DOI:
10.1016/j.semcdb.2018.02.026

Document Version
Peer reviewed version

Candida innate immunity at the mucosa

Jonathan P. Richardson[a*], David L. Moyes[b] Jemima Ho[a] and Julian R. Naglik[a]

[a]Mucosal & Salivary Biology Division, Dental Institute, King's College London, UK. Email: jonathan.richardson@kcl.ac.uk; jemima.ho@kcl.ac.uk; julian.naglik@kcl.ac.uk

[b]Centre for Host-Microbiome Interactions, Mucosal & Salivary Biology Division, Dental Institute, King's College London, UK. Email: david.moyes@kcl.ac.uk

[*] **Corresponding author**: jonathan.richardson@kcl.ac.uk

Postal Address:

Mucosal & Salivary Biology Division

Room 2.67

Hodgkin Building

King's College London

SE1 1UL

United Kingdom

We request that colour be used for Figure 1.

Abstract

The tremendous diversity in microbial species that colonise the mucosal surfaces of the human body is only now beginning to be fully appreciated. Distinguishing between the behaviour of commensal microbes and harmful pathogens that reside at mucosal sites in the body is a complex, and exquisitely fine-tuned process central to mucosal health. The fungal pathobiont *Candida albicans* is frequently isolated from mucosal surfaces with an asymptomatic carriage rate of approximately 60% in the human population. While normally a benign member of the microbiota, overgrowth of *C. albicans* often results in localised mucosal infection causing morbidity in otherwise healthy individuals, and invasive infection that often causes death in the absence of effective immune defence. *C. albicans* triggers numerous innate immune responses at mucosal surfaces, and detection of *C. albicans* hyphae in particular, stimulates the production of antimicrobial peptides, danger-associated molecular patterns and cytokines that function to reduce fungal burdens during infection. This review will summarise our current understanding of innate immune responses to *C. albicans* at mucosal surfaces.

Keywords

Candida albicans; innate immunity; microbiota; Candidalysin.

1. Introduction

In the past, mucosal surfaces were often considered to be merely a static barrier between the body and the external environment. However, recent research has now redefined mucosal barriers and the epithelial cells that comprise them as highly complex and dynamic structures capable of initiating and modulating several crucial host responses required to maintain tissue homeostasis during health and disease. The mucosal surfaces of the human body provide a varied and challenging niche for bacteria, fungi and viruses. The incredible diversity within the microbial communities that colonise the host mucosa makes differentiating between harmless commensalism and pathogenic behaviour difficult, particularly in the context of pathobionts, which can remain passive for extended periods of time before displaying pathogenic behaviour that is damaging to the host.

Fungi, particularly *Candida* species, are frequently isolated from the skin [1] and the mucosal surfaces of the body [2]. While *C. albicans* is often regarded as the most pathogenic of the *Candida* species, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. krusei* and others contribute significantly to morbidity and mortality. Indeed, the recent emergence of fungal pathogens such as *C. auris* [3] highlight the prominence of *Candida* species and the unrelenting threat they pose to human health.

The morphological plasticity of *C. albicans* is a central virulence trait that facilitates mucosal pathogenesis. Overgrowth of *C. albicans* hyphae at mucosal surfaces occurs when host defences are diminished, resulting in localised mucosal infection. *C. albicans* infections of the oral cavity [2] present as creamy-white fungal plaques on the oral mucosa (pseudomembranous candidiasis), painful reddened lesions on the tongue (erythematous candidiasis) and smooth or nodular lesions on any mucosal surface within the mouth (chronic hyperplastic candidiasis). Growth of *C. albicans* on mucosal surfaces and abiotic

substrates results in the formation of biofilms, which are of increasing concern in medical settings [4, 5]. Regular contact between *Candida* biofilm and the hard palate of the oral cavity can result in *Candida*-associated denture stomatitis, and lifestyle choices (particularly smoking) can result in median rhomboid glossitis of the tongue. *Candida* species are frequently isolated from the gastrointestinal tract [6], which is widely regarded as the primary tissue from which the majority of systemic infections are acquired (usually following surgery or major abdominal trauma). Thus, mucosal colonisation by *Candida* species (and *C. albicans* in particular), is a major risk factor for potential life-threatening candidaemia.

The skin [1, 7] and mucosal surfaces of the body have evolved a number of incredibly sensitive and discerning mechanisms that allow appropriate immune defence to be initiated and controlled in response to changes in microbial behaviour. This article will review our current understanding of innate defences against *C. albicans* at mucosal surfaces.

2. The role of the mycobiome in relation to anti-fungal immunity

With the recent advances made in high-throughput sequencing technologies, researchers are now able to accurately characterise the complex microbial communities that develop within human habitats. The astonishing extent and complexity of these communities that has been revealed in these studies has suggested a level of importance in human health and disease that is only now beginning to be understood, with the "superorganism" or "holobiont" hypotheses being proposed [8]. However, despite the advances being made in this field, attention has largely focussed on the bacterial components of these rich microbial communities.

To date, the fungal communities, or *myco*biome, have yet to be systematically investigated in the same way. There are several reasons for this. First, despite their

97 considerable biomass, fungi account for a relatively small percentage of the genes within
98 the microbiome as compared to bacteria and archaea [9, 10]. Second, isolation of high-
99 quality nucleic acids in sufficient quantities from fungal cells in a microbial community is
100 challenging due to the complex cell wall structures that fungal cells possess, and requires a
101 combination of enzymatic, chemical and mechanical lysis steps that vary with different fungi
102 [11]. Finally, discrimination between the different fungal taxa is dependent on the
103 databases and reference genome catalogues that are available. These databases are
104 currently either incomplete or, in the case of reference genome catalogues, not available at
105 present [12, 13]. However, the data that is available points to a critical role for the
106 mycobiome and fungal components within it, in human health and disease [6, 14-16].
107 Indeed, microbiome analysis of HIV-positive and -negative individuals reveal long-
108 term shifts in the mycobiome but not the bacteriome [17]. While some taxa, such as
109 *Candida* and *Penicillium* appeared in all individuals, HIV-negative individuals were
110 specifically associated with *Pichia, Cladosporium* and *Fusarium* species*,* while HIV-positive
111 individuals showed the presence of *Alternaria*, *Epicoccum* and *Trichosporon*. Moreover,
112 species common to both cohorts, including *Candida,* show differences in their relative
113 abundance. These changes arise from complex interactions between individual taxa of the
114 mycobiome and demonstrate that the *Pichia* spp associated with a healthy mycobiota
115 produce factors that suppress the growth of pathogenic fungi such as *Candida* spp that
116 show greater prevalence in HIV-positive individuals [17]. Thus, the loss of *Pichia* in HIV-
117 positive individuals may in part, explain the prevalence of oral candidiasis associated with
118 HIV-positive status, as a natural inhibitor of *Candida* is lost.
119 In general, changes in the mycobiota are associated with modulation of immune
120 responses and disease progression [6, 18], as well as maintenance of microbial population

architecture and host metabolic function [19]. Furthermore, components of the mycobiota interact with bacteria to impact on disease [15]. For example, the microbiota of Crohn's disease patients contains an abundance of *Candida tropicalis* compared with healthy controls, and positively correlates with the production of anti-*Saccharomyces cerevisiae* antibodies; a diagnostic biomarker of Crohn's disease [15]. Furthermore, both *Serratia marcesens* and *Escherichia coli* are elevated in Crohn's patients, while "beneficial" bacteria (e.g. *Faecalibacterium prausnitzii*) show a significant decrease in their abundance.

Strikingly, the abundance of *S. marcesens*, *E. coli* and *C. tropicalis* in patients with Crohn's disease positively correlate with one another; the biomass and thickness of these triple species biofilms are significantly greater than those of single and double species biofilms, with enrichment in the number of *C. tropicalis* hyphae that bind directly to both bacteria through fimbrial connections [15]. Thus, specific interkingdom microbial interactions may be key determinants in Crohn's disease. Although there is mounting evidence that links changes in the micro/mycobiota with disease, there remains much to understand regarding the complex interactions between the mycobiota, the remaining microbiota, and the host. In order for *C. albicans* to cause disease at a mucosal surface, it must first interact with epithelial cells. The interactions that occur between *C. albicans* and epithelial cells are described below.

3. Interaction of *Candida albicans* with the host mucosa

3.1 Adhesion to epithelial cells

Attachment of *C. albicans* yeast and hyphae to epithelial cells is a prerequisite for colonisation and accordingly, a risk factor for the development of mucosal infection. Attachment of *C. albicans* to mucosal sites of the body can be mediated either directly or

indirectly through association with bacterial and fungal components of the microbiota. While *C. albicans* yeast cells are capable of interacting with and adhering to the host mucosa [20], the switch to hyphal growth invokes extensive transcriptional reprogramming of the fungus [21, 22], leading to changes in the composition of the fungal cell wall [23] that enable a more robust interaction with the epithelial surface to be established and maintained [24]. Two key *C. albicans* hypha-associated adhesins in this process are Als3p and Hwp1p, which mediate direct attachment to epithelial cells.

The Agglutinin-Like Sequence (Als) family of *C. albicans* adhesins contains eight members (Als1-7p and Als9p) which are GPI-linked to β-1-6 glucans in the fungal cell wall. Each member of the Als family contains an N-terminal substrate-binding domain, a highly variable central serine/threonine-rich domain comprised of numerous 36 amino acid tandem repeat sequences, and a C-terminal domain containing the GPI anchor [25]. The Als proteins of *C. albicans* exhibit a complex pattern of morphology-dependent and -independent expression that varies between individual clinical specimens, *in vivo* disease models, and fungal culture conditions *in vitro* [25, 26].

Als3p is strongly upregulated during epithelial infection [27], and disruption of *ALS3* reduces epithelial adhesion *in vitro*. Similarly, an *als2*Δ/PMAL2-*ALS2* mutant (where the one remaining wild type copy of *ALS2* in a heterozygous *ALS2* knockout is placed under the control of a regulatable promoter) also exhibited reduced epithelial adhesion [28]. In contrast, deletion of *C. albicans ALS5*, *ALS6* or *ALS7* increases fungal adhesion to the epithelium [29], indicating that the Als proteins have varied roles in mediating adherence to host mucosa. However, despite these findings, conflicting observations have been made regarding the precise role of *ALS1*, *ALS2* and *ALS4-6* in epithelial attachment [30-32].

168 The structural similarity that exists between specific *C. albicans* proteins and those of
169 the host can in some instances be exploited to confer an advantage to the fungus. Hyphal
170 Wall Protein 1 (Hwp1p) is a hypha-associated adhesin that is strongly expressed during
171 colonisation and infection of the oral mucosa [27, 33]. The amino acid sequence of the
172 Hwp1p N-terminal domain closely resembles that of natural substrates for mammalian
173 transglutaminase enzymes [34]. By mimicking a natural host substrate, *C. albicans* exploits
174 host transglutaminase activity, which covalently couples the N-terminal domain of Hwp1p to
175 the epithelial surface [35]. Hwp1p has a greater affinity for terminally differentiated
176 epithelial cells that display SPR3 and keratin 13 when compared with less differentiated cells
177 [36], and deletion of *HWP1* results in reduced epithelial adhesion and virulence in a murine
178 model of oropharyngeal candidiasis (OPC) [35, 37]. However, while the role of Hwp1p in
179 mucosal infection is clearly established, it plays a minimal role in systemic infection and is
180 therefore habitat specific [38].
181 *C. albicans* Int1p is an adhesin with structural similarity to human leukocyte integrin.
182 Int1p is required for hyphal growth, intestinal colonisation in mice and virulence *in vivo* [39].
183 Heterologous expression of *INT1* in the non-adherent yeast *Saccharomyces cerevisiae*
184 confers adhesion to epithelial cells [39, 40], confirming the role of Int1p as a primary
185 adhesin. Phenotypes associated with *INT1* expression are complex and dose dependent, as
186 reintegration of a single copy of wild type *INT1* into an *int1*Δ/Δ null mutant background
187 restores hyphal growth but not epithelial attachment [39].
188 While only a handful of *C. albicans* proteins have been identified that mediate
189 epithelial adhesion directly, numerous factors have been identified that exert an indirect
190 influence on epithelial attachment. Collectively, these factors affect multiple pathways and
191 processes including the expression and appropriate presentation of adhesins on the fungal

cell wall, and the activation of hypha-associated transcriptional circuitry required to induce the expression of morphology-dependent genes required for enhanced epithelial interaction. The factors that indirectly influence the interaction of *C. albicans* with host mucosa are presented in Table 1.

Table 1. Factors that indirectly influence attachment of *C. albicans* to epithelial cells.

Gene	Function	Epithelial Adhesion of Null Mutant	Epithelial Cell Type	Reference
BIG1	Endoplasmic reticulum protein	Decreased	HeLa	[41]
BST1	Inositol deacylase	Decreased	Caco-2 KB	[42]
CDC10	Septin protein	Decreased	HeLa	[43]
CFL1	Ferric reductase	Decreased	HeLa	[44]
CSF4	Putative glycosidase	Decreased	FaDu	[45]
EAP1	GPI-anchored cell wall protein	Decreased	HEK293	[46]
EFG1	Transcription factor	Decreased	Caco-2	[47]
IFF4	GPI-anchored cell wall protein	Overexpression increases adherence	FaDu	[48]
IPT1	Sphingolipid biosynthesis	Decreased	Gingival	[49]
IRS4	Cell wall integrity	Decreased	HT-29 HeLa FaDu	[50]
KRE5	Glucosyl transferase	Decreased	HeLa	[51]
MNT1	Mannosyl transferase	Decreased	Buccal	[52]
MNT2	Mannosyl transferase	Decreased	Buccal	[53]
MP65	Putative β-glucanase enzyme	Decreased	Buccal Caco-2	[54]
NOT5	Putative transcriptional complex component	Decreased	Buccal	[55]
PDE2	Phosphodiesterase	Decreased	Buccal	[56]
PGA1	Putative GPI-anchored protein	Decreased	HT-29	[57]
PHR1	β-(1, 3)-glucanosyltransferase	Decreased	TR146 Caco-2	[58]
PMT1	Protein mannosyltransferase	Decreased	Caco-2	[59]
PRA1	Zinc sequestration	Decreased	HEK293	[60]
SAP1	Aspartic proteinase	Decreased	Buccal	[61]
SAP2	Aspartic proteinase	Decreased	Buccal	[61]
SAP3	Aspartic proteinase	Decreased	Buccal	[61]

SAP4-6	Aspartic proteinases	Increased	Buccal	[61]
SAP9	Aspartic proteinase	Increased	Buccal	[62]
SAP10	Aspartic proteinase	Decreased	Buccal	[62]
SET1	Methyl transferase	Decreased	FaDu HT-29	[63]
SUN41	Putative glycosidase	Decreased	Caco-2	[64]
TUP1	Transcriptional corepressor	Decreased	SCC15	[65]
VAC1	Putative vesicle transport protein	Decreased	SK-LMS-1	[66]

198

199 **3.2 Epithelial recognition of *C. albicans***

200 Physical recognition of *C. albicans* by host mucosa is achieved through the
201 interaction of epithelial pattern recognition receptors (PRRs) with pathogen-associated
202 molecular patterns (PAMPs). Fungal PAMPs include cell wall proteins which contain
203 conserved structural motifs that are projected from the cell wall into the extracellular
204 environment, and intracellular molecules such as nucleic acids. Toll-like receptors (TLRs), C-
205 type lectin receptors (CLRs) and nucleotide-binding domain leucine-rich receptors (NLRs)
206 comprise the three main families of PRR. A successful PRR-PAMP interaction activates
207 epithelial signalling pathways that contribute to innate defence against fungal infection.
208 While the involvement of PRRs in anti-fungal responses is well documented for myeloid cells
209 [67] (and see sections 7 and 8), relatively little is known about the PRRs involved during
210 epithelial recognition of *C. albicans*.

211 The epithelial ephrin type-A receptor 2 (EphA2) is a recently identified non-classical
212 PRR that binds to exposed β-glucans of *C. albicans* yeast and hyphae [68]. β-glucan-induced
213 phosphorylation of EphA2 is dependent upon fungal burden, and a yeast locked
214 (*efg1*/*cph1*Δ/Δ) *C. albicans* mutant stimulates EphA2 phosphorylation within 15 min,
215 indicating that epithelial recognition of fungus through EphA2 is morphology-independent.
216 Activation of EphA2 results in phosphorylation of MEK1/2 and p38 (leading to downstream

activation of c-Fos), phosphorylation of signal transducer and activator of transcription 3 (Stat3), and secretion of human beta defensin-2, chemokine (C-C motif) ligand 20 (CCL20), interleukin (IL)-1α, IL-1β and IL-8 [68]. Thus, epithelial recognition of *C. albicans* β-glucan via EphA2 results in antifungal and pro-inflammatory responses. The importance of EphA2-mediated innate recognition of *C. albicans in vivo* is highlighted by the observation that immune competent *EphA2*$^{-/-}$ knockout mice have higher fungal burdens in the oral cavity when compared to wild type mice [68].

All TLRs (except TLR7) are expressed by reconstituted human oral epithelium, and all except TLR5 and TLR7 are detectable in buccal epithelial cells from healthy donors [69]. Epithelial TLR4 in particular, plays a direct role in mucosal defence against *C. albicans* infection, a process that is dependent upon an intimate relationship with neutrophils. While infection of oral epithelial cells with *C. albicans in vitro* results in cellular damage and a robust pro-inflammatory response, expression of TLR4 remains unchanged compared to uninfected cells [69]. However, in the presence of polymorphonuclear leukocytes, epithelial cells secrete immune modulators that stimulate a robust PMN-mediated upregulation of epithelial TLR4, concomitant with a reduction in epithelial damage and protection against fungal invasion [69].

3.3 Invasion of mucosal barriers

Invasion of mucosal barriers by *C. albicans* is commensurate with localised infection. While yeast and hyphal morphologies of *C. albicans* are capable of adhering to the host mucosa, it is predominantly the hyphal form of the fungus that invades into the epithelial surface. *C. albicans* uses two temporally and mechanistically distinct mechanisms of invasion that together enable the fungus to access the superficial and underlying epithelial

241 tissues. These mechanisms are receptor-mediated induced endocytosis and active
242 penetration.
243
244 **3.4 Receptor-induced endocytosis**
245 Once attached to the epithelial surface, the hyphae of *C. albicans* invade mucosal
246 barriers by initiating a dynamic and complex host-driven process called receptor-induced
247 endocytosis (RIE) [70, 71]. Indeed, the invading fungus remains completely passive during
248 RIE, as hyphae that are rendered metabolically inviable by thimerosal treatment are still
249 endocytosed by epithelial cells [71]. Endocytosis of *C. albicans* hyphae is triggered by
250 epithelial recognition of fungal invasins expressed on the hypha cell wall, and occurs within
251 4 h of initial contact with epithelial cells [72].
252 While several host receptors are implicated in the process of fungal endocytosis,
253 only two fungal invasins have been identified as triggers of internalisation: the adhesin
254 Als3p, and Ssa1p (a member of the heat shock protein (HSP) 70 family of proteins)
255 expressed on the *C. albicans* cell wall [73, 74]. Disruption of either *ALS3* or *SSA1* result in
256 reduced invasion of epithelial cells and attenuated virulence in a murine model of OPC [73-
257 75], with Als3p in particular playing a dominant role in this process. Als3p and Ssa1p are
258 recognised by the epithelial receptor E-cadherin [73, 74], an interaction that stimulates a
259 dynamic, hypha-induced reorganisation of epithelial clathrin, dynamin and cortactin that
260 culminates in the formation of pseudopods that surround the fungus and facilitate
261 internalisation [76]. Interestingly, inhibition of E-cadherin receptor activity results in a
262 partial, but not complete block of fungal endocytosis [77], suggesting the involvement of
263 additional host epithelial receptors and/or pathways in fungal internalisation. Indeed,

remodelling of the actin cytoskeleton in rabbit corneal epithelial cells is dependent on the small GTPases Cdc42, Rac1, RhoA and the tight junction protein ZO-1 [78].

Recognition of *C. albicans* Als3p and Ssa1p can also occur through interaction with a heterodimeric receptor complex comprised of the epidermal growth factor receptor (EGFR/HER1) and HER2 expressed on epithelial cells [77]. Latex beads coated with a recombinant N-terminal region of Als3p or recombinant Ssa1p are rapidly endocytosed by epithelial cells *in vitro* [73, 74], identifying both proteins as ligands that stimulate epithelial internalisation. During infection of oral epithelial cells *in vitro*, *C. albicans* activates the platelet-derived growth factor BB (PDGF BB) and neural precursor-cell-expressed developmentally down-regulated protein 9 (NEDD9) pathways in a cadherin-independent manner [79]. In contrast, analysis of samples obtained during a clinical study of vaginal candidiasis revealed that the PDGF BB, but not NEDD9 pathway is activated in response to infection [79], highlighting the tissue specific nature of epithelial responses to the fungus.

The aryl hydrocarbon receptor (AhR) is a cytoplasmic ligand-activated transcription factor that plays a central role in EGFR-mediated endocytosis of *C. albicans in vitro* and *in vivo* [80]. Infection of oral epithelial cells with *C. albicans* activates the AhR, which in turn leads to phosphorylation of Src family kinases, culminating in EGFR activation and fungal endocytosis. Inhibition of the AhR in immune-competent and immune-suppressed mice was found to reduce the severity of OPC [80], highlighting the contribution of AhR signalling to disease pathology. Given the intracellular location of the AhR, the mechanism of *C. albicans*-mediated receptor activation is likely to be indirect. However, the specific ligand that is induced by *C. albicans* to activate the AhR has yet to be identified. Small interfering RNA (siRNA)-mediated depletion of EphA2 also reduces RIE of *C. albicans* [68]. EphA2 knockdown

and chemical inhibition of receptor activity reduce EGFR phosphorylation, suggesting that EphA2 and EGFR function in the same endocytosis pathway [68].

Knockout studies investigating the role of the transcription factor Rim101p have provided further insight into the fungal proteins required to induce the uptake of *C. albicans* by epithelial cells. A *C. albicans rim101*Δ/Δ mutant was unable to efficiently initiate RIE by oral epithelial cells [81]. Notably, however, overexpression of Cht2p, Pga7p or Zrt1p in a *rim101*Δ/Δ mutant background restored the ability of *C. albicans* to trigger RIE efficiently, implicating these proteins in the process of epithelial internalisation. Despite the great advances made in our understanding of RIE, the molecular signalling events that drive this epithelial response are yet to be characterised in full and the extent of receptor and pathway redundancy between mechanisms remains to be explored in detail. The *C. albicans* factors involved in the processes of epithelial adhesion and RIE are presented in Figure 1A.

3.5 Active penetration of mucosal surfaces

Mucosal surfaces vary in their structure and cellular composition depending on location within the body. The stratified mucosa of the oral and vaginal lumen comprise several layers of epithelial cells, the outermost of which are terminally differentiated, whereas the epithelium that lines the gastrointestinal (GI) tract is composed of a single (non-stratified) layer of cells. Terminally differentiated epithelial cells are non-proliferative and considered less capable of supporting RIE. In order to invade a mucosal barrier that does not readily internalise hyphae, *C. albicans* uses the process of active penetration.

Unlike RIE, where the fungus remains passive during uptake [71], active penetration of host mucosa by *C. albicans* hyphae relies upon physical attributes of the fungus including turgor pressure, physical advancement of the hyphal tip, and secretion of hydrolytic

311 enzymes that facilitate fungal invasion through or between epithelial cells. Paradoxically,
312 while only a single cell thick, the GI epithelium does not support fungal invasion by RIE, but
313 by active penetration only, highlighting specific differences in epithelial responses to *C.*
314 *albicans*. The mucosal barrier of the GI tract is coated with a layer of mucus. *C. albicans*
315 hyphae secrete the aspartic proteinase Sap2p that degrades gastroinestinal mucins [82] and
316 Sap5p that degrades E-cadherin [83], weakening the adherens junctions between epithelial
317 cells, which may facilitate the translocation of fungus across the gut. Despite these
318 contributions however, our understanding of the fungal proteins required for the process of
319 active penetration remains incomplete.
320 Surprisingly, Als3p is not essential for active penetration as an *als3Δ/Δ* null mutant
321 can still invade epithelial cells that are unable to endocytose hyphae [75]. However, Als3p
322 may nevertheless provide points of anchorage on the mucosal surface which enable hyphal
323 pressure upon the epithelial barrier to be sustained. Active penetration of *C. albicans*
324 hyphae through mucosal barriers is delayed in onset compared with RIE and is also
325 mechanistically distinct, as blocking the polymerisation of epithelial actin does not prevent
326 the mucosa from being breached [75, 84]. *In vivo*, it is likely that a combination of active
327 penetration and RIE are required for full invasion of stratified epithelial barriers. Active
328 penetration across the outermost (terminally differentiated) epithelial layers is thought to
329 occur first, and this is followed by RIE, when the invading fungus reaches the underlying
330 (non-terminally differentiated) epithelial cells.
331
332 **4. Candidalysin: epithelial damage and innate immunity**
333 One of the hallmarks of *C. albicans* infection of mucosal surfaces is damage to the
334 superficial epithelium. Damage to the oral and vaginal mucosa is mediated by Candidalysin,

a secreted dual function amphipathic peptide toxin encoded by the extent of cellular elongation gene (*ECE1*) [85, 86]. Candidalysin adopts an alpha helical conformation in solution and intercalates into the plasma membrane of epithelial cells, where it forms heterogeneous and transient lesions that destabilise membrane structure, causing calcium influx and release of intracellular contents (Figure 1B). Importantly, a *C. albicans ece1*Δ/Δ null mutant and a mutant that does not express the Candidalysin-encoding region of *ECE1* (*ece1*Δ/Δ+*ECE1*$_{\Delta 184\text{-}279}$), form hyphae, adhere to and invade epithelial cells normally, but do not cause damage or the secretion of pro-inflammatory cytokines. Moreover, both mutants are attenuated in a murine model of OPC and a Zebrafish swim bladder model of mucosal infection [85].

Epithelial recognition of Candidalysin triggers mucosal immunity predominantly through MAPK signalling, activating the p38 and ERK1/2 pathways that in turn activate the AP-1 transcription factor c-Fos and MAPK phosphatase 1 (MKP1) respectively, alerting the host to the transition from colonising yeast to invasive, toxin-producing hyphae (Figure 1C). Low concentrations of Candidalysin (<15 μM) trigger the release of pro-inflammatory cytokines but do not cause epithelial damage, whereas higher concentrations (70 μM) of toxin induce pro-inflammatory responses and cause extensive damage, demonstrating that Candidalysin has dual functionality in a concentration-dependent manner.

Candidalysin-induced activation of epithelial cells culminates in the release of cytokines including granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), IL-1α, IL-1β and IL-6 (Figure 1D). *C. albicans ECE1* and Candidalysin mutants induce significantly lower levels of neutrophils to the site of infection *in vivo* when compared to wild type controls [85, 86].

A host receptor for Candidalysin-induced signalling has yet to be identified; however, epithelial activation is not mediated through classical PRRs such as Toll-like receptors or C-type lectin receptors [87]. Intriguingly, Candidalysin can permeabilise synthetic lipid bilayers that do not contain an endogenous receptor [85], suggesting that the toxin may damage epithelial cells and activate innate immune responses through distinct mechanisms.

A model of mucosal infection has been proposed [85] in which the hyphae of *C. albicans* invade the epithelial surface, creating an invasion "pocket" [75] into which Candidalysin is secreted. During the initial stages of infection, the concentration of Candidalysin is insufficient to cause appreciable plasma membrane damage, but is nevertheless recognised by the epithelial cells of the host mucosa, stimulating an innate immune response. As infection progresses however, the concentration of Candidalysin within the invasion pocket increases to damage-inducing levels, causing membrane lesions that facilitate infection.

Vulvovaginal candidasis (VVC) is a disease of immune competent women. Approximately 75% of women will experience at least one episode of VVC in their lifetime [88], while almost 9% will suffer from recurrent infection [89]. Symptomatic VVC is characterised by itching, burning, and pain at the vulvovaginal mucosa, often accompanied by odorless vaginal discharge [90]. In contrast to the oral epithelium, recruitment of neutrophils to the site of infection during VVC does not result in fungal clearance but rather, causes an acute exacerbation of symptoms [91].

Similar to TR146 oral epithelial cells, treatment of A431 vaginal cells with Candidalysin causes damage, c-Fos/p-MKP1 signalling and cytokine secretion [86]. Notably, fungal burdens remain equivalent in mice that receive an intravaginal challenge of wild type *C. albicans* or strains unable to express and secrete Candidalysin. However, a significant

decrease in neutrophil recruitment, damage, and pro-inflammatory cytokine expression was observed in response to strains unable to produce the toxin, identifying Candidalysin as the driver of immune pathology in the vaginal environment [86]. Thus, Candidalysin plays a crucial role in the activation of innate defences against *C. albicans* hyphae at disparate mucosal sites in the body.

The pathogenicity of natural *C. albicans* isolates is perhaps, unsurprisingly, correlated with the degree of epithelial damage caused, and release of the damage-associated cytokine IL-1α. Highly variable murine oral responses were observed from several isolates of *C. albicans*, including differences in neutrophil recruitment and the robustness of inflammatory responses [92]. Notably, from a panel of hypha-associated genes tested (*ALS3, SAP4, SAP5, SAP6, HWP1* and *ECE1*), only significant differences in *ECE1* expression (Candidalysin) was observed between isolates. However, *ECE1* expression did not always correlate with a strains' ability to damage epithelial cells [92], but this could be due to differences in adhesion and hypha formation in the individual strains tested and by the utilisation of a single *ECE1* primer set to assess *ECE1* gene expression in all strains.

5. Antimicrobial peptides, alarmins and cytokine responses

A multitude of host factors are known to be rapidly induced in response to *C. albicans* infection, including antimicrobial peptides (AMPs), which are among the first molecules to be released from the mucosal surface. The cathelicidins are a family of broad-spectrum AMPs that are expressed by a variety of epithelial and immune cells. Human cathelicidin (LL-37) and its murine equivalent (mCRAMP), are induced in response to *C. albicans* where they bind to the cell wall of the fungus, resulting in permeabilisation of the fungal plasma membrane [93]. Following secretion, LL-37 can be further processed into

406 shorter peptide fragments (designated RK-31 or KS-30) capable of killing *C. albicans* with
407 equal or greater efficacy when compared to full-length LL-37 [94]. However, cathelicidin
408 does not confer systemic or subcutaneous protection against *C. albicans* [93].
409 Lactoferrin (Lf) also possesses anti-fungal activity and, like LL-37, can be cleaved into
410 distinct peptides to enhance functionality. Full-length Lf, together with two Lf-derived
411 peptides (lactoferricin and lactoferrampin), exert candidacidal activity through mechanisms
412 that involve disruption of the fungal plasma membrane [95-99]. Full-length Lf also induces
413 apoptosis-like processes within the fungus [100] and sequestration of iron to induce
414 fungistasis [101].
415 In contrast to Lf, the cationic salivary protein histatin 5 does not lyse *C. albicans*
416 directly, but binds to β-glucans and cell wall proteins including Ssa1p and Ssa2p [102-105].
417 Once histatin 5 is bound to the *C. albicans* cell wall, it is transported into the fungus by two
418 key polyamine transporters (Dur3p and Dur31p) [106, 107], where it exerts fungicidal
419 activity by disrupting osmotic homeostasis and cell cycle control [102, 108].
420 The defensins are a family of cysteine-rich AMPs that exhibit anti-microbial activity
421 against a wide range of organisms. Several members of the defensin family possess potent
422 anti-*C. albicans* activity, including β-defensin 2 and 3 which kill *C. albicans* through a poorly
423 defined mechanism that does not involve membrane disruption [109], as well as α-defensin
424 6 which blocks adhesion of *C. albicans* to intestinal epithelial cells [110]. The importance of
425 defensins against *C. albicans in vivo* is demonstrated by the observation that mice lacking β-
426 defensin 3 are highly susceptible to OPC [111].
427 Vitamin D is receiving increasing attention as a potent anti-microbial molecule
428 involved in pro-inflammatory responses and cytokine regulation [112, 113] that can
429 counteract pathogen-induced transcriptional changes in host monocytes [114]. Vitamin D3

exhibits direct anti-*C. albicans* activity [115], and although the precise mechanism(s) of action *in vivo* remain to be determined, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), the hormonal form of Vitamin D, induces potent upregulation of LL-37 in tongue and lung epithelial cells, monocytes and neutrophils [116, 117].

Alarmins are endogenous intracellular proteins that are released from host cells following severe trauma and tissue damage. The S100A8 and S100A9 alarmins are released from the oral and vaginal mucosa in response to *C. albicans* infection and contribute to (but are not essential for), recruitment of neutrophils that function to resolve the symptoms of infection in the oral, but not vaginal lumen in a strain specific manner [86, 92, 111, 118, 119].

In addition to AMPs and alarmins, numerous cytokines play a crucial role in the induction and regulation of innate immune defence against *C. albicans*. Signalling mediated through IL-1 and its related cytokines is critical for the induction of effective anti-*C. albicans* immunity. Absence of the IL-1 receptor significantly impairs expression of the neutrophil recruiting molecules CXCL1, CXCL2, CXCL5 and G-CSF and subsequent neutrophil migration [120]. Furthermore, IL-1 receptor deficient mice (*Il1r1*$^{-/-}$) have significantly higher fungal burdens in the oral cavity at 3, 7, 14 and 21 days post-infection when compared to wild type controls [121].

IL-17 has emerged as one of the most important cytokines in mucosal anti-fungal immunity, with manifold functionality. Produced by a variety of lymphoid-derived cells (both innate and adaptive) IL-17 has a dramatic impact on innate immunity. While there are several isoforms of IL-17, each with distinct biological functions, it is IL-17A and IL-17F which play key roles in antifungal immunity. Although it has been suggested that neutrophils may produce IL-17, this does not appear to be the case during OPC [122]. However, one of the

more important roles of the IL-17 cytokines is to activate a neutrophil response. This involves secretion of chemokines that will recruit neutrophils (e.g. CXCL1/2 and CXCL5), as well as cytokines that activate neutrophils once they have been recruited to the site of infection (e.g. G-CSF) [123].

IL-17 is a potent inducer of anti-microbial peptide (AMP) secretion, notably β-defensins 1 and 3 in mice [111, 123], as well as histatins [124, 125]. Thus, given the importance of these AMPs during *Candida* infection [111, 126], the multiple roles of IL-17 in mediating protection against *C. albicans* are clearly established. IL-17A also affects the epithelial cells of the GI tract directly, where it regulates expression of occludins required for epithelial tight junctions and barrier integrity [127, 128]. Collectively, the multiple functionalities of IL-17 cytokines act to drive and regulate a number of essential and non-redundant host mechanisms required for effective defence against *C. albicans* infection at mucosal surfaces.

Collectively, AMPs, alarmins and cytokines exert numerous protective functions at mucosal surfaces in response to *C. albicans* infection, and although our understanding of these complex processes continues to improve, there is much still to learn, particularly with respect to fungi.

6. Mucosal inflammasome responses to *C. albicans*

Inflammasomes are cytosolic multi-protein complexes that play a critical role in immunity. They are comprised of a PRR (either a nucleotide-binding domain leucine-rich receptor (NLR), or an Absent In Melanoma-2 (AIM2) receptor), and are activated in response to innate recognition of exogenous and endogenous PAMPs and danger-associated molecular patterns (DAMPs). NLRs contain an N-terminal region comprised of either a PYRIN

478 or CARD domain, a central nucleotide-binding oligomerisation domain and a C-terminal
479 leucine-rich repeat sequence [129, 130]. Physical association between a NLR and an adaptor
480 protein (apoptosis-associated speck-like protein containing a CARD (ASC)), results in the
481 recruitment and autocatalytic activation of pro-caspase-1, which subsequently cleaves the
482 inactive cytokine zymogens pro-IL-1β and pro-IL-18 [131], to yield biologically active
483 molecules.

484 While numerous inflammasomes exist [132], those most closely associated with
485 innate defence against *C. albicans* at mucosal surfaces are the NLRP3 and NLRC4 complexes
486 [121, 133]. Tissue specific roles have been ascribed to the NLRP3 and NLRC4
487 inflammasomes; the NLRP3 inflammasome is present in both haematopoietic and stromal
488 compartments and plays a crucial role in the prevention of fungal dissemination during oral
489 infection *in vivo* [121] while the NLRC4 complex is important for mucosal defence [133].

490 The production of active IL-1β from the oral mucosa in response to *C. albicans* is
491 dependent upon both NLRP3 and NLRC4, and buccal mucosal tissues upregulate NLRP3 and
492 NLRP4 expression within 72 h during the innate immune response to *C. albicans* infection
493 [133]. Moreover, *Nlrp3*$^{-/-}$ and *Nlrc4*$^{-/-}$ knockout mice exhibit a significant reduction in the
494 expression of IL-17A, IL-17F and antimicrobial peptides in the oral cavity, while the fungal
495 burden of *Nlrc4*$^{-/-}$ mice is significantly higher during OPC when compared to wild type
496 controls [133], highlighting the importance of inflammasome complexes, particularly NLRC4,
497 for oral defence against *C. albicans* infection *in vivo*.

498

499 **7. Neutrophils in antifungal innate immunity**

500 Many protective innate immune responses at mucosal surfaces are mediated by
501 myeloid cells, most notably neutrophils and macrophages, which rapidly infiltrate the site of

infection. Activation of neutrophils and macrophages is triggered by direct recognition of fungal PAMPs [134], by chemokines and AMPs, by cytokines released from epithelial cells in response to Candidalysin (e.g.IL-1α/β, G/GM-CSF, IL-8, CCL20, β-defensin-2/3 and S100A8/9) [85, 87, 123], and by IL-17 released from resident innate Th17 cells or γδ T cells [135]. Neutrophils and macrophages express a range of PRRs including TLR2, TLR4, DC-SIGN, Mincle, Dectin-2 and Dectin-3 that recognise *C. albicans* cell wall mannoproteins, TLR9 that responds to DNA, and Dectin-1 that interacts with cell wall β-glucans, leading to their full activation [134, 136-138].

Activation of PRRs by cognate PAMPs triggers the MAPK and NF-κB intracellular signalling pathways through the activation of MyD88, the inflammasome complex and SYK [134]. This signalling leads to downstream production of pro-inflammatory cytokines and antimicrobial factors, phagocytosis and a unique method of cell death termed NETosis [134, 139]. However, the PAMPs described above are not the only factors that stimulate neutrophil responses. Indeed, the secreted aspartic proteases (Saps) of *C. albicans* have also been shown to recruit neutrophils [140]. Furthermore, the production of IL-17 from innate type 17 cells (Figure 1E) and potentially, γδ T cells, in response to IL-1α/β released from epithelial cells will also lead to activation of infiltrating neutrophils [135], and a key role for IL-1 in coordinating responses to OPC has also been identified [120].

The classical method of neutrophil-mediated killing of *C. albicans* hyphae is phagocytosis followed by a lethal oxidative burst. The interaction between Dectin-1 and insoluble β-glucan leads to the formation of a phagocytic synapse that greatly improves the phagocytosis of *C. albicans* yeast and short hyphae [141]. However, hyphae that are too large to be phagocytosed by neutrophils remain a threat to mucosal tissues. To destroy these larger filaments, neutrophils can undergo NETosis, forming Neutrophil Extracellular

Traps (NETs) [142]. NETosis involves the cell "exploding" to release a web of chromatin coated with granule enzymes, antimicrobial peptides (e.g. calprotectin), and histones [142-144] (Figure 1F). Although both yeast and hypha morphologies of *C. albicans* trigger NETosis, the neutrophil response to hyphae is by far the most rapid.

Several *C. albicans*-associated triggers of NETosis have been identified, including reactive oxygen species (ROS) [145], fibronectin [146] and β-glucan, either through Dectin-1/SYK signalling [147], or through the complement receptor (CD11b/CD18) [146, 148]. The mechanisms of NETosis are now beginning to be elucidated, and appear to involve both autophagy and chromatin de-condensation through the ROS-activated peptidylarginine deiminase 4 (PAD4) [149, 150]. As well as killing fungi, NETs are also capable of slowing hyphal growth, potentially through the sequestration of micronutrients (e.g. zinc) [143].

8. Macrophages in antifungal innate immunity

Although neutrophils are the dominant myeloid cell recruited to the foci of infection, macrophages also infiltrate and perform similar protective functions, phagocytosing the fungus after PRR-PAMP interaction [151], albeit with a lower efficiency of killing when compared to neutrophils.

Intriguingly, *C. albicans* has been observed to survive within macrophages and even escape [152]. Often, this escape involves the formation of hyphae that physically pierce through the membrane of the phagolysosome and rupture the ingesting macrophage [153], although *C. albicans* can also escape macrophages in a non-lytic fashion [154] akin to the vomocytosis process described for *Cryptococcus neoformans*. Whatever the mechanism of escape, macrophages play a lesser role during disseminated *C. albicans* infection in mice when compared with neutrophils [134, 138].

Nevertheless, macrophages phagocytose *C. albicans* and respond through NLR-PAMP interactions that stimulate inflammasome assembly (resulting in the secretion of biologically active IL-1β), and yet another unique form of cell death termed pyroptosis [155]. Notably, the induction of macrophage pyroptosis by *C. albicans* is both a temporally and mechanistically distinct means of escape that precedes hypha-mediated exfiltration [156], and provides an important source of biologically active IL-1β (Figure 1G).

9. Innate immune memory

Conventional wisdom has it that while adaptive immunity 'learns' and has memory, innate immunity has no memory. However, recent findings have begun to overturn this paradigm. From the mid 1950's onwards, numerous reports observed that administration of the *Bacillus* Calmette-Guérin (BCG) vaccine conferred improved resistance to other non-related pathogens, including *Staphylococcus aureus* [157], *Salmonella* [158] and *C. albicans* [159]. Similar observations have been made following infection of mice with an avirulent strain of *C. albicans*, which resulted in improved protection against virulent *C. albicans* and pathogenic bacteria, through a macrophage-dependent, but T cell-independent mechanism [160, 161]. Further to these findings is the landmark observation that mice which receive a sub-lethal infection of *C. albicans* are protected for up to 2 weeks against a subsequent lethal re-infection in a monocyte-dependent, but T and B cell independent manner [162].

Intriguingly, macrophages demonstrate marked plasticity in their effector responses [163]. The importance of macrophage plasticity was made evident by Quintin et al. [162], who demonstrated that pre-exposure of macrophages to *C. albicans* (and particularly to cell wall β-glucan), results in "functional reprogramming" through epigenetic changes to histones [162, 164]. Further studies have demonstrated that this functional reprogramming

574 is driven by a Dectin-1/Raf1/NF-κB signalling circuit [165]. In addition, reprogrammed
575 monocytes show a metabolic shift in glycolysis, akin to that seen in the Warburg effect
576 associated with cancer [166]. The net effect of macrophage reprogramming is an increased
577 production of pro-inflammatory cytokines including TNFα, IL-1β and IL-6.
578
579 **10. Innate type 17 cells**
580 The critical role that IL-17, and particularly the specific lymphocytes that produce it
581 play in innate immunity to *C. albicans* has recently come to light in a series of landmark
582 studies [111, 135, 167]. These studies demonstrate that mice with defects in the IL-17
583 receptor or downstream signalling components are highly susceptible to OPC [111]. Equally,
584 the genetic basis for many cases of chronic mucocutaneous candidiasis (a condition
585 characterised by perpetual *C. albicans* infection of the skin, nails and mucosal surfaces), has
586 now been identified as a collection of loss-of-function mutations in IL-17 signalling [168-
587 170], and auto-antibodies against IL-17 [171, 172].
588 Although IL-17 is produced by Th17 T cells of the classical adaptive immune
589 response, it is a common mistake to regard IL-17 as a cytokine that functions purely in an
590 adaptive capacity. Indeed, detailed and extensive research clearly demonstrates that IL-17 is
591 produced by a broad selection of innate immune cells, including γδ-T cells, natural killer T
592 cells (NKT), type 3 innate lymphoid cells (ILC3) and TCRβ+ 'natural' Th17 cells (nTh17) [173].
593 While ILC3s have been suggested to play a major role in protection against OPC [174],
594 recent research has since indicated that nTh17 and γδ-T cells are the predominant source of
595 IL-17 as *Rag1*$^{-/-}$ mice, which produce ILC3 cells but not nTh17 or γδ-T cells, have the same
596 high susceptibility to OPC as IL-17R$^{-/-}$ mice [167].

The induction of innate type 17 immunity differs considerably from conventional adaptive immune responses to *C. albicans*, which are considered to be activated through CARD9 signalling [175]. Notably, CARD9 signalling is not required to drive innate type 17 responses [176], and innate type 17 cells are observed to be activated in response to the secretion of Candidalysin from invading *C. albicans* hyphae [135]. Indeed, oral infection of mice with an *ece1*Δ/Δ *C. albicans* mutant (does not produce Candidalysin), fail to induce IL-17 production and the characteristic activation of nTh17 cells associated with wild type responses to OPC. Furthermore, Verma et al. [135] identify a causal link between the production of IL-1 cytokines and the activation of innate type 17 responses, a finding that integrates with studies which demonstrate the key role of inflammasomes during murine OPC [121].

11. Conclusions

The tremendous diversity within the microbial populations that comprise the human microbiota provides a dynamic and ever-present immunological challenge for mucosal surfaces. Numerous complex and interconnecting mechanisms function during innate recognition and mucosal responses to *C. albicans*. The complex molecular events that transpire to enable disparate mucosal sites to distinguish between commensalism and pathogenicity are receiving more attention now than ever. Continued research will undoubtedly increase our understanding of the essential mechanisms of innate immunity required to control this most common of mucosal pathobionts.

Funding

This work was supported by grants from the Biotechnology and Biological Sciences Research Council (BB/N014677/1), Medical Research Council (MR/M011372/1), King's Health Partner's Challenge Fund (R170501), the National Institute for Health Research at Guys and St Thomas's NHS Foundation Trust and King's College London Biomedical Research Centre (IS-BRC-1215-20006), and the Rosetrees Trust (M680) to JRN, and the National Institute for Health (R37DE022550) to JRN and DLM. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Figure captions

Figure 1. Innate mucosal immune responses to *C. albicans*.

A) Adhesion of *C. albicans* hyphae to the host epithelium is mediated through two key adhesins; Als3p and Hwp1p. The epithelial PRR EphA2 interacts with β-glucan independently of fungal morphology. EphA2, E-cadherin and EGFR/HER2 receptor complexes function during receptor induced endocytosis (RIE), most notably through the interaction of E-cadherin and EGFR/HER2 with the *C. albicans* invasins Als3p and Ssa1p. **B**) Candidalysin is secreted from the hyphae of *C. albicans* where it inserts into the host epithelial membrane, damaging the cell through the formation of pores that result in loss of intracellular contents (i.e. lactate dehydrogenase (LDH)), and influx of calcium. **C**) Epithelial detection of Candidalysin activates the MAPK signalling pathway (particularly p38) which activates the AP-1 transcription factor c-Fos, driving cytokine expression. Pathway activity is fine-tuned through the action of MKP1 on p38 and JNK. **D**) In response to *C. albicans* infection, epithelial cells secrete antimicrobial peptides (AMPs) and alarmins that combat the invading fungus, together with cytokines and chemokines that recruit and activate myeloid cells

644 including innate type 17 cells, neutrophils and macrophages. **E**) Following infection with *C.*
645 *albicans*, epithelial cells release IL-1 which activates innate type 17 cellular responses,
646 leading to the secretion of IL-17. **F**) Neutrophils interact with *C. albicans* through PRRs (TLRs,
647 CLRs and NLRs), then phagocytose and destroy yeast and short hyphae. Cytokine signals
648 stimulate release of TNF-α from neutrophils which upregulates TLR4 expression on epithelial
649 cells, conferring additional protection. Hyphae that are too large to be phagocytosed
650 stimulate the production of neutrophil extracellular traps (NETs) through a process termed
651 NETosis. **G**) *C. albicans* that is phagocytosed by macrophages may avoid destruction through
652 the induction of pyroptosis and hyphal growth, allowing the fungus to escape from the
653 macrophage. Adapted from [177].
654

655 **References**

656 [1] A. Kuhbacher, A. Burger-Kentischer, S. Rupp, Interaction of *Candida* Species with the Skin,
657 Microorganisms 5(2) (2017) DOI: 10.3390/microorganisms5020032.
658 [2] D. Williams, M. Lewis, Pathogenesis and treatment of oral candidosis, J Oral Microbiol 3 (2011)
659 DOI: 10.3402/jom.v3i0.5771.
660 [3] A. Jeffery-Smith, S.K. Taori, S. Schelenz, K. Jeffery, E.M. Johnson, A. Borman, Candida auris
661 Incident Management Team, R. Manuel, C.S. Brown, *Candida auris*: a Review of the Literature, Clin
662 Microbiol Rev 31(1) (2018) DOI: 10.1128/CMR.00029-17.
663 [4] S. Ganguly, A.P. Mitchell, Mucosal biofilms of *Candida albicans*, Curr Opin Microbiol 14(4) (2011)
664 380-5.
665 [5] C.J. Nobile, A.D. Johnson, *Candida albicans* Biofilms and Human Disease, Annu Rev Microbiol 69
666 (2015) 71-92.
667 [6] I.D. Iliev, V.A. Funari, K.D. Taylor, Q. Nguyen, C.N. Reyes, S.P. Strom, J. Brown, C.A. Becker, P.R.
668 Fleshner, M. Dubinsky, J.I. Rotter, H.L. Wang, D.P. McGovern, G.D. Brown, D.M. Underhill,
669 Interactions between commensal fungi and the C-type lectin receptor Dectin-1 influence colitis,
670 Science 336(6086) (2012) 1314-7.
671 [7] S.W. Kashem, D.H. Kaplan, Skin Immunity to *Candida albicans*, Trends Immunol 37(7) (2016) 440-
672 50.
673 [8] P. Kramer, P. Bressan, Humans as Superorganisms: How Microbes, Viruses, Imprinted Genes, and
674 Other Selfish Entities Shape Our Behavior, Perspect Psychol Sci 10(4) (2015) 464-81.
675 [9] J.L. Baker, B. Bor, M. Agnello, W. Shi, X. He, Ecology of the Oral Microbiome: Beyond Bacteria,
676 Trends Microbiol 25(5) (2017) 362-374.
677 [10] G.B. Huffnagle, M.C. Noverr, The emerging world of the fungal microbiome, Trends Microbiol
678 21(7) (2013) 334-41.

[11] A. Vesty, K. Biswas, M.W. Taylor, K. Gear, R.G. Douglas, Evaluating the Impact of DNA Extraction Method on the Representation of Human Oral Bacterial and Fungal Communities, PLoS One 12(1) (2017) e0169877.
[12] S. Dollive, Y.Y. Chen, S. Grunberg, K. Bittinger, C. Hoffmann, L. Vandivier, C. Cuff, J.D. Lewis, G.D. Wu, F.D. Bushman, Fungi of the murine gut: episodic variation and proliferation during antibiotic treatment, PLoS One 8(8) (2013) e71806.
[13] P.I. Diaz, B.Y. Hong, A.K. Dupuy, L.D. Strausbaugh, Mining the oral mycobiome: Methods, components, and meaning, Virulence 8(3) (2017) 313-323.
[14] J.J. Limon, J.H. Skalski, D.M. Underhill, Commensal Fungi in Health and Disease, Cell Host Microbe 22(2) (2017) 156-165.
[15] G. Hoarau, P.K. Mukherjee, C. Gower-Rousseau, C. Hager, J. Chandra, M.A. Retuerto, C. Neut, S. Vermeire, J. Clemente, J.F. Colombel, H. Fujioka, D. Poulain, B. Sendid, M.A. Ghannoum, Bacteriome and Mycobiome Interactions Underscore Microbial Dysbiosis in Familial Crohn's Disease, MBio 7(5) (2016) DOI: 10.1128/mBio.01250-16.
[16] R.R. Watkins, P.K. Mukherjee, J. Chandra, M.A. Retuerto, C. Guidry, N. Haller, C. Paranjape, M.A. Ghannoum, Admission to the Intensive Care Unit is Associated With Changes in the Oral Mycobiome, J Intensive Care Med 32(4) (2017) 278-282.
[17] P.K. Mukherjee, J. Chandra, M. Retuerto, M. Sikaroodi, R.E. Brown, R. Jurevic, R.A. Salata, M.M. Lederman, P.M. Gillevet, M.A. Ghannoum, Oral mycobiome analysis of HIV-infected patients: identification of *Pichia* as an antagonist of opportunistic fungi, PLoS Pathog 10(3) (2014) e1003996.
[18] D.L. Moyes, J.R. Naglik, The mycobiome: influencing IBD severity, Cell Host Microbe 11(6) (2012) 551-2.
[19] P.C. Seed, The human mycobiome, Cold Spring Harbor perspectives in medicine 5(5) (2014) a019810.
[20] K.C. Hazen, Participation of yeast cell surface hydrophobicity in adherence of *Candida albicans* to human epithelial cells, Infect Immun 57(7) (1989) 1894-900.
[21] A. Nantel, D. Dignard, C. Bachewich, D. Harcus, A. Marcil, A.P. Bouin, C.W. Sensen, H. Hogues, M. van het Hoog, P. Gordon, T. Rigby, F. Benoit, D.C. Tessier, D.Y. Thomas, M. Whiteway, Transcription profiling of *Candida albicans* cells undergoing the yeast-to-hyphal transition, Molecular biology of the cell 13(10) (2002) 3452-65.
[22] Y. Wu, Y.H. Li, S.B. Yu, W.G. Li, X.S. Liu, L. Zhao, J.X. Lu, A Genome-Wide Transcriptional Analysis of Yeast-Hyphal Transition in *Candida tropicalis* by RNA-Seq, PLoS One 11(11) (2016) e0166645.
[23] C.J. Heilmann, A.G. Sorgo, A.R. Siliakus, H.L. Dekker, S. Brul, C.G. de Koster, L.J. de Koning, F.M. Klis, Hyphal induction in the human fungal pathogen *Candida albicans* reveals a characteristic wall protein profile, Microbiology 157(Pt 8) (2011) 2297-307.
[24] R.L. Sandin, A.L. Rogers, R.J. Patterson, E.S. Beneke, Evidence for mannose-mediated adherence of *Candida albicans* to human buccal cells *in vitro*, Infect Immun 35(1) (1982) 79-85.
[25] L.L. Hoyer, C.B. Green, S.H. Oh, X. Zhao, Discovering the secrets of the *Candida albicans* agglutinin-like sequence (ALS) gene family--a sticky pursuit, Med Mycol 46(1) (2008) 1-15.
[26] C.B. Green, X. Zhao, K.M. Yeater, L.L. Hoyer, Construction and real-time RT-PCR validation of *Candida albicans* PALS-GFP reporter strains and their use in flow cytometry analysis of *ALS* gene expression in budding and filamenting cells, Microbiology 151(Pt 4) (2005) 1051-60.
[27] K. Zakikhany, J.R. Naglik, A. Schmidt-Westhausen, G. Holland, M. Schaller, B. Hube, *In vivo* transcript profiling of *Candida albicans* identifies a gene essential for interepithelial dissemination, Cell Microbiol 9(12) (2007) 2938-54.
[28] X. Zhao, S.H. Oh, K.M. Yeater, L.L. Hoyer, Analysis of the *Candida albicans* Als2p and Als4p adhesins suggests the potential for compensatory function within the Als family, Microbiology 151(Pt 5) (2005) 1619-30.
[29] X. Zhao, S.H. Oh, L.L. Hoyer, Deletion of *ALS5*, *ALS6* or *ALS7* increases adhesion of *Candida albicans* to human vascular endothelial and buccal epithelial cells, Med Mycol 45(5) (2007) 429-34.

[30] Y. Kamai, M. Kubota, Y. Kamai, T. Hosokawa, T. Fukuoka, S.G. Filler, Contribution of *Candida albicans ALS1* to the pathogenesis of experimental oropharyngeal candidiasis, Infect Immun 70(9) (2002) 5256-8.
[31] X. Zhao, S.H. Oh, G. Cheng, C.B. Green, J.A. Nuessen, K. Yeater, R.P. Leng, A.J. Brown, L.L. Hoyer, *ALS3* and *ALS8* represent a single locus that encodes a *Candida albicans* adhesin; functional comparisons between Als3p and Als1p, Microbiology 150(Pt 7) (2004) 2415-28.
[32] C. Murciano, D.L. Moyes, M. Runglall, P. Tobouti, A. Islam, L.L. Hoyer, J.R. Naglik, Evaluation of the role of *Candida albicans* agglutinin-like sequence (Als) proteins in human oral epithelial cell interactions, PLoS One 7(3) (2012) e33362.
[33] J.R. Naglik, F. Fostira, J. Ruprai, J.F. Staab, S.J. Challacombe, P. Sundstrom, *Candida albicans HWP1* gene expression and host antibody responses in colonization and disease, Journal of medical microbiology 55(Pt 10) (2006) 1323-7.
[34] J.F. Staab, C.A. Ferrer, P. Sundstrom, Developmental expression of a tandemly repeated, proline-and glutamine-rich amino acid motif on hyphal surfaces on *Candida albicans*, J Biol Chem 271(11) (1996) 6298-305.
[35] J.F. Staab, S.D. Bradway, P.L. Fidel, P. Sundstrom, Adhesive and mammalian transglutaminase substrate properties of *Candida albicans* Hwp1, Science 283(5407) (1999) 1535-8.
[36] G. Ponniah, C. Rollenhagen, Y.S. Bahn, J.F. Staab, P. Sundstrom, State of differentiation defines buccal epithelial cell affinity for cross-linking to *Candida albicans* Hwp1, J Oral Pathol Med 36(8) (2007) 456-67.
[37] P. Sundstrom, E. Balish, C.M. Allen, Essential role of the *Candida albicans* transglutaminase substrate, hyphal wall protein 1, in lethal oroesophageal candidiasis in immunodeficient mice, J Infect Dis 185(4) (2002) 521-30.
[38] J.F. Staab, K. Datta, P. Rhee, Niche-specific requirement for hyphal wall protein 1 in virulence of *Candida albicans*, PLoS One 8(11) (2013) e80842.
[39] C.A. Gale, C.M. Bendel, M. McClellan, M. Hauser, J.M. Becker, J. Berman, M.K. Hostetter, Linkage of adhesion, filamentous growth, and virulence in *Candida albicans* to a single gene, *INT1*, Science 279(5355) (1998) 1355-8.
[40] K.M. Kinneberg, C.M. Bendel, R.P. Jechorek, E.A. Cebelinski, C.A. Gale, J.G. Berman, S.L. Erlandsen, M.K. Hostetter, C.L. Wells, Effect of *INT1* gene on *Candida albicans* murine intestinal colonization, J Surg Res 87(2) (1999) 245-51.
[41] T. Umeyama, A. Kaneko, H. Watanabe, A. Hirai, Y. Uehara, M. Niimi, M. Azuma, Deletion of the Ca*BIG1* gene reduces beta-1,6-glucan synthesis, filamentation, adhesion, and virulence in *Candida albicans*, Infect Immun 74(4) (2006) 2373-81.
[42] W. Liu, Z. Zou, X. Huang, H. Shen, L.J. He, S.M. Chen, L.P. Li, L. Yan, S.Q. Zhang, J.D. Zhang, Z. Xu, G.T. Xu, M.M. An, Y.Y. Jiang, Bst1 is required for *Candida albicans* infecting host via facilitating cell wall anchorage of Glycosylphosphatidyl inositol anchored proteins, Scientific reports 6 (2016) 34854.
[43] A. Gonzalez-Novo, L. Labrador, A. Jimenez, M. Sanchez-Perez, J. Jimenez, Role of the septin Cdc10 in the virulence of *Candida albicans*, Microbiol Immunol 50(7) (2006) 499-511.
[44] Q. Yu, Y. Dong, N. Xu, K. Qian, Y. Chen, B. Zhang, L. Xing, M. Li, A novel role of the ferric reductase Cfl1 in cell wall integrity, mitochondrial function, and invasion to host cells in *Candida albicans*, FEMS yeast research 14(7) (2014) 1037-47.
[45] C. Alberti-Segui, A.J. Morales, H. Xing, M.M. Kessler, D.A. Willins, K.G. Weinstock, G. Cottarel, K. Fechtel, B. Rogers, Identification of potential cell-surface proteins in *Candida albicans* and investigation of the role of a putative cell-surface glycosidase in adhesion and virulence, Yeast 21(4) (2004) 285-302.
[46] F. Li, M.J. Svarovsky, A.J. Karlsson, J.P. Wagner, K. Marchillo, P. Oshel, D. Andes, S.P. Palecek, Eap1p, an adhesin that mediates *Candida albicans* biofilm formation *in vitro* and *in vivo*, Eukaryot Cell 6(6) (2007) 931-9.

[47] C. Dieterich, M. Schandar, M. Noll, F.J. Johannes, H. Brunner, T. Graeve, S. Rupp, *In vitro* reconstructed human epithelia reveal contributions of *Candida albicans EFG1* and *CPH1* to adhesion and invasion, Microbiology 148(Pt 2) (2002) 497-506.
[48] Y. Fu, G. Luo, B.J. Spellberg, J.E. Edwards, Jr., A.S. Ibrahim, Gene overexpression/suppression analysis of candidate virulence factors of *Candida albicans*, Eukaryot Cell 7(3) (2008) 483-92.
[49] M. Rouabhia, P.K. Mukherjee, A.A. Lattif, S. Curt, J. Chandra, M.A. Ghannoum, Disruption of sphingolipid biosynthetic gene *IPT1* reduces *Candida albicans* adhesion and prevents activation of human gingival epithelial cell innate immune defense, Med Mycol 49(5) (2011) 458-66.
[50] H. Badrane, S. Cheng, M.H. Nguyen, H.Y. Jia, Z. Zhang, N. Weisner, C.J. Clancy, *Candida albicans IRS4* contributes to hyphal formation and virulence after the initial stages of disseminated candidiasis, Microbiology 151(Pt 9) (2005) 2923-31.
[51] A.B. Herrero, P. Magnelli, M.K. Mansour, S.M. Levitz, H. Bussey, C. Abeijon, *KRE5* gene null mutant strains of *Candida albicans* are avirulent and have altered cell wall composition and hypha formation properties, Eukaryot Cell 3(6) (2004) 1423-32.
[52] E.T. Buurman, C. Westwater, B. Hube, A.J. Brown, F.C. Odds, N.A. Gow, Molecular analysis of CaMnt1p, a mannosyl transferase important for adhesion and virulence of *Candida albicans*, Proc Natl Acad Sci U S A 95(13) (1998) 7670-5.
[53] C.A. Munro, S. Bates, E.T. Buurman, H.B. Hughes, D.M. Maccallum, G. Bertram, A. Atrih, M.A. Ferguson, J.M. Bain, A. Brand, S. Hamilton, C. Westwater, L.M. Thomson, A.J. Brown, F.C. Odds, N.A. Gow, Mnt1p and Mnt2p of *Candida albicans* are partially redundant alpha-1,2-mannosyltransferases that participate in O-linked mannosylation and are required for adhesion and virulence, J Biol Chem 280(2) (2005) 1051-60.
[54] S. Sandini, A. Stringaro, S. Arancia, M. Colone, F. Mondello, S. Murtas, A. Girolamo, N. Mastrangelo, F. De Bernardis, The *MP65* gene is required for cell wall integrity, adherence to epithelial cells and biofilm formation in *Candida albicans*, BMC Microbiol 11 (2011) DOI: 10.1186/1471-2180-11-106.
[55] S. Cheng, C.J. Clancy, M.A. Checkley, M. Handfield, J.D. Hillman, A. Progulske-Fox, A.S. Lewin, P.L. Fidel, M.H. Nguyen, Identification of *Candida albicans* genes induced during thrush offers insight into pathogenesis, Mol Microbiol 48(5) (2003) 1275-88.
[56] D. Wilson, A. Tutulan-Cunita, W. Jung, N.C. Hauser, R. Hernandez, T. Williamson, K. Piekarska, S. Rupp, T. Young, L. Stateva, Deletion of the high-affinity cAMP phosphodiesterase encoded by *PDE2* affects stress responses and virulence in *Candida albicans*, Mol Microbiol 65(4) (2007) 841-56.
[57] R. Hashash, S. Younes, W. Bahnan, J. El Koussa, K. Maalouf, H.I. Dimassi, R.A. Khalaf, Characterisation of Pga1, a putative *Candida albicans* cell wall protein necessary for proper adhesion and biofilm formation, Mycoses 54(6) (2011) 491-500.
[58] J. Calderon, M. Zavrel, E. Ragni, W.A. Fonzi, S. Rupp, L. Popolo, *PHR1*, a pH-regulated gene of *Candida albicans* encoding a glucan-remodelling enzyme, is required for adhesion and invasion, Microbiology 156(Pt 8) (2010) 2484-94.
[59] C. Timpel, S. Strahl-Bolsinger, K. Ziegelbauer, J.F. Ernst, Multiple functions of Pmt1p-mediated protein O-mannosylation in the fungal pathogen *Candida albicans*, J Biol Chem 273(33) (1998) 20837-46.
[60] D.A. Soloviev, S. Jawhara, W.A. Fonzi, Regulation of innate immune response to *Candida albicans* infections by αMβ2-Pra1p interaction, Infect Immun 79(4) (2011) 1546-58.
[61] H.J. Watts, F.S. Cheah, B. Hube, D. Sanglard, N.A. Gow, Altered adherence in strains of *Candida albicans* harbouring null mutations in secreted aspartic proteinase genes, FEMS Microbiol Lett 159(1) (1998) 129-35.
[62] A. Albrecht, A. Felk, I. Pichova, J.R. Naglik, M. Schaller, P. de Groot, D. Maccallum, F.C. Odds, W. Schafer, F. Klis, M. Monod, B. Hube, Glycosylphosphatidylinositol-anchored proteases of *Candida albicans* target proteins necessary for both cellular processes and host-pathogen interactions, J Biol Chem 281(2) (2006) 688-94.

[63] S.B. Raman, M.H. Nguyen, Z. Zhang, S. Cheng, H.Y. Jia, N. Weisner, K. Iczkowski, C.J. Clancy, *Candida albicans SET1* encodes a histone 3 lysine 4 methyltransferase that contributes to the pathogenesis of invasive candidiasis, Mol Microbiol 60(3) (2006) 697-709.
[64] E. Hiller, S. Heine, H. Brunner, S. Rupp, *Candida albicans* Sun41p, a putative glycosidase, is involved in morphogenesis, cell wall biogenesis, and biofilm formation, Eukaryot Cell 6(11) (2007) 2056-65.
[65] C.C. Villar, H. Kashleva, A. Dongari-Bagtzoglou, Role of *Candida albicans* polymorphism in interactions with oral epithelial cells, Oral Microbiol Immunol 19(4) (2004) 262-9.
[66] K. Franke, M. Nguyen, A. Hartl, H.M. Dahse, G. Vogl, R. Wurzner, P.F. Zipfel, W. Kunkel, R. Eck, The vesicle transport protein Vac1p is required for virulence of *Candida albicans*, Microbiology 152(Pt 10) (2006) 3111-21.
[67] I.M. Dambuza, S.M. Levitz, M.G. Netea, G.D. Brown, Fungal Recognition and Host Defense Mechanisms, Microbiology spectrum 5(4) (2017) DOI: 10.1128/microbiolspec.FUNK-0050-2016.
[68] M. Swidergall, N.V. Solis, M.S. Lionakis, S.G. Filler, EphA2 is an epithelial cell pattern recognition receptor for fungal beta-glucans, Nat Microbiol (2017) DOI: 10.1038/s41564-017-0059-5.
[69] G. Weindl, J.R. Naglik, S. Kaesler, T. Biedermann, B. Hube, H.C. Korting, M. Schaller, Human epithelial cells establish direct antifungal defense through TLR4-mediated signaling, J Clin Invest 117(12) (2007) 3664-72.
[70] L. Drago, B. Mombelli, E. De Vecchi, C. Bonaccorso, M.C. Fassina, M.R. Gismondo, *Candida albicans* cellular internalization: a new pathogenic factor?, International journal of antimicrobial agents 16(4) (2000) 545-7.
[71] H. Park, C.L. Myers, D.C. Sheppard, Q.T. Phan, A.A. Sanchez, E.E. J, S.G. Filler, Role of the fungal Ras-protein kinase A pathway in governing epithelial cell interactions during oropharyngeal candidiasis, Cell Microbiol 7(4) (2005) 499-510.
[72] C.C. Villar, X.R. Zhao, *Candida albicans* induces early apoptosis followed by secondary necrosis in oral epithelial cells, Molecular oral microbiology 25(3) (2010) 215-25.
[73] Q.T. Phan, C.L. Myers, Y. Fu, D.C. Sheppard, M.R. Yeaman, W.H. Welch, A.S. Ibrahim, J.E. Edwards, Jr., S.G. Filler, Als3 is a *Candida albicans* invasin that binds to cadherins and induces endocytosis by host cells, PLoS biology 5(3) (2007) e64.
[74] J.N. Sun, N.V. Solis, Q.T. Phan, J.S. Bajwa, H. Kashleva, A. Thompson, Y. Liu, A. Dongari-Bagtzoglou, M. Edgerton, S.G. Filler, Host cell invasion and virulence mediated by *Candida albicans* Ssa1, PLoS Pathog 6(11) (2010) e1001181.
[75] B. Wachtler, F. Citiulo, N. Jablonowski, S. Forster, F. Dalle, M. Schaller, D. Wilson, B. Hube, *Candida albicans*-epithelial interactions: dissecting the roles of active penetration, induced endocytosis and host factors on the infection process, PLoS One 7(5) (2012) e36952.
[76] E. Moreno-Ruiz, M. Galan-Diez, W. Zhu, E. Fernandez-Ruiz, C. d'Enfert, S.G. Filler, P. Cossart, E. Veiga, *Candida albicans* internalization by host cells is mediated by a clathrin-dependent mechanism, Cell Microbiol 11(8) (2009) 1179-89.
[77] W. Zhu, Q.T. Phan, P. Boontheung, N.V. Solis, J.A. Loo, S.G. Filler, EGFR and HER2 receptor kinase signaling mediate epithelial cell invasion by *Candida albicans* during oropharyngeal infection, Proc Natl Acad Sci U S A 109(35) (2012) 14194-9.
[78] A.N. Atre, S.V. Surve, Y.S. Shouche, J. Joseph, M.S. Patole, R.L. Deopurkar, Association of small Rho GTPases and actin ring formation in epithelial cells during the invasion by *Candida albicans*, FEMS Immunol Med Microbiol 55(1) (2009) 74-84.
[79] Y. Liu, A.C. Shetty, J.A. Schwartz, L.L. Bradford, W. Xu, Q.T. Phan, P. Kumari, A. Mahurkar, A.P. Mitchell, J. Ravel, C.M. Fraser, S.G. Filler, V.M. Bruno, New signaling pathways govern the host response to *C. albicans* infection in various niches, Genome research 25(5) (2015) 679-89.
[80] N.V. Solis, M. Swidergall, V.M. Bruno, S.L. Gaffen, S.G. Filler, The Aryl Hydrocarbon Receptor Governs Epithelial Cell Invasion during Oropharyngeal Candidiasis, MBio 8(2) (2017) DOI: 10.1128/mBio.00025-17.

[81] C.J. Nobile, N. Solis, C.L. Myers, A.J. Fay, J.S. Deneault, A. Nantel, A.P. Mitchell, S.G. Filler, *Candida albicans* transcription factor Rim101 mediates pathogenic interactions through cell wall functions, Cell Microbiol 10(11) (2008) 2180-96.
[82] A.R. Colina, F. Aumont, N. Deslauriers, P. Belhumeur, L. de Repentigny, Evidence for degradation of gastrointestinal mucin by *Candida albicans* secretory aspartyl proteinase, Infect Immun 64(11) (1996) 4514-9.
[83] C.C. Villar, H. Kashleva, C.J. Nobile, A.P. Mitchell, A. Dongari-Bagtzoglou, Mucosal tissue invasion by *Candida albicans* is associated with E-cadherin degradation, mediated by transcription factor Rim101p and protease Sap5p, Infect Immun 75(5) (2007) 2126-35.
[84] F. Dalle, B. Wachtler, C. L'Ollivier, G. Holland, N. Bannert, D. Wilson, C. Labruere, A. Bonnin, B. Hube, Cellular interactions of *Candida albicans* with human oral epithelial cells and enterocytes, Cell Microbiol 12(2) (2010) 248-71.
[85] D.L. Moyes, D. Wilson, J.P. Richardson, S. Mogavero, S.X. Tang, J. Wernecke, S. Hofs, R.L. Gratacap, J. Robbins, M. Runglall, C. Murciano, M. Blagojevic, S. Thavaraj, T.M. Forster, B. Hebecker, L. Kasper, G. Vizcay, S.I. Iancu, N. Kichik, A. Hader, O. Kurzai, T. Luo, T. Kruger, O. Kniemeyer, E. Cota, O. Bader, R.T. Wheeler, T. Gutsmann, B. Hube, J.R. Naglik, Candidalysin is a fungal peptide toxin critical for mucosal infection, Nature 532(7597) (2016) 64-8.
[86] J.P. Richardson, H.M.E. Willems, D.L. Moyes, S. Shoaie, K.S. Barker, S.L. Tan, G.E. Palmer, B. Hube, J.R. Naglik, B.M. Peters, Candidalysin drives epithelial signaling, neutrophil recruitment, and immunopathology at the vaginal mucosa, Infect Immun (2017) DOI: 10.1128/IAI.00645-17.
[87] D.L. Moyes, M. Runglall, C. Murciano, C. Shen, D. Nayar, S. Thavaraj, A. Kohli, A. Islam, H. Mora-Montes, S.J. Challacombe, J.R. Naglik, A biphasic innate immune MAPK response discriminates between the yeast and hyphal forms of *Candida albicans* in epithelial cells, Cell Host Microbe 8(3) (2010) 225-35.
[88] B.M. Peters, J. Yano, M.C. Noverr, P.L. Fidel, Jr., *Candida* vaginitis: when opportunism knocks, the host responds, PLoS Pathog 10(4) (2014) e1003965.
[89] B. Foxman, R. Muraglia, J.P. Dietz, J.D. Sobel, J. Wagner, Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: results from an internet panel survey, Journal of lower genital tract disease 17(3) (2013) 340-5.
[90] J.D. Sobel, Vulvovaginal candidosis, Lancet 369(9577) (2007) 1961-71.
[91] P.L. Fidel, Jr., M. Barousse, T. Espinosa, M. Ficarra, J. Sturtevant, D.H. Martin, A.J. Quayle, K. Dunlap, An intravaginal live *Candida* challenge in humans leads to new hypotheses for the immunopathogenesis of vulvovaginal candidiasis, Infect Immun 72(5) (2004) 2939-46.
[92] F.A. Schonherr, F. Sparber, F.R. Kirchner, E. Guiducci, K. Trautwein-Weidner, A. Gladiator, N. Sertour, U. Hetzel, G.T.T. Le, N. Pavelka, C. d'Enfert, M.E. Bougnoux, C.F. Corti, S. LeibundGut-Landmann, The intraspecies diversity of *C. albicans* triggers qualitatively and temporally distinct host responses that determine the balance between commensalism and pathogenicity, Mucosal Immunol 10(5) (2017) 1335-1350.
[93] B. Lopez-Garcia, P.H. Lee, K. Yamasaki, R.L. Gallo, Anti-fungal activity of cathelicidins and their potential role in *Candida albicans* skin infection, The Journal of investigative dermatology 125(1) (2005) 108-15.
[94] M. Murakami, B. Lopez-Garcia, M. Braff, R.A. Dorschner, R.L. Gallo, Postsecretory processing generates multiple cathelicidins for enhanced topical antimicrobial defense, J Immunol 172(5) (2004) 3070-7.
[95] H. Nikawa, L.P. Samaranayake, J. Tenovuo, K.M. Pang, T. Hamada, The fungicidal effect of human lactoferrin on *Candida albicans* and *Candida krusei*, Arch Oral Biol 38(12) (1993) 1057-63.
[96] E. Ueta, T. Tanida, T. Osaki, A novel bovine lactoferrin peptide, FKCRRWQWRM, suppresses *Candida* cell growth and activates neutrophils, J Pept Res 57(3) (2001) 240-9.
[97] M.I. van der Kraan, K. Nazmi, A. Teeken, J. Groenink, W. van 't Hof, E.C. Veerman, J.G. Bolscher, A.V. Nieuw Amerongen, Lactoferrampin, an antimicrobial peptide of bovine lactoferrin, exerts its

candidacidal activity by a cluster of positively charged residues at the C-terminus in combination with a helix-facilitating N-terminal part, Biological chemistry 386(2) (2005) 137-42.
[98] N. Kondori, L. Baltzer, G.T. Dolphin, I. Mattsby-Baltzer, Fungicidal activity of human lactoferrin-derived peptides based on the antimicrobial αβ region, International journal of antimicrobial agents 37(1) (2011) 51-7.
[99] M. Moniruzzaman, J.M. Alam, H. Dohra, M. Yamazaki, Antimicrobial Peptide Lactoferricin B-Induced Rapid Leakage of Internal Contents from Single Giant Unilamellar Vesicles, Biochemistry 54(38) (2015) 5802-14.
[100] M.T. Andres, M. Viejo-Diaz, J.F. Fierro, Human lactoferrin induces apoptosis-like cell death in *Candida albicans*: critical role of K^+-channel-mediated K^+ efflux, Antimicrob Agents Chemother 52(11) (2008) 4081-8.
[101] C.H. Kirkpatrick, I. Green, R.R. Rich, A.L. Schade, Inhibition of growth of *Candida albicans* by iron-unsaturated lactoferrin: relation to host-defense mechanisms in chronic mucocutaneous candidiasis, J Infect Dis 124(6) (1971) 539-44.
[102] W.S. Jang, J.S. Bajwa, J.N. Sun, M. Edgerton, Salivary histatin 5 internalization by translocation, but not endocytosis, is required for fungicidal activity in *Candida albicans*, Mol Microbiol 77(2) (2010) 354-70.
[103] X.S. Li, M.S. Reddy, D. Baev, M. Edgerton, Candida albicans Ssa1/2p is the cell envelope binding protein for human salivary histatin 5, J Biol Chem 278(31) (2003) 28553-61.
[104] X.S. Li, J.N. Sun, K. Okamoto-Shibayama, M. Edgerton, *Candida albicans* cell wall Ssa proteins bind and facilitate import of salivary histatin 5 required for toxicity, J Biol Chem 281(32) (2006) 22453-63.
[105] J.N. Sun, W. Li, W.S. Jang, N. Nayyar, M.D. Sutton, M. Edgerton, Uptake of the antifungal cationic peptide Histatin 5 by *Candida albicans* Ssa2p requires binding to non-conventional sites within the ATPase domain, Mol Microbiol 70(5) (2008) 1246-60.
[106] R. Kumar, S. Chadha, D. Saraswat, J.S. Bajwa, R.A. Li, H.R. Conti, M. Edgerton, Histatin 5 uptake by *Candida albicans* utilizes polyamine transporters Dur3 and Dur31 proteins, J Biol Chem 286(51) (2011) 43748-58.
[107] F.L. Mayer, D. Wilson, I.D. Jacobsen, P. Miramon, K. Grosse, B. Hube, The novel *Candida albicans* transporter Dur31 Is a multi-stage pathogenicity factor, PLoS Pathog 8(3) (2012) e1002592.
[108] D. Baev, X.S. Li, J. Dong, P. Keng, M. Edgerton, Human salivary histatin 5 causes disordered volume regulation and cell cycle arrest in *Candida albicans*, Infect Immun 70(9) (2002) 4777-84.
[109] S. Vylkova, N. Nayyar, W. Li, M. Edgerton, Human beta-defensins kill *Candida albicans* in an energy-dependent and salt-sensitive manner without causing membrane disruption, Antimicrob Agents Chemother 51(1) (2007) 154-61.
[110] P. Chairatana, I.L. Chiang, E.M. Nolan, Human alpha-Defensin 6 Self-Assembly Prevents Adhesion and Suppresses Virulence Traits of *Candida albicans*, Biochemistry 56(8) (2017) 1033-1041.
[111] H.R. Conti, V.M. Bruno, E.E. Childs, S. Daugherty, J.P. Hunter, B.G. Mengesha, D.L. Saevig, M.R. Hendricks, B.M. Coleman, L. Brane, N. Solis, J.A. Cruz, A.H. Verma, A.V. Garg, A.G. Hise, J.P. Richardson, J.R. Naglik, S.G. Filler, J.K. Kolls, S. Sinha, S.L. Gaffen, IL-17 Receptor Signaling in Oral Epithelial Cells Is Critical for Protection against Oropharyngeal Candidiasis, Cell Host Microbe 20(5) (2016) 606-617.
[112] M. Fukuoka, Y. Ogino, H. Sato, T. Ohta, K. Komoriya, K. Nishioka, I. Katayama, RANTES expression in psoriatic skin, and regulation of RANTES and IL-8 production in cultured epidermal keratinocytes by active vitamin D3 (tacalcitol), The British journal of dermatology 138(1) (1998) 63-70.
[113] D.L. Kamen, V. Tangpricha, Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity, Journal of molecular medicine 88(5) (2010) 441-50.
[114] T.E. Klassert, J. Brauer, M. Holzer, M. Stock, K. Riege, C. Zubiria-Barrera, M.M. Muller, S. Rummler, C. Skerka, M. Marz, H. Slevogt, Differential Effects of Vitamins A and D on the

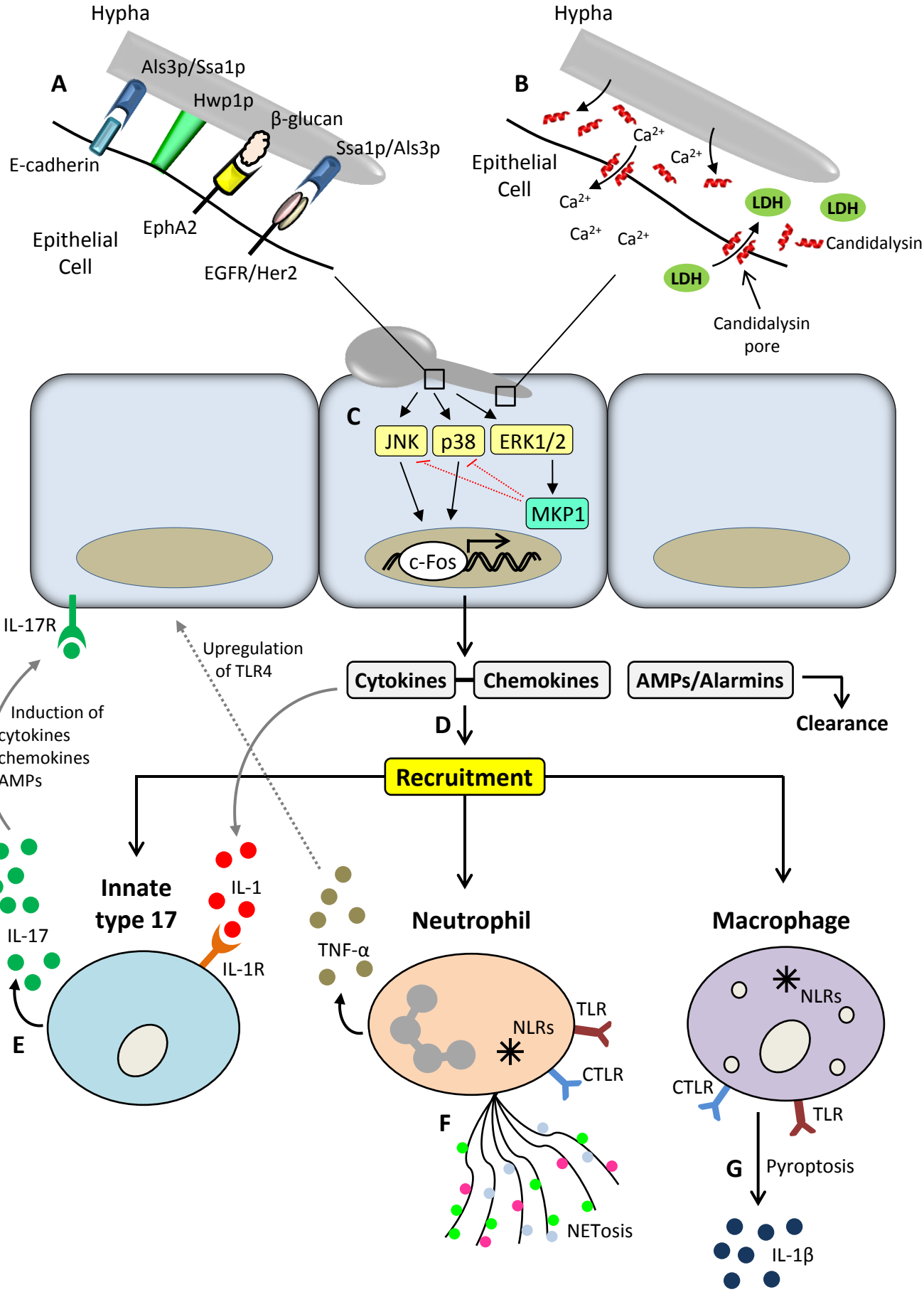
Transcriptional Landscape of Human Monocytes during Infection, Scientific reports 7 (2017) DOI: 10.1038/srep40599.
[115] D. Bouzid, S. Merzouki, M. Bachiri, S.E. Ailane, M.M. Zerroug, Vitamin D3 a new drug against *Candida albicans*, J Mycol Med 27(1) (2017) 79-82.
[116] T.T. Wang, F.P. Nestel, V. Bourdeau, Y. Nagai, Q. Wang, J. Liao, L. Tavera-Mendoza, R. Lin, J.W. Hanrahan, S. Mader, J.H. White, Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression, J Immunol 173(5) (2004) 2909-12.
[117] A.F. Gombart, N. Borregaard, H.P. Koeffler, Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3, FASEB journal : official publication of the Federation of American Societies for Experimental Biology 19(9) (2005) 1067-77.
[118] J. Yano, E. Lilly, M. Barousse, P.L. Fidel, Jr., Epithelial cell-derived S100 calcium-binding proteins as key mediators in the hallmark acute neutrophil response during *Candida* vaginitis, Infect Immun 78(12) (2010) 5126-37.
[119] J. Yano, G.E. Palmer, K.E. Eberle, B.M. Peters, T. Vogl, A.N. McKenzie, P.L. Fidel, Jr., Vaginal epithelial cell-derived S100 alarmins induced by *Candida albicans* via pattern recognition receptor interactions are sufficient but not necessary for the acute neutrophil response during experimental vaginal candidiasis, Infect Immun 82(2) (2014) 783-92.
[120] S. Altmeier, A. Toska, F. Sparber, A. Teijeira, C. Halin, S. LeibundGut-Landmann, IL-1 Coordinates the Neutrophil Response to *C. albicans* in the Oral Mucosa, PLoS Pathog 12(9) (2016) e1005882.
[121] A.G. Hise, J. Tomalka, S. Ganesan, K. Patel, B.A. Hall, G.D. Brown, K.A. Fitzgerald, An essential role for the NLRP3 inflammasome in host defense against the human fungal pathogen *Candida albicans*, Cell Host Microbe 5(5) (2009) 487-97.
[122] A.R. Huppler, A.H. Verma, H.R. Conti, S.L. Gaffen, Neutrophils Do Not Express IL-17A in the Context of Acute Oropharyngeal Candidiasis, Pathogens 4(3) (2015) 559-72.
[123] H.R. Conti, F. Shen, N. Nayyar, E. Stocum, J.N. Sun, M.J. Lindemann, A.W. Ho, J.H. Hai, J.J. Yu, J.W. Jung, S.G. Filler, P. Masso-Welch, M. Edgerton, S.L. Gaffen, Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis, J Exp Med 206(2) (2009) 299-311.
[124] H.R. Conti, O. Baker, A.F. Freeman, W.S. Jang, S.M. Holland, R.A. Li, M. Edgerton, S.L. Gaffen, New mechanism of oral immunity to mucosal candidiasis in hyper-IgE syndrome, Mucosal Immunol 4(4) (2011) 448-55.
[125] S. Tati, P. Davidow, A. McCall, E. Hwang-Wong, I.G. Rojas, B. Cormack, M. Edgerton, *Candida glabrata* Binding to *Candida albicans* Hyphae Enables Its Development in Oropharyngeal Candidiasis, PLoS Pathog 12(3) (2016) e1005522.
[126] J. Tomalka, E. Azodi, H.P. Narra, K. Patel, S. O'Neill, C. Cardwell, B.A. Hall, J.M. Wilson, A.G. Hise, beta-Defensin 1 plays a role in acute mucosal defense against *Candida albicans*, J Immunol 194(4) (2015) 1788-95.
[127] J.S. Lee, C.M. Tato, B. Joyce-Shaikh, M.F. Gulen, C. Cayatte, Y. Chen, W.M. Blumenschein, M. Judo, G. Ayanoglu, T.K. McClanahan, X. Li, D.J. Cua, Interleukin-23-Independent IL-17 Production Regulates Intestinal Epithelial Permeability, Immunity 43(4) (2015) 727-38.
[128] J.R. Maxwell, Y. Zhang, W.A. Brown, C.L. Smith, F.R. Byrne, M. Fiorino, E. Stevens, J. Bigler, J.A. Davis, J.B. Rottman, A.L. Budelsky, A. Symons, J.E. Towne, Differential Roles for Interleukin-23 and Interleukin-17 in Intestinal Immunoregulation, Immunity 43(4) (2015) 739-50.
[129] F. Martinon, K. Burns, J. Tschopp, The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta, Molecular cell 10(2) (2002) 417-26.
[130] E. Meylan, J. Tschopp, M. Karin, Intracellular pattern recognition receptors in the host response, Nature 442(7098) (2006) 39-44.

[131] G. Fantuzzi, C.A. Dinarello, Interleukin-18 and interleukin-1 beta: two cytokine substrates for ICE (caspase-1), J Clin Immunol 19(1) (1999) 1-11.
[132] D.E. Place, T.D. Kanneganti, Recent advances in inflammasome biology, Curr Opin Immunol 50 (2017) 32-38.
[133] J. Tomalka, S. Ganesan, E. Azodi, K. Patel, P. Majmudar, B.A. Hall, K.A. Fitzgerald, A.G. Hise, A novel role for the NLRC4 inflammasome in mucosal defenses against the fungal pathogen *Candida albicans*, PLoS Pathog 7(12) (2011) e1002379.
[134] S.C. Cheng, L.A. Joosten, B.J. Kullberg, M.G. Netea, Interplay between *Candida albicans* and the mammalian innate host defense, Infect Immun 80(4) (2012) 1304-13.
[135] A.H. Verma, J.P. Richardson, C. Zhou, B.M. Coleman, D.L. Moyes, J. Ho, A.R. Huppler, K. Ramani, M.J. McGeachy, I.A. Mufazalov, A. Waisman, L.P. Kane, P.S. Biswas, B. Hube, J.R. Naglik, S.L. Gaffen, Oral epithelial cells orchestrate innate type 17 responses to *Candida albicans* through the virulence factor candidalysin, Sci Immunol 2(17) (2017) DOI: 10.1126/sciimmunol.aam8834.
[136] L.L. Zhu, X.Q. Zhao, C. Jiang, Y. You, X.P. Chen, Y.Y. Jiang, X.M. Jia, X. Lin, C-type lectin receptors Dectin-3 and Dectin-2 form a heterodimeric pattern-recognition receptor for host defense against fungal infection, Immunity 39(2) (2013) 324-34.
[137] P.R. Taylor, S.V. Tsoni, J.A. Willment, K.M. Dennehy, M. Rosas, H. Findon, K. Haynes, C. Steele, M. Botto, S. Gordon, G.D. Brown, Dectin-1 is required for beta-glucan recognition and control of fungal infection, Nat Immunol 8(1) (2007) 31-8.
[138] S. Duhring, S. Germerodt, C. Skerka, P.F. Zipfel, T. Dandekar, S. Schuster, Host-pathogen interactions between the human innate immune system and *Candida albicans*-understanding and modeling defense and evasion strategies, Frontiers in microbiology 6 (2015) DOI: 10.3389/fmicb.2015.00625.
[139] E.F. Kenny, A. Herzig, R. Kruger, A. Muth, S. Mondal, P.R. Thompson, V. Brinkmann, H.V. Bernuth, A. Zychlinsky, Diverse stimuli engage different neutrophil extracellular trap pathways, eLife 6 (2017) DOI: 10.7554/eLife.24437.
[140] E. Gabrielli, S. Sabbatini, E. Roselletti, L. Kasper, S. Perito, B. Hube, A. Cassone, A. Vecchiarelli, E. Pericolini, *In vivo* induction of neutrophil chemotaxis by secretory aspartyl proteinases of *Candida albicans*, Virulence 7(7) (2016) 819-25.
[141] H.S. Goodridge, C.N. Reyes, C.A. Becker, T.R. Katsumoto, J. Ma, A.J. Wolf, N. Bose, A.S. Chan, A.S. Magee, M.E. Danielson, A. Weiss, J.P. Vasilakos, D.M. Underhill, Activation of the innate immune receptor Dectin-1 upon formation of a 'phagocytic synapse', Nature 472(7344) (2011) 471-5.
[142] C.F. Urban, U. Reichard, V. Brinkmann, A. Zychlinsky, Neutrophil extracellular traps capture and kill *Candida albicans* yeast and hyphal forms, Cell Microbiol 8(4) (2006) 668-76.
[143] C.F. Urban, D. Ermert, M. Schmid, U. Abu-Abed, C. Goosmann, W. Nacken, V. Brinkmann, P.R. Jungblut, A. Zychlinsky, Neutrophil extracellular traps contain calprotectin, a cytosolic protein complex involved in host defense against *Candida albicans*, PLoS Pathog 5(10) (2009) e1000639.
[144] T.W. Halverson, M. Wilton, K.K. Poon, B. Petri, S. Lewenza, DNA is an antimicrobial component of neutrophil extracellular traps, PLoS Pathog 11(1) (2015) e1004593.
[145] D. Ermert, C.F. Urban, B. Laube, C. Goosmann, A. Zychlinsky, V. Brinkmann, Mouse neutrophil extracellular traps in microbial infections, J Innate Immun 1(3) (2009) 181-93.
[146] A.S. Byrd, X.M. O'Brien, C.M. Johnson, L.M. Lavigne, J.S. Reichner, An extracellular matrix-based mechanism of rapid neutrophil extracellular trap formation in response to *Candida albicans*, J Immunol 190(8) (2013) 4136-48.
[147] S. Nani, L. Fumagalli, U. Sinha, L. Kamen, P. Scapini, G. Berton, Src family kinases and Syk are required for neutrophil extracellular trap formation in response to beta-glucan particles, J Innate Immun 7(1) (2015) 59-73.
[148] N. Branzk, A. Lubojemska, S.E. Hardison, Q. Wang, M.G. Gutierrez, G.D. Brown, V. Papayannopoulos, Neutrophils sense microbe size and selectively release neutrophil extracellular traps in response to large pathogens, Nat Immunol 15(11) (2014) 1017-25.

[149] S.K. Jorch, P. Kubes, An emerging role for neutrophil extracellular traps in noninfectious disease, Nature medicine 23(3) (2017) 279-287.
[150] S. Kenno, S. Perito, P. Mosci, A. Vecchiarelli, C. Monari, Autophagy and Reactive Oxygen Species Are Involved in Neutrophil Extracellular Traps Release Induced by *C. albicans* Morphotypes, Frontiers in microbiology 7 (2016) DOI: 10.3389/fmicb.2016.00879.
[151] S.G. Filler, *Candida*-host cell receptor-ligand interactions, Curr Opin Microbiol 9(4) (2006) 333-9.
[152] P. Miramon, L. Kasper, B. Hube, Thriving within the host: *Candida* spp. interactions with phagocytic cells, Medical microbiology and immunology 202(3) (2013) 183-95.
[153] C.G. McKenzie, U. Koser, L.E. Lewis, J.M. Bain, H.M. Mora-Montes, R.N. Barker, N.A. Gow, L.P. Erwig, Contribution of *Candida albicans* cell wall components to recognition by and escape from murine macrophages, Infect Immun 78(4) (2010) 1650-8.
[154] J.M. Bain, L.E. Lewis, B. Okai, J. Quinn, N.A. Gow, L.P. Erwig, Non-lytic expulsion/exocytosis of *Candida albicans* from macrophages, Fungal genetics and biology : FG & B 49(9) (2012) 677-8.
[155] M. Wellington, K. Koselny, F.S. Sutterwala, D.J. Krysan, *Candida albicans* triggers NLRP3-mediated pyroptosis in macrophages, Eukaryot Cell 13(2) (2014) 329-40.
[156] N. Uwamahoro, J. Verma-Gaur, H.H. Shen, Y. Qu, R. Lewis, J. Lu, K. Bambery, S.L. Masters, J.E. Vince, T. Naderer, A. Traven, The pathogen *Candida albicans* hijacks pyroptosis for escape from macrophages, MBio 5(2) (2014) e00003-14.
[157] R.J. Dubos, R.W. Schaedler, Effects of cellular constituents of mycobacteria on the resistance of mice to heterologous infections I. Protective effects, J Exp Med 106(5) (1957) 703-17.
[158] J.G. Howard, G. Biozzi, B.N. Halpern, C. Stiffel, D. Mouton, The effect of *Mycobacterium tuberculosis* (BCG) infection on the resistance of mice to bacterial endotoxin and *Salmonella enteritidis* infection, Br J Exp Pathol 40(3) (1959) 281-90.
[159] N.A. Sher, S.D. Chaparas, L.E. Greenberg, S. Bernard, Effects of BCG, *Corynebacterium parvum*, and methanol-extration residue in the reduction of mortality from *Staphylococcus aureus* and *Candida albicans* infections in immunosuppressed mice, Infect Immun 12(6) (1975) 1325-30.
[160] F. Bistoni, A. Vecchiarelli, E. Cenci, P. Puccetti, P. Marconi, A. Cassone, Evidence for macrophage-mediated protection against lethal *Candida albicans* infection, Infect Immun 51(2) (1986) 668-74.
[161] F. Bistoni, G. Verducci, S. Perito, A. Vecchiarelli, P. Puccetti, P. Marconi, A. Cassone, 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(5) (1988) 285-99.
[162] J. Quintin, S. Saeed, J.H.A. Martens, E.J. Giamarellos-Bourboulis, D.C. Ifrim, C. Logie, L. Jacobs, T. Jansen, B.J. Kullberg, C. Wijmenga, L.A.B. Joosten, R.J. Xavier, J.W.M. van der Meer, H.G. Stunnenberg, M.G. Netea, *Candida albicans* infection affords protection against reinfection via functional reprogramming of monocytes, Cell Host Microbe 12(2) (2012) 223-32.
[163] S.K. Biswas, A. Mantovani, Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm, Nat Immunol 11(10) (2010) 889-96.
[164] S. Saeed, J. Quintin, H.H. Kerstens, N.A. Rao, A. Aghajanirefah, F. Matarese, S.C. Cheng, J. Ratter, K. Berentsen, M.A. van der Ent, N. Sharifi, E.M. Janssen-Megens, M. Ter Huurne, A. Mandoli, T. van Schaik, A. Ng, F. Burden, K. Downes, M. Frontini, V. Kumar, E.J. Giamarellos-Bourboulis, W.H. Ouwehand, J.W. van der Meer, L.A. Joosten, C. Wijmenga, J.H. Martens, R.J. Xavier, C. Logie, M.G. Netea, H.G. Stunnenberg, Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity, Science 345(6204) (2014) DOI: 10.1126/science.1251086.
[165] D.C. Ifrim, J. Quintin, L.A. Joosten, C. Jacobs, T. Jansen, L. Jacobs, N.A. Gow, D.L. Williams, J.W. van der Meer, M.G. Netea, Trained immunity or tolerance: opposing functional programs induced in human monocytes after engagement of various pattern recognition receptors, Clin Vaccine Immunol 21(4) (2014) 534-45.

[166] S.C. Cheng, J. Quintin, R.A. Cramer, K.M. Shepardson, S. Saeed, V. Kumar, E.J. Giamarellos-Bourboulis, J.H. Martens, N.A. Rao, A. Aghajanirefah, G.R. Manjeri, Y. Li, D.C. Ifrim, R.J. Arts, B.M. van der Veer, P.M. Deen, C. Logie, L.A. O'Neill, P. Willems, F.L. van de Veerdonk, J.W. van der Meer, A. Ng, L.A. Joosten, C. Wijmenga, H.G. Stunnenberg, R.J. Xavier, M.G. Netea, mTOR- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity, Science 345(6204) (2014) DOI: 10.1126/science.1250684.
[167] H.R. Conti, A.C. Peterson, L. Brane, A.R. Huppler, N. Hernandez-Santos, N. Whibley, A.V. Garg, M.R. Simpson-Abelson, G.A. Gibson, A.J. Mamo, L.C. Osborne, S. Bishu, N. Ghilardi, U. Siebenlist, S.C. Watkins, D. Artis, M.J. McGeachy, S.L. Gaffen, Oral-resident natural Th17 cells and γδ T cells control opportunistic *Candida albicans* infections, J Exp Med (2014) DOI: 10.1084/jem.20130877.
[168] A. Puel, S. Cypowyj, J. Bustamante, J.F. Wright, L. Liu, H.K. Lim, M. Migaud, L. Israel, M. Chrabieh, M. Audry, M. Gumbleton, A. Toulon, C. Bodemer, J. El-Baghdadi, M. Whitters, T. Paradis, J. Brooks, M. Collins, N.M. Wolfman, S. Al-Muhsen, M. Galicchio, L. Abel, C. Picard, J.L. Casanova, Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity, Science 332(6025) (2011) 65-8.
[169] B. Boisson, C. Wang, V. Pedergnana, L. Wu, S. Cypowyj, M. Rybojad, A. Belkadi, C. Picard, L. Abel, C. Fieschi, A. Puel, X. Li, J.L. Casanova, An *ACT1* mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis, Immunity 39(4) (2013) 676-86.
[170] Y. Ling, S. Cypowyj, C. Aytekin, M. Galicchio, Y. Camcioglu, S. Nepesov, A. Ikinciogullari, F. Dogu, A. Belkadi, R. Levy, M. Migaud, B. Boisson, A. Bolze, Y. Itan, N. Goudin, J. Cottineau, C. Picard, L. Abel, J. Bustamante, J.L. Casanova, A. Puel, Inherited IL-17RC deficiency in patients with chronic mucocutaneous candidiasis, J Exp Med 212(5) (2015) 619-31.
[171] S.K. Browne, S.M. Holland, Anti-cytokine autoantibodies explain some chronic mucocutaneous candidiasis, Immunol Cell Biol 88(6) (2010) 614-5.
[172] A.K. Sarkadi, S. Tasko, G. Csorba, B. Toth, M. Erdos, L. Marodi, Autoantibodies to IL-17A may be correlated with the severity of mucocutaneous candidiasis in APECED patients, J Clin Immunol 34(2) (2014) 181-93.
[173] H.R. Conti, S.L. Gaffen, IL-17-Mediated Immunity to the Opportunistic Fungal Pathogen *Candida albicans*, J Immunol 195(3) (2015) 780-8.
[174] A. Gladiator, N. Wangler, K. Trautwein-Weidner, S. LeibundGut-Landmann, Cutting edge: IL-17-secreting innate lymphoid cells are essential for host defense against fungal infection, J Immunol 190(2) (2013) 521-5.
[175] S. LeibundGut-Landmann, O. Gross, M.J. Robinson, F. Osorio, E.C. Slack, S.V. Tsoni, E. Schweighoffer, V. Tybulewicz, G.D. Brown, J. Ruland, C. Reis e Sousa, Syk- and CARD9-dependent coupling of innate immunity to the induction of T helper cells that produce interleukin 17, Nat Immunol 8(6) (2007) 630-8.
[176] S. Bishu, N. Hernandez-Santos, M.R. Simpson-Abelson, A.R. Huppler, H.R. Conti, N. Ghilardi, A.J. Mamo, S.L. Gaffen, The adaptor CARD9 is required for adaptive but not innate immunity to oral mucosal *Candida albicans* infections, Infect Immun 82(3) (2014) 1173-80.
[177] J.R. Naglik, A. Konig, B. Hube, S.L. Gaffen, *Candida albicans*-epithelial interactions and induction of mucosal innate immunity, Curr Opin Microbiol 40 (2017) 104-112.

Figure 1


Hypha
A
Als3p/Ssa1p
Hwp1p
β-glucan
Ssa1p/Als3p
E-cadherin
Epithelial Cell
EphA2
EGFR/Her2
Hypha
B
Epithelial Cell
Ca2+
LDH
Candidalysin
Candidalysin pore
C
JNK
p38
ERK1/2
MKP1
c-Fos
IL-17R
Upregulation of TLR4
Induction of cytokines chemokines AMPs
Cytokines
Chemokines
AMPs/Alarmins
Clearance
D
Recruitment
Innate type 17
IL-17
IL-1
IL-1R
E
TNF-α
Neutrophil
NLRs
TLR
CTLR
F
NETosis
Macrophage
NLRs
CTLR
TLR
G
Pyroptosis
IL-1β