

Review Article

Insights into *Candida Albicans*: A New Perspective on Pathogenic Factors and Regulatory Mechanisms

Mohadeseh Kamali¹ M.D., Mehdi Taheri Sarvtin^{2*} Ph.D.

¹Department of Internal Medicine, Faculty of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran

²Department of Medical Mycology and Parasitology, Faculty of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran

A B S T R A C T

Article history

Received: 15 Jan 2023

Accepted: 24 Apr 2023

Available online: 15 Jun 2023

Keywords

Candida albicans

Pathogenic

Regulatory factors

Candida albicans (*C. albicans*) is a polymorphic fungus that exists as a natural flora in the skin and mucosal surfaces of the body. However, under certain conditions, such as immunodeficiency, mucosal damage, antibiotic use, and cancer, this fungus can cause superficial and systemic infections. *C. albicans* is the most common opportunistic pathogenic fungus in humans and causes 60% of mucosal infections and 40% of candidemia cases. Several pathogenic factors have been identified that contribute to the pathogenic potential of this fungus. Among these factors, we can mention: hypha production, attachment, and biofilm formation, secretion of hydrolase enzymes, acquisition of micronutrients, adaptation to oxygen and nitrogen deficiency conditions, and growth at temperatures above 37 °C. This review article will investigate the pathogenic factors of *C. albicans* and their regulatory factors. For this purpose, articles published in national and international scientific databases, including PubMed/MEDLINE, Google Scholar, Elsevier databases, IranMedex, Scopus, SID, and Science Direct, were used. Keywords such as: “Candida,” “Fungi,” “Pathogenesis,” and “Virulence” were used to find the articles.

Introduction

Fungi are a diverse group of eukaryotic microorganisms that exist in yeast, mold, or a combination of the two forms as natural flora in humans, animals, or the surrounding environment [1, 2]. These microorganisms have diverse life cycle patterns for metabolism and cell shape adaptation, enabling them to adapt to changing ecosystems. However, it is estimated that there are between 1.5 and 5 million species of fungi; only about 72,000 species have been described, and only a few hundred of them have been mentioned as causing human disease. Some fungi, such as *Blastomyces* species, coccidiosis, and paracoccidioides, can cause disease in people without immune deficiency, and some fungi, which are called opportunists, such as *Aspergillus*, *Fusarium*, pseudopodium, and *Candida* species, mainly cause disease in people with immune system defects [3]. The genus *Candida* was isolated for the first time in 1844 from the sputum of a patient with tuberculosis. These fungi can metabolize glucose in aerobic and anaerobic conditions and grow at 37 °C. In addition to the environment, these fungi exist as normal flora in human and animal bodies, and their growth and reproduction are controlled by the immune system. In immune system failure, these fungi can grow on mucosal surfaces or other parts of the body and cause disease. *Candida albicans* (*C. albicans*), *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. auris*, *C. lusitaniae*, *C. krusei*, *C. stellatoidea*, *C. guilliermondii*, *C. famata*, and *C. dubliniensis* are the most

common *Candida* species isolated from clinical cases [4]. *C. albicans* is one of the main causes of superficial infections such as oral, vaginal, skin, and nail candidiasis, as well as systemic infections such as spleen, liver, heart, kidney, central nervous system, and candidemia [3, 5]. In addition, *C. albicans* or other *Candida* species are thought to be a role in triggering or aggravating psoriasis and atopic dermatitis [6-8]. Although an increase in non-*albicans* species of *Candida* has been observed in recent years, *C. albicans* is still the most common cause of candidiasis, especially candidemia [5]. Epidemiological data show that the mortality rate of invasive candidiasis caused by *C. albicans* is still high, and despite treatment, it is reported to be close to 40% [9]. *C. albicans* uses several pathogenic factors such as the production of hyphae, adhesion, and invasion, secretion of hydrolase enzymes, acquisition of micronutrients, adaptation to oxygen and nitrogen deficiency, and growth at temperatures above 37 °C to cause mucosal or systemic disease [3]. This review article will investigate the pathogenic factors of *C. albicans* and its regulatory factors.

In this review, articles published in national and international databases such as PubMed/MEDLINE, Google Scholar, Elsevier databases, IranMedex, Scopus, SID, and Science Direct with keywords including: “*Candida*” “Fungi”, “Pathogenesis,” and “virulence” were searched and related articles found during the years 1990-2022 were reviewed.

Pathogenic factors in *C. albicans***Hypha (mycelium) production**

Although the mycelium form of *C. albicans* can also be seen in the commensal state in tissue samples of patients, the predominant form of this fungus is mycelium. This phenomenon proves that the transformation of yeast into mycelium form is one of the important factors in the pathogenesis of *C. albicans* [3]. In addition, it has been shown that *C. albicans* strains that cannot produce hyphae have little pathogenic power. This indicates that hypha production plays a vital role in the effective pathogenicity of *C. albicans* [10]. The creation of hyphae may be effective for entering the bloodstream and creating candidemia [11]. Hyphae formation in the phagosome can help *C. albicans* escape phagocytosis and killing by macrophages [12]. The creation of hyphae plays a role in forming an optimal biofilm on medical devices and creating iatrogenic candidemia [13]. Host temperature, pH, and the availability of nutrients are environmental factors that play a role in changing the shape of *C. albicans* [14, 15]. The way yeast cells and mycelium grows is different. Mycelium growth mainly occurs in its tip, but in yeast, it mainly occurs in the bud and daughter cells and rarely in the mother cell. Unlike mycelium, which has permanent vertical growth, growth in yeasts grows vertically only at the beginning of separation from the mother cell, and then the growth becomes isotropic [16]. Cyclins are a large and diverse group of regulatory proteins in eukaryotes, each of which prefers specific substrates of the cyclin-dependent kinase

(CDK) complex. The cyclin subunit determines which protein is held close to the CDK and can be converted into a substrate, while the CDK determines where the substrate is phosphorylated. Therefore, while CDKs phosphorylate proteins, cyclins determine the choice of substrate proteins and the time and place of intracellular phosphorylation [17]. Cln1 and Cln2 cyclins are expressed in the G1 phase of the cell cycle. These cyclins in the primary buds of *C. albicans* cause polarization of the actin filaments of the cell skeleton to the bud tip and Vertical growth by concentrating the activity of GTPase (hydrolyzing guanosine triphosphate (GTP) to guanosine diphosphate (GDP) coded by the *cdc42* gene in the bud tip [17, 18]. While in the G2 phase of the cell cycle, meiotic cyclins change the vertical growth to isotropic growth by defocusing *cdc42* and polarizing the actin filaments of the cell skeleton from the tip of the bud [18]. Therefore, the difference in the growth of the yeast and mycelium states of *C. albicans* can be attributed to the difference in the polarization of actin filaments of the cell skeleton [19]. In filamentous fungi, the placement of cell growth in a small area of the cell surface at the tip of the hyphae requires a strong polarization of the cell biosynthetic apparatus, which includes the large-scale movement of membrane-containing vesicles and cell wall precursors towards the tip of the hyphae [20, 21]. This movement depends on the cytoskeleton's microtubule and the actin filaments and is coordinated by a vesicle organizing center (Spitzenkörper) located behind the hyphal tip [16]. Rapid exocytosis of

transferred vesicles increases the length of the hyphal tip, and this exocytosis must be balanced with endocytosis to recover extra membranes and enzymes that participate in cell wall biosynthesis [22, 23]. It is thought that the mechanism of hyphal elongation in *C. albicans* and filamentous fungi is similar; however, important differences are seen; For example, the growth of *C. albicans* hyphae is relatively slower and does not seem to require microtubules [24, 25]. In addition, in the hyphae of *C. albicans*, the movement of most secretory vesicles takes a shorter route than filamentous fungi [26]. Like other fungi, a protein complex called polarisome forms a cap at the growth site of *C. albicans* hyphae and in yeast and hyphae-like cells [27]. Compared with Spitzenkörper, polarisome proteins show much less turnover [28]. Using the Bni1 protein, polarisome may stimulate actin polymerization in hyphal tips [16].

Signaling pathways controlling hyphae production

Hyphae production in *C. albicans* is controlled by several signaling pathways:

Cek mitogen-activated protein kinase (MAPK) pathway

This pathway is activated by factors such as nitrogen deficiency and cell wall damage [29, 30]. Membrane proteins Sho1, Opy2, and Msb2 may also play a role in Cek stimulation [31]. Cyclic adenosine monophosphate protein kinase A (cAMP-PKA) pathway

In addition to morphology, this pathway plays a role in growth, glycogen synthesis, energy metabolism, and mitochondrial activity [32-34]. This pathway is activated by environmental stimuli such as serum, N-acetyl glucose amide (GlcNAc), amino acids, and carbon dioxide [35-37]. The cellular level of cAMP is also regulated by phosphodiesterase and adenylyl cyclase [9] (Fig. 1).

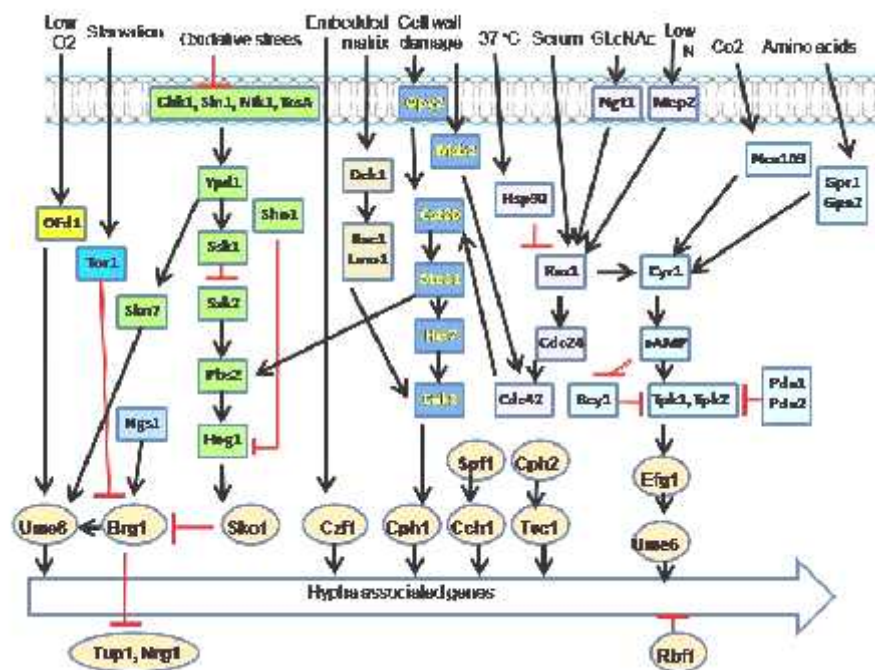


Fig. 1. Signaling pathways controlling hyphae production

High-osmolarity glycerol (HOG) MAPK pathway

This pathway can control mycelium production [9]. Hog1 is activated in high osmotic pressure, and after being phosphorylated, it is transferred to the nucleus, and by affecting the glycerol transporter and changes in transcription, it prevents the transformation of yeast into mycelium [9, 38] (Fig. 1).

Tup1-mediated negative regulatory pathway

Transcription factor Tup1 is a negative regulator of mycelium production. The synergistic effect of Tup1, Nrg1, and Rfg1 has been reported. Tup1 can repress transcription, and mutants lacking Tup1 can efficiently form hyphae without special induction conditions [9] (Fig. 1).

The role of pH in the regulation of hypha production

Acidic pH prevents the transformation of yeast into mycelium, while alkaline and neutral pH stimulate the production of hyphae [39, 40]. *C. albicans* can regulate the pH of the environment by metabolizing nutrients [9]. The *Rim101* gene plays a role in transmitting the pH signal and regulating the transcription of specific pH-dependent enzymes in fungi [9, 41]. Deletion of *Rim101* inhibits mycelia formed in alkaline pH. *PHR1* and *PHR2* genes are involved in synthesizing beta 1 and 3 glucan and beta 1 and 6 glucan and are regulated by *Rim101* at different pH. *PHR1* is expressed at pH less than 5.5 and *PHR2* at more than 5.5 [42]. The mutant strains in *PHR1* have incomplete growth in alkaline pH,

and the mutant strains in *PHR2* have poor growth in acidic pH [43].

Regulation of hypha elongation

Ume6, *Eed1*, and *Hgc1* are essential in hypha elongation [44-46]. *Eed1* is necessary for the expression of *Ume6* and plays an important role in mycelium maintenance [46]. In mutants lacking *Eed1* and *Ume6*, the growth in the liquid medium remains in the induction phase, and the cells cannot continue to grow. In the stable environment, these mutants grow only as yeast without mycelium production [47]. *Hgc1* plays its role along with Cdc28. Mutants lacking *Hgc1* can only produce very short germ tubes [48]. The expression of *Hgc1* is dependent on *Ume6*, and *Hgc1* is expressed in mutants lacking *Ume6*, but it cannot persist [49]. It has been shown that the phosphorylation of *Cek1* MAP kinase increases in mutants lacking *RAP1*; Therefore, *RAP1* may have an inhibitory role in hypha production [50] (Table 1).

Ability to adhere and form a biofilm

After the production of hyphae, the ability to adhere and form a biofilm is among the most important Virulence factors of *C. albicans* [9]. Attachment helps the organism to persist in the host and is, therefore, necessary for the spread and settlement of the fungus [51]. It is estimated that biofilm formation is related to 65 to 80% of microbial infections [52, 53]. 80% of *C. albicans* infections are directly or indirectly related to biofilm formation [54]. The production of hyphae and the ability to adhere together with the secretion of proteases and phospholipases facilitate the invasion of the

fungus into epithelial cells [51]. *C. albicans* have a set of proteins that bind it to host cells, non-living surfaces, and other microorganisms, and biofilm formation [55, 56]. Adhesive molecules called Als (agglutinin-like sequence) have been studied more than others. These proteins form a family with eight members, Als1-7 and Als9 [57]. Als1 is important in binding to epithelial, endothelial cells, and biological surfaces [9, 51]. It has been shown that increasing the expression of this molecule causes a 125% increase in binding [9]. It has been shown that Als3 plays an important role in endocytosis and invasion of host tissues [58-60]. Only Als1 and Als5 in Als family have the same function as Als3 [61]. Strains lacking Als5, Als6, or Als7 have normal binding power but slower growth [62]. Als2, Als4, and Als9 have not been investigated in the laboratory [9]. Hwp1 is another adhesive molecule that plays an important role in the attachment of *C. albicans* to host cells [54]. A synergistic effect for Als1 and Hwp1 has been reported for germ tube formation, an essential step for fungal pathogenesis [62]. It has been shown that the mutants lacking this adhesive molecule show less binding power to oral epithelial cells and also less pathogenic power in systemic candidiasis in mice [57]. Hwp1 does not seem to have a role in binding to endothelial cells [51]. Hwp1 and Als3 cooperate in the formation of biofilm [63].

The regulation of adherence and biofilm formation

Bcr1 plays an important role in regulating *C. albicans* hyphae adhesion molecules [64]. (Table 1, Fig. 2). Als3 is a key target for *Bcr1*

action [65]. Hwp1, which is an epithelial adhesion molecule, is also controlled by *Bcr1*. Mutants lacking *Bcr1* cannot form a significant biofilm in the tongue of immunodeficient mice due to defects in adherence [66]. The *Efg1* gene, which plays an essential role in hypha production, also plays a role in *C. albicans* attachment [61]. This gene's expression is influenced by the immune system. Mutants lacking *Efg1* have defects in cell layer formation on polystyrene surfaces due to changes in surface protein composition. In addition, the lack of *Efg1* function in some *C. albicans* strains, only the formation of pseudohyphae in solid medium and no growth in liquid medium are observed. *Ywp1* is also expressed only at the end of the logarithmic phase of yeast sols and is not found in pseudohyphae and mycelium. Yeasts with *Ywp1* form only one cell layer, while mutants lacking this gene can connect and form biofilm. Therefore, it seems that *Ywp1* has an inhibitory role in the attachment and formation of biofilm. *Sfp1* is another gene that plays an inhibitory role in the binding of *C. albicans* [65]. Increased expression of Als1, Als3, and Hwp1 and, as a result, increased binding strength is observed in mutants lacking *Sfp1*. Increasing the expression of *Sfp1* also decreases the expression of adhesive molecules. *Sfp1* may exert its role through *Bcr1* and *Efg1* and the Rhb1-Tor1 signaling pathway [67]. *CaFEN1* and *CaFEN12* are also involved in adhesion and biofilm formation through the synthesis of sphingolipids, and the deletion of these genes inhibits biofilm formation [65]. It seems that *RAP1* has an

inhibitory role in biofilm formation. It has been shown that mutants lacking *RAP1* form a stronger biofilm than *C. albicans* having this factor [50].

Hydrolase enzymes

Hydrolase enzymes such as: Proteases secreted aspartyl proteinases (SAPs), lipases (LIPs) and phospholipases (PLBs) play a role in providing nutrients for *C. albicans* through protein degradation, facilitating penetration and invasion of host tissues and also evading immune responses [68, 69]. Among the hydrolase enzymes, SAPs have been studied

more deeply. *C. albicans* have 10 genes (*SAP1-SAP10*) encoding this enzyme, which plays an important role in the pathogenesis of this fungus [68]. It has been shown that *SAP1,2,3* are involved in tissue damage during superficial infection, and *SAP4,5,6* are involved in tissue damage during systemic infection [70]. SAPs are also used in diagnosing systemic candidiasis by the enzyme-linked immunosorbent assay method [71]. The key advantage of using SAPs is their ability to differentiate colonization from invasive disease [68].

Table 1. Pathogenic factors of *Candida albicans* and its regulatory genes

Number	Pathogenic factor	Regulatory genes
1	Mycelium production	<i>Ume6</i> · <i>Eed1</i> · <i>Hgc1</i> · <i>Rap1</i>
2	Adherence and formation of biofilm	<i>Bcr1</i> · <i>Efg1</i> · <i>CaFEN1</i> · <i>CaFEN12</i> , <i>Ywp1</i> · <i>Sfp1</i> · <i>Rap1</i>
3	hydrolase enzymes	<i>Cph1</i> · <i>Efg1</i> · <i>Tec1</i> · <i>Hog1</i> <i>Tup1</i> · <i>Mig1</i> · <i>Nrg1</i>
4	Absorption of micronutrients	<i>ZRT1-3</i> · <i>ZRC1</i> · <i>Sef1</i> · <i>Sfu1</i> · <i>CRD1</i>
5	Compatibility with different levels of oxygen	<i>Ofd1</i> · <i>Nrg1</i> · <i>Ume6</i>
6	Growth in nitrogen deficiency conditions	<i>MEP1</i> · <i>MEP2</i> · <i>Ume6</i> · <i>Brg1</i>
7	Growth at a temperature higher than 37 °C	<i>Hms1</i> · <i>Hsf1</i>

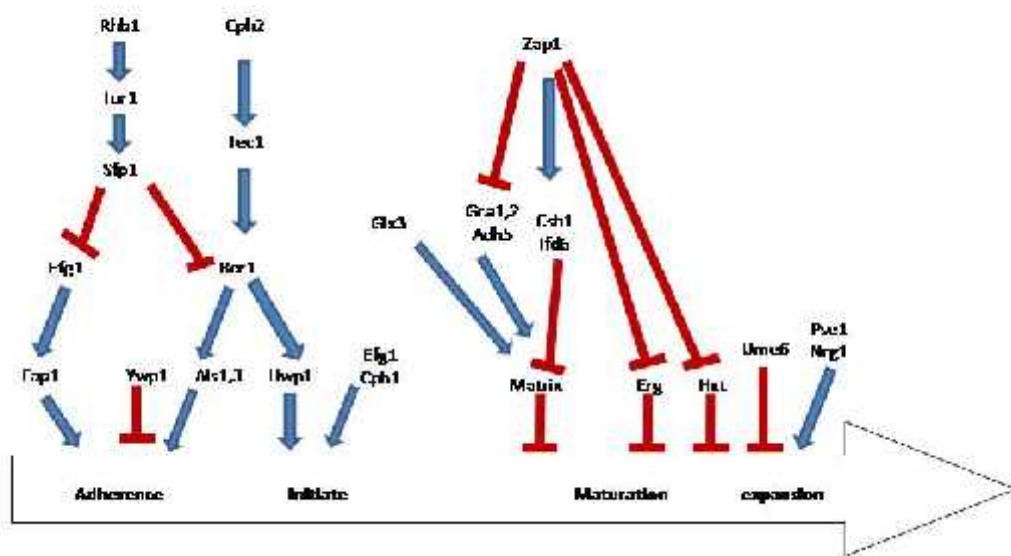


Fig. 2. *Candida albicans* biofilm gene regulation network

SAP2 can be used to make a vaccine to prevent systemic candidiasis in BALB/c mice [72]. It has been shown that using SAP2 protein conjugated with alum adjuvant has brought efficient immune protection with a 20-fold reduction in kidney colonization [68]. The products of *SAP1-8* genes are secreted in the intercellular space, and the products of *SAP9,10* genes are attached to the cell wall [73]. Phospholipases are other enzymes that have four classes of PLBA-D [74]. However, probably only five members of (PLB1-5) are involved in the pathogenesis of *C. albicans*. The expression of phospholipase B has been observed in mucosal, digestive, and systemic infections [75]. Most of the activity of phospholipase B is related to Plb1, and Plb2 has little activity [76]. The lipase family is another enzyme comprising 10 members [LIP1-10] [68]. The expression of LIP5,6,8,9 has been observed in induced peritonitis in mice [77]. It has been reported that the lack of LIP8 expression reduced the pathogenicity of *C. albicans* in mice [78]. Lipase increases the secretion of pro-inflammatory cytokine Interleukin-6 and decreases the secretion of anti-inflammatory cytokine transforming growth factor; therefore, lipase seems to play a role in pathogenesis by causing inflammation [79].

Regulation of hydrolysis enzymes

SAP gene expression depends on other pathogenic factors, such as mycelium production and phenotype change. In addition, pH, type, stage of infection, and substrate availability are effective in the

expression and regulation of *SAP* genes [80]. Biofilm formation is also effective in regulating the expression of *SAP* genes; in this way, *SAP5,6,9* are seen more in biofilm than in planktonic growth [81]. Transcription factors Cph1 and *Efg1* of the *MAP* kinase pathway and the cAMP pathway regulate the production of hyphae and the expression of *SAP4-6* [81, 82]. In addition, it seems that *Efg1* also regulates mycelium-independent *SAP* genes because deletion of *Efg1* decreases the expression of yeast-specific *SAP1* and *SAP3* proteinases [83]. Transcription factor *Tec1*, which is often expressed during mycelium production, It is involved in the expression of *SAP4-6* [84]. The transcription factor *Nrg1*, which Tup1 regulates, can prevent the expression of *SAP5*. Tup1 also regulates transcription factor Mig1 and can prevent the expression of *SAP9*. In addition, the transcription factor *Tup1* can inhibit the expression of *SAP6,7* independently of *Mig1* and *Nrg1* [85]. Therefore, it seems that *Efg1*, *Cph1*, and *Tec1* stimulate the expression of *SAPs*, and *Tup1*, *Mig1*, and *Nrg1* prevent the expression of *SAPs* [80]. The expression of lipases and *PLB1* can be influenced by environmental conditions such as temperature, pH, and nutrients. The expression of *PLB1* is controlled by the transcriptional inhibitory factor *Tup1*. Increased expression of *PLB1* has been observed in mutants lacking *Tup1* [86]. The *hog1* protein kinase signal transduction pathway is also effective in *PLB1* expression.

Mutations in *Hog1* decrease *PLB1* expression [87].

Absorption of micronutrients

The absorption of micronutrients by *C. albicans* plays an important role in the pathogenesis of this fungus [88]. The concentration of iron, zinc, and copper in people is very variable and is influenced by factors such as diet, gender, age, general health, and lifestyle [88-90]. To reduce the growth of microbial agents, the host's body tries to keep nutrients away from them. To neutralize such defense and survive in the host's body, *C. albicans* expresses and regulates several micronutrient acquisition systems [88].

A) Zinc absorption

C. albicans can absorb free zinc in the environment, and zinc bound to host proteins by pH-dependent antigen-1 (Pra1p) [91]. Sap6p can also provide this micronutrient for the fungus by binding to zinc in low-zinc environments [92]. Zinc homeostasis in *C. albicans* is regulated by a transcriptional activator called Zap1p, which controls the expression of several genes, including zinc transporters ZRT1-3 and ZRC1 [93, 94]. (Table 1)

B) Iron absorption

Iron, as a cofactor in metabolic functions, is needed for the survival of most organisms [95]. In addition, iron is also effective in mycelium production and the pathogenicity of *C. albicans* [96]. Since iron does not exist in free form in the body, pathogenic microorganisms have developed complex strategies to obtain this element [95]. *C. albicans* use three systems for iron absorption: hemoglobin absorption, reduced iron absorption, and siderophore collection [88]. Ferric reductases Cfl1p and Fre10p regenerate

Fe³⁺ in transferrin to Fe²⁺ [97, 98]. Then the reduced iron is transported into the cell through permeases Ftr1p, Ftr2p, Fth1p, and Fth2p [99, 100]. *C. albicans* use siderophore transfer protein [Sit1p] to absorb iron from other bacteria and fungi [88]. For survival and successful invasion, *C. albicans* must be able to absorb iron from environments with different concentrations. The concentration of iron in the gastrointestinal tract is high, and in the blood and tissue is low. Iron absorption is controlled by two transcription factors, Sef1 and Sfu1. Sef1 is responsible for increasing iron absorption in environments with low concentrations. Iron absorption pathways are suppressed in environments with high iron [101]. Under high iron conditions, phosphorylated Sfu1 binds to the Sef1 promoter in the nucleus and inhibits transcription, and binds to the Sef1 protein in the cytosol, preparing Sef1 for degradation. As iron concentration decreases, Sef1 is phosphorylated and prevents Sfu1 binding. Then, Sef1-P can enter the nucleus and induce the transcription of genes for the absorption and utilization of iron [102] (Table 1).

C) Copper absorption

Copper is needed for the effective absorption of iron and also the function of proteins [88]. *C. albicans* stimulate the expression of copper transporter (Ctr1p) by using the Mac1p transcription factor [103, 104]. Mutants lacking Ctr1 cannot grow in conditions of iron and copper deficiency [103]. Increasing copper concentration can create toxic conditions for *C. albicans*; therefore, this fungus activates the P1-type ATPase copper pump and removes excess copper from the cell by expressing the

CRD1 gene [88]. Mutants lacking *CRD1* are sensitive to external sources of copper, silver, and cadmium [103]. *Sur7p* plays a role in morphogenesis, cell wall synthesis, actin polymerization, and cell wall resistance against stresses [105-108]. It has been shown that the deletion of *Sur7* increases sensitivity to copper [109] (Table 1).

Compatibility with different levels of oxygen

Adaptation to different oxygen levels is essential for the formation of hyphae and pathogenicity of *C. albicans*. Transcription factor Ume6p increases the length of hyphae in hypoxic conditions in combination with 5% CO₂. On the other hand, hypoxia with 5% CO₂ decreases the expression of NRG1, which is a negative regulator of hypha formation [110]. Ofd1p, part of the 2-oxoglutarate and Fe²⁺-dependent dioxygenases (2-OGDD) enzyme pathway, plays a role in hypha induction in hypoxic conditions. Ofd1p acts as an oxygen sensor through Ume6p. Ofd1p consists of two components, Ofd1N and Ofd1C. Ofd1C induces the degradation of *Ume6p* in high oxygen conditions, and *Ofd1N*, by inhibiting *Ofd1C* in low oxygen conditions, causes the continuation of *Ume6p* activity and the increase in hyphae length [111].

Growth in nitrogen deficiency conditions

Nitrogen deficiency can cause the transformation of yeast into hyphae [110]. Two ammonium permease genes, *MEP1* and *MEP2*, are expressed in nitrogen deficiency conditions and allow growth. These genes cause the activation of signal transmission pathways and, as a result, mycelium

production [112]. The *Tor1* pathway also responds by regulating Brg1p and Ume6p in nitrogen deficiency conditions. This pathway is a negative regulator of mycelium production. Inhibition of this pathway causes mycelium production by activating Brg1p and preventing the activity of *Nrg1p-Tup1p* [110]. RHB1 is another transcription factor that plays a role in stimulating hypha production through MEP2 under nitrogen deficiency conditions [113-115].

Growth at a temperature higher than 37 °C

C. albicans usually produce mycelium at 37-39 °C [110]. At high temperatures, the inhibition of *Ras1p* by *Hsp90p* decreases, which leads to an increase in Ras1GTPase activity. Then *Ras1p* stimulates cAMP production by *Cyr1p*, and finally, the cAMP-PKA pathway is activated to induce mycelium. Hsp90p appears to suppress mycelium production mainly through the cAMP-PKA signaling pathway, as any disruption of the upstream components of the cAMP-PKA pathway that blocks PKA-dependent signaling prevents the induction of hyphal growth [116]. It has been shown that the genetic deletion of Hsp90p reduces the severity of systemic disease in mice [110]. At high temperatures, Hsp90p regulates mycelium production through the transcription factors Hms1p and Hsf1p, independent of the cAMP-PKA pathway [117, 118].

Conclusion

C. albicans's pathogenicity is a multifactorial process regulated by a network of pathogenic factors. Knowledge of the pathogenic factors of this fungus provides the possibility of developing better diagnosis and treatment

methods for infected people. Shape change seems an important phenomenon in pathogenesis; therefore, it is necessary to carefully study the environmental signals and intestinal metabolites that can play a role in this shape change. Knowing how to modify these signals can effectively control commensalism and prevent pathogenicity. Targeting the transformation may also be effective in infection control and treatment. Targeting other pathogenic factors, such as the secretion of hydrolase enzymes and the expression of adhesive molecules, may be a successful strategy in controlling and treating infection; of course, there are many ambiguous points about hydrolase enzymes; for example,

the exact role of *Sap9* and *Sap10* remains unknown. The information about the secreted phospholipases also has fewer details than the *SAP* family. Lipases secreted by *C. albicans* have also received less attention, with many ambiguous points about them. The interaction between host nutrients and the nutrient absorption systems of fungi can be studied. Interference in iron, zinc, copper, oxygen, and nitrogen homeostasis systems may be a suitable therapeutic strategy.

Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgment

None.

References

- [1]. Kamali M, Taheri Sarvtin MA. survey on airborne fungal spores in indoor air and outdoor air of Babol city. *Journal of Jiroft University of Medical Sciences* 2015; 2(1): 116-30.
- [2]. Taheri Sarvtin M, Kamali M, Yazdani J. A review on the risk factors, presentations and treatment of candidemia. *Journal of Jiroft University of Medical Sciences* 2015; 2(2): 55-60.
- [3]. Lopes JP, Lionakis MS. Pathogenesis and virulence of *Candida albicans*. *Virulence* 2022; 13(1): 89-121.
- [4]. Taheri Sarvtin M, Hedayati MT, Ayatollahi Mosavi SA, Afsarian MH. An overview on the role of microbial agents in psoriasis. *Mazand Univ Med Sci.* 23(98): 364-85.
- [5]. Arita GS, Conrado PCV, Sakita KM, Rodrigues-Vendramini FAV, Faria DR, Kioshima ES, et al. Serial systemic candidiasis alters *Candida albicans* macromorphology associated with enhancement of virulence attributes. *Microb Pathog.* 2022; 164: 105413.
- [6]. Taheri Sarvtin M, Shokohi T, Hajheydari Z, Yazdani J, Hedayati MT. Evaluation of candidal colonization and specific humoral responses against *Candida albicans* in patients with psoriasis. *International Journal of Dermatology* 2014; 53(12): 555-60.
- [7]. Taheri Sarvtin M, Hajheydari Z, Hedayati MT. A Review on the role of fungi in atopic dermatitis. *Journal of Mazandarn University of Medical Sciences.* 2012; 22(87): 115-37.
- [8]. Taheri Sarvtin M, Hedayati MT, Abastabar M, Shokohi T. *Debaryomyces hansenii* colonization and its protein profile in psoriasis. *Iranian Journal of Dermatology* 2014; 17(4): 134-37.
- [9]. Hui Chen, Xuedong Zhou, Biao Ren, Lei Cheng. The regulation of hyphae growth in *Candida albicans*. *Virulence* 2020; 11(1): 337-48.
- [10]. Murad AM, Munir A, Leng P, Traffon M, Wishart J, Macaskill S, et al. NRG1 represses yeast-hypha morphogenesis and hypha-specific gene expression in *Candida albicans*. *EMBO.* 2001; 20(17): 4742-752.
- [11]. Koh AY, Köhler JR, Cogshall KT, Van Rooijen N, Pier GB. Mucosal damage and neutropenia are required for *Candida albicans* dissemination. *PLoS pathog.* 2008; 4(2): e35.
- [12]. McKenzie CG, Koser U, Lewis LE, Bain JM, Mora-Montes HM, Barker RN, et al. Contribution of *Candida albicans* cell wall components to recognition by and escape from murine macrophages. *Infect Immun.* 2010; 78 (4): 1650-658.

- [13]. Nobile CJ, Johnson AD. *Candida albicans* biofilms and human disease. *Annu Rev Microbiol.* 2015; 69: 71-92.
- [14]. Lu Y, Su C, Liu H. *Candida albicans* hyphal initiation and elongation. *Trends Microbiol.* 2014; 22 (12): 707-14.
- [15]. Vylkova S, Carman AJ, Danhof HA, Collette JR, Zhou H, Lorenz MC. The fungal pathogen *Candida albicans* autoinduces hyphal morphogenesis by raising extracellular pH. *mBio.* 2011; 2 (3): 55-61.
- [16]. Kornitzer D. Regulation of *Candida albicans* hyphal morphogenesis by endogenous signals. *Fungi (Basel).* 2019; 5(1): 21.
- [17]. Srivastava LM. Cell wall, cell division, and cell growth. Chapter 2. In: *Plant Growth and Development*; 2002. p. 23-74.
- [18]. Chiou JG, Balasubramanian MK, Lew DJ. Cell polarity in yeast. *Annu Rev Cell Dev Biol.* 2017; 33(1): 77-101.
- [19]. Liu H. Transcriptional control of dimorphism in *Candida albicans*. *Curr Opin Microbiol.* 2001; 4(6): 728-35.
- [20]. Steinberg G, Peñalva MA, Riquelme M, Wösten HA, Harris SD. *Cell Biology of Hyphal Growth.* *Microbiol. Spectr.* 2017; 5(2): 1-34.
- [21]. Riquelme M, Aguirre J, Bartnicki-García S, Braus GH, Feldbrügge M, Fleig U, et al. Fungal morphogenesis, from the polarized growth of hyphae to complex reproduction and infection structures. *Microbiol Mol Biol Rev.* 2018; 82(2): e00068-17.
- [22]. Bartnicki-Garcia S, Garduño-Rosales M, Delgado-Alvarez DL, Mouriño-Pérez RR. Experimental measurement of endocytosis in fungal hyphae. *Fungal Genet Biol.* 2018; 118: 32-6.
- [23]. Hernández-González M, Bravo-Plaza I, Pinar M, de Los Ríos V, Arst HN, Peñalva MA. Endocytic recycling via the TGN underlies the polarized hyphal mode of life. *PLoS Genet.* 2018; 14(4): e1007291.
- [24]. Yokoyama K, Kaji H, Nishimura K, Miyaji M. The role of microfilaments and microtubules in apical growth and dimorphism of *Candida albicans*. *J Gen Microbiol.* 1990; 136(6): 1067-1075.
- [25]. Rida PCG, Nishikawa A, Won GY, Dean N. Yeast-to-hyphal transition triggers formin-dependent golgi localization to the growing tip in *Candida albicans*. *Mol Biol Cell.* 2006; 17(10): 4364-378.
- [26]. Weiner A, Orange F, Lacas-Gervais S, Rechav K, Ghugtyal V, Bassilana M, et al. On-site secretory vesicle delivery drives filamentous growth in the fungal pathogen *Candida albicans*. *Cell Microbiol.* 2019; 21(1): 12963.
- [27]. Crampin H, Finley K, Gerami-Nejad M, Court H, Gale C, Berman J, et al. *Candida albicans* hyphae have a Spitzenkörper that is distinct from the polarisome found in yeast and pseudohyphae. *J Cell Sci.* 2005; 118(Pt 13): 2935-947.
- [28]. Jones LA, Sudbery PE. Spitzenkörper, exocyst, and polarisome components in *Candida albicans* hyphae show different patterns of localization and have distinct dynamic properties. *Eukaryot Cell* 2010; 9(10): 1455-465.
- [29]. Cheetham J, Smith DA, da Silva Dantas A, Doris KS, Patterson MJ, Bruce CR, et al. A single MAPKKK regulates the Hog1 MAPK pathway in the pathogenic fungus *Candida albicans*. *Mol Biol Cell.* 2007; 18(11): 4603-614.
- [30]. Roman E, Alonso-Monge R, Gong Q, Li D, Calderone R, Pla J. The Cek1 MAPK is a short-lived protein regulated by quorum sensing in the fungal pathogen *Candida albicans*. *FEMS Yeast Res.* 2009; 9(6): 942-55.
- [31]. Herrero-de-Dios C, Alonso-Monge R, Pla J. The lack of upstream elements of the Cek1 and Hog1 mediated pathways leads to a synthetic lethal phenotype upon osmotic stress in *Candida albicans*. *Fungal Genet Biol.* 2014; 69: 31-42.
- [32]. Giacometti R, Kronberg F, Biondi RM, Passeron S. Catalytic isoforms Tpk1 and Tpk2 of *Candida albicans* PKA have non-redundant roles in stress response and glycogen storage. *Yeast* 2009; 26(5): 273-85.
- [33]. Sun W, Zhang L, Lu X, Feng L, Sun S. The synergistic antifungal effects of sodium phenylbutyrate combined with azoles against *Candida albicans* via the regulation of the Ras-cAMP-PKA signalling pathway and virulence. *Can J Microbiol.* 2019; 65(2): 105-15.
- [34]. Lin CJ, Chen YL. Conserved and divergent functions of the cAMP/PKA signaling pathway in *Candida albicans* and *Candida tropicalis*. *J Fungi (Basel).* 2018; 4(2): 68.
- [35]. Grahl N, Demers EG, Lindsay AK, Harty CE, Willger SD, Piispanen AE, et al. Mitochondrial activity and Cyr1 are key regulators of Ras1 activation of *C. albicans* virulence pathways. *PLoS Pathog.* 2015; 11(8): 1005133
- [36]. Klengel T, Liang WJ, Chaloupka J, Ruoff C, Schröppel K, Naglik JR, et al. Fungal adenylyl cyclase integrates CO₂ sensing with cAMP signaling and virulence. *Curr Biol.* 2005; 15(22): 2021-2026.
- [37]. Xu XL, Lee RTH, Fang HM, Wang, YM, Li R, Zou H, et al. Bacterial peptidoglycan triggers *Candida albicans* hyphal growth by directly activating the adenylyl cyclase Cyr1p. *Cell Host Microbe.* 2008; 4(1): 28-39.
- [38]. Nadal Clanchet ED, Posas Garriga F. The HOG pathway and the regulation of osmoadaptive responses in yeast. *FEMS Yeast Res.* 2022; 22 (1): 13.

- [39]. Biswas S, Van Dijck P, Datta A. Environmental sensing and signal transduction pathways regulating morphopathogenic determinants of *Candida albicans*. *Microbiol Mol Biol Rev.* 2007; 71(2): 348-76.
- [40]. Davis D. Adaptation to environmental pH in *Candida albicans* and its relation to pathogenesis. *Curr Genet.* 2003; 44(1): 1-7.
- [41]. Aréchiga-Carvajal ET, Ruiz-Herrera J. The RIM101/ *pacC* homologue from the basidiomycete *Ustilago maydis* is functional in multiple pH-sensitive phenomena. *Eukaryot Cell.* 2005; 4(6): 999-1008.
- [42]. Davis D, Wilson RB, Mitchell AP. RIM101-dependent and-independent pathways govern pH responses in *Candida albicans*. *Mol Cell Biol.* 2000; 20(3): 971-78.
- [43]. Li M, Martin SJ, Bruno VM, Mitchell AP, Davis, DA. *Candida albicans* Rim13p, a protease required for Rim101p processing at acidic and alkaline pHs. *Eukaryot Cell.* 2004; 3(3): 741-51.
- [44]. Mendelsohn S, Pinsky M, Weissman Z, Kornitzer D. Regulation of the *Candida albicans* hypha-inducing transcription factor Ume6 by the CDK1 cyclins Cln3 and Hgc1. *mSphere* 2017; 2(2): 248-16.
- [45]. Banerjee M, Uppuluri P, Zhao XR, Carlisle, P. L., Vipulanandan G, Villar CC, et al. Expression of UME6, a key regulator of *Candida albicans* hyphal development, enhances biofilm formation via Hgc1 and Sun41-dependent mechanisms. *Eukaryot Cell* 2013; 12(2): 224-32.
- [46]. Martin R, Moran GP, Jacobsen ID, Heyken A, Domey J, Sullivan DJ, et al. The *Candida albicans*-specific gene EED1 encodes a key regulator of hyphal extension. *PLoS One* 2011; 6(4): 18394.
- [47]. Childers DS, Kadosh D, Sturtevant J. Filament condition-specific response elements control the expression of NRG1 and UME6, key transcriptional regulators of morphology and virulence in *Candida albicans*. *PLoS One* 2015; 10(3): 122775.
- [48]. Wang Y. Hgc1-Cdc28-how much does a single protein kinase do in the regulation of hyphal development in *Candida albicans*? *J Microbiol.* 2016; 54(3): 170-77.
- [49]. Carlisle PL, Kadosh D. *Candida albicans* Ume6, a filament-specific transcriptional regulator, directs hyphal growth via a pathway involving Hgc1 cyclin-related protein. *Eukaryot Cell* 2010; 9(9): 1320-328.
- [50]. Wang WH, Lai TX, Wu YC, Chen ZT, Tseng KY, Lan CY. Associations of Rap1 with cell wall integrity, biofilm formation, and virulence in *Candida albicans*. *Microbiol Spectr.* 2022; 10(6): 328522.
- [51]. Maras B, Maggiore A, Mignogna G, D'Erme M, Angiolella L. Hyperexpression of CDRs and HWP1 genes negatively impacts on *Candida albicans* virulence. *Plos One* 2021; 16(6): 252555.
- [52]. Jamal M, Ahmad W, Andleeb S, Jalil F, Imran M, Nawaz MA, et al. Bacterial biofilm and associated infections. *J Chin Med Assoc.* 2018; 81 (1): 7-11.
- [53]. Van Acker H, Van Dijck P, Coenye T. Molecular mechanisms of antimicrobial tolerance and resistance in bacterial and fungal biofilms. *Trends Microbiol.* 2014; 22(6): 326-33.
- [54]. Fanning S, Mitchell AP. Fungal biofilms. *PLoS Pathog* 2012; 8(4): 1002585.
- [55]. Garcia MC, Lee JT, Ramsook CB, Alsteens D, Dufrêne YF, Lipke PN. A role for amyloid in cell aggregation and biofilm formation. *PLoS One* 2011; 6(3): 17632.
- [56]. Verstrepen KJ, Klis FM. Flocculation, adhesion and biofilm formation in yeasts. *Mol Microbiol.* 2006;60(1): 5-15.
- [57]. Mayer FL., Wilson D, Hube B. *Candida albicans* pathogenicity mechanisms. *Virulence* 2013; 4(2): 119-28.
- [58]. Mushi MF, Bader O, Taverne-Ghadwal L, Bii C, Groß U, Mshana SE. Oral candidiasis among African human immunodeficiency virus-infected individuals: 10 years of systematic review and meta-analysis from sub-Saharan Africa. *J Oral Microbiol.* 2017; 9(1): 1317579.
- [59]. Mackenzie A, Marshall NW, Hadjipanteli A, Dance DR, Bosmans H, Young KC. Characterisation of noise and sharpness of images from four digital breast tomosynthesis systems for simulation of images for virtual clinical trials. *Phys Med Biol.* 2017; 62(6): 2376-397.
- [60]. Kullberg BJ, Vasquez J, Mootsikapun P, Nucci M, Paiva JA, Garbino J, et al. Efficacy of anidulafungin in 539 patients with invasive candidiasis: a patient-level pooled analysis of six clinical trials. *J Antimicrob Chemother.* 2017; 72(8): 2368-377.
- [61]. Zhao X, Oh SH, Hoyer LL. Deletion of ALS5, ALS6 or ALS7 increases adhesion of *Candida albicans* to human vascular endothelial and buccal epithelial cells. *Med Mycol.* 2007; 45(5): 429-34.
- [62]. Nas T, Kalkanci A, Fidan I, Hizel K, Bolat S, Yolbakan S, et al. Expression of ALS1, HWP1 and SAP4 genes in *Candida albicans* strains isolated from women with vaginitis. *Folia Microbiol (Praha).* 2008; 53(2): 179-83.
- [63]. Nobile CJ, Schneider HA, Nett JE, Sheppard DC, Filler SG, Andes DR, et al. Complementary adhesion function in *C. albicans* biofilm formation. *Curr Biol.* 2008; 18(14): 1017-1024.

- [64]. Nobile C, Mitchell AP. Regulation of cell-surface genes and biofilm formation by the *C. albicans* transcription factor Bcr1p. *Curr Biol*. 2005; 15(12): 1150-155.
- [65]. Xu Z, Huang T, Du M, Soteyome T, Lan H, Hong W, et al. Regulatory network controls microbial biofilm development, with *Candida albicans* as a representative: From adhesion to dispersal. *Bioengineered* 2022; 13(1): 253-267.
- [66]. Dwivedi P, Thompson A, Xie Z, Kashleva H, Ganguly S, Mitchell AP, et al. Role of Bcr1-activated genes Hwp1 and Hyr1 in *Candida albicans* oral mucosal biofilms and neutrophil evasion. *PLoS One* 2011; 6(1): 16218.
- [67]. Chen HF, Lan CY, Coste AT. Role of SFP1 in the regulation of *Candida albicans* biofilm formation. *PLoS One* 2015; 10(6): 129903.
- [68]. Chin VK, Lee TY, Rusliza B, Chong PP. Dissecting *Candida albicans* infection from the perspective of *C. albicans* virulence and omics approaches on host-pathogen interaction: a review. *Int J Mol Sci*. 2016; 17(10): 1643.
- [69]. de Barros PP, Rossoni RD, De Camargo Ribeiro F, Junqueira JC, Jorge AOC. Temporal profile of biofilm formation, gene expression and virulence analysis in *Candida albicans* strains. *Mycopathologia* 2017; 182(3-4): 285-95.
- [70]. Costa CR, Jesuino RSA, de Aquino Lemos J, de Fátima Lisboa Fernandes O, Hasimoto e Souza LK, Passos XS, et al. Effects of antifungal agents in sap activity of *Candida albicans* isolates. *Mycopathologia* 2010; 169(2): 91-8.
- [71]. Morrison CJ, Hurst SF, Reiss E. Competitive binding inhibition enzyme-linked immunosorbent assay that uses the secreted aspartyl proteinase of *Candida albicans* as an antigenic marker for diagnosis of disseminated candidiasis. *Clin Diagn Lab Immunol*. 2003; 10(5): 835-48.
- [72]. Vilanova M, Teixeira L, Caramalho Í, Torrado E, Marques A, Madureira P, et al. Protection against systemic candidiasis in mice immunized with secreted aspartic proteinase. *Immunology* 2004; 111(3): 334-42.
- [73]. Ilkhanizadeh-Qomi M, Nejatbakhsh S, Jahanshiri Z, Razzaghi-Abyaneh M. Aspartyl proteinase and phospholipase activities of *Candida albicans* isolated from oropharyngeal candidiasis in head and neck cancer patients. *Journal of Jiroft University of Medical Sciences*. 2022; 13(9): 105200.
- [74]. Niewerth M, Korting HC. Phospholipases of *Candida albicans*. *Mycoses* 2001; 44(9-10): 361-77.
- [75]. Schaller M, Borelli C, Korting HC, Hube B. Hydrolytic enzymes as virulence factors of *Candida albicans*. *Mycoses* 2005; 48(6): 365-77.
- [76]. Ilkhanizadeh-Qomi M, Nejatbakhsh S, Jahanshiri Z, Razzaghi-Abyaneh M. Aspartyl proteinase and phospholipase activities of *Candida albicans* isolated from oropharyngeal candidiasis in head and neck cancer patients. *Journal of Jiroft University of Medical Sciences* 2020; 13(9): e105200.
- [77]. Hube B, Stehr F, Bossenz M, Mazur A, Kretschmar M, Schäfer W. Secreted lipases of *Candida albicans*: Cloning, characterisation and expression analysis of a new gene family with at least ten members. *Arch Microbiol*. 2000; 174(5): 362-74.
- [78]. Gácsér A, Stehr F, Kröger C, Kredics L, Schäfer W, Nosanchuk JD. Lipase 8 affects the pathogenesis of *Candida albicans*. *Infect Immun*. 2007; 75(10): 4710-718.
- [79]. Castillo GDV, Aguilar JD, Miró MS, Sotomayor C, Azcurra AI. Role of *C. albicans* LIP in isolates from malignant lesions on in vitro model of human buccal cells. *FO-Congresos*; 2017 Nov; Curitiba; Brasil. Available at: <http://hdl.handle.net/11086/29026>
- [80]. Naglik J, Albrecht A, Bader O, Hube B. *Candida albicans* proteinases and host/pathogen interactions. *Cell Microbiol*. 2004; 6(10): 915-26.
- [81]. Garcia-Sanchez S, Aubert S, Iraqui I, Janbon G, Ghigo JM, d'Enfert C. *C. albicans* biofilms: a developmental state associated with specific and stable gene expression patterns. *Eukaryot Cell* 2004; 3(2): 536-45.
- [82]. Naglik JR, Moyes D, Makwana J, Kanzaria P, Tschlaki E, Weindl G, et al. Quantitative expression of the *Candida albicans* secreted aspartyl proteinase gene family in human oral and vaginal candidiasis. *Microbiology* 2008; 154(11): 3266-280.
- [83]. Korting H, Hube B, Oberbauer S, Januschke E, Hamm G, Albrecht A, et al. Reduced expression of the hyphal-independent *Candida albicans* proteinase genes SAP1 and SAP3 in the *efg1* mutant is associated with attenuated virulence during infection of oral epithelium. *J Med Microbiol*. 2003; 52(Pt 8): 623-32.
- [84]. Schweizer A, Rupp S, Taylor BN, Röllinghoff M, Schröppel K. The TEA/ATTS transcription factor CaTec1p regulates hyphal development and virulence in *Candida albicans*. *Mol Microbiol*. 2000; 38(3): 435-45.
- [85]. Murad AM, Leng P, Straffon M, Wishart J, Macaskill S, MacCallum D, et al. NRG1 represses yeast hypha morphogenesis and hypha-specific gene expression in *Candida albicans*. *EMBO*. 2001; 20(17): 4742-752.
- [86]. Hruskova-Heidingsfeldova O. Secreted proteins of *Candida albicans*. *Front Biosci Landmark* 2008; 13(18): 7227-242.
- [87]. Enjalbert B, Smith DA, Cornell MJ, Alam I, Nicholls S, Brown AJ, et al. Role of the Hog1

- stress-activated protein kinase in the global transcriptional response to stress in the fungal pathogen *Candida albicans*. *Mol Biol Cell*. 2006; 17(2): 1018-1032.
- [88]. Nikou SA, Kichik N, Brown R, Ponde NO, Ho J, Naglik JR, et al. *Candida albicans* interactions with mucosal surfaces during health and disease. *Pathogens* 2019; 8(2): 53
- [89]. Kode MA, Karjodkar FR. Estimation of the serum and the salivary trace elements in OSMF patients. *J Clin Diagn Res*. 2013; 7(6): 1215-218.
- [90]. Kim YJ, Kim YK, Kho HS. Effects of smoking on trace metal levels in saliva. *Oral Dis*. 2010; 16(8): 823-30.
- [91]. Citiulo F, Jacobsen ID, Miramon P, Schild L, Brunke S, Zipfel P, et al. *Candida albicans* scavenges host zinc via Pra1 during endothelial invasion. *PLoS Pathog*. 2012; 8(6): e1002777
- [92]. Kumar R, Breindel C, Saraswat D, Cullen PJ, Edgerton M. *Candida albicans* Sap6 amyloid regions function in cellular aggregation and zinc binding, and contribute to zinc acquisition. *Sci Rep*. 2017; 7(1): 2908.
- [93]. Kim MJ, Kil M, Jung JH, Kim J. Roles of zinc-responsive transcription factor Csr1 in filamentous growth of the pathogenic yeast *Candida albicans*. *J Microbiol Biotechnol*. 2008; 18(2): 242-47.
- [94]. Nobile CJ, Nett JE, Hernday AD, Homann OR, Deneault JS, Nantel A, et al. Biofilm matrix regulation by *Candida albicans* Zap1. *PLoS Biol*. 2009; 7(6): e1000133.
- [95]. Lan CY, Rodarte G, Murillo LA, Jones T, Davis RW, Dungan J, et al. Regulatory networks affected by iron availability in *Candida albicans*. *Mol Microbiol*. 2004; 53(5): 1451-469.
- [96]. Junier A, Weeks A, Alcaraz Y, Kumamoto CA. Bypass of Dfi1 regulation of *Candida albicans* invasive filamentation by Iron Limitation. *mSphere* 2022; 7(1): e0077921.
- [97]. Knight S, Vilaire G, Lesuisse E, Dancis A. Iron acquisition from transferrin by *Candida albicans* depends on the reductive pathway. *Infect Immun*. 2005; 73(9): 5482-492.
- [98]. Hammacott JE, Williams PH, Cashmore AM. *Candida albicans* Cfl1 encodes a functional ferric reductase activity that can rescue a *Saccharomyces cerevisiae* *frel* mutant. *Microbiology* 2000; 146 (Pt 4): 869–876
- [99]. Ramanan N, Wang Y. A high-affinity iron permease essential for *Candida albicans* virulence. *Science* 2000; 288(5468): 1062-1064.
- [100]. Mamouei Z, Zeng G, Wang YM, Wang Y. *Candida albicans* possess a highly versatile and dynamic high-affinity iron transport system important for its commensal-pathogenic lifestyle. *Mol Microbiol*. 2017; 106(6): 986-98.
- [101]. Chen C, Pande K, French SD, Tuch BB, Noble SM. An iron homeostasis regulatory circuit with reciprocal roles in *Candida albicans* commensalism and pathogenesis. *Cell Host Microbe*. 2011; 10(2): 118-35.
- [102]. Chen C, Noble SM. Post-transcriptional regulation of the Sef1 transcription factor controls the virulence of *Candida albicans* in its mammalian host. *PLoS Pathog*. 2012; 8(11): e1002956.
- [103]. Riggle PJ, Kumamoto CA. Role of a *Candida albicans* P1-type ATPase in resistance to copper and silver ion toxicity. *J Bacteriol*. 2000; 182(17): 4899-905.
- [104]. Weissman Z, Berdicevsky I, Cavari BZ, Kornitzer D. The high copper tolerance of *Candida albicans* is mediated by a P-type ATPase. *Proc. Natl Acad Sci USA*. 2000; 97(7): 3520-525.
- [105]. Alvarez FJ, Douglas LM, Konopka JB. The Sur7 protein resides in punctate membrane subdomains and mediates spatial regulation of cell wall synthesis in *Candida albicans*. *Commun Integr Biol*. 2009; 2(2): 76-7.
- [106]. Alvarez FJ, Douglas LM, Rosebrock A, Konopka JB. The Sur7 protein regulates plasma membrane organization and prevents intracellular cell wall growth in *Candida albicans*. *Mol Biol Cell*. 2008; 19(12): 5214-225.
- [107]. Bernardo SM, Lee SA. *Candida albicans* Sur7 contributes to secretion, biofilm formation, and macrophage killing. *BMC Microbiol*. 2010; 10: 133.
- [108]. Wang HX, Douglas LM, Amanianda V, Latge JP, Konopka JB. The *Candida albicans* Sur7 protein is needed for proper synthesis of the fibrillar component of the cell wall that confers strength. *Eukaryot Cell* 2011; 10(1): 72-80.
- [109]. Douglas LM, Wang HX, Keppler-Ross S, Dean N, Konopka JB. Sur7 promotes plasma membrane organization and is needed for resistance to stressful conditions and to the invasive growth and virulence of *Candida albicans*. *MBio* 2012; 3(1): 254-11
- [110]. Villa S, Hamideh M, Weinstock A, Qasim MN, Hazbun TR, Sellam A, et al. Transcriptional control of hyphal morphogenesis in *Candida albicans*. *FEMS yeast Res*. 2020; 20(1): foaa005.
- [111]. Lu Y, Su C, Solis NV, Filler SG, Liu H. Synergistic regulation of hyphal elongation by hypoxia, CO₂, and nutrient conditions controls the virulence of *Candida albicans*. *Cell Host Microbe*. 2013; 14(5): 499-509
- [112]. Biswas K, Morschhauser J. The Mep2p ammonium permease controls nitrogen starvation-induced filamentous growth in *Candida albicans*. *Mol Microbiol*. 2005; 56(3): 649-69.

- [113]. Tsao CC, Chen YT, Lan CY. A small G protein Rhb1 and a GTPaseactivating protein Tsc2 involved in nitrogen starvationinduced morphogenesis and cell wall integrity of *Candida albicans*. *Fungal Genet Biol.* 2009; 46 (2): 126-36.
- [114]. Chen YT, Lin CY, Tsai PW, Yang CY, Hsieh WP, Lan CY. Rhb1 regulates the expression of secreted aspartic protease 2 through the TOR signaling pathway in *Candida albicans*. *Eukaryot Cell* 2012; 11(2): 168-82.
- [115]. Flanagan PR, Liu NN, Fitzpatrick DJ Hokamp K, Köhler JR, Moran GP. The *Candida albicans* TOR-Activating GTPases Gtr1 and Rhb1 coregulate starvation responses and biofilm formation. *mSphere* 2017; 2(6): 477-17.
- [116]. Shapiro RS, Uppuluri P, Zaas AK, Collins C, Senn H, Perfect JR et al. Hsp90 orchestrates temperature-dependent *Candida albicans* morphogenesis via Ras1-PKA signaling. *Curr Biol.* 2009; 19(8): 621-29.
- [117]. Shapiro RS, Sellam A, Tebbji F, Whiteway M, Nantel A, Cowen LE. Pho85, Pcl1, and Hms1 signaling governs *Candida albicans* morphogenesis induced by high temperature or Hsp90 compromise. *Curr Biol.* 2012; 22(6): 461-70.
- [118]. Veri AO, Miao Z, Shapiro RS. Tebbji F, O'Meara TR, Kim SH, et al. Tuning Hsf1 levels drives distinct fungalmorphogenetic programs with depletion impairing Hsp90 function and overexpression expanding the target space. *PLoS Genet.* 2018; 14(3): 1007270.