Colonization is a Crucial Factor in Oral Candidiasis

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Oral candidiasis, or thrush, is usually caused by the fungus Candida albicans. Oral thrush affects a significant proportion of the population, and specifically afflicts the very young, the elderly, and the immunocompromised. Approximately 50 percent of people with full upper dentures will suffer from Candida-associated denture stomatitis (chronic erythematous candidiasis), and oropharyngeal candidiasis is highly prevalent in AIDS patients. An even higher proportion of the total population (up to 60 percent) carry C. albicans in their mouths without clinical symptoms, but usually the yeast are present in low numbers compared to oral bacteria. These observations raise several intriguing questions. Why do some people have the yeast and not get candidiasis? Why do some people appear never to have the yeast in their mouths? And if yeast are normally present in low numbers, could they be prevented from getting a foothold in people’s mouths, thus preventing subsequent or recurrent candidiasis?

There are no simple answers to these questions, but the ability of yeast to stick and grow in people’s mouths (colonization) and our proficiency at stopping this process depend on the yeast’s adherence capabilities and our effectiveness at removing them. The mouth is a dynamic system of interrelated micro-environments that involves micro-organism-, nutrient-, and saliva-flows. Oral colonization with yeast entails acquisition from the environment, attachment to surfaces, and growth/replication. While the micro-organisms are trying to stick around and grow, host defense systems are trying to remove them. The balance among acquisition, growth, and removal determines whether someone is colonized and whether this will lead to candidiasis. Microbial adherence mechanisms play significant roles in determining where this balance lies.1

Acquisition of Yeast from the Environment

C. albicans has been isolated from primates, domesticated and other mammals, marsupials, and birds. It survives better on moist surfaces than dry inanimate objects, but if the degree of contamination is high enough, viable C. albicans cells will remain on dry surfaces for at least twenty-four hours. Candida often colonizes the human epidermis, especially moist webs of skin between fingers or toes, but the gastrointestinal tract and vagina are considered to be the major reservoirs.

It is evident that the most common means of transfer in a clinical setting is contact with carriers, often the hands of health professionals, although various Candida species can be cultured from inanimate objects including food. Indeed, Candida species are relatively common contaminants of both processed and unprocessed foods. In people whose mouths are colonized with C. albicans, the yeast can be found in saliva at an average concentration of 300-500 cells per ml. This will allow transfer during kissing and other direct saliva-saliva contact. There are ample opportunities, therefore, for entry of Candida species into the mouth by manual inoculation, saliva transfer, or contaminated food and drink.

Attachment and Growth of C. albicans

Once in the mouth, C. albicans is presented with a plethora of sites for adhesion to oral surfaces. These include the epithelial cells of buccal muco-
sae, the tongue, tooth surfaces, various oral prostheses such as dentures, and other oral micro-organisms that have already colonized these surfaces. Clinically, *C. albicans* can be cultured from swabs of the buccal mucosa, tongue, teeth, denture surfaces, and dental plaque samples. In colonized individuals with no clinical symptoms of candidiasis, *C. albicans* is most frequently found on the dorsum of the tongue.

Adhesion involves interactions between the yeast cells and host surfaces. The *C. albicans* molecules that mediate binding of cells to other cells (host or microbial), inert polymers, or proteins are termed adhesins. The structures to which the adhesins bind are called ligands or receptors. Several *C. albicans* adhesins have been identified. Most are glycoproteins (proteins with chains of various sugars attached) present in the cell wall of the fungus. Both the protein and carbohydrate portions of glycoprotein adhesins have been implicated in adherence. The interactions between adhesins and receptors can be protein-protein, protein-glycoprotein (lectin-like), ionic or hydrophobic. Some adhesins are specific for a particular ligand; others bind to a variety of ligands that may be present on multiple surfaces. Several gene families have been identified in *C. albicans* that encode proteins similar to those involved in yeast agglutination, or co-aggregation. These proteins are thought to be involved in the adhesion of *C. albicans* to a variety of molecules. The initial interaction between adhesin and receptor involves the shape, charge, and hydrophobicity of both moieties. Subsequently, stronger bonds, such as covalent linkages with epithelial cells, may be formed. These various adhesion interactions may induce a growth response, or an induction of mycelial growth, in the yeast cells.

All oral surfaces adsorb from saliva a thin layer of salivary components. This layer is called the acquired salivary pellicle. Saliva affects the oral adhesion of *C. albicans*. Few salivary proteins bind directly to the yeast cells, but *C. albicans* selectively binds salivary molecules that have adsorbed to oral surfaces such as tooth enamel and oral bacteria (Figure 1).

Growth conditions in the oral cavity are so poor (there is practically no growth of *C. albicans* in saliva unless it is supplemented with glucose) that yeast cells have to adhere in order to be maintained. In addition, for *C. albicans* to cause an infection, it has to multiply and cause tissue damage. *C. albicans* secretes a range of degradative enzymes that may damage host tissues and also provide carbon and nitrogen for growth. The best characterized of these enzymes are the secreted aspartyl proteinases, but lipases and hexosaminidase may also contribute to *C. albicans* pathogenicity. Because *C. albicans* does not have particularly stringent growth requirements, can utilize a variety of carbon and nitrogen sources, and is acid-tolerant this may give it a growth advan-

![Figure 1. Adhesive interactions of *C. albicans* that overcome saliva flow](image)
Evading Host Defense Mechanisms

Host defenses act to remove or kill invading yeast, which is why immune system defects are major risk factors for candidiasis. Innate defenses include the epithelial barrier, the flushing effect of saliva, and anti-candidal salivary components such as lysozyme, histatins, lactoferrin, and calprotectin. Acquired immunity includes the production of immunoglobulins and, if tissues are penetrated, the involvement of macrophages and polymorphonuclear leukocytes. *C. albicans* possesses several features that enable it to evade or overcome host defenses and colonize the mouth. It can adhere to a variety of surfaces and to immobilized saliva components, and thus resist the clearing effect of saliva flow and swallowing (Figure 1). Enzyme secretion and hyphal formation enable tissue destruction and penetration. The abrasion of mucosal surfaces and the penetration of tissues expose *C. albicans* cells to further adhesion receptors and other host defense mechanisms. The yeast can bind to various extracellular matrix (ECM) proteins including fibronectin, laminin, entactin, collagen, and vitronectin, thus aiding tissue colonization. *C. albicans* cells have been shown to possess surface proteins with similarity to human integrin molecules. Such proteins may be involved in adherence to ECM proteins containing the RGD (arginine-glycine-aspartic acid) amino acid motif.

*C. albicans* can be ingested by neutrophils and mononuclear phagocytic cells. Components from the classic and alternative complement pathways enhance yeast phagocytosis by macrophages and neutrophils. *C. albicans* activates the alternate pathway of complement, and both iC3b and C3d fragments can bind to *C. albicans*. Several *C. albicans* wall proteins have been implicated in the binding of iC3b and C3d. One way that *C. albicans* can evade host defenses is by binding iC3b which blocks neutrophil CR3 recognition of iC3b and reduces phagocytosis of iC3b-coated *C. albicans*.

Prospects for Preventing Oral Candidiasis

With a limited range of antifungal drugs available to clinicians and the emergence of drug-resistant *Candida* strains, the prospect of preventing *C. albicans* colonization, thus precluding candidiasis, is becoming increasingly attractive. The prevention of colonization by inhibiting *C. albicans* adherence could be achieved by immunizing the host or by physical interference with adherence mechanisms. Salivary IgA antibodies have been shown to reduce the adherence of *C. albicans* cells to buccal epithelial cells. The stimulation of a mucosal immune response with a *C. albicans* adhesin, possibly expressed by another resident oral microbe, may prevent colonization. Alternatively, application of soluble receptors, ligands, or the domains of these molecules involved in adherence could be used to prevent microbial colonization.

It is evident, however, that *C. albicans* can utilize a number of adherence mechanisms to colonize a variety of oral surfaces. It will be necessary to determine the nature of the principal adherence interactions before the goal of colonization prevention can be attained.

REFERENCE