

From Genes to Networks: The Regulatory Circuitry Controlling *Candida albicans* Morphogenesis



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Abstract *Candida albicans* is a commensal yeast of most healthy individuals, but also one of the most prevalent human fungal pathogens. During adaptation to the mammalian host, *C. albicans* encounters different niches where it is exposed to several types of stress, including oxidative, nitrosative (e.g., immune system),

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osmotic (e.g., kidney and oral cavity) stresses and pH variation (e.g., gastrointestinal (GI) tract and vagina). *C. albicans* has developed the capacity to respond to the environmental changes by modifying its morphology, which comprises the yeast-to-hypha transition, white-opaque switching, and chlamydo-spore formation. The yeast-to-hypha transition has been very well characterized and was shown to be modulated by several external stimuli that mimic the host environment. For instance, temperature above 37 °C, serum, alkaline pH, and CO₂ concentration are all reported to enhance filamentation. The transition is characterized by the activation of an intricate regulatory network of signaling pathways, involving many transcription factors. The regulatory pathways that control either the stress response or morphogenesis are required for full virulence and promote survival of *C. albicans* in the host. Many of these transcriptional circuitries have been characterized, highlighting the complexity and the interconnections between the different pathways. Here, we present the major signaling pathways and the main transcription factors involved in the yeast-to-hypha transition. Furthermore, we describe the role of heat shock transcription factors in the morphogenetic transition, providing an edifying example of the complex cross talk between pathways involved in morphogenesis and stress response.

1 Introduction

Fungal pathogens have become responsible for increasing mortality in humans over the past four decades. In developed countries, fungal infections appear as one of the primary causes of hospital-acquired infections, most of them caused by *Candida* spp.—particularly *Candida albicans*. *Candida* infections range from mild superficial infections to life-threatening invasive infections. Despite the use of antifungals and other therapeutic approaches, *Candida* infections remain associated with a high mortality rate (Kullberg and Arendrup 2016; Pfaller and Diekema 2007).

Numerous studies have shown that morphogenesis is tightly linked to the ability of *C. albicans* to cause disease. Although *C. albicans* displays an extended array of morphological transitions (e.g., chlamydo-spore formation, GUT phenotype, white-opaque switching, gray phenotype), the yeast-to-hypha transition appears to be an important virulence trait (Brown and Gow 1999; Gow et al. 2002; Mukaremera et al. 2017; Nemecek et al. 2006; Peters et al. 2014; Rooney and Klein 2002; Trevijano-Contador et al. 2016). Therefore, particular interest was given to the mechanisms of transition between the unicellular yeast form and either pseudohyphal or hyphal forms, often referred to as filamentous forms (Odds 1987; Sudbery et al. 2004). For instance, the yeast form is required for dissemination into the bloodstream (Bendel et al. 2003; Saville et al. 2003) and adhesion to endothelial cells (Grubb et al. 2009; Yang et al. 2014). In contrast, the filamentous form is needed for tissue invasion and for escaping from immune cells, yielding resistance toward phagocytosis (Erwig and Gow 2016; Fradin et al. 2005; Lorenz et al. 2004; Rooney and Klein 2002).

In this review, we summarize the major signaling pathways that regulate the morphogenetic transition between unicellular yeast form and filamentous forms. We report the differences between *C. albicans* and the model organism *Saccharomyces cerevisiae*, highlighting specific features of *C. albicans* related to morphogenesis and the associated cellular stress response.

2 Stimuli Inducing the Yeast-to-Hypha Transition

The yeast-to-hypha transition is triggered by different environmental cues that reflect the host environment, such as nutrient starvation, N-acetyl glucosamine (GlcNAc), serum, CO₂ levels, neutral pH, temperature, and surface contact. In laboratory conditions, several media are used to mimic these environmental cues, such as GlcNAc-containing medium or Spider medium (Liu et al. 1994; Mattia et al. 1982). However, the most widely used inducer of morphogenesis is serum (Ernst 2000; Gow 1997), whose complex composition makes difficult the identification of the factor(s) responsible for filamentation. Early studies have shown that CO₂ is an inducer of *C. albicans* morphogenesis (Persi et al. 1985) and that physiological CO₂ levels are essential for *C. albicans* pathogenicity (Klengel et al. 2005). Filamentation is favored by pH values close to neutral, but is considerably reduced at pH lower than 6, while the yeast form is predominant at pH 4 (Buffo et al. 1984). High temperatures also promote filamentation via the molecular chaperone Hsp90 (O'Meara et al. 2017; Shapiro et al. 2009) and the transcription factor (TF) Sfl2 (Song et al. 2011). Finally, surface growth triggers several behaviors, such as invasion, thigmotropism, and biofilm formation (Kumamoto 2005; Kumamoto 2008; Kumamoto and Vines 2005).

The yeast-to-hypha transition is also influenced by quorum sensing molecules, such as homoserine lactone (HSL), the 12-carbon backbone molecule dodecanol, farnesol, and tyrosol (Chen et al. 2004; Hogan et al. 2004). These compounds block the hyphal transition by the Ras-cAMP-PKA pathway and impact on cAMP-controlled genes involved in morphogenesis and stress response (Davis-Hanna et al. 2008). In the host, HSL, dodecanol, and farnesol are secreted by bacteria, such as *Pseudomonas aeruginosa*, and regulate *C. albicans* morphogenesis through independent mechanisms (Hall et al. 2011). Additionally, farnesol is produced by *C. albicans* as a by-product of ergosterol biosynthesis (Hornby et al. 2003) and affects many physiological functions, including cell wall maintenance, iron transport and the regulation of genes encoding heat shock proteins (Hsps) (Cao et al. 2005). Recently, it has been reported that farnesol's effect on hyphal morphogenesis is linked to *EED1* gene (see below), since an *eed1* null mutant is hypersensitive to this molecule (Polke et al. 2017). Farnesol and HSL inhibit the activity of the adenylate cyclase (AC) Cyr1, and several evidences suggest that farnesol acts downstream of Ras1 (Feng et al. 1999). On the other hand, dodecanol modulates filamentation and cAMP signaling without affecting AC activity, but through a mechanism involving the transcription factor Sfl1 (Hall et al. 2011), while tyrosol is

continuously released into the culture medium by *C. albicans* itself in order to promote germ tube formation (Chen et al. 2004). Finally, several alcohols, such as amyl alcohol, have been shown to inhibit the yeast-to-hypha morphological transition in a dose-dependent manner (Chauhan et al. 2013).

3 Hypha-Associated Genes (HAGs) and Chromatin Remodeling

The genes induced during hyphal formation have been referred to as hypha-specific genes (HSGs), in contrast to genes involved during yeast growth—yeast-specific genes (YSGs). However, it has been shown that HSGs can also be expressed by yeast cells under certain conditions (Fradin et al. 2005) and that hyphal growth does not require the induction of all HSGs (Naseem et al. 2015); thus, they can be referred to as hypha-associated genes (HAGs). During the morphogenetic transition, HAGs are under the control of several TFs, such as Efg1, Tec1, Nrg1, Tup1, Rim101, Bcr1, and Rfg1 (Eckert et al. 2007; Whiteway and Bachewich 2007). During the yeast-to-hypha morphogenetic transition, Efg1 interacts with the histone acetyltransferase (HAT) NuA4 leading to an increase in histone H4 acetylation at the promoter of HAGs (Lu et al. 2008). The Hos2/Set3 histone deacetylase complex (HDAC) acts as a regulator of hyphal development through the cAMP-PKA pathway (Hnisz et al. 2010) and modulates the expression levels of the transcription regulators *BRG1*, *TEC1*, *NRG1*, and *EFG1*, acting as both repressor and activator (Hnisz et al. 2012). The GATA family TF Brg1 recruits Hda1 to the promoter of HAGs leading to chromatin modifications that prevent the binding of the repressor Nrg1 (Lu et al. 2012; see below).

The Swi/Snf chromatin remodeler complex has been reported to bind to the promoters of HAGs only in hyphae, and this binding is mediated by Efg1 (Lu et al. 2008). Thus, Efg1 recruits NuA4 to the HAGs' promoters, allowing in turn the recruitment of the Swi/Snf complex in order to activate transcription during the morphogenetic transition (Lu et al. 2008). Moreover, deletion of *SWI/SNF* or other subunits of the complex, such as Snf6, prevents hyphal growth; a *swi1* deletion strain is defective in HAGs expression and is avirulent in a mouse model of systemic infection (Mao et al. 2006; Tebbji et al. 2017).

HAGs form a large group of virulence factors that contribute to pathogenesis. These factors are molecules recognized by the host, such as cell wall proteins (adhesins) and hydrolytic enzymes that contribute to penetration and tissue damage within the host (Hiller et al. 2011). In a reconstituted human epithelium (RHE) model, the expression levels of HAGs increased within 30 min after inoculation, leading to cellular damage (Hiller et al. 2011; Spiering et al. 2010).

In order to penetrate the host tissues, *C. albicans* produces hydrolytic enzymes, such as phospholipases, lipases, and secreted aspartyl proteinases (SAPs). Genes encoding Sap4, Sap5, and Sap6 were shown to be among the most upregulated

HAGs induced by serum and elevated temperature, together with genes encoding a cell wall mannoprotein (*HWPI*), required for hyphal development and yeast adhesion to epithelium, and the adhesin-like protein 3 (*ALS3*) (Nantel et al. 2002). The agglutinin-like sequence (ALS) family is composed of glycosylphosphatidylinositol (GPI)-anchored proteins encoded by eight genes (*ALS1-7* and *ALS9*). Among them, *ALS3* is the best studied and behaves both as an adhesin and as an invasin. As an adhesin, it mediates the attachment to epithelial and endothelial cells, and to extracellular matrix; as an invasin, it binds to the E-cadherin and N-cadherin host receptors, inducing endocytosis (Phan et al. 2007). Further, *C. albicans* can use ferritin as a source of iron and Als3 is involved in this process. It has been proposed that *C. albicans*—in its hyphal form—can bind ferritin by Als3, iron release is then facilitated by acidification of the environment, and uptake is promoted by the reductive pathway (Almeida et al. 2008). Among the HAGs, extent of cell elongation 1 (*ECE1*) was identified in a screen of yeast and hyphal cells (Birse et al. 1993). Its expression was not detected in yeast, but within 30 min after hyphal induction. However, despite the association between *ECE1* expression levels and morphogenesis, *ece1* null mutants are not defective for filamentation, showing that *ECE1* is not essential for this process (Birse et al. 1993). Recently, it was shown that Ece1 is critical for epithelial damage and *C. albicans* recognition by the immune system and that *ECE1* encodes a cytolytic peptide toxin, called “Candidalysin,” secreted during infection. *C. albicans* strains lacking this toxin are avirulent in an oropharyngeal candidiasis (OPC) mouse model (Moyes et al. 2016). Hyphal G cyclin 1 (*HGC1*) is another HAG that encodes a cyclin involved in the cell-cycle regulation that plays a role in polarized growth and represses cell separation of hyphae. Mutants lacking *HGC1* are defective for filamentation, but the constitutive expression of *HGC1* is not sufficient to activate morphogenesis (Zheng et al. 2004). Furthermore, the TF Ume6 has a role in *HGC1* regulation, since the *HGC1* expression levels are significantly reduced in *ume6* deletion strains, although there is no evidence of a direct regulation mechanism (Fan et al. 2013).

Morphogenesis is important for the ability of *C. albicans* to cause disease, even if it could be uncoupled to some extent from virulence based on the observation from large-scale studies (Noble et al. 2010; Perez et al. 2013) that some genes that have a role in infectivity do not have an obvious role in morphology and vice versa. Nevertheless, in these large-scale studies, filamentation was tested in only one condition (solid Spider medium), and virulence was only tested in a mouse model of systemic infection (Noble et al. 2010). Therefore, the exact correlation between morphology and virulence remains to be fully appreciated in order to define those factors that contribute independently or simultaneously to these two processes. Yet, the regulation of morphogenesis is critical for *C. albicans* virulence and a detailed understanding of the molecular pathways that regulate the yeast-to-hypha transition will provide important insights into new therapeutic strategies.

4 Morphogenetic Transition: Major Signaling Pathways

Morphogenesis in *C. albicans* is promoted mainly by the cAMP-PKA and the mitogen-activated protein kinase (MAPK) pathways described below. However, other signaling pathways such as the target of rapamycin (TOR) and regulation of Ace2 morphogenesis (RAM) pathways are known to regulate morphogenesis in certain environmental conditions, such as matrix embedding and pH responses (Fig. 1).

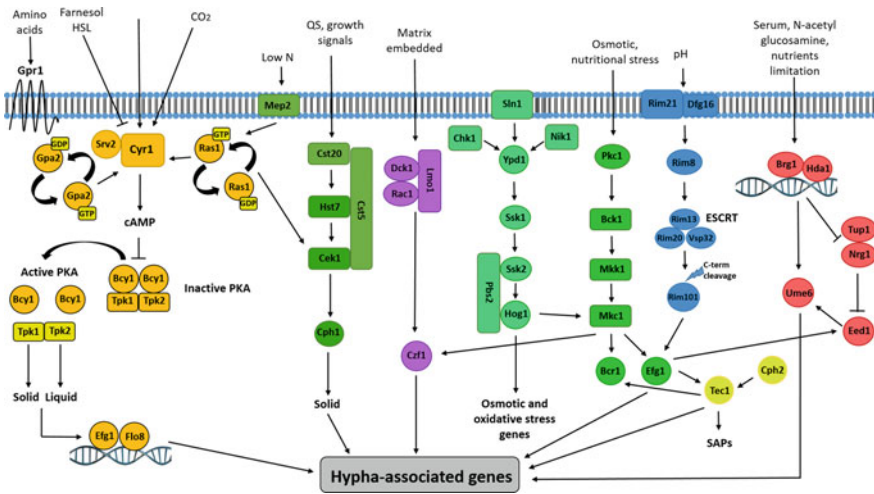


Fig. 1 Major signaling pathways of *C. albicans* morphogenesis. Several environmental factors are known to activate the yeast-to-hypha transition by affecting different components of the represented pathways. The signaling cascades lead to the activation of transcription factors, such as Efg1, Flo8, Cph1, Czf1, Bcr1, and Ume6 that directly influence the expression of hypha-associated genes. Some of these transcription factors are activated in very specific conditions. For instance, Rim101 cleavage and subsequent activation depend on the environmental pH (blue); Czf1 and Cph1 enhance filamentation in matrix-embedded conditions (purple) and on solid media (dark green), respectively. The cAMP-PKA pathway is represented in orange; the adenylate cyclase Cyr1 is directly activated by serum and CO₂. Ras1 activated state also stimulates AC activity, as well as proline and methionine through Gpr1 and Gpa2. Cyr1 associates with Srv2 to increase the intracellular levels of cAMP. cAMP binds to the regulatory subunit of the PKA Bcy1 with the subsequent release of the catalytic subunits Tpk1 and Tpk2, which regulate filamentation in solid and liquid media, respectively. The MAPK pathways are represented in green. The Cek1 pathway leads to the activation of Cph1, the Hog1 pathway whose role in filamentation has not been clarified yet, is involved in the osmotic and oxidative stress response, and the Mkk1 pathway activates several transcription factors, such as Czf1, Bcr1, and Efg1. Activation of the transcription factor Tec1 depends on Cph2 (in yellow) and takes to the SAPs expression, important for virulence. Finally, several stimuli induce the expression of Brg1 (in red), which is recruited at the promoter of HAGs and, together with Hda1, occlude the binding of Nrg1, which represses transcription in a Tup-1-dependent manner. Among the genes subsequently expressed, there is *UME6*, whose expression depends also on the transcription factor Eed1

The cAMP-PKA pathway. The cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) pathway is well conserved across eukaryotes and regulates many cellular processes in fungi. PKA is a heterotetramer consisting of two regulatory subunits that bind and inactivate two catalytic subunits. cAMP activates PKA by a conformational change that occurs upon binding. The cAMP intracellular levels are controlled by the AC Cyr1, which synthesizes cAMP from ATP, and by phosphodiesterases, which in contrast hydrolyze cAMP. AC activity is controlled by G protein-coupled receptors. There are two classes of G proteins: the monomeric small GTPases and the heterotrimeric G protein complexes, consisting of three subunits, namely α , β , and γ . Both G protein types are activated upon GTP binding and inactivated when GDP is bound. The exchange between GDP and GTP is catalyzed by GTPase-activating proteins (GAPs) or guanine exchange factors (GEFs).

In *S. cerevisiae*, the cAMP-PKA pathway is required as the major intermediate by which glucose or other nutrients regulate the cell cycle (Colombo et al. 2017; Fuller and Rhodes 2012). Furthermore, it is involved in pseudohyphal differentiation in response to nitrogen starvation and requires Gpr1, a seven-transmembrane-spanning receptor able to bind glucose (Lorenz et al. 2000), which activates the homolog of the mammalian G- α subunit, Gpa2 (Kubler et al. 1997; Lorenz and Heitman 1997). This signaling culminates in the activation of the TFs Flo8 and Sfl1 (Pan and Heitman 2002). In nitrogen starvation conditions, Gpr1 binds to Gpa2 (Harashima and Heitman 2005; Xue et al. 1998) leading to the activation of cAMP production through the AC Cyr1 (also called Cdc35) upon glucose induction (Colombo et al. 1998; Kraakman et al. 1999; Lorenz et al. 2000). α -Gpa2 does not form a heterotrimeric complex with the known yeast G $\beta\gamma$ subunits Ste4/18, but with Gpb1/2 and Gpg1 proteins (Harashima and Heitman 2005; Kraakman et al. 1999).

Furthermore, the G protein Ras2 can activate cAMP generation by Cyr1 (Minato et al. 1994). In fungi, Ras signaling has been associated to cell shape (Cullen and Sprague 2012), stress response (de la Torre-Ruiz et al. 2010), mating (Alspaugh et al. 2000), and nutrient sensing (Broach 2012). In *S. cerevisiae*, the role of Ras1 and Ras2 is not totally clear: current model suggests that low-level sugar phosphorylation activates the Ras-mediated localization of Cyr1 to the plasma membrane, where Gpr1-Gpa2 can trigger the signaling (Colombo et al. 2004; Thevelein and de Winde 1999). In contrast, Pde1 and Pde2, respectively low- and high-affinity cAMP phosphodiesterases, negatively regulate cAMP levels (Hu et al. 2010; Ma et al. 1999). PKA comprises a single regulatory subunit, Bcy1 (or Sra1) (Toda et al. 1987), and three catalytic subunits Tpk1, Tpk2, and Tpk3 (Toda et al. 1987). The Tpk2 subunit activates pseudohyphal differentiation, whereas Tpk1 and Tpk3 play a negative role, inhibiting filamentous growth (Pan and Heitman 1999; Robertson and Fink 1998). Tpk2 mediates the binding of the TF Flo8 and inhibits the binding of the negative regulator Sfl1 to the promoter of the *FLO11* gene, which encodes a GPI-anchored cell surface adhesin (Kobayashi et al. 1996; Rupp et al. 1999), through Flo8 and Sfl1 phosphorylation (Pan and Heitman 2002).

In *C. albicans*, the cAMP-PKA pathway mediates different cellular processes, such as cell-cycle regulation and stress response (Cao et al. 2017; Giacometti et al. 2009), but it is one of the major pathways that positively regulate filamentation, involving the TFs Efg1 and Flo8 (Bockmuhl and Ernst 2001; Cao et al. 2006) (Fig. 1). Indeed, reduced activity of PKA results in defects in filamentation (Bockmuhl et al. 2001; Sonneborn et al. 2000), and a *flo8* deletion mutant is blocked in filamentation and in the expression of HAGs, leading to avirulence in a mouse model of systemic infection (Cao et al. 2006). Many factors have been described that activate filamentation through this pathway. For instance, amino acids such as proline or methionine stimulate hyphal growth via Gpr1 and Gpa2 (Maidan et al. 2005; Miwa et al. 2004). CO₂ also activates AC by directly stimulating Cyr1 catalytic domain (Klengel et al. 2005; Parrino et al. 2017). Furthermore, serum strongly induces filamentation through the muramyl peptide, which binds to Cyr1 and stimulates AC activity (Xu et al. 2008). The cAMP levels are negatively regulated by the phosphodiesterases Pde1 and Pde2, as reported in *S. cerevisiae* (Hoyer et al. 1994; Jung and Stateva 2003). Ras1 is activated by the GAP Csc25 (also known as Cdc25). The Ras1 active state stimulates the AC activity of Cyr1, which interacts with the AC-associated protein Srv2 (also known as cyclase-associated protein Cap1) in order to increase the intracellular cAMP levels (Fig. 1). Cyr1 physically interacts with Ras1 through the Ras association (RA) domain in the presence of serum (Fang and Wang 2006). The increased cAMP binds to Bcy1 leading to the release of the two PKA catalytic subunits encoded by *TPK1* and *TPK2* (there is no Tpk3 in *C. albicans*). Either Tpk1 or Tpk2 can activate TFs such as Efg1, by phosphorylation (Bockmuhl and Ernst 2001) (Fig. 1). Both subunits have been linked to different cues: Tpk1 is reported to be critical for hyphal development on solid-inducing medium, while Tpk2 has a role in filamentation only in liquid medium (Bockmuhl et al. 2001). Although the mechanisms that activate Ras1-mediated hyphal growth are not fully understood, it is known that incubation at 37 °C induces filamentous growth through the molecular chaperone Hsp90, which has an important role in the regulation of Ras1 and AC activity in response to temperature. However, Hsp90 works via effectors downstream of PKA and distinct from Efg1 (Shapiro et al. 2009).

The Ras-cAMP-PKA pathway has been involved in virulence (Bahn et al. 2003; Hogan and Sundstrom 2009; Leberer et al. 2001). For instance, Tpk2 is required for germination and engulfment in epithelial cells and for virulence in a mouse model of OPC (Sanchez AA 2005). This pathway regulates Efg1, which is considered as the major regulator of the morphogenetic transition in *C. albicans* (Braun and Johnson 2000). *EFG1* encodes a basic helix-loop-helix (bHLH) TF that belongs to the APSES family of fungus-specific regulators (Doedt et al. 2004). The role of Efg1 in filamentation is complex: Loss of *EFG1* results in a defect in filamentation under hypha-inducing conditions (Lo et al. 1997); however, under microaerophilic or embedded conditions, hyphal development is normal in an *efg1* deletion strain (Giusani et al. 2002). Therefore, under hypoxic conditions, Efg1 functions as a repressor of hyphal growth on agar at temperatures below 35 °C (Setiadi et al. 2006), while under normoxia, Efg1 is a strong inducer of hyphal growth (Lo et al.

1997; Stoldt et al. 1997). The hypoxic repressor function is mediated by modifications at the Efg1 N-terminus (Desai et al. 2015). Genome-wide chromatin immunoprecipitation (ChIP) analysis showed that the promoter regions bound by Efg1 in yeast-form cells are different from those bound in hyphal cells (Lassak et al. 2011). These evidences suggest a double role for Efg1, either as a repressor or as an activator of filamentation, depending on the environmental cues. Indeed, while in a model of systemic bloodstream infection (increased oxygen levels) the *efg1* mutant was much less virulent than the WT (Bendel et al. 2003; Lo et al. 1997), in hypoxic niches, as in the mouse gut, the *efg1* mutant was hyperproliferative (Pande et al. 2013; White et al. 2007). Additionally, it was reported that the changes in *EFG1* expression, depending on histone modifying enzymes, are important to allow *C. albicans* to better adapt in the host, establishing optimal survival strategies (Tyc et al. 2016). A transcriptomic analysis showed an overlap between the targets of Flo8 and Efg1, and a physical interaction between these two proteins was demonstrated (Cao et al. 2006).

The MAPK pathways. The mitogen-activated protein kinase (MAPK) signal transduction pathway comprises a conserved module of three kinases: the MAP kinase kinase kinase (MAPKKK), the MAP kinase kinase (MAPKK), and the MAP kinase (MAPK). The signaling depends on three phosphotransfer steps, where the MAPKKK becomes phosphorylated and phosphorylates the MAPKK, which in turn phosphorylates the MAPK.

In *S. cerevisiae*, the MAPK cascade is used to mediate various cellular functions, such as osmolarity adaptation (Hohmann 2009), mating (Schrick et al. 1997), cell wall integrity (Levin 2005), and filamentation. Indeed, the genome of *S. cerevisiae* encodes multiple MAPKs. In order to activate morphogenesis, the G protein Ras2 stimulates the activity of the G protein Cdc42, upon nitrogen starvation signals. Cdc42 binds to GTP, becomes active, and interacts with the p21-activated kinase (PAK) Ste20, which needs to be dissociated from its negative regulator Hsl17 (Fujita et al. 1999). The Cdc42-Ste20 dimer activates the MAPK cascade: Ste11 (MAPKKK), Ste7 (MAPKK), and Kss1 (MAPK) (Cook et al. 1996; Madhani et al. 1997). Once activated, Kss1 removes repressor activity of Dig1/Dig2 dimer (also known as Rst1/Rst2) on the TF Ste12 through Dig1/Dig2 phosphorylation (Bardwell et al. 1998a, b; Cook et al. 1996). Ste12 cooperates with the TF Tec1 to bind the enhancers called filamentation and invasion response elements (FREs) and to start the transcriptional program required for filamentous growth by the activation of genes, such as *FLO11* (Chou et al. 2006; Lo and Dranginis 1998; Madhani and Fink 1997). In *C. albicans*, three different MAPK pathways have been described: the Hog1-MAPK, the Mkc1-MAPK, and Cek1/Cek2 (see below). All the MAPK signaling pathways serve as a pattern of cascades essential for *C. albicans* morphogenesis, but they are also required under different conditions and they are activated by different stimuli. Hence, in contrast to *S. cerevisiae* the MAPK pathways of *C. albicans* show a broader function, and all of them play a role in morphogenesis, suggesting the importance of phenotypic plasticity for *C. albicans* in order to adapt and survive in different host niches.

The Hog1-MAPK pathway. Activation of the Hog1-MAPK pathway culminates in the phosphorylation, activation, and nuclear translocation of Hog1. In *S. cerevisiae*, this pathway is involved in osmolarity adaptation. Two separate branches have been described, where independent transmembrane osmosensors converge at the MAPKK Pbs2, which activates the Hog1 MAPK (Hohmann 2009). The Sln1 branch, the so-called two component system, is controlled by the plasma membrane-localized sensor Sln1, a histidine kinase active under low osmolarity conditions. Sln1 inactivates Ssk1 via the phosphorelay protein Ypd1. When osmolarity increases, Sln1 is inactivated, the phosphorylation steps are interrupted, and the unphosphorylated form of Ssk1 accumulates. Ssk1 binds to the regulatory domain of Ssk2 and Ssk22 MAPKKs, triggering their autophosphorylation and activation (Posas and Saito 1998). Then, Ssk2 and Ssk22 phosphorylate and activate Pbs2 MAPKK, which in turn phosphorylate the MAPK Hog1 (de Nadal et al. 2002; Hohmann 2002; Maeda et al. 1995; Posas et al. 1996). The Sho1 branch is controlled by two mucin-like transmembrane sensors, namely Msb2 and Hkr1 (de Nadal et al. 2007; Tatebayashi et al. 2007). These sensors might monitor the movements between the cell wall and the plasma membrane, since mucins connect the cell interior with the cell wall. Sho1 is a membrane-localized scaffold protein, recruiting components to the cell surface where remodeling is necessary (Reiser et al. 2000). Sho1 is activated under high osmolarity conditions, and the signaling to Pbs2 requires the Ste11 MAPKKK, which interacts with Ste50, Ste20, and the small GTPase Cdc42 (de Nadal et al. 2002; Posas et al. 2000).

S. cerevisiae harbors only one transmembrane histidine kinase (Sln1), but three are found in *C. albicans*, namely Sln1, Nik1, and Chk1 (Calera et al. 1999; Nagahashi et al. 1998) (Fig. 1). Deletion of *CaSLN1* only slightly affects the osmotic stress tolerance (Nagahashi et al. 1998). The second putative kinase, Nik1, is the homolog of *Neurospora crassa Nik1* and is required for osmotolerance and filamentation (Alex et al. 1996; Alex et al. 1998; Srikantha et al. 1998). Finally, *CaChk1* modulates the expression of cell surface components (Kruppa et al. 2004), showing a role in virulence and morphogenesis (Calera et al. 1999; Calera and Calderone 1999).

Homologs of *S. cerevisiae* components of the osmotic stress pathway (*PBS2*, *SSK1* and *SHO1*) have also been identified in *C. albicans*, but they exhibit different functions as compared to their counterparts in *S. cerevisiae*. Deletion of *PBS2* prevents the relay of both osmotic and oxidative stress signals to Hog1 (Arana et al. 2005). In contrast, deletion of *SSK1* prevents activation of Hog1 in response to oxidative stress. This contrasts with the observations in *S. cerevisiae* where inactivation of both the Sho1- and the Sln1 osmosensing branches prevents relay of osmotic stress signals to Hog1 (Maeda et al. 1995). Furthermore, *sho1* mutants are sensitive to oxidative stress, but Sho1 has a minor role in the transmission of the phosphorylation signal to Hog1 in response to oxidative stress, which probably occurs through the Sln1-Ssk1 branch (Roman et al. 2005). However, which histidine kinase regulates Ssk1 in response to oxidative stress is unclear, since *sln1* mutant are still able to activate the pathway in response to H₂O₂ (Li et al. 2004; Roman et al. 2005). Furthermore, a *sho1* null mutant is sensitive to cell wall

interfering compounds, showing modifications in the cell wall architecture (Roman et al. 2005). Therefore, in *C. albicans* the Hog1 pathway is involved not only in both osmotic (Arana et al. 2005; San Jose et al. 1996) and oxidative (Alonso-Monge et al. 2003; Correia et al. 2017; Du et al. 2005) stresses, but also in cell wall biosynthesis (Alonso-Monge et al. 1999, 2001; Monge et al. 2006; O'Rourke and Herskowitz 1998). Additionally, it plays a role in morphogenesis: *hog1* and *pbs2* mutants show enhanced filamentation in non-inducing conditions (Alonso-Monge et al. 1999; Arana et al. 2005). However, a direct role of Hog1 in the regulation of morphogenetic gene targets has not been established yet.

The Mkc1-MAPK pathway. In *S. cerevisiae*, protein kinase C (Pkc1) is involved in response to a large number of stresses, including osmotic (Garcia-Rodriguez et al. 2005) and nutritional (Vilella et al. 2005) stresses. Pkc1 activation leads to a MAPK module consisting of the bypass of C protein kinase (Bck1) MAPKKK that activates the Mkk1 MAPKK, which in turn phosphorylates the Mpk1 MAPK. In *C. albicans*, *pkc1* mutants are sensitive to osmotic stress, but do not display any filamentation defect (Paravicini et al. 1996), whereas Pkc1 activates the Mkc1 pathway that in contrast has a role in morphogenesis (Navarro-Garcia et al. 1995). The MAPK Mkc1, the homolog of ScMpk1, plays a role in cellular integrity and cell wall formation (Navarro-Garcia et al. 1995) and is essential for invasive growth under embedded conditions and for biofilm formation (Kumamoto 2005). This suggests that Mkc1 signaling is relevant for processes dependent on physical interaction with external surfaces (Eisman et al. 2006). Further, *mkc1* mutants are sensitive to high temperatures, lytic enzyme preparations, and cell wall antifungals, indicating an additional role of Mkc1 in the construction of the cell wall (Navarro-Garcia et al. 1995; Navarro-Garcia et al. 1998). Mkc1 is also phosphorylated upon oxidative stress (as described for Hog1), osmotic stress, antifungal treatment, in the presence of calcium and at low temperatures. The targeted TFs or those indirectly induced by Mkc1 remain to be identified, but possible candidates are Efg1, Czf1, and Bcr1 (Biswas et al. 2007) (Fig. 1). Bcr1 is involved in *C. albicans* hyphal development and virulence; its expression depends on the hyphal regulator Tec1 (Nobile and Mitchell 2005), a member of the TEA/ATTS family of TFs. Tec1 regulates virulence because it is required for the expression of the SAPs and for filamentation in order to escape macrophages (Schweizer et al. 2000). The SAP gene family encodes at least nine members (Sap1 to Sap9), considered putative virulence factors. Sap activity has been demonstrated to be important for attachment and penetration in the host during infection (Borg and Ruchel 1988; Ollert et al. 1993). The Sap4, Sap5, and Sap6 proteins are activated during hyphal formation (Hube et al. 1994), while the *sap4 sap5 sap6* triple mutant is avirulent in vivo (Sanglard et al. 1997). *TEC1* expression has been shown to be regulated by Efg1, providing an edifying example of how *C. albicans* can converge different signals to regulate a common set of differentially expressed genes (Lane et al. 2001) (Fig. 1).

In *C. albicans*, *TEC1* transcription might depend on a TF named Cph2 (Lane et al. 2001). Cph2 belongs to the myc subfamily of bHLH proteins and regulates hyphal growth independently of either the MAPK or the cAMP-PKA pathways.

A *cph2* deletion strain shows medium-specific impairment in hyphal growth (Lane et al. 2001). Further, ectopic expression of *TEC1* suppressed the filamentation defects in *cph2* null mutant, suggesting that Cph2 function in hyphal growth is mediated, in part, through Tec1. Furthermore, Cph2 may also play a direct role in the transcriptional activation of some HAGs (Lane et al. 2001).

The Cek1-MAPK pathway. The *Candida* ERK-like kinase (Cek1) MAPK pathway was first discovered in *C. albicans* because of its ability to confer a cell-cycle-specific arrest when overexpressed in *S. cerevisiae* (Whiteway et al. 1992). *S. cerevisiae* homolog of Cek1, Fus3, is part of a pathway participating in mating (Elion 2000), invasive growth (Palecek et al. 2002), and vegetative growth (Cullen et al. 2000; Lee and Elion 1999). In *C. albicans*, the Cek1-MAPK pathway ends up with the activation of the TF Cph1, a Ste12 homolog (Liu et al. 1994) (Fig. 1). Interestingly, Cph1 is required for filamentation on solid media, but not in liquid (Leberer et al. 1996; Liu et al. 1994) and is dispensable for virulence in a murine model of systemic candidiasis (Liu et al. 1994). The *efg1 cph1* double mutant fails to form filaments in hypha-inducing conditions and is avirulent in a systemic mouse model of candidiasis (Lo et al. 1997). However, under certain conditions, such as matrix-embedded, the *efg1 cph1* double mutant is still able to filament, suggesting the presence of other pathways for hyphal development that involve other TFs (e.g., Czf1). Several studies have highlighted the involvement of the Cek1-MAPK pathway in morphogenesis and filamentation. For instance, deletion of *CEK1* results in filamentation defects in media where nitrogen source is limiting (Csank et al. 1998). As mentioned before, nitrogen starvation is one of the signals that trigger the morphogenetic transition (Csank et al. 1998; Tripathi et al. 2002). *C. albicans* has two genes encoding ammonium permeases (*MEP1* and *MEP2*) that, in addition to their role as transporters, enable growth when limiting concentrations of ammonium are the only available nitrogen source. Mep2 has also a central role in the induction of filamentation on solid surface under limiting nitrogen conditions (Biswas and Morschhauser 2005). It has been proposed that Mep2 triggers the Cph1/Cek1-mediated pathway in a Ras1-dependent manner (Biswas and Morschhauser 2005), and mutations of components of this pathway lead to reduced virulence (Marcil et al. 2002). Finally, Cek1-MAPK is also activated by growth signals (Roman et al. 2005), by quorum sensing (Sato et al. 2004), and is involved in cell wall biogenesis (Roman et al. 2005) and in mating (Magee et al. 2002).

Negative regulators of morphogenesis and chromatin remodeling. The hyphal induction program is also under negative regulation by the TFs Nrg1, Rfg1 (Kadosh and Johnson 2005), and Sfl1 (see below). Another negative regulator is Tup1, but this protein does not directly bind DNA. In *S. cerevisiae*, Tup1 regulates genes involved in glucose homeostasis, DNA damage, and oxygen stress response (DeRisi et al. 1997), forming a transcriptional corepressor complex with Ssn6 (Smith and Johnson 2000). In *C. albicans*, the *tup1* mutant constitutively grows in a filamentous form, in the absence of hypha-inducing conditions (Braun and Johnson 1997). However, Tup1 is not only a repressor of filamentation, since the *tup1*

deletion strain has misshapen cell wall and is not able to grow at 42 °C (Braun and Johnson 2000).

SSN6 encodes a global transcriptional repressor, whose overexpression increases filamentation and decreases virulence (Hwang et al. 2003). As stated above, the Ssn6–Tup1 corepressor complex does not interact directly with DNA, but is targeted to specific promoters through interaction with sequence-specific DNA-binding proteins (i.e., TFs) (Keleher et al. 1992; Smith and Johnson 2000). An independent role of Ssn6 has been reported, namely through its interaction with the HDAC Rpd31. The *ssn6 rpd31* double mutant is able to form elongated cells, but is unable to extend filaments, suggesting that Ssn6 has a dual role in filamentation depending on the interaction with Rpd31 (Lee et al. 2015).

The Nrg1 TF contains a highly conserved zinc finger domain. In *C. albicans*, Nrg1 represses transcription in a Tup1-dependent manner (Braun and Johnson 2000; Murad et al. 2001). Ectopic overexpression of *NRG1* blocks hyphal growth in all conditions (Sanchez AA 2005) and attenuates virulence in a systemic infection mouse model (Saville et al. 2006). Another TF interacting with the Tup1–Ssn6 complex is repressor of filamentous growth 1 (Rfg1), homolog of ScRox1 (Khalaf and Zitomer 2001). However, *RFG1* overexpression does not inhibit hyphal development in vitro or in vivo and drives pseudohyphal formation under yeast-growth conditions (Cleary et al. 2010).

Molecular mechanisms involved in the initiation and extension of hyphal development. The two phases of hyphal development, namely initiation and maintenance, are sustained in *C. albicans* by two parallel pathways active either in air or in hypoxia plus CO₂ (Fig. 2) (Lu et al. 2013). Serum, GlcNAc, or nutrient limitation induce the expression of the activator Brg1, which is recruited to the promoter of HAGs through changes in chromatin that occlude the binding of the repressor Nrg1 (Fig. 2). Both hyphal elongation pathways require the initiation step with a transient downregulation of Nrg1 via the cAMP-dependent PKA pathway; at the same time, Brg1 and the hypha-specific TF Ume6 are upregulated (Fig. 2). Recently, Hir1, a subunit of the HIR histone chaperone complex, has been shown to be involved in hyphal initiation, providing evidence of the tight control of gene expression during yeast-to-hypha transition (Jenull et al. 2017). Afterward, a window of opportunity permits to choose the maintenance phase: either involving Brg1 and Hda1 (air), or initiating a positive feedback loop by stabilizing Ume6 (hypoxia plus high CO₂ levels) (Fig. 2) (Lu et al. 2013). In the first case, maintenance needs the HDAC Hda1 recruitment to promoters, allowing a chromatin remodeling that blocks Nrg1 access at the promoters of HAGs (Lu et al. 2011, 2014). Brg1 recruits Hda1 to promoters of HAGs under reduced Tor1 signaling for hyphal maintenance (Lu et al. 2012). In the feed-forward regulation of hyphal development, Brg1 regulates the expression of Ume6 (Lu et al. 2012). Hyphal extension and maintenance depend on the TF Ume6 and the Eed1/Def1 protein.

In *C. albicans*, *UME6* encodes a filament-specific transcription regulator sufficient to direct hyphal growth in the absence of hypha-inducing conditions (Zeidler et al. 2009). This differs greatly from *S. cerevisiae* Ume6, whose function is to regulate arginine catabolism (Messenguy et al. 2000), DNA repair (Sweet et al.

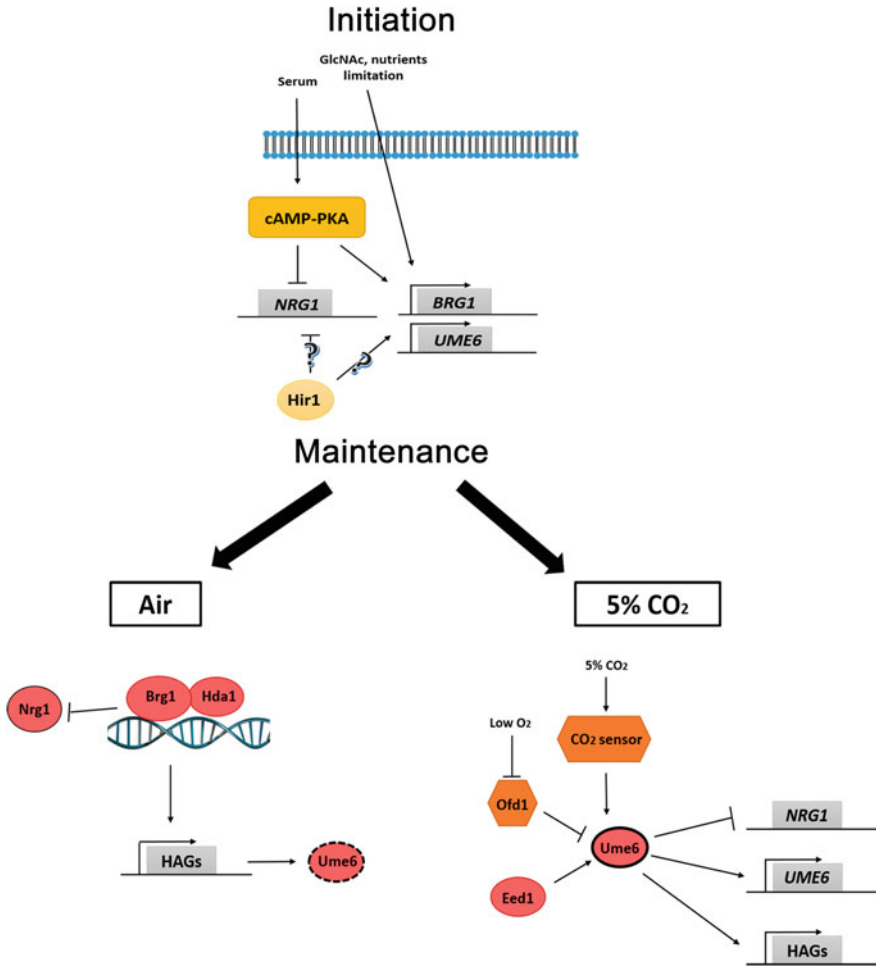


Fig. 2 Hyphal initiation and maintenance. Both hyphal elongation pathways require the initiation step characterized by a transient downregulation of *Nrg1* via the cAMP-dependent PKA pathway, and upregulation of *Brg1* and *Ume6*. Serum, GlcNAc, or nutrient limitation induce the expression of *Brg1*. *Hir1*, a subunit of the HIR histone chaperone complex, has been shown to be involved in hyphal initiation, but its exact function remains to be elucidated. The maintenance phase consists of two parallel pathways active either in normoxia or hypoxia + CO₂. In normoxia, *Brg1* recruits the HDAC *Hda1* to the promoters of *HAGs*, allowing a chromatin remodeling that prevents *Nrg1* binding to these promoters. *Brg1* regulates the expression of *Ume6*, which is unstable under normoxia and is degraded (dashed lines). Under hypoxia and in the presence of 5% CO₂, the oxygen sensor *Ofd1* and an uncharacterized CO₂-sensing pathway stabilize *Ume6* (thick full line), leading to hyphal development through a positive feedback loop where *Ume6* binds to its own promoter, regulates *HAGs* expression, and inhibits *NRG1* expression. Furthermore, *Ume6* is regulated by *Eed1*

1997), and meiosis (Rubin-Bejerano et al. 1996). *C. albicans ume6* deletion mutants are defective in hyphal growth and are attenuated in virulence (Banerjee et al. 2008), while constitutive overexpression promotes hyperfilamentation in the absence of filament-inducing conditions, tissue invasion, and virulence (Banerjee et al. 2008; Carlisle et al. 2009; Zeidler et al. 2009). Ectopic overexpression of *UME6* is able to rescue the hyphal growth defects observed in *brg1* and *hda1* mutants (Lu et al. 2012).

As described before, hyphal maintenance can occur through two different pathways (air or hypoxia plus CO₂). In response to hypoxia and 5% CO₂, the oxygen sensor *Ofd1* and an uncharacterized CO₂-sensing pathway stabilize *Ume6*, leading to hyphal development through a positive feedback loop where *Ume6* binds to its own promoter (Fig. 2). Furthermore, *Ume6* is degraded under normoxia, while very stable in hypoxia or hypercapnia: it was reported that deleting *Ofd1* resulted in stabilizing *Ume6* in 5% CO₂, but not in air (Lu et al. 2013). Additionally, *UME6* has one of the longest 5' untranslated regions (UTRs) identified in fungi, which is predicted to form a complex and stable secondary structure. The 5' UTR region functions to inhibit *Ume6* protein expression under several filamentous-inducing conditions. Overall, the translational efficiency mechanism has evolved to fine-tune morphogenesis, and in this case, the 5' UTR region of *UME6* is found to regulate the protein translational efficiency (Childers et al. 2014). Furthermore, *Ume6* is regulated posttranslationally by the cell-cycle kinase *Cdc28/Cdk1*, which reduces *Ume6* activity, and the cyclin *Cln3*, an essential promoter of yeast proliferation, suppresses hyphal induction through *Ume6* (Mendelsohn et al. 2017).

In addition to the TFs already described, *UME6* expression depends on epithelial escape and dissemination (*EED1*, also known as *DEF1*) (Martin et al. 2011) (Fig. 1). *EED1* was identified in a genome-wide analysis in a RHE model. It was shown that an *eed1* mutant strain was still able to invade superficial oral epithelial cells, but in these cells the mutant grew as yeasts, without dissemination in tissues (Zakikhany et al. 2007). *EED1* is unique to *C. albicans*, and no homolog has been detected in the genomes of the species that belong to the CUG clade, including species closely related to *C. albicans* (Butler et al. 2009), even if orthologs of its flanking genes exist in other fungi (Martin et al. 2011). Furthermore, it seems that *EED1* does not have any DNA-binding domain; however, it is one of the key outputs of the signal transduction pathways that lead to activation of HAGs (Sudbery 2011). The reason why *EED1* has evolved specifically in *C. albicans* could be linked to its importance in the biology of filamentation and possibly to pathogenesis. In fact, *Eed1* is important for hyphal development on solid media and for the interaction with host cells, but ectopic overexpression of *UME6* restored hyphal defects of *eed1* loss of function (Martin et al. 2011). The suggested model proposes that *Eed1* expression is regulated by *Efg1* (Martin et al. 2011) and by *Nrg1* (Doedt et al. 2004; Martin et al. 2011), and this is the primary element of a cycle controlling hyphal extension. The second step involves *UME6* activation by *Eed1*, and this may be required to keep *NRG1* expression at low levels to allow hyphal maintenance (Martin et al. 2011). The mechanism by which *Eed1* regulates *Ume6* remains unclear, and it might require additional players.

5 Morphogenetic Transition: Other Signaling Pathways

The matrix-embedded response. The ability to respond to the matrix-embedding environment is significant for *C. albicans* growing within host tissues. As already mentioned, the TF Czf1 is involved in the regulation of hyphal growth under these conditions (Brown et al. 1999), but the master regulator Efg1 and the TF Cph1 are also associated with the response to the matrix (Fig. 1). Ectopic expression of *CZF1* in embedded cells promotes hyphal formation. However, *czf1* mutants exhibit a defect in filamentation only in some embedding conditions (low temperature, in the absence of strong inducers of hyphal growth). Mutants lacking both *EFG1* and *CPH1*, although defective in germ tube formation under many laboratory conditions (Lo et al. 1997), were still able to filament in the tongues of immunosuppressed gnotobiotic piglets and in embedded conditions (Riggle et al. 1999). In contrast, strains lacking both *CPH1* and *CZF1* displayed the most defective phenotype in a matrix-embedding environment, suggesting that these genes play an important role in hyphal growth under these conditions (Brown et al. 1999). Efg1 is a positive regulator of *CZF1* expression, as it binds to its promoter, and deletion of *EFG1* abolishes *CZF1* expression. On the other hand, *CZF1* expression is negatively autoregulated, through direct binding to own promoter (Vinces et al. 2006). This suggests that a different genetic program is involved in filamentous growth in embedded conditions (Vinces et al. 2006).

Another signaling pathway regulating filamentation in embedded conditions involves the G protein Rac1 (Hope et al. 2008) (Fig. 1). Rac1 is required for filamentous growth in an agar matrix (Basilana and Arkowitz 2006) and is activated upon interaction with the GEF Dck1 (Hope et al. 2008). Rac1 and Dck1 function together with Lmo1, a protein similar to the human engulfment and cell motility (ELMO1) protein, upstream the Cek1 and Mkc1 MAP kinase pathways for invasive filamentous growth and cell wall integrity (Hope et al. 2010) (Fig. 1).

The pH-dependent response. *C. albicans* is highly tolerant to a wide range of pH conditions encountered in several niches within the human body. As already mentioned, pH fluctuations drive the morphological transition; moreover, *C. albicans* actively neutralizes the environment from either acidic or alkaline pHs. Under acidic conditions, the fungus is able to raise the pH from 4 to >7 in less than 12 h, resulting also in yeast-to-hypha transition (Vylkova et al. 2011).

In the pH-dependent filamentation, the Rim101 TF (also called Prr2 for pH response regulator) has a central role, by inducing the expression of alkaline-specific genes and repressing the expression of acid-specific genes (Fonzi 1999; Ramon et al. 1999). The extracellular pH is sensed by the transmembrane proteins Rim21 and Dfg16 (Barwell et al. 2005; Penalva et al. 2002) (Fig. 1). The protein Rim8 (or Prr1) has a crucial role, since its expression is activated in low pH conditions and mutants lacking *RIM8* are defective in pH-dependent regulation of gene expression (Porta et al. 1999). Rim20 and Rim13 are also part of the pathway: They form the endosomal sorting complexes required for transport (ESCRT), required for endocytic trafficking, and together with Vps32 (also called Snf7)

activate the transcription factor Rim101 by proteolytic cleavage of its C-terminal domain (Cornet et al. 2005; Kullas et al. 2004) (Fig. 1). Under alkaline conditions, Rim101 is active in its shorter form, while in acidic conditions, it is processed in a longer form whose function is not known (Li et al. 2004). Once activated, Rim101 binds to the promoter regions of different genes, activating *PRA1* and *PHR1* and repressing *PHR2* (Ramon et al. 1999; Ramon and Fonzi 2003; Baek et al. 2006). *PHR1* and *PHR2* are required for normal morphology at pH above or below 5.5, respectively. These genes encode GPI-anchored glycosidases that localize at the plasma membrane and are involved in cross-linking cell wall glucans (Fonzi 1999; Muhlschlegel and Fonzi 1997). *PRA1* encodes a cell wall protein whose deletion is associated to morphological defects in alkaline-induced filamentation (Sentandreu et al. 1998) and host zinc acquisition (Citiulo et al. 2012). The pH response represents another example of the dynamic interaction and adaptation of *C. albicans* to its host environment.

The Target of Rapamycin (TOR) pathway. Rapamycin, produced by the bacterium *Streptomyces hygroscopicus*, was discovered in a screen for antimicrobial activity against *C. albicans* and later found to have a potent immunosuppressive activity (Baker et al. 1978; Vezina et al. 1975). Rapamycin binds to its intracellular receptor FKBP (FK506-binding protein), and this complex inhibits the activity of a phosphatidylinositol 3-kinase-related kinase, the target of rapamycin (TOR), which is important for cell growth (Schmelzle and Hall 2000). There are two highly homologous TOR proteins in *S. cerevisiae*, Tor1 and Tor2 (Kunz et al. 1993). In addition to rapamycin-dependent function, Tor2 also regulates cytoskeletal dynamics during polarized cell growth (Helliwell et al. 1998). Furthermore, two different TOR complexes have been found in *S. cerevisiae* (Loewith et al. 2002; Reinke et al. 2004; Wullschleger et al. 2005): target of rapamycin complex 1 (TORC1), which contains either Tor1 or Tor2 and mediates the TOR-shared, rapamycin-sensitive pathway, and target of rapamycin complex 2 (TORC2), which contains Tor2 and mediates a TOR2-unique, rapamycin-insensitive, pathway. Within the TORC1 complex, Tor1 is conserved from yeast to humans. In *C. albicans*, Tor1 participates in a signaling pathway involved in cellular growth in response to nutrient availability (Rohde et al. 2008; Rohde and Cardenas 2004) and it mediates repression in cell–cell adhesion (Bastidas et al. 2009). In fact, Tor1 controls the expression of adhesion genes by interacting with the transcriptional activators Bcr1 and Efg1. In addition, it promotes the expression of the transcriptional repressors Nrg1 and Tup1 (Fig. 3) (Bastidas et al. 2009). Tor1 signaling during hyphal initiation activates the expression of the transcription factor Brg1, which recruits the HDAC Hda1 to the promoters of hypha-specific genes (Fig. 3) (Su et al. 2013). One of the TORC1 substrates is the kinase Sch9, which in *C. albicans* is involved in cellular growth, stress response, and filamentation under certain conditions. In particular, CaSch9 regulates filamentation differentially in liquid and solid media (Liu et al. 2010). This observation appears consistent with the fact that CaTor1 is required for filamentation on agar surface, but not in liquid medium (Bastidas et al. 2009). Further, Sch9 controls hypha formation in response to oxygen and CO₂ levels: *sch9* mutants showed a striking hyperfilamentation

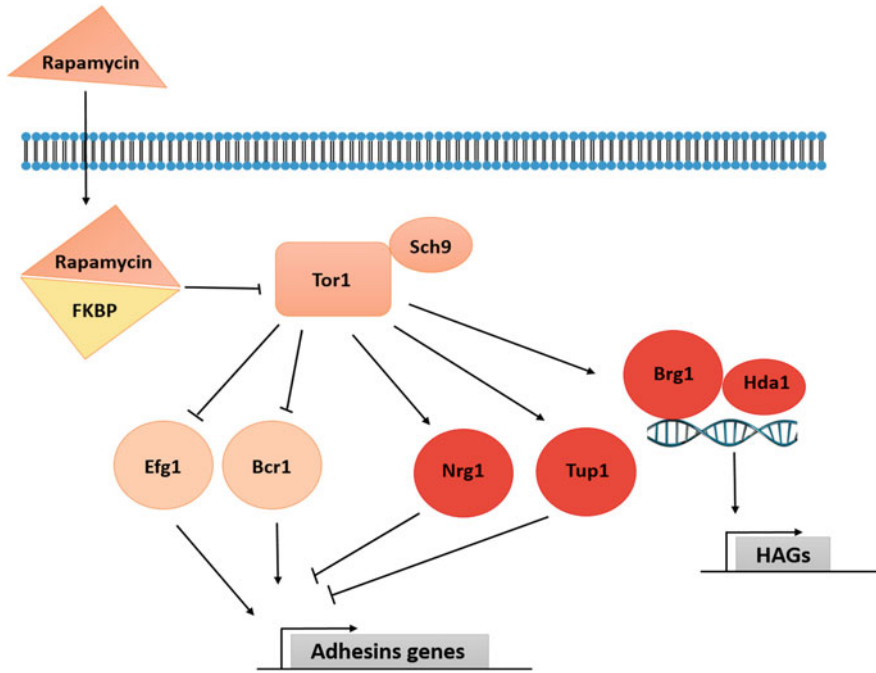


Fig. 3 TOR pathway during morphogenesis. Rapamycin binds to its intracellular receptor FKBP forming a complex that inhibits the activity of Tor1. Tor1 regulates adhesins genes expression by interacting with Bcr1 and Efg1 and promotes the expression of Nrg1 and Tup1. During hyphal initiation, Tor1 signaling activates the expression of Brg1, which recruits the HDAC Hda1 to the promoters of HAGs

under hypoxia, but only in the presence of elevated CO_2 levels (>1%) and at a high temperature (>37 °C). Notably, to generate this hyperfilamentous phenotype, the transcription factors Czf1 and Ace2, as well as both protein kinase A isoforms, were required (Stichternoth et al. 2011).

The Regulation of Ace2 and Morphogenesis (RAM) pathway. The RAM signaling pathway is involved in the regulation of polarized morphogenesis, cellular separation, and bud development in *S. cerevisiae* (Nelson et al. 2003). This pathway converges in the activation of Ace2, a TF whose activity is regulated by a set of six proteins that include the Cbk1 kinase, its activator Mob2, Tao3 (Pag1), Hym1, Sog2, and the Ste20-like protein kinase Kic1 (Fig. 4) (Bidlingmaier et al. 2001; Colman-Lerner et al. 2001; Du and Novick 2002; Nelson et al. 2003; Weiss et al. 2002). During cellular division, the Cbk1–Mob2 complex blocks Ace2 in the nucleus of the daughter cell where Ace2 accumulates and drives the expression of genes that are not expressed in the mother cell (Colman-Lerner et al. 2001; Mazanka et al. 2008; Weiss et al. 2002). In *C. albicans*, the RAM pathway is also involved in morphogenesis and cell polarity (McNemar and Fonzi 2002; Song et al. 2008). It was shown that mutations of the RAM genes lead to hypersensitivity to

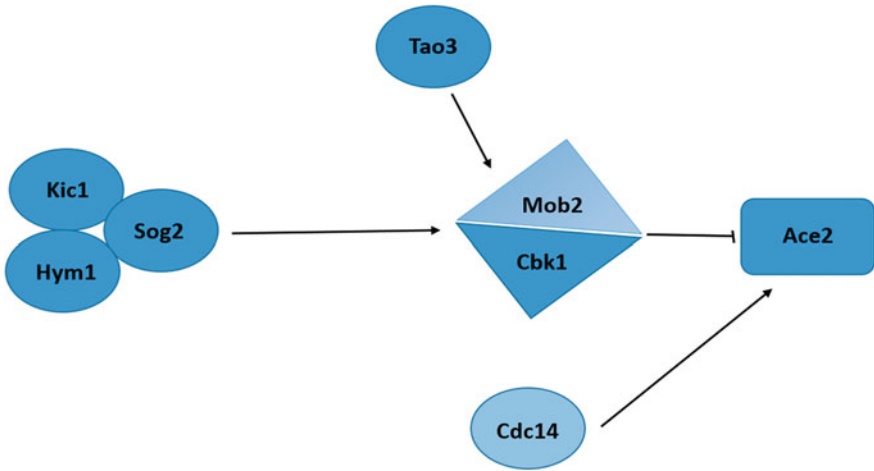
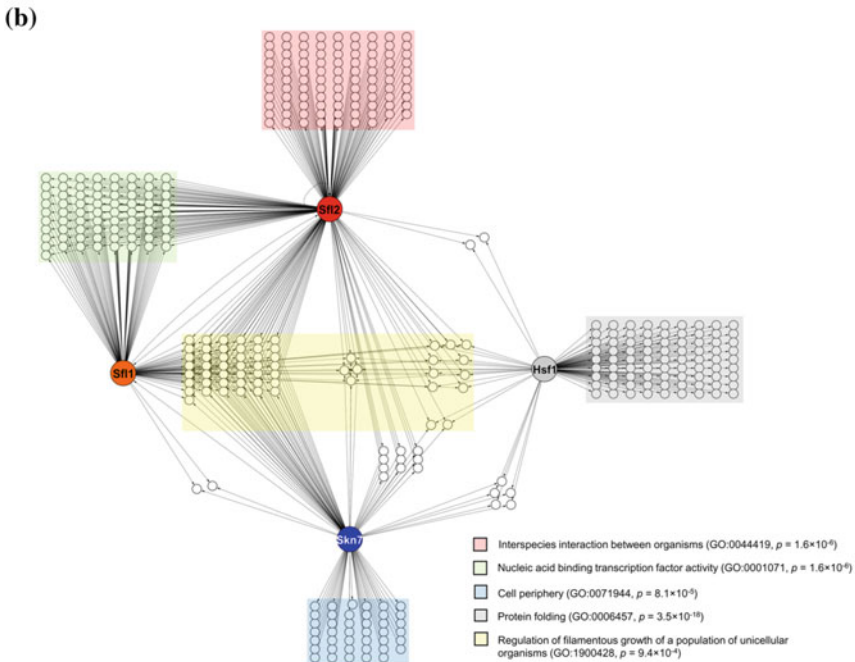
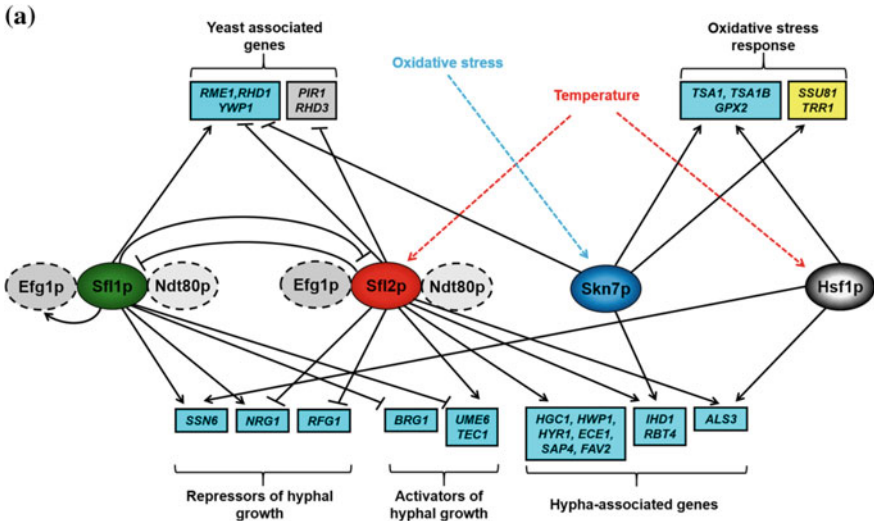


Fig. 4 Activation of RAM pathway during morphogenesis. During morphogenesis, the TF Ace2 is regulated by the kinase Cbk1 associated to its activator Mob2. This complex, whose formation is a key event for hyphal growth, is regulated by Hym1, Sog2 and the Ste20-like protein kinase Kic1 complex, together with Tao3. In addition, Ace2 localization depends on the protein phosphatase Cdc14

cell wall or membrane stresses, defects in cell separation, and loss of cell polarity. In particular, the Cbk1–Mob2 interaction is a key event for hyphal growth (Song et al. 2008). In addition, Ace2 localization depends on the protein phosphatase Cdc14 in both yeasts (Fig. 4) (Clemente-Blanco et al. 2006; Weiss et al. 2002). Furthermore, deletion of *CaACE2* caused an increased invasion of solid agar medium and led to abnormal pseudohyphal growth, even in the absence of external inducers. The mutant cells were also impaired for adherence to plastic surface, biofilm formation, and virulence (Kelly et al. 2004). Finally, Ace2 is found in two isoforms: a full-length Ace2L, involved in the septin ring formation during hyphal development that avoids cell separation, and a shorter form Ace2S, that regulates the expression of cell separation genes (Calderon-Norena et al. 2015).

6 Role of the Heat Shock Factors in *C. albicans* Morphogenetic Transition

In response to heat stress, cells activate an ancient signaling pathway leading to the transient expression of heat shock or heat stress proteins (Hsps). Hsps display very complex protection mechanisms, but the most conserved Hsps are molecular chaperones that prevent protein misfolding and the formation of non-specific protein aggregates, and assist proteins in the acquisition of their native structures (Richter et al. 2010).



Specific heat shock TFs are required to upregulate *HSPs*. Heat shock TFs share a common structure characterized by an N-terminal DNA-binding domain (DBD) followed by a cluster of hydrophobic amino acids organized in heptad repeats that form leucine zippers, and C-terminal heptad repeats (Su et al. 2013). In eukaryotes, *HSP* expression depends on the heat shock TF Hsf1, conserved from

◀**Fig. 5 a HSF-type regulators transcriptional network.** Sfl1 and Sfl2 regulate the expression of yeast-associated genes, and genes encoding repressors and activators of hyphal growth (blue boxes indicate common targets), by direct binding or together with Efg1 and Ndt80 (gray, dashed lines indicate hypothetical interaction). Sfl1 (dark green) induces the expression of yeast-associated genes (*RME1*, *RHD1*, *YWP1*) and of genes encoding repressors of hyphal growth (*SSN6*, *NRG1*) and represses genes encoding activators of hyphal growth (*BRG1*, *UME6*, *TEC1*). Sfl2 (red) is activated by temperature increase and negatively regulates yeast-associated genes, that are either common targets of Sfl1 (*RME1*, *RHD1*, *YWP1*) or unique targets of Sfl2 (*PIR1*, *RDH3*). Conversely, Sfl2 negatively regulates the expression of genes encoding repressor of hyphal growth, also regulated by Sfl1 (*SSN6*, *NRG1*, *RFG1*), and positively the expression of activators of hyphal growth also regulated by Sfl1 (*UME6*, *TEC1*), as well as hypha-associated genes (*HGCI*, *HWPI*, *HYR1*, *ECE1*, *SAP4*, *FAV2*, *IHD1*, *RBT4*, *ALS3*). Sfl1 and Sfl2 negatively regulate each other. Skn7 (dark blue) is activated during morphogenesis and oxidative stress; Skn7 induces the expression of hypha-associated genes, also targets of Sfl2 (*IHD1*, *RBT4*), negatively regulates yeast-associated genes also regulated by Sfl2 (*RME1*, *RHD1*, *YWP1*), and regulates the expression of several oxidative stress response genes (*TSA1*, *TSA1B*, *GPX2*, *SSU81*, *TRR1*). Hsf1 (dark gray) is activated upon temperature increase as Sfl2 and shares common targets with Sfl1 (*SSN6*), Sfl2 (*ALS3*), and Skn7 (*TSA1*, *TSA1B*, *GPX2*). **b Transcriptional circuitry of HSF-type Regulators Hsf1, Sfl2, Sfl1 and Skn7.** Hsf1 (gray sphere), Sfl2 (red sphere), Sfl1 (orange sphere), and Skn7 (blue sphere) share common direct transcriptional targets (open spheres, highlighted with green shading for Sfl1 and Sfl2 common targets and yellow shading for targets involving at least 3 HSF-type regulators). Targets that are specific to each regulator are highlighted with red (Sfl2), blue (Skn7), and gray (Hsf1) shadings. The associated functional categories (GO terms) that are significantly enriched are shown at the bottom right part of the figure. GO term enrichment analyses were conducted using the GO Term Finder algorithm (<http://www.candidagenome.org/cgi-bin/GO/goTermFinder>) at the *Candida* Genome Database. Binding data were taken from references (Leach et al. 2016) (Hsf1) (Znaidi et al. 2013) (Sfl2, Sfl1) and (Basso et al. 2017) (Skn7). Transcriptional network was constructed using Cytoscape version 3.4.0

yeasts to humans (Sorger and Pelham 1987; Wiederrecht et al. 1987). In response to temperature upshift, Hsf1 binds to a short highly conserved DNA sequence, namely the heat shock element (HSE), consisting of short tandem repeats of the sequence AGAAN (N is any nucleotide) found in the promoters of many heat shock genes (Fernandes et al. 1995).

Heat shock transcription factors in eukaryotes contain a helix-turn-helix DBD. In *S. cerevisiae*, the DBD is important not only to bind DNA, but also for regulation of Hsf1 function. In *C. albicans*, in addition to Hsf1, there are three transcription factors containing an HSF-type DBD, namely Sfl1, Sfl2, and Skn7 (Fig. 5). These transcription factors play a role in morphogenesis, as reflected in the overrepresentation of genes involved in the regulation of filamentous growth among their common targets (Fig. 5b).

Hsf1. In *C. albicans*, Hsf1 is required for virulence and HSE-containing genes are activated upon systemic infection (Nicholls et al. 2011), demonstrating that the connection between heat shock response and pathogenicity is crucial. In response to an acute temperature upshift, *C. albicans* induces classical heat shock genes and some other stress-regulated genes (Fig. 5a and b) (Enjalbert et al. 2003). In *C. albicans* as in other yeasts, Hsf1 is also essential for viability (Nicholls et al. 2009), and the Hsf1-HSE regulon is critical for the modulation of genes involved in protein folding under basal conditions, including the chaperone-encoding *HSP70*,

HSP90, and *HSP104* genes, as well as in response to heat stress (Leach et al. 2012; Nicholls et al. 2009).

Hsf1 physically interacts with the heat shock proteins Hsp70 and Hsp90 (Leach et al. 2012). Hsp70 and Hsp90 contribute to the Hsf1 autoregulatory circuit: in the absence of stress, Hsp90 represses Hsf1, but under thermal stress, the repression is released and Hsf1 can become active, leading to an increase in Hsp90 levels (Jarosz et al. 2010; Leach et al. 2012).

Heat shock regulation also influences *C. albicans* morphogenesis, since a mild heat shock is normally used to stimulate the yeast-to-hypha transition in experimental conditions (Fig. 1) (Odds 1988). The levels of the chaperone Hsp90 are increased during the yeast-to-hypha transition (Swoboda et al. 1995), and Hsp90 was demonstrated to regulate morphogenesis, since compromising its function induces the yeast-to-hypha transition via the Ras1-PKA pathway and attenuates virulence in systemic infection mouse model (Shapiro et al. 2009). Recently, it has been shown that *hsf1* mutants display defective filamentation on various solid hyphal inducing media (Nair et al. 2017) and that tuning the expression level of *HSF1* has a significant impact on morphogenesis (Veri et al. 2018). Indeed, overexpression of *HSF1* was sufficient to drive expression of the morphogenetic regulators *UME6* and *BRG1*, while loss of either *UME6* or *BRG1* was sufficient to block filamentation in response to *HSF1* overexpression (Song and Carlson 1998).

Sfl1 and Sfl2. *Sfl1* (Suppressor gene for flocculation (*SFL1*)) was first identified in *S. cerevisiae* where it encodes a repressor for invasion and pseudohyphal formation (Robertson and Fink 1998), and it binds specifically to GAA triplet motif of the HSE elements (Zhu et al. 2009). *Sfl1* behaves as a repressor of flocculation-related genes, such as *FLO11*, *STAI*, and *SUC2* (Kim et al. 2004; Robertson and Fink 1998; Song and Carlson 1998). However, this transcription factor can also act as a positive regulator of stress-responsive genes (Conlan and Tzamarias 2001; Galeote et al. 2007). Inhibition of transcription by *Sfl1* is likely due to its interaction with the Ssn6-Tup1 corepressor complex. Besides, repression of gene expression by *Sfl1* and Ssn6-Tup1 might involve a negative regulation of RNA polymerase II, since some components of the RNA polymerase II mediator complex, such as Sin4 and Srb10, are needed for full repression by *Sfl1* (Conlan and Tzamarias 2001; Song and Carlson 1998). Tpk2 inhibits *Sfl1* binding to DNA (Conlan and Tzamarias 2001; Pan and Heitman 2002) and, in parallel, activates Flo8 in the cAMP-signaling pathway (Conlan and Tzamarias 2001; Fujita et al. 1989). In *C. albicans*, two structural homologs of Sc*Sfl1* have been identified, namely *Sfl1* and *Sfl2*, and their role in morphogenesis and virulence were proven (Bauer and Wendland 2007; Song et al. 2011; Spiering et al. 2010). In fact, deletion of *CaSFL1* leads to flocculation and promotes hyphal development, through HAGs and cell adhesion genes induction, while its overexpression blocks filamentation (Bauer and Wendland 2007; Li et al. 2007). Therefore, *Sfl1* and Flo8 antagonistically regulate hyphal development in a mechanism similar to the one described in *S. cerevisiae*, where they can bind the same regions depending on phosphorylation by Tpk2 (Li et al. 2007). However, in the absence of Flo8, *Sfl1* acts as a repressor at high temperature, and as an activator at low temperature, proving its dual function: in

embedded agar at 24 °C, overexpression of *SFL1* enhances filamentation, whereas deletion of *SFL1* blocks filamentous growth in a *flo8* deletion mutant (Li et al. 2007). Interestingly, both deletion and overexpression of Sfl1 attenuate *C. albicans* virulence during systemic infection (Li et al. 2007).

Sfl2 is a positive regulator of filamentous growth in *C. albicans*, displaying high amino-acid sequence homology with Sfl1 (Song et al. 2011). Both TFs are probably the products of a gene duplication event from a shared unique ancestor and have diverged to exert antagonistic functions in filamentous growth. Interestingly, exchanging the HSF-DNA-binding domains of Sfl1 and Sfl2 almost completely reversed the repressor/activator functions of the hybrids generated from the domain swapping (Song et al. 2011), suggesting that their antagonistic functions are conferred by their ability to bind DNA. A comprehensive model for Sfl1 and Sfl2 transcriptional network was recently provided (Fig. 5a and b) (Znaidi et al. 2013). According to this model, Sfl1 and Sfl2 positively and negatively regulate a common set of targets that can be divided into three categories: repressors of hyphal growth (*SSN6*, *NRG1*, *RFG1*), activators of hyphal development (*UME6*, *BRG1*, *TEC1*), and yeast-specific genes (YSGs) (*RME1*, *RHD1*, *YWP1*). In particular, while the two transcription factors can act both as repressor and activator for the first two gene categories described above, only Sfl1 upregulates and Sfl2 downregulates the yeast-specific gene category (Fig. 5a). Furthermore, Sfl1 and Sfl2 directly repress each other's expression. Lastly, Sfl1 and Sfl2 behave as «switch on/off» regulators, with Sfl1 turning off the expression of hyphal positive regulators expression and turning on the YSGs and the hyphal repressors, whereas Sfl2 turns off the YSGs and negative regulators of hyphal development and turns on activators of hyphal growth, as well as a set of HAGs, not regulated by Sfl1 (Fig. 5a). Moreover, motif discovery analyses suggest an interaction between Sfl1 and Sfl2 with the transcriptional regulators Ndt80 and Efg1, proving the complexity of the circuitry that regulates morphogenesis (Znaidi et al. 2013). Finally, evidences of the reminiscent heat shock response of these two transcription factors are reported. For instance, Sfl1 and Sfl2 can bind to the promoter of *HSP104* and *HSP70* (Znaidi et al. 2013), and one potential Sfl1 binding motif is similar to that for ScHsf1 (MacIsaac et al. 2006; Morozov and Siggia 2007). Taken together, these data suggest the specific needs of *C. albicans* to survive and adapt in warm-blooded animals, converting temperature-sensing inputs into morphogenesis output by the HSF-type transcription factors.

Skn7. The third *C. albicans* transcription factor that shares the HSF-DBD homology with Hsf1, Sfl1, and Sfl2 is named Skn7. Skn7 is highly conserved among fungi, displaying a uniform architecture consisting in an N-terminal HSF-DBD and a C-terminal receiver domain (Fassler and West 2011). Within the HSF domain, two residues known to be involved in contacting DNA and critical in combination for the protein function are conserved, namely phenylalanine 76 and leucine 83 (Basso et al. 2017; Fassler and West 2011). However, Skn7 presents a very interesting peculiarity when compared with the other HSF-type transcription factors: the presence of a response-regulator domain. This domain confers an additional regulation for transcriptional activity via phosphorylation of conserved

residues within the protein and distinguishes Skn7 from the other HSF-type DBD proteins (Hsf1, Sfl1, and Sfl2). In *C. albicans*, the mechanisms that regulate Skn7 are not known. Nevertheless, it has been reported that Skn7 is involved in the oxidative stress response (Basso et al. 2017; Singh et al. 2004) and morphogenesis (Basso et al. 2017; Chauvel et al. 2012; Singh et al. 2004) (Fig. 5a and b), but how it regulates either the adaptation to oxidative stress or the morphogenetic transition has not been defined so far. *C. albicans* adaptation to oxidative stress depends on the TF Cap1 (Wang et al. 2006; Zhang et al. 2000), and Skn7 does not share common targets with Cap1 (Basso et al. 2017; Znaidi et al. 2009), suggesting that the role of these TFs in the oxidative stress response is different. However, Skn7 seems to prevent the accumulation of reactive oxygen species (ROS) occurring during filamentation on solid medium and, interestingly, the morphogenesis regulation appears uncoupled from the protection against intracellular ROS (Basso et al. 2017). Furthermore, Skn7 positively regulates the expression of other TFs, such as Brg1, Cph1, Czf1, Eed1, Sfl2, Tec1, and Ume6, and is required for Cph1, Tec1, and Ume6 function (Basso et al. 2017), highlighting its deep interconnection with other regulators of morphogenesis.

7 Conclusion

C. albicans exhibits remarkable morphological features of adaption to host niches that differ in terms of temperature, pH, oxygen/CO₂ levels, and nutrient availability. Such environmental fluctuations are a source of stress, requiring the activation of regulatory pathways and transcriptional circuits that impact on *C. albicans* morphogenesis and promote survival within body organs. Some of the transcriptional circuitries governing *C. albicans* morphogenesis have been characterized in detail. They already highlight the complexity that lies behind modulation of their activity. As stated above, turning on and off gene expression by TFs in response to a variety of stimuli is tightly orchestrated by a series of cascades and highly interconnected signal transduction pathways, including the cAMP/PKA, the Hog1/Mkc1/Cek1-MAPK pathways or those responding to matrix embedding, pH variation, and heat shock. Through deciphering the components of the cascades activated upstream of TFs, one could provide important clues on how signals that trigger filamentous growth and stress response are sensed and transduced. On the other hand, through studying TF function and modeling the transcriptional circuitries that operate during morphogenesis, one could identify important effectors and determinants of morphological switching that act downstream of TFs, as illustrated in Fig. 5b. The knowledge gathered from deciphering the regulatory circuitries involved in morphogenesis and/or stress response in *C. albicans* could open up new avenues for identifying potential molecular targets for future antifungal drug development.

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