary to avoid or overcome the defence mechanisms of the host (discussed as ‘The commensal school’ in [4]). It is also likely that the human host has evolved to recognize and deal with a potential fungal invader so that the evolved state is one of commensalism. Many of the genes that have been the focus of this co-evolution encode cell wall components and concomitantly, the morphology, of the fungus. The way in which these components orchestrate the ecology of the fungus in the human host is the subject of this review.

Fungal mechanisms associated with commensalism and pathogenicity

It is not known whether commensal proliferation of *C. albicans* on mucosal surfaces occurs mostly within the mucous layer, like other members of the microbial flora, or whether fungal cells are in physical contact with epithelial cells. During pathogenesis, three different and dynamic stages can be discriminated: (i) adhesion, (ii) invasion, and (iii) damage [5,6,7]. During these processes, inflammation – a characteristic of fungal disease – is initiated. However, it remains to be elucidated which of these stages are truly characteristic for pathogenesis and can be taken as representing the transition from a commensal to a parasitic interaction with the host.

Adhesion to other fungal or bacterial or host cells is required for both commensalism and pathogenesis. In *Candida* species, adhesion is mediated by some well characterized adhesion factors such as members of the Als family, Hwp1, Eap1, and others [8]. Several of these are glycosylphosphatidylinositol (GPI)-proteins (linked to cell wall glucan, see below) or GPI-anchored proteins (linked to the cell membrane), which are exposed at the

cell surface. Adhesins such as Als3 and Hwp1 are predominantly expressed during hypha formation making this morphology particularly adherent. Dysfunction in cell wall regulation may cause inappropriate exposure or aberrant surface localization of adhesins and thus can reduce adhesion properties [7[•],9].

Invasion of *C. albicans* into non-professional phagocytic cells is hypha-dependent and can occur via two different routes: induced endocytosis or active penetration. Induced endocytosis is a host-driven activity by which hypha-associated invasins, in particular Als3, bind to a host receptor on epithelial or endothelial cells (E-cadherin, N-cadherin) to trigger fungal up-take [10]. Active penetration, either directly into host cells or between host cells, requires fungal turgor, normal vacuole formation, cell wall integrity, hyphal extension and other physical forces [7[•],11]. Fungal cells can sense the topography of the host surface and respond by thigmotropic orientation [12]. They may also communicate with other fungal cells by quorum sensing mechanisms [13]. Quorum sensing not only regulates morphology (yeast or hypha growth), but may also orchestrate deep invasion into tissues since histological analyses frequently show almost synchronized parallel invasion of hyphae (Figure 1).

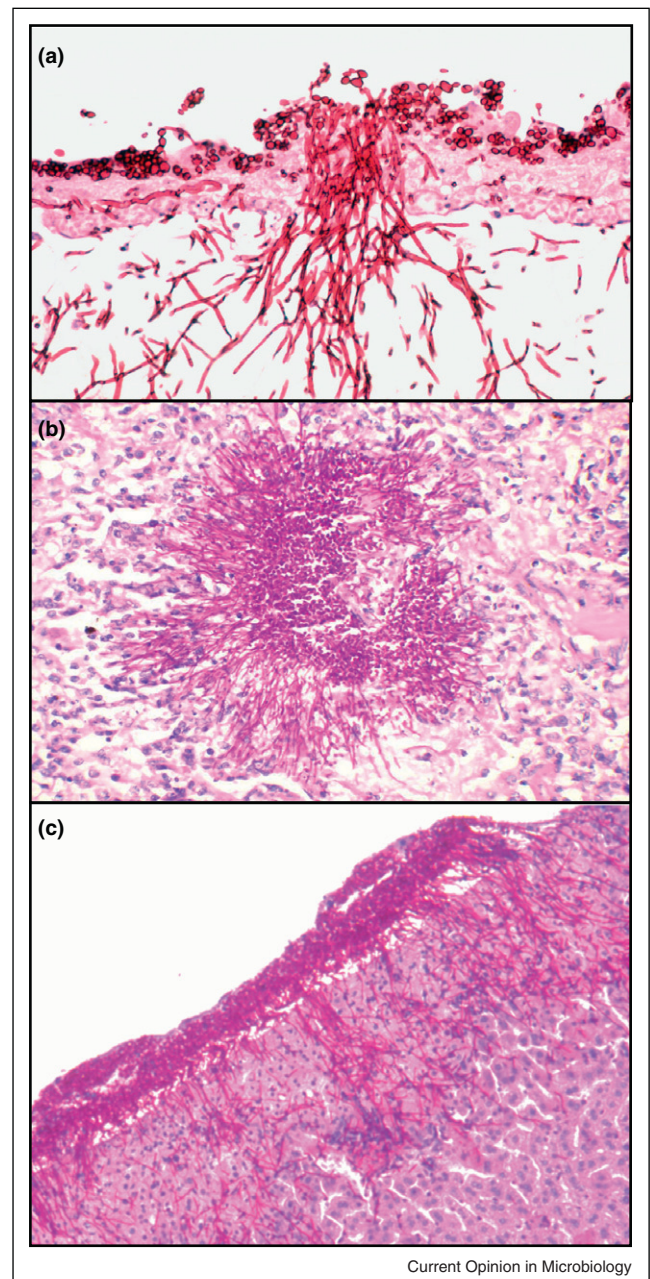
Although it seems obvious that invasion is a truly pathogenic stage, it may be that *C. albicans* moderately invades epithelial cells even in the commensal phase in order to maintain a foothold on proliferating epithelia and to avoid being sloughed off from epithelial surfaces. This would explain immunological data indicating continuous interactions exist between *C. albicans* and the host [3,14]. Furthermore, invasion via induced endocytosis does not inevitably cause damage since killed fungal hyphae with no potential to cause disease can be taken up via this mechanism [7[•],15].

By contrast, induction of host damage is a key characteristic of pathogenesis. Damage directly caused by the fungus occurs when hyphae invade deep into or through host cells (interepithelial invasion) and is potentiated by virulence factors such as the secretion of hydrolases, unknown damaging factors and some attributes which are also characteristic for active penetration, for example hyphal extension [7[•],11]. However, tissue damage and disease occurs not only by direct fungal activities, but may also be the result of an overactivation of the immune system, for example massive infiltration of neutrophils or, finally, an inappropriate and unbalanced systemic response causing life threatening sepsis. Thus, immune recognition may not only be beneficial and crucial for fighting invading fungi, but may also be an integral part of the disease process.

Immune recognition and cell wall structure

The *C. albicans* cell wall is 90% carbohydrate and 10% protein. As a generalization, the carbohydrates dominate immune recognition and the proteins have the key role in

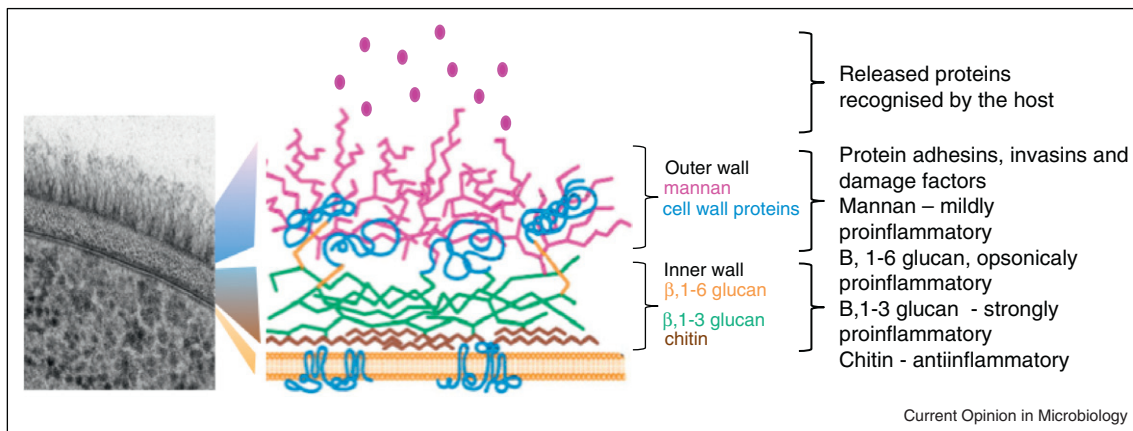
Figure 1



Invasive properties of hyphae of *C. albicans*. (A) Invasion of a model epithelium from the chick chorioallantoic membrane by hyphae of *C. albicans* (Gow N.A.R., with permission), (B) the ramification of hyphae from a human lung lesion, (C) invasion into murine liver after intraperitoneal infection. Note the almost parallel invasion potentially indicating communication between hyphae (from Das A. (B) and Jacobsen I.D. (C), with permission).

adhesive interactions with cell host surfaces. However, cell wall proteins are relevant as antigens and therefore vaccine targets, for example Als3 [16], and it is known that cell wall associated or secreted proteins such as the aspartic proteases are recognized by immune cells [17].

Figure 2



Transmission electron micrograph showing a section of the *C. albicans* cell wall and a cartoon showing the arrangement of the major components and (on the rhs) the role of those components in immune activation and suppression. TEM by Walker L., adapted from [35] with permission.

The polysaccharides are in three major forms: (i) mannans (*O*-linked and *N*-linked), which are post-translational modifications of the cell wall proteins; (ii) β -glucans (which comprise two types β -1,3 glucan and β -1,6 glucan); and (iii) chitin and/or its deacetylated form chitosan. The mannoproteins form a fibrillar outer layer, while the β -glucan/chitin layer lies under the mannoprotein outer layer (Figure 2). It has also been suggested recently that some of the mannan is free in the cell wall [18].

The cell wall proteins are mostly attached via GPI-remnants to β -1,3 glucan via β -1,6 glucan, which acts as a linker molecule (or anchored via GPI with the membrane, as discussed above). Chitin and β -1,3 glucan are structural polysaccharides in the inner cell wall layer. Both of these molecules convey strength and shape to the cell wall. By contrast, the mannans of the outer cell wall are less structured, but have low permeability and porosity. Therefore, the mannan layer affects the resistance of the wall to attack by host molecules and the permeability of the wall to antifungal drugs, but does not influence cell shape.

All of the polysaccharides of the cell wall contribute to the immunological signature of *C. albicans* [19]. *O*-linked and *N*-linked mannans are pathogen associated molecular patterns (PAMPs) that engage a wide range of Toll like receptor (TLR) and C-type lectin Pattern Recognition Receptors (PRRs) [20]. In myeloid cells *O*-linked mannans are recognized by TLR4, whilst *N*-mannan is recognized by the Mannose Receptor Protein (MRP), Galectin-3, as well as Mincle and DC-SIGN. Mannans include both α -linked and β -linked sugars. It is clear that the C-type lectin Galectin-3 has an affinity for β -mannose in the form of β -1,2, oligomannosides whilst most of the other receptors are presumed to bind predominantly α -linked mannose oligosaccharides [19]. The major PRR for β -1,3 glucan is the C-type lectin Dectin-1 [21] which can

collaborate with TLR2, perhaps by forming a co-receptor complex, which together amplify recognition responses triggered by the Syk kinase and TLR/MyD88 dependent pathways [22]. Dectin-1- β -glucan interactions are also critical for the activation of inflammasome complexes [23^{**},24^{*}]. Phospholipomannan in the wall is recognized by Galectin-3, which may be coupled to TLR2 and is likely to be of special importance in recognizing *C. albicans* in the gut mucosa. β -1,6 Glucan, which acts as a linker between the GPI-proteins of the wall and the β -1,3 glucan skeletal polysaccharide, is an opsonic receptor of neutrophils [25]. β -1,3 Glucan is a major pro-inflammatory mediator and conditions that enhance its exposure at the surface of the cell increase the amount of pro-inflammatory cytokines that are induced. The overlying mannan layer is not strictly an 'immunological shield' since it too is recognized by a plethora of PRRs (see above), but it is true that damage to the integrity of the mannan layer with consequential exposure of more β -1,3 glucan at the cell surface enhances the strength of the pro-inflammatory signal. This enhanced β -1,3 glucan-exposure can occur after exposure to echinocandins and during the progression of an infection as host enzymes act on the fungal cell surface [26]. It should be noted that most of these studies were done with myeloid cells, such as macrophages. Recognition by epithelial (or other cell types) have been much less well studied and are likely to differ in many key respects.

Chitin and its deacetylated form chitosan also participate in immune recognition, activation and attenuation [27^{*},28,29]. The C-type lectin RegIIIg (HIP/PAD) in the neutrophil-like Paneth cells of the small intestine, and FIBCD1, a calcium-dependent acetyl group-binding tetrameric protein have been implicated as chitin-binding receptors [30], however, the chitin binding receptor of myeloid cells has yet to be identified. The role of chitin in

immune recognition remains to be fully clarified. It induces both pro-inflammatory and anti-inflammatory responses and the type of response is very dependent on the size of the chitin particle (see [27*]; and summary in [31]). A significant proportion of chitin is deacetylated to chitosan in the walls of zygomycetes and other fungi such as the basidiomycete yeast *Cryptococcus neoformans*. It is likely that chitin and chitosan have separate immune recognition mechanisms. For example, chitosan, but not its acetylated form chitin, activates the NLRP3 inflammasome in a phagocytosis-dependent manner [32] and dendritic cells can be activated by chitosan, and not chitin via a mechanism that involves TLR4 [33]. The next few years are likely to lead to further discoveries of the cognate receptors for both chitin and chitosan by cells that participate in the primary innate immune response.

Recognition during morphogenesis, commensalism and pathogenesis

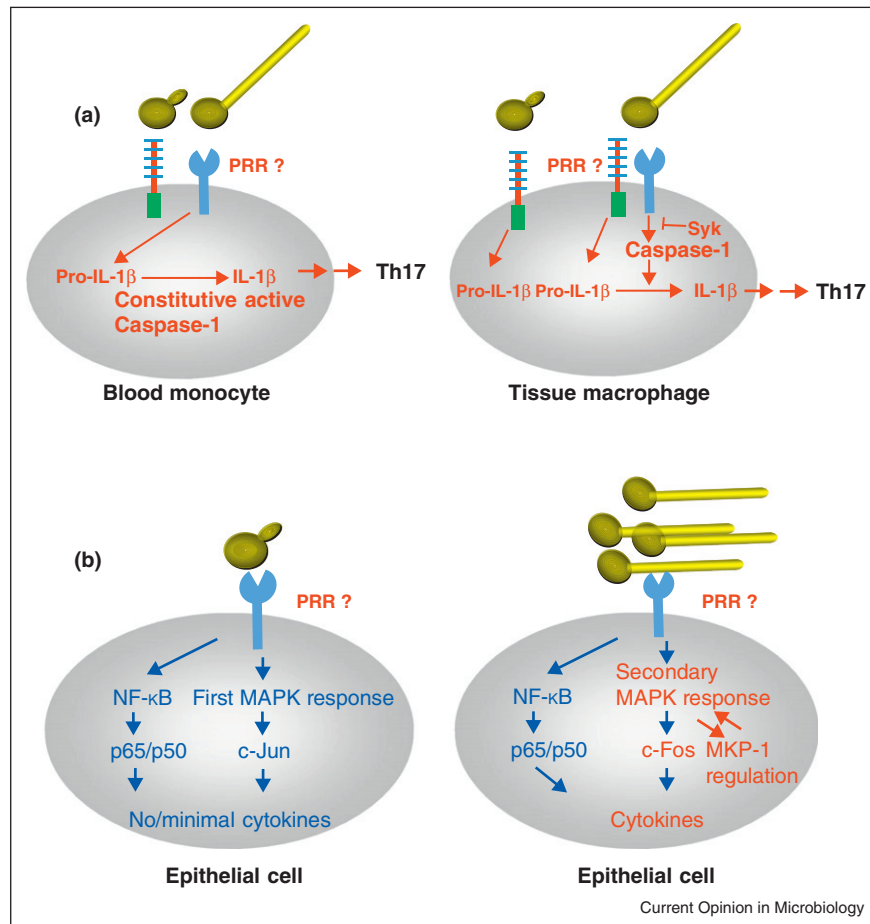
One of the key characteristics and predominant virulence attributes of *C. albicans* is the ability to switch between yeast and hyphal growth [34]. These morphological forms differ in growth dynamics, cellular structure, gene expression pattern, cell surface molecules, dissemination and invasion potential [35]. Some of the hypha-associated factors are clearly linked with virulence potential, for example Hwp1 (adhesion) [36], Als3 (adhesion, invasion, iron acquisition) [15,37,38], Sod5 (detoxification of reactive oxygen species) [39–41], or Sap4-6 (proteases involved in several aspects of interaction with the host) [42]. It is clear that yeast and hyphae are differentially recognized by immune cells [43*] and that the cytokine signature induced by yeast and hyphal cells differs significantly. Hyphae induce low levels of IL-12 and IFN γ from DCs but higher levels of IL-4, and hyphae are not recognized by TLR4 [44].

Because hyphae do not form bud scars, which have surface-exposed β -1,3 glucan, they also do not induce a strong Dectin-1 mediated pro-inflammatory response [45]. Dectin-2 mediated recognition of mannans from hyphae and yeast cells has also been suggested to differ [46]. The mannans of yeast and hyphae differ physically and chemically (e.g. [23**]) and this may contribute to the differential immune reactivity of these two morphological forms together with morphology associated proteins [47,48**]. For example, surface-associated pH-regulated antigen 1 protein (Pra1), a predominantly hypha-associated protein, plays a pivotal role in the recognition of *C. albicans* by human neutrophils and enhances neutrophil antimicrobial responses. However, the fungus can counteract some of these defence mechanisms by releasing soluble Pra1 [49]. Recognition of Pra1p occurs via the leucocyte receptor integrin α (M) β ₂ and complement receptor 3 [49,50]. Furthermore, Pra1 can bind human complement inhibitors and thus may mediate fungal complement evasion [51].

Recently, mechanisms have emerged that enable an understanding of how colonizing (yeast cells) and invasive (hyphal) forms of *C. albicans* are discriminated by epithelial cells and the underlying mucosa. It was shown that fungal burden and the transition from yeast to hypha have a profound influence on immune activation of epithelial cells [52**]. Initial immune recognition of *C. albicans* was found to be cell wall dependent, but morphology-independent, and involved activation of the NF- κ B pathway and the MAPK-mediated transcription factor c-Jun. However, this response appears to be transient and does not result in epithelial cytokine induction. Full epithelial activation with concomitant cytokine induction is only induced when hyphal burdens increase, but not yeast burdens, providing a mechanism that would facilitate discrimination between the colonizing and invading forms of the fungus. Recognition of increased hyphal burdens occurs in both oral and vaginal epithelial cells and results in the activation of two key proteins: the transcription factor c-Fos, which is activated by the p38 pathway, and the MAPK phosphatase MKP1, which is activated via the MEK1/2–ERK1/2 pathway and regulates the MAPK-mediated cytokine response. c-Fos and MKP1 activation is contact dependent but independent of viability and avidity of adherence. The hypha-associated moieties that induce c-Fos and MKP1 activation are unknown, but cell wall polysaccharides (mannan, β -glucan, chitin) are unlikely to be the activating factors as these only activate NF- κ B and c-Jun [52**,53].

For mucosal immunity, Th-17 cell subsets and their associated cytokines, IL-17A, IL-17F and IL-22, play key roles in discriminating colonization and invasive disease [54,55]. Human Th-17 differentiation in memory CD4 T cells is induced by IL-1 β , IL-6 and TGF β 1 cytokines (and maintained by IL-23) from antigen-presenting cells. While yeast cells and hyphae both induce IL-23 and IL-6, only hyphae induce IL-1 β in macrophages. In addition, alterations in tryptophan metabolism by *C. albicans* hyphae can also down regulate the Th-17 response [56]. The hypha-specific induction of IL-1 β is mediated by the NLRP3 inflammasome and *C. albicans* yeast-locked mutants do not activate the inflammasome and therefore do not induce IL-1 β secretion by macrophages. In myeloid cells, activation of IL-1 β requires the pro-form of the cytokine to be processed by the caspase-1 protease that is activated via the Dectin-1 pathway. Whilst both yeast cells and hyphae induce pro IL-1 β mRNA and protein, only hyphae induce caspase-1 and hence secretion of active IL-1 β and subsequent IL-17 secretion by Th-17 cells leading to recruitment of neutrophils (Figure 3) [23**,35]. Recently the NLRC4 inflammasome has also been shown to be protective for mucosal immunity to *C. albicans* [57]. Overall, this suggests that the transition from colonizing yeast cells to tissue-invading hyphae signals the activation of a protective Th-17 response in the mucosa. IL-22 pro-

Figure 3



Two host danger response pathways that indicate the shift from *C. albicans* commensal growth to infection. **(A)** Monocytes recognize both yeast and hyphal cells which both induce caspase-1 formation that processes pro-IL-1 β to the mature form of IL-1 β . This induces T cell differentiation to Th17 cells, while with macrophages only hyphae induce pro-IL-1 β processing by caspase-1. Consequently, in the mucosa, yeast cells do not induce a strong pro-inflammatory response, but invasive hyphal cells induce protective Th-17 immunity [35]. **(B)** Oral epithelial cells are able to discriminate between yeast and hypha via a bi-phasic MAPK response. Low burden of colonising yeasts cells are recognized by an unknown PRR causing activation of NF- κ B and weak, early and transient activation of a first MAPK response and c-Jun. In a second phase, high burden of hyphae are recognized which results in continued activation of NF- κ B along with further, stronger activation of a secondary MAPK response and activation of c-Fos, which causes cytokine expression. The MKP1 phosphatase acts in a negative feedback loop and prevents an over-reaction of the immune system [52**].

duction is presumed to augment this protective response by inducing epithelial cells to produce defensins. It may be that epithelial damage caused by penetrating hyphae also leads to the release of cellular ATP, which is known to also drive Th-17 cell differentiation. Therefore, hyphae may have several roles in inducing immune responses in: (a) specifically activating the p38/c-Fos and ERK/MKP1 pathways leading to immune activation and regulation; (b) enhancing the secretion of Th-17-type cytokines; (c) causing damage and release of ATP that activates the inflammasome of immune cells; and (d) inducing IL-22 production by Th-17 cells that enhances the production of defensins in the epithelium. The nature of the morphology-specific PAMPs that drive these polarization in immune response remain to be discovered.

Conclusions

The transition from *C. albicans* commensalism to invasive growth is not an event, but rather a shift in dynamic equilibrium between host and pathogen associated factors. For the fungus to be retained on the healthy surface of a host tissue it must be able to counter the effects of the sentinel activity of mucosal immunity mechanisms, to compete with other microbes for space and nutrients, and the sloughing off of the cellular substrate to which it is tethered. To do this it must have evolved mechanisms for retention and immune avoidance that in a different context (e.g. immunosuppression) can be seen as traits that also promote pathogenesis. Emerging evidence does, however, support a view that yeast cells on the surface of the mucosa do not trigger strong inflammatory

responses. By contrast, infiltrating hyphae induce cellular damage, activate inflammasome complexes and MAP kinase pathways and induce the recruitment of neutrophils that operate to counter their further ramification at the attempted site of infection. Many of these mechanisms of homeostasis and innate immune activation are controlled or triggered by molecules of the fungal cell wall. Cell wall proteins represent many of the key pathogen virulence attributes (adhesins, invasins, hydrolases, etc.), but may also be recognized by the host. Cell wall carbohydrates act predominantly as PAMPS that induce both protective immunity and potentially pathogenic overactivation of the inflammatory response. The complexity of this interaction of the host is also expressed at subsequent phases of infection, for example during invasive growth. In all these dynamic processes the cell wall plays a central role in defining the equilibrium between commensalism and disease.

Acknowledgements

The authors wish to thank Drs Ashim Das and Ilse Jacobsen for images used in Figure 1. Our own research is supported by the Wellcome Trust, EC (ALLFUN, Ariadne) BBSRC and MRC (to NG) and the Federal Ministry of Education and Research (BMBF: ERA Net PathoGenoMics CandiCol 0315901B), the Center for Sepsis Control and Care (CSCC – BMBF 01EO1002), the Deutsche Forschungsgemeinschaft (DFG Hu 528/15, 16 and 17), the European Union (CaInfectome PIEF-GA-2008-219406, FinSysB MCRTN FP7-214004), the Jena School for Microbial Communication (JSMC), the International Leibniz Research School for Microbial and Biomolecular Interactions (ILRS) and the company Bayer Vital (to BH).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Moran G, Coleman D, Sullivan D: **An introduction to the medically important *Candida* species.** In *Candida and Candidiasis*, edn 2. Edited by Calderone RA, Clancy CJ. ASM Press; 2012:11-25.
 2. Netea MG, Gow NAR: **Innate immunity to *Candida* infections.** In *Candida and Candidiasis*, edn 2. Edited by Calderone RA, Clancy CJ. ASM Press; 2012:155-170.
 3. Mochon AB, Jin Y, Kayala MA, Wingard JR, Clancy CJ, Nguyen MH, Felgner P, Baldi P, Liu H: **Serological profiling of a *Candida albicans* protein microarray reveals permanent host-pathogen interplay and stage-specific responses during candidemia.** *PLoS Pathog* 2010, **6**:e1000827.
 4. Hube B: **Fungal adaptation to the host environment.** *Curr Opin Microbiol* 2009, **12**:347-349.
 5. Martin R, Wächtler B, Schaller M, Wilson D, Hube B: **Host-pathogen interactions and virulence-associated genes during *Candida albicans* oral infections.** *Int J Med Microbiol* 2011, **301**:417-422.
 6. Naglik JR, Moyes DL, Wächtler B, Hube B: ***Candida albicans* interactions with epithelial cells and mucosal immunity.** *Microbes Infect* 2011, **13**:963-976.
 7. Wächtler B, Wilson D, Haedicke K, Dalle F, Hube B: **From attachment to damage: defined genes of *Candida albicans* mediate adhesion, invasion and damage during interaction with oral epithelial cells.** *PLoS ONE* 2011, **6**:e17046.
- First systematic study, which suggests that adhesion, invasion and damage are mediated by distinct factors of *Candida albicans*.
8. Zordan R, Cormack B: **Adhesins in opportunistic fungal pathogens.** In *Candida and Candidiasis*, edn 2. Edited by Calderone RA, Clancy CJ. ASM Press; 2012:243-259.
 9. Martinez-Lopez R, Park H, Myers CL, Gil C, Filler SG: ***Candida albicans* Ecm33p is important for normal cell wall architecture and interactions with host cells.** *Eukaryot Cell* 2006, **5**:140-147.
 10. Liu Y, Filler SG: ***Candida albicans* Als3, a multifunctional adhesin and invasin.** *Eukaryot Cell* 2011, **10**:168-173.
 11. Dalle F, Wächtler B, L'Ollivier C, Holland G, Bannert N, Wilson D, Labruere C, Bonnin A, Hube B: **Cellular interactions of *Candida albicans* with human oral epithelial cells and enterocytes.** *Cell Microbiol* 2010, **12**:248-271.
 12. Brand A, Gow NA: **Mechanisms of hypha orientation of fungi.** *Curr Opin Microbiol* 2009, **12**:350-357.
 13. Singh A, Del Poeta M: **Lipid signalling in pathogenic fungi.** *Cell Microbiol* 2011, **13**:177-185.
 14. Hube B: **From commensal to pathogen: stage- and tissue-specific gene expression of *Candida albicans*.** *Curr Opin Microbiol* 2004, **7**:336-341.
 15. Phan QT, Myers CL, Fu Y, Sheppard DC, Yeaman MR, Welch WH, Ibrahim AS, Edwards JE Jr, Filler SG: **Als3 is a *Candida albicans* invasin that binds to cadherins and induces endocytosis by host cells.** *PLoS Biol* 2007, **5**:e64.
 16. Spellberg BJ, Ibrahim AS, Avanesian V, Fu Y, Myers C, Phan QT, Filler SG, Yeaman MR, Edwards JE Jr: **Efficacy of the anti-*Candida* rAls3p-N or rAls1p-N vaccines against disseminated and mucosal candidiasis.** *J Infect Dis* 2006, **194**:256-260.
 17. Pietrella D, Rachini A, Pandey N, Schild L, Netea M, Bistoni F, Hube B, Vecchiarelli A: **The inflammatory response induced by aspartic proteases of *Candida albicans* is independent of proteolytic activity.** *Infect Immun* 2010, **78**:4754-4762.
 18. Kruppa M: **Quorum sensing and *Candida albicans*.** *Mycoses* 2009, **52**:1-10.
 19. Netea MG, Brown GD, Kullberg BJ, Gow NA: **An integrated model of the recognition of *Candida albicans* by the innate immune system.** *Nat Rev Microbiol* 2008, **6**:67-78.
 20. Netea MG, Gow NA, Munro CA, Bates S, Collins C, Ferwerda G, Hobson RP, Bertram G, Hughes HB, Jansen T *et al.*: **Immune sensing of *Candida albicans* requires cooperative recognition of mannans and glucans by lectin and Toll-like receptors.** *J Clin Invest* 2006, **116**:1642-1650.
 21. Brown GD: **Innate antifungal immunity: the key role of phagocytes.** *Annu Rev Immunol* 2011, **29**:1-21.
 22. Dennehy KM, Ferwerda G, Faro-Trindade I, Pyz E, Willment JA, Taylor PR, Kerrigan A, Tsoni SV, Gordon S, Meyer-Wentrup F *et al.*: **Syk kinase is required for collaborative cytokine production induced through Dectin-1 and Toll-like receptors.** *Eur J Immunol* 2008, **38**:500-506.
 23. Cheng SC, van de Veerendonk FL, Lenardon M, Stoffels M, Plantinga T, Smeekens S, Rizzetto L, Mukaremera L, Preechasuth K, Cavalieri D *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 Leukoc Biol* 2011, **90**:357-366.
 24. Gringhuis SI, Kaptein TM, Wevers BA, Theelen B, van der Vliet M, Boekhout T, Geijtenbeek TB: **Dectin-1 is an extracellular pathogen sensor for the induction and processing of IL-1beta via a noncanonical caspase-8 inflammasome.** *Nat Immunol* 2012, **13**:246-254.
- This report shows that, in addition to the activation of NLRP3-caspase-1 inflammasome, *Candida albicans* can also trigger IL-1 β via a non-canonical caspase-6 inflammasome via a dectin-1 dependent mechanism.
25. Rubin-Bejerano I, Fraser I, Grisafi P, Fink GR: **Phagocytosis by neutrophils induces an amino acid deprivation response in *Saccharomyces cerevisiae* and *Candida albicans*.** *Proc Natl Acad Sci USA* 2003, **100**:11007-11012.

26. Wheeler RT, Kombe D, Agarwala SD, Fink GR: **Dynamic, morphotype-specific *Candida albicans* beta-glucan exposure during infection and drug treatment.** *PLoS Pathog* 2008, **4**:e1000227.
27. Mora-Montes HM, Netea MG, Ferwerda G, Lenardon MD, Brown GD, Mistry AR, Kullberg BJ, O'Callaghan CA, Sheth CC, Odds FC *et al.*: **Recognition and blocking of innate immunity cells by *Candida albicans* chitin.** *Infect Immun* 2011, **79**:1961-1970.
- In this report the presence of pure *C. albicans* chitin is shown to block the production of a number of pro-inflammatory cytokines when monocytes are exposed to yeast cells. Caspofungin-treated cells, with high levels of chitin exposed at the cell surface, are shown to also be attenuated in cytokine production.
28. Nagatan K, Wang S, Llado V, Lau CW, Li Z, Mizoguchi A, Nagler CR, Shibata Y, Reinecker H-C, Rodrigo Mora J *et al.*: **Chitin microparticles for the control of intestinal inflammation.** *Inflamm Bowel Dis* 2012 <http://dx.doi.org/10.1002/ibd.22874>.
29. Reese TA, Liang HE, Tager AM, Luster AD, Van Rooijen N, Voehringer D, Locksley RM: **Chitin induces accumulation in tissue of innate immune cells associated with allergy.** *Nature* 2007, **447**:92-96.
30. Schlosser A, Thomsen T, Moeller JB, Nielsen O, Tornøe I, Mollenhauer J, Moestrup SK, Holmskov U: **Characterization of FIBCD1 as an acetyl group-binding receptor that binds chitin.** *J Immunol* 2009, **183**:3800-3809.
31. Lenardon MD, Munro CA, Gow NA: **Chitin synthesis and fungal pathogenesis.** *Curr Opin Microbiol* 2010, **13**:416-423.
32. Bueter CL, Lee CK, Rathinam VA, Healy GJ, Taron CH, Specht CA, Levitz SM: **Chitosan but not chitin activates the inflammasome by a mechanism dependent upon phagocytosis.** *J Biol Chem* 2011, **286**:35447-35455.
33. Villiers C, Chevallet M, Diemer H, Couderc R, Freitas H, Van Dorselaer A, Marche PN, Rabilloud T: **From secretome analysis to immunology: chitosan induces major alterations in the activation of dendritic cells via a TLR4-dependent mechanism.** *Mol Cell Proteomics* 2009, **8**:1252-1264.
34. Gow NA, Brown AJ, Odds FC: **Fungal morphogenesis and host invasion.** *Curr Opin Microbiol* 2002, **5**:366-371.
35. Gow NA, van de Veerdonk FL, Brown AJ, Netea MG: ***Candida albicans* morphogenesis and host defence: discriminating invasion from colonization.** *Nat Rev Microbiol* 2011, **10**:112-122.
36. Sudbery PE: **Growth of *Candida albicans* hyphae.** *Nat Rev Microbiol* 2011, **9**:737-748.
37. Almeida RS, Brunke S, Albrecht A, Thewes S, Laue M, Edwards JE, Filler SG, Hube B: **The hyphal-associated adhesin and invasive Als3 of *Candida albicans* mediates iron acquisition from host ferritin.** *PLoS Pathog* 2008, **4**:e1000217.
38. Hoyer LL, Green CB, Oh SH, Zhao X: **Discovering the secrets of the *Candida albicans* agglutinin-like sequence (ALS) gene family – a sticky pursuit.** *Med Mycol* 2008, **46**:1-15.
39. Fradin C, De Groot P, MacCallum D, Schaller M, Klis F, Odds FC, Hube B: **Granulocytes govern the transcriptional response, morphology and proliferation of *Candida albicans* in human blood.** *Mol Microbiol* 2005, **56**:397-415.
40. Frohner IE, Bourgeois C, Yatsyk K, Majer O, Kuchler K: ***Candida albicans* cell surface superoxide dismutases degrade host-derived reactive oxygen species to escape innate immune surveillance.** *Mol Microbiol* 2009, **71**:240-252.
41. Martchenko M, Alarco AM, Harcus D, Whiteway M: **Superoxide dismutases in *Candida albicans*: transcriptional regulation and functional characterization of the hyphal-induced SOD5 gene.** *Mol Biol Cell* 2004, **15**:456-467.
42. Naglik JR, Challacombe SJ, Hube B: ***Candida albicans* secreted aspartyl proteinases in virulence and pathogenesis.** *Microbiol Mol Biol Rev* 2003, **67**:400-428 table of contents.
43. Wozniak I, Hornbach A, Schmitt C, Frosch M, Einsele H, Hube B, Löffler J, Kurzai O: **Induction of ERK-kinase signalling triggers morphotype-specific killing of *Candida albicans* filaments by human neutrophils.** *Cell Microbiol* 2008, **10**:807-820.
- Study that suggests that neutrophils are predominantly attracted by *Candida albicans* hyphae, but not by yeast cells.
44. d'Ostiani CF, Del Sero G, Bacci A, Montagnoli C, Spreca A, Mencacci A, Ricciardi-Castagnoli P, Romani L: **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* 2000, **191**:1661-1674.
45. Gantner BN, Simmons RM, Underhill DM: **Dectin-1 mediates macrophage recognition of *Candida albicans* yeast but not filaments.** *EMBO J* 2005, **24**:1277-1286.
46. Sato K, Yang XL, Yudate T, Chung JS, Wu J, Luby-Phelps K, Kimberly RP, Underhill D, Cruz PD Jr, Ariizumi K: **Dectin-2 is a pattern recognition receptor for fungi that couples with the Fc receptor gamma chain to induce innate immune responses.** *J Biol Chem* 2006, **281**:38854-38866.
47. Murciano C, Moyes DL, Runglall M, Islam A, Mille C, Fradin C, Poulain D, Gow NA, Naglik JR: ***Candida albicans* cell wall glycosylation may be indirectly required for activation of epithelial cell proinflammatory responses.** *Infect Immun* 2011, **79**:4902-4911.
48. van der Graaf CA, Netea MG, Verschueren I, van der Meer JW, Kullberg BJ: **Differential cytokine production and Toll-like receptor signaling pathways by *Candida albicans* blastoconidia and hyphae.** *Infect Immun* 2005, **73**:7458-7464.
- This paper shows that hyphae stimulate far less IFN γ from human monocytes than yeast cells and that this discrimination may be due to a loss of TLR4-mediated recognition during hyphal development.
49. Losse J, Svobodova E, Heyken A, Hube B, Zipfel PF, Jozsi M: **Role of pH-regulated antigen 1 of *Candida albicans* in the fungal recognition and antifungal response of human neutrophils.** *Mol Immunol* 2011, **48**:2135-2143.
50. Soloviev DA, Jawhara S, Fonzi WA: **Regulation of innate immune response to *Candida albicans* infections by alphaMbeta2-Pra1p interaction.** *Infect Immun* 2011, **79**:1546-1558.
51. Zipfel PF, Skerka C, Kupka D, Luo S: **Immune escape of the human facultative pathogenic yeast *Candida albicans*: the many faces of the *Candida* Pra1 protein.** *Int J Med Microbiol* 2011, **301**:423-430.
52. Moyes DL, Runglall M, Murciano C, Shen C, Nayar D, Thavaraj S, Kohli A, Islam A, Mora-Montes H, Challacombe SJ *et al.*: **A biphasic innate immune MAPK response discriminates between the yeast and hyphal forms of *Candida albicans* in epithelial cells.** *Cell Host Microbe* 2010, **8**:225-235.
- First study suggesting a mechanism by which epithelial cells may discriminate between colonizing and pathogenic *Candida albicans* cells.
53. Moyes DL, Murciano C, Runglall M, Islam A, Thavaraj S, Naglik JR: ***Candida albicans* yeast and hyphae are discriminated by MAPK signaling in vaginal epithelial cells.** *PLoS ONE* 2011, **6**:e26580.
54. van de Veerdonk FL, Joosten LA, Shaw PJ, Smeekens SP, Malireddi RK, van der Meer JW, Kullberg BJ, Netea MG, Kanneganti TD: **The inflammasome drives protective Th1 and Th17 cellular responses in disseminated candidiasis.** *Eur J Immunol* 2011, **41**:2260-2268.
55. van de Veerdonk FL, Marijnissen RJ, Kullberg BJ, Koenen HJ, Cheng SC, Joosten I, van den Berg WB, Williams DL, van der Meer JW, Joosten LA *et al.*: **The macrophage mannose receptor induces IL-17 in response to *Candida albicans*.** *Cell Host Microbe* 2009, **5**:329-340.
56. Romani L: **Cell mediated immunity to fungi: a reassessment.** *Med Mycol* 2008, **46**:515-529.
57. Tomalka J, Ganesan S, Azodi E, Patel K, Majmudar P, Hall BA, Fitzgerald KA, Hise AG: **A novel role for the NLRP4 inflammasome in mucosal defenses against the fungal pathogen *Candida albicans*.** *PLoS Pathog* 2011, **7**:e1002379.