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# *Candida albicans*–epithelial interactions and induction of mucosal innate immunity

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*Candida albicans* is a human fungal pathogen that causes millions of mucosal and life-threatening infections annually. *C. albicans* initially interacts with epithelial cells, resulting in fungal recognition and the formation of hyphae. Hypha formation is critical for host cell damage and immune activation, which are both driven by the secretion of Candidalysin, a recently discovered peptide toxin. Epithelial activation leads to the production of inflammatory mediators that recruit innate immune cells including neutrophils, macrophages and innate Type 17 cells, which together work with epithelial cells to clear the fungal infection. This review will focus on the recent discoveries that have advanced our understanding of *C. albicans*-epithelial interactions and the induction of mucosal innate immunity.

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## Introduction

*Candida albicans* is normally a harmless commensal organism within the normal microbiota in approximately half the world's population. In the commensal phase, *C. albicans* most likely resides in the mucus layer of mucosal surfaces. However, occasionally and under certain circumstances, *C. albicans* may encounter host cells directly, which may result in the attachment of the fungus to epithelial cells. Depending on the strain of *C. albicans* and the physiological and immune status of the host, this interaction event can lead to superficial overgrowth and epithelial invasion, followed by disease and immune activation. *C. albicans* is the most prevalent *Candida* species causing infections in humans and is the causative agent of oral and vaginal candidiasis (e.g. thrush), giving rise to severe morbidity in millions of individuals worldwide. Given that potentially fatal systemic infections can arise from breaches of the mucosal barrier (predominantly from the gut) it is of paramount importance to understand how *C. albicans* interacts with cells of the innate immune system and how this fungus is restricted to the mucosal surface in health. Critical to this is an understanding of how epithelial cells are able to discriminate between harmless (commensal) and dangerous (pathogenic) *C. albicans* cells, which determines whether a mutually beneficial commensal relationship or immune activation takes place.

## *C. albicans* interaction with epithelial cells: adhesion and invasion

Epithelial cells at mucosal surfaces are the first point of contact with *C. albicans* and constitute the first line of defence. Although fungal pathogenicity depends on the type of mucosal tissue, there are common virulence mechanisms and principles. *C. albicans* adhesion to epithelial cells is mediated through the interaction of fungal cell wall moieties and surface proteins with host receptors (Table 1). *C. albicans* yeast cells are recognized by oral epithelial cells (in the TR146 cell line) and induce three signaling pathways within 15 min; the nuclear factor-kappaB (NF-κB) pathway, the phosphatidylinositol-4,5-bisphosphate 3-kinase (Pi3K), and all three mitogen-activated protein kinase (MAPK) pathways (p38, JNK (c-Jun N-terminal kinase) and ERK1/2 (extracellular signal-regulated protein kinase)). This results in the activation of the p65/p50 transcription factor via NF-κB, the c-Jun transcription factor via JNK and ERK1/2, and AKT (protein kinase B) and mTor (mammalian target of rapamycin) via Pi3K signaling [1,2]. Initial binding may constitute recognition of fungal cell wall mannans and β-glucans but this does not fully activate epithelial cells as proinflammatory cytokines were not induced [2]. Lack of activation by *C. albicans* cell wall polysaccharides was also found in skin keratinocytes [3], suggesting that fungal polysaccharides play a limited role in inducing epithelial/

**Table 1**

***C albicans* genes involved during interactions with epithelial cells**

| Fungal component/gene | Epithelial function or target receptors | Reference |
|---|---|---|
| **Structural polysaccharides** | | |
| β-Glucan | Induces epithelial signaling. | [2] |
| Mannans | Induces epithelial signaling. Receptors not identified. | [2] |
| Chitin | Induces epithelial signaling. Receptors not identified. | [2] |
| **Adhesins** | | |
| *HWP1* | Adhesion to epithelial cells via transglutaminase activity. Specific host receptors unknown. | [8] |
| *ALS1-9* | Adhesin family. Structural studies indicate this family has multiple epithelial targets. | [14,80,81,82,83] |
| *INT1* | Interaction with epithelial integrins. | [84] |
| **Toxins** | | |
| *ECE1* | Parent protein of Candidalysin. Induces c-Fos and MKP1 signaling. Receptor activation indicated but not identified. | [22••] |
| **Endocytosis** | | |
| *ALS3* | Activation of or interaction with E-cadherin, EGFR/Her2, AhR, NEDD9 and PDGF BB | [13,15,16,18•,20•] |
| *SSA1* | HSP70 family member. Activation of or interaction with EGFR/Her2 | [15] |
| **Active penetration/hydrolysis** | | |
| *SAP1-8* | Secreted aspartic proteases — digestion of epithelial tissues. Sap5 degrades E-cadherin | [85,86] |
| *PLB1* | Phospholipase B1 — digestion of epithelial tissues | [87] |
| *LIP1-10* | Lipase family — digestion of epithelial tissues | [88] |

keratinocyte immune responses. While many other yeast-associated secreted/cell-surface proteins (e.g. Sap1-3/9/10, Als1/3/4/9, Mp65, Phr1, Iff4, Sun41, Pra1, Eap1, Utr2 and Ecm33), cell wall processing proteins (e.g. Big1, Mnt1/2, Mnn9), and protein trafficking/vesicle transport proteins (e.g. Vps11) are thought to promote epithelial adhesion, this is likely to be via indirect mechanisms given that these proteins possess complex, multi-factorial functions that contribute to cell wall integrity and hypha formation [4–7].

Adhesion of *C. albicans* to an epithelial cell is a strong inducer of hypha formation. The formation of hyphae occurs within 30–60 min and this is accompanied by the expression of hypha-associated proteins, which are known to possess critical roles in adhesion, invasion, damage induction and immune activation/evasion. The two key hyphal proteins that promote epithelial adhesion are Hwp1 (hyphal wall protein 1) [8] and Als3 (agglutinin-like sequence 3) [9,10]. Hwp1 is highly expressed in human oral infections [11] and acts as a substrate for epithelial transglutaminases, enabling strong covalent links with other epithelial proteins [12]. Als3 is both an adhesin and an invasin, and together with Ssa1 (heat shock protein) promotes the endocytosis of *C. albicans* into epithelial cells via E-cadherin [13–15] and the EGFR/Her2 (epidermal growth factor receptor/human epidermal growth factor 2) complex [16]. Endocytosis is an entirely host driven process and does not require viable hyphae [17]. Other pathways that promote *C. albicans* endocytosis include the PDGF BB (platelet-derived growth factor BB) and NEDD9 (neural precursor-cell-expressed developmentally downregulated protein 9) pathways, which both require hypha formation and Als3 expression [18•]. However, despite possessing adhesion/invasin activities, Als3 does not directly induce epithelial cell damage or cytokine production [19]. The AhR (aryl hydrocarbon receptor) also contributes to the endocytosis of *C. albicans* via Src family kinase phosphorylation of EGFR, but AhR is not involved in epithelial damage or cytokine induction by *C. albicans* and it is unknown how AhR is activated [20•]. Currently, the level of redundancy between these different pathways (E-cadherin, EGFR/Her2, AhR, PDGF BB and NEDD9) and how they communicate to promote *C. albicans* endocytosis is unclear. It is important to note that induced endocytosis is not the only invasion route of *C. albicans*. Indeed, active penetration, which does not require host activities, seems to be the dominant invasion route depending on the type of epithelial cell [21].

## Epithelial damage and immune activation by Candidalysin

While *C. albicans* adhesion and invasion leads to fungal recognition and signal pathway activation, surprisingly this does not translate into epithelial damage or innate immune activation [2,17]. Recently, it was discovered that *C. albicans* hyphae induce both epithelial damage and innate immunity through the secretion of a cytolytic peptide toxin called Candidalysin, which is encoded by