The polymorphic fungus *Candida albicans* is a member of the normal human microbiome. In most individuals, *C. albicans* resides as a lifelong, harmless commensal. Under certain circumstances, however, *C. albicans* can cause infections that range from superficial infections of the skin to life-threatening systemic infections. Several factors and activities have been identified which contribute to the pathogenic potential of this fungus. Among them are molecules which mediate adhesion to and invasion into host cells, the secretion of hydrolytic enzymes, the yeast-to-hypha transition, contact sensing and thigmotropism, biofilm formation, phenotypic switching and a range of fitness attributes. Our understanding of when and how these mechanisms and factors contribute to infection has significantly increased during the last years. In addition, novel virulence mechanisms have recently been discovered. In this review we present an update on our current understanding of the pathogenicity mechanisms of this important human pathogen.

**Introduction**

The total number of eukaryotic species on Earth has recently been estimated at 8.7 million, with fungi making up approximately 7% (611,000 species) of this number. Of all fungi, only around 600 species are human pathogens. This relatively small group encompasses fungi that cause relatively mild infections of the skin (e.g., dermatophytes and *Malassezia* species), fungi that cause severe cutaneous infections (e.g., *Sporotrich schenckii*) and fungi that have the potential to cause life-threatening systemic infections (e.g., *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Candida albicans*). Indeed, *Candida* spp are the fourth most common cause of hospital-acquired systemic infections in the United States with crude mortality rates of up to 50%. *C. albicans* can cause two major types of infections in humans: superficial infections, such as oral or vaginal candidiasis, and life-threatening systemic infections (for a comprehensive description of *C. albicans* infections see the second edition of *Candida and Candidiasis*).

*C. albicans* and to a lesser extent other *Candida* species are present in the oral cavity of up to 75% of the population. In healthy individuals this colonization generally remains benign. However, mildly immunocompromised individuals can frequently suffer from recalcitrant infections of the oral cavity. These oral infections with *Candida* species are termed “oral candidiasis” (OC). Such infections are predominantly caused by *C. albicans* and can affect the oropharynx and/or the esophagus of persons with dysfunctions of the adaptive immune system. Indeed, HIV is a major risk factor for developing OC. Further risk factors for developing OC include the wearing of dentures and extremes of age.

It is estimated that approximately 75% of all women suffer at least once in their lifetime from vulvovaginal candidiasis (VVC), with 40–50% experiencing at least one additional episode of infection. A small percentage of women (5–8%) suffer from at least four recurrent VVC per year. Predisposing factors for VVC are less well defined than for OC and include diabetes mellitus, use of antibiotics, oral contraception, pregnancy and hormone therapy. Despite their frequency and associated morbidity, superficial *C. albicans* infections are non-lethal. In stark contrast, systemic candidiasis is associated with a high crude mortality rate, even with first line antifungal therapy. Both neutropenia and damage of the gastrointestinal mucosa are risk factors for the development of experimental systemic (disseminated) candidiasis. Further risk factors include central venous catheters, which allow direct access of the fungus to the bloodstream, the application of broad-spectrum antibacterials, which enable fungal overgrowth, and trauma or gastrointestinal surgery, which disrupts mucosal barriers.

During both superficial and systemic infection, *C. albicans* relies on a battery of virulence factors and fitness attributes. The major factors and fitness traits are discussed below.

**Pathogenicity Mechanisms**

The ability of *C. albicans* to infect such diverse host niches is supported by a wide range of virulence factors and fitness attributes. A number of attributes, including the morphological transition between yeast and hyphal forms, the expression of adhesins and invasins on the cell surface, thigmotropism, the formation of biofilms, phenotypic switching and the secretion of hydrolytic enzymes are considered virulence factors. Additionally, fitness attributes include rapid adaptation to fluctuations
C. albicans, the main quorum sensing molecules include farnesol, tyrosol and dodecanol. Due to quorum sensing, high cell densities (> 10^7 cells ml^-1) promote yeast growth, while low cell densities (< 10^7 cells ml^-1) favor hyphal formation. The transition between yeast and hyphal growth forms is termed dimorphism and it has been proposed that both growth forms are important for pathogenicity. The hyphal form has been shown to be more invasive than the yeast form. On the other hand, the smaller yeast form is believed to represent the form primarily involved in dissemination.

Mutants that are unable to form hyphae under in vitro conditions are generally attenuated in virulence. However, hypha formation is linked to the expression of a subset of genes encoding virulence factors that are not involved in hyphal formation per se. Such hypha-associated proteins include the hyphal wall protein Hwp1, the agglutinin-like sequence protein Als3, the secreted aspartic proteases Sap4, Sap5 and Sap6 and the hypha-associated proteins Ece1 and Hyr1. Deletion of \textit{HGC1}, which encodes a hypha-specific G1 cyclin-related protein, results in cells that grow normally in the yeast form but fail to produce hyphae. Nevertheless, the \textit{hgc1ΔΔ} mutant cells still express at least four

**Figure 1.** An overview of selected \textit{C. albicans} pathogenicity mechanisms. Yeast cells adhere to host cell surfaces by the expression of adhesins. Contact to host cells triggers the yeast-to-hypha transition and directed growth via thigmotropism. The expression of invasins mediates uptake of the fungus through induced endocytosis. Adhesion, physical forces and secretion of fungal hydrolases has been proposed to facilitate the second mechanism of invasion, i.e., fungal-driven active penetration into host cells by breaking down barriers. The attachment of yeast cells to abiotic (e.g., catheters) or biotic (host cells) surfaces can give rise to the formation of biofilms with yeast cells in the lower part and hyphal cells in the upper part of the biofilm. Phenotypic plasticity (switching) has been proposed to influence antigenicity and biofilm formation of \textit{C. albicans}. In addition to these virulence factors, several fitness traits influence fungal pathogenicity. They include a robust stress response mediated by heat shock proteins (Hsps); auto-induction of hyphal formation through uptake of amino acids, excretion of ammonia (NH3) and concomitant extracellular alkalinization; metabolic flexibility and uptake of different compounds as carbon (C) and nitrogen (N) sources; and uptake of essential trace metals, e.g., iron (Fe), zinc (Zn), copper (Cu) and manganese (Mn).
hypha-associated genes (HWPI, ECE1, HYR1 and ALS3). The finding that an hgc1Δ/Δ mutant was attenuated in a mouse model of systemic infection, supported the view that hyphal formation per se is an important virulence attribute.

Adhesins and invasions. C. albicans has a specialized set of proteins (adhesins) which mediate adherence to other C. albicans cells to other microorganisms, to abiotic surfaces and to host cells. Arguably the best studied C. albicans adhesins are the agglutinin-like sequence (ALS) proteins which form a family consisting of eight members (Als1–7 and Als9). The ALS genes encode glycosylphosphatidylinositol (GPI)-linked cell surface glycoproteins. Of the eight Als proteins, the hypha-associated adhesin Als3 is especially important for adhesion. Another important adhesin of C. albicans is Hwp1, which is a hypha-associated GPI-linked protein. Hwp1 serves as a substrate for mammalian transglutaminases and this reaction may covalently link C. albicans hyphae to host cells. An hwp1Δ/Δ mutant displayed reduced adherence to buccal epithelial cells and displayed attenuated virulence in a mouse model of systemic candidiasis.

Hwp1 and Als3 were also demonstrated to contribute to biofilm formation by acting as complementary adhesins. Morphology-independent proteins can also contribute to adhesion. These include GPI-linked proteins (Eap1, Iff4 and Ecm33), non-covalent wall-associated proteins (Mp65, a putative β-glucanase, and Phr1, a β-1,3 glucanosyl transferase), cell-surface associated proteases (Sap9 and Sap10) and the integrin-like surface protein Int.

C. albicans is a remarkable pathogen as it can utilize two different mechanisms to invade into host cells: induced endocytosis and active penetration. For induced endocytosis, the fungus expresses specialized proteins on the cell surface (invasins) that mediate binding to host ligands (such as E-cadherin on epithelial cells and N-cadherin on endothelial cells), thereby triggering engulfment of the fungal cell into the host cell. Indeed, even killed hyphae are taken up, indicating that induced endocytosis is a passive process that does not require the activities of viable fungal cells. Two invasins have been identified so far, namely Als3 (which also functions as an adhesin, see above) and Ssa1. Als3 and Ssa1 bind to host E-cadherin and likely induce endocytosis by a clathrin-dependent mechanism; however, macropinocytosis has also been implicated in C. albicans induced endocytosis. In contrast, active penetration is a funga-driven process and requires viable C. albicans hyphae. It is still unclear exactly which factors mediate this second route of invasion into host cells. Fungal adherence and physical forces are believed to be crucial. Secreted aspartic proteases (Saps) have also been proposed to contribute to active penetration. Lipases and phospholipases, on the other hand, have not been shown to contribute to this process.

In summary, invasion into host cells by C. albicans relies on two likely complementary mechanisms: induced endocytosis mediated by Als3 and Ssa1 and active penetration mediated by yet undefined molecular mechanisms.

Biofilm formation. A further important virulence factor of C. albicans is its capacity to form biofilms on abiotic or biotic surfaces. Catheters, dentures (abiotic) and mucosal cell surfaces (biotic) are the most common substrates. Biofilms form in a sequential process including adherence of yeast cells to the substrate, proliferation of these yeast cells, formation of hyphal cells in the upper part of the biofilm, accumulation of extracellular matrix material and, finally, dispersion of yeast cells from the biofilm complex. Mature biofilms are much more resistant to antimicrobial agents and host immune factors in comparison to planktonic cells. The factors responsible for heightened resistance include the complex architecture of biofilms, the biofilm matrix, increased expression of drug efflux pumps and metabolic plasticity. Dispersion of yeast cells from the mature biofilm has been shown to directly contribute to virulence, as dispersed cells were more virulent in a mouse model of disseminated infection. The major heat shock protein Hsp90 was recently identified as a key regulator of dispersion in C. albicans biofilms. In addition, Hsp90 was also required for biofilm antifungal drug resistance.

Several transcription factors control biofilm formation. These include the transcription factors Bcr1, Tc1 and Efg1. In a recent study, Nobile et al. investigated the transcriptional network regulating biofilm formation and identified further, previously unknown regulators of biofilm production. These novel factors include Ndt80, Rob1 and Brg1. Deletion of any of these regulators (BCR1, TEC1, EFG1, NDT80, ROBI or BRG1) resulted in defective biofilm formation in vivo rat infection models.

Extracellular matrix production is controlled by additional factors. The zinc-responsive transcription factor Zap1 negatively regulates β-1,3 glucan, the major component of biofilm matrix. Glucoamylases (Gca1 and Gca2), glucan transferases (Bgl2 and Pbr1) and the exo-glucanase, Xog1, are positive regulators of β-1,3 glucan production. While expression of GCA1 and GCA2 are controlled by Zap1, the enzymes Bgl2, Pbr1 and Xog1 function independently of this key negative regulator. Biofilms formed by mutants lacking BGL2, PHR1 or XOG1 were shown to be more susceptible to the antifungal agent, fluconazole, both in vitro and in vivo. Furthermore, recent studies indicate that C. albicans biofilms are resistant to killing by neutrophils and do not trigger production of reactive oxygen species (ROS). Evidence suggests that β-glucans in the extracellular matrix protect C. albicans from these attacks.

Contact sensing and thigmotropism. An important environmental cue that triggers hypha and biofilm formation in C. albicans (see above) is contact sensing. Upon contact with a surface, yeast cells switch to hyphal growth. On certain substrates, such as agar or mucosal surfaces, these hyphae can then invade into the substratum. Contact to solid surfaces also induces the formation of biofilms. On surfaces with particular topologies (such as the presence of ridges) directional hyphal growth (thigmotropism) may occur.
Brand et al. demonstrated that thigmotropism of *C. albicans* hyphae is regulated by extracellular calcium uptake through the calcium channels Cch1, Mid1 and Fig1. Additional mechanisms include the polarisome Rsr1/Bud1-GTPase module. Brand et al. also provided evidence that *C. albicans* thigmotropism is required for full damage of epithelial cells and normal virulence in mice.

Therefore, the correct sensing and response to both abiotic (biofilm formation) and biotic (invasion) surfaces is important for pathogenicity.

**Secreted hydrolases.** Following adhesion to host cell surfaces and hyphal growth, *C. albicans* hyphae can secrete hydrolases, which have been proposed to facilitate active penetration into these cells. In addition, secreted hydrolases are thought to enhance the efficiency of extracellular nutrient acquisition.

Three different classes of secreted hydrolases are expressed by *C. albicans*: proteases, phospholipases and lipases.

The family of secreted aspartic proteases (Saps) comprises ten members, Sap1–10. Sap1–8 are secreted and released to the surrounding medium, whereas Sap9 and Sap10 remain bound to the cell surface. Sap1–3 have been shown to be required for damage of reconstituted human epithelium (RHE) in vitro, and for virulence in a mouse model of systemic infection. However, the relative contribution of Saps to *C. albicans* pathogenicity is controversial. Recent results indicate that Saps are not required for invasion into RHE and that Sap1–6 are dispensable for virulence in a mouse model of disseminated candidiasis.

However, the observed expansion of Sap-encoding genes in *C. albicans* compared with its less pathogenic relatives suggests a role for these proteases in virulence. Indeed, the large size of the Sap family itself makes it likely that a certain degree of functional redundancy may exist.

The family of phospholipases consists of four different classes (A, B, C, and D). Only the five members of class B (PLB1–5) are extracellular and may contribute to pathogenicity via disruption of host membranes. Both *plb1Δ/Δ* and *plb5Δ/Δ* mutants have been shown to be attenuated in virulence in a mouse model of systemic infection.

The third family of secreted hydrolases, the lipases, consists of 10 members (*LIP1*–10). A *lip8Δ/Δ* mutant had reduced virulence in a mouse model of systemic infection, supporting a role for these extracellular hydrolases in *C. albicans* pathogenicity.

**pH-sensing and regulation.** In the human host, *C. albicans* is exposed to a surrounding pH ranging from slightly alkaline to acidic. Additionally, depending on the host niche, the environmental pH can be very dynamic. Therefore, *C. albicans* must be able to adapt to changes in pH. The pH of human blood and tissues is slightly alkaline (pH 7.4), while the pH of the digestive tract ranges from very acidic (pH 2) to more alkaline (pH 8), and the pH of the vagina is around pH 4. Neutral to alkaline pH can cause severe stress to *C. albicans*, including malfunctioning of pH-sensitive proteins, and impaired nutrient acquisition (as a consequence of a disrupted proton gradient). Among the first proteins identified as being important for adaptation to changing pH were the two cell wall β-glycosidases Phrl and Phr2. *PHR1* is expressed at neutral-alkaline pH. In contrast, *PHR2* is mainly expressed at acidic pH. Correspondingly, Phr1 is required for systemic infections, and Phr2 is essential for infections of the vagina. *C. albicans* senses pH via the Rim101 signal transduction pathway. In this pathway, environmental pH is gauged by the plasma membrane receptors Dlg16 and Rim21. Activation of these receptors leads to induction of a signaling cascade, finally leading to activation of the major pH-responsive transcription factor Rim101 via its proteolytic cleavage. Rim101 then enters the nucleus and mediates pH-dependent responses. A *dfg16Δ/Δ* mutant had reduced virulence in a mouse infection model of systemic candidiasis, and a *rim20Δ/Δ* mutant had attenuated virulence in a mouse corneal infection model. Finally, a *rim101Δ/Δ* mutant had reduced virulence in both a systemic mouse model of hematogenously disseminated candidiasis and a murine model of oropharyngeal candidiasis. Together these data demonstrate that the Rim101 pathway, and pH sensing in general, are critical for *C. albicans* virulence.

*C. albicans* is not only able to sense and adapt to environmental pH, but can also modulate extracellular pH, actively alkalizing its surrounding environment under nutrient starvation and, thereby, autoinducing hypha formation. The molecular mechanisms underlying this are beginning to be uncovered and appear to involve the uptake of amino acids and probably other amine-containing molecules, such as polyamines, in the absence of glucose. *C. albicans* then cleaves these substrates intracellularly with the urea amidolyase Dur1,2, and exports the resulting ammonia through the Ato (ammonia transport outward) export proteins. The extrusion of ammonia leads to an alkalinization of the extracellular milieu, which in turn promotes hyphal morphogenesis. Hyphal formation itself is considered a key virulence factor of *C. albicans* as non-filamentous mutants are attenuated in virulence (see above). Therefore, *C. albicans* senses, adapts to and, strikingly, also actively modulates extracellular pH. All these features contribute to its remarkable capacity to co-exist as a commensal, and to prevail as a fungal pathogen in humans.

**Metabolic adaptation.** Nutrition is a central and fundamental prerequisite for survival and growth of all living organisms. Metabolic adaptability mediates the effective assimilation of alternative nutrients in dynamic environments. This metabolic flexibility is particularly important for pathogenic fungi during infection of different host niches. Glycolysis, gluconeogenesis and starvation responses are all thought to contribute to host colonization and pathogenesis, but their specific contribution may be highly niche-specific and is still only partially understood. In healthy individuals *C. albicans* is predominantly found as part of the gastrointestinal microbiome. Although the concentration of nutrients in this environment can be naturally high, growth of the fungus is believed to be controlled through competition with other members of the intestinal microbial flora. During disseminated candidiasis in susceptible individuals, *C. albicans* gains access to the bloodstream. Blood is relatively rich in glucose (6–8 mM), the preferred nutrient source of most fungi. However, phagocytic cells (macrophages and neutrophils) can efficiently phagocytose *C. albicans*. Once
inside a macrophage or neutrophil, however, the nutritional environment completely changes for the fungus. Not only does the phagocyte produce highly reactive intermediates like ROS, reactive nitrogen species (RNS) and antimicrobial peptides (AMPs), it also restricts the availability of nutrients, thereby creating an environment of nutrient starvation. Prompt and efficient metabolic plasticity is therefore required for adaptation of C. albicans to such a hostile host milieu. Inside macrophages, the fungus initially switches from glycolysis to gluconeogenesis and a starvation response (activation of the glyoxylate cycle). Lipids and amino acids are proposed to serve as nutrient sources within macrophages.93

In addition to metabolic flexibility, the fungus has also evolved ways to escape from macrophages by inhibiting the production of antimicrobial effectors and inducing hyphal formation. Hyphae formed inside phagocytic cells can pierce through the host immune cell by mechanical forces and can permit escape.93,94 During systemic candidiasis, fungal cells can disseminate to virtually every organ within the human host, each with potentially different availability of nutrients. In the liver for example, C. albicans has access to large quantities of glycogen, the main storage molecule of glucose. The brain has high concentrations of glucose and vitamins as potential nutrient sources.93 In other tissues, C. albicans faces relatively poor glucose concentrations and uses alternative metabolic pathways to utilize host proteins, amino acids, lipids and phospholipids. The fungus can use secreted proteases (see above) to hydrolyse host proteins. It was recently shown that adaptation to different nutrient sources by C. albicans not only promotes survival and growth, but also affects virulence.95 Growth on alternative carbon sources, such as lactate or amino acids, rendered the fungus more resistant to environmental stresses and increased its virulence potential in both a mouse model of systemic candidiasis, and a murine vaginal infection model.95 Furthermore, the glyoxylate cycle has been shown to be required for full virulence in C. albicans.96 Uptake of amino acids, and likely also polyamines, affects the virulence of C. albicans by allowing the fungus to autoinduce hypha formation through extracellular alkalinaization (Fig. 1).97,98

In summary, during infection the main nutrient sources for C. albicans are likely to be host-derived glucose, lipids, proteins and amino acids, depending on the anatomical niche. Besides being able to use these different nutrients individually, the ability of C. albicans to rapidly and dynamically respond to host and pathogen-induced changes in micro-environmental nutrient availability contributes to its success as a pathogen.

Environmental stress response. A robust stress response contributes to the survival and virulence of C. albicans by facilitating the adaptation of the fungus to changing conditions and protecting it against host-derived stresses. Phagocytic cells of the immune system produce oxidative and nitrosative stresses. pH stress occurs, for example, in the gastrointestinal and urogenital tract.99 Stress-responsive regulatory pathways, as well as downstream targets, were shown to be essential not only for efficient stress adaptation, but also for full virulence of the fungus.99 In fact, several mutants lacking genes encoding regulators of stress response or detoxifying enzymes are attenuated in virulence. Cellular responses to stresses include heat shock-, osmotic-, oxidative- and nitrosative-stress responses.99

The heat shock response is mediated by heat shock proteins (see below) which act as molecular chaperones to prevent deleterious protein unfolding and aggregation. Additionally, thermal stress leads to trehalose accumulation in C. albicans, which is thought to act as a “chemical chaperone” by stabilizing proteins prone to unfolding.95 However, the exact function of trehalose accumulation following thermal insults remains unknown.

The osmotic stress response results in intracellular accumulation of the compatible solute glycerol to counteract loss of water due to the outward-directed chemical gradient. Glycerol biosynthesis is mediated by the glycerol 3-phosphatase Gpp1 and the glycerol 3-phosphate dehydrogenase Gpd2.96 Both gpp1Δ/Δ and gpd2Δ/Δ mutants were shown to have reduced capacity to damage oral epithelial cells in vitro. However, this was probably due to an inability to generate hyphal turgor pressure and mechanical forces (see above) rather than heightened sensitivity to osmotic stress in this infection model.96

Reactive oxygen species (ROS), such as peroxide, superoxide anions, and hydroxyl radicals, induce an oxidative stress response.99 Catalase Cta1 and superoxide dismutases, Sod1 and Sod5, are crucial for efficient detoxification of ROS in C. albicans, and are required for full virulence in mouse models of systemic candidiasis.97-99

Neutrophils also produce reactive nitrogen species (RNS), which induce a nitrosative stress response in phagocytosed C. albicans cells. The major protein implicated in detoxification of RNS is the flavohemoglobin-related protein Yhb1. Deletion of Yhb1 renders C. albicans cells sensitive to RNS and attenuates virulence in a mouse model of systemic candidiasis.100

In fungi, environmental signals, including stress signals, are sensed and transmitted by mitogen-activated protein (MAP) kinase pathways through sequential phosphorylation events.101 The three main MAP kinase signaling pathways in C. albicans are the Mkc1-, Hog1- and Cek1-MAP kinase pathway.101

The Mkc1 (MAP kinase from C. albicans) pathway is primarily involved in maintaining cellular integrity, cell wall biogenesis, invasive growth under embedded conditions and biofilm formation.100 Mkc1 is activated upon oxidative and osmotic stress conditions.

The Hog1 (High osmolarity glycerol response) pathway mediates the response to osmotic, oxidative and thermal stress, morphogenesis and cell wall formation.101 Under osmotic stress, activated Hog1 leads to glycerol accumulation.101

The Cek1 (Candida ERK-like kinase) pathway mediates filamentation, mating and likely also adaptation to thermal stress.101,102 Mutants in all three pathways (mkc1Δ, hog1Δ or cek1Δ) were all attenuated in virulence in mouse infection models, highlighting the importance of the stress response during infection.103-105

In addition to the sequential cascade of activation in the three MAP kinase pathways, environmental signals also trigger cross-talk between these pathways. For example, activated Hog1 both represses the Cek1-pathway and activates the Mkcl pathway.101 Moreover, certain signals, like oxidative or osmotic stress are
sensed by more than one pathway. This interweaved MAP kinase sensing network probably engenders fine-tuning of a robust adaptive response.

**Heat shock proteins.** The heat shock response is a conserved reaction of living organisms to stressful conditions such as high temperature, starvation and oxidative stress.\(^{106,107}\) Such stresses can induce protein unfolding and nonspecific protein aggregation, ultimately leading to cell death. In order to prevent this detrimental fate, cells produce heat shock proteins (Hsps).\(^{106}\) These specialized proteins act as chaperones and prevent protein unfolding and aggregation by binding to their clients and stabilizing them.\(^{108}\) Six major Hsps have been identified in *C. albicans*: Hsp104, Hsp90, Hsp70, two Hsp70 proteins (Ssa1 and Ssa2) and Hsp60. \(^{109}\) HSPI04 encodes a Hsp required for proper biofilm formation, and virulence in a *Caenorhabditis elegans* infection model.\(^{109}\) Hsp90 is a major Hsp in *C. albicans* and regulates drug resistance, morphogenesis, biofilm formation and virulence.\(^{5,109-111}\) HSP78 encodes an uncharacterized Hsp that is transcriptionally upregulated in response to phagocytosis by macrophages.\(^{9}\) The two *C. albicans* Hsp70 family members, Ssa1 and Ssa2 (stress-70 subfamily A), are expressed on the cell surface and function as receptors for antimicrobial peptides, e.g., Ssa2 binds histatin 5.\(^{1,114-116}\) An *ssa2Δ*Δ mutant had increased resistance to histatin 5, but was dispensable for virulence in mouse models of disseminated and oropharyngeal candidiasis.\(^{9,114-116}\) Ssa1 also acts as an invasin.\(^{39}\) An *ssa1Δ*Δ mutant had attenuated virulence in mouse models of both disseminated and oropharyngeal candidiasis.\(^{49}\) Finally, HSP60 encodes a putative mitochondrial Hsp of unknown function. An *hsp60Δ/HSP60* heterozygous mutant has increased sensitivity to elevated temperatures, indicating that Hsp60 might be required for thermal stress tolerance.\(^{117}\)

Expression of Hsps is mainly controlled by the transcription factor heat shock factor 1 (Hsf1).\(^{118,119}\) Hsf1 is phosphorylated in response to heat stress and induces transcription of Hsp-encoding genes via binding to heat shock element (HSEs) in their promoters.\(^{119}\) *C. albicans* Hsf1 is essential for viability and a mutant that is unable to activate Hsf1 displays attenuated virulence in a mouse model of systemic candidiasis.\(^{15}\)

**Small heat shock proteins.** In addition to the above mentioned heat shock proteins, six small Hsps (sHsps) have also been identified in *C. albicans*.\(^{120}\) sHsps are low-molecular-mass chaperones that prevent protein aggregation.\(^{121,122}\) Upon heat, or other forms of stress, cells express sHSPs which transition from an oligomeric to a multimeric state and bind aggregated proteins.\(^{123}\) In these chaperone-aggregate complexes, client proteins are held ready for disaggregation and refolding by other major Hsps, such as Hsp104.\(^{124}\)

*C. albicans* is predicted to encode six sHsps: Hsp31, Hsp30, Hsp21, two Hsp12 proteins and Hsp10.\(^{125}\) As yet only Hsp12 and Hsp21 have been investigated. Hsp12 is expressed in response to different stresses, including heat shock and oxidative stress. Deletion of both *HSPI2* genes did not influence virulence of *C. albicans* in a Drosophila infection model.\(^{125}\) It should be noted, however, that the fly infection experiment was performed at 30°C, and it remains to be investigated how the mutant behaves at physiological temperature in a mammalian host.

We recently investigated the function of Hsp21 and showed that this Hsp is crucial for regulation of intracellular levels of trehalose. Deletion of HSP21 resulted in impaired thermostolerance, enhanced sensitivity toward oxidative stress, and strongly attenuated virulence in a mouse model of systemic candidiasis.\(^{126}\) Importantly, Hsp21 is not found in humans. These results indicate that sHsps can act as virulence factors and might represent attractive drug targets.

**Metal acquisition.** Trace metals are essential for the growth and survival of all living organisms including humans, animals, plants, bacteria and fungi. Among the most important metals are iron, zinc, manganese and copper, all of which are essential for the proper function of a large number of proteins and enzymes. Pathogenic microorganisms, as well as their respective hosts, have evolved elaborate mechanisms to acquire or restrict access to these metals.\(^{126}\)

To date, the most widely investigated transition metal with regard to pathogenesis is iron. *C. albicans* acquires this metal by different strategies, including a reductive system, a siderophore uptake system and a heme-iron uptake system.\(^{127}\) The reductive system mediates iron acquisition from host ferritin, transferrin or the environment. The adhesin and invasin Als3 (see above) was shown to be the receptor for ferritin.\(^{30}\) Despite the fact that an *als3Δ*Δ mutant had normal virulence in a mouse infection model of disseminated candidiasis, deletion of *ALS3* resulted in reduced capacity to damage oral epithelial host cells in vitro, suggesting that Als3-mediated iron acquisition from host ferritin contributes to iron acquisition depending on the stage of the infection.\(^{30,31}\) Although *C. albicans* does not synthesize its own siderophores, the fungus uses an uptake system to steal iron from siderophores produced by other microorganisms, also known as xeno-siderophores. The only described siderophore transporter in *C. albicans* is Sit1. A *sit1Δ*Δ mutant exhibited normal virulence in a mouse model of disseminated candidiasis. However, the mutant was strongly impaired in its capacity to damage ex vivo human keratinocyte tissue.\(^{129}\) Finally, the heme-iron uptake system promotes iron acquisition from hemoglobin and heme-proteins and is mediated by the heme-receptor gene family members *RBT5*, *RBT31*, *CSA1*, *CSA2* and *PAG7* (*RBT6*).\(^{127,128}\) An *rbt5Δ*Δ mutant has normal virulence in mice, however, this may be due to functional redundancy.\(^{127,131}\) The role of the other four heme-binding proteins (*Rbt51*, *Csa1*, *Csa2* and *Pga7*) in virulence has not yet been investigated.

Zinc is the second most abundant metal in most living organisms.\(^{126}\) Our group has recently uncovered a previously undescribed mechanism of zinc acquisition by *C. albicans*.\(^{132}\) The fungus secretes the zinc-binding protein Pral1 (*pH*-regulated antigen 1), which, analogous to siderophore-mediated iron acquisition, acts as a zincophore by binding extracellular zinc and re-associating with the fungal cell. Re-association of Pral1 is mediated by the zinc transporter Zrt1.\(^{132}\) Despite enhanced virulence of a *pral1Δ*Δ mutant in mice,\(^{133}\) deletion of *PRA1* strongly reduces the capacity of *C. albicans* to damage endothelial cells in vitro in the absence of exogenous zinc, suggesting that zinc acquisition plays an important role during certain steps of infection.\(^{132}\) Copper and manganese are also essential for fungal growth; however,
the mechanisms by which *C. albicans* acquires these metals is currently poorly understood. A putative manganese transporter, Ccc1, and a copper transporter, Ctr1, have been identified, although their roles in virulence have not yet been determined. Therefore, future studies are required to elucidate the role of these other essential metals in *C. albicans* pathogenicity.

## Conclusions

Understanding the pathogenicity mechanisms that *C. albicans* uses during infection is crucial for the development of new antifungal therapies and diagnostics. Classically, antifungal drugs were designed to exert fungicidal activities, i.e., to kill the pathogenic microorganism. Recently however, specifically targeting virulence factors has been proposed as a new and promising antifungal strategy. Several virulence factors, such as dimorphism, the secretion of proteases and the expression of adhesins and invasins, have been suggested as attractive targets, and recent investigations have further broadened our understanding of the *C. albicans* factors and activities which contribute to virulence. The heat shock response, including major and small heat shock proteins, has emerged as a promising drug target. Specifically, those Hsps that are unique to fungi and do not occur in humans (for example, Hsp21) represent good candidates for specific drug targets. Another avenue of research is the interplay between host nutritional immunity and fungal nutrient acquisition systems. In particular, interfering with the iron, zinc, manganese or copper homeostasis mechanisms of pathogenic microorganisms may represent promising therapeutic strategies. As our detailed understanding of fungal pathogenicity mechanisms improves, the potential for developing novel therapeutic and diagnostic strategies expands.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Acknowledgments

Our work on *C. albicans* pathogenicity mechanisms was supported as follows: F.L.M. and B.H. were supported by the International Leibniz Research School for Microbial and Biomolecular Interactions (ILRS) as part of the excellence graduate school Jena School for Microbial Communication (JSMC). D.W. and B.H. were supported by the ERA-NET PathoGenoMicS Program (Candidol; BMBF 0315 901 B). B.H. was also supported by the Center for Septis Control and Care (CSCC; BMBF 01EO1002) and the Deutsche Forschungsgemeinschaft (DFG Hu 528/15, 16 and 17). We apologize to all colleagues in the field of *Candida albicans* research whose work we were unable to cite due to space limitations.

## References

1. Mora C, Tresnerev DP, Adi S, Simpson AGB, Worm B. How many species are there on Earth and in the ocean? PLoS Biol. 2011; 9:e1001127; PMID:21886479; http://dx.doi.org/10.1371/journal.pho.1001127.
2. Brown GD, Denning DW, Levitz SM. Tackling fungal infections. Science 2012; 336:336-47; PMID:22582229; http://dx.doi.org/10.1126/sci.1222256.
3. Pfäffle MA, Diekema DJ. Epidemiology of invasive mycoses in North America. Crit Rev Microbiol 2010; 36:1-53; PMID:20088682; http://dx.doi.org/10.3109/10408410903241444.
4. Pfäffle MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev 2007; 20:133-63; PMID:17223626; http://dx.doi.org/10.1128/CMR.00029-06.
5. Calderone RA, Clancy CJ. *Candida* and Candidiasis: ASM Press, Washington, DC, 2012.
6. Ruhnke M, Skin and mucous membrane infections. In: Calderone RA, ed. *Candida and Candidiasis*; ASM Press, Washington, DC, pp. 307-325., 2002.
7. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr., Calandra TF, Edwards JE Jr., et al.; Infectious Diseases Society of America. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:503-35; PMID:19865975; http://dx.doi.org/10.1086/596977.
8. Hurley R, De Louvois J. *Candida* vaginitis. Postgrad Med J 1979; 55:645-7; PMID:5233955; http://dx.doi.org/10.1136/pgmj.55.647.645.
9. Sobel JD. Vulvovaginal candidiasis. Lancet 2007; 369:1691-71; PMID:17560449; http://dx.doi.org/10.1016/S0140-6736(07)60917-9.
10. Foxman B, Marsh JH, Gillespie B, Sobel JD. Frequency and response to vaginal symptoms among white and African American women: results of a random digit dialing survey. J Womens Health 1998; 7:1167-74; PMID:9861594; http://dx.doi.org/10.1089/jwh.1998.7.1167.
11. Fidel PL Jr. History and new insights into host defense against vaginal candidiasis. Trends Microbiol 2004; 12:220-7; PMID:15120141; http://dx.doi.org/10.1016/j.tim.2004.03.006.
12. Perillo J, Choi J, Spellberg B. Nosocomial fungal infections: epidemiology, diagnosis, and treatment. Med Mycol 2007; 45:321-46; PMID:17510856; http://dx.doi.org/10.1080/13693780701218689.
13. Koh AY, Kohler KR, Coggshall KT, Van Roojen N, Pier GB. Mucosal damage and neutrophilia are required for Candida albicans dissemination. PLoS Pathog 2008; 4:e35; PMID:18292097; http://dx.doi.org/10.1371/journal.ppat.0040035.
14. Spellberg B, Marr K, Filler SG. Candida: What Should Clinicians and Scientists Be Talking About? In: Calderone RA, Clancy CJ, ed. *Candida and Candidiasis*; ASM Press, Washington, DC, pp. 225-242., 2012.
15. 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; PMID:20817114; http://dx.doi.org/10.1016/j.fgb.2010.08.010.
16. Berman J, Sudbery PE. *Candida albicans*: a molecular revolution built on lessons from budding yeast. Nat Rev Genet 2002; 3:918-30; PMID:12459722; http://dx.doi.org/10.1038/nrg948.
17. Sudbery P, Gow N, Berman J. The distinct morphogenetic states of *Candida albicans*. Trends Microbiol 2004; 12:317-24; PMID:15223059; http://dx.doi.org/10.1016/j.tim.2004.05.008.
18. Schübel P, Morrischüezer J, Chlamydospore formation in Candida albicans and Candida dubliniensis—an enigmatic developmental programme. Mycoses 2007; 50:1-12; PMID:17302741; http://dx.doi.org/10.1111/j.1439-0507.2006.01308.x.
19. Soll DR. Why does *Candida albicans* switch? FEMS Yeast Res 2009; 9:973-89; PMID:19744246; http://dx.doi.org/10.1111/j.1567-1364.2009.00562.x.
20. Odds FC. *Candida* and Candidoides. second ed. Bailliere Tindall, London, United Kingdom, 1988.
29. Zheng X, Wang Y, Wang Y. Hgf1, a novel hypha-specific G1 cyclin-related protein regulates Candida albicans hyphal morphogenesis. EMBO J 2004; 23:1845-56; PMID:15071502; http://dx.doi.org/10.1038/ sjo.embj.2004.176.

30. Sundstrom PS, Bruneke S, Albrecht A, Theves S, Laue M, Edwards JE, et al. The hyphal-associated adhesion and invasion Als1 of Candida albicans mediates iron acquisition from host ferritin. PLoS Pathog 2008; 4:e1000217; PMID:19025418; http://dx.doi.org/10.1371/journal.ppat.1000217.

31. Garcia MC, Lee JT, Ramsook CB, Alsteens D, Dufrêne EC. A role for cell microtubules in the regulation of Candida albicans hyphal formation. Cell Microbiol 2010; 12:273-82; PMID:19919567; http://dx.doi.org/10.1111/j.1462-8802.2009.01412.x.

32. Dalle F, Wächter B, Löffler C, Holland G, Hube B, Köhler JR, et al. Cellular interactions of Candida albicans with human oral epithelial cells and enterocytes. Cell Microbiol 2010; 12:248-71; PMID:19863559; http://dx.doi.org/10.1111/j.1462-8802.2009.01394.x.

33. Phan QT, Franti RA, Pradavski NV, Edwards JE Jr., Fuller SG. N-cadherin mediates endocytosis of Candida albicans by endothelial cells. J Biol Chem 2005; 280:10455-61; PMID:15632157; http://dx.doi.org/10.1074/jbc.M41292200.

34. Park H, Myers CL, Sheppard DC, Phan QT, Sanchez AA, E. Edwards JE, et al. Role of the fungal Ras-protein kinase A pathway in governing epithelial-cell interactions during oopharyngeal candidiasis. Cell Microbiol 2005; 7:499-510; PMID:15760450; http://dx.doi.org/10.1111/j.1462-8802.2004.00476.x.

35. Sun JN, Solis NV, Phan QT, Bajwa JS, Kashleva H, Thompson A, et al. Calcium signaling and virulence mediated by Candida albicans Hwp1. Science 1999; 283:1535-40; PMID:10499848; http://dx.doi.org/10.1126/science.283.5407.1535.

36. Finkel JS, Mitchell AP. Genetic control of Candida albicans biofilm development. Nat Rev Microbiol 2011; 9:109-18; PMID:21189476; http://dx.doi.org/10.1038/nrmicro2783.

37. Uppuluri P, Chaturvedi AK, Sinivasan A, Banerjee M, Ramasubramaniam AK, Köhler JR, et al. Dispersion and biofilm formation. J Clin Microbiol 2010; 48:10088-92; PMID:20360962; http://dx.doi.org/10.1128/JCM.010088-10.

38. Robbins N, Uppuluri P, Nett J, Rajendran R, Ramasubramaniam AK, et al. An evolutionarily conserved transcriptional control network is regulated by a calcium-dependent mechanism for dispersal from Candida albicans biofilms. Proc Natl Acad Sci U S A 2011; 108:6431-6; PMID:21373185; http://dx.doi.org/10.1073/pnas.1013436108.

39. Choi H, Yoon JH, Kwon HJ, Park J, Cho Y, Kim J, et al. Identification of a gene essential for both cellular processes and host-pathogen interactions. J Cell Biol 2012; 198:823-36; PMID:22505414; http://dx.doi.org/10.1083/jcb.201103175.

40. Albrecht A, Felk A, Pichova I, Naglik JR, Schaller M, de Groot P, et al. Glycophosphatidylinositol-anchored proteases of Candida albicans target proline necessary for both cellular processes and host-pathogen interactions. J Biol Chem 2012; 287:2955-63; PMID:22363181; http://dx.doi.org/10.1074/jbc.M111.319054.

41. Brand A, Hoonhout D, Schnall M, Biesemeier A, Schweier A, Röllinghoff M, et al. Induction of SAP7 correlates with virulence in an intravenous infection model of candidiasis but not in a vaginal infection model in mice. Infect Immun 2005; 73:7698-7701; PMID:16177793; http://dx.doi.org/10.1128/IAI.73.10.7696-7701.2005.

42. Chang SM, Lee S, Choe K, Go H, Park J, et al. A specific G1 cyclin-related protein regulates cdc5 cells necessary for both cellular processes and host-pathogen interactions. J Cell Sci 2010; 123:4501-13; PMID:20608572; http://dx.doi.org/10.1242/jcs.070747.

43. Lonneman W, Mummery D, Hoyer LL. Comparison between Candida albicans agglutinin-like sequence (Als) proteins in human oral epithelial cell interactions. PLoS One 2012; 7:e33562; PMID:22428031; http://dx.doi.org/10.1371/journal.pone.0033562.

44. Nobiale CJ, Schneider HA, Nett JE, Sheppard DC, Fuller SG, Andes DR, et al. Complementary adhesion function in C. albicans biofilm formation. Curr Biol 2008; 18:1017-24; PMID:18635588; http://dx.doi.org/10.1016/j.cub.2007.09.034.

45. Zbudziak F, Wächter B, Cutler JE, Staab JF, et al. The role of the hyphal-associated adhesion and invasion Als1 of Candida albicans mediates iron acquisition from host ferritin. PLoS Pathog 2008; 4:e1000217; PMID:19025418; http://dx.doi.org/10.1371/journal.ppat.1000217.

46. Garcia MC, Lee JT, Ramsook CB, Alsteens D, Dufrêne EC. A role for cell microtubules in the regulation of Candida albicans hyphal formation. Cell Microbiol 2010; 12:273-82; PMID:19919567; http://dx.doi.org/10.1111/j.1462-8802.2009.01412.x.

47. Park H, Myers CL, Sheppard DC, Phan QT, Sanchez AA, E. Edwards JE, et al. Role of the fungal Ras-protein kinase A pathway in governing epithelial-cell interactions during oopharyngeal candidiasis. Cell Microbiol 2005; 7:499-510; PMID:15760450; http://dx.doi.org/10.1111/j.1462-8802.2004.00476.x.

48. Sun JN, Solis NV, Phan QT, Bajwa JS, Kashleva H, Thompson A, et al. Calcium signaling and virulence mediated by Candida albicans Hwp1. Science 1999; 283:1535-40; PMID:10499848; http://dx.doi.org/10.1126/science.283.5407.1535.
74. Theiss S, Ishdorj G, Brenton A, Kretschmar M, Lan CY, Nietlicher 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; PMID:16761460; http://dx.doi.org/10.1016/j.ijmm.2006.03.003.

75. Fu Y, Ibrahim AS, Fonzi W, Zhou X, Ramos CF, Gánca A, Stehr F, Kröger C, Kredics L, Schäfer W, Hube B, Stehr F, Bossenz M, Mazur A, Kretschmar M, Yuan X, Mitchell BM, Hua X, Davis DA, Wilhelmus KR. The RIM101 signal transduction pathway regulates virulence. Int J Med Microbiol 2006; 296:405-20; PMID:16761460; http://dx.doi.org/10.1016/j.ijmm.2006.04.007.

76. Hube B, Stehr F, Bossenz M, Mazur A, Kretschmar M, Schaller M, Filler G, Nosanchuk JD. Lipase \( \text{PHR1} \) affects the pathogenesis of Candida albicans. Infect Immun 2000; 174:362-74; PMID:11131027; http://dx.doi.org/10.1128/iai.74.3.362-374.2000.

77. Gácser A, Stehr F, Kogler G, Kredics L, Schafer W, Nosanchuk JD. Lipase \( \text{PHR2} \) of Candida albicans encode putative glycosidases required for proper cross-linking of beta-1,3- and beta-1,6-glucans. J Bacteriol 1999; 181:7070-9; PMID:10559174.

78. Mikhailcheg F, Fossini WA, PHR2 of Candida albicans encodes a functional homolog of the pH-regulated gene \( \text{PHR1} \) with an inverted pattern of pH-dependent expression. Mol Cell Biol 1997; 17:5960-7; PMID:9315694.

79. Thewes S, Kretschmar M, Park H, Lorenz MC, Bender JA, Fink GR. Transcriptional response of Candida albicans upon internalization by macrophages. Eukaryot Cell 2004; 3:1076-87; PMID:15492540; http://dx.doi.org/10.1128/EC.3.5.1076-1087.2004.

80. Gómez S, Navarathna DH, Roberts DB, Cooper JT, Arkin AL, Petro TM, et al. Arginine-induced germ tube formation in Candida albicans is essential for escape from murine macrophage line RAW 264.7. Infect Immun 2009; 77:1596-605; PMID:19188839; http://dx.doi.org/10.1128/IAI.01452-08.

81. Ene IV, Adya AK, Weinheier S, Brand AC, MacCallum DM, Gow NA, et al. Host carbon sources modulate cell wall architecture, drug resistance and virulence in a fungal pathogen. Cell Microbiology 2012; 14:1319-35; PMID:22587014; http://dx.doi.org/10.1111/j.1462-5822.2012.01813.x.

82. Lorenz MC, Fink GR. The glycolytic cycle is required for fungal virulence. Nature 2001; 412:83-6; PMID:11452311; http://dx.doi.org/10.1038/35083594.

83. Wysong DR, Christlin L, Sugar AM, Robbins PW, Diamond RD. Cloning and sequencing of a Candida albicans catalase gene and effects of disruption of this gene. Infect Immun 1996; 66:1993-6; PMID:9573857.

84. Hwang CS, Rhie GE, Oh JH, Huh WK, Yim HS, Cho JG, et al. The fungal pathogen Candida albicans encodes a functional homolog of the pH-regulated transcription factor \( \text{YHB1} \) and virulence of Candida albicans in nitrosative stress and virulence. YHB1 is required for host-pathogen interactions. Infect Immun 2007; 75:4710-22; PMID:17646357; http://dx.doi.org/10.1128/mBio.00055-11.

85. Zhan H, Chu HJ, Yang ZW, Cheng Z, Ge X, Liu M, et al. Mitogen-activated protein kinase Hog1p in morphogenesis and virulence of Candida albicans. J Bacteriol 1999; 181:3058-68; PMID:10522006.

86. Caekebeke SC, Schoutep K, Lebere E, Harcus D, Mohamed O, Meloche S, et al. Roles of the Candida albicans mitogen-activated protein kinase homolog, Cek1p, in hyphal development and systemic candidiasis. Infect Immun 1998; 66:2713-21; PMID:9395738.

87. Lindquist S. Heat-shock proteins and stress tolerance in microorganisms. Curr Opin Genet Dev 1992; 2:748-55; PMID:1458023; http://dx.doi.org/10.1006/s1539-437X(05)80135-2.

88. Alonso-Monge R, Navarro-García F, Molero G, Diez-Orejas R, Gustin M, Pla J, et al. Role of the mitogen-activated protein kinase Ssk1p in Candida albicans. Mol Biol Cell 2005; 16:4814-26; PMID:16030247; http://dx.doi.org/10.1128/mBio.00055-11.

89. Alonso-Monge R, Navarro-García F, Molero G, Diez-Orejas R, Gustin M, Pla J, et al. Role of the mitogen-activated protein kinase Ssk1p in Candida albicans. Mol Biol Cell 2005; 16:4814-26; PMID:16030247; http://dx.doi.org/10.1128/mBio.00055-11.

90. Brock M. Fungal metabolism in host niches. Curr Opin Microbiol 2009; 12:371-6; PMID:19385543; http://dx.doi.org/10.1016/j.molcel.2010.10.006.

91. Bok A, Pinczyński S, Czuchra A, Pluta S, Bacusa R, Köhler K, et al. The heat-induced molecular disaggregate Hop14 of Candida albicans plays a role in biofilm formation and pathogenicity in a worm infection model. Eukaryot Cell 2012; 11:1012-20; PMID:22563920; http://dx.doi.org/10.1128/EC.00147-12.

92. Congen LE, Singh SD, Kohler JR, Collins C, Zas AK, Schwel WA, et al. Harnessing Hsp90 function as a powerful, broadly effective therapeutic strategy for fungal infectious disease. Proc Natl Acad Sci U S A 2009; 106:2628-33; PMID:19190673; http://dx.doi.org/10.1073/pnas.0813934106.

93. Lafayette SL, Collins C, Zas AK, Schwel WA, Betancourt-Quiruoza M, Gunaratika AA, et al. PKC signal-regulating drug resistance of the fungal pathogen Candida albicans via circuitry comprised of Mek1, calcineurin, and Hsp90. PLoS Pathog 2010; 6:e1001069; PMID:20865172; http://dx.doi.org/10.1371/journal.ppat.1000106.

94. Shapiro RS, Upaduri P, Zas AK, Collins C, Senn H, Perfect JR, et al. Hsp90 orchestrates temperature-independent Candida albicans morphogenesis via Ria-PKA signaling. Curr Biol 2009; 19:621-9; PMID:19327993; http://dx.doi.org/10.1016/j.cub.2009.03.017.

95. Singh SD, Robbins N, Zas AK, Schwel WA, Perfect JR, Congen LE. Hsp90 governs echinocandin resistance in the pathogenic yeast Candida albicans via calcineurin. PLoS Pathog 2009; 5:e1000532; PMID:19649312; http://dx.doi.org/10.1371/journal.ppat.1000532.

96. Li XS, Reddy MS, Bae D, Edgerton M. Candida albicans Sas12p is the cell envelope binding protein for human salivary histatin 5. J Biol Chem 2003; 278:25553-61; PMID:12761219; http://dx.doi.org/10.1074/jbc.M300608200.

97. Li XS, Sun JN, Okamoto-Shibayama K, Edgerton M. Candida albicans Sas12p is a cell envelope binding protein for human salivary histatin 5. J Biol Chem 2003; 278:25553-61; PMID:12761219; http://dx.doi.org/10.1074/jbc.M300608200.

98. Cooper JE Jr, Watanabe M, Ayer WA. The pH of the host niche controls gene expression and differences in substrate utilization. Int J Med Microbiol 2009; 298:561-74; PMID:19095643; http://dx.doi.org/10.1016/j.ijmm.2009.04.007.

99. Davis DA. How human pathogenic fungi sense and adapt to pH: the link to virulence. Curr Opin Microbiol 2002; 5:467-70; PMID:12632443; http://dx.doi.org/10.1016/S0959-437X(05)80135-2.
117. Leach MD, Sted DA, Argo E, Brown AJ. Identification of sumoylation targets, combined with inactivation of SMT3, reveals the impact of sumoylation upon growth, morphology, and stress resistance in the pathogen Candida albicans. Mol Biol Cell 2011; 22:687-702; PMID:21209135; http://dx.doi.org/10.1091/mbc.E10-07-0632.

118. Sorger PK, Pelham HR. Purification and characterization of a heat-shock element binding protein from yeast. EMBO J 1987; 6:3035-41; PMID:3319580.

119. Sorger PK, Pelham HR. Yeast heat shock factor is an essential DNA-binding protein that exhibits temperature-dependent phosphorylation. Cell 1988; 54:855-64; PMID:3044613; http://dx.doi.org/10.1016/S0092-8674(88)91219-6.

120. 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; PMID:22064682; http://dx.doi.org/10.1093/nar/gkr945.

121. Narberhaus F. Alpha-crystallin-type heat shock proteins: socializing minichaperones in the context of a multichaperone network. Microbiol Mol Biol Rev 2002; 66:64-93; PMID:11875128; http://dx.doi.org/10.1128/MMBR.66.1.64-93.2002.

122. Halbeek M, Walke S, Storzer T, Ehrupeger M, White HE, Chen S, et al. Hsp26: a temperature-regulated chaperone. EMBO J 1999; 18:6744-51; PMID:10581247; http://dx.doi.org/10.1093/emboj.18.23.6744.

123. Eyles SJ, Gierasch LM. Nature’s molecular sponges: small heat shock proteins grow into their chaperone roles. Proc Natl Acad Sci U S A 2010; 107:2727-8; PMID:20313678; http://dx.doi.org/10.1073/pnas.0915160107.

124. Cashikar AG, Duennwald M, Lindquist SL. A chaperone pathway in protein disaggregation. Hsp26 alters the nature of protein aggregates to facilitate refolding by Hsp104. J Biol Chem 2005; 280:23869-75; PMID:15845555; http://dx.doi.org/10.1074/jbc.M502854200.

125. Fu MS, De Sordi L, Mulhchlele FA. Functional characterization of the small heat shock protein Hsp12p from Candida albicans. PLoS One 2012; 7:e42894; http://dx.doi.org/10.1371/journal.pone.0042894.

126. Hood MI, Skaar EP. Nutritional immunity: transition metals at the pathogen-host interface. Nat Rev Microbiol 2012; 10:525-37; PMID:22796883; http://dx.doi.org/10.1038/nrmicro2836.

127. Almeida RS, Wilson D, Hube B. Candida albicans iron acquisition within the host. FEMS Yeast Res 2009; 9:1000-12; PMID:19788558; http://dx.doi.org/10.1111/j.1567-1364.2009.00570.x.

128. 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; PMID:22064682; http://dx.doi.org/10.1093/nar/gkr945.

129. Leach MD, Sted DA, Argo E, Brown AJ. Identification of sumoylation targets, combined with inactivation of SMT3, reveals the impact of sumoylation upon growth, morphology, and stress resistance in the pathogen Candida albicans. Mol Biol Cell 2011; 22:687-702; PMID:21209135; http://dx.doi.org/10.1091/mbc.E10-07-0632.

130. Weissman Z, Kornitzer D. A family of Candida cell surface haem-binding proteins involved in haem and haemoglobin-iron utilization. Mol Microbiol 2004; 53:1209-20; PMID:15306022; http://dx.doi.org/10.1111/j.1365-2958.2004.04199.x.

131. Braun BR, Head WS, Wang MX, Johnson AD. Identification and characterization of TUP1-regulated genes in Candida albicans. Genetics 2000; 156:31-44; PMID:10978273.

132. Citiulo F, Jacobsen ID, Miramón P, Schild L, Brunke S, Zipfel P, et al. Candida albicans scavenges host zinc via Pral during endothelial invasion. PLoS Pathog 2012; 8:e1002777; PMID:22761575; http://dx.doi.org/10.1371/journal.ppat.1002777.

133. Soloviev DA, Jawhara S, Fonzi WA. Regulation of innate immune response to Candida albicans infections by αMβ2-Pra1p interaction. Infect Immun 2011; 79:1546-58; PMID:21245270; http://dx.doi.org/10.1128/IAI.00650-10.

134. Marvin ME, Williams PH, Cashmore AM. The Candida albicans CTR1 gene encodes a functional copper transporter. Microbiology 2003; 149:1461-74; PMID:12777486; http://dx.doi.org/10.1099/mic.0.26172-0.

135. Gauwerky K, Borelli C, Korting HC. Targeting virulence: a new paradigm for antifungals. Drug Discov Today 2009; 14:214-22; PMID:19152839; http://dx.doi.org/10.1016/j.drudis.2008.11.013.

136. Cashikar AG, Duennwald M, Lindquist SL. A chaperone pathway in protein disaggregation. Hsp26 alters the nature of protein aggregates to facilitate refolding by Hsp104. J Biol Chem 2005; 280:23869-75; PMID:15845555; http://dx.doi.org/10.1074/jbc.M502854200.

137. Leach MD, Sted DA, Argo E, Brown AJ. Identification of sumoylation targets, combined with inactivation of SMT3, reveals the impact of sumoylation upon growth, morphology, and stress resistance in the pathogen Candida albicans. Mol Biol Cell 2011; 22:687-702; PMID:21209135; http://dx.doi.org/10.1091/mbc.E10-07-0632.

138. Weissman Z, Kornitzer D. A family of Candida cell surface haem-binding proteins involved in haem and haemoglobin-iron utilization. Mol Microbiol 2004; 53:1209-20; PMID:15306022; http://dx.doi.org/10.1111/j.1365-2958.2004.04199.x.

139. Braun BR, Head WS, Wang MX, Johnson AD. Identification and characterization of TUP1-regulated genes in Candida albicans. Genetics 2000; 156:31-44; PMID:10978273.

140. Citiulo F, Jacobsen ID, Miramón P, Schild L, Brunke S, Zipfel P, et al. Candida albicans scavenges host zinc via Pral during endothelial invasion. PLoS Pathog 2012; 8:e1002777; PMID:22761575; http://dx.doi.org/10.1371/journal.ppat.1002777.

141. Soloviev DA, Jawhara S, Fonzi WA. Regulation of innate immune response to Candida albicans infections by αMβ2-Pra1p interaction. Infect Immun 2011; 79:1546-58; PMID:21245270; http://dx.doi.org/10.1128/IAI.00650-10.

142. Marvin ME, Williams PH, Cashmore AM. The Candida albicans CTR1 gene encodes a functional copper transporter. Microbiology 2003; 149:1461-74; PMID:12777486; http://dx.doi.org/10.1099/mic.0.26172-0.

143. Gauwerky K, Borelli C, Korting HC. Targeting virulence: a new paradigm for antifungals. Drug Discov Today 2009; 14:214-22; PMID:19152839; http://dx.doi.org/10.1016/j.drudis.2008.11.013.