Oral Health and Candidiasis Development

Subjects: Microbiology
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Oral fungal infection is one of the most researched medical challenges today, being critically related to the development of oral candidiasis, the dissemination of *Candida* sp. in oromucosal tissues, overcoming barriers such as antifungal drug resistance, and repurposing new pathways and mechanisms to alleviate resilient infections.

oral candidiasis | cellular response | epithelial damage | immune response

1. Introduction

Nowadays, oral disease management has become of significant concern in human health and is defined by serious disorders with a life-threatening pattern, affecting over 3.5 billion people worldwide, according to the World Health Organization [1]. Generally, tooth decay, periodontal disease, oral cancer, and oral candidiasis are important pathological conditions that warrant permanent attention and prevention. On the other hand, oral pathologies may trigger systemic diseases in the absence of care and prophylactic treatments. It is well known that tooth decay is directly related to the development of periodontal disease, both being linked to poor nutritional support for the patient [2]. Individuals suffering from periodontal disease are at high risk of developing severe cardiovascular events [3], heart attack, and stroke, which are responsible for a high mortality rate or health complications affecting the quality of life [4][5]. Furthermore, periodontal disease, characterized by chronic inflammatory events, was closely studied due to an additional risk of developing oral cancer in relation to habits such as smoking or alcohol intake [6]. In a cascade fashion, pathogenic microbial colonization in the oral cavity favors mycotic development and the occurrence of oral candidiasis.

The development of oral candidiasis is determined by several mechanisms that induce imbalances in the oral epithelium homeostasis. Poor local defense and a delayed immune system response are detrimental to cellular restoration. As a result, pathogenic fungal colonies disseminate and form resistant mixed biofilms by entailing bacterial pathogens and cellular fragments, promoting serious challenges in initiating a proper therapeutic protocol [7].

Multidrug resistance was established as a serious concern that creates unsuccessful results following treatment with classic topical drugs, particularly polyenes and azoles. Enzymes' structural modifications, efflux pumps, gene regulation, and mutations are the main mechanistic pathways of *Candida* sp. implied in drug resistance [8]. One of the main components that arouse interest in studying new antifungal agents is the fungi cell wall. The cell wall represents the indwelling place of key proteins implied in gene regulation and related to adhesion, dissemination,

and immune response [9]. Hence, this research of the literature aimed to discuss possibilities and new trends through antifungal therapy for the buccal route. Many studies have explored the antifungal activity of new agents or synergic components that may enhance the effect of classic drugs by targeting molecular levels.

The most studied mechanisms related to the antifungal activity proposed the modification of the cell wall structure, the passage through the inner layers, triggering alterations in the cytoplasmic membrane, and cellular death. It was found that these events can be connected with the presence of genuine surface stabilizers selected in nanocolloids development, particularly micro-/nanoemulsions [10]. Incorporating poorly water-soluble compounds in the formulation process of nanoparticulate agents can improve drug passage through the oral tissue, permitting targeted action in the affected site [11]. Inorganic nanoparticles synthesized from various natural resources represent new biomaterials that can be adequately processed to promote oxidative stress and fungi death or provide a gene regulation capacity without inducing cytotoxicity in healthy cells [12][13]. Combining nanoparticles with organic graphene-oxide-based scaffolds or polymeric supports defines a new beginning to developing smart biomaterials for delivering antifungals such as clotrimazole [14] or miconazole [15], the most selected azoles for oral applications.

2. Oral Health and Candidiasis Development

Oral fungal infection is one of the most researched medical challenges today, being critically related to the development of oral candidiasis, the dissemination of *Candida* sp. in oromucosal tissues, overcoming barriers such as antifungal drug resistance, and repurposing new pathways and mechanisms to alleviate resilient infections. The discovery of new targeted therapeutic agents exhibiting intelligent mechanisms of action remains of major concern, especially in the case of chronic and immunocompromised patients [16][17].

As a part of the gastrointestinal tract, the oral cavity is usually a pleasant environment for commensal microorganisms in the absence of health imbalances [18]. Mycotic infection of the oral mucosa acts as an invasive pathology that involves the development of opportunistic pathogens in the structure of the healthy tissue of the host. Depending on the predisposing factors, the presence of systemic disease, and the status of the immune system, infection with *Candida* can become life-threatening, with a reserved prognosis and a high mortality rate of 71–79%, especially in patients with indwelling catheters or following immunosuppressive treatments [16][19].

Infection with *Candida albicans* is one of the most encountered types of oral mycosis in 95% of cases [20] and is known usually as oral candidiasis, oropharyngeal candidiasis, or oral thrush [21], affecting not only the extremes of ages—neonates and elderly individuals—but also the adult population with comorbidities [16]. Its development leads to the formation of white patterns with a cotton-like feeling at the level of the epithelium of the mouth and throat, accompanied by inflammatory lesions, discomfort, and limitations in swallowing [22]. Other species reported in the literature as promotors for candidiasis occurrence are *C. glabrata*, *C. tropicalis*, *C. pseudotropicalis*, *C. krusei*, *C. lusitaniae*, *C. dubliniensis*, *C. parapsilosis*, or *C. stellatoidea* [16][20]. In severe cases related to immunocompromised diseases, pathogens such as *Cryptococcus neoformans* were found to produce unexpected tongue lesions in an HIV patient [23], while mucormycosis caused by mucormycetes was recently reported with a

high incidence in COVID-19 patients [24][25], along with candidiasis [26]. The newly developed infections that occurred in the new context of the COVID-19 pandemic were analyzed as multifactorial cases, and an immediate action was taken to combat fungi resistance and avoid the death of hospitalized patients.

Hence, it can be appreciated that the development of oral candidiasis is influenced by several local and systemic factors, which will be briefly pointed out, as shown in **Table 1**. Thus, the main local triggers involved in oral candidiasis pathogenesis are related to the presence of imbalances in the normal salivary flow [27], the use of dentures or dental prosthesis [28][29], diet factors [30], poor local defense at the epithelial level [31], oral dysbiosis [32][33], the use of inhalator corticosteroids [34], smoking [35], or the presence of other local oral lesions which predispose the oral mucosa to abnormal changes [36]. On the other side, the influence of a series of systemic factors such as deficiencies in the normal levels of vitamins and minerals [37], the presence of metabolic disorders [38], menopause [39], HIV infection [40], the completion of prolonged antibiotherapy [21] and immunosuppressive treatments, especially related to weakened immunity in cancer patients who followed chemotherapy [41] and radiotherapy of the head and neck [42], and not least those who suffered from COVID-19 and associated comorbidities [26], may induce the development of chronic candidiasis, which is hard to control with conventional therapy.

Table 1. Local and systemic triggers defined by surface and molecular changes, involved in candidiasis development and pathogenesis.

Local Factors Factors	Surface and Molecular Effects	Ref.
Imbalances in salivary flow	A high number of *C. albicans* colonies were found in patients with xerostomia, which indicates alterations in normal microbiota. These changes are signaled by a modified pH in oral mucosa and the loss of antimicrobial proteins such as lysozyme, lactoperoxidase, immunoglobulin, histatins, and lactoferrin.	[27] [43] [44]
Dentures	Dentures decrease O_2 supply at the epithelial level and reduce the salivary flow, creating a favorable acidic medium for yeast development. The fungi have an increased affinity for the roughened hydrophobic surfaces of acrylic resins of dentures, encouraging biofilm generation and the initiation of stomatitis. The adhesion process is promoted by a gradual replacement of interfacial water. Intimate mechanisms involved in biofilm formation are the roughness of the surface, hydrophobicity, and electrostatic nature of interactions prior to promoting protein adsorption and adhesion, Lifshitz–van der Waals forces, Brownian motion, and receptor–ligand binding.	[28] [45] [46]
Prosthesis	Dental implants favor the localization of *C. albicans* in the subgingival sulcus and the initiation of pathogenic periodontitis (peri-implantitis). Poor oral hygiene acts in the sense of promoting colonization of periodontal pathogens. The virulence of *C. albicans* is related to the activity of aspartyl proteinase as a promotor for adhesion. In addition, secretion of candidalysin will harm the epithelial cells and bind the epithelial growth factor ^{1} ErbB1 (Her1). The damage to the tissues of the peri-implant area is favored by metallopeptidase (95 kDa),	[29]

Local Factors Factors	Surface and Molecular Effects	Ref.
	targeting type I collagen, type IV collagen, fibronectin, and basement membrane.	
Pre-existing oral pathologies	Denture stomatitis is promoted by modification in E-cadherin, collagen VII and fibronectin, combined with the presence of *C. albicans* colonies in the oral mucosa. Biopsy studies highlighted disorganization of the epithelial cells, with an irregular arrangement of keratinocytes and inflammatory phenomena in connective tissue.	[36] [46]
Poor epithelial local defense	Reduced response of the host immune defense elements (Toll-like receptors, C-type lectin receptors, and [2] NOD-like receptors) induces dissemination of virulence factors, specific for *C. albicans* growth: dimorphism, adhesion, phenotypic switching, polymorphism, and secretion of hydrolytic enzymes such as lipases, phospholipases, and proteinases. A deficiency of epithelial antimicrobial peptides (AMP) was correlated with candidiasis development.	[31] [47] [48]
Oral dysbiosis	The oral microbiome covers a large number of microorganisms, up to 700 species, of which more than 60 are fungi species. A reduction in the number of native fungi that normally harbor the buccal mucosa was associated with the risk of developing oral infections. The interactions between fungal entities and bacteria such as streptococci favor the development of mixed biofilms and modulate the mechanisms implied in polymorphism and host immune response. The interactions of streptococci with *C. albicans* are made through the cell wall surface proteins of the Csh protein family and streptococcal surface proteins A and B. For its part, *C. albicans* supports the interactions through [3] ALS1, [4] ALS3, and [5] HWP1. Other interactions are governed by carbohydrate and extracellular polysaccharides, quorum-sensing molecules, and metabolic events. Dietary sucrose increases *C. albicans* virulence and the symbiotic relationship with streptococcus species.	[32] [33] [49]
Inhalator corticosteroids	The treatment with inhalator corticosteroids causes a poor epithelial local defense of the immune system and was thought to elevate salivary glucose levels as a substrate for fungi growth. Oral candidiasis development was dependent on dose and the device used in administration.	[34] [50]
Smoking	Several theories consider the epithelial damage induced by smoking. In a more profound understanding, a concentration of 1–2 mg/mL of nicotine was found to assure the process of fungi cell multiplication, and it was correlated with an increase in HWP1 and ALS3 expression, implied in hyphae expansion and biofilm formation.	[16] [35]
Carbohydrate-based diet	The intake of dietary and sugar-based foods represents a substrate for candidiasis development. High glucose levels in diabetic patients influence oral candidiasis development as well. Low blood glucose levels (~0.1%) stimulate hyphae growing as the invasive form of candidiasis. This is the result of the regulation of secreted aspartyl proteinases (SAP) genes under the signals of the [6] cAMP/PKA pathway and [7] MAP kinase cascade. MAP kinase pathway was recognized as a trigger for adhesion, invasion, and reorganization of the epithelial level.	[16] [50] [51]

Local Factors Factors	Surface and Molecular Effects	Ref.
Systemic Factors		
Factors	**Surface and Molecular Effects**	**Ref.**
Vitamin and mineral deficiencies	Candidiasis development can be promoted by vitamin A, B_6, and B_{12} deficiency, iron deficiency, or a reduced level of essential fatty acids, folic acid, magnesium, selenium, or zinc. Concerning iron metabolism, it represents an essential element for cell differentiation, oxygen transport, and the normal activity of immune cells. The atrophy of oral mucosa and candidiasis were frequently discovered in anemic patients.	[16] [37] [52]
Metabolic disorders	Diabetic patients are highly predisposed to oral candidiasis, which can be seen as a pathological result of an accumulation of factors: poor oral hygiene, xerostomia, pH imbalances, increase in serum glucose levels, and poor epithelial local defense alike.	[38] [53]
Menopause	A decrease in estrogen hormone levels in menopausal women can counteract the normal state of the oral mucosa. A hormonal change can induce a cascade of local effects involving the modification in salivary secretion, lysozyme decrease, poor local immune activity, and an increase in oxidative stress.	[39]
HIV immunodeficiency	Immunosuppression that can be quantified by a decreased number of CD4+ immune cells entails an increased risk of developing candidiasis. A decrease in histatins level contributes to the severity of the pathology.	[18] [21] [40]
Prolonged antibiotherapy	Administration of broad-spectrum antibiotics yields dysbiosis, affecting the normal oral flora and transforming the commensal microorganisms into pathogenic entities. Imbalances in oral microbiota were related to a decrease in salivary antibody content. Salivary proteins expressed as mucins, salivary IgA, cystatin S, basic proline-rich proteins, or statherins are implied in a dynamic process concerning adhesion/aggregation/clearance of fungal cells.	[21] [54] [55]
Immunosuppressive treatments	Immunosuppressive and cytotoxic treatments of malignancies promote a weakening of the immune system, with repercussions for epithelial cell defense. Resistance to antifungal therapy was observed due to the formation of biofilms with persistent *C. albicans* or *C. glabrata* cells. [22]	[41] [42] [56]
COVID-19	COVID-19 induces immunosuppression by decreasing CD4+ and CD8+ T immune cells. In addition, candidiasis development in its invasive form has a [19] multifactorial pattern, drawn by the presence of comorbidities (diabetes mellitus, pulmonary disorders, and malignancies) and concomitant [41] treatments with immunosuppressants, corticosteroids, or antibiotics. Once more, a decrease in the salivary level of AMP was considered to be a robust marker for both superficial and intrusive infections.	[57] [58]

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C. albicans may exist in four classic states—yeast, pseudohyphae, hyphae, and chlamydospores, characterized by dynamic morphological switching. However, up to nine morphologies have been described to date, of which the opaque (a/α), grey, and gastrointestinally induced transition yeast-like cells were studied for their behavior in the process of pathogenesis [59].

Note: [1] ErbB1 (Her1) represents eukaryotic ribosome biogenesis protein, [2] NOD-like receptors—nucleotide-binding and oligomerization domain receptors, [3] ALS1—agglutinin-like sequence-1, [4] ALS3—agglutinin-like sequence-3, [5]

C. albicans infection is the host-1 by [6] to MAPK/PKA represents the specific, as in contrast to the receptor-kinase A pathway, and [7] MAP kinase, or antigen activated protein kinase [60]. Other mechanisms were previously described, with specific attention paid to the passage of *C. albicans* in the presence of Flu1 efflux pumps. The efflux pumps protect *C. albicans* by host defense peptides via SAPs. Subsequently, proteolytic degradation of the intercellular junctions sustains *C. albicans* passage and completes its invasive character. The affinity of the fungi for bacterial entities and the secretion of toxin-like candidalysin determine the high virulence and an enhanced capacity to invade the epithelial tissue [61]. However, in the absence of triggers, *C. albicans* inhabits the lining mucosa, along with other microorganisms, as part of commensal microflora in a calm and friendly environment.

Thereby, in a normal state, the oral mucosa acts as a physiological barrier against physical and chemical agents due to its well-arranged epithelial structure, which forms the entry lining of the gastrointestinal tract [62]. As well as in the case of skin structure, oral mucosa plays a major role as an immunological and microbiological defense gate, but its structural peculiarities create a unique environment imagined as a mosaic of cellular arrangements, a key factor in the oral pathogenesis of candidiasis, the process of response to infection, and drug delivery [62][63]. The oral mucosa has a thickness of 500–800 µm, covering the entire surface of the oral cavity. It is a stratified, non-keratinized epithelium connected with flexible connective tissue, specific to the buccal, soft palate, and sublingual mucosa. Then, the mucosa is continued with a stratified, keratinized epithelium in the hard palate and gingival areas, being linked with collagenous connective tissue as the intimate lining in the proximity of maxillofacial bone tissues [64].

At the epithelium level, cells are connected by tight junctions, gap junctions, and anchoring junctions, providing integrity for the entire lining [62]. A rapid epithelial clearance, along with salivary flow produced by salivary glands, presents a protective function to avoid the adhesion and invasion of microorganisms [65]. Moreover, the barrier effect is strengthened by the presence of nanometric membrane granules which release lipidic compounds in the intercellular spaces [66]. From an in-depth perspective, the lipidic component contains a high proportion of phospholipids [67], ceramides, and small levels of cholesterol sulfate and glycerol ceramides [64].

As exemplified in **Table 1**, several factors, such as cytotoxic agents, radiation, and immunosuppressants, provoke local imbalances in the normal homeostasis of the epithelia, followed by the destabilization of cell arrangement, triggering a cascade of immunological reactions. This event acts in favor of *C. albicans* pathogenesis and invasion, from local development through systemic disease [68]. Lesions occurring in the oral mucosa and the gastrointestinal tract may determine the dissemination of the fungi in organs such as the lungs, liver, kidney, spleen, or brain [69]. In severely immunocompromised patients receiving chemotherapy and in the absence of appropriate treatment, it was stated that oral candidiasis can expand its development through the pharynx and esophagus, reaching the bloodstream by accessing the intestinal epithelium [70][71].

C. albicans is characterized by smart structural behavior. This fact represents the basis of antifungal drug resistance and its ability to interact with the host immune system and invade healthy tissues. Here, the most important mechanisms related to the multidrug resistance and the narrowing of treatment options will be briefly presented, taking into consideration *C. albicans* morphology.

C. albicans grows as yeast—in round to oval structures with an important role in adhesion—and as pseudohyphae or hyphae structures—tubular cells with filamentous patterns [72]. Their development is quite sensitive to ambient factors, specifically body temperature, local pH, salivary flow, human serum, CO_2/O_2 tension, and the presence of commensal Gram-positive and Gram-negative bacterial species [44][73]. This symbiotic relationship offers advantages for both microbial entities, capitalizing on the formation of polymicrobial films [74]. To exemplify, streptococci offer a carbon substrate from lactate excretion for *C. albicans* development, while in reverse, the fungal colonies assure a reduced oxygen tension for living bacteria [21][75]. *Streptococcus mitis*, *S. oralis*, and *S. gordoni* interact with *C. albicans* by cell surface proteins, which have an affinity for the cell wall of the fungus containing adhesins [75]. Furthermore, *Staphylococcus aureus* has an attraction to the hyphal structure of *C. albicans*, and by default, their interactions increase the virulence of the biofilm [74].

As a mechanistic pathway, the transition through the hyphal state is mediated by multiple transcriptor factors via gene regulation [73]. Under ambient stimuli, *C. albicans* will express hypha-specific genes in numerous pathways, namely: the cAMP/PKA primary pathway mediated by the stimulation of CO_2 and serum, the chaperone heat shock protein 90 (Hsp90) pathway mediated by temperature, the Rim 101 pathway, specific under the effect of acidic pH [76], and, in the last case, the pescadillo homolog (Pes 1) pathway, responsible for hyphal to yeast inversion [76][77].

Considering the previously detailed aspects, a concise presentation of the main processes implied in oral candidiasis pathogenesis is rendered and described in **Figure 1**. The emphasis is on the impairment to normal homeostasis and the implications of the adhesion regulators for *C. albicans* yeast-like colonization, followed by changes in the oral epithelium under the effect of hyphae invasion.

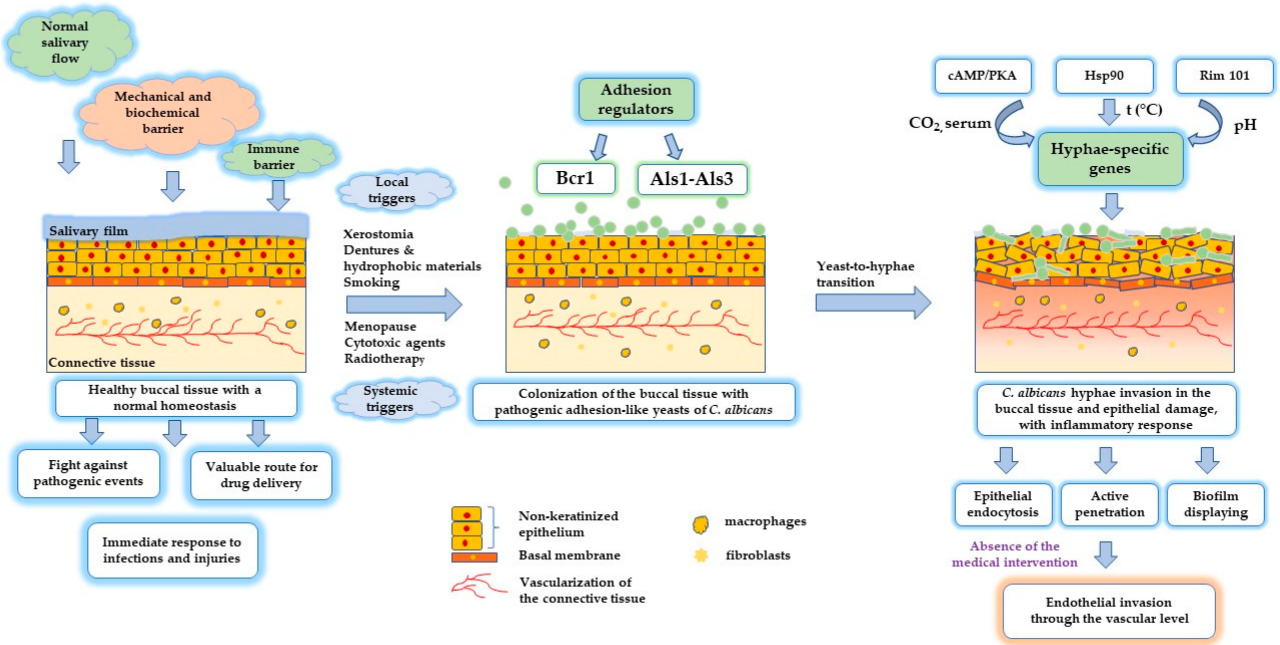


Figure 1. Dynamics in the colonization process of the oral mucosa with *C. albicans* and molecular processes, triggering yeast to hyphae transition and invasion.

The bi-layered cell wall represents a fundamental structure that assures the protection and adhesion of the fungi at the level of the epithelial host cells. Its composition, based on immunogenic elements such as chitin, β (1–3) glucan, β (1–6) glucan, mannan, and mannoproteins, creates an interface to interact with the host immune cells via glycoconjugates, representing the main target of antifungal drugs from the echinocandins' class [78]. The cell wall provides protection against shocks, having a rigid structure [79]. On the other side, elasticity and flexibility were found to be part of the adaptable nature of the fungi to modulate the tensile strength in response to environmental stress conditions such as osmotic shocks [79][80]. Several methods were proposed to study the cell wall's morphology and chemical structure. Lenardon, M.D. et al. offered a valuable interpretation by appealing to 3D modeling and molecular scaling [81]. Thus, in the inner layer of the cell wall, chitin microfibrils coexist with the cell wall proteins, providing vital activity for fungi growth. Chitin microfibrils are crossed by β (1–3) and β (1–6) glucan helices and then interconnected with the cell wall proteins through covalent bonds [81][82]. N-mannan structures define the outer layer of the cell wall as a fibrillar layer and bind the proteins positioned on the inner side. Glycosylphosphatidylinositol proteins, defined as Als3, Als9-2, Sod5, Sap1, Sap3, endoglucanase, exoglucanase, and chitinase, are two sides grafted with both N-mannan and O-mannans and covalently attached to chitin microfibrils by β (1–6) glucan. Pir proteins are attached to N-mannans and covalently linked to an alkali-sensitive bond. The cell membrane integrates proteins with catalytic and transport activity [78][81]. At this level, lipids continue to build the cellular membrane of fungi, promoting structural integrity and protection. Cell morphology, the yeast to hyphae transition, and the biofilm dynamics depend on plasma membrane composition, specifically sterol, sphingolipid, and phospholipid content, which is of paramount importance for the adhesion process and fungi resistance. The higher the polar lipid level in the cell membrane, the better the consolidation of the biofilm will be [83]. A graphical interpretation of the cell wall structure of *C. albicans* is presented in **Figure 2**, with attention paid to the main targets of the host immune defense.

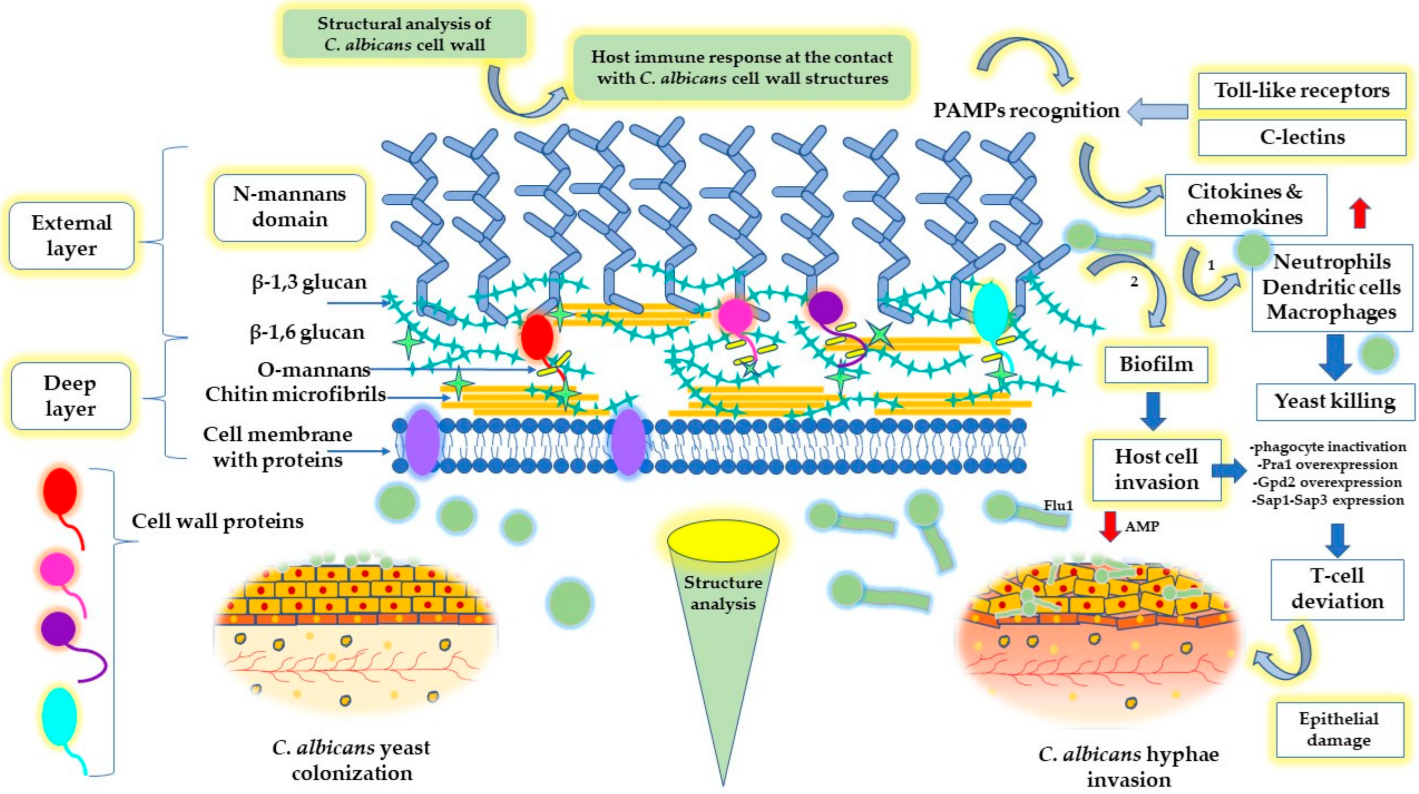


Figure 2. Cell wall structure and host immune defense in *C. albicans* epithelial infection.

The adhesion process of the yeasts at the level of epithelial surfaces or abiotic areas of dental biomaterials with a hydrophobic nature is strengthened by the biofilm generation displayed in the presence of protein-based adhesion regulators, namely Bcr1 via Hwp1 gene [84], Als1 and Als3 [7][85]. This process is continued with the development of hyphal cells, which contribute with a series of regulator factors known as Efg1, Tec1, Ndt1, and Rob1 to consolidate the biofilm [86], create a powerful barrier against host immune system intervention, and disseminate by building a favorable environment for the proliferation of mixed biofilms in the presence of other microbial species [7]. In the maturation process of the biofilm, an expansion by the extracellular matrix was observed, and the engulfment of singular structures such as yeasts, pseudohyphae, hyphae, conglomerates containing *C. albicans* lysed particles after the action of the immune system, host cells, erythrocytes, epithelial cells, dead cells, neutrophils and polysaccharides [87][88]. The proliferation of *C. albicans* biofilm is continued with the dispersion of yeast-like cells under the effect of transcriptional regulators such as Nrg1, Ume6 [89], Pes1 [83], Hsp90 [90], and cell wall protein Ywp1 [91], in a similar manner to that of the planktonic phase, but exhibiting a high virulence [7].

The destructuration of the oral epithelium represents a sign of symptomatic candidiasis, marked by a rapid expansion through the use of extracellular matrix and blood constituents to promote dissemination and invasion [60]. The polymorphism represents the ability of *C. albicans* to pass from an adhesion-like state of yeast—implied in the attachment at the level of the epithelial cells—through an intermediate pseudohyphal and filamentous hyphal-based morphology [21][60]. The hyphal form invades the epithelium by passing the tight junctions and creating depressions when active penetration occurs, or membrane ripples and protrusions, particularly for endocytosis, as was emphasized in the TEM and SEM microscopic analysis of Wächtler, B. et al., and Dalle, F. et al. [60][92]. This process is mediated by the lytic enzymes (proteases) and invasins secreted by hyphal cells, which bind and

degrade E-cadherin and other structural proteins implied in cell stability and their interaction. Agglutinin-like sequence-3 (Als3) represents one of the invasins implied in endocytosis [93], along with the heat shock protein Ssa1 from the Hsp70 family [90][94].

The immunological pattern of *C. albicans* has for years opened a broad area of research intending to propose specific mechanisms implied in growing fungi cells, discovering their vulnerabilities. According to previous reports, important mechanisms that create a cycle of fungi invasion and interaction with the host immune cellular pathways will be further described. At the contact with the antigen, the innate immune system initiates a defense against the pathogens. Phagocytes are activated and will recognize the pathogen-associated molecular patterns through the pattern-recognition receptor pathways (PAMPs) [7][95], followed by signal-mediated transcription. These PAMPs are the structural elements of the cell wall expressed as N-mannans and β-glucans, easily identified by the C-lectins and Toll-like receptors of the host [95]. In this way, the immune system's inflammatory response will be quantified by an increased level of cytokines and chemokines. An increase in the level of neutrophils, macrophages, and dendritic cells is favorable for killing the pathogen and activating the adaptive immune response [7]. The immune response is higher in the yeast form and reduced in the hyphal state, where the transcriptional regulators of the cell wall proteins will act in the sense of host cell invasion [96]. The adaptive immune system releases antibodies to counteract PAMPs activity. On the other hand, the success of an immediate reaction of the host immune system is limited in the case of biofilm attachment, evolving resistance, and a higher virulence, which results in the underestimated activity of neutrophils [97]. Besides the penetration activity, hyphal cells sustain the inactivation of the immune response by destroying phagocytes [7]. In the biofilm state, the overexpression of pH-regulated antigen 1 (Pra1) and glycerol-3-phosphate dehydrogenase 2 (Gpd2), together with the aspartyl proteinases Sap1-Sap3 activity, sustain complement inactivation. Pra1 protein acts in multiple ways, favoring *C. albicans* infection. As a pH-dependent zincophore, it attaches to the immune cells (e.g., CD4+ T cells) and deviates their action to reduce the cytokine cascade. Gpd2 targets the epithelial and endothelial cells, while Sap1-Sap3 attaches complement proteins and degrades them via proteolytic reactions [98]. Subsequently, it was found that Msb2 glycoprotein degrades the AMP, while Sap's degradative injuries assure the release of nutrients that sustain *C. albicans* development [99]. The mechanism was proposed as the cleavage of Msb2 under the action of Saps. Consequently, the extracellular domain of Msb2 is released in the invasive medium of fungal cells. However, this complex inactivates human cathelicidin LL-37, histatin-5, hNP-1, and hBD-1. Similarly, polyamine efflux transporter Flu1 reduces AMP activity through the efflux of histatin-5 [99][100].

On the other side, another essential component of the oral mucosa sustains the immune cells' defense. The mucus generated by salivary activity promotes protection against pathogens due to its composition based on mucins [44]. In the study of Kavanaugh, N.L. et al. mucins were evaluated as potent glycopolymers to decrease fungi virulence. It was discovered that the coded MUC2, MUC5AC, and MUC5B mucins suppress *C. albicans* virulence related to hyphal activity, suppress filamentation, and inhibit adhesion [101]. Generally, the response of innate immunity can be increased with several defense proteins identified in the saliva. Besides mucins, lysozymes, statherins, cystatins, or proline-rich proteins act synergistically to counteract tissue imbalances. Salivary immunoglobulin and salivary chaperonin stimulate the activity of both innate and acquired immunity [65].

In a pathological state, when the immune response is weakened, the invasive mechanisms of *C. albicans* favor the epithelial damage and the development of acute, chronic, or chronic mucocutaneous candidiasis [21]. Acute candidiasis is characterized by pseudomembranous and erythematous forms, being specific for chronic conditions as well. Pseudomembranous infection is commonly recognized as a complex of damaged epithelial cells and necrotic tissue braided with hyphal cells in a plaque-like architecture. After debridement, a bleeding tissue is disclosed [102]. More frequently encountered after using broad-spectrum antibiotics, acute erythematous candidiasis or atrophic candidiasis is perceived in the form of acute painful and swollen oral lesions with a red appearance on the dorsum of the tongue and palate. For patients wearing dentures or orthodontic retainers, chronic atrophic candidiasis (denture stomatitis) usually occurs [103]. Likewise, a complex of stable non-detachable plaque type and erythematous lesions with nodular appearance better describes the chronic development of hyperplastic candidiasis on the oral mucosa and lateral area of the tongue. These patients are at risk of developing epithelial dysplasia and cancerous lesions [104]. Other lesions associated with *C. albicans* development target the commissures of the lips in angular cheilitis or the dorsum area of the tongue, where symmetrical disposal of the lesions determines the shaping of median rhomboid glossitis. The lesions can appear independently or in mixed pathologies associated with pseudomembranous and erythematous candidiasis and constitute a real challenge for an appropriate therapeutic purpose [105].

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