Oral *Candida*: Clearance, Colonization, or Candidiasis?

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Abstract. *Candida albicans* is frequently isolated from the human mouth, yet few carriers develop clinical signs of candidiasis. Oral candidiasis presents clinically in many forms. This reflects the ability of the yeast to colonize different oral surfaces and the variety of factors which predispose the host to *Candida* colonization and subsequent infection. Colonization of the oral cavity appears to be facilitated by several specific adherence interactions between *C. albicans* and oral surfaces which enable the yeast to resist host clearance mechanisms. Thus, *Candida* has been shown to adhere to complement receptors, various extracellular matrix proteins, and specific sugar residues displayed on host or bacterial surfaces in the oral cavity. Oral candidiasis results from yeast overgrowth and penetration of the oral tissues when the host's physical and immunological defenses have been undermined. Tissue invasion may be assisted by secreted hydrolytic enzymes, hyphal formation, and contact sensing. While these and other phenotypic characteristics may endow certain *Candida* species or strains with a competitive advantage in the oral cavity, it is the host's immune competence that ultimately determines whether clearance, colonization, or candidiasis occurs.

Key words: *Candida albicans*, oral candidiasis, colonization, pathogenicity.

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Introduction

Colonization of the mouth by *Candida* species has a long recorded history. Hippocrates, as early as 377 BCE, reported oral lesions that were probably caused by *Candida* (Odds, 1988). The genus *Candida* is comprised of about 150 fungal species that are assigned to the family deuteromycetes, since almost all lack a sexual stage. Seven of these species (*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. kefyr*, *C. glabrata*, and *C. guilliermondii*) are recognized as medically important pathogens. *C. albicans* is the most prevalent yeast isolated from the human body as a commensal or as an opportunistic pathogen. Other *Candida* species are usually regarded as opportunists. Although *C. albicans* survives poorly on dry surfaces (Odds, 1988), it can remain viable for some time on moist objects. For example, it is isolated from the toothbrushes of most people who carry the yeast in their mouths, and it survives in hand cream, cosmetics, and on clothing. *Candida* often colonizes the human epidermis, especially moist webs of skin between fingers or toes, but the gastro-intestinal tract is considered to be the major reservoir (Odds, 1988). The existence of such reservoirs ensures regular seeding of the oral cavity. While a considerable proportion of the population carries detectable numbers of yeast in the mouth, very few of those people suffer from oral *Candida* infections. The objective of this review is to examine the selective nature of colonization and candidiasis and to discuss molecular approaches that may eventually produce prophylactic therapies.

Carriage of oral yeast

Many yeast species have been isolated from the oral cavity. The majority of isolates are *Candida*, and the most prevalent species is *C. albicans* (Table 1). Yeast such as *Rhodotorula glutinis* and *Saccharomyces cerevisiae* are found in the oral cavity rarely and are not known to cause oral infections. *Cryptococcus neoformans* is occasionally isolated from the mouth, but usually from patients with pulmonary cryptococcosis (Stenderup, 1990). It is important to note that

the isolation of *C. albicans* or other *Candida* species from the oral cavity, in the absence of lesions, does not constitute evidence of clinical candidiasis. Whether cumbersome imprint sampling methods (Olsen and Stenderup, 1990) or less sensitive saliva sampling and oral rinse procedures (Coulter *et al.*, 1993) are used, none of these techniques usefully locates or confirms colonization (Olsen and Stenderup, 1990). Reported rates of yeast carriage in the human mouth vary widely (from 25 to 75%), depending on the population sampled and the sensitivity of the sampling technique (Odds, 1988).

Host factors reported to be associated with increased oral carriage rates of yeast include: reduced saliva flow rate (Parvinen and Larmas, 1981); low saliva pH (Arendorf and Walker, 1980); blood group O and non-secretion of blood group antigens (Burford-Mason *et al.*, 1988); smoking (Arendorf and Walker, 1980); and increased saliva glucose concentration (Knight and Fletcher, 1971). However, evidence for the involvement of these factors in increased carriage rates is equivocal, and conflicting reports can be found. A comparison between surveys of 'healthy' people and surveys conducted on hospital patients shows that *C. albicans* carriage by the latter group is significantly higher (Odds, 1988). While candidiasis can be a nosocomial infection (Vazquez *et al.*, 1993), this factor does not account for the overall difference in carriage rates; it is evident that the immune competence of individuals and/or the presence of other predisposing factors can affect colonization by *C. albicans* (Hauman *et al.*, 1993).

C. albicans colonizes several surfaces in the oral cavity. The organism is most frequently found on the dorsum of the tongue, but can also be cultured from swabs of cheek and tooth surfaces (Arendorf and Walker, 1980). Despite considerable research on caries and periodontal disease, there are few reports of *Candida* in the periodontitis or plaque microbiota (Arendorf and Walker, 1980; Slots *et al.*, 1988; Rams and Slots, 1991; Coulter *et al.*, 1993). This may reflect either a low abundance of *Candida* in these niches or deficiencies in the detection methods. If a small quantity of yeast were incorporated into plaque, it might serve as a reservoir, in addition to other regions of the gastro-intestinal tract, for recurrent episodes of oral candidiasis.

The oral surfaces colonized by *C. albicans* are bathed in saliva and adsorb salivary proteins. The clean tooth surface, which by itself binds *C. albicans* poorly, rapidly acquires a pellicle of proteins which contains amylase, lysozyme, bacterial glucosyltransferases and glucans, albumin, immunoglobulins, cystatins, proline-rich proteins (PRPs), and lactoferrin, and may contain serum factors such as fibronectin and C3 fragments (Levine *et al.*, 1985; Lamkin and Oppenheim, 1993). Some of these proteins promote binding of *C. albicans* to the tooth, while other salivary factors inhibit yeast growth. Epithelial surfaces also have salivary proteins attached. For example, a membrane-bound epithelial enzyme, transglutaminase, covalently cross-links acidic PRPs to epithelial surface proteins (Bradway *et al.*, 1992). If the oral mucosal surface is damaged, other receptors that can mediate *Candida* adherence, such as fibronectin and laminin, may be exposed. *Candida* also interacts with other microbes and microbial products in the complex biofilm covering oral surfaces (Holmes *et al.*, 1995a). The uneven distribution of *C. albicans* in the mouth presumably reflects the distribution and accessibility of ligands to which *Candida* can adhere.

Table 1. Yeast species isolated from the mouth (adapted from Odds, 1988)

Yeast Species	Percentage of Yeast Isolates
Candida albicans	47-75
Candida tropicalis	7
Candida glabrata	7
Candida krusei	< 5
Candida parapsilosis	< 5
Candida guilliermondii	< 5
Rhodotorula spp.	< 4
Saccharomyces cerevisiae	< 2
Cryptococcus spp.	< 1

Longitudinal studies have tested whether carriage in the oral cavity is continuous or if regular re-seeding is required to maintain oral *Candida* populations. Daily sampling showed that carriage was continuous in a significant proportion of healthy *C. albicans* carriers and that carriage recurred in a majority of the remaining subjects (Gergely and Uri, 1966; Williamson, 1972). Since the strains carried were not biotyped, it is not known whether single or multiple strains were maintained or whether strain replacement occurred. In immunocompromised hosts, *Candida* infections are often caused by a resident strain (Powderly *et al.*, 1993; Voss *et al.*, 1994), and the same strain can cause recurrent infections (Miyasaki *et al.*, 1992). In another report, resident strains were supplanted by strains responsible for the candidiasis (Schmid *et al.*, 1992). Epidemiological studies using DNA fingerprint biotyping have shown that a large proportion of the strains responsible for infections in a particular locale are often genetically similar (Schmid *et al.*, 1990, 1992; Vazquez *et al.*, 1993). Presumably, such strains have properties that make them more effective at colonizing the host and/or causing disease.

Oral candidiasis

Oral lesions of candidal origin that may be encountered by dentists are described in Table 2, along with conditions that may predispose individuals to such infections. Many factors can predispose individuals to oral candidiasis (reviewed by Samaranayake, 1990; Scully *et al.*, 1994). Some are mechanical, such as ill-fitting dentures; some are short-term, such as courses of antibiotic therapy; while other types of predisposition may be deep-seated and related to the underlying disease status of the individual. AIDS, malignancy, impaired granulocyte function, anti-cancer treatments, and long-term antibiotic therapy are all factors which markedly increase the host's susceptibility to oral candidiasis. Pseudomembranous candidiasis is the most common form of oral thrush. This presentation is seen in from 10 to 15% of debilitated, elderly people (Odds, 1988) and also in neonates whose immune system is immature

Table 2. Predisposing factors for, and pathology associated with, oral candidiasis

Predisposing Factors[a]	Oral Candidiasis	Pathology
Age (neonates and the elderly) Nutritional deficiency Broad-spectrum antibiotics Oral/systemic steroids Malignancy Chemotherapy Phagocyte dysfunction CMI[b] deficiencies AIDS	Pseudomembranous candidiasis (Oral thrush)	Creamy/white patches on the surface of oral mucosa and the tongue; forming confluent, curd-like pseudomembranes at later stages. Pseudomembranes can be scraped off to reveal raw, erythematous base.
Denture-wearing Habitual thumb sucking	Chronic atrophic candidiasis (Denture stomatitis)	Chronic erythema and edema of upper palate localized to occluded/traumatized tissues.
	Angular cheilitis[c] (Perlèche)	Fissures and encrustations at corners of mouth; most commonly associated with denture stomatitis.
Asthma/corticosteroid aerosols Broad-spectrum antibiotics	Acute atrophic candidiasis (Antibiotic sore tongue)	Small lesions, usually on tongue, with reddening/inflammation of surrounding tissues.
Cellular hyperplasia Oral cancer Smoking Denture-wearing	Chronic hyperplastic candidiasis (*Candida* leukoplakia)	Chronic, nodular, hard lesions on surface of tongue or inside of cheek. *Candida* associated with host epithelial cell hyperplasia

[a] Factors most commonly reported as underlying conditions in oral candidiasis; the list is not exhaustive.
[b] Cell-mediated immunity.
[c] Not necessarily of candidal origin

and whose gastro-intestinal microflora has not been established. In these conditions, fungal cells invade the stratum corneum, but do not penetrate beyond the stratum spinosum. *Candida*-associated denture stomatitis affects many (from 25 to 65%) denture wearers (Budtz-Jörgensen, 1990a). As with pseudomembranous candidiasis, there is no fungal penetration beyond the spinus layers, but neutrophil and lymphocyte infiltration are induced (Odds, 1988). Less common forms of oral candidiasis include acute atrophic candidiasis, and *Candida* leukoplakia. In oral candidiasis, most tissue damage results from the host inflammatory response, although additional damage may be due to enzymes secreted from *Candida*.

Oropharyngeal candidiasis is an important disease of immunocompromised individuals such as organ transplant recipients, cancer patients (Bodey, 1988), and individuals with AIDS (Coleman *et al.*, 1993). Oral candidiasis is one of the earliest indicators of the progression from HIV seropositive status to AIDS. Esophageal lesions in AIDS patients can be extensive, requiring systemic fluconazole therapy (Millon *et al.*, 1994), and these lesions can be a source of infection for other forms of oral candidiasis that are often seen in AIDS patients (Holmstrup and Samaranayake, 1990). The high frequency of oral *Candida* carriage (Hauman *et al.*, 1993) and candidiasis in immunocompromised individuals emphasizes that a fully functional immune system is needed to prevent candidiasis. Dentists should be aware that visible infection by *Candida* can be an early indicator of immune dysfunction. It should prompt a review of the patient's clinical background. Host factors influence not only colonization but also the form of candidal infection that is likely to be established. The pathology of some *Candida* infections reflects a particular predisposing condition(s). In certain clinical situations, therefore, oral candidiasis can be of diagnostic and prognostic value for patients who already have, or are at high risk of developing, serious underlying disease. In general, the infection of subepithelial oral tissues is an ominous indicator of immune incompetence.

Factors contributing to the persistence of *Candida*

No single factor appears to be responsible for the pathogenicity of *C. albicans*. It has been proposed that a combination of different factors contributes at each stage of infection (Cutler, 1991; Calderone, 1994; Matthews, 1994; Odds, 1994).

Adherence

Adherence of *Candida* species to host surfaces is required for

initial colonization and contributes to persistence within the host (Fig.). Without attachment, the growth rate of *C. albicans* (about 1.5 hours *per* generation in a rich growth medium) is insufficient to maintain carriage in the mouth or gastro-intestinal tract. Continued adherence could also be important during the progression from colonization to infection. The balance between colonization and overt infection (Fig.) may be tipped toward infection in compromised individuals by changes in the expression of adherence ligands and receptors.

Candida cells adhere to several host cell types, including epithelia (Critchley and Douglas, 1985; Fukayama and Calderone, 1991), endothelia (Edwards *et al.*, 1992; Ghannoum *et al.*, 1992; Klotz, 1994), and phagocytic cells (Diamond, 1993; Kanbe and Cutler, 1994). Adherence mechanisms known to be used by *Candida* are summarized in Table 3, and many have been characterized at the molecular level (Tronchin *et al.*, 1991; Calderone, 1993a,b; Hostetter, 1994). *C. albicans* expresses adhesins that recognize extracellular matrix proteins, including laminin, collagen, fibrinogen, fibronectin, and entactin (Bouchara *et al.*, 1990; Klotz and Smith, 1991; Klotz *et al.*, 1993; López-Ribot and Chaffin, 1994; Nègre *et al.*, 1994). Some research suggests that these adhesins are identical, with common or multiple ligand-binding sites (Klotz *et al.*, 1993), while other studies suggest separate adhesins that recognize discrete domains on target molecules (Nègre *et al.*, 1994). *C. albicans* possesses cell surface proteins with similarity to the mammalian integrins αMβ2, αXβ2, and α5β1 (Hostetter, 1994; Santoni *et al.*, 1994). These bind to epithelial and endothelial receptors such as iC3b, and to fibronectin. *C. albicans* lectin-like adhesins include surface proteins that bind fucosyl or *N*-acetyl-D-glucosamine determinants (Critchley and Douglas, 1987; Tosh and Douglas, 1992) or galactosides (Jimenez-Lucho *et al.*, 1990; Brassart *et al.*, 1991; Yu *et al.*, 1994a,b) on buccal epithelial cells. A *Candida* lectin that binds streptococcal polysaccharide has recently been described (Holmes *et al.*, 1995b). In addition, the carbohydrate moieties on *Candida* mannoproteins may be receptors for host glycoproteins on splenic macrophages (Kanbe and Cutler, 1994). Of particular importance to oral candidiasis may be the adherence of *Candida* cells to saliva-coated surfaces (Vasilas *et al.*, 1992; Hoffman and Haidaris, 1994; Cannon *et al.*, 1995), including prosthetic devices (Nikawa *et al.*, 1993a), and to oral bacteria (Jenkinson *et al.*, 1990).

The composition of the *C. albicans* cell surface is dynamic. The pattern of macromolecules surface-exposed *in vitro* depends on environmental conditions (Kennedy and Sandin, 1988; Cutler and Kanbe, 1993), and recent evidence has confirmed that *C. albicans* cell surface modulation occurs *in vivo* (De Bernardis *et al.*, 1994). These surface changes may enable a commensal yeast strain to escape immune surveillance (Diamond, 1993) or adhere to different host receptors, thereby promoting candidiasis. Changes in surface protein glycosylation may expose hydrophobic protein structures at the cell surface (Hazen and Glee, 1994), in turn affecting adherence properties. Yeast cell surface changes may be brought about by *Candida*/host interactions. For example, adherence to human buccal epithelial cells induced the synthesis of new proteins in *C. albicans* and the expression of signal proteins (Bailey *et al.*, 1995). An understanding of adherence mechanisms, the signals they generate and the processes that they induce, may therefore lead to specific preventive treatments for individuals predisposed to candidiasis.

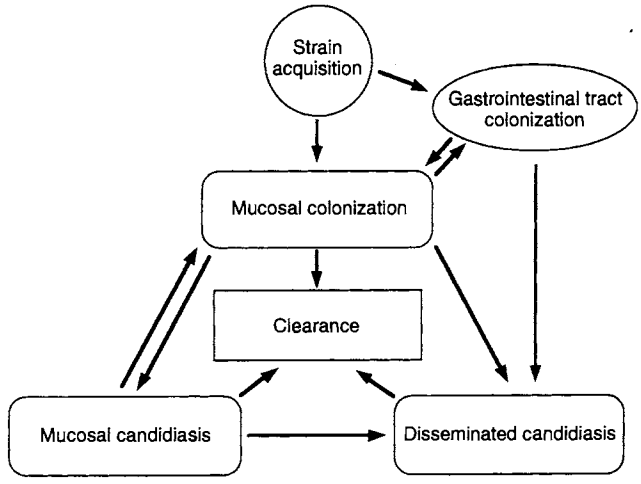

Figure. Relationship among strain acquisition, colonization, infection, and yeast eradication for oral *Candida*.

In vitro studies show that changing environmental conditions can induce morphogenesis of *C. albicans* (reviewed by Odds, 1988) and that the cell surface of the hyphal form of *C. albicans* displays a number of proteins that are either absent or masked in the yeast form (Ollert and Calderone, 1990; Ponton *et al.*, 1993). The hyphal form also exhibits increased adherence properties (Kimura and Pearsall, 1980; Samaranayake and MacFarlane, 1982; Odds, 1994) which appear to correlate with increased expression of the α5β1-like fibronectin receptor in cells forming hyphae (Santoni *et al.*, 1994). Divalent cation-dependent aggregation also occurs during the yeast-hyphal transition (Holmes *et al.*, 1992), which complicates many adherence assays. For this reason, most of the *Candida* adhesins that have been isolated are from yeast cells.

The yeast/host cell interaction is also affected by external factors such as drug treatment. Antibiotic treatment can cause *C. albicans* overgrowth in the oral cavity by eliminating competing micro-organisms and exposing additional sites suitable for colonization. Antifungals, however, can reduce the adherence of *C. albicans in vitro* (Darwazeh *et al.*, 1991; Gottlieb *et al.*, 1991; Ghannoum *et al.*, 1992). This effect may enhance drug efficacy. Pre-treatment of prostheses or mucosae may also help to prevent infection by reducing yeast adherence. Adhesion of *C. albicans* has promise as a target for antifungal drug design, because animal studies indicate that administration of adhesin receptors can ameliorate colonization (Ghannoum *et al.*, 1991; Klotz *et al.*, 1992).

Morphogenesis

C. albicans is a fungus that can grow in a number of morphological forms, ranging from yeast to hyphae.

Table 3. Adherence mechanisms of *Candida*

Adherence Mechanism	*Candida* Adhesin	Receptor/Ligand	Host Tissue/Surface	Reference
Hydrophobicity	Surface proteins	Hydrophobic surfaces	Epithelial cells, dental materials	Nikawa *et al.*, 1992; Hazen and Glee, 1994
Protein-protein	"Integrin-like" surface proteins, *e.g.*, αMβ2, αXβ2, α5β1	iC3b; C3d; RGD-containing polypeptides[a] (*e.g.*, fibronectin)	Epithelial cells, extracellular matrix, endothelial cells, blood	Calderone,1993a; Hostetter, 1994; Santoni *et al.*, 1994
	Surface proteins	C3d; extracellular matrix proteins (*e.g.*, fibrinogen, collagen, laminin, fibronectin, entactin)	Epithelial cells, extracellular matrix, endothelial cells, blood	Bouchara *et al.*,1990; Calderone,1993a; Klotz *et al.*, 1993; López-Ribot and Chaffin, 1994; Nègre *et al.*, 1994
Lectin-like	Surface proteins	Fucose or GlcNAc residues on host glycoproteins Fucα1-2Galβ residues	Epithelial cells	Critchley and Douglas, 1987; Brassart *et al.*, 1991; Tosh and Douglas, 1992
	Surface proteins?	Oral streptococcal polysaccharide(s)	Colonized epithelial cells, dental plaque?	Holmes *et al.*, 1995b
	"Fimbriae" mannoprotein	Glycosphingolipid receptors (βGalNAc(1-4)βGal)	Epithelial cells	Yu *et al.*, 1994b
Undefined	Unknown	Glycosphingolipids	Epithelial cells	Jimenez-Lucho *et al.*, 1990
	Carbohydrate moiety of cell wall mannoprotein	Unknown	Macrophages	Kanbe and Cutler, 1994

[a] Polypeptides containing the sequence Arg-Gly-Asp.

Pseudohyphal forms are also seen, and this morphology can be assumed by several other *Candida* species (Odds, 1988). There is a common belief that the hyphal form is invasive and pathogenic, while the yeast is the commensal non-pathogenic form. Evidence for this is equivocal (Kerridge, 1993; Odds, 1994). Histopathological examination of candidiasis lesions indicates that hyphae are not always present. Recently, it was shown that hyphae are capable of contact-sensing or thigmotropism (Sherwood *et al.*, 1992). *C. albicans* hyphae incubated on perforated filters over agar plates grew through the pores and along grooves. This property could facilitate the penetration of some tissues. Certain *C. albicans* strains exhibit high-frequency switching of colony morphology when nutritionally stressed. This is accompanied by changed cellular morphology and, in some cases, by chromosomal translocation (reviewed by Soll, 1992). High-frequency phenotypic switching can simultaneously affect expression of many potential virulence factors and may be a genetic mechanism that allows the asexual *C. albicans* to adapt to environmental change.

Secreted hydrolytic enzymes

Secreted hydrolytic enzymes often contribute to the pathogenesis of microbial disease (Volkmann, 1990). *C. albicans* has been reported to secrete several enzymes. These include a phospholipase, lipase, phosphomonoesterase, hexosaminidase, and at least three separate aspartic proteinases (White *et al.*, 1993; Odds, 1994). Of these enzymes, the proteinases have been studied most. Proteinase activity is produced by only the most pathogenic *Candida* species (*C. albicans*, *C. tropicalis*, and *C. parapsilosis*) and shows a broad substrate specificity. Secreted aspartic proteinase activity has been suggested as a virulence factor on the basis of studies using proteinase-deficient mutants (Ross *et al.*, 1990) and because it can be immunodetected in clinical samples (De Bernardis *et al.*, 1990). However, there is no conclusive

evidence that proteinase activity is always associated with infection, and genetic factors other than the proteinase deficiency may limit the pathogenicity of proteinase-mutant strains. It has been suggested instead that proteinase is just one factor used at a particular stage in *Candida* infections (Odds, 1994).

Interaction of *C. albicans* with the host immune system

Innate primary defense mechanisms play key roles in preventing yeast colonization of the oral cavity. These primary defenses include: the physical barrier of the epithelia; lingual antimicrobial peptide, a defensin with broad-spectrum antimicrobial activity that is expressed in epithelia surrounding oral lesions (Schonwetter *et al.*, 1995); secretory IgA, which aggregates yeasts and assists in clearance; and salivary factors (Challacombe, 1990; Scully *et al.*, 1994). Saliva flow rate affects microbial clearance, and specific salivary molecules—such as lysozyme (Togbi *et al.*, 1988), histatins (Lal *et al.*, 1992), and lactoferrin (Nikawa *et al.*, 1993b)—have candidacidal properties.

Phagocytes provide the second line of defense against invasive *Candida* infection. In the immunocompetent host, neutrophils, eosinophils, and monocytes phagocytose yeast and hyphal forms of *C. albicans* that gain access to deeper tissues (Heimdahl and Nord, 1990). During acute inflammatory responses to *Candida* infection, neutrophils predominate numerically and in candidacidal activity. Both oxidative and non-oxidative mechanisms are involved in the intracellular killing of *Candida* (Diamond, 1993), but these are not always effective. For maximum killing efficiency, granulocytes and macrophages require augmentation by cytokines such as interferon-gamma, granulocyte-macrophage colony-stimulating factor, and interleukin-1 and -2, produced by T-cells (Greenfield, 1992; Diamond, 1993). A significant factor in the pathogenicity of *C. albicans* is the ability of surface molecules, such as mannoproteins and complement receptors, to modulate phagocyte responses (Diamond, 1993). The importance of cell-mediated immunity in resistance to *Candida* infection is illustrated by the severe mucosal candidiasis seen as a result of T-cell dysfunction in AIDS patients and in many people with chronic mucocutaneous candidiasis (Odds, 1988). This contrasts with neutropenic patients, who are at greater risk of disseminated infection. Humoral immunity, in the form of serum antibodies, plays a lesser role in the defense against infection.

Molecular analysis of pathogenicity

Definitive evidence for the role of potential virulence factors in pathogenicity can be obtained by gene disruption experiments that specifically inactivate one or more genes. Rudimentary tools for undertaking gene disruption and controlled gene expression experiments are available (Kelly *et al.*, 1988; Cannon *et al.*, 1990, 1992; Herreros *et al.*, 1992; Fonzi and Irwin, 1993), but the diploid nature of *C. albicans* and the lack of positive selection markers for transformation are limiting. Genes encoding potential virulence factors have been cloned from *C. albicans*. These include the hexosaminidase gene *HEX1* (Cannon *et al.*, 1994), several genes encoding aspartic proteinases (*SAP1* - Hube *et al.*, 1991; *SAP2* - Mukai *et al.*, 1992; *SAP3* - White *et al.*, 1993; *SAP4* - Miyasaki *et al.*, 1994), and a gene that confers adherence properties on *S. cerevisiae* (Barki *et al.*, 1993). None of these genes has been successfully insertionally inactivated. Two genes (*CPH1* and *PHR1*) involved in hyphal formation, however, have been disrupted (Liu *et al.*, 1994; Saporito-Irwin *et al.*, 1995). Null mutants of either gene were impaired in hyphal formation under certain, but not all, conditions. It remains to be seen whether the disruption of these genes in *C. albicans* affects pathogenicity.

Control of infection

The antifungal agents commonly used to treat oral candidiasis patients target either the high ergosterol content of *Candida* plasma membranes or the enzymes involved in ergosterol biosynthesis. The membrane-active polyenes nystatin and amphotericin B are fungicidal and for oral candidiasis are usually administered as a suspension or lozenges, while the ergosterol biosynthesis inhibitors (imidazoles and triazoles) are administered as tablets (miconazole, ketoconazole, and fluconazole), as a gel (miconazole), or as troches (clotrimazole) (Budtz-Jörgensen, 1990b; Martin, 1990). Such treatments usually eliminate oral candidiasis. Fluconazole, a fungistatic triazole which has superior pharmacokinetic properties and greater solubility than the imidazoles, is widely used for the oropharyngeal candidiasis seen in AIDS patients. Fluconazole and amphotericin B dominate the treatment of disseminated or recurrent fungal infections. However, amphotericin B can cause undesirable side-effects, including significant renal toxicity, while prophylactic exposure to fluconazole can lead to resistance or overgrowth by naturally resistant organisms like *Candida krusei* and *Candida glabrata* (Vanden Bossche *et al.*, 1994). The limitations and restricted target range of existing antifungals, particularly with regard to the treatment of disseminated rather than superficial disease, have led to a search for more effective antifungals (Georgopapadakou and Walsh, 1994; Monk and Perlin, 1994). Biosynthesis of cell wall glucan polymers is the target for the echinocandins and pneumocandins that are now approaching clinical trial (Sternberg, 1994), while another target under investigation is the plasma membrane proton pumping ATPase (Monk and Perlin, 1994), an enzyme which appears to be essential for fungal viability.

Given the diversity of clinical conditions predisposing for oral candidiasis, are there any simple preventive measures that can help avoid disease? Prophylactic fluconazole treatment of individuals seropositive for HIV is a short-term solution, but this approach is less than satisfactory in the longer term. Technological developments, such as the inclusion of *Candida* adhesins, ligands, or antibodies in toothpastes or mouthwashes, may ultimately help tip the balance between colonization and clearance (Fig.). In the meantime, the dentist should be aware of the ways that candidiasis presents in the oral cavity and that a particular disease presentation can reflect the host condition. Clearly, the encouragement of sensible dental hygiene for those at risk, particularly the immunocompromised, AIDS patients,

asthmatics, and those undergoing long-term broad-spectrum antibiotic treatment, is the most useful preventive measure that is currently available.

Conclusions

The pathogenesis of *Candida* infections is complex, involving both yeast and host factors. This aspect of the host-fungus relationship is illustrated by the spectrum of clinical presentations of oral candidiasis. The repertoire of adherence mechanisms exhibited by *C. albicans* enables it to colonize many oral niches. The ability of a *Candida* strain to overcome the host clearance mechanisms and to colonize surfaces (Fig.) depends on the effectiveness of those mechanisms, the avidity of the yeast adherence, and the yeast growth rate. Progression from adherent replicating yeast to a mucosal infection again depends on adherence and growth rate but also involves tissue penetration. Secreted hydrolytic enzymes, hyphal formation, and contact-sensing are factors that could facilitate this process. For an infection to persist, the host immune system must fail to contain the growth of the yeast. The balance among clearance, colonization, or candidiasis therefore depends on the ability of *Candida* strains to modulate expression of virulence factors in response to environmental change, combined with the competence of the host immune system. The precarious nature of this balance is evidenced by the significant number of people for whom oral candidiasis is a recurrent problem. The key role played by adherence mechanisms suggests that further molecular analysis of *C. albicans* cell surface macromolecule expression and related functions will ultimately provide the information needed for effective prevention of oral candidiasis. For the moment, however, the inter-relationship between host status and the clinical presentations of oral candidiasis means that the dentist can gain useful insight into the overall health of the patient. In addition to suggesting appropriate antifungal treatment, such insights may also help in the early diagnosis and treatment of more serious underlying disease.

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