Candida-Host Interactions in HIV Disease: Implications for Oropharyngeal Candidiasis

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ABSTRACT

Oropharyngeal candidiasis (OPC), caused primarily by *Candida albicans*, is the most common oral infection in HIV⁺ persons. Although Th1-type CD4⁺ T cells are the predominant host defense mechanism against OPC, CD8⁺ T cells and epithelial cells become important when blood CD4⁺ T cells are reduced below a protective threshold during progression to AIDS. In an early cross-sectional study, OPC⁺ tissue biopsied from HIV⁺ persons had an accumulation of activated memory CD8⁺ T cells at the oral epithelial-lamina propria interface, with reduced expression of the adhesion molecule E-cadherin, suggesting a protective role for CD8⁺ T cells but a dysfunction in the mucosal migration of the cells. In a subsequent 1-year longitudinal study, OPC⁺ patients with high oral *Candida* colonization (indicative of a preclinical OPC condition), had higher numbers of CD8⁺ T cells distributed throughout the tissue, with normal E-cadherin expression. In OPC⁺ patients, where lack of CD8⁺ T cell migration was associated with reduced E-cadherin, subsequent evaluations following successful treatment of infection revealed normal E-cadherin expression and cellular distribution. Regarding epithelial cell responses, intact oral epithelial cells exhibit fungistatic activity via an acid-labile protein moiety. A proteomic analysis revealed that annexin A1 is a strong candidate for the effector moiety. The current hypothesis is that under reduced CD4⁺ T cells, HIV⁺ persons protected from OPC have CD8⁺ T cells that migrate to the site of a preclinical infection under normal expression of E-cadherin, whereas those with OPC have a transient reduction in E-cadherin that prohibits CD8⁺ T cells from migrating for effector function. Oral epithelial cells concomitantly function through annexin A1 to keep *Candida* in a commensal state but can easily be overwhelmed, thereby contributing to susceptibility to OPC.

Oropharyngeal candidiasis (OPC) is an opportunistic fungal infection that can involve the hard and soft palate, tongue, buccal mucosa, and floor of the mouth. It primarily presents as white curdlike lesions (pseudomembranous, also known as *thrush*) or reddened patches (erythematous; Calderone, 2002). OPC is defined as superficial candidiasis with shallow levels of tissue invasion. As a result, chewing and swallowing can be difficult. Infections can be acute or recurrent, and they are common in immunocompromised patients—especially, those infected with the human immunodeficiency virus (HIV; reviewed in Fidel, 2002). OPC is one of the first clinical signs of underlying HIV infection, and it will occur in 50% to 95% of all HIV⁺ persons sometime during their progression to AIDS (Rabeneck *et al.*, 1993). OPC is also a common manifestation of chronic mucocutaneous candidiasis, and it occurs in patients with lymphoma, in those undergoing steroid therapy, and in transplant recipients (reviewed in Deslauriers *et al.*, 1997; Calderone, 2002). Although OPC will occur under several immunocompromising conditions, it appears to be much more common in HIV⁺ persons than in the other named conditions. The use of highly active antiretroviral therapy in those with HIV has significantly reduced the incidence of OPC (Palella *et al.*, 1998). This is postulated to be due to increased immune responsiveness as well as direct action on the organism by protease inhibitors (Cassone *et al.*, 1999; Gruber *et al.*, 1999; Calderone and Fonzi, 2001).

OPC is caused primarily by *Candida albicans*, a ubiquitous dimorphic fungal organism that is part of the normal microflora of the gastrointestinal and reproductive tracts of healthy individuals. For asymptomatic carriers, the approximate rate of oral yeast carriage in HIV-negative persons is 50% to 60%, with *C. albicans* present in 85% of isolates recovered (Glick and Siegel, 1999). In HIV⁺ individuals, the asymptomatic colonization rate is higher, approaching 76% (Leigh *et al.*, 1998; Wozniak *et al.*, 2002). Colonization with *C. albicans* is assumed to be responsible for acquired immune responsiveness. Anti-*Candida* antibodies—circulating immunoglobulin G and mucosal immunoglobulins A and G—can be detected in most healthy individuals (Witkin *et al.*, 1988, 1989; Regulez *et al.*, 1994; Wozniak *et al.*, 2002). Moreover, greater than 80% of healthy persons have positive cutaneous skin test reactivity to *Candida* antigen, and peripheral blood lymphocytes from more than 90% of healthy individuals proliferate *in vitro* to *Candida* antigen (Kirkpatrick *et al.*, 1971; Mathur *et al.*, 1977; Fidel *et al.*, 1993; Deslauriers *et al.*, 1997).

Key Words

AIDS, *Candida albicans*, epithelial cells, T cells, mucosal immunity, cytokines.

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These acquired host responses in conjunction with innate resistance (*i.e.*, epithelial cells, polymorphonuclear leukocytes and macrophages) presumably play a significant role in restricting *C. albicans* to mucosal surfaces in an asymptomatic commensal state. But under immunocompromised conditions, *C. albicans*—along with its virulence factors, such as proteases, morphologic transition, phenotypic switching, biofilm formation—can convert into an opportunistic pathogen with significant morbidity. The following section offers a brief review of published data regarding host defenses present in those with and without OPC relative to T cells, cytokines, and epithelial cells; it follows with new, unpublished data from the Fidel laboratory, as presented at the Sixth World Workshop on Oral Health and Disease in AIDS, which together provide potential explanations for the resistance and susceptibility to OPC.

HOST DEFENSE AGAINST OPC

Previously Reported Data

The majority of data suggest that CD4⁺ Th1-type cells are critical for host defense against OPC. Clinically, OPC is most common in HIV⁺ persons when CD4⁺ cell numbers drop below 200 cells/ μ L (Rabeneck *et al.*, 1993; Nielsen *et al.*, 1994; Schuman *et al.*, 1998; Greenspan *et al.*, 2000). In *in vitro* immune analyses, peripheral blood mononuclear cells from most individuals, including HIV⁺ persons, respond to *Candida* antigens with Th1-type cytokines (Kunkl *et al.*, 1998; Leigh *et al.*, 2001). These results suggest that the *Candida*-specific T cells were not becoming defective with immunosuppression but that a threshold number of CD4⁺ T cells is required to protect the oral cavity against infection by this commensal organism. Below this threshold number of cells, other systemic and/or local immune mechanisms must function exclusively. Resistance and susceptibility to OPC then depends on the status of these alternative immune mechanisms.

Several aspects of local immunity have been clinically evaluated. In support of the Th1/Th2 dichotomy concept, Leigh *et al.* (1998) reported that HIV⁻ individuals had Th1/Th0 cytokines in their saliva, whereas HIV⁺ individuals had primarily Th2-type cytokines, which was more profound in those patients with OPC. Lymphocytes have also been examined in the OPC lesions. Although both CD4⁺ and CD8⁺ cells have been identified (Romagnoli *et al.*, 1997), we reported an accumulation of CD8⁺ T cells at a considerable distance from *Candida*, superficially located at the outer epithelium (Myers *et al.*, 2003), thus suggesting a role for CD8⁺ T cells against infection but with a potential problem in cell trafficking or the microenvironment that promotes susceptibility to OPC. Increases in mRNA for several CD8 cell-associated cytokines (IL-2 and IL-15) and chemokines (IP-10, RANTES, and MCP-1; Lilly *et al.*, 2004) supported a role for reactivity by CD8 T cells. A murine AIDS model showed a rate of 30% recurrent OPC, with a predominance of CD8⁺ T cells recruited into the oral tissues (Deslauriers *et al.*, 1997). The tissue-associated CD8⁺ T cells primarily possess the $\alpha\beta$ T-cell receptor (McNulty *et al.*, 2005). The CD8 T cells present in the lesions are activated memory T cells, as evidenced by cell surface activation markers (CD69, CD45RO)

that are transitioning between central and effector memory status (CD27^{Hi}, CCR7^{Lo}, CD62L^{Lo}; Leigh *et al.*, 2006). Hence, the CD8 T cells appear as normal activated memory cells recruited into the oral mucosa from the periphery but inhibited from migrating further through the mucosa to the outer epithelium.

The issue of cellular migration was addressed through the study of homing receptor/adhesion molecules and chemokine receptors. Chemokine receptor expression was similar in HIV⁺ OPC⁺ persons and HIV⁺ OPC⁻ persons (Lilly *et al.*, 2006). Cellular migration is controlled by chemokine receptors as well as cellular heterodimer homing receptors (integrins) and reciprocal tissue-associated adhesion molecules. Some homing receptor–adhesion molecule interactions ($\alpha_4\beta_7$ /MAdCAM, $\alpha_4\beta_1$ /VCAM-1) govern migration of cells out of blood and into mucosal tissues, whereas others govern migration through mucosal tissues ($\alpha_6\beta_7$ /E-cadherin). The CD8⁺ T cells present in OPC⁻ and OPC⁺ tissue had positive integrin expression in varying combinations but no discernible difference in OPC⁻ versus OPC⁺ tissue. In contrast, MAdCAM expression was significantly increased in OPC⁺ tissue, in support of the increased presence of T cells, whereas E-cadherin was significantly decreased in OPC⁺ tissue (McNulty *et al.*, 2005). The reduced E-cadherin provides an explanation for the inability of the CD8⁺ T cells to migrate to the outer epithelium and so represents a putative dysfunction in those with OPC, lending to the susceptibility to OPC.

Humoral immunity does not appear to play a role in protection against or susceptibility to OPC. There is no evidence to date that a deficiency in *Candida*-specific antibodies is present in HIV⁺ persons that could account for the increased prevalence of OPC (Wray *et al.*, 1990; Millon *et al.*, 2001; Wozniak *et al.*, 2002).

Innate cellular defenses also play a role in host defense. Our laboratory has studied the role of epithelial cells for a number of years. These studies have shown that oral epithelial cells can inhibit up to 80% of the *Candida* growth *in vitro* by a fungistatic mechanism via cell contact by intact but not necessarily live epithelial cells through an acid-labile protein receptor (Steele *et al.*, 1999, 2000, 2001; Nomanbhoy *et al.*, 2002; Yano *et al.*, 2005). Analysis of oral epithelial cells in HIV⁺ persons showed significantly reduced activity by cells from patients with OPC compared to that from patients without OPC, providing support as an innate protective mechanism against infection (Steele *et al.*, 2000). Additionally, epithelial cells produce cytokines and chemokines in response to *Candida*, which may contribute to the innate and/or adaptive immune response (Rouabhia *et al.*, 2002; Schaller *et al.*, 2002; Steele and Fidel, Jr., 2002; Dongari-Bagtzoglou and Kashleva, 2003a, 2003b).

On the basis of these data, we propose that several secondary lines of defense are important for protection against OPC when the primary defense by CD4⁺ cells are below the protective threshold. These include CD8 T cells and oral epithelial cells. The Figure illustrates a diagram depicting this hypothesis. In HIV⁺ persons with < 200 CD4 cells/ μ L and OPC⁻, it is postulated that although the CD4⁺ T cells are below the protective threshold, epithelial cells have activity against *Candida* to hold it “in check,” and CD8⁺ T cells are able to migrate to the outer epithelium to aid in protection. However, in those susceptible to OPC, the CD8⁺ T cells are inhibited from migrating to the outer

Fig. Proposed immune function of the oral mucosa in HIV⁺ individuals with and without oropharyngeal candidiasis (OPC) and < 200 CD4 cells/ μ L. Left frame depicts the protective mechanisms associated with the HIV⁺ OPC⁻ individual colonized with *Candida albicans* when the primary defense of CD4⁺ T cells is below the protective threshold (200 cells/ μ L). The secondary defense consists of CD8⁺ T cells migrating to the outer epithelium under normal expression of E-cadherin and functional oral epithelial cell anti-*Candida* activity that together keep *Candida* "in check" and prevent symptomatic infection. Th1 cytokines in saliva may also act in protection against infection, along with cytokines in tissue. Right frame depicts the condition of OPC. In this scenario, when CD4⁺ T cells are below the protective threshold, CD8⁺ T cells are inhibited from migrating to *Candida* for effector function because of a transient reduction in E-cadherin, and the epithelial cells have reduced capacity to inhibit *Candida*, resulting in *Candida* overgrowth and symptomatic infection. Reduced Th1 cytokines in saliva may also contribute to the susceptibility.

epithelium because of reduced E-cadherin with reduced levels of epithelial cell anti-*Candida* activity, resulting in bouts of OPC.

New Findings

Based on the cross-sectional data with the CD8 T cells and E-cadherin (reviewed in Fidel, 2006), the next important step was to conduct a longitudinal analysis of CD8⁺ T cells in the tissue of those HIV⁺ patients who have not acquired OPC, who have had sporadic cases of OPC, or who have recurrent OPC. The objective was to confirm the cross-sectional findings and determine whether the reduction in E-cadherin in those with OPC was permanent or transient. Oral swabs were taken every 2 weeks and biopsies every 2 months to track changes in the CD8⁺ T cells and adhesion molecule expression before, during, and after OPC episodes. In total, the results to date have shown that although OPC⁻ patients with low oral fungal burden revealed an unremarkable presence of CD8⁺ T cells and normal E-cadherin expression, OPC⁻ patients who had increased oral *Candida* colonization (indicative of a potential preclinical OPC condition) had higher numbers of CD8⁺ T cells throughout the tissue with normal E-cadherin expression. In patients with reduced E-cadherin expression and an acute episode of OPC where CD8⁺ T cells were accumulated at the epithelial-lamina propria interface, evaluation of E-cadherin following successful

antifungal treatment revealed a return to normal expression. These results suggest that under conditions of CD4⁺ T-cell deficiency, CD8⁺ T cells typically migrate to the site of a preclinical infection via normal expression of E-cadherin and reduced E-cadherin expression in those with OPC is not permanent. The reduction in E-cadherin that we have observed in patients with OPC is consistent with 2 independent studies showing that *Candida* can cleave or degrade E-cadherin (Frank and Hostetter, 2007; Villar *et al.*, 2007). Hence, the reduction in E-cadherin may be a virulence mechanism for *Candida* that, when adherent to the epithelium, promotes subsequent invasion. We postulate that increases in *Candida* levels lead to increased degradation of E-cadherin, which creates an environment more conducive to infection and invasion and the onset of OPC.

The metabolic state of the epithelial cells is important in understanding the interaction of *Candida* with E-cadherin, as is the cellular localization of the epithelial cells. Phan *et al.* (2007) showed that an adhesin (Als3) on *C. albicans* hyphae can bind E-cadherin on metabolically active epithelial cells, which induces endocytosis. Thus, it appears that *Candida* can either degrade or use E-cadherin. We hypothesize that these 2 conditions can and do occur depending on the location of the epithelial cells. If *Candida* gains access to basal epithelial cells that are metabolically active, it will use E-cadherin to gain intracellular access through endocytosis. But if *Candida* remains on the

apical epithelium, it will likely degrade E-cadherin to occupy and superficially attach to the outer epithelium rather than be released from the epithelium inside metabolically inactive sloughing cells. In any event, it appears that *Candida* has the ability to modulate E-cadherin rather than become modulated by a host-dependent mechanism (transient or permanent). If so, immunotherapeutic strategies directed toward restoring normal E-cadherin expression would allow CD8⁺ T cells to migrate to the outer epithelium, where antifungal effector activity would be critical to reducing the incidence of OPC in susceptible populations. Current studies are focusing on the mechanism of action by CD8⁺ T cells.

In other studies, the objective was to identify the antifungal effector moiety on oral epithelial cells; accordingly, the acid treatment that abrogates the antifungal activity was used. The strategy involved extracting surface-associated glycoproteins from the epithelial cells treated with and without periodic acid. The extracted glycoproteins were then incubated with *Candida*, and any bound epithelial proteins were then eluted from *Candida* and separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis. Because this method could result in contamination of samples with *Candida* cell surface-associated proteins, we labeled the epithelial cell surface proteins with biotin before the acid treatment and protein extraction, which allowed for the use of Western blots to focus only on epithelial cell proteins. Results revealed 2 protein bands (approximately 33 and 45 kDa) eluted from *Candida* blastoconidia or hyphae that are present in phosphate buffered saline–treated cells but not periodic acid–treated epithelial cells.

Proteomic analysis was then conducted on the unique bands from phosphate buffered saline–treated cells. Results showed that the 45-kDa protein for the phosphate buffered saline–treated cells was an actin molecule, whereas the 33-kDa protein was annexin A1. The latter is a viable candidate for the effector molecule because it functions through signaling cascades to inhibit cellular processes, including growth (Croxtall *et al.*, 2003; Liu *et al.*, 2007). Further studies showed that annexin A1 but not actin (as expected) was present on the epithelial cell surface. Functional studies are underway to confirm the role of annexin A1 and elucidate the mechanism of action.

Finally, the extracted epithelial cell surface proteins were evaluated for antifungal activity. Results demonstrated that proteins extracted from phosphate buffered saline–treated cells but not periodic acid–treated cells were capable of inhibiting the growth of *Candida*, similar to intact epithelial cells. These data are consistent with the fact that live epithelial cells are not required despite the need for cell contact.

CONCLUSIONS

Our data suggest that protection against OPC involves primary and secondary host defense mechanisms. The primary and most critical host defense against OPC involves CD4⁺ T cells. However, the role of CD4⁺ T cells is lessened as cell counts fall in association with the progression to AIDS. During CD4⁺ T-cell deficiency, secondary host defenses become critical (*i.e.*, primary) in providing protection against OPC. These secondary defenses include cytokines in saliva

that can promote protection (Th1 type or proinflammatory), the epithelial cell anti-*Candida* activity, and tissue-associated CD8⁺ T cells with the appropriate homing receptors and adhesion molecules that allow them to maximize their migration and effector function. Progress has been made in elucidating the mechanism of the epithelial cell effector activity. The lack of a requirement for live metabolically active epithelial cells suggests that the growth inhibitory signal (or signals) is mediated by cascades in *Candida* and not the epithelial cells as part of a sophisticated symbiosis where *Candida* sacrifices growth for protection against killing by some other immune activity (immune evasion). In regard to the mechanism of the putative CD8 T-cell effector activity, standard cytotoxic T-lymphocyte activity would not be predicted. Rather, we postulate that the effector activity of CD8 T cells occurs via a non-MHC-restricted mechanism similar to that reported for murine CD8⁺ T cells cultured with IL-2 (Beno and Mathews, 1992; Beno *et al.*, 1995). A similar mechanism was also reported against HIV (Stranford *et al.*, 1999; Mackewicz *et al.*, 2000). Interestingly, IL-2 mRNA has been shown to be present in the tissue of OPC⁺ HIV⁺ individuals and increased in OPC⁺ HIV⁺ patients (Lilly *et al.*, 2004). Thus, if the CD8⁺ T cells were present and the E-cadherin could promote adequate migration of the CD8⁺ activated memory T cells, an effective response against OPC could occur despite other factors that promote OPC. That E-cadherin is not permanently reduced in those susceptible to OPC, as evidenced by the longitudinal analyses, suggests that immunotherapeutic strategies can be developed to enhance E-cadherin that would in turn reduce OPC in vulnerable populations such as HIV⁺ patients.

Taken together, our previous and current work continue to support the overall hypothesis that CD8⁺ T cells and oral epithelial cells represent important anti-*Candida* oral host defenses when CD4⁺ T cells drop below protective levels and that the oral microenvironment can be enhanced by immunotherapeutic strategies to optimize their protective capacity.

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