

Review articles

Adherence of *Candida* sp. to host tissues and cells as one of its pathogenicity features[1]

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ABSTRACT. The ability of *Candida* sp. cells to adhere to the mucosal surfaces of various host organs as well as synthetic materials is an important pathogenicity feature of those fungi which contributes to the development of infection. This property varies depending on the species of the fungus and is the greatest for *C. albicans*. The process of adhesion depends on plenty of factors related to the fungal and host cells as well as environmental conditions. The main adhesins present on the fungal cell wall are: Als, Epa, Hwp1, but also Eap1, Sun41, Csh1 and probably Hyr1; for adhesion significant are also secreted aspartyl proteases Sap. Various researchers specify a range of genes which contribute to adhesion, such as: CZF1, EFG1, TUP1, TPK1, TPK2, HGC1, RAS1, RIM101, VPS11, ECM1, CKA2, BCR1, BUD2, RSR1, IRS4, CHS2, SCS7, UBI4, UME6, TEC1 and GAT2. Influence for adherence have also heat shock proteins Hsp70, Mediator Middle domain subunit Med31 and morphological transition. Among factors affecting adhesion related to host cells it is necessary to mention fibronectins and integrins (receptors for *Candida* sp. adhesins), type of epithelial cells, their morphology and differentiation phase. To a lesser degree influence on adhesion have non-specific factors and environmental conditions.

Key words: *Candida albicans*, virulence factors, adhesion, adhesins, adhesion genes

Introduction

The ability of *Candida* sp. cells to adhere to a range of materials, primarily the mucosal surfaces of various organs of a host, but also to synthetic materials, affects the ability of the fungus to colonize (Fig. 1). This colonization represents the first stage of infection, whose development proceeds via the post-adherence formation of filamentous forms and biofilm, which determines increased resistance to both host defense mechanisms and antifungal drugs. By preventing the fungal cells from, *inter alia*, being washed into the human gastrointestinal tract by saliva, adhesion is essential to their survival and further development in the oral cavity. Apart from being leached with saliva, the fungal cells can also be removed during mastication or continuous renewal of epithelial cells; similar removal processes can be observed in the vagina by the secretion of mucus, and in the urinary system by the outflow of urine [1–6].

Some differences in the degree of adherence have been observed for individual *Candida* species; *C. albicans* has been found to demonstrate greater *in vitro* adhesion to epithelial cells of the oral cavity than other *Candida* species, followed by *C. tropicalis* and then *C. parapsilosis* [2,7]. Lima-Neto et al. [7] suggest that *C. albicans* has a higher affinity for epithelial cells than *C. parapsilosis* due to the presence of more α-L-fucose residues. Fidel et al. [8] also showed that *C. albicans* demonstrates the greatest adhesion to the vascular endothelium, followed by *C. tropicalis* and *C. krusei*, and then *C. parapsilosis*, *C. glabrata* and *C. kefyr*. The authors speculate that the reduced capacity of *C. glabrata* to adhere to these substrates results from a lack of the adhesins occurring in *C. albicans*. In addition, a study conducted by Negri et al. [9] indicates that

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C. tropicalis blastospores adhere better to the epithelial cells than to the surface of silicone, but this ability varies according to the strain.

The mechanism of adhesion is based on the interaction between the fungal cell wall and the surface of the host cell, and depends on a number of factors related to three key aspects: the fungal cells, the host cells and the environmental conditions [6].

Factors affecting adherence related to fungal cells

The presence of specific proteins in the fungal cell wall, i.e. the so-called adhesins (polysaccharides, glycoproteins, most of which belong to the class of GPI-CWPs, i.e. glycosylphosphatidylinositol – cell wall proteins, e.g., Epa, Als, Hwp), which promote adhesion to the proteins or carbohydrates in the host cell wall [2,3,10]. One of the most important genes responsible for the adhesion process, whose expression is induced by physical contact between the fungal and epithelial cells, is HWP1. It encodes hyphal wall protein 1 (Hwp1), a fungal cell wall mannoprotein specific for germ-tubes and hyphal forms, which on the basis of molecular mimicry forms a stable complex with transglutaminase active on the host epithelial surface [2,11–13]. Hwp1 adhesin (the first known protein required in the process of biofilm formation) is regulated by Kex2 endoproteinase, which itself also regulates the activity of *C. albicans* proteinases, indicating its role for the fungus in providing virulence and drug resistance [14–16]. As HWP1 is detected both in carriers of *C. albicans* and patients with candidosis of the oral cavity or vagina, the fungal filamentous forms can be said to be present in both cases, however, expression of this gene is higher among strains isolated from persons with candidosis [17].

ALS (agglutinin-like sequence) are genes encoding a fungal cell-surface glycoproteins, a type of adhesins that exhibit similarity to immunoglobulins, bind to peptide ligands of human cells and form aggregates with other microorganisms potentially pathogenic to man, which may lead to mixed infections. This family includes eight genes, although not all are present in each strain: ALS1-7 and ALS9, from which ALS1-4 encode adhesins specific for germ tubes and hyphae, while ALS5-7 and ALS9 are associated with blastospores. Their expression varies not only depending on the morphological form, but also on the stage of fungal growth or the type of medium. Individual proteins have some differences in the structure, which may result in their functional diversity, increasing the ability to colonize the host cells [2,18–21].

The genes most frequently reported to be involved in adherence for *C. albicans* are ALS1, ALS3 and ALS5, which are characterized by their ability to adhere to a wide variety of substrates [2,22]. According to Murciano et al. [19] of the Als proteins, only Als3 is responsible for the adherence of *C. albicans* to cells of the oral cavity epithelium, in cases of squamous cell carcinoma, and for the subsequent onset of invasion and destruction of the host cells. It is also believed to be responsible for triggering an immune response involving cytokines (CSF, GM-CSF, IL-6, IL-1α), whose induction is directly proportional to the number of fungal cells adjacent to the epithelium and the stability of this connection, and is also dependent on the hyphal penetration into the epithelium. The contribution of the Als3 protein probably results from their large number and their wide distribution over the entire surface of the germ tubes and hyphae, which facilitates interaction with the epithelial cells. The expression of ALS3, as well as other genes that affect the properties of the *Candida* sp. hyphal cell wall, such as HYR1 or HWP1, is regulated by Bcr1p transcription factor [23]. Murciano et al. [19] do not report the participation of other Als proteins in the adhesion process, which may indicate that they affect adherence only when present in large numbers. Zhao et al. [24] conclude that while both the ALS1 and ALS3 genes play a role in adhesion to the human umbilical vein endothelium, ALS3 also influence adhesion to the oral cavity epithelium: cells of strains lacking ALS3 adhere to the surface of host cells to a far lower degree than fungi without ALS1. These researchers also note that both genes are transcribed at a different time, causing the first Als1 to be formed and Als3 to be activated only after the formation of germ tubes. Als3 (not detected in other fungi of the genus *Candida*) is also essential for the formation of organized biofilm and providing virulence of *C. albicans* [22].

Zhao et al. [25] describe the role of ALS2 and ALS4 genes in adherence, noting that both contribute to *C. albicans* cell adhesion to the vascular endothelium and do not affect adhesion to the oral cavity epithelium. However, ALS2 is important for interaction with the oral reconstituted human epithelium (RHE), causing its destruction.

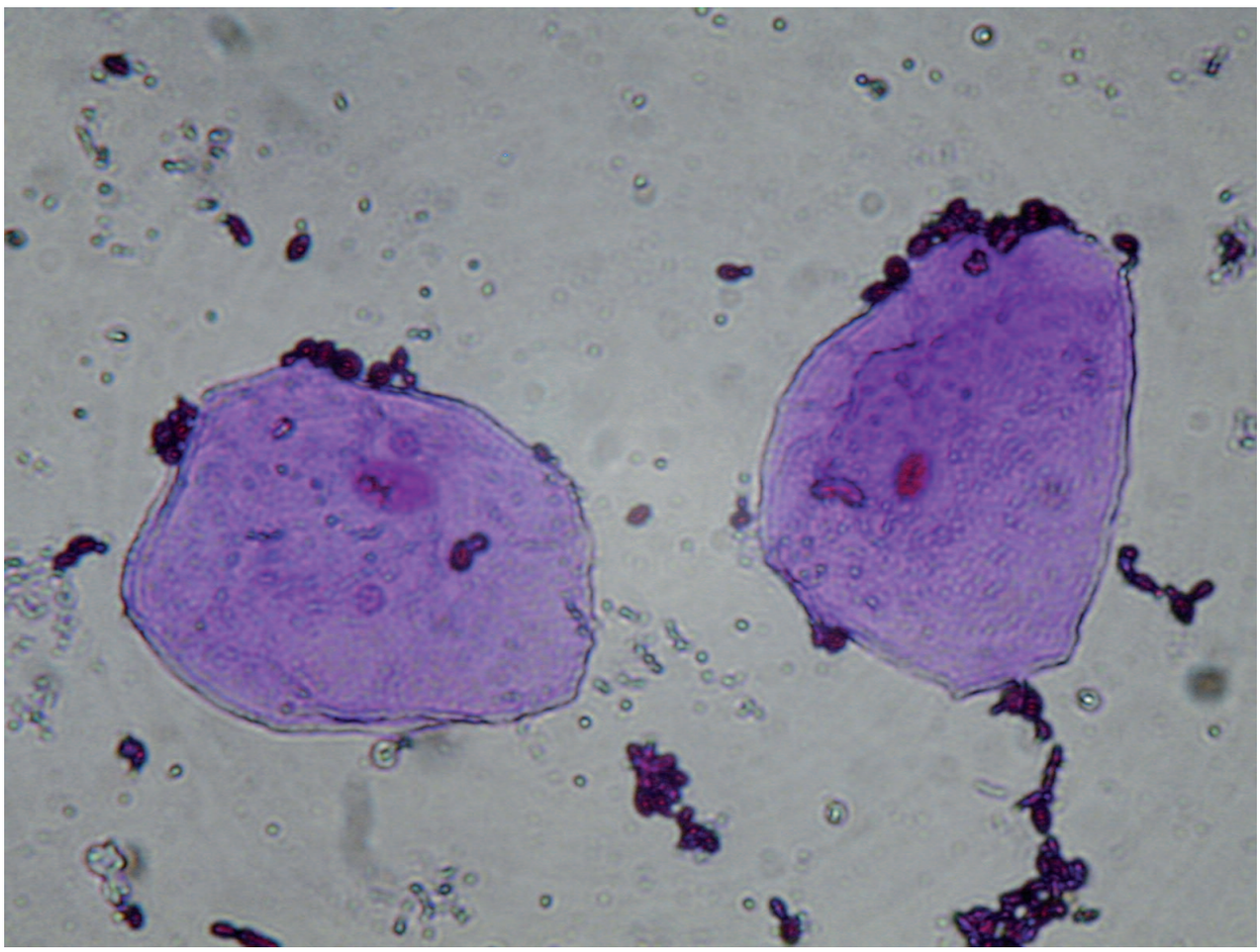

Fig. 1. *Candida* sp. blastospores adhering to human oral epithelial cells (original by Barbara Modrzewska)

ALS2, unlike ALS4 is relevant in the formation of biofilm. The authors also note increased expression of one gene in the absence of the other. ALS5-7 genes are produced in smaller quantities than the other genes of this group, and their experimental elimination from the genotype of *C. albicans* strains contributes to the increase in cell adhesion [21]. ALS9 is characterized by the largest allelic variability of this group, and in *C. albicans*, the ALS9-2 allele is the most common [26]. ALS9, especially ALS9-2, rather than ALS9-1, contributes to the adhesion to the vascular endothelium. However, adhesion to the oral epithelium or to plastic surfaces coated with laminins, is mediated by Als3 [22,25].

The EPA (epithelial adhesin) gene family, which encodes proteins with a similar structure to the Als, has been shown to play an important role in the adhesion of *C. glabrata* cells, for which the ALS genes were not observed. This gene family may comprise 17–23 genes depending on the strain, however the most important role in encoding adhesins is played by EPA1, EPA6 and EPA7. Epa1 lectin is dependent on calcium ions, but its mediated adherence may be lower in the presence of lactose [2,10,27–29].

Another important role in adherence is played by secreted aspartyl proteinases (Sap), which are encoded by genes located on the same chromosomes as ALS, occur in similar numbers and are regulated by similar mechanisms [2].

Some authors also note the importance of such adhesins as Eap1, Sun41, Csh1 (increases the hydrophobicity of the cells) and Hyr1 in adherence [6,10–12,30], however, Wächtler et al. [13] suggest that HYR1 is irrelevant to the interaction with epithelial cells of the oral cavity. Eap1, observed only in *C. albicans*, participates in adhesion to plastics with a hydrophobic surface (e.g., polystyrene); it is also necessary in the process of biofilm formation [10].

All genes of importance in the subsequent stages of *C. albicans* infection were described by Wächtler et al. [13]. The following genes known to contribute

to yeast adhesion were chosen, all of which also affect the subsequent invasion and damage of oral cavity epithelial cells: CZF1, EFG1, TUP1, TEC1, TPK1, TPK2, HGC1, RAS1, RIM101 (controllers of morphology and / or gene expression), VPS11 (gene encoding factors involved in the morphogenetic plasticity), ALS3 and ECM1. Of these genes, ECM1 and EFG1 enhance the process of invasion much more than adhesion, and despite the significant relationship between adherence and tissue invasion, other additional factors are known to play a role in the latter. Some genes that affect the adhesion and damage of host tissues but not the invasion process are CKA2 (performing a role in maintaining cell polarity, its oriented growth, the flow of calcium and homeostasis), BCR1 (activating the ALS1, ALS3 and HWP1 genes), BUD2, RSR1 (both encoding the factors responsible for thigmotropism) and HWP1. It may suggest that the invasion itself is not sufficient to cause the destruction of the epithelium [13,31].

The adherence of *C. albicans* is also significantly affected by heat shock proteins (Hsp) Ssa1 and Ssa2, which belong to the Hsp70 family and are present on the surface of blastospores as well as hyphae. As SSA1 shows greater expression than SSA2, its role in the adherence to epithelial and endothelial cells is more significant, and the Ssa1 protein acts in a similar way to Als3, causing endocytosis by binding to host cell cadherins [32].

The Mediator protein complex (Med31 – Mediator Middle domain subunit) is also known to be an important factor affecting the adherence of *C. albicans* by regulating the expression of ALS1, ALS3 and EAP1 genes, which encode cell wall adhesins, and by regulating the expression of the transcription factors related to those genes (EFG1, TEC1, CPH1). Med31 also plays a positive role in the process of germination and biofilm formation [33].

Badrane et al. [34] report that the strains experimentally deprived of the IRS4 gene, encoding an immunogenic protein, presented an altered distribution of chitin in the cell wall, which resulted in reduced adherence to esophageal adenocarcinoma cells (FaDu), cervical cells (HeLa) and colon carcinoma cells (HT-29) and led to the limited formation of hyphae. It has been noted that IRS4 contributes to the virulence of the fungus: the influence is dependent on location, insofar that IRS4 was found to have no influence in mice with oropharyngeal candidosis, but was necessary in intravenously disseminated candidosis; it was also found to be dependent on the duration of the infection at a given site: IRS4 action in the kidneys is observed after the first stages of disseminated candidosis.

Wang et al. [6] describe another genes positively affecting the adhesion and the formation of hyphae: CHS2 – responsible for the synthesis of chitin, SCS7 – taking part in the formation of cell membrane sphingolipids (encoding α-hydroxylase) and UBI4 – contributing to ubiquitination, which plays role in various cellular processes that determine the virulence of *C. albicans* [6,35]. Du et al. [36] as genes playing a role in adherence and filamentation mention: UME6, TEC1 and GAT2 (they also take part in the biofilm formation) and CPH1 (that does not enhance biofilm production, but contributes to mating).

The morphological transition of *C. albicans* between blastospores and filamentous cells affects its ability to adhere [2], but no such relationship has been reported for *C. tropicalis* [9]. However, it can be stated with some certainty that various adhesion mechanisms are associated with subsequent stages of *Candida* sp. growth (e.g., Als1 or Ala1 adhesins in the yeast phase, Hwp1 in the germ tube and hyphal phase). Germ tubes were also found to demonstrate greater adherence to epithelial cells and form more stable complexes with them than blastospores, which may be associated with the presence of antigens specific to those forms [4,12].

A thick layer (glycocalyx) was also found to be present on the cell wall of *Candida* sp. blastospores adhering to the epithelial surface, which is considered a binder. It is derived from an epithelial fibrin and disappears after internalization by the epithelium [3].

Factors affecting adherence related to host cells

Fibronectins and integrins are proteins of host epithelial cells that function as receptors which bind *Candida* sp. adhesins. Their role in adherence is described in detail by Henriques et al. [2]. Adhesion is also known to be determined by the type of epithelial cells, their morphology and differentiation stage (e.g. due to differences in physiological activity between younger and older cells) [37]. Various species of the genus *Candida* differ in their ability to adhere to enterocytes of newborns and adults: the greatest adherence to both newborns' and

adults' enterocytes being demonstrated by *C. albicans* followed by *C. parapsilosis* in the case of newborns, while *C. glabrata* and *C. tropicalis* in the case of adults [38].

The adherence to epithelial cells of the oral cavity may be influenced by their tissue-like organization. This may increase adherence by providing a greater surface area available to the fungal cells, and by periodically expressing additional factors that promote adhesion [37].

Adherence to the epithelium of the gastrointestinal tract has been found to be associated with the lysis of microvilli, which facilitates the colonization of this region. The adhesion may also be facilitated by the mucus present in the gastrointestinal tract and is accompanied by the lysis of mucous secretions, which confirms the mucinolytic activity of *Candida* sp. extracellular enzymes. Such a mucinous substance (cohesin) has also been observed in studies of cutaneous candidosis – it covers both blastospores and hyphae, and enables adhesion to corneocytes. These fungi were also observed to demonstrate proteolytic activity, which contributes to the degradation of keratin and the formation of cavitations on the corneocytes. Such a change in the structure of the epithelial surface further enhances the adhesion of the fungus, which settles in the resulting cavitations [3].

In response to invasion by *Candida* sp. cells, the human organism produces a number of substances, such as antimicrobial peptides (AMPs) as an immune response. One AMP is LL-37, which binds to such fungal cell wall polysaccharides as mannans, and causes the aggregation of *Candida* sp. cells followed by their detachment from the colonized surface, thus decrease in adherence to the epithelium (oral, urinary bladder) or polystyrene; at higher concentrations, LL-37 leads to the elimination of pathogenic cells. Other peptides, such as histatin 5 (the most effective among histatins, transported by Dur31, secreted by the epithelial cells) and β-defensin 3, also have fungicidal activity, but do not share the same properties as LL-37, thus they do not affect adhesion [39–41].

Environmental conditions as factors affecting adherence

A number of environmental factors influence *Candida* sp. adhesion, such as: the temperature (greater adherence occurs at 25°C than 37°C), the pH value (optimal adherence is seen at pH 3, which is typically found under dental prostheses), the type of the medium (cell binding is better in Sabouraud agar than broth) and inoculum concentration (the minimal inoculum concentration required to observe adhesion is 10^4 cells/ml; the most commonly used concentration under experimental conditions is 10^7 cells/ml). The presence in the medium of carbohydrates such as sucrose, glucose, fructose and, to a lesser extent, maltose also enhances the adhesion: *Candida* adherence is promoted by its reduction of environmental pH via the degradation of carbohydrates in the saliva [2,42,43]. Host saliva can influence the adhesion to polystyrene (which is used, *inter alia,* in the production of prostheses) depending on the morphological form of the fungus: it increases adhesion of blastospores and decreases adhesion of germ tubes, but does not affect the process of germination itself. The presence of secretory IgA (sIgA) in saliva is known to impair the adhesion of germ tubes by blocking the adhesins on the surface of the *C. albicans* cell wall; this substantiates the reduced ability of the saliva of patients undergoing chemotherapy for oral carcinoma, which contains less sIgA, to inhibit the adhesion of fungi [44]. Other factors influencing adherence include human serum (which decreases the adhesion to the epithelium), induced endocytosis and the degree of cell damage, whereas the presence of urine favors colonization of silicone catheters by *C. glabrata* [1,45].

To a lesser extent, the process of *Candida* sp. adhesion to host cells is influenced by non-specific factors, such as the surface hydrophobicity of the pathogen (hydrophobic cells adhere better), which is itself dependent on the temperature of the environment, the interaction of fungal cell wall components, such as chitin, mannan and glucan, with their corresponding receptors on the host cell, and least importantly, electrostatic and van der Waals forces [1,2,5,8,11,18].

As is apparent from the above data, the ability of *Candida* sp. to adhere to various substrates is determined by many genes and is influenced by a range of factors related to the fungus, host and environment. It is a property of fundamental importance for the fungus, without which its survival and development in the host organism, tissue colonization and development of the infection would not be possible.

References

[1] Fisher J.F., Kavanagh K., Sobel J.D., Kauffman C.A., Newman C.A. 2011. *Candida* urinary tract infection: pathogenesis. *Clinical Infectious Diseases* 52: S437-S451.

[2] Henriques M., Azeredo J., Oliveira R. 2006. *Candida* species adhesion to oral epithelium: factors involved and experimental methodology used. *Critical Reviews in Microbiology* 32: 217-226.

[3] Jayatilake J.A.M.S. 2011. A review of the ultrastructural features of superficial candidiasis. *Mycopathologia* 171: 235-250.

[4] Machado A.G., Komiyama E.Y., Santos S.S.F., Jorge A.O.C., Brighenti F.L., Koga-Ito C.Y. 2011. *In vitro* adherence of *Candida albicans* isolated from patients with chronic periodontitis. *Journal of Applied Oral Science* 19: 384-387.

[5] Trofa D., Gácser A., Nosanchuk J.D. 2008. *Candida parapsilosis*, an emerging fungal pathogen. *Clinical Microbiology Reviews* 21: 606-625.

[6] Wang Y.C., Huang S.H., Lan C.Y., Chen B.S. 2012. Prediction of phenotype-associated genes via a cellular network approach: a *Candida albicans* infection case study. *PLoS One* 7: e35339.

[7] Lima-Neto R.G., Beltrão E.I.C., Oliveira P.C., Neves R.P. 2011. Adherence of *Candida albicans* and *Candida parapsilosis* to epithelial cells correlates with fungal cell surface carbohydrates. *Mycoses* 54: 23-29.

[8] Fidel P.L.Jr., Vazquez J.A., Sobel J.D. 1999. *Candida glabrata*: review of epidemiology, pathogenesis, and clinical disease with comparison to *C. albicans*. *Clinical Microbiology Reviews* 12: 80-96.

[9] Negri M., Martins M., Henriques M., Svidzinski T.I.E., Azeredo J., Oliveira R. 2010. Examination of potential virulence factors of *Candida tropicalis* clinical isolates from hospitalized patiens. *Mycopathologia* 169: 175-182.

[10] ten Cate J.M., Klis F.M., Pereira-Cenci T., Crielaard W., de Groot P.W.J. 2009. Molecular and cellular mechanisms that lead to *Candida* biofilm formation. *Journal of Dental Research* 88: 105-115.

[11] Martin R., Wächtler B., Schaller M., Wilson D., Hube B. 2011. Host-pathogen interactions and virulence-associated genes during *Candida albicans* oral infections. *International Journal of Medical Microbiology* 301: 417-422.

[12] Sundstrom P. 1999. Adhesins in *Candida albicans. Current Opinion in Microbiology* 2: 353-357.

[13] Wächtler B., Wilson D., Haedicke K., Dalle F., Hube B. 2011. From attachment to damage: defined genes of *Candida albicans* mediate adhesion, invasion and damage during interaction with oral epithelial cells. *PLoS One* 6: e17046.

[14] Bader O., Schaller M., Klein S., Kukula J., Haack K., Mühlschlegel F., Korting H.C., Schäfer W., Hube B. 2001. The KEX2 gene of *Candida glabrata* is required for cell surface integrity. *Molecular Microbiology* 41: 1431-1444.

[15] Naglik J.R., Albrecht A., Bader O., Hube B. 2004. *Candida albicans* proteinases and host/patogen interactions. *Cellular Microbiology* 6: 915-926.

[16] Nobile C.J., Nett J.E., Andes D.R., Mitchell A.P. 2006. Function of *Candida albicans* adhesion Hwp1 in biofilm formation. *Eukaryotic Cell* 5: 1604-1610.

[17] Naglik J.R., Fostira F., Ruprai J., Staab J.F., Challacombe S.J., Sundstrom P. 2006. *Candida albicans* HWP1 gene expression and host antibody responses in colonization and disease. *Journal of Medical Microbiology* 55: 1323-1327.

[18] Williams D.W., Kuriyama T., Silva S., Malic S., Lewis M.A.O. 2011. *Candida* biofilms and oral candidosis: treatment and prevention. *Periodontology 2000* 55: 250-265.

[19] Murciano C., Moyes D.L., Runglall M., Tobouti P., Islam A., Hoyer L.L., Naglik J.R. 2012. Evaluation of the role of *Candida albicans* agglutinin-like sequence (Als) proteins in human oral epithelial cell interactions. *PLoS One* 7: e33362.

[20] Sheppard D.C., Yeaman M.R., Welch W.H., Phan Q.T., Fu Y., Ibrahim A.S., Filler S.G., Zhang M., Waring A.J., Edwards J.E.Jr. 2004. Functional and structural diversity in the Als protein family of *Candida albicans. Journal of Biological Chemistry* 279: 30480-30489.

[21] Zhao X., Oh S.H., Hoyer L.L. 2007. Deletion of ALS5, ALS6 or ALS7 increases adhesion of *Candida albicans* to human vascular endothelial and buccal epithelial cells. *Medical Mycology* 45: 429-434.

[22] Liu Y., Filler S.G. 2011. *Candida albicans* Als3, a multifunctional adhesion and invasion. *Eukaryotic Cell* 10: 168-173.

[23] Nobile C.J., Mitchell A.P. 2005. Regulation of cell-surface genes and biofilm formation by the *C. albicans* transcription factor Bcr1p. *Current Biology* 15: 1150-1155.

[24] Zhao X., Oh S.H., Cheng G., Green C.B., Nuessen J.A., Yeater K., Leng R.P., Brown A.J.P., Hoyer L.L. 2004. ALS3 and ALS8 represent a single locus that encodes a *Candida albicans* adhesion; functional comparisons between Als3p and Als1p. *Microbiology* 150: 2415-2428.

[25] Zhao X., Oh S.H., Yeater K.M., Hoyer L.L. 2005. Analysis of the *Candida albicans* Als2p and Als4p adhesions suggests the potential for compensatory function within the Als family. *Microbiology* 151: 1619-1630.

[26] Zhao X., Oh S.H., Hoyer L.L. 2007. Unequal contribution of ALS9 alleles to adhesion between *Candida albicans* and human vascular endothelial cells. *Microbiology* 153: 2342-2350.

[27] Alves C.T., Wei X.Q., Silva S., Azeredo J., Henriques M., Williams D.W. 2014. *Candida albicans* promotes

invasion and colonisation of *Candida glabrata* in a reconstituted human vaginal epithelium. *Journal of Infection* 69: 396-407.

[28] Filler S.G. 2006 *Candida*-host cell receptor-ligand interactions. *Current Opinion in Microbiology* 9: 333-339.

[29] Sundstrom P. 2002. Adhesion in *Candida* spp. *Cellular Microbiology* 4: 461-469.

[30] Karkowska-Kuleta J., Rapala-Kozik M., Kozik A. 2009. Fungi pathogenic to humans: molecular bases of virulence of *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*. *Acta Biochimica Polonica* 56: 211-224.

[31] Blankenship J.R., Mitchell A.P. 2006. How to build a biofilm: a fungal perspective. *Current Opinion in Microbiology* 9: 588-594.

[32] Sun J.N., Solis N.V., Phan Q.T., Bajwa J.S., Kashleva H., Thompson A., Liu Y., Dongari-Bagtzoglou A., Edgerton M., Filler S.G. 2010. Host cell invasion and virulence mediated by *Candida albicans* Ssa1. *PLoS Pathogens* 6: e1001181.

[33] Uwamahoro N., Qu Y., Jelicic B., Lo T.L., Beaurepaire C., Bantun F., Quenault T., Boag P.R., Ramm G., Callaghan J., Beilharz T.H., Nantel A., Peleg A.Y., Traven A. 2012. The functions of Mediator in *Candida albicans* support a role in shaping species-specific gene expression. *PLoS Genetics* 8: e10002613.

[34] Badrane H., Cheng S., Nguyen M.H., Jia H.Y. Zhang Z., Weisner N., Clancy C.J. 2005. *Candida albicans* IRS4 contributes to hyphal formation and virulence after the initial stages of disseminated candidiasis. *Microbiology* 151: 2923-2931.

[35] Cheon S.A., Bal J., Song Y., Hwang H.M., Kim A.R., Kang W.K., Kang H.A., Hannibal-Bach H.K., Knudsen J., Ejsing C.S., Kim J.Y. 2012. Distinct roles of two ceramide synthases, CaLag1p and CaLac1p, in the morphogenesis of *Candida albicans*. *Molecular Microbiology* 83: 728-745.

[36] Du H., Guan G., Xie J., Sun Y., Tong Y., Zhang L., Huang G. 2012. Roles of *Candida albicans* Gat2, a GATA-type zinc finger transcription factor, in biofilm formation, filamentous growth and virulence. *PLoS One* 7(1): e29707.

[37] Dalle F., Wächtler B., L'Ollivier C., Holland G., Bennert N., Wilson D., Labručre C., Bonnin A., Hube B. 2010. Cellular interactions of *Candida albicans* with human oral epithelial cells and enterocytes. *Cellular Microbiology* 12: 248-271.

[38] Falgier C., Kegley S., Podgorski H., Heisel T., Storey K., Bendel C.M., Gale C.A. 2011. *Candida* species differ in their interactions with immature human gastrointestinal epithelial cells. *Pediatric Research* 69: 384-389.

[39] Gropp K., Schild L., Schindler S., Hube B., Zipfel P.F., Skerka C. 2009. The yeast *Candida albicans* evades human complement attack by secretion of aspartic proteases. *Molecular Immunology* 47: 465-475.

[40] Mayer F.L., Wilson D., Jacobsen I.D., Miramón P., Große K., Hube B. 2012. The novel *Candida albicans* transporter Dur31 is a multi-stage pathogenicity factor. *PLoS Pathogens* 8: e1002592.

[41] Tsai P.-W, Yang C.-Y., Chang H.-T., Lan C.-Y. 2011. Human antimicrobial peptide LL-37 inhibits adhesion of *Candida albicans* by interacting with yeast cell-wall carbohydrates. *PLoS One* 6: e17755.

[42] Emira N., Mejdi S., Dorra K., Amina B., Eulogio V. 2011. Comparison of the adhesion ability of *Candida albicans* strains to biotic and abiotic surfaces. *African Journal of Biotechnology* 10: 977-985.

[43] Salerno C., Pascale M., Contaldo M., Esposito V., Busciolano M., Milillo L., Guida A., Petruzzi M., Serpico R. 2011. *Candida*-associated denture stomatitis. *Medicina Oral Patologia Oral y Cirugia Bucal* 16: e139-e143.

[44] San Millán R., Elguezabal N., Regúlez P., Moragues M.D., Quindós G., Pontón J. 2000. Effect of salivary secretory IgA on the adhesion of *Candida albicans* to polystyrene. *Microbiology* 146: 2105-2112.

[45] Wächtler B., Citiulo F., Jablonowski N., Förster S., Dalle F., Schaller M., Wilson D., Hube B. 2012. *Candida albicans*-epithelial interactions: dissecting the roles of active penetration, induced endocytosis and host factors on the infection process. *PLoS One* 7: e36952.

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