Epithelial Cell Innate Response to *Candida albicans*

J.R. Naglik* and D. Moyes

Department of Oral Immunology, Dental Institute, King's College London, London, United Kingdom; *corresponding author, julian.naglik@kcl.ac.uk

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ABSTRACT

With the advent of treatments and diseases such as AIDS resulting in increasing numbers of patients with suppressed immune systems, fungal diseases are an escalating problem. *Candida albicans* is the most common of these fungal pathogens, causing infections in many of these patients. It is therefore important to understand how immunity to this fungus is regulated and how it might be manipulated. Although work has been done to identify the receptors, fungal moieties, and responses involved in anti-*Candida* immunity, most studies have investigated interactions with myeloid or lymphoid cells. Given that the first site of contact of *C. albicans* with its host is the mucosal epithelial surface, recent studies have begun to focus on interactions of *C. albicans* with this site. The results are startling yet in retrospect obvious, indicating that epithelial cells play an important role in these interactions, initiating responses and even providing a level of protection. These findings have obvious implications, not just for fungal pathogens, but also for identifying how host organisms can distinguish between commensal and pathogenic microbes. This review highlights some of these recent findings and discusses their importance in the wider context of infection and immunity.

With the advent of the AIDS epidemic, with modern medical interventions such as cancer therapy and allogeneic transplantation, we have witnessed a rapid rise in the prevalence of fungal infections. This is the combined result of reducing the CD4⁺ lymphocyte population of the cell-mediated immune system and using immunosuppressive therapies (*i.e.*, steroids). The predisposition of certain patient groups to a multitude of opportunistic fungal infections led to a notable increase in basic research into pathogenic fungi, predominantly on *Candida* sp., *Cryptococcus neoformans*, and *Aspergillus fumigatus* (Odds, 2000). The outcome of this research has led to the unraveling of many fundamental biological processes that take place

during host-fungal interactions, particularly with regard to *Candida albicans*.

EPITHELIAL INNATE IMMUNITY AND *C. ALBICANS*

Innate immunity plays the vital role of gatekeeper of the mucosal epithelia. It is required to maintain homeostatic function and coordinate immunologic reactions against commensal and pathogenic microbes. The specialized interaction among resident microbes, epithelial cells, and local immune cells results in either a degree of mutualism (commensalism) or a breach of the mucosal barrier and subsequent cell injury (pathogenicity). Of particular interest are “opportunistic” microbes such as *C. albicans*, the most common fungal pathogen of humans. *Candida* spp. reside as commensal organisms in the normal oral, vaginal, and gut flora in approximately half the population. However, if the balance of the normal flora is disrupted or the immune defenses are compromised, *Candida* spp. often become pathogenic, causing mucosal disease in a significant proportion of immunosuppressed individuals and women of fertile age (Sobel, 1992). The majority of patients experience only superficial forms of mucosal candidiasis—most commonly, thrush. Determining exactly how this transformation from “commensal to pathogen” takes place and how it can be prevented is a continuing challenge. Although many virulence attributes have been suggested to contribute to *Candida* infections (Naglik *et al.*, 2003), hyphal formation and subsequent invasion have been the most widely studied and most compelling (Calderone and Fonzi, 2001; Zakikhany *et al.*, 2007). Currently, one of the most fundamental immunologic issues is to determine how the host distinguishes between commensal colonization and virulent infection and between the yeast and hyphal form of this fungus. Here, we examine the mechanisms by which the major constituent of any mucosal surface, the epithelial cell, responds to the human fungal pathogen *C. albicans*.

PATTERN RECOGNITION OF *C. ALBICANS*

Detection of pathogens at mucosal surfaces is primarily an innate immune-mediated event, using a multitude of detection systems. Detection almost invariably involves recognition of pathogen-associated molecular patterns—either secreted by or present on the surface of microbes—by a large group of receptors

Key Words

HIV/AIDS, mycology, innate immunity, oral epithelium, fungal pathogens.

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Table. Classes of Pattern Recognition Receptors

PRR	Location	Recognition Molecules	Role in Fungal Responses
TLR			
1/2	Surface	Lipoproteins; triacylated lipopeptides; zymosan?	Possibly
2	Surface	Peptidoglycan; lipoproteins; glycolipids; lipoaribomannan; zymosan	Yes
3	Endosomal	dsRNA; poly (I:C)	Possibly
4	Surface/cytoplasmic	Lipopolysaccharide; lipid A; fungal O-mannan	Yes
5	Surface	Flagellin	No
6/2	Surface	Diacylated lipopeptides; zymosan?	Possibly
7	Endosomal	ssRNA; imidazoquinolines	No
8	Endosomal	ssRNA; imidazoquinolines	No
9	Endosomal	Unmethylated CpG DNA, fungal DNA?	Yes?
10	Surface?	Unknown	No
Lectins			
C-type ^a	Surface/extracellular	Variable; fungal β -glucans and mannan	Yes
Galectins	Cytoplasm/nucleus; extracellular	β -Galactosides (variety of complex N-glycans)	Yes
Siglecs	Surface	Variable; sialic acids	No
Pentraxins ^b	Body fluids	Variable; bind and activate the complement system	Probably
LBP	Extracellular	Lipopolysaccharide	Possibly
NLR			
NOD1/2	Cytoplasmic	Muramyl dipeptide	Possibly
NALP1	Cytoplasmic	Variable	Probably
NALP3	Cytoplasmic	Variable	Probably
RLH			
RIG-I	Cytoplasmic	5'-triphosphate ssRNA	No
MDA-5	Cytoplasmic	ssRNA	No

Poly (I:C), polyriboinosinic:polyribocytidylic acid; LBP, lipopolysaccharide binding protein; NOD1/2, nucleotide-binding oligomerization domain containing 1 or 2; NALP1/3, NACHT, LRR, and pyrin domain containing protein 1 or 3; RLH, retinoic acid-inducible gene I-like helicases; RIG-I, retinoic acid-inducible gene I; MDA-5, melanoma differentiation-associated gene 5.

^aDectin-1/2, MR, DC-SIGN.

^bPTX3 (Pentraxin 3), CRP (C-reactive protein), SAP (serum amyloid protein), MBL (mannose binding lectin), C1q and C3 (complement components).

termed *pattern recognition receptors* (PRRs) (Table). These PRRs include the well-known Toll-like receptors (TLRs), the C-type lectin receptors, and the Nod-like receptors (Kumagai *et al.*, 2008; Hollmig *et al.*, 2009) and have varying cellular locations. Although these 3 families constitute the majority of the currently known PRRs, others exist and more are being discovered each year. Thus, the PRRs form a large arsenal of receptors, all detecting different aspects of a microbial organism.

The known PRRs utilized by myeloid cells to detect *C. albicans* pathogen-associated molecular patterns are reasonably well defined—they include TLR2 (phospholipomannan), TLR4 (O-bound mannans), mannose receptor (N-bound mannans), dectin-1 (β -glucans), dectin-2 (hypha-specific high-mannose containing structures), DC-SIGN (dendritic cell-specific intercellular adhesion molecule 3—grabbing nonintegrin: α -linked mannans), galectin-3 (β -1,2 mannosides), and potentially, TLR9 (fungal DNA) (Netea *et al.*, 2008; Roeder *et al.*, 2004a). However, recognition is complex, and although each receptor can function individually, synergy exists between these receptors. In particular, TLR2 and dectin-1 work in conjunction to regulate cytokine responses and phagocytosis (Gantner *et al.*, 2003). However, the PRR-mediated recognition systems that initiate innate responses in epithelial cells are still largely unknown or undefined.

PRR EPITHELIAL RESPONSES TO *C. ALBICANS*

We and others have shown that epithelial cells express a range of PRRs, including TLR 1-6 and 8-10, dectin-1 and galectins, as well as adaptors and coreceptors, such as CD14 and MyD88 (Weindl *et al.*, 2007; Backhed and Hornef, 2003; Hornef and Bogdan, 2005). In further work, we compared TLR expression profiles in oral (TR146) and vaginal (A431) epithelial cells and discovered that the range of TLR expression was similar in both types (unpublished data). TLR 2 and 5 were expressed at high levels, which is notable because stimulation of these TLRs has been associated with epithelial repair, growth, and survival (Shaykhiev *et al.*, 2008; Rhee *et al.*, 2005). In comparison with vaginal epithelial cells (A431 epidermal lineage), oral epithelial cells (TR146 buccal lineage) generally expressed higher levels of most TLRs—particularly, TLR 1, 3, and 6. Interestingly, TLR4 was undetectable or expressed at extremely low levels in both epithelial cells, confirming published reports (Backhed and Hornef, 2003) and indicating that mucosal tissues might be unresponsive to TLR4 stimulation. Indeed, we have demonstrated that oral and vaginal epithelial cells are unresponsive to *Escherichia coli* lipopolysaccharide (unpublished data). Infection of epithelial cell monolayers and reconstituted human epithelium with *C. albicans* resulted in strong downregulation

Fig. 1. Signal pathway activation by different surface PRRs. All known PRRs activate MAPK and NF- κ B signal pathways but may differ in the extent to which they activate these pathways or which combination of these pathways are activated, thus allowing differences in the responses generated. Here we show the different upstream mechanisms by which different families of PRRs activate these pathways. TLRs are the best-described family and utilize Toll/IL-1 receptor domain-containing adapter proteins such as MyD88, MAL, TRAM, and TRIF. The other surface PRRs usually signal using ITAM and ITIM domains. Examples of ITAM domain-containing PRRs include the C-type lectin dectin-1. These proteins either contain an ITAM domain within their cytoplasmic region (as with dectin-1) or associate with an ITAM-containing transducing protein (e.g., dectin-2 with Fc γ). Dectin-1 utilizes Src kinases and Syk kinase to activate a complex containing CARD9, MALT1, and Bcl10 to activate the downstream signal pathways. ITIM domain-containing PRRs are generally considered to be inhibitory, activating the inhibitory phosphatases SHP1 and SHP2, although there is some evidence to suggest that they may also play a role in activation. Examples of these proteins include the S-type lectins or Siglecs.

of most TLRs, specifically in oral epithelial cells. TLR2 was the only upregulated TLR but only in oral epithelial cells and not vaginal cells. Because the TLRs are generally downregulated and TLR2 has been shown to exhibit a negative or suppressive role (Netea *et al.*, 2004), the data suggest that *C. albicans* may negatively regulate TLR-mediated sensing in oral epithelial cells. This induction of negative regulation by *C. albicans* does not occur in myeloid cells, which suggests a specific response in mucosal tissues.

Although epithelial TLR profiles may be modified by *C. albicans*, the PRRs that epithelial cells utilize to initially recognize *C. albicans* are currently undefined, although several have been suggested. We have demonstrated that initial activation of epithelial cells is unlikely to be through TLR2, TLR4, or dectin-1, because blocking of these receptors with antibodies does not appear to alter the epithelial cytokine profile (Weindl *et al.*, 2007). Given that mannans and β -glucans are the classic fungal moieties recognized by TLR2, TLR4, or dectin-1 in myeloid cells, these data further confirm that epithelial cell PRR responsiveness is different from that of myeloid cells.

PRR-INDUCED EPITHELIAL SIGNALLING

PRR ligation of *Candida* pathogen-associated molecular patterns results in the activation of intracellular signaling pathways, leading to transcriptional activation of genes in the nucleus and, ultimately, the production of novel proteins (Fig. 1). Initiation of signaling involves several potential mechanisms, depending on the PRR (Ivashkiv, 2008; Kenny and O'Neill, 2008; O'Neill, 2008; Tsoni and Brown, 2008). TLRs, for example, contain a Toll/IL-1 receptor domain in their cytoplasmic region that interacts with adaptor proteins—most commonly, MyD88 (myeloid differentiation 88) but also TRIF (Toll/IL-1 receptor domain-containing adaptor-inducing interferon β), TRAM (TRIF-related adaptor molecule), and MAL (MyD88 adapter-like protein). This interaction leads to the activation of the IRAK (IL-1 receptor-associated kinase) proteins and TRAF6 (TNF receptor-associated factor 6). In turn, this leads to activation of the NF- κ B and MAPK pathways (respectively, nuclear factor kappa light chain enhancer of activated B cells and mitogen-activated protein kinase), as well as IRF (interferon regulatory factor) signaling via IRF 3, 5, and 7.

The MAPK pathways constitute 3 arms: p38, JNK (c-Jun N-terminal kinase), and ERK1/2 (extracellular signal-regulated kinase 1/2). However, C-type lectin receptors are thought to signal through activation of ITAM/ITIM cytoplasmic domains (immunoreceptor tyrosine-based activation/inhibition motif)—through their own (e.g., dectin-1) or through a coreceptor, such as DAP12 (DNAX activation protein of 12 kDa) and FcR γ (Fc gamma chain receptor; e.g., dectin-2). Ligation of these receptors leads to activation of a different set of early adaptors—predominantly, Src family kinases such as Src, Lyn, and Fyn. In the case of dectin-1, this leads to activation of Syk kinase and the downstream activation of the CARD9/Bcl10/MALT1 signaling complex (caspase recruitment domain family/B-cell CLL-lymphoma 10/mucosa-associated lymphoid tissue lymphoma translocation gene 1). Irrespective of the C-type lectin receptor pathways and adapters used, the result is the activation of the NF- κ B and MAPK pathways.

Further regulation of these pathways is achieved by activation of other signal-associated proteins. For example, specific regulation of MAPK responses occurs via the action of dual specificity phosphatases, also known as MKPs (MAPK phosphatases; Liu *et al.*, 2007). In the case of ITIM activation, the SHP protein tyrosine phosphatases are activated, which generally suppresses signaling. Which of these pathways and proteins are induced depends on the PRR activated and the heterogeneity of responses generated by the different PRRs will manifest through differences in the activation of alternative elements of these pathways. For example, one pathway may lead to the activation of p38 and JNK but not ERK1/2 MAPK signaling, whereas another may lead to JNK and ERK1/2 but not p38 signaling, with similar differences in the NF- κ B elements activated. However, irrespective of the signal pathways activated, there may be cell-specific differences resulting from different expression levels of the various proteins. The majority of studies defining the PRR-mediated pathways were performed using myeloid or lymphoid cells, but detailed analysis of PRR-mediated pathways in other cell types—specifically, epithelial cells—may yet identify novel and unusual mechanisms of pathogen recognition and control at mucosal surfaces.

To this end, the majority of epithelial cell work has been bacterial based and has identified NF- κ B and MAPK as the main pathways activated (Kinane *et al.*, 2008; Handfield *et al.*, 2008). NF- κ B is also thought to be a likely signaling candidate in the activation of epithelial cells to *Candida* (Pivarcsi *et al.*, 2003; Roeder *et al.*, 2004b). However, in a recent study using oral epithelial cells we demonstrated that the innate response to *C. albicans* is via both NF- κ B and MAPK pathways (Moyes *et al.*, 2010). We found that NF- κ B activation appears to be independent of morphology and results from generic recognition of fungal moieties present on all *Candida* spp. and, probably, fungi in general. The MAPK network appears to elicit the “danger response” and is dependent on hyphal recognition and fungal dose. Further detailed characterization of these signaling pathways in epithelial cell types is required, which will advance our understanding of how human mucosal surfaces recognize, respond to, and control these important fungal pathogens.

C. ALBICANS-INDUCED EFFECTOR RESPONSES

The terminal stages of PRR ligation is the activation of an “effector response” profile in the target cell, which depends on the cell type. In the case of myeloid cells, it usually results in the activation of immune-specific responses, including production of either proinflammatory or anti-inflammatory cytokines. For example, activation of TLR4 on macrophages by lipopolysaccharide leads to the release of IL-1 α , TNF α , and IFN γ (Iwasaki and Medzhitov, 2004). Recognition of *Candida* is similar in this respect, with IL-12, TNF α , and IL-1 (as well as other commonly induced cytokines) being released after stimulation of immune cells (Netea *et al.*, 2008). Also, activation via TLR2 (potentially in conjunction with dectin-1) on macrophages leads to the secretion of IL-12 and TNF α .

With respect to epithelial cells, we and others have shown the secretion of a general profile of proinflammatory cytokines and chemokines after stimulation with *C. albicans*, which includes IL-1 α/β , IL-6, G-CSF, GM-CSF, and TNF α , as well as the chemokines IL-8 and RANTES (Weindl *et al.*, 2007; Schaller *et al.*, 2004; Villar *et al.*, 2005; Dongari-Bagtzoglou and Fidel, 2005). Unlike myeloid and lymphoid cells, epithelial cells do not produce IL-12, IFN γ , IL-4, or IL-13. The effect that these cytokines have on epithelial function and protective responses against *Candida* is currently unclear. However, it is unwise to assume that epithelial cells work independently from other cells. The mucosal surface, though predominantly made up of epithelial cells, includes a variety of other immune cells, such as dendritic cells and neutrophils. Indeed, the naturally high levels of IL-8 released by epithelial cells will actively recruit neutrophils into mucosal tissues, which may constitute an immune surveillance mechanism. The importance of this becomes apparent in the light of recent work that we have described with our collaborators, demonstrating a protective interaction between these 2 cell types against oral candidiasis (Weindl *et al.*, 2007).

Using 3-dimensional organotypic oral (TR146) models, when applied alone, *C. albicans* induces a proinflammatory cytokine response but fails to signal through or significantly modulate TLR expression. However, addition of polymorphonuclear (PMN) cells to the *C. albicans*-infected model strongly upregulates TLR4 (~100-fold) and protects the epithelium against fungal invasion and cell damage. No alteration in TLR4 expression or protection was observed when PMN cells were added in the absence of *C. albicans*. Of note, *C. albicans*-induced epithelial cell damage was abolished in the presence of PMN cells irrespective of whether the PMN cells were applied apically or basally. This demonstrated that (1) PMN-dependent protection against *C. albicans* infection was independent of PMN migration or direct cell-cell contact with oral epithelial cells and (2) 3-way communication among all 3 cell types (pathogen, epithelial cell, and immune cell) was essential for TLR4 upregulation and subsequent protection. Furthermore, *Candida* invasion and cell injury could be restored by TLR4 blockade (antibody) or “knockdown” of TLR4 using siRNA (short interfering RNA), even in the presence of PMN cells, demonstrating a direct role of epithelial TLR4 in antifungal

Fig. 2. Model for protective innate immune responses against *C. albicans* at oral epithelial surfaces *in vivo*. *C. albicans* induces cytokine and chemokine production from the epithelium, predominantly through activation of NF- κ B and MAPK signaling pathways. This is dose dependent and relies on hypha formation and probably invasion. PMN cells are recruited from blood vessels and secrete TNF α (and other cytokines), which leads to the upregulation of epithelial TLR4 and, subsequently, the protection against *C. albicans* tissue damage and invasion through an as-yet-unknown mechanism.

protective responses. Our data indicate that although epithelial TLR4 does not seem to be utilized in the initiation of responses to *C. albicans*, it is nevertheless involved in mediating a secondary protective effect against *C. albicans* infection in the presence of PMN cells. This is the first description of such a PMN-dependent TLR4-mediated protective mechanism at epithelial surfaces (Fig. 2.). It also indicates that, far from being passive cells, epithelial cells can play a major part in host defense against invading pathogens and may provide significant insights into how fungal infections are managed and controlled in the oral mucosa.

CONCLUSIONS

The host epithelial mechanisms enabling discrimination between the commensal and pathogenic states of this fungus are not fully understood. Different *Candida* spp. and different morphologic forms of *C. albicans* appear to induce a variety of signaling pathways and effector profiles in epithelial cells. We believe that hypha formation and cell invasion are key determinants in activating the MAPK-based danger response pathways, whereas NF- κ B activation constitutes generic recognition of fungal moieties present on all *Candida* spp. and is independent of hypha formation. Further work into how the yeast and hyphal phases of *C. albicans* induce MAPK-based responses will be crucial to determine whether activation of these signaling networks results in a protective host phenotype *in vivo*. Likewise, it will be vital to identify the yeast- and hypha-specific moieties that subvert or activate protective host mechanisms against *C. albicans*. This will significantly advance our understanding of how epithelial cells respond to this and, potentially, other fungal mucosal pathogens. Ultimately, the successful targeting of specific epithelial signaling networks or novel fungal processes/proteins resulting in the prevention or control of infection could provide

a basis for novel therapeutic strategies against a multitude of mucosal pathogens.

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