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Candida and the Human Host: Who Wins the Battle?

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Abstract

Candida species are part of the commensal human flora and are mostly harmless. However, under certain circumstances, *Candida* spp. can cause superficial, mucocutaneous, or systemic life-threatening infections. The interaction between *Candida* and the host is a complex process that involves immune strategies to confine the pathogen and evasion tactics of *Candida* to achieve host cell invasion and colonization. Understanding this complex interplay may lead to new therapeutic strategies; this is a primary goal in an era of increasing antifungal resistance of *Candida* species. This review summarizes the different aspects of the *Candida*-host relationship and highlights the factors that enable Candida's survival in the host.

Keywords: *Candida*, pathogenesis, immunity, NETosis, scavenging, phagocytosis.

Introduction

Candida species are part of the commensal human flora that colonizes healthy human skin, mucosa, and the reproductive tract. *Candida* is the fourth cause of nosocomial systemic infections, with a mortality ranging from 11 to 33% [1, 2]. *Candida albicans*, the most common species, can cause superficial-mucocutaneous and life-threatening systemic infections in humans. Systemic infections are encountered mainly in neutropenic patients with disrupted gastrointestinal mucosa and patients in intensive care units with central venous catheters or abdominal surgery [3].

During infection, the interplay between *C. albicans* and the host involves varied virulence factors and adaptation mechanisms to the changing environment [4].

C. albicans is a polymorphic fungus that can grow as budding yeasts, pseudo-hyphae, or true hyphae. The transition between yeast and hyphal growth (dimorphism) has a central role in pathogenicity [5] and biofilm formation [6, 7]. The hyphal form is considered more invasive [6], whereas the smaller yeast is associated with attachment and dissemination [8, 9]. Hyphal morphogenesis is a crucial mechanism in biofilm formation, host invasion, and evasion of killing by phagocytic cells [7, 9]. It is induced by varied factors, such as high pH (>7), amino acids availability, starvation, presence of N-acetylglucosamine, Co_2, and temperature [10]. In addition, quorum sensing molecules promote yeast growth at high densities (>10^7 cells mL^{-1}), whereas low densities favor hyphal growth [11, 12]. Other important inter-players with *Candida* in pathogenesis are: 1) Adhesins, glycosylphosphatidylinositol (GPI)-linked cell surface proteins that mediate adherence of *Candida* cells to other *Candida* cells, microorganisms, host cells, and abiotic surfaces [13, 14]. Specifically, the hyphae surface protein Als3 is expressed during oral epithelial cell infection and vaginal infection [15-18], and Hwp1 facilitates the linkage of *C. albicans* cells to host cells. 2) Invasins, mainly Als3 and Ssa1, mediate binding to host E-cadherin and N-cadherin on epithelial and endothelial host cells, respectively, and trigger the engulfment of the fungal cell into the host cell [19-21]. Invasion into host cells is augmented by *Candida* proteases, phospholipases, and lipases [17]. 3) Environmental adaptation of *Candida* also has an important role in pathogenicity. The host environmental pH is different in various compartments (acidic pH in the vagina and alkaline pH in tissues and blood) (4), and *Candida* cells sense and adapt to the host pH by Rim1 signal transduction and cell wall β-

glycosidases [22-24]. In addition, depleted glucose sources trigger *Candida* to activate the glyoxylate cycle with gluconeogenesis and usage of lipids and amino acids as nutrient sources [25, 26]. This allows *Candida* to transform into a more virulent hypha [27, 28]. Fungal heat shock response to environmental stresses includes synthesis of heat shock proteins (Hsps) that stabilize proteins and prevent their damage (4). Important Hsps in *Candida* are Hsp104 that was shown to be required for biofilm formation [29], Hsp90, which regulates drug resistance, morphogenesis, and biofilm formation [30, 31], and Hsp70 members that function as receptors for antimicrobial peptides [32].

Candida virulence factors determine the extent and severity of the disease it may cause. Thus, its understanding is essential both biologically and as a means of developing new antifungal strategies. The development of new therapies is critical, as the current antifungal arsenal is limited in the face of an increased rate of triazole-resistant *Candida* species during the last decades. For the same purpose, it is equally important to understand the interplay between *Candida* and the host's innate and adaptive immunity, including the interaction of the fungus with the tissues it inhabits, as a potential port of entry for invasive infections.

Aims

The aim of this review is to summarize the different aspects of the interplay between *Candida* and the host's immunity and to highlight the factors that enable *Candida's* survival in the host.

Materials and Methods

This review summarizes our current knowledge of the interaction between *Candida* and the host's immunity. A search of papers published between January 1970 and January 2021 was performed using PubMed and Web of Science databases. The terms: *Candida*, innate, adaptive, immunity, complement, NETosis, oxygen scavenging, and saliva were used as keywords for database searches.

The role of innate and adaptive immunity in response to *Candida albicans*

Body clearance of fungi like *C. albicans* involves phagocytosis by fixed tissue macrophages, infiltrating monocytes, and neutrophils. The interaction of *Candida* with epithelial cells causes the release of cytokines and chemokines that recruit and activate inflammatory and immune cells, including phagocytes, antigen-presenting cells (APCs), and T cells. The first immune cells to contact *C. albicans* are the mast cells. Mast cells play a key role in maintaining the balance between the host and the commensal *C. albicans* limiting pathological fungal growth and modulating the response of resident macrophages during infection [33]. Through phagocytosis, the fungi are confined and killed by the oxidative and non-oxidative antimicrobial systems. These include oxygen-derived reactive species generated from the activation of the NADPH oxidase complex and granule constituents. At the site of infection, myeloperoxidase released from neutrophils activates macrophages and induces microbicidal activity. These mechanisms are responsible for the damage to hyphal forms of *C. albicans* [34]. The defense against *C. albicans* by autophagy involves a complex process. A former study has shown that phagocytized *C. albicans* leads to the inhibition of basal autophagic flux via MTOR-independent mechanisms [35].

The APCs process *Candida* antigens and migrate to the lymph nodes to present them, in the context of the MHC Class II molecule, to naive CD4 T cells, which are then activated and differentiate to either a Th1-type or a Th17-type cell. The prevailing cytokine milieu probably determines the dominant outcome (Th1 or Th17). On reaching the infected site, Th1 effector cells release cytokines that orchestrate infection containment in the mucosal surfaces and prevent dissemination [34]. IL-12 is a cytokine produced by the innate immunity components that links the innate and adaptive immunity systems. In mice, its deletion leads to acute susceptibility to oral infection with *C. albicans*, whereas such mice are resistant to systemic disease. However, it is an essential component of the adaptive response that leads to the generation of Th1-type cytokine responses and protection against disseminated disease [36]. Th17 cells release IL-17, thereby enhancing the candidacidal activity of neutrophils. Thus, both innate and adaptive components of the immune system work cooperatively to provide an effective defense against the invading yeast [34, 37].

The complement

Complement promotes phagocytosis through interaction with a series of complement receptors, including the recently described complement receptor immunoglobulin [38]. However, it is also evident that the killing of yeast and hyphal forms can occur in a complement-independent manner. Phagocytosis and killing of *Candida* are enhanced by the cytokine network, such as tumor necrosis factor-α and interferon-γ. Patients with primary immunodeficiency diseases who have phagocytic deficiencies, for example, defects in the NADPH oxidase complex, are predisposed to fungal infections, providing evidence for the critical role of phagocytes in antifungal immunity. Secondary immunodeficiencies can arise as a result of treatment with anti-cancer or other immunosuppressive drugs. These agents may also predispose patients to fungal infections due to their ability to compromise the antimicrobial activity of phagocytes.

Candida-complement interplay occurs in disseminated disease and locally on skin or mucous membranes in the oral cavity and vagina; the mechanisms can be supposed to be the same. Activation of the complement system by *Candida* is facilitated by directly triggering the three dominant pathways, but also indirectly via the coagulation and fibrinolysis systems. The complement-mediated anti-*Candida* effects induced thereby clearly affect chemotaxis, opsonization, and phagocytosis. Even the membrane attack complex formed on the fungal surface plays a modulatory role, although lysis of the yeast per se cannot be induced due to the thick fungal cell wall. Several evasion mechanisms have evolved during co-evolution, including the avoidance of recognition and destruction, to elude the hostile action of complement. Some examples are the cleavage of complement proteins by yeast enzymes and the exploitation of regulatory proteins, such as factor H, by recruiting them to the cell wall. The rationale is that the fluid phase regulators, when on the fungal cell surface, down-regulate complement locally [39].

Interestingly, however, evasion protein knockout strains do not necessarily lead to an attenuated disease. Thus, the effect is likely more complex in vivo than initially thought. The interactions between complement and non-*albicans Candida* species also deserve attention, especially *Candida auris*, a recently identified drug-resistant species of medical importance. Deciphering these interactions may lead to alternative antifungal therapies that directly target the molecular mechanisms [39, 40].

Host endocytosis and NETosis

When phagocytes arrive at the infected sites, neutrophils, which can detect large microorganisms such as *C. albicans*, undergo a specialized form of cell death named netosis. The NETS (traps) formed are rich in nucleosome and bactericidal highly cationic histones, elastase, defensins, cathelicidin, LL37, lysozyme, and proteinases, all highly toxic to bacterial and fungal cells such as *C. albicans* [41, 42]. In 1981, a novel explanation was proposed for the role of netosis in the pathogenicity of microbial infections and autoimmune disorders such as lupus, atopic dermatitis, psoriasis, rheumatic fever, rheumatoid arthritis, and autoimmune nephritis [43, 44]. It was suggested that negatively-charged *C. albicans* is pre-opsonized with **cationic histone** that acts similarly to antibodies, and in this way, is internalized by macrophages. It was also demonstrated that the process could be inhibited by anionic heparin, which neutralized the histone action [43]. Like antibodies, the polycation can bind by strong electrostatic force to negatively charged domains present on *C. albicans* cells, facilitating endocytosis of *Candida* cells [45]. This allows the fungus to survive unharmed in macrophages and most probably also in skin keratinocytes and mucosal cells. Survival of intracellular *Candida* may be due to their thick glucan layers. Of great importance is that, unlike bacteria, *C. albicans* and other fungal cells lack autolytic wall enzyme systems, which, in bacteria, can be activated by cationic peptides such as lysozyme and certain bacteriolytic antibiotics [46-49]. On the other hand, phagocytosis also induces a switch from yeast to hyphae that puncture the macrophage membrane allowing *Candida* to escape [6]. *C. albicans* can also evade the effect of net enzymes by releasing DNAse to the extracellular medium or by forming biofilms which render fungal cells less accessible to immune cells [41, 42].

In the oropharyngeal form of mucocutaneous candidiasis, mucosal cells phagocytize *Candida.* It occurs when the balance between host, *Candida,* and microbiota is disturbed and is usually related to cancer or a weakened immune system (e.g., acquired immunodeficiency syndrome, AIDS) [45]. In vaginal candidiasis**,** the epithelium of the vagina can engulf *Candida* cells. Although the mechanism by which these cells engulf *Candida* is still unclear, it has been suggested that since vaginitis is always accompanied by the accumulation of high numbers of neutrophils, endocytosis can be effective via the cationic peptides generated by neutrophil NETS [50]. Keratinocytes are the principal cells in the skin that engulf but do not significantly injure *C. albicans*, suggesting that they may survive undamaged until the host's immune system is compromised. *Candida* invasion of other non-phagocytic host cells, such as epithelial cells during mucosal and respiratory infection, with subsequent invasion of endothelial cells during hematogenous infection, is mediated by fungal induction of its own uptake. *C. albicans* hyphae interact with endothelial cells in vitro by binding to N-cadherin on the endothelial cell surface. This binding induces rearrangement of endothelial cell microfilaments, resulting in the organism's endocytosis [46].

Cationic antimicrobial peptides

Since invasive fungal infections in humans are generally associated with high mortality, choosing the right antifungal drug is crucial. The limited spectrum of antifungals available and the development of drug resistance represent the main concerns for the current antifungal treatments, requiring alternative strategies, such as antimicrobial peptides (AMPs). Upon contact with *C. albicans*, the human host utilizes efficient complex immune responses that lead to the production of soluble effectors, including AMPs and cytokines, or to the activation of complement, which can directly damage the pathogen. *C. albicans* defends itself against various innate immune components, including AMPs [48, 51]. Although most AMPs exert their activity through membrane interaction, other mechanisms have been identified, including cell wall inhibition and nucleic acid binding [51]. Cationic peptides are good AMP candidates for developing alternative antimicrobial agents. Notably, they show negligible host toxicity and low resistance rates. Most of the current literature focuses on peptides

with antibacterial activity, but fewer studies focus on their anti-*Candida* properties. The classification of the cationic peptides is based on their mode of action, including cell wall inhibition and nucleic acid-binding. Therefore, the elucidation of such mechanisms can be helpful to identify novel drug targets and, possibly, serve as the templates for the synthesis of new antimicrobial compounds with increased activity and reduced host toxicity. The cationic antimicrobial peptide LL-37, a member of the cathelicidin family, is highly present in NETS and was found to have a protective role against C. *albicans* [51].

Candida interaction with epithelial cells, keratinocytes, and endothelial cells

One of the most critical virulence strategies of *C. albicans* is their ability to invade epithelial cells and keratinocytes, where they can survive unharmed.

The mucosal epithelium is the first line of host defense after the initial contact with the invading pathogen. The interaction between the epithelia and the microorganism either causes commensalism or violates the superficial barrier on mucosal surfaces. The infection process of *C. albicans* consists of adhesion, invasion, and cell damage. During the adherence of *C. albicans* to human epithelial surfaces, a significant number of specialized adhesins are needed to build their attachment to the host. Additionally, upon recognizing *C. albicans*, epithelial cells can secrete antimicrobial peptides, such as defensins, cathelicidins, and histatin.

Diverse fungal species commonly colonize the human skin. Some *Candida* species, especially *C. albicans*, reside on the skin surface as commensals and cause infections by growing into the colonized tissue. However, defense mechanisms at the skin barrier level are very efficient, involving residential non-immune and immune cells and immune cells specifically recruited to the site of infection [52]. Therefore, the skin is an effective barrier against fungal infection. While most studies about commensal and pathogenic interaction of *Candida* species with host epithelia focus on the interaction with mucosal surfaces, such as the vaginal and gastrointestinal epithelia, less is known about the mechanisms underlying *Candida* interaction with the skin [52]. Human keratinocytes kill *C. albicans in vitro*, but the killing mechanism is not yet understood. It was demonstrated that spontaneous, ultraviolet-B-light-induced,αmelanocyte-stimulating hormone-induced and interleukin-8-induced *Candida* killing by keratinocytes could be inhibited with mannan and mannosylated bovine serum albumin (Man-BSA). It was also shown that the presence of the mannose receptor on human keratinocytes is actively involved in *C albicans* killing [53].

In immune-compromised hosts, *C. albicans* can disseminate from blood and migrate from the circulation, causing extensive organ damage and systemic candidiasis. *C. albicans* that fail to be eliminated by phagocytes and fungicidal factors have to adhere to and penetrate endothelial cells before disseminating in organs [54]. At the initiation of hematogenous infections, vascular endothelium acts as a barrier to prevent pathogen dissemination. *C. albicans* must face two main difficulties to enter the tissues successfully: adhering to endothelial cells and gaining access to endothelial layers. There is evidence that morphogenetic transformation occurs during the adhesion process [54].

Candida mechanisms of survival in the host: oxidant scavenging ability

Both the planktonic and hyphal forms of *Candida* can recruit large numbers of phagocytes, which can engulf mainly the planktonic forms. By doing so, they can be activated to release large numbers of pro-inflammatory agents such as reactive oxygen and nitrogen species, cationic proteinases, and membrane–puncturing phospholipases [55-57]. However, unlike bacteria, the lack of autolytic wall enzymes in *Candida* does not allow lysis of the rigid glucan cell walls. This was also clearly demonstrated by electron microscopy (Ginsburg I, unpublished data).

In addition, to secure their survival in the host, *C. albicans* elaborate catalase as a significant antioxidant agent. Catalase, an iron-containing enzyme, detoxifies hydrogen peroxide and plays a vital role in protecting C. *albicans* against reactive oxygen species and neutrophil killing. High basal catalase expression increased the resistance of this yeast to oxidative and combinatorial oxidative plus cationic stresses. However, rather than enhancing the virulence of C. *albicans,* as predicted, high basal catalase expression decreased fungal colonization in some iron-limiting tissues. Catalase inactivation did not significantly perturb the virulence of C. *albicans* in models of systemic infection [58]. It is of note that catalase, which is considered a powerful virulence factor in many microbiotas, paradoxically rescues anaerobic catalase-negative periodontal pathogens from peroxide and oxygen radicals generated by leukocytes migrating to inflamed sites. Therefore, the role of H_2O_2 in oral pathophysiology and its cell signaling properties are vital in host and parasite interrelationships under normal and pathological conditions [59].

The effect of various agents on the oxygen scavenging ability of *Candida* cells

Chlorhexidine (CHX) induces oxygen scavenging ability (OSA) of C. albicans

A marked enhancement of OSA occurs in the presence of the cationic microbicide chlorhexidine (CHX) digluconate.

The OSA of *C. albicans* treated by CHX increases with unstimulated saliva, polyphenols, cationic peptides, and fresh blood [59]. When tested with CHX, large amounts of H_2O_2 (50 -100 mM) neither kill *Candida* cells nor affect their catalase activity. However, as little as 2.5 μM of hypochlorous acid (HOCl) totally inactivates *Candida* OSA and kills all the fungal cells. However, AAPH, a donor of peroxyl radicals, significantly increased the OSA of *Candida* treated by CHX and failed to kill the fungal cells. Large amounts of CHX killed all fungal cells tested [44, 59].

Reactive oxygen enhancement by CHX depends on the Candida cultivation medium

In a former work, various species of *C. albicans* were cultivated on nine different media and tested for their OSA in the presence of CHX. CHX markedly increased OSA of *Candida* grown on some media (sensitive) but failed to do so when grown on others (resistant). Interestingly, *Candida* that grew on resistant media, when passaged to a sensitive medium, fully regained their ability to decompose peroxide. Phase microscopy showed no apparent changes in cell morphology of *Candida* grown on any of the media [59]. These results suggest that this is an epigenetic phenomenon.

C. albicans disrupted by sonication were analyzed for the ability to decompose H_2O_2. Supernatant fluids from sonicated *Candida* grown on sensitive media readily decomposed peroxide, depressed luminescence, and were inhibited by azide, indicating the role of catalase and additional heme enzymes. However, no OSA was detected in supernatants from *Candida* grown on the resistant media treated with CHX, suggesting that some not yet defined ingredients of the resistant media signaled a lack of catalase activity [59].

The combined effect of CHX, saliva, and blood on OSA

Local application of CHX on oral lesions always encounters the whole saliva and its proteins mucin, albumin, and polyphenols from nutrients. Saliva may also contain variable amounts of blood due to capillary injury [60]. Non-inhibitory amounts of saliva, mixed with CHX, markedly enhanced OSA. Similar to saliva, mucin markedly enhanced OSA of *Candida* treated with CHX [60]. In addition, saliva contains cationic agents such as histatin and lysozyme, and in inflammatory sites also cationic peptides such as LL-37 and other neutrophil-derived lysosomal polycations. Coating *Candida* cells with polycations showed a substantial decline in OSA, which was reversed with anionic heparin [59].

In a former work (59), the OSA of *C. albicans* was tested by a luminescence test. CHX induced a low luminescence inhibition but adding RBCs combined with mucin, albumin, and polyphenols induced a potent OSA activity, which was partially abolished by the heme protein inhibitor sodium azide. This finding implies that maintaining a proper redox status in the oral cavity requires synergism among multiple agents. In human blood, it was shown that polyphenols enhance the total oxidant-scavenging capacity by binding to RBCs [61]. Human erythrocytes can carry oxygen and bind avidly to their surfaces a large variety of polyphenol antioxidants, which lead to enhanced total oxidant-scavenging capacities (TOSC) [61]. It was also postulated that circulating erythrocytes and other blood cells might be constantly coated by polyphenols from supplemented nutrients, which act as antioxidant depots and can thus act as protectors against the harmful consequences of oxidative stress [61]. Further studies are needed to determine the fate of polyphenols in circulation and their sequestration in the spleen [61].

The role of polyphenols as oxidant-scavengers

Several microbial species can irreversibly bind a large variety of polyphenols (flavonoids) found in many colored fruits and vegetables and enhance their total oxidant-scavenging capacities (TOSC). The binding of flavonoids to microbial surfaces is further increased by the cationic poly-L-histidine, chlorhexidine, and Copaxone [62]. The possibility is considered that clinically, microbial cells in the oral cavity and the gastrointestinal tract, complexed with antioxidant polyphenols from nutrients and with cationic ligands, might increase the protection of mammalian cells against damage induced by excessive generation of reactive oxygen species during infections and inflammation [62]. *C. albicans*, as well as Streptococcus mutans, are two significant contributors to dental caries. They have a symbiotic relationship that allows them to create an enhanced biofilm. In a former study, we examined whether two natural polyphenols (Padma hepaten (PH) and a polyphenol extraction from green tea (PPFGT)) could inhibit the caries-inducing properties of these pathogens. Both PPFGT and PH dose-dependently inhibited biofilm formation and exopolysaccharide production without affecting planktonic growth [63, 64].

Polyphenols enhance the oxidant-scavenging capacities of red blood cells

Salivary antimicrobial peptides are considered an essential part of the host innate defense system in preventing microbial oral cavity colonization. Histatin-5 has exhibited potent activity against *C. albicans* [65]. Previous studies have shown that histatin-5 levels are significantly reduced in the saliva of HIV-positive individuals [66]. *C. albicans* efficiently and rapidly degrade histatin-5, resulting in loss of its anti-candidal potency, indicating an essential role for histatin-5 in keeping *C. albicans* in its commensal stage [67]. The versatility in the pathogenic potential of *C. albicans* is the result of its ability to adapt through the regulation of

virulence determinants, mainly proteolytic enzymes involved in tissue degradation. The histatin-5 activity is due to proteolysis by a member of the secreted aspartic proteases (Sap) family involved in *C. albicans* pathogenesis. The proteolysis was attributed to Sap9, identifying histatin-5 as the first host-specific substrate for that isoenzyme [67]. These pioneer findings demonstrated the ability of a specific *C. albicans* enzyme to degrade and deactivate a host antimicrobial peptide involved in the protection of the oral mucosa against *C. albicans*, thereby providing new insights into the factors directing the transition of *C. albicans* from commensal to pathogen, with important clinical implications for alternative therapies [67].

Murine tumor cells were induced to phagocytize either *C. albicans* or group A streptococcal cells [44]. The presence of microbial cells within the tumor cell cytoplasm did not affect in vitro tumor cell growth. However, when C. albicans-infected tumor cells were injected into syngeneic mice, they formed tumors that grew faster, invaded the surrounding normal tissue more rapidly, and metastasized more quickly than control tumor cells. In contrast, tumor cells infected with group A streptococcal particles did not grow faster or show increased malignant behavior [44]. These data indicate that the in vivo behavior of malignant tumor cells can be modulated by microbial cells, which are often present in the microenvironment of the growing tumor [44].

The effect of saliva on *Candida albicans* growth

The effect of lysozyme on *Candida* growth

C. albicans interacts with saliva, which contains the cationic histatin and lysozyme enzyme. Like other polycations, these cationic enzymes can bind by strong electrostatic forces to *Candida* cells, promoting phagocytosis mainly by neutrophils and macrophages [68].

When *C. albicans* is grown in a lysozyme-glucose solution, scattered small colonies are seen on the agar surface, compared with the thick full growth of the control culture incubated without lysozyme. A constant quantity of lysozyme destroyed Candida cells to an equal degree, regardless of varying glucose concentrations. The presence of NaCl prevented the lysis of Candida by lysozyme in various solutions [68].

Microscopic observations revealed drastic changes in *Candida* cell morphology following exposure to lysozyme. Most of the cells were seen swollen, degenerated, and some were destroyed. The gram-positive characteristics of *Candida* cells changed to gram-negative. The combined activity of lysozyme, complement, and antibody may also play an important role in the protection against candidiasis in vivo [69].

The effect of lysozyme on *Candida* biofilm formation

The in vitro effect of lysozyme on *C. albicans* biofilm development was investigated using a reference strain and ten clinical isolates from dentures. Lysozyme affected biofilm formation to a greater extent than it affected growth. For the reference strain, lysozyme acted as a biofilm promotor on polystyrene at the highest concentration tested. When the reference strain was investigated on acrylic resin support, lysozyme worked as a significant biofilm promotor on rough resin [68]. In 10 wild strains, different patterns of biofilm formation on polystyrene were observed in the presence of lysozyme. Some strains, characterized by large amounts of biofilm formation in the presence of high lysozyme, were poor biofilm producers at low concentrations of lysozyme. In contrast, some strains that were poor biofilm producers with a high lysozyme concentration were more inhibited by low lysozyme concentrations [69]. This investigation emphasized the need to develop strategies for biofilm control based on in vitro experiments and to implement these in clinical trials before the approval of hygiene products enriched with exocrine proteins, such as lysozyme.

Interactions of *Candida* with oral bacteria and salivary molecules in oral biofilms

Candida aggregates with various streptococcal species; this interaction may promote oral colonization. *C. albicans* and *C. tropicalis* are the yeasts most frequently isolated from the human oral cavity, and both species were shown to bind to Streptococcus gordonii [70]. For 21 strains of *C. albicans*, there was a positive correlation between the ability to adhere to *S. gordonii* and adherence to experimental salivary pellicle. Whole saliva either stimulated or slightly inhibited the adherence of *C. albicans* to *S. gordonii* depending on the streptococcal growth conditions. The results suggested that the major salivary adhesins and coaggregation adhesins of *C. albicans* are co-expressed [70].

Conclusion

The interplay between *Candida* and the host is a complex process that involves immune strategies to confine the pathogen and evasion tactics of *Candida* to achieve host cell invasion and colonization. Neutrophil traps rich in cationic histones at the site of infection assist endocytosis of *Candida* by phagocytes. However, the fungus can survive unharmed by switching to hyphal forms to evade macrophages. The oxygen scavenging ability of *Candida* helps its survival in the host and can be enhanced by various agents, such as chlorhexidine, saliva, and polyphenols. This process has the potential to mitigate inflammation-induced damage and is not necessarily associated with virulence. Various factors balance the interaction of *Candida* with barrier tissues.

The saliva has a protective role against *Candida* infection through cationic lysozymes that promote phagocytosis and antagonizes biofilm formation, and the mannose receptor on keratinocytes mediates *Candida* killing. Understanding this complex interplay may lead to new therapeutic strategies; this is a primary goal in an era of increasing antifungal resistance of *Candida* species.

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