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Review

# The metabolic basis of *Candida albicans* morphogenesis and quorum sensing

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ABSTRACT

*Candida albicans* is a polymorphic fungus that has the ability to rapidly switch between yeast and filamentous forms. The morphological transition appears to be a critical virulence factor of this fungus. Recent studies have elucidated the signal transduction pathways and quorum sensing molecules that affect the morphological transition of *C. albicans*. The metabolic mechanisms that recognize, and respond to, such signaling molecules and promote the morphological changes at a system level, however, remain unknown. Here we review the metabolic basis of *C. albicans* morphogenesis and we discuss the role of primary metabolic pathways and quorum sensing molecules in the morphogenetic process. We have reconstructed, *in silico*, the central carbon metabolism and sterol biosynthesis of *C. albicans* based on its genome sequence, highlighting the metabolic pathways associated with the dimorphic transition and virulence as well as pathways involved in the biosynthesis of important quorum sensing molecules.
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## 1. Introduction

*Candida albicans* is a human commensal fungus that can be isolated from approximately 70% of the healthy population (Mavor et al., 2005). In the majority of cases *C. albicans* is harmless, however, if the person is immunocompromised, it can be an opportunistic pathogen (Wingard et al., 1979). *C. albicans* is the fourth leading cause of nosocomial bloodstream infections (Pfaller and Diekema, 2007), with an attributable mortality of 37–44% in severely immunocompromised patients (Wisplinghoff et al., 2004; Leroy et al., 2009; Moran et al., 2010).

*C. albicans* and other polymorphic fungi (e.g. *Histoplasma capsulatum*) have the remarkable ability to grow in several distinct morphological forms: yeast, hyphae, and pseudohyphae, according to environmental conditions (Bastidas and Heitman, 2009; Sudbery et al., 2004). The true hyphae and pseudohyphae (chains of elliptical cells with constrictions at the septa) are often referred to as filamentous forms (Odds, 1988). The ability to switch rapidly from yeast-to-filamentous growth or vice versa in response to certain environmental cues is considered to be a critical virulence factor for these fungi (Lo et al., 1997; Mitchell, 1998; Brown and Gow, 1999; Gow et al., 2002; Rooney and Klein, 2002; Nemecek et al., 2006). In *C. albicans*, each morphology is believed to confer discrete advantages in the course of infection. The yeast form is important for dissemination through the bloodstream (Bendel et al., 2003; Saville et al., 2003), and adheres to endothelial surfaces (Grubb et al., 2009). The filamentous forms, on the other hand, are more adapted for invasion through the host epithelial tissue (Rooney and Klein, 2002), and also have a higher resistance to phagocytosis due to their morphology. Indeed, an engulfed *C. albicans* yeast cell can destroy a macrophage if filamentous growth is triggered after phagocytosis (Arai et al., 1977; Lorenz et al., 2004), and filamentous forms have a higher resistance to neutrophil killing (Smail et al., 1992; Fradin et al., 2005). Moreover, experimental studies support the hypothesis that the morphological transition is an essential virulence factor for *C. albicans*. For instance, a reduced mortality rate has been reported in animal infection models for mice inoculated with *C. albicans* mutants unable to undergo the yeast-to-filamentous transition (Lo et al., 1997; Gale et al., 1998). In addition, the induction of hyphal gene expression promoted virulence in a mouse model of systemic candidiasis (Carlisle et al., 2009).

The morphogenesis of *C. albicans* is predominately determined by environmental signaling. The yeast-to-filamentous transition can be triggered by serum, proline, N-acetylglucosamine, different carbon sources, and other cues as summarized in Table 1. However, there is a lack of understanding about how *C. albicans* regulates its morphogenesis in response to these environmental changes. In addition, the synchronised morphogenesis of *C. albicans* cells, and other dimorphic fungi, seems to be coordinated within the cell population by chemical signals (Chen and Fink, 2006; Hogan, 2006a,b; Nickerson et al., 2006; Chen et al., 2007). Dimorphic fungi are known to produce several signaling metabolites. Farnesol, which suppresses filamentous formation in *C. albicans*, is the best characterized of these molecules (Hornby et al., 2001), but the mechanism by which farnesol is sensed by *C. albicans* is not yet clear. Tyrosol is another signaling molecule produced by *C. albicans* and it stimulates the yeast-to-hypha conversion (Chen et al., 2004). Other metabolites such as estradiol (mammalian metabolite) and

**Table 1**
The effect of environmental cues on the morphogenesis of *C. albicans*.

| Environmental cues | Effect on morphogenesis | References |
|---|---|---|
| 25 °C or lower | ↑Yeast formation | Lee and Mitchell (1979) |
| 37 °C or higher | ↑Pseudohypha formation (maintains the yeast form at pH 4.5) | Lee and Mitchell (1979) and Lee et al. (1999) |
| 5–15% CO2 | ↑Predominantely pseudohypha formation | Bahn and Mühlschlegel (2006), Klengel et al. (2005), Mock et al. (1990) and Sims (1986) |
| | ↑Hypha formation | Brown et al. (1999) |
| $Ca^{2+}$ | ↓Hypha formation (absence of other divalent ions)<br>↑Hypha formation (in presence of $Mg^{2+}$) | Holmes et al. (1991) and Sabie and Gadd (1989) |
| D-glucose | ↑Hypha formation (at 37 °C and pH 7–8) | Hrmova and Drobnica (1981), Hudson et al. (2004) and Vidotto et al. (1996a) |
| 0.2% of glucose, galactose, fructose or sucrose | ↑Hypha formation | Maidan et al. (2005b) |
| Fructose | ↑Hypha formation (in the absence of nitrogen source) | Vidotto et al. (1996b) |
| Lee's medium | ↑Hypha formation (at 37 °C)<br>↓Hypha formation (at 25 °C) | Lee et al. (1975) |
| Lithium | ↓Hypha formation (except in liquid culture and requires at least 15 mM LiCl) | Martins et al. (2008) |
| Low ammonia medium | ↑Hypha formation (at pH 6.7) | Eisman et al. (2006) and Holmes and Shepherd (1987) |
| N-acetylglucosamine | ↑Hypha formation (inhibited when pH < 4.5) | Holmes and Shepherd (1987) and Sullivan and Shepherd (1982) |
| pH 4.5 (acid pH) | ↑Yeast formation (in the presence of glucose) | Lee and Mitchell (1979) and Pollack and Hashimoto (1987) |
| pH 6–8 | ↑Pseudohypha formation (but maintains the yeast form at 25 °C) | Lee and Mitchell (1979) and Pollack and Hashimoto (1987) |
| Proline | ↑Hypha formation (not observed when pH < 5.0) | Dabrowa et al. (1976) and Holmes and Shepherd (1987) |
| Serum | ↑Hypha formation | Hilmioglu et al. (2007) and Reynolds and Braude (1956) |
| Spider medium | ↑Hypha formation | Liu et al. (1994) and Toenjes et al. (2005) |
| 3-oxo-C12-homoserine lactone | ↓Hypha formation<br>↓Pseudohypha formation | Hogan et al. (2004) |
| Dodecanol | ↓Hypha formation<br>↓Pseudohypha formation | Hogan et al. (2004) |
| Human blood without white blood cell | ↑Hypha formation | Fradin et al. (2005) |
| Phagocytosis or surrounded by neutrophils | ↓Hypha formation | Barelle et al. (2006), Fradin et al. (2005) and Rubin-Bejerano et al. (2003) |
| Phagocytosis by macrophages | ↑Hypha formation | Barelle et al. (2006), Fradin et al. (2005), Lorenz et al. (2004) and Rubin-Bejerano et al. (2003) |
| Parenteral lipid emulsion | ↑Germ tube formation | Swindell et al. (2009) |

*Note*: ↑: inducing, ↓: suppressing

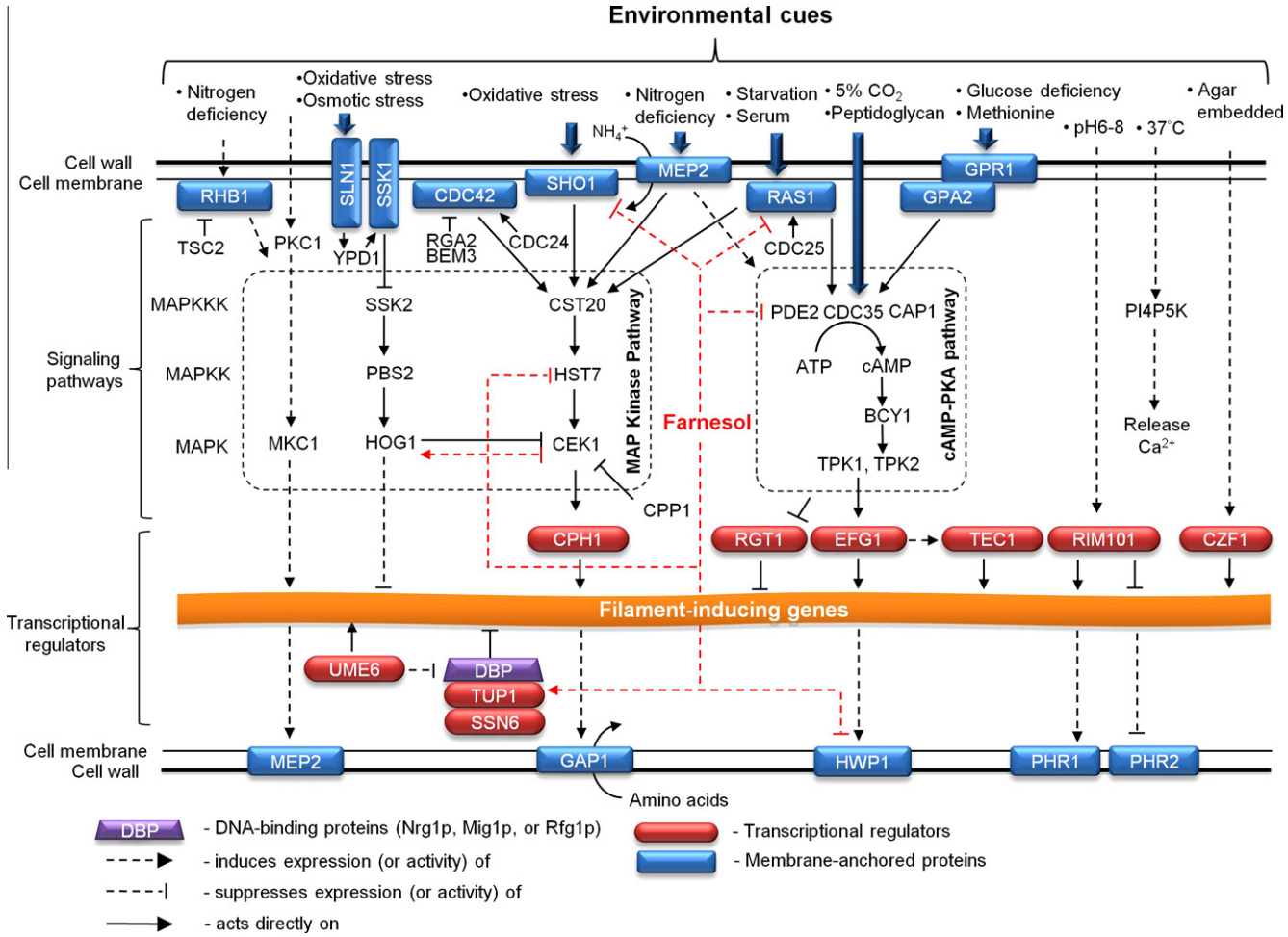


**Fig. 1.** Signal transduction pathways and transcriptional regulators that affect the filamentous growth of *C. albicans* and the effect of farnesol on some of these pathways. In response to filamentous-inducing conditions, GTPases (Gpa2p, Ras1p, and Cdc42p) activate two well-characterized signaling pathways; the Cek1p mediated MAP kinase pathway and cAMP-PKA pathway. These lead to the activation of transcriptional regulators Cph1p and Efg1p, respectively, which promote filamentous growth. Nitrogen starvation activates both the MAP Kinase and cAMP-PKA pathways via ammonium permease (Mep2p). Adenylyl cyclase (Cdc35p) not only responds to Ras1p, it is also activated in response to G-proteins (Gpr1p and Gpa2p), which are activated by glucose deficiency and the presence of methionine. Cdc35p also acts as a sensor for $CO_2$ and peptidoglycans. Oxidative stress and osmotic stress are sensed by a two component system (Sln1p and Ssk1p), which in turn suppresses Hog1p MAP kinase pathways. At 37 °C, Pi4p5kp synthesizes phosphatidylinositol 4,5-bisphosphate ($PIP_2$) to promote the release of intracellular $Ca^{2+}$. The role of other individual genes are summarized in Table 2. Quorum sensing molecule farnesol inhibits filamentous growth by suppressing the expression of *RAS1, SHO1 HST7, CEK1, PDE2*, and *HWP1*, while it upregulates filamentous-suppressing genes such as *TUP1* and *HOG1*. Blue boxes represent the membrane-anchored proteins, red boxes represent the transcriptional regulators, and the purple box indicates DNA-binding proteins (Nrg1p, Mig1p, or Rfg1p). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dibutyryl cAMP are also known to affect *C. albicans* morphogenesis (Niimi et al., 1980; White and Larsen, 1997; Cheng et al., 2006). Despite many studies showing the effect of small molecules on fungal morphogenesis, the pathways that recognize such signals and their effect on virulence are poorly characterized. Thus, this article reviews our current knowledge of *C. albicans* morphogenesis from a metabolic point of view and relates it to the activity of central carbon metabolism and the biosynthesis of quorum sensing molecules.

## 2. Signaling pathways and transcriptional regulators associated with *C. albicans* morphogenesis

In the last 10 years, the use of gene knockout mutagenesis and transcriptional studies have revealed signaling pathways, transcriptional factors, as well as other regulatory components that collectively drive the yeast-to-hyphal transition, or its reversion (Gow, 2009). The roles of signaling pathways and transcriptional regulators on *C. albicans* morphogenesis have been discussed in many review articles (Alonso-Monge et al., 2009b; Bahn et al., 2007; Biswas et al., 2007; Brown and Gow, 1999; Dhillon et al., 2003; Enrst, 2000; Hogan and Sundstrom, 2009; Lengeler et al., 2000; Liu, 2001, 2002; Navarro-García et al., 2001; Román et al., 2007; Wang, 2009). An important class of proteins involved early in signaling pathways is the GTPase superfamily. These G-proteins bind and hydrolyse guanosine triphosphate (GTP) in response to certain environmental stimuli (e.g. glucose, proline, pH, nitrogen deficiency, serum, and oxidative stress), and regulate downstream signal transduction. In *C. albicans*, the GTPases that regulate morphogenesis include G-protein-coupled receptor Gpr1p (Maidan et al., 2005), and the following members of the Ras superfamily: Rho-type Cdc42p (Johnson, 1999); RHeb-type Rhb1p (Tsao et al., 2009); and a small GTPase, Ras1p (Feng et al., 1999; Leberer et al., 2001).

GTPases are thought to be the main regulators that activate the two best-studied signaling pathways involved in *C. albicans* morphogenesis: the cAMP-Protein Kinase A (PKA), and the Mitogen-Activated Protein Kinase (MAPK), pathways (Fig. 1). The cAMP-PKA pathway involves adenylyl cyclase (Cdc35p) (Rocha et al.,

**Table 2**
Genes involved in the morphogenesis of *C. albicans*.

| Genes | Gene functions | Involvement in morphogenesis | References |
|---|---|---|---|
| *Signaling pathway genes* | | | |
| *BCY1* | The regulatory subunit of PKA | ↑Hypha formation | Cassola et al. (2004) |
| *CAP1* | Adenylate cyclase-associated protein | ↑Hypha formation | Bahn and Sundstrom (2001) |
| *CDC42* | Rho-type GTPase; a main regulator of cell polarity in fungi with two forms; CDC42-GTP and CDC42-GDP. CDC42-GTP activates *CST20* and promotes septin ring formation | Only CDC42-GTP: ↑hypha formation | Bassilana et al. (2003), Su et al. (2005) and Court and Sudbery (2007) |
| *CDC24* | The GDP-GTP exchange factor for *CDC42*; promotes CDC42-GTP formation | ↑Hypha formation | Bassilana et al. (2003) |
| *RGA2, BEM3* | CDC42 GTPase-activating proteins; promotes *CDC42*-GDP formation | ↓Hypha formation | Court and Sudbery (2007) and Wang (2009) |
| *CDC35 or CYR1* | Adenylyl cyclase, a sensor that responds to $CO_2$ and bacterial peptidoglycan (PGN)-like molecules | ↑Hypha formation<br>↑Pseudohypha formation | Rocha et al. (2001) and Klengel et al. (2005)<br>Xu et al. (2008) |
| *CDC53* | Encodes cullin, part of ubiquitin-ligase complex SCF | ↓hypha formation | Trunk et al. (2009) |
| *CST20* | MAPKK kinase of *CEK1* pathway | ↑Hypha formation | Leberer et al. (1996) |
| *HST7*[a] | MAPK kinase of *CEK1* pathway | ↑Hypha formation | Leberer et al. (1996) |
| *CEK1*[a] | MAP kinase of *CEK1* pathway; phosphorlyation is prevented by farnesol | ↑Hypha formation | Csank et al. (1998) and Román et al. (2009) |
| *CPP1* | Cek1p phosphatase, Inactivates the Cek1p | ↓Hypha formation | Csank et al. (1997) |
| *CRK1*[a] | Cdc2-related kinase, suppressed by farnesol | ↑Hypha formation | Chen et al. (2000) and Sato et al. (2004) |
| *GPA2* | A G-protein α subunit | ↑Hypha formation | Sánchez-Martínez and Pérez-Martín (2002) and Maidan et al. (2005) |
| *MKC1* | MAPK kinase; maintains cell wall integrity | ↑Hypha formation | Navarro-García et al. (1998) |
| *YPD1* | A phosphohistidine intermediate protein that transfers a phosphate from Sln1p to Ssk1p | Expressed in both yeast and hyphal forms | Payne et al. (2000) |
| *SSK1* | Response regulator of two component system; suppresses *HOG1*-mediated MAPK pathways and it is associated with cell wall synthesis and oxidative-stress response | ↑Hypha formation | Calera et al. (2000) and Menon et al. (2006) |
| *SSK2* | MAPKK Kinase of *HOG1* pathway | ↓Hypha formation | Cheetham et al. (2007) |
| *PBS2* | MAPK Kinase of *HOG1* pathway, essential for oxidative-stress response | ↓Hypha formation | Arana et al. (2005) |
| *HOG1*[a] | High osmolarity glycerol MAP kinase; responds to osmotic stress, temperature upshift, oxidative stress. Represses the activity of *CEK1*, regulates respiratory metabolism, and upregulated by farnesol | ↓Hypha formation | José et al. (1996) and Eisman et al. (2006) Alonso-Monge et al. (2003), Smith et al. (2004) and Alonso-Monge et al. (2009a) |
| *PDE2*[a] | Phosphodiesterase, suppressed by farnesol | ↑Hypha formation<br>↑Pseudohypha formation | Bahn et al. (2003) and Sato et al. (2004)<br>Smith et al. (2004) |
| *PI4P5 K* | phosphatidylinositol-4 phosphate 5-kinase; synthesizes phosphatidylinositol 4,5-bisphosphate (PIP2) in response to high temperature | ↑Hypha formation | Hairfield et al. (2002) |
| *RAD53* | The kinase involved in mediating DNA damaged–induced hyphal growth | ↑Hypha formation | Shi et al. (2007) |
| *RAS1*[a] | A member of the GTPase superfamily; responds to nitrogen starvation, glucose and serum. Suppressed by farnesol | ↑Hypha formation | Feng et al. (1999) |
| *CDC25* | *RAS1* guanine exchange factor; responds to glucose and induces cAMP signaling pathway | ↑Hypha formation | Enloe et al. (2000) |
| *RHB1* | Rheb of Ras superfamily, involves in the nitrogen starvation inducing filamentous growth | ↓Hypha formation | Tsao et al. (2009) |
| *TSC2* | Homolog of human tuberous sclerosis protein 2, negatively regulates the GTPase activity of *RHB1* | ↑hypha formation | Tsao et al. (2009) |
| *SHO1* | An adaptor protein that responds to oxidative stress and cell wall biosynthesis, It activates *CEK1* Kinase pathway. | ↑Hypha formation | Román et al. (2005) |
| *TPK1* | The catalytic subunit of PKA | ↑Hypha formation | Cloutier et al. (2003) |
| *TPK2* | The catalytic subunit of PKA | ↑Hypha formation | Cloutier et al. (2003) |
| *YAK1* | Ser/Thr protein kinase; Upstream of Tup1p | ↑Hypha formation | Goyard et al. (2008) |
| *Transcription factor genes* | | | |
| *CPH1* | Transcription factor that is activated by MAPK pathway; responds to starvation and GlcNAc | ↑Hypha formation<br>↑Pseudohypha formation | Lo et al. (1997) |
| *CZF1* | Putative zinc finger transcription factor; responds to agar-embedded growth conditions | ↑Hypha formation | Brown et al. (1999) |
| *EFG1* | Transcription factor that is activated by PKA pathway; responds to serum, upregulates glycolysis and downregulates TCA cycle | ↑Hypha formation<br>↑Pseudohypha formation | Stoldt et al. (1997) and Leng et al. (2001) |
| *TEC1* | A transcription factor - member of the TEA/ATTS family; regulated by *EFG1* | ↑Hypha formation | Schweizer et al. (2000) and Lane et al. (2001) |
| *TUP1*[a] | A general transcriptional repressor; regulates glycolysis and TCA cycle. Upregulated by farnesol | ↓Hypha formation | Braun and Johnson (1997), Cao et al. (2005) and Kebaara et al. (2008) |
| *SSN6* | A general transcriptional repressor forms a complex with *TUP1* | ↓Pseudohypha formation | Hwang et al. (2003) |
| *MIG1* | DNA-binding protein (DBP) binds to *TUP1* | ↓Hypha formation | Murad et al. (2001) |
| *NRG1* | DBP binds to *TUP1* | ↓Hypha formation<br>↓Pseudohypha formation | Braun et al. (2001) and Murad et al. (2001) |

**Table 2** (*continued*)

| Genes | Gene functions | Involvement in morphogenesis | References |
|---|---|---|---|
| *RFG1* | Repressor for filamentous growth; DBP binds to *TUP1* | ↓Hypha formation<br>↓Pseudohypha formation | Kadosh and Johnson (2001) and Khalaf and Zitomer (2001) |
| *RIM101* | pH-response regulator, activated by alkaline conditions and regulates both *PHR1* and *PHR2*. It is required for ARO9 pH dependent expression and required for virulence during systemic infection | ↑Hypha formation | Ramon et al. (1999) and Nobile et al. (2008) |
| *RGT1* | A transcriptional repressor for genes that encode hexose transporters, N-acetylglucosamine transporter (*NGT1*), and downregulates glycolysis | ↓Hypha formation | Sexton et al. (2007) |
| *GCN4* | General amino acid control; regulates both morphogenesis and metabolic responses to amino acid starvation | ↑Hypha formation<br>↑Pseudohypha formation | Tripathi et al. (2002) |
| *UME6* | A transcriptional regulator; encodes zinc finger DNA-binding protein | ↑Hypha formation<br>↑Pseudohypha formation | Strich et al. (1994) and Banerjee et al. (2008) |
| *Receptor genes* | | | |
| *CDR1, CDR2* | Multidrug transporters of the ABC family: an efflux pump that removes estradiol from the cell | ↑Germ tube is formed in the present of estradiol | Cheng et al. (2006) |
| *GAP1* | General amino acid permease; the expression of transporter is induced by GlcNAc and Cph1p. | ↑Hypha formation | Biswas et al. (2003) |
| *HGT4* | Glucose and galactose sensor | ↑Hypha formation | Brown et al. (2006) and Brown et al. (2009) |
| *GPR1* | G-protein-coupled receptor; upstream of cAMP-PKA pathway, senses methionine and proline | ↑Hypha formation | Maidan et al. (2005) and Maidan et al. (2005) |
| *HGT4* | Glucose sensor; induces the expression of hexose transporters (e.g. *HGT12*, *HXT12* and *HGT7*) | ↓Hypha formation<br>↓Pseudohypha formation | Brown et al. (2006) |
| *CHK1*[a]/*NIK1*/*SLN1* | Histidine kinase of two component system; *SLN1* is the upstream components of Hog1-mediated MAPK pathway. The *CHK1* mutant overcomes the hyphal-suppressing effect of farnesol | ↑Hypha formation | Nagahashi et al. (1998) and Calera and Calderone (1999), Yamada-Okabe et al. (1999) and Kruppa et al. (2004) |
| *NGT1* | N-acetylglucosamine transporter | In a homozygous NGT1 deletant, hyphal growth cannot be induced by GlcNAc | Alvarez and Konopka (2007) |
| *MEP2* | Ammonium permease; senses nitrogen starvation. Expression is suppressed by: 10 mM of $NH_4^+$, overexpression of *RHB1*, and *TSC2* deletion. It activates both MAP kinase pathway and cAMP-PKA pathway | ↑Pseudohypha formation | Biswas and Morschhäuser (2005) and Tsao et al. (2009) |
| *Metabolic genes* | | | |
| *ALO1* | D-arabinono-1,4-lactone oxidase; catalyzies the last step of D-erythroascorbic acid biosynthesis | ↑Hypha formation | Huh et al. (2001) |
| *ATC1* | Cell wall-linked acid trehalase, converts exogenous galactose into glucose. | ↑Hypha formation<br>↑Pseudohypha formation | Pedreño et al. (2007) |
| *GAL10* | UDP-galactose-4-epimerase; converts galactose into glucose | ↓Hypha formation | Singh et al. (2007) |
| *PDX1* | Pyruvate dehydrogenase | ↑Hypha formation<br>↑Pseudohypha formation | Vellucci et al. (2007) |
| *TSP1* | Trehalose-6-phosphate synthase; involved in trehalose biosynthesis. | ↑Hypha formation | Zaragoza et al. (1998) |
| *Cell wall genes* | | | |
| *ALS1* | Adhesin; hypha specific gene | ↑Hypha formation<br>↑Pseudohypha formation | Fu et al. (2002) |
| *HWP1*[a] | Cell wall protein; hyphal-specific gene, involved in cellular adhesion during biofilm formation, and suppressed by farnesol | ↑Hypha formation | Sharkey et al. (1999) and Ramage et al. (2002), Enjalbert and Whiteway (2005) and Padovan et al. (2009) |
| *INT1* | Integrin-like, role in adhesion | ↑Hypha formation<br>↑Pseudohypha formation | Gale et al. (1998) and Asleson et al. (2001) |
| *PHR1* | GPI-anchored glycosidase; cell wall structure, expressed at pH 5.5 or alkaline pH | ↑Hypha formation<br>↑Pseudohypha formation | Ghannoum et al. (1995) and De Bernardis et al. (1998) |
| *PHR2* | GPI-anchored glycosidase; cell wall structure, expressed at acidic pH | ↑Hypha formation | Mühlschlegel and Fonzi (1997) and De Bernardis et al. (1998) |
| *PMT1* | Mannosyltransferase | ↑Hypha formation | Timpel et al. (1998) |
| *PMT6* | Mannosyltransferase, role in adhesion and antifungal resistance | ↑Hypha formation | Timpel et al. (2000) |
| *Cell cycle-associated genes* | | | |
| *CDC28* | Cyclin-dependent kinase; phosphorylates *Cdc11* p(septin gene) in association with either *CCN1* or *HGC1*. *CDC28-HGC1* negatively regulates *RGA2* and also phosphorylates Efg1p | ↑Hypha formation | Sinha et al. (2007) and Wang et al. (2009) |
| *HGC1* | Hyphal-specific G1 cyclin related protein; maintains the localization of polarity proteins (e.g. actin) on hyphal tip, regulated by cAMP-PKA pathway and Tup1p | ↑Hypha formation | Zheng and Wang (2004) |
| *CCN1* | $G_1$ cyclin; role in maintaining hyphal growth | ↑Hypha formation | Loeb et al. (1999) |

(*continued on next page*)

**Table 2** (*continued*)

| Genes | Gene functions | Involvement in morphogenesis | References |
|---|---|---|---|
| *CLN3* | $G_1$ cyclin; is important for yeast budding and negatively regulates the yeast-to-hyphal transition | ↓Hypha formation | Bachewich and Whiteway (2005) and Lazo et al. (2005) |
| *CLB2, CLB4* | B-cyclins that are negative regulators of polarized growth | ↓Hypha formation<br>↓Pseudohypha formation | Bensen et al. (2005) |
| *Others genes* | | | |
| *CDC10, CDC11* | Non-essential septin genes | cdc10 and cdc11 mutants show abnormal hyphal structure | Warenda et al. (2003) |

*Note*: ↑: induction,↓: suppression.
Observations are based on knockout mutagenesis studies.
[a] The expression of these genes is regulated by farnesol.

2001) and PKA (Bcy1p, Tpk1p and Tpk2p) (Cassola et al., 2004; Cloutier et al., 2003) (Table 2, Fig. 1). Eventually, the PKA pathway activates an important transcription factor encoded by *EFG1* (Stoldt et al., 1997) that induces the expression of hyphal-specific genes (e.g. *HWP1*, *HYR1* and *ALS1*) (Fu et al., 2002; Leng et al., 2001; Sharkey et al., 1999). MAPK pathways typically consist of three kinases; MAPKKK, MAPKK, and MAPK that are sequentially activated one after the other by phosphorylation. There are several different MAPK pathways that have been described and linked to the morphological changes of *C. albicans* (e.g. Cek1p, Hog1p, and Mkc1p MAPK pathways) (Alonso-Monge et al., 2009b; Cheetham et al., 2007; Csank et al., 1998; Eisman et al., 2006; Leberer et al., 1996, 2001; Navarro-García et al., 1998). Fig. 1 illustrates how these signaling pathways and regulatory components are interconnected, and Table 2 summarizes how these components lead to modifications in cell wall organization, cell polarity, metabolism, cell cycle, virulence factors, and morphogenesis. Furthermore, transcriptome studies have identified several hyphal-suppressing genes in *C. albicans*. These repressor genes, such as *TUP1*, *SSN6*, *NRG1*, *MIG1*, and *HOG1*, are involved in the regulation of central carbon metabolism (Braun and Johnson, 1997; Hwang et al., 2003; José et al., 1996; Murad et al., 2001) as illustrated in Table 3. There are many other genes that are known to be involved in the morphological switch of *C. albicans*. The role of those genes and how they may influence, or have their expression changed during, morphogenesis are briefly summarized in Table 2.

## 3. Quorum sensing molecules and *C. albicans* morphogenesis

The phenomenon of "quorum sensing" is being increasingly recognized as a fundamental aspect of microbial cell-to-cell communication and signaling. Fuqua et al. (1994) first coined this term to describe the cooperative behaviour of bacterial cells that can only take place when a certain cell population density threshold is reached. Quorum sensing is often referred to as autoinduction, a process by which individual cells release small diffusible molecules into their environment and these molecules are sensed by all cells in the population (Gray et al., 1994; Hense et al., 2007; Nealson, 1977). When high cell density is reached, these autoinducing molecules accumulate above a certain threshold level, activating and/or repressing certain genes (Fuqua et al., 1994), which in turn induce complex cellular behaviour such as secretion of extracellular enzymes (Rosenberg et al., 1977), bioluminescence (Eberhard, 1972; Eberhard et al., 1981; Fuqua et al., 1994), plasmid transfer (Piper et al., 1993), antibiotic biosynthesis (Bainton et al.,

**Table 3**
The effect of morphogenesis-related genes, and farnesol, on *Candida albicans* metabolism based on DNA array studies or large-scale protein analyses*.

| Metabolism of: | *EFG1* | *GCN4* | *HOG1* | *TUP1* | *MIG1* | *NRG1* | *RIM101* | *SSN6* | *NGT1* | Farnesol |
|---|---|---|---|---|---|---|---|---|---|---|
| Alanine | | | | | | | | | | |
| Arginine | | ↑ | | | | | ↑pH8 | | | |
| Asparagine | | ↑ | | | | | ↓pH4 | | | |
| Aspartate | | | | | | | | | | |
| Cysteine | | | | | | | | | | |
| Ergosterol biosynthesis | ↓ | | | | | ↓ | | | | |
| Glutamate | ↓ | ↑ | | ↓ | ↓ | ↓ | ↑pH8 | | | |
| Glutamine | | | | | | | | | | |
| Glycine | | | | | | | | | | ↑ |
| Glycolysis | ↑ | ↑ | ↑ | | | | | ↓ | ↓ | ↓ |
| Glyoxylate shunt | | | | | | | | | | ↓ |
| Histidine | | ↑ | | ↓ | | | ↓pH4<br>↑pH8 | | | |
| Isoleucine | | ↑ | | | | | ↓ pH8 | | | |
| Leucine | | ↑ | | ↓ | ↓ | ↓ | | | | |
| Lysine | | ↑ | | | | | | ↓ | | |
| Methionine | | ↑ | | | | | | | | |
| Pentose phosphate | | ↑ | | | | | | | | |
| Phenylalanine | | ↑ | | | | | | | | |
| Proline | | ↑ | | | | | | | | |
| Serine | | ↑ | | | | | | | | |
| TCA cycle | ↓ | ↑ | ↓ | | | | | | | |
| Threonine | | ↑ | | | | | | | | |
| Tryptophan | | ↑ | | | | | | | | |
| Tyrosine | | ↑ | | | | | | | | |
| Valine | | ↑ | | | | | | | | |

*Note*: ↑: gene/farnesol upregulates one or more enzymes in a particular biochemical pathway.
↓: gene/farnesol downregulates one or more enzymes in a particular biochemical pathway $\downarrow^{pH4}$: assayed at pH 4, $\uparrow^{pH8}$: assayed at pH 8.

1992), biofilm development (Alem et al., 2006), and morphological switches (Hornby et al., 2001). Despite quorum sensing being well-characterized and evolutionarily-conserved between diverse bacterial species (Gray and Garey, 2001; Gray et al., 1994), only a few quorum sensing like-responses have been reported in eukaryotes, such as *H. capsulatum* (Kügler et al., 2000), *C. albicans* (Chen et al., 2004; Hornby et al., 2001), and *Saccharomyces cerevisiae* (Chen and Fink, 2006). Curiously, in each of these studies quorum sensing was associated with the morphological switch from yeast-to-filamentous forms, or vice versa.

Eukaryotic quorum sensing is best studied in *C. albicans*. This fungus has the greatest number of quorum sensing molecules (QSMs) identified to date. Tryptophol and phenylethyl alcohol were the first QSMs identified in *C. albicans* (Lingappa et al., 1969). These QSMs are produced by *C. albicans* and inhibit both cell growth and germ tube formation - whether the inhibition of germ tube formation is due to the inhibition of growth remains unclear. In recent years, three additional QSMs have been isolated from *C. albicans*; farnesol, tyrosol and farnesoic acid (Chen et al., 2004; Hornby et al., 2001; Hornby and Nickerson, 2004; Oh et al., 2001), although farnesoic acid has only been reported in one *C. albicans* strain (ATCC 10231, Oh et al., 2001) and has a lower activity than farnesol (Hornby and Nickerson, 2004).

Farnesol is the best characterized QSM in *C. albicans* and it is known to block the yeast-to-filamentous transition at high cell density, as well as under other hyphal-inducing conditions (e.g. serum, proline, and N-acetylglucosamine) (Hornby et al., 2001); but it is incapable of stopping the elongation of pre-existing hyphae (Mosel et al., 2005; Navarathna et al., 2005). Moreover, farnesol is continuously released into the environment during growth, and its accumulation in the medium is roughly proportional to the cell density (Hornby et al., 2001). It has been proposed that farnesol is secreted by the cells to inhibit germ tube formation in the late stage of biofilm development where there is a high density of interwoven filamentous cells, and, therefore, it promotes the dispersal of yeast cells to colonize new environments (Alem et al., 2006). After farnesol was discovered in *C. albicans* cultures, several studies have been undertaken to investigate the mechanisms by which QSMs affect morphogenesis. For instance, Sato et al. (2004) used RT-PCR to show that farnesol inhibited MAP kinase cascades via the suppression of *HST7* and *CPH1* gene expression (Fig. 1). Hog1p phosphorylation also increased in the presence of farnesol (Smith et al., 2004). Cao et al. (2005) demonstrated that several morphogenesis-associated genes were downregualted (e.g. *CRK1* and *PDE2*) and some upregulated (e.g. *TUP1*) by the presence of farnesol. It has been suggested that hyphal formation induced by the cAMP-PKA pathway can be repressed by farnesol which suppresses the *RAS1-CDC35* pathway (Davis-Hanna et al., 2008). Kebaara et al. (2008) showed that farnesol inhibits hyphal formation by upregulating the global repressor of *TUP1* because it failed to suppress hyphal development in *tup1*/*tup1* and *nrg1*/*nrg1* null-mutants. Recently, Román et al. (2009) showed that farnesol prevents the activation of Cek1p, which is a part of the MAPK cascade. In summary, the studies to date show that farnesol inhibits *C. albicans* morphogenesis by suppressing both MAPK and cAMP-PKA pathways and promoting the expression of hyphal-suppressor genes such as *TUP1* and *HOG1* (Fig. 1). How yeast cells sense farnesol, however, is still unclear.

Tyrosol is another QSM produced by *C. albicans*. It has been observed that when a dense culture of *C. albicans* is diluted into fresh medium there is long lag-phase before exponential growth initiates (Chen et al., 2004). This lag period can be shortened, and germ tube formation can be enhanced, when tyrosol is supplied (Chen et al., 2004). Alem et al. (2006) also suggested that tyrosol stimulated hypha formation in the early and intermediate phases of *C. albicans* biofilm formation. It seems that tyrosol does not induce germ tube formation when *C. albicans* grows under non-filamentous-inducing conditions but rather accelerates the morphological switch from yeast-to-hyphal growth under favourable environmental conditions (Chen et al., 2004). In contrast to farnesol, little is known about how tyrosol exerts its effects. A study of gene expression profiles of *C. albicans* cells at different cell densities with and without tyrosol suggested that the acceleration of germ tube formation may simply be due to upregulation of genes associated with DNA replication (e.g. DNA polymerase, chromosome-separation factor) and the cell cycle (e.g. cell cycle checkpoint protein) (Chen et al., 2004).

Together, these studies demonstrate that the morphogenesis of *C. albicans* is under the positive and negative regulation of QSMs in response to cell density. QSMs such as tryptophol, phenylethyl alcohol, and farnesol suppress hyphal formation when cells grow at high density. The QSM tyrosol accelerates germ tube formation at low cell density (Fig. 2). QSMs appear to have other roles in addition to affecting morphogenesis. Farnesol, for example, enhances *C. albicans* resistance to oxidative stress (Westwater et al., 2005), and tyrosol can act as an antioxidant, protecting *C. albicans* cells during phagocytosis by neutrophils (Cremer et al., 1999). Moreover, when growing in the human body *C. albicans* often grows in a polymicrobial environment and QSMs appear to be also involved in inter-species competition (Shank and Kolter, 2009). Farnesol not only inhibits filament formation in other *Candida* species (e.g. *Candida dubliniensis* and *Candida tropicalis*) (Henriques et al., 2007; Zibafar et al., 2009), it also induces apoptosis in some fungi (e.g. *S. cerevisiae*, *Aspergillus nidulans*, and *Penicillium expansum*), and suppresses the growth of *Paracoccidioides brasiliensis* (Derengowski et al., 2009; Fairn et al., 2007; Liu et al., 2009; Semighini et al., 2006). In contrast, when *C. albicans* is exposed to other QSMs such as 3-OXO-C12 homoserine lactone from *Pseudomonas aeruginosa*, its filamentous growth is suppressed (Hogan et al., 2004). Interestingly, farnesol seems to be also involved in *C. albicans*-host interactions. Proteomic approaches have shown that farnesol triggers apoptosis in both human oral carcinoma cells and *C. albicans* itself via classic apoptotic pathways (Scheper et al., 2008; Shirtliff et al., 2009). It appears that *C. albicans* is more susceptible to farnesol-mediated cell death when log-phase cells grow under nutrient-poor conditions (Langford et al., 2010). Dècanis et al. (2009) demonstrated that farnesol upregulates the expression of toll-like receptor 2, and increases the production of interleukin-6 and β-defensin 2 in the engineered tissue of human oral mucosa. The same authors suggest that farnesol promotes epithelial cell immunity against *C. albicans* (Dècanis et al., 2009). Moreover, Ghosh et al. (2010) showed that farneosl induces the expression of inflammatory cytokines in the macrophage. Therefore, these studies clearly demonstrate that QSMs play complex roles in *C. albicans*-host and *C. albicans*-interspecies interactions.

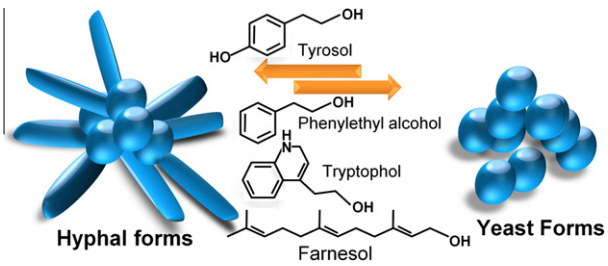


**Fig. 2.** The effect of quorum sensing molecules on the dimorphic transition of *C. albicans*. Tyrosol accelerates hypha formation, while farnesol, tryptophol, and phenylethyl alcohol suppress hypha development.

## 4. *In silico* reconstruction of the central carbon metabolism of *C. albicans* and the biosynthesis of quorum sensing molecules

The central carbon metabolism of most organisms is highly conserved comprising both catabolic and anabolic biochemical reactions. Central carbon metabolism is indispensable for cellular growth and any major cellular event, such as morphogenesis, will certainly be accompanied by significant changes in these important pathways. Therefore, knowledge of the different biochemical pathways involved in the central carbon metabolism of *C. albicans*, as well as how they are affected by the morphogenetic process, is crucial to understand the mechanisms of morphogenesis in this fungus.

Most of the genes thought to encode enzymes involved in the central carbon metabolism of *C. albicans* have been annotated by individual *in vitro* studies and by high-throughput transcriptomics (Bensen et al., 2004; Doedt et al., 2004; Enjalbert et al., 2006; Fradin et al., 2005; García-Sánchez et al., 2004; García-Sánchez et al., 2005; Harcus et al., 2004; Hromatka et al., 2005; Karababa et al., 2004; Lan et al., 2004; Lorenz et al., 2004; Murad et al., 2001; Nantel et al., 2002; Nett et al., 2009; Rogers and Barker, 2002; Sexton et al., 2007; Shirtliff et al., 2009; Singh et al., 2005; Swoboda et al., 1994; Tournu et al., 2005) and proteomics studies (Cabezón et al., 2009; Fernández-Arenas et al., 2007; Hernández et al., 2004; Kusch et al., 2008; Pitarch et al., 2004; Shirtliff et al., 2009; Thomas et al., 2006; Urban et al., 2003; Yin et al., 2004). We have reconstructed *in silico* the central carbon metabolism of *C. albicans* directly from its non-annotated genome sequence available from GenBank, using a program called IdentiCS (Sun and Zeng, 2004). Then the metabolic pathways were curated based on three publicly available online-databases: the *Candida* Genome Database – CGD (http://www.candidagenome.org/), the *Saccharomyces* Genome Database – SGD (http://www.yeastgenome.org/), and the Kyoto Encyclopedia of Genes and Genomes-KEGG (http://www.genome.jp/kegg/) (Fig. 3).

### 4.1. Glycolysis

Genes encoding all glycolytic enzymes in *C. albicans* have been identified and are conserved across fungi. Although the mRNA expression of glycolytic genes is not regulated tightly and fluctuates during the yeast-to-hyphal switch (Swoboda et al., 1994), some differences in the activities of glycolytic enzymes have been correlated with yeast and hyphal growth (Schwartz and Larsh, 1982). For instance, the specific activity of hexokinases in the hyphal form is almost twice that in the yeast form (Schwartz and Larsh, 1982). This might indicate a higher glycolytic flux during hyphal growth. Several glycolytic genes are regulated by signaling pathways associated with morphogenesis. These include enzymes such as hexokinase II (upregulated by Efg1p and downregulated by Ssn6p and Rgt1p) (Doedt et al., 2004; García-Sánchez et al., 2005; Sexton et al., 2007), phosphofructokinase (downregulated by Rgt1p) (Sexton et al., 2007), glucose-6-phosphote isomerase (upregulated by Efg1p) (Doedt et al., 2004), fructose–bisphosphate aldolase (upregulated by Efg1p, Gcn4p, Hog1p) (Doedt et al., 2004; Enjalbert et al., 2006; Yin et al., 2004), phosphoglycerate kinase (upregulated by Gcn4p and Hog1p) (Enjalbert et al., 2006; Yin et al., 2004), and pyruvate kinase (upregulated by Gcn4p and Hog1p) (Enjalbert et al., 2006; Yin et al., 2004). In addition, Shirtliff et al. (2009) used a proteomic analysis to demonstrate that several glycolytic enzymes (e.g. glyceraldehyde 3-phosphate dehydrogenase, enolase, phosphoglycerate mutase and pyruvate kinase) were downregulated when *C. albicans* was exposed to farnesol.

### 4.2. Pentose phosphate pathway

In anaerobic respiration, the pentose phosphate pathway is coupled with glycolysis to generate both cytosolic NADPH and ribose. The NADPH provides oxidizing energy for biosynthetic reactions (e.g. synthesis of amino acids, fatty acids, and sugar alcohols) while ribose is used in the biosynthesis of nucleotides (e.g. nucleic acids and redox cofactors). The conversion of glucose 6-phosphate to 6-phosphogluconolactone by a NADP-dependent glucose 6-phosphate dehydrogenase (G6PDH) is the first reaction, and the key-regulatory step, in the pentose phosphate pathway. A putative G6PDH is encoded by the *ZWF1* gene in *C. albicans* and its expression is upregulated by Gcn2p and Gcn4p (Tournu et al., 2005).

### 4.3. Pyruvate dehydrogenase

In aerobic respiration, pyruvate produced by glycolysis and the pentose phosphate pathway is mainly oxidatively decarboxylated to acetyl-CoA by the pyruvate dehydrogenase multi-complex enzyme. This enzyme is highly conserved across species, and the *C. albicans* genome contains genes with high homology to the *S. cerevisiae* operon encoding all subunits of pyruvate dehydrogenase. Disruption of one of the pyruvate dehydrogenase subunit genes (*PDX1*) in *C. albicans* resulted in a deficiency in filamentous growth (Vellucci et al., 2007). Thus the availability of acetyl-CoA may be required for the morphogenesis of *C. albicans.*

### 4.4. TCA cycle

The tricarboxylic acid (TCA) cycle is a central hub of carbon metabolism (Fig. 3) and, under aerobic conditions, acetyl-CoA formed from pyruvate is oxidized completely to carbon dioxide, water, and chemical energy through this pathway. This process is catalyzed by a series of conserved enzymes. All genes involved in the TCA cycle have been found in the *C. albicans* genome and all the TCA cycle enzymes have been extracted from *C. albicans* cells (Rao et al., 1962). Some TCA cycle enzymes are regulated by signaling pathways. For example, α-ketoglutarate dehydrogenase, succinate dehydrogenase, fumarase, citrate synthase, and malate dehydrogenase are repressed by the Efg1p transcription factor (Doedt et al., 2004), which appears to be involved in hyphal formation (Leng et al., 2001; Stoldt et al., 1997). Citrate synthase is downregulated by Hog1p and cis-aconitase is upregulated by Gcn4p (Enjalbert et al., 2006). The TCA cycle is, however, *amphibolic* because the cycle not only catabolically decarboxylates pyruvate but it also has anabolic functions. Intermediate compounds of the TCA cycle are used as precursors for the biosynthesis of building blocks for the cell (e.g. amino acids and lipids). Therefore, a constant inflow of carbon to supply intermediate compounds for amino acid and lipid biosynthesis is essential for cell growth. An example of a metabolic strategy to maintain the supply of TCA cycle intermediates is the glyoxylate shunt.

### 4.5. Glyoxylate shunt

The glyoxylate shunt assimilates two-carbon molecules such as ethanol and acetate into the TCA cycle; this process not only supplies TCA cycle substrates but also allows microbial growth in environments where only two-carbon compounds are available. The glyoxylate shunt can be considered as a shortcut version of the TCA cycle. The cycle bypasses two decarboxylation steps and directly converts isocitrate to malate using two enzymes: isocitrate lyase (encoded by *ICL1*) and malate synthase (encoded by *MLS1*) (Fig. 3). The regulation of the glyoxylate shunt is primarily via the activity of isocitrate lyase, which is downregulated by the presence of the quorum sensing molecule farnesol (Enjalbert and Whiteway, 2005) and is usually repressed by glucose in fungi. Although there has been no direct report on the role of the glyoxylate shunt in *C. albicans* morphogenesis, Lorenz and Fink (2001)

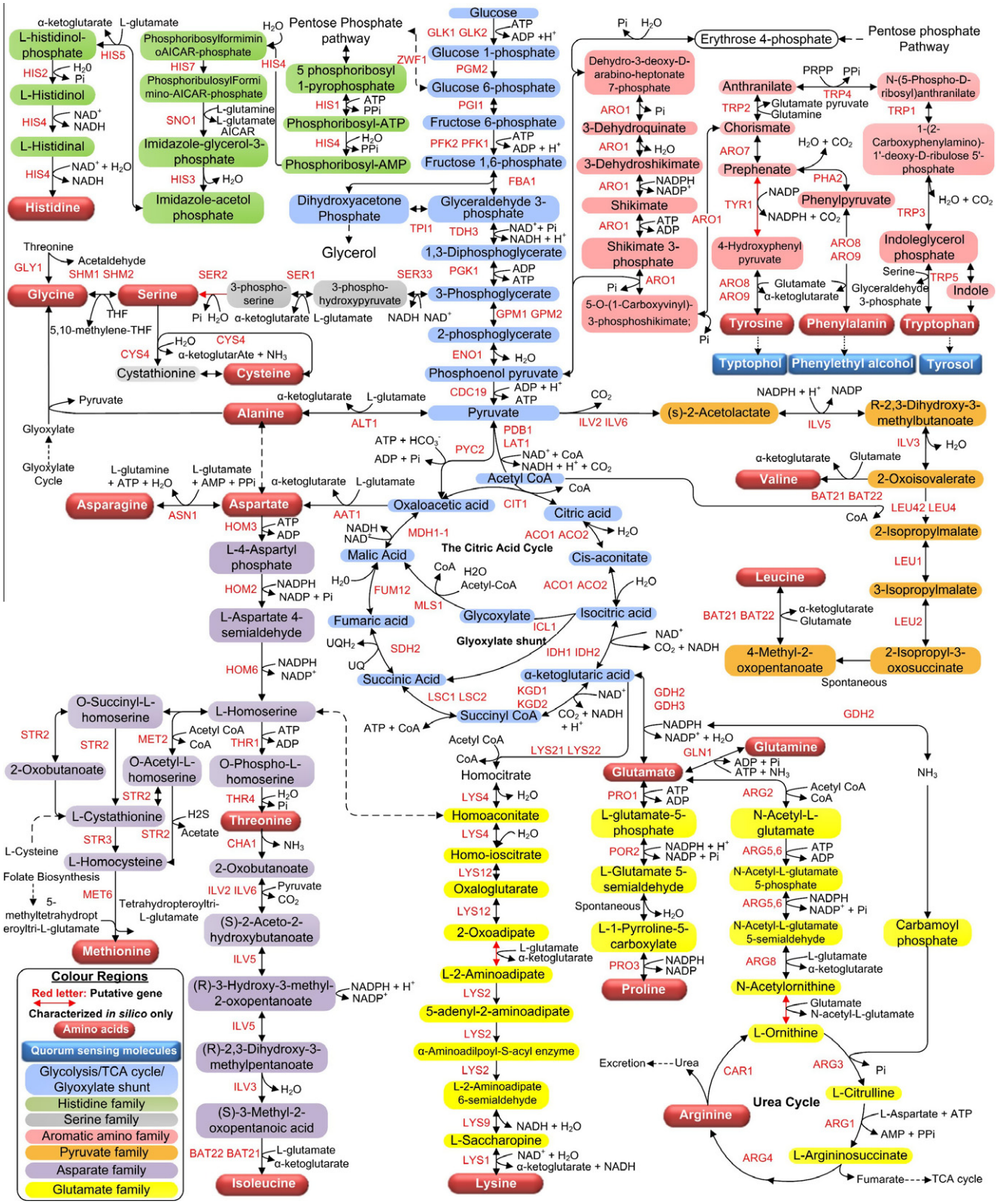


**Fig. 3.** The *in silico* reconstruction of the central carbon metabolism of *C. albicans*. Blue shading indicates the intermediate metabolites of glycolysis and the TCA cycle that act as key precursors for the biosynthesis of amino acids. The intermediates for biosynthesis of individual amino acids are differentiated by different colours and red 3D boxes represent the final amino acid products. Blue 3D boxes indicate quorum sensing molecules derived from aromatic amino acids and the putative genes encoding enzymes are in red text. The few reactions not verified by *in vitro* studies are indicated by red lines.

showed that the disruption of both *ICL1* and *MLS1* reduced *C. albicans* virulence using a mouse model of intravenous infection.

### 4.6. Amino acid biosynthesis

The biosynthesis of amino acids is achieved through a series of biochemical reactions that can be classified into six distinct pathways. Each amino acid pathway derives its carbon skeleton from a common precursor which is an intermediate compound of glycolysis or the TCA cycle. In *C. albicans*, the glycolytic pathway provides precursors for the biosynthesis of four amino acid families: the histidine, serine, pyruvate and aromatic families. Only the aspartate and glutamate family precursors are derived from the TCA cycle (Fig. 3).

#### 4.6.1. Glutamate biosynthesis

Glutamate is synthesized directly from α-ketoglutarate by an NADPH-dependent glutamate dehydrogenase (GDH). This is an important reaction in central carbon metabolism because it serves to assimilate ammonia for the biosynthesis of several other amino acids and at the same time it maintains the redox equilibrium in the cell. The NADH-dependent glutamate dehydrogenase (Gdh2p) favors the catabolic deamination of glutamate to α-ketoglutarate. Therefore, Gdh2p is an important enzyme in the biosynthesis of other amino acids (e.g. aspartate, tyrosine, phenylalanine, etc.). Three glutamate dehydrogenase genes have been identified in *S. cerevisiae* but only *GDH2* and *GDH3* have orthologues in the *C. albicans* genome. NADH-dependent *GDH2* is transcriptional repressed by Tup1p, Nrg1p and Mig1p (Murad et al., 2001). NADP-dependent *GDH3* is downregulated by Efg1p (Doedt et al., 2004), and upregulated 2-fold by Rim101p at pH 8 (Bensen et al., 2004).

#### 4.6.2. Aromatic amino acid and quorum sensing molecule biosynthesis

The discovery that extracellular aromatic alcohols act as quorum sensing molecules during fungal morphogenesis makes aromatic amino acid biosynthesis an important component of the central carbon metabolism regarding morphogenesis. But how the aromatic alcohols are synthesized from aromatic amino acids in *C. albicans* is still unclear. In contrast, the production of aromatic alcohols in *S. cerevisiae* has been well-characterized. Aromatic alcohols are derived from aromatic amino acid catabolism via the Ehrlich pathway (Felix, 1907). This process in *S. cerevisiae* involves three consecutive enzymatic steps; a transaminase (encoded by *ARO8, ARO9*), a decarboxylase (encoded by *ARO10*), and reduction by alcohol dehydrogenase (encoded by *ADH*) (Hazelwood et al., 2008; Sentheshanmuganathan, 1960). It is proposed that the biosynthesis of aromatic alcohols such as tyrosol, tryptophol, and phenylethyl alcohol in *C. albicans* (Fig. 2), follows the same biosynthetic pathway as in *S. cerevisiae* (Ghosh et al., 2008). This study demonstrated that the biosynthesis of aromatic alcohols by *C. albicans* decreased when the *ARO80* gene, which encodes a transcriptional activator known to increase the expression of Aro9p and Aro10p in *S. cerevisiae*, was deleted (Ghosh et al., 2008).

#### 4.6.3. Regulation of global amino acid biosynthesis

There are several morphology-associated genes that also regulate multiple amino acid biosynthetic pathways in response to starvation and pH changes. When amino acids are limiting growth, *C. albicans* switches from yeast to filamentous growth (Tripathi et al., 2002). This phenomenon is regulated by the transcriptional activator Gcn4p in an *EFG1*-dependent fashion (Tripathi et al., 2002). The double deletion *gcn4*/*gcn4* blocks amino acid starvation from inducing morphogenesis, but the *efg1*/*efg1* knockout mutants fail to express this *GCN4* phenotype (Tripathi et al., 2002). Gcn4p is not only involved in the dimorphic switch of *C. albicans*, but it also acts as a global regulator of metabolism in response to amino acid starvation (Tournu et al., 2005; Tripathi et al., 2002). Tripathi et al. (2002) found from DNA microarray analysis that, under amino acid starvation conditions, Gcn4p upregulates numerous enzymes involved in amino acid biosynthesis, except those responsible for the biosynthesis of cysteine, glycine, alanine, aspartate and glutamine (Table 3) (Tournu et al., 2005). Rim101p is a pH-response regulator that is activated at alkaline pH (Li and Mitchell, 1997). In turn, Rim101p regulates the expression of pH-response regulators (Phr1p and Phr2p) involved in the pH-dependent morphogenesis of *C. albicans* (Ramon et al., 1999). Bensen et al. (2004) compared transcriptional profiles between *rim101*/*rim101* null-mutants and the wild type strain. They found that Rim101p upregulates arginine, glutamine, and histidine biosynthetic enzymes at pH 8, while asparagine and histidine biosynthetic enzymes are downregulated at pH4, respectively (Table 3).

The *in silico* reconstruction of central carbon metabolic pathways based on the *C. albicans* genome (Fig 3) enables us to integrate post-genomic studies into a metabolic network that helps elucidate the physiological and biochemical mechanisms governing the morphological switch of *C. albicans*.

## 5. Central carbon metabolism, virulence, and morphogenesis of *C. albicans*

In additional to its role in morphogenesis, central carbon metabolism has increasingly been recognized for its importance in fungal pathogenicity. It has been shown that the deletion of glycolytic transcriptional regulators (*TYE7*, *GAL4*), a gluconeogenic gene (*FBP1*), glyoxlate cycle genes (*ICL1, MLS1*), or a β-oxidation gene (*FOX2*), attenuates the virulence of *C. albicans* in a murine model of systemic infection (Askew et al., 2009; Lorenz and Fink, 2001; Piekarska et al., 2006; Ramírez and Lorenz, 2007). Interestingly, *C. albicans* appears to modulate these carbon assimilatory pathways during infection. When glucose is at similar levels to that found in the bloodstream there is an activation of glycolysis and repression of both the glyoxylate cycle and gluconeogenesis in *C. albicans* (Barelle et al., 2006; Rodaki et al., 2009). In contrast, several transcriptomic studies have demonstrated that following the phagocytosis of *C. albicans* by neutrophils or macrophages, there is a downregulation of glycolysis, and an upregulation of the glyoxlate cycle, gluconeogensis, and β-oxidation (Fradin et al., 2005; Lorenz et al., 2004; Rubin-Bejerano et al., 2003). Since all these metabolic pathways involve the utilization of non-fermentable carbon sources (e.g. amino acids, ethanol, acetate, and fatty acids), it seems likely that *C. albicans* can alter its central carbon metabolism to utilize alternative carbon sources in response to host defences or to changes in the environment, and this metabolic reprogramming is important for the virulence of *C. albicans*. Although the morphological switch from yeast-to-hyphae is observed after *C. albicans* is engulfed by macrophages, Lorenz et al. (2004) suggested that those underling metabolic changes are independent from morphogenesis.

Lorenz et al. (2004) also demonstrated that genes for L-arginine biosynthesis and degradation were upregulated after *C. albicans* cells were engulfed by macrophages, and other groups have shown that concentrations of $CO_2$ greater than 50% (v/v) enhanced filamentous growth (Bahn and Mühlschlegel, 2006; Klengel et al., 2005; Mock et al., 1990; Sims, 1986). Ghosh et al. (2009) have proposed a mechanism, involving arginine, which connects these two observations. They suggest that arginase (Car1p) converts arginine to urea, which in turn is cleaved into $NH_3$ and $CO_2$ by the amidolyase enzyme (Dur1,2p [sic]). They show that the *dur1,2*/*dur1,2* null-mutant cannot form germ tubes in macrophages, and that the phenomenon of arginine-induced hyphal formation is not

observed in *efg1*/*efg1* strains. Therefore, once inside a macrophage, it is proposed that *C. albicans* produces arginine and arginine degradation produces $CO_2$. The $CO_2$ may then activate adenylyl cyclase (Cdc35p), which in turn activates the cAMP-PKA signaling pathway and Efg1p to induce the yeast-to-hyphal transition (Fig. 1) and thereby *C. albicans* escapes from the macrophage (Klengel et al., 2005).

## 6. The effect of metabolic genes on the utilization of carbon sources

There are several metabolic genes associated with morphogenesis or virulence that seem to affect the ability of *C. albicans* to utilize carbon sources. Firstly, trehalose-6-phosphate synthase (*TPS1*) is a gene involved in the first step of trehalose biosynthesis and it regulates glucose influx (Ernandes et al., 1998). The *tps1*/*tps1* null-mutant is unable to grow on glucose or fructose as a sole carbon source but this mutant is capable of growing on other carbon sources such as galactose or glycerol (Zaragoza et al., 1998). In addition, this mutant is impaired in hyphal formation (Zaragoza et al., 1998). Another gene related to trehalose biosynthesis is the cell wall-linked acid trehalase (*ATC1*) (Pedreño et al., 2004). The *atc1*/*atc1* null-mutant is incapable of growing on exogenous trehalose as sole carbon source and the mutant has diminished capacity to form hyphae in various media (e.g. serum, spider medium and Lee's medium) (Pedreño et al., 2007).

Galactose metabolism also plays a role in the morphogenesis of *C. albicans.* UDP-galactose-4-epimerase (*GAL10*) is a key enzyme in galactose metabolism that converts UDP-galactose into UDP-glucose. The glucose generated can then be fed into glycolysis as a carbon and energy source. The *gal10*/*gal10* null-mutant is unable to grow on galactose as sole carbon source (Singh et al., 2007). Compared to wild type, the mutant also exhibits increased hyphal formation in rich media, Lee's medium and spider medium (Singh et al., 2007). Recently, Hgt4p has been reported as a galactose and glucose sensor. Indeed, the *hgt4*/*hgt4* null-mutant cannot grow on either glucose or galactose in the presence of the respiration inhibitor antimycin A (Brown et al., 2009, 2006). The *hgt4*/*hgt4* mutant is hypo-filamentous and less virulent in a mouse model of disseminated candidiasis (Brown et al., 2006).

In addition, carnitine biosynthesis and acetyl-CoA metabolism can affect the ability of *C. albicans* to utilize different carbon sources. Carnitine is an essential metabolite that acts as a shuttle to transport fatty acids and acetyl groups between intracellular compartments. Mutants lacking carnitine synthetic enzymes (e.g. trimethyl-lysine dioxygenase, trimethylaminobutyraldehye dehydrogenease, and butyrobetaine dioxygenase) or lacking carnitine acetyltransferase, which transfers the acetyl group from acetyl-CoA to carnitine, are unable to utilize non-fermentable carbon sources such as fatty acids, acetate, or ethanol as sole carbon sources (Strijbis et al., 2009; Zhou and Lorenz, 2008). Moreover, Carman et al. (2008) have shown that a *C. albicans* mutant strain with acetyl-CoA synthase (*ACS2*) deleted was unable to utilize glucose, acetate, or ethanol but the mutant cells were viable when given fatty acids or glycerol. The same authors deleted acetyl-CoA hydrolase (*ACH1*), an enzyme which hydrolysis acetyl-CoA to acetate, but this strain was fully virulent in a mouse model of disseminated candidiasis.

## 7. *In silico* reconstruction of the sterol biosynthetic pathway and farnesol biosynthesis in *C. albicans*

The sterol biosynthesis pathway generates compounds necessary for the maintenance of cellular structure. These sterols, such as ergosterol in fungi and cholesterol in mammalian cells, are essential for membrane integrity and permeability. The sterol biosynthesis pathway is targeted by several antifungal agents. In addition, sterol biosynthesis is potentially involved in the quorum sensing of dimorphic fungi because this pathway generates farnesol, the most well-characterized quorum sensing molecule involved in *C. albicans* morphogenesis.

Adopting the same approach we used for the central carbon metabolism, we have reconstructed, *in silico*, the *C. albicans* sterol biosynthetic pathway (Fig. 4). The first step in sterol biosynthesis is the condensation of acetyl-CoA and acetoacetyl-CoA into 3-hydroxy-3-methylglutaryl-CoA by hydroxymethylglutaryl-CoA synthase. Seven sequential reactions are then involved in the synthesis of farnesyl pyrophosphate, which is the precursor for the biosynthesis of farnesol. Surprisingly, the enzyme that synthesizes farnesol has not been fully described, but Hornby et al. (2003) claimed to have extracted an enzyme from *C. albicans* possessing this activity. Fungal and mammalian cells share a common sterol biosynthetic pathway from acetyl-CoA through farnesyl pyrophosphate to zymosterol (Fig. 4). From this point there are different pathways in fungi and mammals. 24-C-methyltransferase converts zymosterol into fecosterol leading to the biosynthesis of ergosterol in fungi, whereas 24-dehydrocholesterol reductase directs sterol biosynthesis into the production of cholesterol which serves as a precursor for steroid hormones (e.g. androgens and estrogens) in mammalian cells. In general, the biosynthesis of ergosterol is conserved between *C. albicans* and *S. cerevisiae.*

Interestingly, the presence of estrogens has been reported to have a profound effect on the morphogenesis of dimorphic fungi (Cheng et al., 2006; White and Larsen, 1997). Estrogen may contribute to the gender bias in human infection by another dimorphic and pathogenic fungus, *P. brasiliensis*, for which, contrary to *C. albicans,* the yeast form is the pathogenic state. In healthy individuals, *P. brasiliensis* infects mainly adult males (Borges-Walmsley et al., 2002). Estrogen has been shown to suppress the hyphal-to-yeast transition in *P. brasiliensis* and, thus, it has been proposed that adult women are less prone to infection by *P. brasiliensis* due to higher levels of estrogen in their bodies compared to males (Borges-Walmsley et al., 2002).

On the other hand, healthy women often develop recurrent vaginal candidosis, especially during pregnancy (Tarry et al., 2005). Clinical studies have shown that women are more likely to have symptomatic *Candida* infections when estrogen levels are high (Tarry et al., 2005), and estrogen has been shown to promote germ tube formation in *C. albicans* (Cheng et al., 2006; White and Larsen, 1997) which is the first step in the yeast-to-hypha transition (Whiteway and Bachewich, 2007). Low estrogen levels may be one reason why healthy adult males do not commonly develop candidosis.

Therefore estrogen, which seems to promote *Candida* infection in women, protects them from *P. brasiliensis* infection because this hormone induces the filamentous growth of both fungi. What is intriguing from the metabolic point of view is the fact that estrogens are synthesized by mammalian cells via the sterol biosynthetic pathway, which is used by fungi to synthesize farnesol (Nickerson et al., 2006). Thus, the sterol pathway appears to have an important role in both fungal morphogenesis and in pathogenesis.

## 8. The integration of quorum sensing and central carbon metabolism in *C. albicans*

QSMs are products of the central carbon metabolism of *C. albicans*. They function as communication signals and coordinately regulate the growth of *C. albicans* cells, in response to cell density. Their production, however, may simply reflect the flux within the central carbon metabolism pathways and their accumulation and

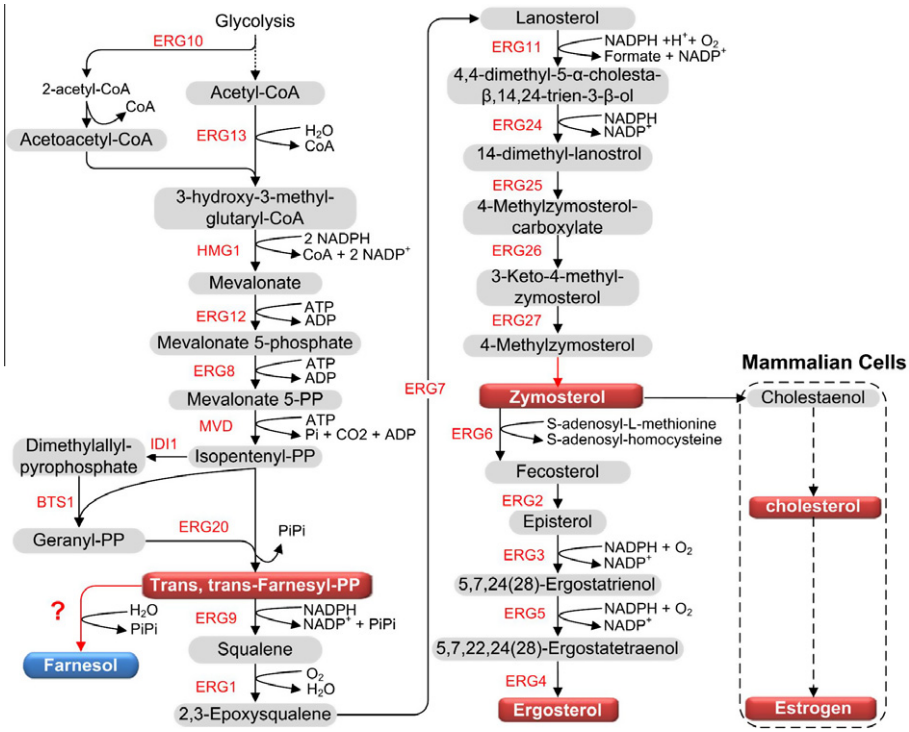


**Fig. 4.** The *in silico* reconstruction of the sterol pathway of *C. albicans* and mammalian cells. Farnesol, which suppress germ tube formation in *C. albicans*, is produced via the sterol pathway, but some enzymes involved in its biosynthesis are still to be identified. Mammals use the same pathway to synthesize estrogens, which promote germ tube formation in *C. albicans*.

signaling may provide feedback to these pathways to optimise growth under the particular environmental conditions. For example, if carbon and nitrogen sources are available to the cells this may stimulate flux though the pathways for the biosynthesis of QSMs such as farnesol that will repress the filamentous growth of *C. albicans* and, if carbon and/or nitrogen sources become scarce, flux through other pathways involved in the biosynthesis of QSMs that accelerate hypha formation, such as tyrosol, may be activated.

The metabolic hubs of central carbon metabolism are metabolites that take part in more than twenty different pathways and include pyruvate, NADH, NADPH, and ATP (Villas-Bôas et al., 2007). Thus, central carbon metabolism is highly interconnected and forms a metabolic network that responds very quickly to any environmental change. This is the part of cell metabolism most likely to include metabolic reactions involved in cell responses to QSMs in the environment. Indeed, several observations support the idea that central carbon metabolism provides the carbon sources for the synthesis of QSMs. As discussed above, farnesol, tyrosol, tryptophol, and phenyethyl alcohol are derived from glycolytic products. Aromatic QSMs are derived from phosphoenolpyruvate and farnesol is derived from acetyl-CoA. Therefore, if these molecules are synthesized as part of central carbon metabolism, their concentrations are likely to affect the flux distribution in these primary metabolic pathways by suppressing or inducing specific metabolic reactions. In addition, N-acyl homoserine lactones, which are common QMSs produced by many bacteria (e.g. *Pseudomonas corrugata*, *Erwina carotovora* and others (Dong et al., 2001; Licciardello et al., 2007; Schaefer et al., 1996)), are synthesized directly from methionine, which is derived from oxaloacetic acid in the TCA cycle, and are thus also part of central carbon metabolism. Moreover, the production of QSMs seems to be affected by the availability of their precursors. For instance, the presence of aromatic amino acids increases the level of tyrosol, tryptophol, and phenyethyl alcohol in *C. albicans* (Ghosh et al., 2008).

Despite the obvious connection between quorum sensing and central carbon metabolism, the role of primary metabolism in the mechanism of quorum sensing has not been investigated. We hypothesize that once extracellular QSMs reach a certain concentration, their passive diffusion across the cell membrane could affect the expression of specific genes or the activity of specific enzymes involved in morphogenesis. Indeed, fluorescently labeled farnesol analogs supplied to *C. albicans* cultures have been found in the cytoplasm of *C. albicans* (Shchepin et al., 2003). Thus, QSMs could rapidly up- and down-regulate particular metabolic pathways (e.g. aromatic amino acid biosynthesis and sterol biosynthesis), redistributing the metabolic flux of carbon through central carbon metabolism and inducing the morphological switch by altering the biosynthesis of cell wall components. Several transcriptomics studies have shown that the metabolic pathways from central carbon metabolism are highly affected by the presence of quorum sensing molecules (Table 3). Therefore, the study on the effect of QSMs on *C. albicans* morphogenesis in the context of central carbon metabolism has the potential to unravel important metabolic mechanisms underlying the morphogenetic process, and thus, should be pursued further.

## 9. Final remarks

The ability to study the behaviour of biological systems *in vivo* under different environmental conditions has increased with recent developments in genomics and post-genomic tools. Gene knockout experiments can demonstrate the involvement of individual genes in biological processes, but often it is unclear how the genes mediate their effects. Proteomic studies can confirm that changes in transcription associated with gene disruption, or environmental changes, result in altered protein expression. The integration of gene knockout, transcriptomic and proteomic studies has elegantly elucidated signaling pathways involved in *C. albicans* morphogenesis. This still, however, only gives a linear view of morphogenesis. This review has used the *C. albicans* genome data to

reconstruct the network of metabolic pathways involved in central carbon, sterol, and QSM metabolism. This will provide a framework which can guide the interpretation of metabolomic data and thus generate the fluxome and a more *three-dimensional* appreciation of how QSMs and environmental cues mediate their effects on morphology.

Morphogenesis is considered to be an important virulence factor for *C. albicans* and other dimorphic fungi. Central carbon metabolism and sterol biosynthesis not only supply carbon and lipid sources to generate the building blocks of new cellular structures in response to morphogenesis, but also supply precursors for the biosynthesis of the quorum sensing molecules involved in cell-cell communication and the coordinated dimorphic transition in a population of *C. albicans* cells. Together, the pre-existing genomic sequences and the *in silico* reconstruction of *C. albicans* biochemical pathways should enable a powerful systems biology study of this fungus that would be the cornerstone to assist in the elucidation of the metabolic mechanisms responsible for *C. albicans* morphogenesis and virulence.

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