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Review Article

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

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A B S T R A C T

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.

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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. stellatoidae*, *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.

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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

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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).

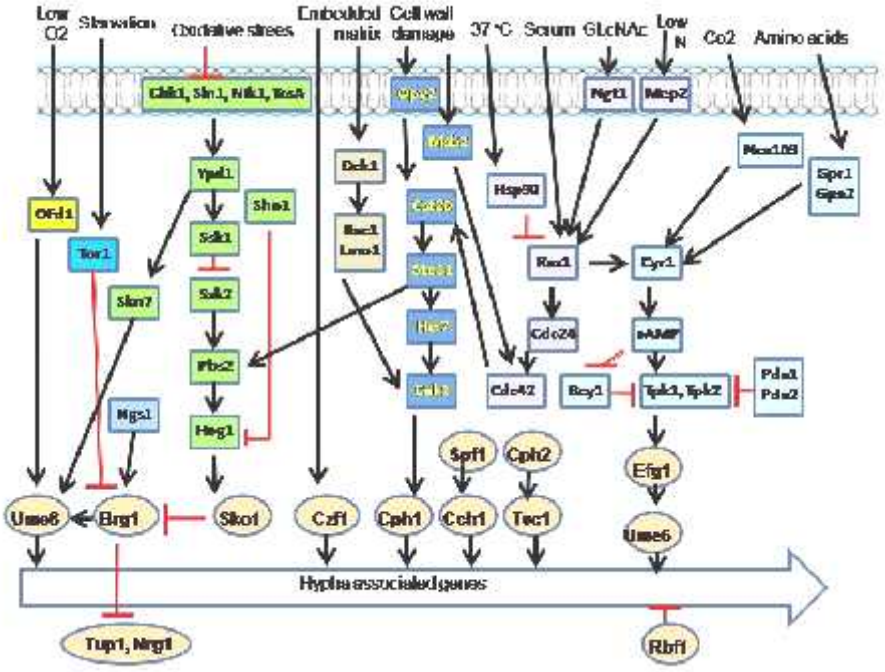

Fig. 1. Signaling pathways controlling hyphae production

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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 Tupl 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

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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 Al's 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

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

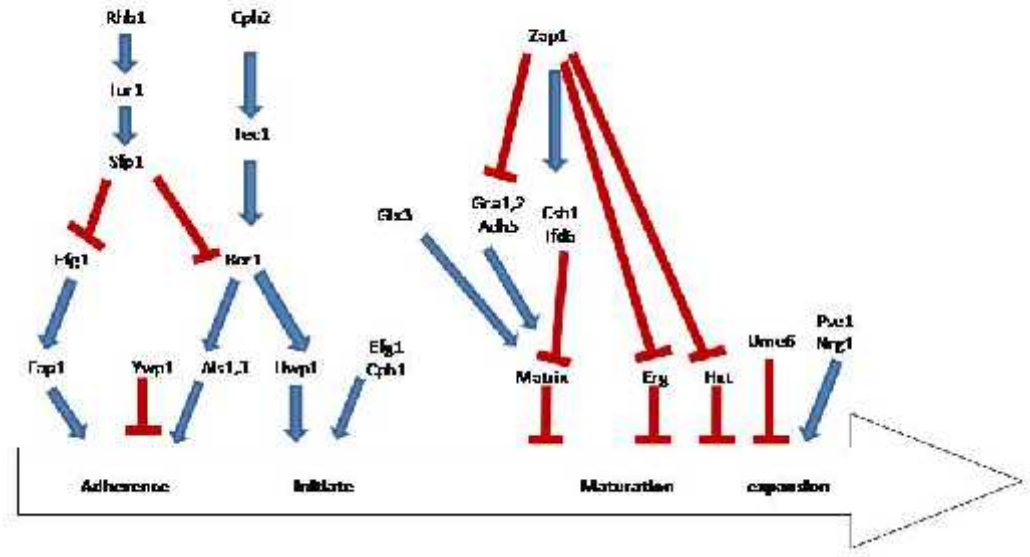

Fig. 2. *Candida albicans* biofilm gene regulation network

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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.

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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

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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. albican'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

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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.

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