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Host responses to Candida albicans. A review

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SUMMARY

Candida albicans is the most prevalent human fungal pathogen, that is component of the commensal microbial flora of the mouth. Under certain conditions, *C. albicans* can cause severe diseases, septicaemia, and death. The mass of infections made by this pathogen are connected with biofilm growth. This survey highlights the pathogenicity mechanisms of *C. albicans* and how this may lead to the induction of a protective immune response. The survey is based on the most recent and important literature available from the Medline database.

Key words: Candida albicans, biofilm, immunity.

INTRODUCTION

Fungi can be found everywhere, and in our life period we are displayed to many of possibly infective contagious species, such as Candida (1). *Candida albicans* and distinct Candida species are present in the mouth of up to 75% of the populace without any symptom of disease (2, 3). This fungus is an opportunistic and decisive human pathogen residing as a commensal in the genitourinary tract, the gastrointestinal tract, on the skin as well (4-7). The main reserve for *C. albicans* in humans is considered to be the gastrointestinal tract. Systemic infections mostly originate from this source, when *C. albicans* cells intrude through the epithelial hurdle of the gut into the bloodstream, disseminate throughout the body (8).

This colonisation in healthy individuals ordinarily remains harmless, and the capability to cope with the regular exposition to fungal pathogens refers that our immune system has operative mechanisms for impeding infections with these structures (1, 4, 6, 9-11). Most people are usually believed to have a single strain of Candida in diverse places of the body for an extended period. Some individuals, however, have above than one strain or species at the equal time, and hospitalised patients commonly prove this (12).

Mildly immunocompromised individuals, however, those with genetic predispositions, gained immunodeficiencies, like therapies which include an altered microbial flora, damaged physical barriers, also patients treated with immunosuppressive materials, due to organ transplantation, cancer, lasting catheterization, usage of steroids, broad spectrum antibiotics, or diseases like AIDS, can constantly suffer from regular infections with Candida species, which are entitled "oral candidiasis" (2, 4, 13-41). Statistics state that about 10% of oldish patients, 5% of newborns and nearly 90% of HIV-contaminated individuals unwrap oral pseudomembranous candidiasis (29, 43, 49). Also, Peterson *et al.* noticed that the occurrence of oral yeasts in the saliva of hospitalized inmates was 55%. In patients with progressive cancer, this quantity hesitated between 47% and 87% of the populace (26, 44). In diabetic patients, the existence of Candida species in the oral mucous membrane gained up to 80% (44).

C. albicans contagions can be distributed into four distinct stages: colonisation, superficial infections, deep-settled infections, systemic infections. Colonised *C. albicans* live as a commensal with the natural microbial flora on mucous mambrane surfaces causing no damage to its host. *C. albicans* asymptomatically colonise the mass of the human populace, superficial contagions, however, can occur when the microbiotic equilibrium is destroyed, and the host immune system is jeopardized (21). Systemic infections can be caused by this pathogenic yeast crossing cell or tissue hurdles, invading into deeper tissues as well (4, 45). Furthermore, disseminated candidiasis is mostly caused by a yeast form (29). Unfortunately, this infectious yeast can still cause unacceptably high mortality and morbidity – even 40%–50% and ranks 4th between all pathogens

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distinguished from the nosocomial infections and the bloodstream (4, 27, 46-51).

In this paper we are going to review the main features of *C. albicans* pathogenicity, with special regard to host defence and the management of oral candidiasis. This article is based on the most recent and important literature available from the Medline database.

CANDIDA ALBICANS PATHOGENICITY MECHANISMS

Different morphological forms

Morphological forms of *C. albicans* can grow differently, involving yeast cells (round to ovoid in shape and detached from each other), pseudohyphal cells (elongated ellipsoid cells remaining fixed at a compacted separation site), parallel-sided true hyphae, which are important during infection (7, 21, 22, 25, 37, 40, 52-67). It is known that this fungus is bigger than bacteria, smaller than epithelial cells, 5-50 μm (length) and 2-5 μm (diameter) in hyphae shape and 5-25 μm (diameter) in yeast shape (68).

Virulence needs yeast and hypha to be able changeover (6, 53, 55, 60, 61, 65, 67). What is important for the formation of biofilms is the invasive hyphal form, that empowers the organism to obviate phagocytic cells and to run away from blood vessels as well. However, yeast cells are believed to be significant for spreading in the holder via the bloodstream (6, 21, 25, 67, 69, 70). *C. albicans* hyphae contain unique glucan constructions that are not established in yeast (61). To add, Candida hyphae show boosted adherence features and greater immunity to phagocytosis collated with yeast (71, 72). It was also demonstrated in vitro that yeast can make N-nitrosobenzylmethylamine and the carcinogenic nitrosamine from appropriate predecessor molecules (73).

Distinct virulence functions, such as adhesion, invasion, oxidative stress response, proteolysis and ferritin binding are moderated by the yeast-to-hypha conversion and the expression of hyphae connected genes (21, 53, 70). Moreover, this transition is controlled by a regulatory network, incorporating the transcription factors Efg1, Cph1 and Tup1, activated by the existence of amino sugar N-acetylglucosamine, serum, peculiar amino acids and the interplay with innate immune cells (70). *C. albicans* hyphae contaminating humans and animals, however dominate at the primal site of infiltration of epithelial cell tissues and layers, yeast cells however are established likewise on the epithelial cell superficies or wrenching from penetrative hyphae which infiltrate tissues (66).

Mating, biofilm molding, adaptability to host surroundings can also essentially use *C. albicans* which form chlamydospores, spore-like constructions, made under individual conditions, and sustain phenotypic switching among opaque and white morphologies (21, 40). These two cell sorts deviate in virulence properties, shape, gene expression section, and colony look. Opaque cells are the sexually qualified shape of *C. albicans*; they can settle skin, run away macrophage revealing, and have much higher mating productivity than white cells, which are more liable to induce bloodstream infections. Despite white-opaque transition, that occurs ingenuously every 104 generations, the whole process can be caused by peculiar environmental states, like usage of GlcNAc as a carbon origin, large CO_2 concentration, genotoxic and oxidative stress. Temperature variations from 25◦C to 37◦C can be prompted by the reverse conversion, from opaque to white cells (40).

Adherence

Candida cells connect to some host cell sorts, involving endothelial epithelial, phagocytic cells (71). *C. albicans* adhesion to epithelial cells is an important event in both the pathogenic and commensal way of life (3, 71, 74-78). It is vital for colonisation and later induction of mucosal disease, which can lead to disseminated candidiasis (71, 74).

Non-specific factors, which include hydrophobic interplay, Brownian movement forces, appealing Lifshitzvan der Waals forces, the repulsive actions of the electrical double layer of cells can mediate the primal connection of Candida cells and be stimulated by fungal cell superficies or indirectly, via different microorganisms (12, 24, 75, 79, 80). This fungus represents multiple various surface constructions that moderate adhesion to epithelial cells by distinct mechanisms and play a significant role in the infective process (67, 74, 81, 82).

C. albicans cell wall is established to be composed of 80-90% of carbohydrates, like β-1,6-glucan, β-1,3-glucan, a small part of chitin, various wall proteins. The latter are arranged into two stratums: an outer layer of β-1,6-glucan, cell wall proteins attached to the skeletal stratum via a glycosylphosphatidylinositol (GPI) remnant and an inner skeletal stratum of chitin, β1, 3-linked glucan (66, 67, 81, 83-87). *C. albicans* yeast cells consist of chitin which usually forms ~2% of the cell wall dry weight, whilst β-1,6 glucan and β-1,3 glucan report for 20% and 40%, accordingly. Hyphal cells possess about 3-5 times more chitin than yeast cells and the bud scars have the greatest amount of chitin

in yeast cells (66). β-glucans are exposed in some places of the surface, especially in regions where yeast cells proliferate during mother-daughter cell segregation (86). Carbohydrates have the responsibility for wall's mechanical potency, while the proteins incorporate cell wall reshaping enzymes and proteins which are vital for adhesion and biofilm formation (77, 84, 88).

Some adhesins are extruded differently, some only by hyphae, others – by both yeast-phase and hyphae entities (11, 74, 80). Diverse genes such as HWP1, ALS, EAP1 that code a well-described type of cell wall proteins that settle a glycosylphosphatidylinositol anchorage motif in their C-terminal areas and a signal peptide at their N-termini moderate *C. albicans* adherence and growing commanding to biofilm molding (11, 89). The adhesion of *C. albicans* to diverse surfaces are moderated by these terminal domains (26). Also Als1, Als3, Als5 moderate adhesion to a diversity of host components (11, 90). Many proteins found on the superficies of *C. albicans* have no classical secretion signal peptides, they are duplex function proteins, that operate as enzymes in the cytoplasm and as invasins, adhesins, immunogens when externalized on the cell superficies (67).

The inhibition of single cell wall part into the fungi cell wall, which is a dynamic construction, can direct to a compensatory increment in other, like remodelling injured cell walls by boosting chitin amount to support cell wall entity (91). Being physically strong the cell wall must be also resilient enough to allow cell enlargement, cell distribution, morphogenesis (84, 87). Furthermore, the wall must likewise be pervious to let exit of excluded proteins and the importation of solutes, however impervious sufficiently to preserve the inner skeletal stratum from environmental hydrolases (84).

There is no doubt that hyphal formation and adhesion are essentially connected: touch of *C. albicans* to host cells or abiotic sheets promotes the hyphal molding and the synchronous induction of hyphal-related adhesins. The whole process improves the adhesiveness of the fungus to superficies (21).

It is important to mention, that *C. albicans* hyphae produce hydrolases within adherence, thus facilitating active penetration. The efficacy of extracellular nutrient purchase is enhanced by secreted hydrolases. *C. albicans* express three distinct classes of secreted hydrolases: lipases, proteases, phospholipases (2).

Invasion

C. albicans have two diverse mechanisms that can spread and cause damage to epithelial cells (8, 59, 74, 79, 92). One mechanism is the endocytosis, which is a microorganism-induced, clathrin-moderated, epithelial-driven, actin-reliant, passive, a zipper-like process (9, 52, 74, 93). Endocytosis is neccesary for primary cell entrance, enabling the fungus to induce injury through the process of active penetration (94). The host cell is forced to make pseudopod-like constructions that encircle the fungus and involve it into the cell in a operation that partially includes the E-cadherin path through induced endocytosis (8, 52, 74, 93). It should be noted that *C. albicans* exploits more than one invasin to generate endocytosis (79). During the pathologic process of induced endocytosis, invasins, as Ssa1 and Als3, uttered on the superficies of a *C. albicans* hypha, moderate the bonding to host ligands (host epithelial superficies proteins), such as N-cadherin onto endothelial cells, E-cadherin onto epithelial cells, EGF receptor (EGFR). The above mentioned invasins also promotes concentration of dynamin, clathrin, cortactin in host cells to the places where hypha goes in the epithelial cells, consistently stimulating the actin cytoskeleton reconstruction (52, 74, 79, 93). Viable fungi is not required for this process and it seems to be critical at the precocious stadiums of invasion (Wächtler *et al.*, 2011; 2012; Zhu *et al.*, 2012) (59). Moreover, actin cytoskeletons give the strength needed for fungal internalisation (52, 79). It is important to mention, that fatal candidemia can be caused by the reformation of actin cytoskeleton, involving filament collection and polymerization (52).

Another invasion mechanism, which demands fungal vitality, is the active penetration. During this invasion *C. albicans* hyphae gradually lengthen and physically press their path into or between epithelial cells (74, 93). This process does not need endocytosis (74). It has been established that induced endocytosis collaborates to the early stadiums (regularly per 4 hrs) of invasion, whilst active penetration reflects the dominant path of epithelial cell entrance (Villar and Zhao 2010; Wachtler *et al.* 2012) (52, 79). Actively penetrating, the organism manage likewise intrude into an epithelial cell not provoking the molding of epithelial cell pseudopods or go over via the intercellular juncture among epithelial cells (74). *C. albicans* can exclude for the invasion three classes of hydrolases: phospholipases class B, aspartic proteases, lipases (8, 52, 62, 71, 74). The epithelial cell juncture proteins degrades principally via proteolysis by secreted aspartyl proteinases, which exhibit proteolytic effect exclusively under acid terms (pH<4.0) (8, 52, 71, 74). Moreover, the phospholipase action is boosted while hyphae are in direct touch with host tissue (71). Pulling down

barriers physical forces, adhesion, excretion of fungal hydrolases lighten the fungal-driven active penetration into host cells (2).

During oropharyngeal candidiasis and due to fungal intrusion, the demolition and deprivation of the superficial oral epithelium can be found (74). Moreover, epithelial cells respond to the hyphal superficies, and to the caused injury, by excluding pro-inflammatory cytokines, which demarcate the conversion to a pathogenic style of living (59, 95-97). These accidents infuse neutrophils and macrophages, which can battle and destroy intruding *C. albicans* (49, 59). Accordingly, intense neutrophil infiltration is representative for *C. albicans* contagions (59).

C. albicans probably intrudes epithelial cells from diverse anatomic places via distinct mechanisms (74). For example, the fungus intrudes oral epithelial cell margins by both active penetration and induced endocytosis, while a gastrointestinal epithelial cell margin is only intruded by active penetration (52, 74). The organism is passive in this process because destroyed hyphae are endocytosed correspondingly to alive hyphae (74). There is no evidence showing that yeast cells actively penetrate into epithelial cells or manifest to cause their proper uptake into epithelial cells, representing that hypha-connected factors provoke active penetration and induced endocytosis (52).

By the way, host cell intrusion can also be made easier by linking extracellular matrix or serum proteins like bridging molecules. *C. albicans* can connect human serum components like Factor H equally the extracellular matrix proteins fibronectin, entactin, laminin, collagen, tenascin, vitronectin (79).

Moreover, vascular dissemination follows the epithelial intrusion. The process includes hyphal permeation of blood vessels and disseminating of the blood with yeast pieces. Blood-borne *C. albicans* connect to the vascular endothelium and make colonies traced by hyphal permeation into the tissues (61).

Once *C. albicans* hyphae have purchased accession to sub-mucosal stratums or epithelial cells, the induction of tissue injury is the terminal peculiarity of the intrusion process. Two distinct mechanisms may cause the process: apoptosis and necrosis. Necrosis is described by enhanced plasma membrane penetrability, mitochondrial swell, and is triggered by agents exterior to cells where *C. albicans* hyphal agents cause this directly. The apoptosis includes a clear biochemical collapse of the cell into membrane-related apoptotic bodies and induces cellular dying. Whereas apoptosis can give beneficial effects to the owner, necrosis is actually always harmful (94). It is established, that terminal epithelial cell dying is usually due to necrosis at tardy time periods of infection (92).

Thermal adaptation

The main fungal pathogen of humans, *C. albicans*, has preserved a heat shock response, although warm-blooded animals are connected with this yeast. The evolutionarily preserved heat shock transcription factor Hsf1 moderate heat shock proteins gene stimulation in *C. albicans*. This heat shock adjustment makes *C. albicans* cells combine the levels of significant chaperones to their medium growing temperature (98).

The heat shock reply in *C. albicans* is essential for many explications. Firstly, mutations that interlock Hsf1 stimulation in *C. albicans* critically lower the virulence of this fungus and preclude thermal adaptability. Secondly, temperature up-shifts encourage morphological conversions from the yeast to hyphal growing shapes. Thirdly, immunogenic *C. albicans* heat shock proteins impinge host-pathogen reactions during contagion. Fourthly, antifungal medicament resistance is removed by higher temperatures in fevered inmates and by Hsp90 inhibitors. Eventually, autoantibodies against Hsp90 are immunodefensive against *C. albicans* contagions (98).

To sum up, the heat shock replay of fungal pathogens is essential for virulence, and present aims for perspective therapeutical strategics (98).

SPECIFICITY OF BIOFILM FORMATION

Various niches and adequate provision of nutritives in the human mouth create the surroundings conductive for the unlimited molding of ordinary microbial biofilms (99).

It has been evaluated that fully 65% of all human contagions are connected to microbial biofilms (100). Biofilms are mixed three-spatial structure communes of microorganisms that are fixed to biotic or abiotic surfaces and are placed in a self-made extracellular matrix (12, 40, 73, 101-106). In vitro, the basal biofilm stratum is made of yeast cells from which filamentous cells rise. In vivo, biofilm structure is more irregular, with inserted filamentous cells, yeast and an extracellular matrix with host immune cells (43). The biofilm matrix consists of proteins, carbohydrates, hexosamines and phosphorus (12, 88).

Being in the mouth sticked, biofilm cells are preserved from the ordinary mechanical flushing

activity of saliva and gingival crevicular liquid. The biofilm itself is a protective hurdle against permeation of provided antimicrobials and host immune agents (12, 48, 63, 71, 88, 100, 102, 103, 105, 107-110). Biofilm antimicrobial immunity has some mechanisms including adaptive stress replies, long permeation of the antimicrobial factor into the biofilm, the existence of a little populace of especially resistant cells, variations in the chemical microenvironment inside the biofilm (62, 108). It was reported by numerous researchers, that Candida biofilms show immunity to antifungals (71).

The molding of a biofilm is influenced by quite many factors consisting of temperature, oxygen provision, pH, the enviroment structure, osmolarity, accessibility of nutritives, the microorganisms, the existence of conditioning film or saliva, the fungal strain and typies, the existence of host immune agents and antimicrobial elements, the extracellular polymeric material (12, 88, 102, 108). It is the mouth, where, the coherence between oral bacteria and *C. albicans* is decisive for *C. albicans* settlement and vitality (99, 111). The streptococci can give adherence places and exclude lactate, that operates as a carbon origin for yeast growing, which, by turns, diminishes oxygen tenseness to standarts preferred by streptococci and stimulates growing agents for the bacteria (99).

Dentures influence the character of the oral cavity microenvironment by reducing the saliva flux ration, salivary pH and hampering the mechanical purification of the soft tissue surfaces with the tongue (104, 106, 112, 113). Therefore, dentures generated injury may lessen tissue immunity against contagion because the penetrability of the epithelium to fusible candidal toxins and antigens is enhanced (41, 104, 113, 114). It was established, that the prevalence frequency of oral *C. albicans* in inmates with dentures was higher than in inmates without dentures (41, 112, 114). Improper denture clean can be the reason of the growth on the denture surface of a biofilm holding microorganisms from the concentration of denture plaque and may also induce systemic diseases and allergic reactions (23, 113, 115). These microorganisms have a great part of *C. albicans* (23). Moreover, several studies have announced that in 33– 82% cases oral candidiasis conducts denture stomatitis representing with glossitis and angular stomatitis, moreover swell and flush of the mucosal tissue beneath the denture basis (23, 107). In addition, biofilm growing develops above the denture superficies, causing inflammation, and has a negatory effect on a patient's capability to speak and eat (107, 115).

In vitro, biofilm molding can be distributed into some growing stages: early (0 to 11 h), intermediate (12 to 30 h) and mature (12to 30 h) (101, 105, 108).

Through the early phase, blastospores (yeast cells) stick to a suitable superficies and endure morphogenesis (105, 108). Cell-superficies parts and other superficies become adherent. This process is moderated by electrostatic and non-specific hydrophobic forces (108). It was determined that the adherence stage is the key step influencing the entire development of biofilm molding (116). Moreover, adherence to abiotic surfaces, first of all, is influence by hydrophobic interactions. Microbial adhesion to biological surfaces however is managed by adhesins, like glycoproteins depending to the agglutinin-like sequence family (108). Also, mutants of *C. albicans* create less adhesive biofilms than wild-type biofilms (105).

The intermediate phase includes extracellular matrix manufacture from cell wall proteins, polysaccharides and persisted hyphal growing (105). The joined cells exhibit a modified phenotype (like enhanced immunity, diminished activity) and initiate to proliferate and connect into communes. This untimely biofilm is fixed to the superficies by more irreversible powers like Van der Waals forces (108).

Mature *C. albicans* biofilms have a yeast basis, with hyphal units enclosed in an extracellular matrix expanding far from the superficies, and represents a hypoxic medium (105). The mixed set-up of aged biofilms lets an inflow of nutritives and water, and outflow of waste commodities (102, 108). The bulk of mature biofilms has been evaluated to fluctuate from 25 up to more than 250 μm (108). In subsequent stadiums, cells can separate from the superficies (in assemblies or sole cells), turn planktonic and accommodate novel surfaces (dispersion of the biofilm) (21, 108). Furthermore, yeast cells dispeled from biofilms exhibit enhanced adherension in comparison with their planktonic coupies (21).

IMMUNITY MECHANISMS AGAINST FUNGUS *CANDIDA ALBICANS*

The human body does not have cell wall proteins and carbohydrates that are represent in the cell wall of *C. albicans* (66). These cell wall elements symbolise a perfect immunological aim to separate non-self from self (56, 66). Upon connection by a contagious pathogen the human body employs a powerfull immune protection which strives attack, exterminates an invader, suspends distribution into deeper tissues, keeps homoeostasis (4, 56, 82, 85). This reply concerning the time of act is separated

into adaptive and innate immunity (4, 46, 82, 117). In details, the innate immunity, which constitutes of immune cells, antimicrobial peptides, the complement system, is persuaded by the adaptive immune system, the latter demands some days to permit production, election, and ripening of antigen-peculiar B and T lymphocytes (4, 46, 82, 117-119). Also, the inborn immune system can strike and simply destroy a contagious pathogen (4, 53, 120). It should be noted, that in candidiasis the distinct mechanisms of the immune system work synergistically - they collaborate with and inflect each other in order to fight fungal contagion (121).

The complement system is stimulated and can strike straightway any intruding contagious provocative, thus playing an important role in anti-C. albicans host protection (4, 53, 119, 120). Candida can activate the complement system within three ways: the lectin pathway (LP), the alternative pathway (AP), the classical pathway (CP) (83). Once stimulated – the cascade is increased and makes some activation commodities like C3a, C3b/iC3b, C4a, C5a, C5b. These commodities start peculiar immune effector responses and functions. The stimulated complement cascade marks and opsonizes the superficies of an alien pathogen with iC3b or C3b, alleviating adherence, intake, and phagocytosis (4, 120, 122). Once an alien is phagocytosed and confronts the unfriendly medium of the phagosome, this pathogen is usually destroyed (4). The inflammatory reply is acquired through the minor complement activation peptides, C5a and C3a, that attach to peculiar macrophages' and neutrophils' receptors (4, 123, 124). The C4a and C3a peptides demonstrate antifungal and antimicrobial action (4).

Besides, *C. albicans* fungus has designed effectual methods to operate human complement activation: firstly, via connecting of complement moderators on the cell wall protein to suppress complement activation; secondly, directly destroying complement parts by excluded aspartic proteases; thirdly, stopping the stimulation of complement by pH-regulated antigen 1 or surface mannan (82, 120).

Microbial pathogens are identified by lymphoid/myeloid cells (monocytes, neutrophils, macrophages, dendritic cells) pattern-recognition receptors (PRRs), involving the Nod-like (NLR), Toll-like (TLR), RIG-I like (RLR), CLR receptor families. All of them identify molecular constructions widely distributed by pathogens, and prominent as pathogen-interacted molecular patterns (PAMPs) (1, 4, 15, 31, 46, 49, 53, 56, 57, 73, 81, 84, 86, 121, 125-134). Diverse PRRs may identify the same PAMP (126, 135). Due to fungal contagions, resistance to pathogens is first moderated by participants of the C-type lectin receptor family, involving Mincle, Dectin-1, Dectin-2, that connect to almost all fungal types which provoke illness in humans (1, 35, 69, 135-137). The main carbohydrate constructions that are discovered in fungal cell borders are identified by the above – mentioned receptors. However, there yet exists somewhat specificity in identification by these receptors. It is due to the disclosure of diverse carbohydrate constructions by the distinct fungal species or morphological shapes of the same organism. For instance, Dectin-1 can exclusively identify the yeast shape of Candida (1). Besides, PRR stimulation might paradoxically induce a few contagions and provoke tissue injury (130).

Furthermore, Candida species have multiplex PAMPs, as chitin, mannan, proteins, β-glucan, nucleic acids, that may promote or adjust the active host reply during contagion (31, 126, 133, 136). Toll-like receptors identify diverse pathogen-connected molecular patterns (PAMPs) like proteoglycans, lipopolysaccharides, nucleic acids (136). Not long ago, another *C. albicans* cell border glycosylated parts, like -mannans (dectin-2), high-mannose constructions (DC-SIGN and dectin-2), have been established as being aims of myeloid cell PRRs as well. Moreover, polysaccharide elements of the *C. albicans* cell border are powerful stimulators of lymphoid/myeloid cells (81). Connecting of fungal PAMPs to PRRs may be the sign of phagocytosis also promoting the emission of peculiar cytokines and extracellular reactive oxygen species, lastly stimulating inherent effector cells (1, 3, 4, 21, 56, 69, 75, 138). Immune cells from the blood and extra fusible immune elements are concentrated by the anaphylatoxins in conjunction with relieved cytokines to the place of infection and boost ignition (4). Cytokine stimulation is correlated with hypha molding because those Candida types or *C. albicans* strains being incapable to generate or sustain hyphae do not stimulate immune replies (21, 92). This immune identification and reply happens per seconds or minutes beyond an infection, usually managing and removing an infectious pathogen (4).

Basing on PAMP identification, PRRs produce a lot of many signalling schemes that perform the initial margin of host defense replies (75, 126, 136). PRR signal at the same time stimulates developing of dendritic cells (DCs), which are accountable for warning admission of the second margin of host protection – adaptive immunity (73, 126). DCs communicate with fungus which directs to phagocytosis of either hyphal and yeast shapes of *C. albicans* and DC stimulation (73, 139). After phagocytosis,

DCs move to the lymph nodes wherein the Candida antigen is altered and submitted on the superficies of the DC to CD4T-cells. Because of the connection between T-cells and DCs, the T-cells begin to individuate into ripe, powerful T-cells (73). The class of T-cell developed is believed to be in accordance with the diversion of the DC, and illustrations of powerful T-cells involve regulatory T-cells, T-helper 17 (Th17), T-helper 2 (Th2), T-helper 1 (Th1) as well (73, 140, 141). According to the evidence, a Th17 reply is ascendant controlling systematic fungal contagions and preserving the mucosa, over the stimulation of phagocytes by GM-CSF and IFN-γ (1, 73, 142). Th17 immunity has diverse defects, like mutations in IL17RA, IL-17, STAT3, STAT1, which have been connected to receptivity to confirmed mucocutaneous candidiasis (1, 134, 143, 144). T-cells in invasive candidiasis behave differently. Th1-influenced immune replies correlate with opposition and protective immunity, whilst Th2 – influenced replies direct to disease become worse (134, 142). What concerns to PRRs, another cell-superficies proteins, like Epidermal Growth Factor Receptor (EGFR) and E-cadherin, can identify Candida as well. Not surprising, they are involved in Candida endocytosis and adhesion (75).

Once the immune system response is stimulated, neutrophils, macrophages, and another phagocytic cells function against fungal pathogens by generating great levels of nitric oxide (NO), reactive oxygen species (ROS), which follows in nitrosative and oxidative stress (40, 82, 86, 92, 137, 145). It should be stressed that the stimulation of anti-oxidant replies is a main approach consequent to internalisation by phagocytes (140). After phagocytosis, *C. albicans* can avoid oxidative-kill by neutrophils and macrophages changing from budding to filamentous cells, which are able to perforate the phagosomal casing (2, 20). Thus, the pathogen is enabled to run away and destroy the phagocyte (2, 20, 21, 64, 146). *C. albicans* can detoxicate the superoxide anion, which is made by the enzyme compound NADPH oxidase, available in all sorts of phagocytes (21, 64). For this reason, *C. albicans* contains a family of superoxide dismutases that convert superoxide into hydrogen peroxide. Also, *C. albicans* holds proteins, such as Thioredoxin, which can detect the existence of oxidants (64).

To follow, neutrophils are one of the precocious inflammatory cells, that move to the place of microbial contagion and grant the initial margin of protection of the inherent immune system by phagocytosing, destroyng, digesting fungi. They also represents phagocytic receptors on their superficies, involving dectin-1, TLR4, TLR2. The latters moderate the identification of fungal cells, whilst next receptors, like Fcγ-receptors (FcγRs) and complement receptor 3 (CR3), lighten intake into the fungus (50, 64, 75, 93, 121, 141). It is essential for opsonization and chemotaxis of *C. albicans* to have complement stimulation (121). A strongly opsonized element is resorted into the phagocytic vacuole during 20 s, and is practiclly directly destroyed (93). The acid hydrolases come in the vacuole following approximately 5 min while the pH has begun to drop to levels suitable for the excellent action of these enzymes (40, 64, 83, 93). The neutrophils can generate large enough contents of oxidants in a procedure prominent how the respiratory burst (20, 40, 64, 83). The procedure incorporates the collection of the enzyme compound NADPH oxidase, on the phagosomal casings of the phagocyte and plasma. This enzyme compound makes the extremely reactive superoxide anion, which is hereafter burned to create hydrogen peroxide. Another responsive species, like peroxynitrite, hypochlorous acid are generated in the neutrophil (64). Investigators have reported that the NADPH oxidase raises the pH to approximately 7.8–8.0 in the initial 3 min later phagocytosis, then it step by step drops to approximately 7.0 after 10–15 min. These enzymes demolish regular tissues, and organs can endure recovery in one or two weeks. Apoptosis eliminate several of the neutrophils, however majority mortify releaving their granules (93). So, degranulation incoporates the excretion of enzymes and peptides collected in the neutrophil granules. Lactoferrin, myeloperoxidase, azurocidin as granule elements are realised to possess candidacidal characteristitics (64). Alkalinity and hypertonicity connected in inflammatory hearth lessens the poisonousness of granules relieved into the tissues (93). Further, dendritic cells phagocytosing either hyphae and yeast, destroy, however, yeast cells more easily (21). Contrariwise, neutrophils are better infused to hyphae but destroy hyphae and yeast equally (21, 147). In addition, neutrophils hold infection made by neutrophil extracellular traps (NETs) (64). Thus, scaffolding net-like constructions are included (64, 94).

It is important to mention, that phagocytic cells, like neutrophils and macrophages, are fundamental parts of defensive antifungal immunity. The deprivation of these cells or deficiencies in their antimicrobial creator techniques outcomes in sensibility (1, 83).

In addition, it should be taken into account that saliva is a body liquid, excluded by three couples of major salivary glands (submandibular, parotid,

sublingual) and by mass of minor salivary glands, which grant the funtamental initial margin of protection against *C. albicans* (51, 148). Most salivary protection proteins may improve concentrations to "effective" levels in particular places in the mouth, despite the fact, that mass of them are concentrated less-than-efficiently (148). Salivary antimicrobial proteins (AMPs), like histatins (Hsts) and defensins, have the straight candidacidal action employing to restrict *C. albicans* overgrowth and connection to the oral epithelium, even if they are concentrated lower than effective (51, 107, 148). More, saliva proteins, like mucins, make it also easier to connect assimilating to Candida or covering the oral appliance (63, 107, 149). So, salivary antibodies proceed in the initial margin of protection. They are excluded into the saliva and the mouth (148). There are two pivotal antibody typies in human saliva - secretory IgG and IgA (107, 148). The salivary immunoglobulins can allay fungi within coneccting and agglutination of elements (148). In this way connecting and agglutination may preclude mucosal adherence of pathogens and their toxins, also prevent intrusion of the underlying tissues, and can direct to purifying towards the acidic assimilation in the stomach (51, 148). Antigen connecting and agglutination may guide to phagocytosis, degranulation, cytokine manufacture in the existence of immune-qualified cells (148).

IMPORTANT HOST CONDITIONS FOR *CANDIDA ALBICANS*

Medium variations have a close relation with cell wall fix up, involving pH, nutrient availability, temperature (Sosinska *et al.*, 2008; Heilmann *et al.*, 2013; Ene *et al.*, 2015) (87, 150). Ene *et al.* (2015) study displayed significant cell wall conversion following merely thirty seconds in reply to hyperosmotic stress. The variations were seen in cell border extent, involving an increment of the internal chitin and β-glucan stratums, as well as retraction of the mannoprotein stratum. These changes demand enzymatic action of synthesis, deterioration and transitory molecules (87). The molding of hyphae is due to existence of physiological temperature, serum or N-acetylglucosamine and CO_2 (2).

In the person body, pH can differ extensively, from pH ~2 to lightly acidic and actually alkaline (2, 65). *C. albicans* flourish in maximum of these places and absolutely brook a broad diapason of medium pH states, from pH of 2 to pH of 10 (65). The host medium pH has impacts on *C. albicans* anatomy and their capacity to reply to stress (65, 67, 150). Neuter to alkalic pH can induce serious stress to *C. albicans*, so pH-susceptible proteins do not operate correctly (2). Fungi cell border proteins possess a pH optimum for action (2, 55, 65, 67). The budding morphological type dominates at low pH (< 6) or low temperatures, whilst the hyphal morphological type dominates at high pH (> 7) and high temperatures (2, 55, 65).

A great quantity of carbohydrate in the mouth has a lot of negative effects on *C. albicans* acid manufacture, and pH, thus stimulation of extracellular phospholipases and acid proteinases (121). Consequently, *C. albicans* can burn a wide diapason of sugars and can exploit entire amino acids how only nitrogen origins (59).

As Candida spp. have adjusted to endure in two situations, they can vegetate both anaerobically or aerobically. Oxygen causes an oxidative stress reply as it can make reactive commodities following a contagion. *C. albicans* can be cured with weak strength of superoxide making materials, like hydrogen peroxide. This process causes a redox potential stimulating antioxidant ferments, which preserve cells from the mortal impacts of a later provocation with greater strength of these oxidants (44).

A fortunate contagion can also be preconditioned by micronutrients, particularly metals, such as zinc and iron, that are subjugate to a procedure – 'nutritional immunity' (Hood and Skaar, 2012) (59). Inwardly oral epithelial cells, 30% of whole iron is accumulated through ferritin, and is not generally available to infective microbes (11, 21, 40). Also, iron grades in person serum are kept as below as 10-24 M, strictly limiting its accesibility to pathogens (59). It should be taken into account that iron is a vital nutritive for majority microorganisms, and its assimilation may perform a particular part in stimulating contagions (11, 40, 44). *C. albicans* get iron by diverse schemes: a siderophore assimilation system, a reductive system, a heme-iron assimilation system (2, 11, 21, 40, 151). The reductive system with its broad gene families of oxidases, reductases, iron permeases moderates iron purchase from host transferrin, ferritin, or the medium (2, 11, 59). With the help of these systems *C. albicans* can powerfully exploit almost entire inartificial iron origins either of ambient microbes within commensal growing and the host within contagion (59). Moreover, *C. albicans* does not generate its proper siderophores. It exploits a consumption system to thieve iron from siderophores manufactured by another microorganisms, such as xeno-siderophores (2, 59). This fungus can externalize haemolysins that destroy globules and then connect and use haemoglobin (12, 59). Hy-

phal intrusion and the progress of spread candidiasis becomes easier because of excretion of haemolysin and iron purchase (21, 44). Almeida *et al.* revealed that *C. albicans* hyphae, not yeast-stage cells, can connect to cleaned ferritin as well as ferritin held inside epithelial cells (11). The rise in blood glucose strength may enhance hemolysin action between *C. albicans* isolates in diabetic inmates (44). The host likewise energetically restricts zinc through contagions, though it can be exploited by *C. albicans* through a newly revealed 'zincophore' system utilizing the zinc-binding protein Pra1 (2, 59). Manganese and copper likewise stimulate fungal growing (2).

Enviromental elements like smoking may encourage Candida contagions as well (89, 152). There are a few theories why tobacco usage enlarges Candida expansion. Tobacco consumption reduces stature of salivary immunoglobulin A, enlarges bulk of epithelial keratinized stratum, inhibits activity of polymorphonuclear leukocytes. In this way the reproduction of Candida types becomes easier (153). It is supposed that cigarette bloat improves adherence, growing and biofilm molding of *C. albicans* (89, 153). Precisely, it has been demonstrated that cigarette bloat interposes with *C. albicans* and S. mutants adherence, following in biofilm molding, which suggests that cigarette consumers are more sensitive to life-warning oral contagions involving candidiasis (89, 154). Secondly, it is also hypothesed that tobacco substance provokes the media which lightens the generation of Candida types. To continue, several another theories suggest that nicotine triggers anatomical and functional changes in keratinocytes. Another ingredients of tobacco direct to a reduction in epithelial elements, antifungal action (153).

It can be concluded, that the great metabolic versatility of *C. albicans* may be component of its contagion strategy, which empower this fungus to remain and rise in the majority transformating and diverse host corners it faces (8, 59).

ORAL EPITHELIUM IMPORTANCE

The oral epithelial role is especially important in the mouth, because the mucosa performs a crucial preservative effect standing as an alloy among exterior and interior medium. A physicochemical hurdle is determined, where some immunological factors interflow to preserve the intrusion of pathogenic creatures (21, 50, 82, 94, 121, 138, 155). Oral epithelial cells can discover diverse Candida types and *C. albicans* in its hyphal or yeast shape. Primary discovery does not depend on fungal vitality. It proposes that stimulation of epithelial warning is the outcome of peculiar identification of the fungus and not surely a property of intrusion or injury induction (92). Furthermore, host reply greatly depends on fungal loads, reflecting the "danger reply" system. This system allows mucosal tissues to stay quiet if low fungal loads are present, however it replies actively and specially to injury-promoting hyphae while loads enlarge (21, 56, 92, 128, 156). The system was underlined by studies demonstrating the MAPK and NF-κB moderated biphasic reply versus *C. albicans* (43, 81, 156). Also, if there are the comparably little amount of yeast cells existing it does not cause epithelial cell injury, and does not provoke a cytokine reply in mucosal macrophages either epithelial cells (66).

Antigen supplying cells, like dendritic and Langerhans cells settle on the mucosal superficies and actually the healthy have a large flow of neutrophil granulocytes via the gingival sulcus in the saliva (148, 157). Firstly *C. albicans* are attached to the oral epithelium (either keratinocytes) in the colonisation development, then it promotes the relaxation of chemokines and cytokines that concentrate and stimulate immune and inflammatory cells, involving antigen presenting cells (APCs), phagocytes, T cells (10, 50, 74, 92, 94, 121, 128, 158). Oral epithelial cells manage stimulate antimicrobial peptides, like cathelicidins, defensins, histatins, which operate *C. albicans* growing and contagion (82, 128).

Also, the oral epithelium is constantly brought back to its previous level. It means that Candida must be existing in the oral cavity in enough amount and with a quite great growing speed permit their prolonged persistency (71).

It has been proposed that manufacture of carcinogenic acetaldehyde by Candida promotes oral carcinogenesis and epithelial dysplasia. When levels reach over 100 μM they are capable to make DNA crosslinks, DNA adducts, chromosomal deviations and alterations in the p53 tumour suppressor gene, sister chromatid variations. Oral leukoplakia, oral lichenoid wound, oral lichen planus are posssibly carcinogenic oral conditions where population by Candida is prevalent. Alcohol intake and cigarette smoking may support adaptation variations which follow in the adjustment of candidal acetaldehyde metabolism (159).

It is important to mention that epithelial replies to Candida not always come out in a potent host immune reply and inflammation. In fact, particular candidal elements, likewise proteins made by epithelial cells, may cause anti-inflammatory actions and later immune toleration. Alas, it still persists

unclear whether the specific properties that establish epithelial cells provoke inflammation or are obedient towards *C. albicans* (75).

FUTURE PERSPECTIVES OF ORAL CANDIDIASIS TREATMENT

Investigators have been encouraged by the immunity of biofilm cells to antifungals or traditional antibiotics to concentrate more on the character of the medical appliance than on trials to eliminate or destroy the micro-organisms (71, 88, 108). Scientists make attempts to change the polymer superficies exploiting active and passive approaches for the impediment of biofilm molding (71, 108). They have designed coats, like denture acrylic or silicone gum, which modify the physicochemical features of the superficies and diminish or actually inhibit biofilm growth (108, 160). Inert coats of different polymers, like hydrophilic polyurethanes, polyethylene oxide brushes, polyethylene glycol can be used to transform polymers. Moreover, diverse antimicrobial compositions, like polyethyleneimines, nitric oxide, antifungals, antibodies, antibiotics, silver ions either nanoparticles, quaternary ammonium compounds can be added into polymers (71, 108, 160). Fine-film polymer formations with involved antifungals (amphotericin either nystatin) have also lately been demonstrated to suppress *C. albicans* biofilm growing on denture substances (71). The altered substance should relieve extremely concentrated antimicrobial in precocious stages, fight precocious population and maintain this relieve through a long-term duration. Silver charged polymers, developed to proceed as a storage of Ag+, which is antibacterial and seldom acquires immunity, can relieve this cation for expanded time of more than ninety days (108). There is a possibility in the perspective to exploit quorum sensing molecules to destroy biofilms as they progress. It has been demonstated that farnesol has harmful impact on Candida biofilms, making aged biofilms instable (71). However, cytotoxicity trials are prerequisite to prove that the transformed materials are not poisonous when imposed in inmates (108).

In the mouth the cleaning impact of the oral musculature and the attenuating impact of saliva can vary in drug strength which changes the primary therapeutic strength, commonly creating it subtherapeutic (24). Cure with antifungal medicaments occasionally causes drug immunity, which can come by chromosome missegregation either reorganization (161). Suppression of the yeast-to-hyphal switch may be a beneficial choice, as well as the regulation of morphogenesis giving a method to effect virulence of *C. albicans* uniquely (21, 162). For instance, affecting pathogen-peculiar elements may be quite useful act with a weak prevalence of microbial immunity and little side effects (21). In this way there is also a possibility to maintain an opportunistic fungus in control specially (21, 162). We should have in mind that *C. albicans* population has advantageous impact by promoting and educating our immune system. In the perspective, we could prevent the morphological conversion from yeast-to-hyphal growing which would be a greatly desirable choice for uniquely monitoring *C. albicans* contagions prophylactically and as a cure. By preventing this conversion we could preclude adherence, intrusion, injury of endothelial and epithelial cells. We may preclude runaway from the bloodstream and macrophages, also diminish the iron purchase capability of the fungus. In addition, the prevention may be exploited to modulate the immune reply, escaping exaggerated inflammation within superficial contagions, either overreacting and potentially lethal sepsis within systemic candidiasis (21).

Immunotherapeutic procedures, mainly – inoculation and adoptive T-cell transfer - could restrict fungal contagions and improve the pathogen-peculiar immune system (96, 142). Seasons can have a meaningful impact on T helper replies inviting to speculate whether inoculation programmes within winter period may be more effective than those within the summer months (96). This unlocks a novel field of clinical investigation, and future researches are required (96, 142).

Possibly, another methods could include the usage of probiotics, which would generate a complemented microbiological stress on Candida inside the mouth and may stimulate local immune action as well (71, 73). Probiotics have been beneficial in the control of Candida biofilms and have been notified for reducing the Candida spread in the mouth (73).

Till now, we have no clinically accessible vaccines opposing fungi either any fungal pathogens, although trial vaccines opposing Candida, another fungal types demand Th17 cells (30, 151).

Besides, if invasive candidemia is revealed early, there can be a favorable prognosis, with death rates rising from 15% (antifungal cure begun straight following positive blood culture), to 40% while cure is postponed by 72 h (Garey *et al.*, 2006). In spite the fact that novel disorder diagnostics are established, Candida contagions are still difficult to identify. The newest diagnosis is grounded on the non-invasive identification of floating polysaccharides from the fungal cell border in blood specimens. The diag-

nostic investigations concentrate on β-glucan and floating mannan levels (84).

CONCLUSIONS

C. albicans complies a scenario of 'overwhelm and frighten' when the situation has transformed from commensal to pathogen. Epithelium is severely intruded while the conditions allow and stimulates stronger immune replies, which it appears to resist in many events. The epithelial cells are fundamental for a proper reply to Candida. They can discriminate among the intruding and the commensal stadium responding diversely to intruding hyphae and yeast. Presence of denture in the mouth can stimulate Candida colonization. Micro- and macronutritives from injured host tissue are collected by a broad diapason of purchase systems. The molding of hyphae may destroy the protecting macrophages. There is a subtile equilibrium among microbial immune avoiding replies and defensive immunity of the human host that can outcome in contagion and disorders. The positive result relies on the capacity of the host to fight microbial contagion either the capacity of a microbial pathogen to oppose, prevent and to avoid host immune protection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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