Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.e-biomedicine.com

Review article

Study of *Candida albicans* and its interactions with the host: A mini review

Pei-Wen Tsai [a], Yu-Ting Chen [a], Po-Chen Hsu [a], Chung-Yu Lan [a,b,c,*]

[a] Institute of Molecular and Cellular Biology, National Tsing Hua University, Hsinchu 30013, Taiwan, ROC
[b] Department of Life Science, National Tsing Hua University, Hsinchu 30013, Taiwan, ROC
[c] Graduate Institute of Molecular Systems Biomedicine, China Medical University, Taichung 40402, Taiwan, ROC

ARTICLE INFO

Article history:
Received 21 November 2012
Received in revised form
30 November 2012
Accepted 30 November 2012
Available online 5 January 2013

Keywords:
Candida albicans
candidiasis
host–pathogen interactions

ABSTRACT

Candida albicans is an important fungal pathogen in humans. The interaction between *C. albicans* and its host is dynamic and complex. This pathogen exhibits multifaceted strategies for growth, proliferation, and survival within the host accompanied with mechanisms to escape from the host defense. The host triggers complex immune responses in response to *C. albicans*. This review outlines selected aspects in the current understanding of *C. albicans* pathogenesis and its interactions with the host, and presents several experimental tools developed in the postgenomic era to study these topics.

1. Introduction

Mycoses are diseases caused by fungi. With the increase in the population of patients with immunodeficiency or undergoing immunosuppressive therapy, mycoses have become a growing problem in modern medical care. In addition, the diagnosis of these diseases can be problematic, drug resistance is of great concern, and fewer drugs are available compared to bacterial or viral diseases [1–3]. Fungal infections lead to various diseases that can be local, superficial, allergic, or systemic [1]. Systemic infections are particularly serious and potentially life-threatening [4–6].

Of the more than 1.5 million estimated species of fungi, fewer than 150–200 species can cause disease in humans [7]. The fungal pathogens involved in systemic infections are either acquired from the surrounding environments of the host or constitute part of the normal flora in humans. The former include *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma duboisii*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Penicillium marneffei* [8,9]. The latter are opportunistic, and include *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* [8,9]. Among the opportunistic pathogens in humans, *C. albicans* is one of the most studied.

Yeasts are unicellular fungi, and the *Candida* species represents one of the yeast species of special importance to human health [10]. *Candida* is a part of the normal flora in healthy individuals, and is usually confined to the skin and mucosal surfaces of the oral cavity, gastrointestinal and urogenital tracts, and vagina [10]. However, *Candida* spp. can

* *Corresponding author*. Institute of Molecular and Cellular Biology, National Tsing Hua University, 101, Section 2, Kuang Fu Road, Hsinchu 30013, Taiwan, ROC.
E-mail address: cylan@life.nthu.edu.tw (C.-Y. Lan).

2211-8020/$ – see front matter
http://dx.doi.org/10.1016/j.biomed.2012.12.004

cause a wide variety of infections on mucosal surfaces under certain conditions. The most common examples include oropharyngeal candidiasis (OPC) and vulvovaginal candidiasis (VVC). OPC is associated with underlying illness such as diabetes [10]. In addition, OPC was one of the first manifestations of HIV-induced immunodeficiency to be recognized [11] and is a sentinel indicator for HIV disease progression before the appearance of more severe symptoms [12,13]. *C. albicans* is the most common cause of OPC [14,15]. However, *Candida glabrata*, *Candida tropicalis*, and *Candida dubliniensis* are also associated with OPC [14,15]. *C. albicans* causes approximately 90% of VVC cases, and *C. glabrata* is responsible for the remaining 10% of this infection [16]. Although the relationship between VVC and HIV is unclear, VVC is an important concern for women infected with HIV [17]. The majority of *C. albicans* isolates causing disease in AIDS patients are derived from strains originally associated with commensal infections, and disease recurrence can result from the same strains of *C. albicans* [18,19].

In addition to causing mucosal diseases, *Candida* spp. can also cause systemic and invasive infections in which *Candida* penetrates and traverses the epithelial barrier to gain entry into the bloodstream (known as candidemia) [20]. Once in the bloodstream, *Candida* can disseminate to infect almost any organs. Consequently, *Candida* has emerged as the fourth most common cause of blood-borne infection in the United States [21]. The mortality associated with these invasive infections for adults ranges from 14.5% to 49% [22,23], and *C. albicans* is estimated to be responsible for 50–60% of the cases of invasive candidiasis [24,25]. As such, *C. albicans* is the most prevalent fungal pathogen in humans. Therefore, here we only review our current understanding of *C. albicans* and its interactions with the host.

2. Virulence factors of *C. albicans* in pathogen–host interactions

To establish an infection successfully, *C. albicans* must adapt to different niches at various anatomic sites of the host and express infection-associated genes. The products of infection-associated genes contribute to *C. albicans* pathogenicity, and function as virulence factors [26]. Researchers have reported several virulence factors for *C. albicans*, including morphological transition, adhesins, secreted hydrolytic enzymes, and phenotypic switching [20,26,27]. This review focuses on several important findings related to virulence factors. For other details, the reader should refer to other recent reviews [28–35].

2.1. *Morphological transition in C. albicans*

The ability of *C. albicans* to switch reversibly between a single-celled budding yeast (blastospore) and an elongated filament form (both pseudohyphae and true hyphae) plays a crucial role in infections [36]. Hyphal cells may promote tissue invasion, whereas yeast cells facilitate dissemination of the pathogen [37–40]. *C. albicans* morphogenesis is controlled by a complex network of signaling pathways that is commonly accompanied by the regulation of genes associated with the morphological states [34]. The signaling and regulatory network is activated by various environmental signals, including serum, N-acetyl-D-glucosamine, neutral pH, a physiological temperature of 37°C, 5% CO_2, and nutrient starvation [28,35,41,42].

The cyclic AMP–protein kinase A (cAMP–PKA) pathway is involved in *C. albicans* yeast–hyphae transition. The cAMP–PKA pathway transfers environmental signals through the adenylyl cyclase Cyr1, which activates cAMP production. In the case of serum-induced hyphae formation, signals pass through the small GTPase Ras1, which subsequently activates Cyr1 by direct interaction between Ras1 and the Ras-association domain of Cyr1. Alternatively, G protein-coupled receptor 1 (Gpr1) seems to sense amino acids such as methionine and activates Cyr1 through Gpa2 (the associated G protein α2 subunit), independent of Ras1 [43]. The activation of Cyr1 increases intracellular levels of cAMP, which binds to the regulatory subunit (Bcy1) of PKA to release and thereby activate the catalytic subunits (Tpk1 and Tpk2) of PKA [44]. Consequently, the active form of PKA controls the transcription factor Efg1 to enhance expression of hypha-specific genes, such as *HGC1*, *ALS3*, and *HWP1*. The Als3 and Hwp1 are both cell wall proteins and relevant to cell adhesion (see the descriptio below). The *HGC1* gene encodes a hypha-specific G1 cyclin, which associates with the cyclin-dependent protein kinase Cdc28 to phosphorylate septin cytoskeleton proteins such as Cdc11. This in turn promotes polarized growth, cell separation, and hyphae formation [45].

The mitogen-activated protein kinase (MAPK) cascade is another important signaling pathway regulating *C. albicans* morphogenesis. The cascade controlling morphogenesis consists of Cst20 (MAPK kinase kinase kinase), Ste11 (MAPK kinase kinase), Hst7 (MAPK kinase), and Cek1 (MAPK). The activation of Cek1 through the signaling cascade subsequently activates the downstream transcription factor Cph1, through phosphorylation. Although the deletion of the *CPH1* gene reduces hyphal growth on solid medium, it still forms hyphae in liquid culture and after serum induction [46]. The *cph1/efg1* double deletion mutant is defective in filamentous growth even in the presence of serum and is avirulent in a mouse model of systemic infection [39]. In addition to activators, there are also negative regulators of filamentation. Mutants lacking *TUP1*, *RFG1*, *MIG1*, or *NRG1* genes exhibit the phenotype of constitutive filamentation [47–50].

Nitrogen availability also affects the morphological transition of *C. albicans*. In the case of nitrogen limitation, upregulation is involved in the expression of the *MEP2* gene that encodes a permease and sensor for ammonium, a preferred nitrogen source for *C. albicans* [51,52]. The Mep2 protein receives the signal and may induce morphogenesis by activating the cAMP–PKA pathway and the Cph1-dependent MAPK pathway [53]. Recent research has indicated that the small GTPase Rhb1 and target of rapamycin (TOR) signaling is also involved in regulating *MEP2* expression and low nitrogen-mediated morphogenesis [54]. The *C. albicans* transcription factors Gat1 and Gln3 control the expression of *MEP2* [52]. The *gln3*- and *gat1*-deleted mutants exhibit reduced sensitivity to rapamycin [55], a TOR kinase inhibitor, suggesting that these regulators are also involved in *C. albicans* TOR signaling. Ambient pH also affects *C. albicans* morphogenesis through

a conserved signal transduction pathway with Rim101 as the key regulator [56,57]. Rim101 is a zinc-finger-containing transcription factor that is full length and inactive under acidic conditions [58,59]. However, at neutral to alkaline conditions, Rim13 cleaves the C-terminal portion of Rim101, activating the protein that alters gene expression [60]. Hypoxia and embedding cells in a matrix can also promoter *C. albicans* morphogenesis. The Efg1 and Cfz1 transcription factors are involved in hypoxia-induced and matrix-dependent hyphae formation, respectively [61–63].

C. albicans integrates multiple environmental cues into complex signaling networks that coordinate various transcription factors to control hypha-specific genes. Consequently, *C. albicans* differentially express various cell surface proteins and virulence factors. This may be significant for the pathogen to penetrate into deep tissues to acquire nutrients or escape from the host defense, and may also hinder detection by the host immune systems.

2.2. Adhesins of C. albicans

The adherence to host cells and tissues is the initial and critical step in microbial infections. In the case of mucosal infections, *C. albicans* first colonizes and proliferates on the mucosal surfaces of epithelial cells. This may be followed by invasion, dissemination, and tissue damage [38,64]. The outmost layer of *C. albicans*, the cell wall, contains diverse carbohydrates and proteins that may contact with host proteins, epithelial, and endothelial cells [65–67]. In addition, *C. albicans* can adhere to abiotic substrates, such as medical devices, and form surface-associated cell communities known as biofilms [68]. Biofilm and planktonic cells differ in many aspects, including their susceptibility to host immune defense and antifungal agents [69–73]. Biofilm is also a dense colonial source of cells, which are continually released into the immediate environment, providing a reservoir for persistent sources of infection.

Previous research has shown several *C. albicans* molecules related to adherence, known as adhesins. The agglutinin-like sequence (Als) protein family is the most recognized of these adhesins [26,30]. Eight *ALS* genes (*ALS1–ALS7* and *ALS9*) encode cell-wall-associated glycoproteins with similar structures. The N terminus of Als proteins, which contains a signal sequence, an immunoglobulin-like domain, and a threonine-rich domain, is involved in ligand binding [74–76]. These proteins also include a central domain containing a variable number of 36-amino-acid tandem repeats rich in serine and threonine residues [75]. Finally, the C terminus of the Als proteins contains a glycosylphosphatidylinositol (GPI) anchorage sequence [77]. Studies on the *ALS*-deletion mutants of *C. albicans* or heterologous expression of *C. albicans ALS* genes in *Saccharomyces cerevisiae* have suggested that a subset of Als proteins is involved in adherence to host surfaces. For example, the heterologous expression of *C. albicans ALS1* or *ALS5* genes in nonadhesive *S. cerevisiae* causes cell binding to extracellular matrix proteins (e.g., fibronectin, laminin, and type IV collagen) and buccal and pharyngeal epithelial and vascular endothelial cells [77,78]. *ALS4* deletion decreases *C. albicans* adherence to endothelial cells, but not to epithelial cells [79]. In addition, Als6 can bind to collagen and Als9 to laminin [80].

Other proteins related to *C. albicans* adhesion include Hwp1, Eap1, and Int1 [26,31]. Hwp1 is a major protein on the hyphal cell wall and is able to adhere to epithelium mediated by host transglutaminase [81]. Hwp1 is also required for biofilm formation [82–84]. Eap1 is a GPI-anchored cell wall protein required for biofilm formation and binding to a polystyrene surface or host cells. However, its host ligands are still unknown [85,86]. Int1 is an integrin-like protein, and the deletion of the *INT1* gene reduces *C. albicans* colonization on the murine intestinal epithelium [87].

2.3. Secreted hydrolytic enzymes

Researchers have identified many types of secreted hydrolytic enzymes in *C. albicans*. These enzymes help *C. albicans* in nutrient acquisition and dissemination within the host. These enzymes can also modulate host immune responses and cause host tissue damage [88].

Secreted aspartyl proteases (Saps) are encoded by 10 members of the *SAP* gene family, *SAP1–SAP10* [89]. These *SAP* genes are differentially expressed in different *C. albicans* cell types and during various stages of *C. albicans*–host interaction. *SAP1–3* and *SAP4–6* are highly expressed in yeast and hyphal cells, respectively [32,90]. The expression of *SAP7* has been detected in some clinical samples of human oral infection [91] and *SAP8* appears at high levels in human vaginal infection [89]. *SAP9* and *SAP10* are expressed in both yeast and hyphae. Their gene products contain N-glycosylation sites and putative GPI-anchor attachment sequences, suggesting their association with the cell wall [92,93]. Moreover, *C. albicans* biofilms secrete more Sap proteins than planktonic cells [94]. When proteins are the only available nitrogen source, TOR signaling also helps regulate *SAP2* transcription and Sap2 protein levels, coordinated with the small GTPase Rhb1 [95]. Under these conditions, the transcription factors Gat1 and Gln3 induce the expression of the *STP1* gene, which encodes a proteolytically activated transcription factor that subsequently mediates *SAP2* gene expression [96].

Different Sap proteins possess unique enzymatic characteristics and substrate specificities [89]. Sap1–3 proteins exhibit the highest activity at pH 3–5, whereas Sap4–6 are most active at pH 5–7. These enzymes may help the pathogen to develop infections at different anatomical sites in humans [32,97]. For example, Sap2 is capable of digesting human albumin, hemoglobin, keratin, and secreted IgA [98]. Sap2 digests proteins into oligopeptides that are subsequently taken up by oligopeptide transporters encoded by the *OPT* gene family [99]. Therefore, Sap2 and other Saps may be critical for cell growth in humans using host proteins as a nitrogen source. The degradation of human proteins also allows *C. albicans* to destroy host barriers and is followed by deep penetration into tissues or the bloodstream.

The four secreted phospholipase A to D (PLA, PLB, PLC and PLD) hydrolyze one or more ester linkages of glycerophospholipids on the host cell membrane, and are critical factors in tissue invasion. PLB represents the major activity of *C. albicans* phospholipase, and contains both hydrolase and lysophospholipase–transacylase activities [100,101]. PLB

proteins have broad substrate specificity and hydrolase activity releases fatty acids from phospholipids and lysophospholipids by hydrolyzing acyl ester bonds and further catalyzing lysophospholipase–transacylase reactions [102]. Previous studies on several *C. albicans PLB* genes have implicated *PLB1* and *PLB5* in *C. albicans* virulence [102–104]. In addition to Saps and phospholipases, *C. albicans* also secretes a serine peptidase and at least nine lipases. The peptidase degrades human serum proteins and extracellular matrix components [105], and the lipases hydrolyze the ester bonds of mono-, di-, and triacylglycerols [88].

2.4. Phenotypic switching in C. albicans

Phenotypic switching helps *C. albicans* adapt to changing environments at different anatomic loci in the host. Phenotypic switching enables *C. albicans* cells to spontaneously and reversibly switch phenotypes at a high frequency. The most studied switching system is the WO-1 strain, which alters between white hemispherical colonies (designated as white, W) and gray flat colonies (designated as opaque, O). W–O switching also changes the shape and size of cells, their ability to form hyphae, cell surface properties (e.g., adhesion and permeability), membrane composition, protease secretion, biofilm formation, sensitivity to phagocytes and oxidants, antigenicity, drug susceptibility, and metabolism [31,106–109]. Moreover, misexpression of the opaque-phase-specific gene *PEP1* in the white phase of *C. albicans* confers increased virulence in a mouse model of cutaneous infection [110]. A murine model for systemic infection shows that considerably more W cells colonize the kidneys than O cells, and most of the cells recovered from the kidneys switch from O to W [111].

C. albicans has long been designated as an asexual yeast; however, there is a mating type-like locus (*MTL*) in the *C. albicans* genome [112]. Interestingly, *C. albicans* strains with subtle changes at the *MTL* locus can mate after inoculation into a mammalian host [113]. Recent research has linked the *MTL* to W–O switching. Only cells homozygous at the *MTL* can switch from the W phase to the O phase and mate with other O cells, producing progeny [114–116]. In addition, DNA microarray analysis indicates that W and O cells have distinct gene expression profiles [106] and Wor1 is a master transcription regulator for W–O switching [117–120]. Deletion of the *WOR1* gene disables switching and locks the cells in the white phase. Subsequent studies have identified additional transcription factors (Wor2, Efg1, and Czf1) that function with Wor1 in a network of feedback loops [121,122]. A sophisticated regulatory network controls phenotypic switching. Phenotypic switching helps *C. albicans* survive within the host and makes the cells become more virulent and effective during infection.

2.5. Other factors related to C. albicans virulence

In addition to the factors discussed previously, other factors are closely related to *C. albicans* virulence. One important example is the ability of *C. albicans* to acquire iron from the host during infection. Several types of evidence support the correlation between iron acquisition and virulence. The iron-free forms of host lactoferrin and transferrin inhibit cell growth and render cells more susceptible to damage by neutrophils [123]. Iron deprivation also affects the adhesive properties and cell wall antigen compositions of *C. albicans* cells [124,125]. The hypha-associated adhesin Als3 mediates iron acquisition from host ferritin [126], and other cell surface proteins including Rbt51 are involved in hemin and hemoglobin-iron utilization [127]. Studies on suspension cultures and biofilm cells indicate that iron availability affects the drug resistance of *C. albicans* [124,128–131]. For example, iron limitation contributes to the antifungal activity of ciclopirox olamine, a topical antimycotic drug of the hydroxypyridone class [132–134]. The siderophore transporter (Arn1) is also required for epithelial invasion and penetration, and endothelial cell injury caused by *C. albicans* is iron dependent [135]. More importantly, the deletion mutants lacking the high-affinity iron permease Ftr1 are unable to establish systemic infection in mice, indicating that Ftr1-mediated iron acquisition is an important factor in *C. albicans* virulence [136]. In response to iron availability, the control of iron acquisition is complex and mediated by a regulatory circuit consisting of transcription factors such as Sfu1, Hap43, and Sef1 [137–141].

2.6. Host responses to C. albicans

The interaction between a pathogen and its host is complex and dynamic [142]. This is particularly true for a pathogen like *C. albicans*, which can establish chronic, long-lasting, and recurrent infections and persist in both latent and active forms. To establish an infection, *C. albicans* adopts various strategies to overcome host defense systems. These strategies allow the pathogen to survive and proliferate within the host by sensing and responding to host environments and by expressing virulence factors. In response to the pathogen, the host triggers defense mechanisms consisting of innate and acquired (or adaptive) immunity.

2.7. Recognition between C. albicans and the host cell

The interaction of *C. albicans* and the host begins with cell–cell recognition. In *C. albicans*, several cell wall components can act as pathogen-associated molecular patterns (PAMPs). These PAMPs include *O*- or *N*-linked mannans, mannoproteins, α- or β-glucans, and chitin. Conversely, human cells have pattern recognition receptors (PRRs) to recognize pathogens and activate host defenses. Previous research has described several PRR families including Toll-like receptors (TLRs), C-type lectin receptors, Nacht-like receptors, RIG-like receptors (RLRs), and the galectin family [143–146]. The complexity of *C. albicans*–host interaction arises from the many ways that PRRs recognize PAMPs. Although a PAMP may be only recognized by a particular PRR, other PAMPs can be recognized by more than one PRR. For example, β-glucans can be recognized by both Dectin-2 and TLR 2 [147], whereas PRRs such as Dectin-2 are able to recognize more than one ligand, including α-glucans and *N*-linked mannans [148]. Different PRRs, such as TLR2 and Dectin-1, can work independently or together [144,145,149]. The complexity of *C. albicans*–host interaction is enhanced by the expression of different sets of PRRs in various cell types and locations within the human host. Phenotypic switching and morphological plasticity may

also change the distributions of *C. albicans* cell-surface PAMPs within distinct host niches.

2.8. Host innate immunity to C. albicans

The integration of innate and acquired responses protects the host against pathogens. The innate system acts early during infection, recognizing and destroying most pathogens. Therefore, this article only focuses on some key points of innate defenses against *C. albicans*. Discussion of other relevant topics and acquired immunity is available in several excellent reviews [150–154].

Many cell types including epithelial cells and phagocytic cells such as polymorphonuclear neutrophils (PMNs), monocytes/macrophages, and dendritic cells (DCs), are involved in innate responses. During mucosal infections, the epithelium provides the first line of defense against *C. albicans*, acting as a passive physical barrier [155]. However, epithelial cells can also activate immune responses and secrete antimicrobial peptides such as β-defensins and human cathelicidin. Recent studies have shown that LL-37, the active form of human cathelicidin, inhibits *C. albicans* adhesion by interacting with cell wall carbohydrates and the β-1,3-exoglucanase Xog1 [156,157]. In response to *C. albicans*, epithelial cells secrete various proinflammatory cytokines and chemokines that recruit and activate various immune cells, such as PMNs [152,158]. The recruitment of PMNs is not only mediated by epithelial cytokines and chemokines, but also by cytokines from other cells and by other factors. For example, interleukin (IL)-17 from T helper (Th)17 cells plays a crucial role in recruiting neutrophils to the site of infection [159]. The importance of Th17 cells in immunity to *C. albicans* has recently been reviewed [160,161]. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are also involved in the recruitment and activation of PMNs [162–164]. Neutrophils can effectively take up and kill *C. albicans* cells using oxidative mechanisms, including the generation of reactive oxygen and nitrogen intermediates [152,165]. Interestingly, neutrophils prefer to attract and kill hyphae rather than yeast cells, by activating extracellular signal-regulated kinase signaling [166]. In addition to killing *C. albicans* through endocytosis, neutrophil extracellular traps containing the antimicrobial peptide calprotectin can also inhibit cell growth of *C. albicans* [165].

Based on previous studies, neutrophils may account for more of the innate immunity defense than mononuclear phagocytes [167]. The elimination of mouse splenic macrophages results in a slower clearance of *C. albicans* from blood [168]. However, another study has indicated that monocytes or exudate macrophages do not play important roles in resistance against *C. albicans* in systemic infection [169]. DCs are antigen-presenting cells and the interface between innate and acquired immunity [170]. These cells can ingest both yeast and hyphal cells of *C. albicans*, leading to maturation and activation of DCs to present *Candida*-specific antigens [171]. DCs can also induce the differentiation of Th cells. The ingestion of yeasts primes Th1 cells, whereas hyphae inhibit IL-12 and Th1 differentiation and favor Th2 differentiation [155,172]. Th1 cells then secrete tumor-necrosis factor-β and interferon-γ to recruit other leukocytes to the site of inflammation. In contrast, Th2 cells produce cytokines, such as IL-4, to promote the synthesis of IgE in B cells [172].

3. Postgenomic approaches to studying *C. albicans* and its interactions with the host

3.1. Whole genome sequencing of C. albicans and non-albicans Candida spp.

The genome sequencing of the SC5314 strain was a significant and recent achievement in studying *C. albicans* [173] and a human-curated annotation for the *Candida* genome is now available [174]. Genome sequencings of various strains of *C. albicans* and several non-*albicans Candida* spp. have also emerged recently [175–178]. These genome sequences provide a great challenge and opportunity for genome comparisons. This genome information can be accessed on the internet-based Candida Genome Database (CGD; http://www.candidagenome.org).

The development of new and more efficient strategies for genetic analysis has also promoted the study of *C. albicans*. Examples include the genome-wide construction of deletion mutants [179–183], and emerging technologies for global measurement of steady state mRNA concentrations [184] and protein expression levels/phosphorylation states [185–187]. With this armamentarium of methods and technologies, researchers are better able to develop *C. albicans* as an easily accessible model for understanding mechanisms in opportunistic fungal pathogenesis and fungal pathogen–host interaction. This review presents several developments in methodologies and technologies for studying *C. albicans* as follows.

3.2. Transcriptional profiling by DNA microarray, RNA-seq and others

DNA microarray-based studies have been used to study various aspects of *C. albicans* biology, physiology, and pathogenesis. Some of these studies were related to morphogenesis [188–190], susceptibility to antifungal drugs [191,192], signaling and stress responses [95,193–195], metabolism [139,140,196,197], mating type [198,199], phenotypic switching [106], biofilms [200–202], and cell responses to environmental changes [203].

Meanwhile, microarray analysis has begun to show the interactions of *C. albicans* with different host cells [204,205]. Gene expression is detected in the pathogen side during pathogen–host interactions. For example, *C. albicans* genes encoding the key enzymes of the glyoxylate cycle and proteins with nonmetabolic functions are upregulated when the pathogen is ingested by a mammalian macrophage [205,206]. After challenging with human blood, *C. albicans* expresses unique sets of genes at different stages of the model, mimicking bloodstream infections. The functions of these genes are related to the general stress response, antioxidative response, glyoxylate cycle, and virulence attributes [204]. A previous study has analyzed the transcriptome of *C. albicans* isolated from the mammalian kidney [207]. Compared to the

control cells, *C. albicans* from infected tissues shows upregulation of genes related to adhesion, stress responses, and the assimilation of alternative carbon sources. However, genes involved in morphogenesis, fermentation, and translation are downregulated [207]. In addition, the basic leucine zipper (bZIP) transcription factor Rca1 activates *C. albicans* carbonic anhydrase during contact with mammalian phagocytes [208]. Moreover, gene expression for the host side is also detected when pathogen–host interactions occur. For example, human DCs sense diverse pathogens of *C. albicans*, *Escherichia coli*, and influenza virus, and elicit pathogen-specific immune responses [209]. With the treatment of *C. albicans* cell wall β-glucan, human leukocytes activate genes that relate to various categories, including those that encode effectors with proinflammatory properties [210]. A study of *Candida*–granulocyte interaction has shown that *C. albicans* modulates the HL60 granulocytoid response by downregulating known antimicrobial genes at a high pathogen–host ratio [211]. Endothelial cells respond differently to low and high densities of *C. albicans* [212]. In response to heat-killed *C. albicans*, miRNA transcription in macrophages is differentially regulated to modulate PRR signaling [213]. Experimental keratomycosis shows that TLR and proinflammatory chemokines are differentially regulated in murine corneas with *C. albicans* inoculation [214,215].

Except for using DNA microarrays alone, chromatin immunoprecipitation coupled with microarray analysis (ChIP-chip) have also recently been developed to study *in vivo* protein–DNA association in *C. albicans* at the whole genome level. Some examples include studies of transcriptional control of W–O switching [122], the regulation of gene expression of ribosome proteins and carbohydrate metabolism [196,216], and the regulation of morphogenesis by the transcription factors Efg1 and Hms1 [217,218],

RNA-seq (deep-sequencing of cDNA) has been used to identify novel transcribed regions, detect new splicing events, and quantify gene expression [219–223]. This method reduces some common concerns in using DNA microarray such as platform-related effects, and is significantly more sensitive than a microarray. More recently, this approach has been used to study *C. albicans* and its interaction with host. Bruno et al have used RNA-seq to generate a high-resolution map of the *C. albicans* transcriptome, to determine all the regions transcribed under various environmental conditions [224]. They have identified 602 novel transcriptionally active regions in the genome; many of which are expressed in a condition-specific manner. They also have shown several novel introns not present in the current genome annotation [224]. The RNA-seq technology has also been used to compare the transcriptomes of a drug-resistant clinical isolate and its isogenic drug-sensitive counterpart [225]. There are 228 genes differentially expressed, and many of them have never been linked to the phenotype of drug resistance. The acquisition of drug resistance is also correlated with an overexpression of the *CZF1* gene, which encodes a transcription factor. The *czf1*-deleted mutants are susceptible to many drugs, independently of known multidrug resistance mechanisms [225]. Tierney et al have demonstrated the use of RNA-seq to profile simultaneously genome-wide gene expression of both *C. albicans* and the host [226]. Although each technology of DNA microarray, ChIP-chip and RNA-seq is powerful in studying *C. albicans* and its interaction with the host, combined tools have been used to study the complex transcription network in regulation of *C. albicans* biofilm development [227].

3.3. *Proteomic research*

Several researchers have reviewed the use of the proteomic approach in studying *C. albicans* and its interaction with the host [185–187,228–230], and this article highlights only a few recent applications. The *C. albicans* cell wall consists of polysaccharides and many integral and covalently attached proteins. Proteomic approaches make it possible to study the *C. albicans* cell wall in detail. For example, the cell wall proteome is affected by hypoxic conditions, iron restriction, ambient pH, and hyphal growth [231–233]. Moreover, many antifungal drugs target *C. albicans*. The proteomic approach also shows the effects of fluconazole on cell wall proteome and integrity [234]. It seems that *C. albicans* adapts to the environmental conditions by changing the protein composition of its cell wall, and some cell wall proteins identified may be candidates for vaccine development [235]. After interaction with heat-killed *C. albicans*, proteins differentially expressed in murine macrophages are shown by comparison to the control. These proteins function in various cellular processes, including cytoskeletal organization, signaling, metabolism, protein synthesis, and stress response. Many of them are known to be involved in the inflammatory process [236]. The responses of murine macrophages are further analyzed using live cells of *C. albicans* and enriched fractions of cytosol, organelle/membrane, and nucleus from the macrophages. This study has identified 17 new differentially expressed proteins, including two mitochondrial proteins, a membrane receptor, galectin-3, and several endoplasmic-reticulum-related proteins [237]. These proteins are also involved in the proinflammatory and oxidative responses, immune response, unfolded protein response, and apoptosis. These processes may increase the host response to the pathogen or may arise from *C. albicans* resistance to phagocytosis [237].

3.4. *Network and systems biology*

Although understanding the functions of individual genes and proteins remains necessary, the importance of studying the structure and dynamics within a cell or an organism has become increasingly recognized. In a single cell or an organism, genes and proteins not only function individually, but also form networks with interconnectivity between genes and proteins in response to environmental conditions [238]. Systems biology approaches aim to understand networks such as those that regulate signaling, metabolism, and gene transcription, showing the basis of gene or protein interactions. Furthermore, systems biology studies correlate biological networks with various cellular processes. In the past few years, methodologies of network and systems biology have been used to study *C. albicans* and its interaction with the host [226,239–241]. This review presents several recent cases to illustrate how approaches of network and systems biology can be used to study *C. albicans* and pathogen–host interactions.

Case 1. An integrative systems biology approach to show the regulation of *C. albicans* adaptation to thermal conditions. *C. albicans* lives in warm-blooded animals, and the heat shock response is essential for its survival. This response is also correlated to *C. albicans* infection [242]. For example, the heat shock protein Hsp90 orchestrates temperature-dependent morphogenesis, which is an important virulence factor of *C. albicans* [243]. Mutations blocking the activity of the heat shock transcription factor Hsf1 prevent thermal adaptation and significantly reduce *C. albicans* virulence [244]. However, the detailed mechanisms of thermal adaptation in *C. albicans* are still not yet fully understood. This study presents a dynamic model of heat shock adaptation, followed by experimental validation. Results indicate that Hsf1 and the chaperone protein Hsp90 are dynamically autoregulated [245]. In addition, this model shows that Hsf1 is activated during thermal transitions that mimic fever, and also explains evolutionary conservation of the heat shock response in *C. albicans* [245].

Case 2. A cellular network approach to predict genes associated with phenotypes during mucosal infection of *C. albicans*. Mucosal infections caused by *C. albicans* can be roughly divided into three stages: adhesion, invasion, and host cell damage [89,184]. Using a cellular network approach, a recent study has aimed to predict phenotype-associated genes during these three stages and their roles in *C. albicans*–host interactions. Assumptions applied to this study are that proteins that lie closer to one another in a protein interaction network are more likely to have similar functions, and that genes regulated by the same transcription factors tend to have similar functions [246]. From this study, 19 genes have been identified to relate to adhesion-, invasion-, and damage-associated functions. Moreover, the predicted genes suggest that cell surface components are critical for cell adhesion, and morphogenesis is crucial for cell invasion [246].

Case 3. Identification of the hubs in regulatory networks of *C. albicans*. Within a biological network, hubs are the nodes with high connectivity (degree) and play significant roles in maintaining topology and functional flow of the network. Removing hubs may break the network and makes the hubs potential drug targets or biomarkers for developing a new therapy. In a recent study, scale-free gene regulatory networks have been inferred to identify hubs from collections of gene expression data of *C. albicans* [247]. One hundred and twenty-six genes with an outward degree of at least seven are further examined, including 16 hubs sensitive to antifungal treatment [147]. In addition, the transcriptional network controlling biofilm formation is also inferred using combined information from genetic screenings, genome-wide approaches, and two animal models. The network consists of six transcription regulators that control approximately 1000 target genes [227].

Case 4. A robust network inference map to predict interactions between pathogen and host. This study presents an inferred regulatory network to predict novel interactions between *C. albicans* and mouse DCs during phagocytosis [226]. Results indicate that the subnetworks comprising the transcription factor Hap3 in *C. albicans*, and pentraxin (Ptx3) and metastasis-associated protein (Mta2) in the host cell are interdependent. *C. albicans* Hap3 is a component of the CCAAT-binding complex, which regulates gene expression. Murine Ptx3 is a soluble PRR that acts as an endogenous modulator of the inflammatory response. Murine Mta2 is a component of a nucleosome remodeling deacetylase complex, involved in transcriptional regulation. To verify the predictions from network inference, recombinant Ptx3 has been prepared and found to bind to the cell wall of *C. albicans* and to alter expression of Hap3 target genes. Moreover, *C. albicans* preincubated with recombinant Ptx3 significantly attenuates the expression of Mta2-regulated cytokines, such as IL-2 and IL-4, in a Hap3-dependent manner. Together, this study indicates that the pathogen–host interplay can cause remodeling of the pathogen and the pathogen affects the host immune response. This study demonstrates the usefulness of the systems biology approach to decipher mechanisms of microbial pathogenesis [226].

4. Conclusions

The interactions between *C. albicans* and host are critical for persistence and pathogenesis of the pathogen and the immune defense of the host. To establish infection successfully, *C. albicans* uses multiple ways to attach, colonize, and even penetrate the host tissues. For example, cell surface adhesins, hyphae formation, and secreted hydrolytic enzymes are associated with these processes. Phenotypic switching also helps *C. albicans* adapt to changing environments within the host. To recognize *C. albicans*, different host cells have developed diverse PRRs that function independently or synergistically. Consequently, the host triggers immune responses to defend against *C. albicans*. This review presents an outline of several important topics on these processes. With the complement of the genome sequences of *C. albicans* and humans, the development of genome-wide technologies for analyzing pathogen–host interactions has dramatically increased. These developments will no doubt broaden our view of the pathogen–host relationship and the processes during infection. A better understanding of *C. albicans*–host interactions will provide important insights for other fungal pathogens.

Acknowledgments

This work was supported by grant NSC101-2311-B-007-010-MY3 (to CYL) from the National Science Council (Taiwan, ROC).

REFERENCES

[1] Blanco JL, Garcia ME. Immune responses to fungal infections. Vet Immunol Immunopathol 2008;125:47–70.
[2] Sanglard D, White TC. Molecular principles of antifungal drug resistance. In: Heitman J, Filler SG, Edwards JR JE, Mitchell AP, editors. Molecular principles of fungal pathogenesis. Washington DC: ASM Press; 2006. p. 191–212.
[3] Miceli MH, Lee SA. Emerging moulds: epidemiological trends and antifungal resistance. Mycoses 2011;54:e666–78.

[4] Richardson MD. Changing patterns and trends in systemic fungal infections. J Antimicrob Chemother 2005;56(Suppl. 1):i5–11.
[5] Richardson M, Lass-Florl C. Changing epidemiology of systemic fungal infections. Clin Microbiol Infect 2008; 14(Suppl. 4):5–24.
[6] Miceli MH, Díaz JA, Lee SA. Emerging opportunistic yeast infections. Lancet Infect Dis 2011;11:142–51.
[7] Perfect JR, Casadevall A. Fungal molecular pathogenesis: what can it do and why do we need it? In: Heitman J, Filler SG, Edwards Jr JE, Mitchell AP, editors. Molecular principles of fungal pathogenesis. Washington DC: ASM Press; 2006. p. 3–11.
[8] Chakrabarti A. Microbiology of systemic fungal infections. J Postgrad Med 2005;51(Suppl. 1):S16–20.
[9] Pfaller MA, Pappas PG, Wingard JR. Invasive fungal pathogens: current epidemiological trends. Clin Infect Dis 2006;43(Suppl. 1):S3–14.
[10] Moran G, Coleman D, Sullivan D. An introduction to the medically important *Candida spp*. In: Calderone RA, Clancy CJ, editors. *Candida* and candidiasis. 2nd ed. Washington DC: ASM Press; 2012. p. 11–25.
[11] Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, et al. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 1981;305:1425–31.
[12] Klein RS, Harris CA, Small CB, Moll B, Lesser M, Friedland GH. Oral candidiasis in high-risk patients as the initial manifestation of the acquired immunodeficiency syndrome. N Engl J Med 1984;311:354–8.
[13] Dodd CL, Greenspan D, Katz MH, Westenhouse JL, Feigal DW, Greenspan JS. Oral candidiasis in HIV infection: pseudomembranous and erythematous candidiasis show similar rates of progression to AIDS. AIDS 1991;5:1339–43.
[14] Coleman DC, Bennett DE, Sullivan DJ, Gallagher PJ, Henman MC, Shanley DB, et al. Oral Candida in HIV infection and AIDS: new perspectives/new approaches. Crit Rev Microbiol 1993;19:61–82.
[15] Vargas KG, Joly S. Carriage frequency, intensity of carriage, and strains of oral yeast species vary in the progression to oral candidiasis in human immunodeficiency virus-positive individuals. J Clin Microbiol 2002;40:341–50.
[16] Sobel JD. Vulvovaginitis due to *Candida glabrata*. An emerging problem. Mycoses 1998;41(Suppl. 2):18–22.
[17] Fichtenbaum C, Aberg J. Candidiasis and HIV. HIV InSite knowledge base chapter. Available from: http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-05-02-03 [accessed 18.10.06].
[18] Miyasaki SH, Hicks JB, Greenspan D, Polacheck I, MacPhail LA, White TC, et al. The identification and tracking of *Candida albicans* isolates from oral lesions in HIV-seropositive individuals. J Acquir Immune Defic Syndr 1992; 5:1039–46.
[19] Soll DR. *Candida* commensalism and virulence: the evolution of phenotypic plasticity. Acta Trop 2002;81: 101–10.
[20] Lim CS, Rosli R, Seow HF, Chong PP. *Candida* and invasive candidiasis: back to basics. Eur J Clin Microbiol Infect Dis 2012;31:21–31.
[21] Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309–17.
[22] Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis 2005;41:1232–9.
[23] Gudlaugsson O, Gillespie S, Lee K, Vande Berg J, Hu J, Messer S, et al. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 2003;37:1172–7.
[24] Perlroth J, Choi B, Spellberg B. Nosocomial fungal infections: epidemiology, diagnosis, and treatment. Med Mycol 2007; 45:321–46.
[25] Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev 2007;20:133–63.
[26] Karkowska-Kuleta J, Rapala-Kozik M, Kozik A. Fungi pathogenic to humans: molecular bases of virulence of *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*. Acta Biochimica Polonica 2009;56:211–24.
[27] Martin R, Wächtler B, Schaller M, Wilson D, Hube B. Host–pathogen interactions and virulence-associated genes during *Candida albicans* oral infections. Int J Med Microbiol 2011;301:417–22.
[28] Biswas S, Van Dijck P, Datta A. Environmental sensing and signal transduction pathways regulating morphopathogenic determinants of *Candida albicans*. Microbiol Mol Biol Rev 2007;71:348–76.
[29] Gow NA, van de Veerdonk FL, Brown AJ, Netea MG. *Candida albicans* morphogenesis and host defence: discriminating invasion from colonization. Nat Rev Microbiol 2011;10: 112–22.
[30] Hiller E, Zavrel M, Hauser N, Sohn K, Burger-Kentischer A, Lemuth K, et al. Adaptation, adhesion and invasion during interaction of *Candida albicans* with the host – focus on the function of cell wall proteins. Int J Med Microbiol 2011;301: 384–9.
[31] Morschhäuser J. Regulation of white-opaque switching in *Candida albicans*. Med Microbiol Immunol 2010;199:165–72.
[32] Naglik J, Albrecht A, Bader O, Hube B. *Candida albicans* proteinases and host/pathogen interactions. Cell Microbiol 2004;6:915–26.
[33] Shapiro RS, Robbins N, Cowen LE. Regulatory circuitry governing fungal development, drug resistance, and disease. Microbiol Mol Biol Rev 2011;75:213–67.
[34] Sudbery PE. Growth of *Candida albicans* hyphae. Nat Rev Microbiol 2011;9:737–48.
[35] Whiteway M, Bachewich C. Morphogenesis in *Candida albicans*. Annu Rev Microbiol 2007;61:529–53.
[36] Walther A, Wendland J. PCR-based gene targeting in *Candida albicans*. Nat Protoc 2008;3:1414–21.
[37] Chaffin WL, López-Ribot JL, Casanova M, Gozalbo D, Martínez JP. Cell wall and secreted proteins of *Candida albicans*: identification, function, and expression. Microbiol Mol Biol Rev 1998;62:130–80.
[38] Filler SG, Sheppard DC. Fungal invasion of normally non-phagocytic host cells. PLoS Pathog 2006;2:e129.
[39] Lo HJ, Köhler JR, DiDomenico B, Loebenberg D, Cacciapuoti A, Fink GR. Nonfilamentous *C. albicans* mutants are avirulent. Cell 1997;90:939–49.
[40] Thompson DS, Carlisle PL, Kadosh D. Coevolution of morphology and virulence in *Candida* species. Eukaryot Cell 2011;10:1173–82.
[41] Cottier F, Mühlschlegel FA. Sensing the environment: response of *Candida albicans* to the X factor. FEMS Microbiol Lett 2009;295:1–9.
[42] Eckert SE, Sheth CC, Mühlschlegel FA. Regulation of morphogenesis in *Candida* species. In: d'Enfert C, Hube B, editors. *Candida*: comparative and functional genomics. Wymondham, UK: Caister Academic Press; 2007. p. 263–91.
[43] Maidan MM, De Rop L, Serneels J, Exler S, Rupp S, Tournu H, et al. The G protein-coupled receptor Gpr1 and the Galpha protein Gpa2 act through the cAMP-protein kinase A pathway to induce morphogenesis in *Candida albicans*. Mol Biol Cell 2005;16:1971–86.

[44] Cloutier M, Castilla R, Bolduc N, Zelada A, Martineau P, Bouillon M, et al. The two isoforms of the cAMP-dependent protein kinase catalytic subunit are involved in the control of dimorphism in the human fungal pathogen *Candida albicans*. Fungal Genet Biol 2003;38:133–41.
[45] Sinha I, Wang YM, Philp R, Li CR, Yap WH, Wang Y. Cyclin-dependent kinases control septin phosphorylation in *Candida albicans* hyphal development. Dev Cell 2007;13: 421–32.
[46] Liu H, Köhler J, Fink GR. Suppression of hyphal formation in *Candida albicans* by mutation of a *STE12* homolog. Science 1994;266:1723–6.
[47] Braun BR, Johnson AD. Control of filament formation in *Candida albicans* by the transcriptional repressor TUP1. Science 1997;277:105–9.
[48] Braun BR, Kadosh D, Johnson AD. NRG1, a repressor of filamentous growth in *C. albicans*, is down-regulated during filament induction. EMBO J 2001;20:4753–61.
[49] Khalaf RA, Zitomer RS. The DNA binding protein Rfg1 is a repressor of filamentation in *Candida albicans*. Genetics 2001;157:1503–12.
[50] Murad AM, d'Enfert C, Gaillardin C, Tournu H, Tekaia F, Talibi D, et al. Transcript profiling in *Candida albicans* reveals new cellular functions for the transcriptional repressors CaTup1, CaMig1 and CaNrg1. Mol Microbiol 2001;42:981–93.
[51] Biswas K, Morschhäuser J. The Mep2p ammonium permease controls nitrogen starvation-induced filamentous growth in *Candida albicans*. Mol Microbiol 2005;56:649–69.
[52] Dabas N, Morschhäuser J. Control of ammonium permease expression and filamentous growth by the GATA transcription factors GLN3 and GAT1 in *Candida albicans*. Eukaryot Cell 2007;6:875–88.
[53] Morschhäuser J. Nitrogen regulation of morphogenesis and protease secretion in *Candida albicans*. Int J Med Microbiol 2011;301:390–4.
[54] Tsao CC, Chen YT, Lan CY. A small G protein Rhb1 and a GTPase-activating protein Tsc2 involved in nitrogen starvation-induced morphogenesis and cell wall integrity of *Candida albicans*. Fungal Genet Biol 2009;46:126–36.
[55] Liao WL, Ramón AM, Fonzi WA. GLN3 encodes a global regulator of nitrogen metabolism and virulence of *C. albicans*. Fungal Genet Biol 2011;45:514–26.
[56] Davis D, Edwards Jr JE, Mitchell AP, Ibrahim AS. *Candida albicans* RIM101 pH response pathway is required for host-pathogen interactions. Infect Immun 2000;68:5953–9.
[57] Davis DA. How human pathogenic fungi sense and adapt to pH: the link to virulence. Curr Opin Microbiol 2009;12: 365–70.
[58] Lamb TM, Xu W, Diamond A, Mitchell AP. Alkaline response genes of *Saccharomyces cerevisiae* and their relationship to the RIM101 pathway. J Biol Chem 2001;276:1850–6.
[59] Lamb TM, Mitchell AP. The transcription factor Rim101p governs ion tolerance and cell differentiation by direct repression of the regulatory genes NRG1 and SMP1 in *Saccharomyces cerevisiae*. Mol Cell Biol 2003;23:677–86.
[60] Li M, Martin SJ, Bruno VM, Mitchell AP, Davis DA. *Candida albicans* Rim13p, a protease required for Rim101p processing at acidic and alkaline pHs. Eukaryot Cell 2004;33:741–51.
[61] Kumamoto CA. A contact-activated kinase signals *Candida albicans* invasive growth and biofilm development. Proc Natl Acad Sci USA 2005;102:5576–81.
[62] Setiadi ER, Doedt T, Cottier F, Noffz C, Ernst JF. Transcriptional response of *Candida albicans* to hypoxia: linkage of oxygen sensing and Efg1p-regulatory networks. J Mol Biol 2006;361:399–411.
[63] Stichternoth C, Ernst JF. Hypoxic adaptation by Efg1 regulates biofilm formation by *Candida albicans*. Appl Environ Microbiol 2009;75:3663–72.
[64] Tronchin G, Pihet M, Lopes-Bezerra LM, Bouchara JP. Adherence mechanisms in human pathogenic fungi. Med Mycol 2008;46:749–72.
[65] Klis FM, Brul S, De Groot PW. Covalently linked wall proteins in ascomycetous fungi. Yeast 2010;27:489–93.
[66] Bowman SM, Free SJ. The structure and synthesis of the fungal cell wall. Bioessays 2006;28:799–808.
[67] Zhu W, Filler SG. Interactions of *Candida albicans* with epithelial cells. Cell Microbiol 2010;12:273–82.
[68] Ramage G, Martínez JP, López-Ribot JL. Candida biofilms on implanted biomaterials: a clinically significant problem. FEMS Yeast Res 2006;6:979–86.
[69] Al-Fattani MA, Douglas LJ. Biofilm matrix of *Candida albicans* and *Candida tropicalis*: chemical composition and role in drug resistance. J Med Microbiol 2006;55:999–1008.
[70] Douglas LJ. *Candida* biofilms and their role in infection. Trends Microbiol 2003;11:30–6.
[71] Kuhn DM, Ghannoum MA. Candida biofilms: antifungal resistance and emerging therapeutic options. Curr Opin Investig Drugs 2004;5:186–97.
[72] Kumamoto CA, Vinces MD. Alternative *Candida albicans* lifestyles: growth on surfaces. Annu Rev Microbiol 2005;59: 113–33.
[73] Nett J, Andes D. *Candida albicans* biofilm development, modeling a host-pathogen interaction. Curr Opin Microbiol 2006;9:340–5.
[74] Liu Y, Filler SG. *Candida albicans* Als3, a multifunctional adhesin and invasin. Eukaryot Cell 2011;10:168–73.
[75] Loza L, Fu Y, Ibrahim AS, Sheppard DC, Filler SG, Edwards Jr JE. Functional analysis of the *Candida albicans* ALS1 gene product. Yeast 2004;21:473–82.
[76] Rauceo JM, De Armond R, Otoo H, Kahn PC, Klotz SA, Gaur NK, et al. Threonine-rich repeats increase fibronectin binding in the *Candida albicans* adhesin Als5p. Eukaryot Cell 2006;5:1664–73.
[77] Gaur NK, Klotz SA. Expression, cloning, and characterization of a *Candida albicans* gene, ALA1, that confers adherence properties upon *Saccharomyces cerevisiae* for extracellular matrix proteins. Infect Immun 1997;65: 5289–94.
[78] Fu Y, Rieg G, Fonzi WA, Belanger PH, Edwards Jr JE, Filler SG. Expression of the *Candida albicans* gene ALS1 in *Saccharomyces cerevisiae* induces adherence to endothelial and epithelial cells. Infect Immun 1998;66:1783–6.
[79] Zhao X, Oh SH, Yeater KM, Hoyer LL. Analysis of the *Candida albicans* Als2p and Als4p adhesins suggests the potential for compensatory function within the Als family. Microbiology 2005;151:1619–30.
[80] Sheppard DC, Yeaman MR, Welch WH, Phan QT, Fu Y, Ibrahim AS, et al. Functional and structural diversity in the Als protein family of *Candida albicans*. J Biol Chem 2004;279: 30480–9.
[81] Staab JF, Bradway SD, Fidel PL, Sundstrom P. Adhesive and mammalian transglutaminase substrate properties of *Candida albicans* Hwp1. Science 1999;283:1535–8.
[82] Nobile CJ, Andes DR, Nett JE, Smith FJ, Yue F, Phan QT, et al. Critical role of Bcr1-dependent adhesins in *C. albicans* biofilm formation *in vitro* and *in vivo*. PLoS Pathog 2006;2:e63.
[83] Nobile CJ, Nett JE, Andes DR, Mitchell AP. Function of *Candida albicans* adhesin Hwp1 in biofilm formation. Eukaryot Cell 2006;5:1604–10.
[84] Nobile CJ, Schneider HA, Nett JE, Sheppard DC, Filler SG, Andes DR, et al. Complementary adhesin function in *C. albicans* biofilm formation. Curr Biol 2008;18:1017–24.
[85] Filler SG. Candida–host cell receptor–ligand interactions. Curr Opin Microbiol 2006;9:333–9.
[86] Li F, Svarovsky MJ, Karlsson AJ, Wagner JP, Marchillo K, Oshel P, et al. Eap1p, an adhesin that mediates *Candida*

albicans biofilm formation *in vitro* and *in vivo*. Eukaryot Cell 2007;6:931–9.
[87] Kinneberg KM, Bendel CM, Jechorek RP, Cebelinski EA, Gale CA, Berman JG, et al. Effect of *INT1* gene on *Candida albicans* murine intestinal colonization. J Surg Res 1999;87: 245–51.
[88] Schaller M, Borelli C, Korting HC, Hube B. Hydrolytic enzymes as virulence factors of *Candida albicans*. Mycoses 2005;48:365–77.
[89] Naglik JR, Challacombe SJ, Hube B. *Candida albicans* secreted aspartyl proteinases in virulence and pathogenesis. Microbiol Mol Biol Rev 2003;67:400–28.
[90] White TC, Agabian N. *Candida albicans* secreted aspartyl proteinases: isoenzyme pattern is determined by cell type, and levels are determined by environmental factors. J Bacteriol 1995;177:5215–21.
[91] Naglik JR, Newport G, White TC, Fernandes-Naglik LL, Greenspan JS, Greenspan D, et al. *In vivo* analysis of secreted aspartyl proteinase expression in human oral candidiasis. Infect Immun 1999;67:2482–90.
[92] Hube B, Naglik J. *Candida albicans* proteinases: resolving the mystery of a gene family. Microbiology 2001;147: 1997–2005.
[93] Albrecht A, Felk A, Pichova I, Naglik JR, Schaller M, de Groot P, et al. Glycosylphosphatidylinositol-anchored proteases of *Candida albicans* target proteins necessary for both cellular processes and host–pathogen interactions. J Biol Chem 2006;281:688–94.
[94] Mendes A, Mores AU, Carvalho AP, Rosa RT, Samaranayake LP, Rosa EA. *Candida albicans* biofilms produce more secreted aspartyl protease than the planktonic cells. Biol Pharm Bull 2007;30:1813–5.
[95] Chen YT, Lin CY, Tsai PW, Yang CY, Hsieh WP, Lan CY. Rhb1 regulates the expression of secreted aspartic protease 2 through the TOR signaling pathway in *Candida albicans*. Eukaryot Cell 2012;11:168–82.
[96] Dabas N, Morschhäuser J. A transcription factor regulatory cascade controls secreted aspartic protease expression in *Candida albicans*. Mol Microbiol 2008;69:586–602.
[97] Chaffin WL. *Candida albicans* cell wall proteins. Microbiol Mol Biol Rev 2008;72:495–544.
[98] Hube B. Possible role of secreted proteinases in *Candida albicans* infections. Rev Iberoam Micol 1998;15:65–8.
[99] Reuss O, Morschhäuser J. A family of oligopeptide transporters is required for growth of *Candida albicans* on proteins. Mol Microbiol 2006;60:795–812.
[100] Ghannoum MA. Potential role of phospholipases in virulence and fungal pathogenesis. Clin Microbiol Rev 2000; 13:122–43.
[101] Yang YL. Virulence factors of *Candida* species. J Microbiol Immunol Infect 2003;36:223–8.
[102] Theiss S, Ishdorj G, Brenot A, Kretschmar M, Lan CY, Nichterlein T, et al. Inactivation of the phospholipase B gene PLB5 in wild-type *Candida albicans* reduces cell-associated phospholipase A2 activity and attenuates virulence. Int J Med Microbiol 2006;296:405–20.
[103] Leidich SD, Ibrahim AS, Fu Y, Koul A, Jessup C, Vitullo J, et al. Cloning and disruption of caPLB1, a phospholipase B gene involved in the pathogenicity of *Candida albicans*. J Biol Chem 1998;273:26078–86.
[104] Mukherjee PK, Chandra J, Kuhn DM, Ghannoum MA. Differential expression of *Candida albicans* phospholipase B (*PLB1*) under various environmental and physiological conditions. Microbiology 2003;149:261–7.
[105] dos Santos AL, de Carvalho IM, da Silva BA, Portela MB, Alviano CS, de Araújo Soares RM. Secretion of serine peptidase by a clinical strain of *Candida albicans*: influence of growth conditions and cleavage of human serum proteins and extracellular matrix components. FEMS Immunol Med Microbiol 2006;46:209–20.
[106] Lan CY, Newport G, Murillo LA, Jones T, Scherer S, Davis RW, et al. Metabolic specialization associated with phenotypic switching in *Candida albicans*. Proc Natl Acad Sci USA 2002;99:14907–12.
[107] Lohse MB, Johnson AD. Differential phagocytosis of white versus opaque *Candida albicans* by *Drosophila* and mouse phagocytes. PLoS One 2008;3:e1473.
[108] Soll DR. Why does *Candida albicans* switch? FEMS Yeast Res 2009;9:973–89.
[109] Sahni N, Yi S, Daniels KJ, Srikantha T, Pujol C, Soll DR. Genes selectively up-regulated by pheromone in white cells are involved in biofilm formation in *Candida albicans*. PLoS Pathog 2009;5:e1000601.
[110] Kvaal C, Lachke SA, Srikantha T, Daniels K, McCoy J, Soll DR. Misexpression of the opaque-phase-specific gene *PEP1 (SAP1)* in the white phase of *Candida albicans* confers increased virulence in a mouse model of cutaneous infection. Infect Immun 1999;67:6652–62.
[111] Kvaal CA, Srikantha T, Soll DR. Misexpression of the white-phase-specific gene *WH11* in the opaque phase of *Candida albicans* affects switching and virulence. Infect Immun 1997; 65:4468–75.
[112] Hull CM, Johnson AD. Identification of a mating type-like locus in the asexual pathogenic yeast *Candida albicans*. Science 1999;285:1271–5.
[113] Hull CM, Raisner RM, Johnson AD. Evidence for mating of the "asexual" yeast *Candida albicans* in a mammalian host. Science 2000;289:307–10.
[114] Bennett RJ, Johnson AD. Mating in *Candida albicans* and the search for a sexual cycle. Annu Rev Microbiol 2005;59: 233–55.
[115] Lockhart SR, Zhao R, Daniels KJ, Soll DR. Alpha-pheromone-induced "shmooing" and gene regulation require white-opaque switching during *Candida albicans* mating. Eukaryot Cell 2003;2:847–55.
[116] Miller MG, Johnson AD. White-opaque switching in *Candida albicans* is controlled by mating-type locus homeodomain proteins and allows efficient mating. Cell 2002;110: 293–302.
[117] Huang G, Wang H, Chou S, Nie X, Chen J, Liu H. Bistable expression of WOR1, a master regulator of white-opaque switching in *Candida albicans*. Proc Natl Acad Sci USA 2006; 103:12813–8.
[118] Srikantha T, Borneman AR, Daniels KJ, Pujol C, Wu W, Seringhaus MR, et al. TOS9 regulates white-opaque switching in *Candida albicans*. Eukaryot Cell 2006;5:1674–87.
[119] Tuch BB, Mitrovich QM, Homann OR, Hernday AD, Monighetti CK, De La Vega FM, et al. The transcriptomes of two heritable cell types illuminate the circuit governing their differentiation. PLoS Genet 2010;6:e1001070.
[120] Zordan RE, Galgoczy DJ, Johnson AD. Epigenetic properties of white-opaque switching in *Candida albicans* are based on a self-sustaining transcriptional feedback loop. Proc Natl Acad Sci USA 2006;103:12807–12.
[121] Vinces MD, Kumamoto CA. The morphogenetic regulator Czf1p is a DNA-binding protein that regulates white opaque switching in *Candida albicans*. Microbiology 2007;153: 2877–84.
[122] Zordan RE, Miller MG, Galgoczy DJ, Tuch BB, Johnson AD. Interlocking transcriptional feedback loops control white-opaque switching in *Candida albicans*. PLoS Biol 2007; 5:e256.
[123] Okutomi T, Abe S, Tansho S, Wakabayashi H, Kawase K, Yamaguchi H. Augmented inhibition of growth of *Candida albicans* by neutrophils in the presence of lactoferrin. FEMS Immunol Med Microbiol 1997;18:105–12.

[124] Paul TR, Smith SN, Brown MR. Effect of iron depletion on cell-wall antigens of *Candida albicans*. J Med Microbiol 1989; 28:93–100.
[125] Sweet SP, Douglas LJ. Effect of iron deprivation on surface composition and virulence determinants of *Candida albicans*. J Gen Microbiol 1991;137:859–65.
[126] Almeida RS, Brunke S, Albrecht A, Thewes S, Laue M, Edwards JE, et al. The hyphal-associated adhesin and invasin Als3 of *Candida albicans* mediates iron acquisition from host ferritin. PLoS Pathog 2008;4:e1000217.
[127] Weissman Z, Kornitzer D. A family of *Candida* cell surface haem-binding proteins involved in haemin and haemoglobin-iron utilization. Mol Microbiol 2004;53: 1209–20.
[128] Baillie GS, Douglas LJ. Matrix polymers of *Candida* biofilms and their possible role in biofilm resistance to antifungal agents. J Antimicrob Chemother 2000;46:397–403.
[129] Fiori A, Van Dijck P. Potent synergistic effect of doxycycline with fluconazole against *Candida albicans* is mediated by interference with iron homeostasis. Antimicrob Agents Chemother 2012;56:3785–96.
[130] Hameed S, Dhamgaye S, Singh A, Goswami SK, Prasad R. Calcineurin signaling and membrane lipid homeostasis regulates iron mediated multidrug resistance mechanisms in *Candida albicans*. PLoS One 2011;6:e18684.
[131] Prasad T, Chandra A, Mukhopadhyay CK, Prasad R. Unexpected link between iron and drug resistance of *Candida* spp.: iron depletion enhances membrane fluidity and drug diffusion, leading to drug-susceptible cells. Antimicrob Agents Chemother 2006;50:3597–606.
[132] Lee RE, Liu TT, Barker KS, Lee RE, Rogers PD. Genome-wide expression profiling of the response to ciclopirox olamine in *Candida albicans*. J Antimicrob Chemother 2005;55: 655–62.
[133] Niewerth M, Kunze D, Seibold M, Schaller M, Korting HC, Hube B. Ciclopirox olamine treatment affects the expression pattern of *Candida albicans* genes encoding virulence factors, iron metabolism proteins, and drug resistance factors. Antimicrob Agents Chemother 2003;47: 1805–17.
[134] Sigle HC, Thewes S, Niewerth M, Korting HC, Schäfer-Korting M, Hube B. Oxygen accessibility and iron levels are critical factors for the antifungal action of ciclopirox against *Candida albicans*. J Antimicrob Chemother 2005;55:663–73.
[135] Heymann P, Gerads M, Schaller M, Dromer F, Winkelmann G, Ernst JF. The siderophore iron transporter of *Candida albicans* (Sit1p/Arn1p) mediates uptake of ferrichrome-type siderophores and is required for epithelial invasion. Infect Immun 2002;70:5246–55.
[136] Ramanan N, Wang Y. A high-affinity iron permease essential for *Candida albicans* virulence. Science 2000;288: 1062–4.
[137] Chen C, Pande K, French SD, Tuch BB, Noble SM. An iron homeostasis regulatory circuit with reciprocal roles in *Candida albicans* commensalism and pathogenesis. Cell Host Microbe 2011;10:118–35.
[138] Chen C, Noble SM. Post-transcriptional regulation of the Sef1 transcription tactor controls the virulence of *Candida albicans* in its mammalian host. PLoS Pathog 2012;8: e1002956.
[139] Hsu PC, Yang CY, Lan CY. *Candida albicans* Hap43 is a repressor induced under low-iron conditions and is essential for iron-responsive transcriptional regulation and virulence. Eukaryot Cell 2011;10:207–25.
[140] Lan CY, Rodarte G, Murillo LA, Jones T, Davis RW, Dungan J, et al. Regulatory networks affected by iron availability in *Candida albicans*. Mol Microbiol 2004;53:1451–69.
[141] Singh RP, Prasad HK, Sinha I, Agarwal N, Natarajan K. Cap2-HAP complex is a critical transcriptional regulator that has dual but contrasting roles in regulation of iron homeostasis in *Candida albicans*. J Biol Chem 2011;286:25154–70.
[142] Cottier F, Pavelka N. Complexity and dynamics of host–fungal interactions. Immunol Res 2012;53:127–35.
[143] Akira S. TLR signaling. Curr Top Microbiol Immunol 2006; 311:1–16.
[144] Moyes DL, Naglik JR. Mucosal immunity and *Candida albicans* infection. Clin Dev Immunol 2011;2011:346307.
[145] Netea MG, Van der Meer JW, Kullberg BJ. Recognition of pathogenic microorganisms by Toll-like receptors. Drugs Today (Barc) 2006;42(Suppl. A):99–105.
[146] Netea MG, Brown GD, Kullberg BJ, Gow NA. An integrated model of the recognition of *Candida albicans* by the innate immune system. Nat Rev Microbiol 2008;6:67–78.
[147] Gantner BN, Simmons RM, Canavera SJ, Akira S, Underhill DM. Collaborative induction of inflammatory responses by dectin-1 and Toll-like receptor 2. J Exp Med 2003;197:1107–17.
[148] Levitz SM. Innate recognition of fungal cell walls. PLoS Pathog 2010;6:e1000758.
[149] Dennehy KM, Willment JA, Williams DL, Brown GD. Reciprocal regulation of IL-23 and IL-12 following co-activation of Dectin-1 and TLR signaling pathways. Eur J Immunol 2009;39:1379–86.
[150] Fidel PL, Noverr M. Mucosal immunity to *Candida albicans*. In: Calderone RA, Clancy CJ, editors. *Candida* and candidiasis. 2nd ed. Washington DC: ASM Press; 2012. p. 137–54.
[151] Grubb SE, Murdoch C, Sudbery PE, Saville SP, Lopez-Ribot JL, Thornhill MH. *Candida albicans*-endothelial cell interactions: a key step in the pathogenesis of systemic candidiasis. Infect Immun 2008;76:4370–7.
[152] Naglik JR, Moyes DL, Wächtler B, Hube B. *Candida albicans* interactions with epithelial cells and mucosal immunity. Microbes Infect 2011;13:963–76.
[153] Romani L. Immunity to fungal infections. Nat Rev Immunol 2011;11:275–88.
[154] Romani L. Immunology of invasive candidiasis. In: Calderone RA, Clancy CJ, editors. *Candida* and candidiasis. 2nd ed. Washington DC: ASM Press; 2012. p. 127–36.
[155] Cheng SC, Joosten LA, Kullberg BJ, Netea MG. Interplay between *Candida albicans* and the mammalian innate host defense. Infect Immun 2012;80:1304–13.
[156] Tsai PW, Yang CY, Chang HT, Lan CY. Human antimicrobial peptide LL-37 inhibits adhesion of *Candida albicans* by interacting with yeast cell-wall carbohydrates. PLoS One 2011;6:e17755.
[157] Tsai PW, Yang CY, Chang HT, Lan CY. Characterizing the role of cell-wall β-1,3-exoglucanase Xog1p in *Candida albicans* adhesion by the human antimicrobial peptide LL-37. PLoS One 2011;6:e21394.
[158] Dongari-Bagtzoglou A, Fidel Jr PL. The host cytokine responses and protective immunity in oropharyngeal candidiasis. J Dent Res 2005;84:966–77.
[159] Ye P, Rodriguez FH, Kanaly S, Stocking KL, Schurr J, Schwarzenberger P, et al. Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. J Exp Med 2001; 194:519–27.
[160] Hernández-Santos N, Gaffen SL. Th17 cells in immunity to *Candida albicans*. Cell Host Microbe 2012;11:425–35.
[161] Gaffen SL, Hernández-Santos N, Peterson AC. IL-17 signaling in host defense against *Candida albicans*. Immunol Res 2011;50:181–7.

[162] Kullberg BJ, Netea MG, Curfs JH, Keuter M, Meis JF, van der Meer JW. Recombinant murine granulocyte colony-stimulating factor protects against acute disseminated *Candida albicans* infection in nonneutropenic mice. J Infect Dis 1998;177:175–81.
[163] Lieschke GJ, Burgess AW. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor (1). N Engl J Med 1992;327:28–35.
[164] Lieschke GJ, Burgess AW. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor (2). N Engl J Med 1992;327:99–106.
[165] Urban CF, Ermert D, Schmid M, Abu-Abed U, Goosmann C, Nacken W, et al. Neutrophil extracellular traps contain calprotectin, a cytosolic protein complex involved in host defense against *Candida albicans*. PLoS Pathog 2009;5:e1000639.
[166] Wozniok I, Hornbach A, Schmitt C, Frosch M, Einsele H, Hube B, et al. Induction of ERK-kinase signalling triggers morphotype-specific killing of *Candida albicans* filaments by human neutrophils. Cell Microbiol 2008;10:807–20.
[167] Du C, Calderone RA. Phagocytosis and killing assays for *Candida* species. Methods Mol Biol 2009;499:17–26.
[168] Qian Q, Jutila MA, Van Rooijen N, Cutler JE. Elimination of mouse splenic macrophages correlates with increased susceptibility to experimental disseminated candidiasis. J Immunol 1994;152:5000–8.
[169] van't Wout JW, Linde I, Leijh PC, van Furth R. Contribution of granulocytes and monocytes to resistance against experimental disseminated *Candida albicans* infection. Eur J Clin Microbiol Infect Dis 1988;7:736–41.
[170] Hoebe K, Janssen E, Beutler B. The interface between innate and adaptive immunity. Nat Immunol 2004;5:971–4.
[171] Romagnoli G, Nisini R, Chiani P, Mariotti S, Teloni R, Cassone A, et al. The interaction of human dendritic cells with yeast and germ-tube forms of *Candida albicans* leads to efficient fungal processing, dendritic cell maturation, and acquisition of a Th1 response-promoting function. J Leukoc Biol 2004;75:117–26.
[172] d'Ostiani CF, Del Sero G, Bacci A, Montagnoli C, Spreca A, Mencacci A, et al. Dendritic cells discriminate between yeasts and hyphae of the fungus *Candida albicans*. Implications for initiation of T helper cell immunity *in vitro* and *in vivo*. J Exp Med 2000;191:1661–74.
[173] Jones T, Federspiel NA, Chibana H, Dungan J, Kalman S, Magee BB, et al. The diploid genome sequence of *Candida albicans*. Proc Natl Acad Sci USA 2004;101:7329–34.
[174] Braun BR, van Het Hoog M, d'Enfert C, Martchenko M, Dungan J, Kuo A, et al. A human-curated annotation of the *Candida albicans* genome. PLoS Genet 2005;1:36–57.
[175] Butler G, Rasmussen MD, Lin MF, Santos MA, Sakthikumar S, Munro CA, et al. Evolution of pathogenicity and sexual reproduction in eight *Candida* genomes. Nature 2009;459:657–62.
[176] Inglis DO, Arnaud MB, Binkley J, Shah P, Skrzypek MS, Wymore F, et al. The *Candida* genome database incorporates multiple *Candida* species: multispecies search and analysis tools with curated gene and protein information for *Candida albicans* and *Candida glabrata*. Nucleic Acids Res 2012;40(Database issue):D667–74.
[177] Jackson AP, Gamble JA, Yeomans T, Moran GP, Saunders D, Harris D, et al. Comparative genomics of the fungal pathogens *Candida dubliniensis* and *Candida albicans*. Genome Res 2009;19:2231–44.
[178] Riccombeni A, Vidanes G, Proux-Wéra E, Wolfe KH, Butler G. Sequence and analysis of the genome of the pathogenic yeast *Candida orthopsilosis*. PLoS One 2012;7:e35750.
[179] Homann OR, Dea J, Noble SM, Johnson AD. A phenotypic profile of the *Candida albicans* regulatory network. PLoS Genet 2009;5:e1000783.
[180] Nobile CJ, Mitchell AP. Large-scale gene disruption using the *UAU1* cassette. Methods Mol Biol 2009;499:175–94.
[181] Noble SM, Johnson AD. Genetics of *Candida albicans*, a diploid human fungal pathogen. Annu Rev Genet 2007;41:193–211.
[182] Noble SM, French S, Kohn LA, Chen V, Johnson AD. Systematic screens of a *Candida albicans* homozygous deletion library decouple morphogenetic switching and pathogenicity. Nat Genet 2010;42:590–8.
[183] Hernday AD, Noble SM, Mitrovich QM, Johnson AD. Genetics and molecular biology in *Candida albicans*. Meth Enzymol 2010;470:737–58.
[184] Wilson D, Thewes S, Zakikhany K, Fradin C, Albrecht A, Almeida R, et al. Identifying infection-associated genes of *Candida albicans* in the postgenomic era. FEMS Yeast Res 2009;9:688–700.
[185] Diez-Orejas R, Fernández-Arenas E. *Candida albicans*-macrophage interactions: genomic and proteomic insights. Future Microbiol 2008;3:661–81.
[186] Kniemeyer O, Schmidt AD, Vödisch M, Wartenberg D, Brakhage AA. Identification of virulence determinants of the human pathogenic fungi *Aspergillus fumigatus* and *Candida albicans* by proteomics. Int J Med Microbiol 2011;301:368–77.
[187] Thomas DP, Pitarch A, Monteoliva L, Gil C, Lopez-Ribot JL. Proteomics to study *Candida albicans* biology and pathogenicity. Infect Disord Drug Targets 2006;6:335–41.
[188] Doedt T, Krishnamurthy S, Bockmühl DP, Tebarth B, Stempel C, Russell CL, et al. APSES proteins regulate morphogenesis and metabolism in *Candida albicans*. Mol Biol Cell 2004;15:3167–80.
[189] Lane S, Birse C, Zhou S, Matson R, Liu H. DNA array studies demonstrate convergent regulation of virulence factors by Cph1, Cph2, and Efg1 in *Candida albicans*. J Biol Chem 2001;276:48988–96.
[190] Nantel A, Dignard D, Bachewich C, Harcus D, Marcil A, Bouin AP, et al. Transcription profiling of *Candida albicans* cells undergoing the yeast-to-hyphal transition. Mol Biol Cell 2002;13:3452–65.
[191] De Backer MD, Ilyina T, Ma XJ, Vandoninck S, Luyten WH, Vanden Bossche H. Genomic profiling of the response of *Candida albicans* to itraconazole treatment using a DNA microarray. Antimicrob Agents Chemother 2001;45:1660–70.
[192] Rogers PD, Barker KS. Genome-wide expression profile analysis reveals coordinately regulated genes associated with stepwise acquisition of azole resistance in *Candida albicans* clinical isolates. Antimicrob Agents Chemother 2003;47:1220–7.
[193] Enjalbert B, Moran GP, Vaughan C, Yeomans T, Maccallum DM, Quinn J, et al. Genome-wide gene expression profiling and a forward genetic screen show that differential expression of the sodium ion transporter Ena21 contributes to the differential tolerance of *Candida albicans* and *Candida dubliniensis* to osmotic stress. Mol Microbiol 2009;72:216–28.
[194] Harcus D, Nantel A, Marcil A, Rigby T, Whiteway M. Transcription profiling of cyclic AMP signaling in *Candida albicans*. Mol Biol Cell 2004;15:4490–9.
[195] Srinivasa K, Kim J, Yee S, Kim W, Choi W. A MAP kinase pathway is implicated in the pseudohyphal induction by hydrogen peroxide in *Candica albicans*. Mol Cells 2012;33:183–93.
[196] Askew C, Sellam A, Epp E, Hogues H, Mullick A, Nantel A, et al. Transcriptional regulation of carbohydrate metabolism in the human pathogen *Candida albicans*. PLoS Pathog 2009;5:e1000612.
[197] Hauser NC, Dukalska M, Fellenberg K, Rupp S. From experimental setup to data analysis in transcriptomics:

copper metabolism in the human pathogen *Candida albicans*. J Biophotonics 2009;2:262–8.
[198] Bennett RJ, Uhl MA, Miller MG, Johnson AD. Identification and characterization of a *Candida albicans* mating pheromone. Mol Cell Biol 2003;23:8189–201.
[199] Tsong AE, Miller MG, Raisner RM, Johnson AD. Evolution of a combinatorial transcriptional circuit: a case study in yeasts. Cell 2003;115:389–99.
[200] García-Sánchez S, Aubert S, Iraqui I, Janbon G, Ghigo JM. d'Enfert C. *Candida albicans* biofilms: a developmental state associated with specific and stable gene expression patterns. Eukaryot Cell 2004;3:536–45.
[201] Murillo LA, Newport G, Lan CY, Habelitz S, Dungan J, Agabian NM. Genome-wide transcription profiling of the early phase of biofilm formation by *Candida albicans*. Eukaryot Cell 2005;4:1562–73.
[202] Sellam A, Al-Niemi T, McInnerney K, Brumfield S, Nantel A, Suci PA. A *Candida albicans* early stage biofilm detachment event in rich medium. BMC Microbiol 2009;9:25.
[203] Bensen ES, Martin SJ, Li M, Berman J, Davis DA. Transcriptional profiling in *Candida albicans* reveals new adaptive responses to extracellular pH and functions for Rim101p. Mol Microbiol 2004;54:1335–51.
[204] Fradin C, Kretschmar M, Nichterlein T, Gaillardin C, d'Enfert C, Hube B. Stage-specific gene expression of *Candida albicans* in human blood. Mol Microbiol 2003;47: 1523–43.
[205] Lorenz MC, Fink GR. The glyoxylate cycle is required for fungal virulence. Nature 2001;412:83–6.
[206] Lorenz MC, Bender JA, Fink GR. Transcriptional response of *Candida albicans* upon internalization by macrophages. Eukaryot Cell 2004;3:1076–87.
[207] Walker LA, Maccallum DM, Bertram G, Gow NA, Odds FC, Brown AJ. Genome-wide analysis of *Candida albicans* gene expression patterns during infection of the mammalian kidney. Fungal Genet Biol 2009;46:210–9.
[208] Cottier F, Raymond M, Kurzai O, Bolstad M, Leewattanapasuk W, Jiménez-López C, et al. The bZIP transcription factor Rca1p is a central regulator of a novel CO_2 sensing pathway in yeast. PLoS Pathog 2012;8:e1002485.
[209] Huang Q, Liu D, Majewski P, Schulte LC, Korn JM, Young RA, et al. The plasticity of dendritic cell responses to pathogens and their components. Science 2001;294:870–5.
[210] Ishibashi K, Miura NN, Adachi Y, Ogura N, Tamura H, Tanaka S, et al. DNA array analysis of altered gene expression in human leukocytes stimulated with soluble and particulate forms of *Candida* cell wall beta-glucan. Int Immunopharmacol 2004;4:387–401.
[211] Mullick A, Elias M, Harakidas P, Marcil A, Whiteway M, Ge B, et al. Gene expression in HL60 granulocytoids and human polymorphonuclear leukocytes exposed to *Candida albicans*. Infect Immun 2004;72:414–29.
[212] Lim CS, Rosli R, Seow HF, Chong PP. Transcriptome profiling of endothelial cells during infections with high and low densities of *C. albicans* cells. Int J Med Microbiol 2011;301: 536–46.
[213] Monk CE, Hutvagner G, Arthur JS. Regulation of miRNA transcription in macrophages in response to *Candida albicans*. PLoS One 2010;5:e13669.
[214] Yuan X, Wilhelmus KR. Toll-like receptors involved in the pathogenesis of experimental *Candida albicans* keratitis. Invest Ophthalmol Vis Sci 2010;51:2094–100.
[215] Yuan X, Hua X, Wilhelmus KR. Proinflammatory chemokines during *Candida albicans* keratitis. Exp Eye Res 2010;90:413–9.
[216] Lavoie H, Sellam A, Askew C, Nantel A, Whiteway M. A toolbox for epitope-tagging and genome-wide location analysis in *Candida albicans*. BMC Genomics 2008;9:578.
[217] Lassak T, Schneider E, Bussmann M, Kurtz D, Manak JR, Srikantha T, et al. Target specificity of the *Candida albicans* Efg1 regulator. Mol Microbiol 2011;82:602–18.
[218] Shapiro RS, Sellam A, Tebbji F, Whiteway M, Nantel A, Cowen LE. Pho85, Pcl1, and Hms1 signaling governs *Candida albicans* morphogenesis induced by high temperature or Hsp90 compromise. Curr Biol 2012;22:461–70.
[219] Marioni JC, Mason CE, Mane SM, Stephens M, Gilad Y. RNA-seq: an assessment of technical reproducibility and comparison with gene expression arrays. Genome Res 2008; 18:1509–17.
[220] Mortazavi A, Williams BA, McCue K, Schaeffer L, Wold B. Mapping and quantifying mammalian transcriptomes by RNA-Seq. Nat Methods 2008;5:621–8.
[221] Sultan M, Schulz MH, Richard H, Magen A, Klingenhoff A, Scherf M, et al. A global view of gene activity and alternative splicing by deep sequencing of the human transcriptome. Science 2008;321:956–60.
[222] Trapnell C, Williams BA, Pertea G, Mortazavi A, Kwan G, van Baren MJ, et al. Transcript assembly and quantification by RNA-Seq reveals unannotated transcripts and isoform switching during cell differentiation. Nat Biotechnol 2010;28:511–5.
[223] Wu CY, Rolfe PA, Gifford DK, Fink GR. Control of transcription by cell size. PLoS Biol 2010;8:e1000523.
[224] Bruno VM, Wang Z, Marjani SL, Euskirchen GM, Martin J, Sherlock G, et al. Comprehensive annotation of the transcriptome of the human fungal pathogen *Candida albicans* using RNA-seq. Genome Res 2010;20:1451–8.
[225] Dhamgaye S, Bernard M, Lelandais G, Sismeiro O, Lemoine S, Coppée JY, et al. RNA sequencing revealed novel actors of the acquisition of drug resistance in *Candida albicans*. BMC Genomics 2012;13:396.
[226] Tierney L, Linde J, Müller S, Brunke S, Molina JC, Hube B, et al. An interspecies regulatory network inferred from simultaneous RNA-seq of *Candida albicans* invading innate immune cells. Front Microbiol 2012;3:85.
[227] Nobile CJ, Fox EP, Nett JE, Sorrells TR, Mitrovich QM, Hernday AD, et al. A recently evolved transcriptional network controls biofilm development in *Candida albicans*. Cell 2012;148:126–38.
[228] Pitarch A, Nombela C, Gil C. Contributions of proteomics to diagnosis, treatment, and prevention of candidiasis. Methods Biochem Anal 2006;49:331–61.
[229] Pitarch A, Nombela C, Gil C. *Candida albicans* biology and pathogenicity: insights from proteomics. Methods Biochem Anal 2006;49:285–330.
[230] Premsler T, Zahedi RP, Lewandrowski U, Sickmann A. Recent advances in yeast organelle and membrane proteomics. Proteomics 2009;9:4731–43.
[231] Sosinska GJ, de Groot PW, Teixeira de Mattos MJ, Dekker HL, de Koster CG, Hellingwerf KJ, et al. Hypoxic conditions and iron restriction affect the cell-wall proteome of *Candida albicans* grown under vagina-simulative conditions. Microbiology 2008;154:510–20.
[232] Sosinska GJ, de Koning LJ, de Groot PW, Manders EM, Dekker HL, Hellingwerf KJ, et al. Mass spectrometric quantification of the adaptations in the wall proteome of *Candida albicans* in response to ambient pH. Microbiology 2011;157:136–46.
[233] Heilmann CJ, Sorgo AG, Siliakus AR, Dekker HL, Brul S, de Koster CG, et al. Hyphal induction in the human fungal pathogen *Candida albicans* reveals a characteristic wall protein profile. Microbiology 2011;157:2297–307.
[234] Sorgo AG, Heilmann CJ, Dekker HL, Bekker M, Brul S, de Koster CG, et al. Effects of fluconazole on the secretome, the wall proteome, and wall integrity of the clinical fungus *Candida albicans*. Eukaryot Cell 2011;10:1071–81.
[235] Klis FM, de Koster CG, Brul S. A mass spectrometric view of the fungal wall proteome. Future Microbiol 2011;6:941–51.

[236] Martínez-Solano L, Reales-Calderón JA, Nombela C, Molero G, Gil C. Proteomics of RAW 264.7 macrophages upon interaction with heat-inactivated *Candida albicans* cells unravel an anti-inflammatory response. Proteomics 2009;9:2995–3010.
[237] Reales-Calderón JA, Martínez-Solano L, Martínez-Gomariz M, Nombela C, Molero G, Gil C. Sub-proteomic study on macrophage response to *Candida albicans* unravels new proteins involved in the host defense against the fungus. J Proteomics 2012;75:4734–46.
[238] Balázsi G, Oltvai ZN. Sensing your surroundings: how transcription-regulatory networks of the cell discern environmental signals. Sci STKE 2005;2005:pe20.
[239] Horn F, Heinekamp T, Kniemeyer O, Pollmächer J, Valiante V, Brakhage AA. Systems biology of fungal infection. Front Microbiol 2012;3:108.
[240] Rizzetto L, Cavalieri D. Friend or foe: using systems biology to elucidate interactions between fungi and their hosts. Trends Microbiol 2011;19:509–15.
[241] Santamaría R, Rizzetto L, Bromley M, Zelante T, Lee W, Cavalieri D, et al. Systems biology of infectious diseases: a focus on fungal infections. Immunobiology 2011;216:1212–27.
[242] Brown AJ, Leach MD, Nicholls S. The relevance of heat shock regulation in fungal pathogens of humans. Virulence 2010;1:330–2.
[243] Shapiro RS, Uppuluri P, Zaas AK, Collins C, Senn H, Perfect JR, et al. Hsp90 orchestrates temperature-dependent *Candida albicans* morphogenesis via Ras1-PKA signaling. Curr Biol 2009;19:621–9.
[244] Nicholls S, MacCallum DM, Kaffarnik FA, Selway L, Peck SC, Brown AJ. Activation of the heat shock transcription factor Hsf1 is essential for the full virulence of the fungal pathogen *Candida albicans*. Fungal Genet Biol 2011;48: 297–305.
[245] Leach MD, Tyc KM, Brown AJ, Klipp E. Modelling the regulation of thermal adaptation in *Candida albicans*, a major fungal pathogen of humans. PLoS One 2012;7:e32467.
[246] Wang YC, Huang SH, Lan CY, Chen BS. Prediction of phenotype-associated genes via a cellular network approach: a *Candida albicans* infection case study. PLoS One 2012;7:e35339.
[247] Altwasser R, Linde J, Buyko E, Hahn U, Guthke R. Genome-wide scale-free network inference for *Candida albicans*. Front Microbiol 2012;3:51.