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Immunopathogenesis of Oropharyngeal Candidiasis in Human Immunodeficiency Virus Infection

Louis de Repentigny,[1,2]* Daniel Lewandowski,[1] and Paul Jolicoeur[3]

Department of Microbiology and Immunology, Faculty of Medicine, University of Montreal,[1] Sainte-Justine Hospital,[2] and Laboratory of Molecular Biology, Clinical Research Institute of Montreal,[3] Montreal, Quebec, Canada

INTRODUCTION

Oropharyngeal candidiasis (OPC) is the most frequent opportunistic fungal infection among human immunodeficiency virus (HIV)-infected patients, and it has been estimated that more than 90% of HIV-infected patients develop this often debilitating infection at some time during progression of their disease (374, 375). Although the incidence of OPC in HIV infection has been significantly reduced since the introduction of highly active antiretroviral therapy (HAART) (280), it remains a common opportunistic infection in HIV-infected patients. Clinically, OPC in HIV infection has been classified as exhibiting pseudomembranous and erythematous variants, or angular cheilitis (2). The pseudomembranous form of HIV-associated OPC is characterized by the presence of multifocal

* Corresponding author. Mailing address: Department of Microbiology and Immunology, Sainte-Justine Hospital and University of Montreal, 3175 Côte Sainte-Catherine, Montreal, Quebec H3T 1C5, Canada. Phone: (514) 345-4643. Fax: (514) 345-4860. E-mail: louis.de.repentigny@umontreal.ca.

smooth white papular lesions that can usually be rubbed away, leaving a red surface, and surface pseudohyphae can be readily detected. The erythematous form of OPC typically presents as diffuse and multiple foci of macular erythema involving the palate, oropharynx, buccal mucosa, and dorsal tongue, but hyphae are frequently absent. OPC is frequently complicated by esophageal candidiasis, which may limit food consumption and lead to weight loss, threatening the general health and well-being of HIV-infected patients (428). Furthermore, clinical and in vitro resistance to antifungal azoles frequently occurs in OPC when $CD4^+$ cell counts fall to <200 cells/mm^3 of blood, either by selection or acquisition of resistant strains of *Candida albicans* or by infection with inherently resistant species of *Candida* other than *C. albicans* (273, 332, 343, 344, 354, 380, 445). Of added concern, the full potential impact of antiretroviral therapy on the ability to reconstitute immunity (10, 21, 22, 55, 111, 292, 323, 324, 395) and therefore to reduce the incidence of OPC and esophageal candidiasis (67, 68, 470) has been hampered (362, 429) by suboptimal adherence (235, 441, 443), toxicity (125), and resistance (316, 337) to antiretrovirals, as well as the limited availability of these treatments in developing countries where most HIV-infected patients reside (104).

The leading cause of candidiasis, *C. albicans*, is an imperfect diploid dimorphic fungus that resides as a commensal of the mucosae and the gastrointestinal tract. Intraoral *C. albicans* is found in ~40% of healthy humans (16). However, colonization often leads to opportunistic mucosal or life-threatening deep-organ infection in immunocompromised hosts. Invasion of the human gastrointestinal mucosa by *C. albicans* and its passage across the bowel wall into the bloodstream is an important portal of entry for this opportunistic pathogen into the neutropenic host, leading to systemic or disseminated candidiasis (114, 451). Hematogenous candidiasis is a frequent complication in the treatment of patients with acute leukemia (2, 278). In contrast, *Candida* fungemia is infrequent in HIV-infected patients and is confined mainly to the late stage of HIV infection (247, 333, 438).

The predisposition for OPC and esophageal candidiasis among HIV-infected patients, initially attributed to T-cell impairment, is enigmatic (72, 74, 240, 446). Colonization of oral mucosal surfaces and symptomatic disease are closely correlated with the development and progression of the cellular immunodeficiency of HIV infection (230, 311, 414). However, because *Candida* colonization of the keratinocyte surface occurs without invasion of the submucosa, the occurrence of this superficial fungal disease in a T-cell-poor environment has not been adequately explained. The onset of lesions depends on imbalances between *Candida* virulence attributes and progressively impaired host mucosal defenses in the sequential development of HIV infection, but the exact pathways leading to this imbalance are still unclear. The enhanced risk of OPC and esophageal candidiasis in HIV infection stands in striking contrast to the unenhanced incidence of vaginal candidiasis in HIV-infected women (255, 389), indicating that mucosal immune defense mechanisms and/or their perturbations which favor candidiasis in HIV infection are anatomically compartmentalized (158, 160, 250).

A large body of work conducted with experimentally infected intact or congenitally immunodeficient mice has provided a foundation for understanding the critical roles of Th1 $CD4^+$ T cells, $CD8^+$ T cells, γδ T cells, macrophages, and polymorphonuclear leukocytes (PMNs) in host defense against mucosal and systemic candidiasis (19, 29, 149, 150, 213, 446). The results of these investigations indicated that protection against mucosal candidiasis involves the recruitment and interactive collaboration of several cell populations which, together, can prevent invasion of mucosal surfaces by *C. albicans* in the normal host. It is thus evident that multiple, rather than single, defects in host defense mechanisms potentially underlie mucosal candidiasis in HIV-infection.

In this review, the salient clinical features of OPC and esophageal candidiasis are correlated with mucosal immune defense mechanisms against *C. albicans* and their perturbations in HIV infection. We also describe how a novel experimental model of oroesophageal candidiasis in transgenic (Tg) mice expressing HIV and developing an AIDS-like disease (116, 363) can be used as a new and powerful tool to investigate critical issues regarding innate and acquired immunity at the level of the oral and esophageal mucosa.

OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASES IN THE SETTING OF HIV INFECTION

Clinical Features and Pathology

The pseudomembranous and erythematous variants of OPC represent the most common clinical presentations of mucosal candidiasis associated with HIV-infection (12). Further clinical variants include angular cheilitis (12), exfoliative cheilitis (360), and *Candida*-associated palatal papillary hyperplasia (359). Recognition of these specific forms of oral candidiasis in HIV-infected patients is facilitated by utilizing established clinical diagnostic criteria (12, 178). Symptoms may include burning pain, altered taste sensation, and difficulty swallowing liquids and solids (155). The pseudomembranous form can be easily diagnosed by demonstrating the presence of candidal yeast and pseudohyphae on wet mounts or stained smears of material obtained by swabbing the lesions and is confirmed by isolation of *Candida* species on culture. In the erythematous form, however, the sparse presence of *Candida* at the mucosal surface frequently requires a biopsy and periodic acid-Schiff staining to establish a formal diagnosis.

At least 75% of HIV-infected patients with OPC have concurrent AIDS-associated (70a) esophageal candidiasis (263) confirmed by histopathology of biopsy material obtained at endoscopic examination (355). While 30 to 43% of these patients may not have symptoms of esophageal involvement, a majority have symptoms including dysphagia and odynophagia (80, 428). For this reason, the combination of OPC and these symptoms of esophagitis is highly predictive of esophageal involvement, and these patients can receive empirical antifungal therapy without confirmation of the diagnosis by endoscopy (15, 349, 428). However, patients who fail to respond to antifungal treatment require esophageal biopsy to assess the possibility of azole-resistant *Candida*, other opportunistic pathogens including herpes simplex virus and cytomegalovirus, and lymphoma or Kaposi's sarcoma.

Because procurement of oral tissue samples is restricted for ethical reasons (358), only a limited number of studies have been conducted to determine the histopathologic and ultrastructural features of OPC in HIV infection (147, 357, 358, 367). In erythematous candidiasis, *Candida* hyphae are few while blastoconidia may be found on an atrophic epithelial surface. In contrast, hyphae are numerous and extend into the spinous cell layer in pseudomembranous candidiasis, accompanied by parakeratosis, acanthosis, and spongiosis of the infected superficial epithelium (357). Of interest, hyphae have been observed to penetrate through intercellular spaces, suggesting that *Candida* can engage in thigmotropism (contact guidance), a phenomenon commonly seen in plant fungi and also recognized in *C. albicans* in vitro (398). In some cases, hyphae are seen to traverse spinous cells and display appressoria-like appendages at their extremities, another common feature in plant fungi which enhances the strength of attachment of the exploring fungal tip (357). Intercellular penetration of hyphae is also facilitated by the detachment of epithelial cell desmosomes, presumably by *C. albicans* secretory aspartyl proteinases (SAPs) and/or phospholipase (357). This particular feature is also observed in non-HIV-infected patients with OPC (294). In addition to the marked contrast in penetration of the epithelium by *C. albicans* in pseudomembranous and erythematous candidiasis, these two forms of OPC are distinguished by the nature and intensity of the mucosal inflammatory cell response (147, 357, 358, 367). The erythematous form in both HIV-infected and uninfected patients is characterized by abundant neutrophilic microabcesses in the parakeratin layer of the epithelium, while microabcesses are rarely found in pseudomembranous candidiasis, even underneath foci of extensive hyphal colonization of the parakeratin layer (147, 358, 367). Indeed, some HIV-infected patients with pseudomembranous candidiasis have almost no epithelial inflammatory response (147, 357). In both clinical forms, however, an abundant mononuclear cell response is observed in the submucosa with no significant difference between HIV-infected and -uninfected patients with the exception of an enhanced infiltration in HIV-infected compared to HIV-uninfected patients with pseudomembranous candidiasis. Immunohistochemical analysis has demonstrated that the inflammatory response in both forms of OPC consists predominantly of $CD8^+$ T cells and $CD1a^+$ Langerhans cells (367). The mechanisms which govern the more intense inflammatory response in erythematous compared to pseudomembranous candidiasis remain unknown but are probably independent of HIV infection and its progression since these differences are also observed in patients who are not infected with HIV (147).

Epidemiology

The development of molecular biology-based methods for discriminating *Candida* strains (121) has provided a vital tool to determine the relationships between progression of HIV infection; acquisition, maintenance, and clonality of oral candidal populations; and selection of resistant *C. albicans* or non-*albicans* species of *Candida* following sustained treatment with antifungal azoles. Using these methods, a number of longitudinal studies have been conducted with HIV-infected patients to prospectively examine the molecular epidemiology of recurrent OPC (32, 246, 344, 354, 380, 445). The majority of patients (77 to 100%) with OPC are infected with *C. albicans*, while the remaining patients are infected with one or more non- *albicans* species of *Candida*, either alone or in combination with *C. albicans* (32, 246, 344, 354, 380, 445). A diversity of non-*albicans* species of *Candida* are found, including *Candida tropicalis*, *Candida parapsilosis*, *Candida guillermondii*, *Candida glabrata*, and *Candida dubliniensis*. However, among these species only *C. dubliniensis* has been specifically associated with and recognized as the sole cause of OPC in HIV infection (88, 246, 290, 386, 422, 445). Analysis of serial isolates has revealed that throughout each episode of OPC, the majority of patients are infected with a unique strain of *C. albicans*, originally present as a commensal of the oral cavity (32, 246, 269, 445). In a minority of patients, other patterns of recurrence are found, including strain replacement with a new genotype of *C. albicans* and species replacement with non-*albicans* species of *Candida* (344, 354, 380, 445). Fluconazole resistance may occur through acquisition of a new resistant genotype of *C. albicans* or by development of resistance in a previously susceptible strain (380). Surprisingly, *C. albicans* strains colonizing HIV-infected patients prior to the first episode of OPC and antifungal therapy exhibit an increased frequency of phenotypic switching which increases the proportion of phenotypes in the colonizing population which are resistant to fluconazole (444). After the first OPC episode, risk factors for the emergence of recurrent OPC caused by fluconazole-resistant *C. albicans* include lower $CD4^+$ cell counts, a greater number of treated episodes of OPC, and a greater duration of prior fluconazole treatment (156, 273). Although colonization with azole-resistant *C. glabrata* increases after treatment with fluconazole (402) it is rarely if ever isolated as the sole cause of recurrent OPC (159, 273, 380, 445). In vitro resistance to fluconazole is strongly correlated with clinical failure of fluconazole treatment of OPC in HIV-infected patients (273, 354, 380) and failure to respond to fluconazole therapy in experimental OPC and esophageal candidiasis (450). The molecular mechanisms of resistance to azole antifungals in *C. albicans* strains isolated from HIV-infected patients are multifactorial, with a predominance of overexpression of genes (*MDR1* and *CDR*) encoding efflux pumps, detected in 85% of all resistant isolates (332). Alterations in the gene encoding the target lanosterol 14-α-demethylase enzyme, including functional amino acid substitutions and overexpression of the gene that encodes the enzyme (*ERG11*), are detected in 65 and 35% of the resistant isolates, respectively (332). Overall, multiple mechanisms of resistance are combined in 75% of the isolates displaying high-level fluconazole resistance (332). Although azole-resistant *C. albicans* strains usually remain confined to a single patient with HIV infection and OPC, the potential for transmission of resistant isogenic strains of *C. albicans* among couples (33, 380) and family members including children (301) has been clearly established.

Although HIV-infected women may develop both OPC and vaginal candidiasis, the risk of OPC alone is enhanced by HIV-infection (255, 389). Molecular typing of *C. albicans* colonizing HIV-infected women revealed that concurrent oral and vaginal isolates were in all cases dissimilar, suggesting that the dominant strains of *C. albicans* colonizing these different mucosal sites are distinct (102). These differences may indicate

an ability of specific genotypes of *C. albicans* to colonize different ecological niches or may result from interhuman transmission of different genotypes to separate mucosal sites.

Correlation with Progression of HIV Infection

OPC and esophageal candidiasis can occur at any time during the course of HIV infection, including primary HIV infection (82, 330), the chronic asymptomatic phase and overt AIDS (1, 80, 152, 177, 237, 277, 285, 329, 366, 389). During the chronic asymptomatic phase, both erythematous and pseudomembranous candidiases are predictive of progressive immunodeficiency and onset of AIDS, independently of the $CD4^+$ cell count (129, 224, 230, 311). Oral burdens of *C. albicans* are augmented in HIV-infected patients even prior to the first episode of OPC (439, 445, 467), and the intensity of carriage increases significantly in the progression from asymptomatic *Candida* carrier to an episode of OPC (445). These observations indicate that normal defenses against *Candida* are perturbed early in the progression of HIV infection before any marked depletion of $CD4^+$ cells has occurred. However, the prevalence of the pseudomembranous form of OPC (152, 237, 277, 285, 329, 445) and esophageal candidiasis (1) increases dramatically in advanced HIV disease associated with $CD4^+$ cell counts of $<200/mm^3$, while erythematous candidiasis and angular cheilitis are less strongly associated with late disease (152, 329, 366). The association of lower $CD4^+$ cell counts and OPC has also been established in HIV-infected women (177, 389) and children (80). Higher HIV RNA burdens are also associated with an enhanced risk of OPC and esophageal candidiasis (1, 53, 277, 329) and inversely correlated with $CD4^+$ cell counts, especially in the absence of treatment with HAART. Overall, these findings suggest that while depletion of $CD4^+$ cells below a critical threshold of 200 cells/mm^3 most often triggers the onset of OPC and esophageal candidiasis, other as yet unidentified perturbations of mucosal immunity against *Candida* appear early during the progression of HIV infection.

Impact of Antiretroviral Therapy

The introduction in 1996 of HAART including protease inhibitors dramatically reduced the prevalence of OPC (17, 68, 127, 280) and esophageal candidiasis (120, 207, 222) in HIV-infected patients. Over a period of 12 months after starting antiretroviral treatment including a protease inhibitor, significant decreases were found in the prevalence of OPC (from 30–56% to 1–9%) (17, 68, 127, 280), the number of relapses of OPC (127), the rate of asymptomatic oral carriage of *C. albicans* (280), and oral candidal burdens (17). An equally striking diminution in the incidence of *Candida* esophagitis ranging from 29 to 42% occurred during the period from 1996 to 1998 compared with the first half of the decade (pre-HAART) (120, 207, 222). A comparable decline in the incidence of esophageal candidiasis has been observed in HIV-infected children since the introduction of HAART (222).

The mechanisms underlying the dramatic impact of HAART on the incidence of OPC and esophageal candidiasis have received close attention (10, 17, 21, 39, 67, 68, 127, 292) and provide valuable insights into understanding the perturbations of mucosal defense mechanisms against *C. albicans* in HIV-infection. Several observations indicate that increases in $CD4^+$ cell counts in response to HAART confer immunologic reconstitution and a decreased incidence of opportunistic infections. Episodes of OPC and esophageal candidiasis that continue to occur despite HAART have done so at low $CD4^+$ cell counts, and patients whose $CD4^+$ cell counts have increased in response to HAART are at lower risk (17, 127, 222, 280), establishing a correlation between $CD4^+$ cell recovery and a decreased incidence of mucosal candidiasis. A three-phase T-cell reconstitution has been demonstrated after HAART, with an early rise in the number of memory $CD4^+$ cells, an improved $CD4^+$ cell reactivity to recall antigens, and a late rise in the number of naive $CD4^+$ cells (21, 22, 292). In addition, proliferative responses to the mitogen phytohemagglutinin develop in the majority of patients in whom responses were absent at baseline (10, 292), and there is increasing interleukin-2 (IL-2), IL-12, and IL-10 production (10). It could therefore be hypothesized that HAART reduces the incidence of mucosal candidiasis by reconstituting delayed-type hypersensitivity to *C. albicans* antigens and a protective mucosal Th1 response to *C. albicans* (42, 70, 211) and rectifying the shift to a nonprotective Th2 response resulting from HIV infection (83). However, in contrast to the frequent recovery of a proliferative response to phytohemagglutinin, treatment with HAART results only in late and inconsistent recovery of anticandidal cellular immunity, as assessed either by skin test reactivity for delayed-type hypersensitivity or by a proliferative response to *C. albicans* antigens (17, 67, 68, 292). These findings, associated with the resolution of refractory OPC in some HAART-treated patients well before the recovery of $CD4^+$ cell counts and response to *Candida* antigens (67, 68), indicate that the decreased incidence of OPC in patients receiving HAART cannot be fully accounted for by reconstitution of *Candida* cell-mediated immunity (67, 68). Indeed, decrease of the viral load after HAART therapy (10) may also ameliorate mucosal candidiasis by correcting a dysfunction of neutrophils induced by HIV envelope glycoprotein gp41 (143, 168, 454) or by increasing the neutrophil count in HIV-infected patients with neutropenia (127, 471). Evidence has also been presented that HAART has an early, immune reconstitution-independent inhibitory effect on *C. albicans* Saps in the oral cavities of HIV-infected patients (67), and that HIV protease inhibitors attenuate adherence of *C. albicans* to epithelial cells in vitro (39). It has been shown that *C. albicans* strains from HIV-infected patients with OPC have increased expression of Saps (107, 321), possibly enhanced by HIV envelope gp160 and gp41 binding to *C. albicans* (180). Therefore, inhibition of *C. albicans* Saps by HIV protease inhibitors may also contribute to the amelioration of OPC and esophageal candidiasis in HIV-infected patients treated with HAART.

HISTOLOGY OF THE ORAL MUCOSA

The oral mucosa has histological features in common with the vaginal and esophageal mucosas, including a superficial stratified squamous epithelium and an underlying lamina propria of dense collagenous connective tissue, separated by a basal membrane. However, the mucosa of the oral cavity varies in cellular layer composition, depending on the position and function (145, 369, 408). The lining mucosa, including that

found on the cheeks, floor of the mouth, underside of the tongue, and soft palate, represents 60% of the surface area of the oral mucosa. The stratified squamous epithelium in these areas contains a germinating layer (stratum basale) overlying the basal membrane, a spinous layer (stratum spinosum), and a superficial granular layer (stratum granulosum) and is generally nonkeratinized and therefore similar to the esophageal epithelium. The cells undergo structural differentiation as they migrate from the stratum basale to the epithelial surface (408). The masticatory mucosa, found on the gingiva and hard palate, represents 25% of the surface area of the oral mucosa and has an additional keratinized or parakeratinized surface layer resembling that of the skin but lacking a stratum lucidum (145, 369). The specialized stratified squamous epithelium of the dorsum of the tongue (15% of the surface area of the oral mucosa) contains abundant lingual papillae differentiated into four different types: filiform, fungiform, circumvallate, and foliate. The outer surface of the papillae is covered by keratinized epithelium and thus resembles the hard palate, while the interpapillary region is covered by nonkeratinized epithelium similar to that of the lining mucosa (388). The oral epithelium thus varies in the degree of keratinization, cornification, and orthokeratinous and parakeratinous layer thickness found in areas (gingiva, hard palate, and dorsal surface of the tongue) where frictional forces created by biting, chewing, or movement of food occur. Although the thickness of the human oral stratified squamous epithelium shows regional variation ranging from 190 ± 40 μm (floor of the mouth) to 580 ± 90 μm (cheeks) (388), the width of the epithelium is three to five times less in the mouse oral mucosa at each site (197).

Keratinocyte proliferation is stimulated by epidermal growth factor, transforming growth factor α, platelet-derived growth factor, and IL-1 (408). The switch between proliferation and differentiation is modulated by extracellular calcium, phorbol esters, retinoic acid, and vitamin D_3 (408). To ensure a 14- to 20-day median turnover time of oral epithelial cells (408), the keratinocytes attached to the basal membrane lose integrin expression, leading to progressive morphologic changes during migration to the mucosal surface (408). Interestingly, the turnover times of mouse palate and cheek epithelia are slightly shorter than that of tongue epithelium, and the times for all of these tissues are threefold that for epidermis (197). Keratinocytes are linked by desmosomes, which increase in number from the basal to the superficial layer of the epithelium, and by nexus-like (gap) junctions (388, 392). Polygonal and more flattened, upwardly migrating cells discharge the contents of membrane-coating granules by an exocrine process into the intercellular space, forming broad lipid lamellae containing ceramides and acylceramides which serve as a permeability barrier in the keratinized stratified squamous epithelium (399, 408, 455). In nonkeratinized epithelium, intercellular lipid is nonlamellar, contains mainly cholesterol and glycosphingolipids but no acylceramides and only small amounts of ceramide, and provides a less efficient permeability barrier (399, 408, 455). Continuous desquamation of surface keratinocytes of the oral epithelium plays a pivotal role in maintaining a healthy oral mucosa and in limiting candidal colonization and infection (378).

In several regions of the oral cavity, there are nodules of lymphoid tissue consisting of crypts formed by invagination of the epithelium into the lamina propria. These areas are extensively infiltrated by lymphocytes, which play an important role in host defense against oral infections.

ALTERATIONS IN MECHANISMS OF ORAL INNATE RESISTANCE TO *C. ALBICANS* IN HIV INFECTION

The skin and mucosal tissues represent the primary portal of entry for opportunistic pathogens, leading to life-threatening systemic dissemination in the immunocompromised host. In the normal host, however, several redundant immunological and nonimmunological defense mechanisms directly limit the proliferation of pathogenic microorganisms, thus reducing the burden of organisms available for binding to potential attachment sites. In the oral cavity, the flow and composition of saliva establish a dynamic equilibrium between *C. albicans* (361) and other members of the commensal microbiota, preventing the establishment of oral candidiasis in the normal host (37). Salivary flow protects the oral cavity by dislodging yeasts and bacteria, which are then removed by swallowing, and studies have provided evidence that this process may be facilitated by binding of *C. albicans* to salivary mucins (139, 140) or to a nonmucin proteoglycan (198, 199). In patients with Sjögren's syndrome, however, decreased salivary flow and buffering capacity are associated with an increased frequency of carriage of *C. albicans* (361) and of oral candidiasis (7). The prevalence of oral candidiasis in these patients has been estimated at about 35% (7). A similar effect is observed in patients with advanced HIV infection, in whom the salivary flow rate is reduced by 40% and is also correlated with enhanced recovery of *Candida* from saliva (258). The incidence of oral candidiasis is also enhanced in patients with acidic saliva (373), and a low pH increases the adherence of *C. albicans* to epithelial surfaces in vitro (377). Glucose supplementation of saliva augments the growth rate of *C. albicans* in vitro, and the resulting acidic pH provides the required environment for activity of *Candida* Saps, which enhance virulence by degrading a wide variety of host substrates including the mucins, which play an important role in lubrication of epithelial surfaces and host defense (89, 115, 253, 307, 363, 376, 384). The pH of the mucosa also regulates the expression of the *C. albicans* virulence genes *PHR1* and *PHR2* (108) and is thus a significant environmental signal in determining the virulence capacity of *Candida* and/or modulation of the host defenses (372). Finally, biofilm formation by *C. albicans* has been implicated in the ability of the fungus to cause persistent infection on bioprosthetic materials, including denture acrylic, as well as mucosal surfaces (75, 76). However, there were no significant quantitative differences in biofilm formation between *C. albicans* oral isolates from HIV-infected and noninfected patients, indicating that the biofilm-forming ability of *C. albicans* is unlikely to contribute to high levels of oral yeast carriage in cases of HIV infection (212).

Several salivary anticandidal proteins, including lysozyme, lactoferrin, the histatins, calprotectin, and antileukoprotease, inhibit the growth of *C. albicans* and its attachment to the oral epithelium. Because saliva from HIV-infected patients shows decreased anticandidal activity (258), several investigations have focused on identifying putative defects in salivary antimicrobial proteins which may favor oral candidiasis in HIV infection. Lysozyme and lactoferrin are two major nonimmu-

nological antimicrobial proteins in saliva which possess concentration-, time-, and strain-dependent fungicidal activity against *C. albicans* in vitro (379, 466). Lysozyme is found at a concentration range of 1.5 to 57 μg/ml of saliva (350, 419), and its antifungal properties are thought to be mediated by the enzymatic hydrolysis of N-glycosidic linkages in the microbial cell wall and injury to the cytoplasmic membrane following direct cationic-protein binding (279). Interestingly, concentrations of salivary lysozyme are increased in HIV-infected patients with or without oral candidiasis (20, 199, 274, 467), and a trend toward progressive in vitro resistance to lysozyme has been observed in genetically similar, sequential oral *C. albicans* isolates from patients infected with HIV (379). Because the concentration of lysozyme is increased in HIV-infected patients while the anticandidal activity of saliva is decreased, the contribution of salivary lysozyme to limiting the proliferation of *C. albicans* in the oral cavity of these patients appears doubtful.

Lactoferrin is a member of the transferrin family of nonheme iron-binding glycoproteins and is found at the mucosal surface, where it functions as a prominent component of the first line of host defense against infection (452). The concentration of lactoferrin in unstimulated saliva is about 7 to 20 μg/ml (126, 371), and its fungicidal activity against *C. albicans* (404) has been attributed not only to sequestration of ferrous ions (284) but also to structural damage to the fungal cell wall (313) and activation of intracellular autolytic enzymes (243). Salivary concentrations of lactoferrin in patients with HIV infection have been variously reported to be increased (20, 258), unchanged (276), or decreased (266, 300). These variable results have been at least partly ascribed to the source of the saliva, because increased concentrations of lactoferrin in HIV infection have been found in submandibular but not parotid saliva (20, 258, 274). The predisposition to oral candidiasis in HIV-infected patients is thus not convincingly associated with defective production of lactoferrin. In contrast to lysozyme, serial genotypically identical oral isolates of *C. albicans* from HIV-infected patients did not develop progressive in vitro resistance to lactoferrin (379). The therapeutic potential of lactoferrin for the treatment of OPC has recently led to the development of mucoadhesive lactoferrin tablets with fungicidal activity against *C. albicans* and *C. glabrata* (239). This novel approach to the treatment of mucosal candidiasis will require further validation in clinical trials.

The family of salivary histatins consists of at least 12 low-molecular-weight, structurally related, histidine-rich, cationic proteins, which also contribute to nonimmunological host defense of the oral mucosa (138, 437). The histatins have broad fungicidal activity against pathogenic fungi, including *C. albicans, Cryptococcus neoformans*, and *Aspergillus fumigatus* (194), and are present at 50 to 425 μg/ml (244) in the saliva of healthy adults. Histatin 5, which exerts potent candidacidal activity (138), is internalized by *C. albicans*, inhibits the respiration of mitochondria, and induces the formation of reactive oxygen species leading to mitochondrial and cytoplasmic membrane damage, efflux of ATP and other nucleotides, and cell death (183, 194). The mechanism of action of the histatins is thus distinct from that of other cationic peptides such as the defensins, which can directly insert into and disrupt cell membranes because of the strongly amphipathic nature of their α-helical structures (138). The concentration of histatins in the saliva of HIV-infected patients has been determined to be increased (20) unchanged (258), or decreased (244, 274), and these seemingly discordant results may have been caused by the different stages of HIV infection among the patients under study as well as by the analytical methods employed. However, decreased concentrations of histatins appeared to correlate with an increased tendency to oral candidiasis in a subgroup of HIV-infected patients (274), suggesting that decreased histatin concentrations and/or an inability of these proteins in saliva to interact with *C. albicans* may contribute to the defective salivary anticandidal activity seen in HIV-infected patients (244). Interestingly, transfer of the gene encoding histatin 3 in the salivary glands of rats by using recombinant adenovirus vectors resulted in its expression at up to 1,045 μg/ml of saliva, suggesting that a gene transfer approach to overexpression of naturally occurring antifungal proteins may be potentially useful in the management of mucosal candidiasis (317).

The heterodimeric calcium- and zinc-binding protein calprotectin is produced by PMNs, monocytes, macrophages and mucosal keratinocytes (54, 73, 403). In vitro, calprotectin quantitatively inhibits the growth of *C. albicans* by depriving the fungus of zinc, which is essential for microbial growth (138). Salivary calprotectin concentrations and oral keratinocyte expression of calprotectin are augmented in response to oral candidiasis, in both HIV-infected and -uninfected patients (146, 231, 424). However, the results of two independent studies demonstrated that salivary concentrations of calprotectin are deficient in HIV-infected patients with oral candidiasis or high salivary *Candida* counts compared to those in HIV-infected patients without oral candidiasis or with low salivary *Candida* counts (298, 424). These results suggested that a diminution of this antimicrobial factor may predispose to oral candidiasis in HIV infection. On examination of the oral mucosa of HIV-infected patients with OPC, however, *Candida* hyphae were found to penetrate through the epithelial parakeratin layer yet did not extend beyond the zone of spinous-layer keratinocyte calprotectin expression (147). Further studies are required to determine whether reduced salivary calprotectin is not simply associated with but directly contributes to the predisposition to oral candidiasis in HIV-infected patients.

Antileukoprotease (436), also known as secretory leukocyte protease inhibitor (141), is produced by keratinocytes (457) and constitutes the last member of the family of antimicrobial proteins involved in nonimmunological defense against *C. albicans* at mucosal sites. Like other cationic antimicrobial polypeptides, the antimicrobial activity of antileukoprotease is limited to conditions of low ionic strength. In addition to its inhibition of leukocyte-derived proteinases, antileukoprotease has fungicidal activity by an unknown mode of action against *C. albicans* which is localized primarily in the NH_2-terminal domain (436) and it may thus play an important role in the innate mucosal defense. Interestingly, antileukoprotease exhibits anti-HIV-1 activity in vitro and may contribute to the antiviral activity of saliva associated with the infrequent oral transmission of HIV-1 (287).

ORAL MUCOSAL IMMUNE SYSTEM AND HOST DEFENSES AGAINST *C. ALBICANS*

Cells with Immune Potential in the Oral Mucosa

The oral mucosa is continuously challenged by the resident microbial flora and occasionally by microbial pathogens; it is therefore armed with several cell populations which individually, or in association, can produce a protective innate or acquired immune response. Mucosal cell populations with immune potential include Langerhans' cells, macrophages, αβ- and γδ-T cells, keratinocytes, and PMNs. We now review the specific properties of these cell populations and their role in host defense.

Lymphoid cells. The oral mucosal immune system possesses features in common with both the skin immune system and the mucosal immune system (442). The normal oral mucosa shares with normal skin an absence of B lymphocytes, which are present in the mucosal immune system (50, 442). In contrast to the skin, however, T lymphocytes in the normal human oral mucosa are not organized in rows around postcapillary venules of the superficial and deep vascular networks (50) but are distributed singly or in small clusters on both sides of the basal membrane (442). In addition, T lymphocytes are only rarely found in the more superficial layer of the epithelium. The oral mucosal epithelium contains about 37 times as many T lymphocytes as the epidermis of normal skin (442). The vast majority of T lymphocytes in the oral mucosa express the memory $CD45R0^+$ phenotype (86, 340). T lymphocytes within the oral epithelium are not activated ($CD25^-$), in contrast to $CD25^+$ T cells in the underlying stroma (86). The conversion of T cells from the naive $CD45RA^+$ to the memory $CD45R0^+$ phenotype requires repeated antigenic stimulation, suggesting that apoptotic $CD25^-$, $CD45RA^+$ intraepithelial T cells die after unsuccessful antigen presentation by Langerhans' cells (86).

The CD4/CD8 ratio of 1:2 in the human oral epithelium and 1:4 in the skin indicates the preferential presence of the $CD8^+$ subset in both sites, but $CD4^+$ cells are proportionately more frequent in the oral mucosa than in the skin (442). However, a CD4/CD8 ratio of 1 within the epithelium of the normal human gingiva indicates regional variation in the oral cavity (86). In contrast to normal humans, $CD4^+$ cells are twice as numerous as $CD8^+$ cells in the normal murine oral mucosa (47). $CD4^+$ T cells are required for a Th1-type protective response against oral candidiasis in mice (149) and therefore play a central role in host defense against OPC.

Of direct relevance to host defense against OPC in HIV infection, the buccal epithelium is an inductive site for the generation of cytotoxic T-lymphocyte responses mediated by major histocompatibility complex (MHC) class I-restricted $CD8^+$ T cells, independent of $CD4^+$ cell help (119). It has been suggested that $CD8^+$ T lymphocytes are attracted to the epithelium by IL-8 produced by keratinocytes (267, 442). Moreover, IL-2 (but not gamma interferon [IFN-γ])-activated $CD8^+$ cells exert direct growth inhibition against the hyphal form of *C. albicans* (40). However, $CD8^+$ cells may not be in proximity to *C. albicans* hyphae, which are usually confined to the upper layers of the epithelium (72, 147, 357). Alternatively, $CD8^+$ cells may produce cytokines which enhance the antimicrobial activity of macrophages and neutrophils against *C. albicans*. In addition, MHC class I molecules expressed constitutively on keratinocytes may represent a target for $CD8^+$ cytotoxic T lymphocytes after internalization by keratinocytes of microbial pathogens (448).

γδ T cells represent at most 2% of the T-cell population in the human oral epithelium (331). Oral mucosal γδ T cells display ultrastructural features typical of large granular lymphocytes, also found in cytotoxic $CD8^+$ and NK cells (267), and probably represent a first immunologic line of defense. γδ T cells are located within the epithelium in both normal and inflamed gingiva, often in close proximity to $CD1a^+$ and/or $CD1c^+$ Langerhans' cells and keratinocytes (268). In inflamed mucosa the γδ T cells show the phenotype of activated cells ($CD45RO^+$, $CD8^+$, or $CD4^+$), whereas in normal mucosa the cells are $CD4^-$ $CD8^-$ and express CD45RA (268). In the connective tissue, under the basal membrane, $V\delta2^+$ γδ T cells are predominant, whereas the epithelium contains mostly $V\delta1^+$ γδ T cells (206, 331). γδ T cells participate in the immune response to microbial pathogens including *C. albicans* by producing cytokines such as IFN-γ (213, 267) or by direct cell-to-cell contact leading to cytotoxicity (267, 303). Increases in the numbers of γδ T cells have been found in the oral mucosa soon after mice are colonized and infected with *C. albicans* (71), coinciding with resolution of infection.

Finally, natural killer (NK) cells are large granular lymphocytes which represent 6 to 39% of human gingival (268) and 3% of lower lip (283) mononuclear cells. NK cells are cytotoxic in vitro to certain tumor cell lines and to virally infected cells (72) and have direct antimicrobial activity against *Cryptococcus neoformans* (256) but little or no effect against *C. albicans* hyphae in vitro (40).

Langerhans' cells. Langerhans' cells develop from bone marrow stem cells as one of three distinct subsets of dendritic cells (DCs) which home in to selected tissues (30, 99, 448). The bone marrow stem cells appear to be common precursors of both macrophages and DCs (30). Serving as an essential link between innate and acquired immunity, dendritic cells function as antigen-presenting cells (APCs) that patrol all tissues of the body, capturing pathogens for processing and presentation to T cells in the secondary lymphoid organs. Two subsets of human DCs, Langerhans' cells and interstitial (or dermal) DCs, belong to the myeloid lineage, while the third subset is composed of lymphoid DCs (99). Culture of human $CD34^+$ hematopoietic progenitors in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor alpha (TNF-α) gives rise to $CD1a^+$ DCs related to Langerhans' cells and $CD14^+$ DCs closely related to interstitial DCs, which can differentiate into macrophages in the presence of M-CSF (69). DCs are thus phenotypically and functionally heterogeneous depending on their specific differentiation pathways (11, 468, 469). Serving as sentinels for pathogen entry at the epithelium of the skin and mucosa, Langerhans' cells, identified by expression of CD1a, Lag, and langerin, are localized on the basal and suprabasal layers and represent 2 to 4% of the cells in the epithelium (6, 34, 49, 59, 96, 99, 103, 216, 245, 262, 351, 356, 365, 390, 391, 442). These cells express MHC class II molecules and are also $CD11b^+$ and $CD11c^+$. Langerhans' cells have a pronounced dendritic shape and contain rod-shaped organelles called Birbeck granules. Immature epithelial Langerhans' cells are equipped to capture antigens by

phagocytosis, macropinocytosis, and receptor-mediated absorptive endocytosis, including the macrophage mannose receptor, DEC-205, as well as Fcγ and Fcε receptors (30). The loose interaction of DC-specific, ICAM-3 grabbing, nonintegrin (DC-SIGN) with ICAM-3 establishes the initial contact of the Langerhans' cell with a resting T cell in the apparent absence of foreign antigen (416). To successfully present antigens for T-cell activation, Langerhans' cells must undergo a maturation process (334) triggered by whole bacteria, bacterial lipopolysaccharide, cytokines such as TNF-α and IL-1β, or the T-cell CD40 ligand (CD40L) (30, 99, 216, 458). Mature Langerhans' cells lose the ability to take up antigens but express surface molecules required for communication with T cells at the immunologic synapse (416). During maturation, Langerhans' cells express high levels of surface MHC class I and II and the costimulatory molecules CD54, CD58, and CD86 that interact with receptors on T cells to enhance adhesion (30, 99, 416). In addition, high CD40 expression on mature Langerhans' cells favors binding to CD40L on T cells, which in turn up-regulates the expression of CD80 and CD86, secretion of IL-12, and release of chemokines such as IL-8 and macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β) (30). Antigen presentation via MHC class II molecules in the presence of IL-12 and collaborating IL-18 induces $CD4^+$ cells to differentiate into IFN-γ-producing Th1 cells, leading to activation of the antimicrobial properties of macrophages, and is therefore critical to the induction of a protective acquired cell-mediated immune response (30, 99, 308). Furthermore, Langerhans' cells receiving T-cell help mediated by CD40-CD40L interactions (385) can also present antigen on MHC class I molecules to cytotoxic $CD8^+$ cells, which can be loaded through both endogenous and exogenous pathways (30, 99). More recent work, however, indicates that Langerhans' cells do not need to receive a signal from T cells to become fully mature DCs capable of stimulating $CD4^+$ T cells and cytotoxic $CD8^+$ T cells (110). Interestingly, the murine oral mucosa is an inductive site for priming class I-restricted $CD8^+$ cytotoxic T cells in vivo (119). The expression of MIP-3α by TNF-α-stimulated keratinocytes in the spinous layer (77, 435) and the production of defensins (464), which both recognize the CCR6 chemokine receptor in immature DCs, may explain the positioning of Langerhans' cells in the epidermis and their ready access to microbial pathogens (99). The mobilization of Langerhans' cells and their migration via afferent lymphatics to draining lymph nodes for antigen presentation (208) is governed by the upregulation of the chemokine receptor CCR7 and the production of MIP-3β (405). In addition, IL-18 produced by Langerhans' cells and keratinocytes also contributes to the regulation of Langerhans' cell migration by a TNF-α and IL-1β-dependent mechanism (98).

In normal humans, the density of Langerhans' cells in nonkeratinized oral mucosa is apparently the same as in the skin, but keratinized oral mucosa has fewer Langerhans' cells (96, 103, 442). Although murine palate implants are repopulated by Langerhans' cells within 2 weeks (365), the numerical densities of Langerhans' cells in old mice is reduced compared with that in young mice (364). At the ultrastructural level, murine and human Langerhans' cells in the oral mucosa exhibit no significant differences (59). In the normal human oral mucosa, however, Langerhans' cells present a highly variable morphology according to their epithelial location (391). In contrast to the upper epithelium, where $CD1a^+$ Langerhans' cells have long dendrites forming a network, Langerhans' cells in the basal layer are more rounded and have very few short dendrites. Functionally, the well-developed dendritic morphology of Langerhans' cells in the upper epithelium could reflect optimal immune surveillance (391). Conventionalization of germfree mice with a bacterial flora results in enhanced migration of Langerhans' cells to the oral epithelium (49), and the densities of oral epithelial Langerhans' cells are increased in patients with chronic periodontitis compared to healthy controls (216), demonstrating that Langerhans' cells are recruited to the oral epithelium in response to a bacterial challenge. Purified human (35) or rat (192) oral mucosal Langerhans' cells can serve as APCs in vitro and are more efficient than skin Langerhans' cells in providing costimulatory signals to T cells (193). *C. albicans*-specific T-cell activation by human epidermal Langerhans' cells (85, 223) requires not only the ligation of the T-cell receptor to the antigen-MHC complex but also costimulation by the combination of adhesion molecules CD54 and CD58 with CD11a and CD2 on T cells, respectively (433). As described in further detail below, productive infection of oral mucosal Langerhans' cells by HIV-1 may contribute to their selective depletion (81) and perturb their ability to generate a primary immune response (44), which may impair protective mucosal immunity against colonization and infection by opportunistic microbial pathogens. In addition, Langerhans' cells serve as the portal of entry for HIV-1 at mucosal sites and are critical to the initiation and subsequent spread of infection to draining lymphoid tissue (340).

Keratinocytes. Keratinocytes are of primary importance in the pathogenesis of OPC since they constitute a physical barrier after adhesion of *C. albicans* to the epithelial surface. In addition to their role as a mechanical barrier, epithelial keratinocytes function as fixed or immobile immunocytes and are capable of producing a number of soluble factors and expressing receptors that are involved in up-regulating and down-regulating immune responses (179, 415, 440). The major growth factors produced include basic fibroblast growth factor, platelet-derived growth factors, transforming growth factors α and β, and TNF-α. Keratinocytes also produce several cytokines including IL-1, IL-3, IL-6, IL-7, IL-8, IL-10, IL-12, IL-15, IL-18, and IL-20, and a number of CSFs such as GM-CSF, G-CSF, and M-CSF (14, 45, 179, 440, 448). Under normal conditions, most of these mediators are not constitutively produced (162), but their gene expression and release is up-regulated during inflammation by a variety of external stimuli derived from leukocytes, Langerhans' cells, and keratinocytes themselves, including IFN-γ, TNF-α and IL-17 (14, 241, 257, 282, 432, 448). Interestingly, mRNA expression of IL-1α, IL-1β, IL-8, GM-CSF, and TNF-α is up-regulated in experimental cutaneous *C. albicans* infection with reconstituted human epidermis, demonstrating that the fungus induces a brisk cytokine response by host keratinocytes (383). *C. albicans* also triggers the production of IL-1α and TNF-α (410), as well as GM-CSF (131), by primary oral epithelial cells and oral epithelial cell lines in vitro. In addition, proteolytic activation of the IL-1β precursor by *C. albicans* Sap (38) suggests that candidal proteinases may contribute to the activation and maintenance of the inflammatory response at the epithelial surface. IL-1, IL-8,

and IL-12 possess attractant effects on PMNs, macrophages, and lymphocytes (448). In addition, some of the cytokines produced by keratinocytes (IL-1 and TNF-α) promote the maturation of DCs and therefore could differentially modify the ability of Langerhans' cells to respond to antigens (448). Keratinocyte-derived IL-7 and IL-15 are involved in epidermal T-cell trafficking (179, 448). In addition to the production of soluble factors, keratinocytes express the adhesion molecules CD54 and CD58, and CD54 expression is increased by IFN-γ (136, 448). MHC class I molecules are expressed constitutively and may be a target for $CD8^+$ T cells (448). MHC class II molecules are not expressed constitutively but can be induced by IFN-γ produced by infiltrating T lymphocytes (448). Keratinocytes may function as accessory cells in antigen presentation and interact with lymphocytes to produce a Th2 cytokine response (448).

Of potential relevance to the fragile equilibrium between epithelial colonization and infection, IFN-γ promotes expression of the glycoprotein desquamin, a cell adhesion molecule in the stratum corneum of the human epidermis which possesses lectin-like properties for amino sugars (58), as well as trypsin-like serine proteinase (57) and RNase (393) activity. Desquamin may thus play a crucial role in desquamation and shedding of *Candida* from the superficial portion of the epithelium.

In addition to these indirect mechanisms, keratinocytes possess several potential antimicrobial mechanisms which may directly contribute to host defense against *Candida*. (i) Keratinocytes have been shown to express inducible nitric oxide synthase activity (43), and NO has been associated with candidacidal activity and resistance to mucosal candidiasis (213). (ii) Human oral keratinocytes produce numerous antimicrobial peptides, including β-defensins 1 to 3 (134, 135, 191, 261, 281, 387), cathelicidins (132, 166, 167, 182, 465), adrenomedullin (220, 221), calprotectin (54, 73, 146, 147, 231, 298, 370, 403, 424), and bactericidal/permeability-increasing protein (BPI) (61), which, as natural antibiotics, contribute to the innate immunity of the epithelium (170, 453). β-Defensins exhibit potent antimicrobial activity against *Candida* (387), and their expression by keratinocytes at the mRNA and protein level is enhanced by TNF-α, IL-1β, whole bacteria, and bacterial lipopolysaccharide (191, 261, 281, 387). Although epithelial injury or inflammatory disorders augment the expression and release of the human cathelicidin LL-37 from keratinocytes (132, 166), its antimicrobial activity in vitro has so far been demonstrated only against bacteria and the MBCs against *Candida* species are >100 μg/ml (182). In addition to their direct antimicrobial properties, human β-defensins and the cathelicidin LL-37 are chemotactic for immature DCs and neutrophils and for monocytes and T cells, respectively (465). Secretion of the vasoactive peptide adrenomedullin from oral keratinocytes is stimulated by IL-1α, IL-1β, TNF-α, LPS, and live bacteria but not by *C. albicans* (220, 221). Although adrenomedullin possesses antimicrobial properties, it is not yet known whether it contributes to host defense against oral candidiasis. As outlined previously in this review, oral keratinocytes also express calprotectin, a heterodimer of MRP8 and MRP14 with antimicrobial activity against *C. albicans*. The up-regulated expression of calprotectin by oral keratinocytes in response to infection has been investigated in vitro and appears to be independent of IL-1β (370). Finally, keratinocytes express on their cell membranes BPI, which is also an abundant constituent of PMNs (61, 170). BPI on keratinocytes contributes to the killing of gram-negative bacteria that become closely adherent to epithelial cells (61, 170). The role, if any, of BPI in limiting *C. albicans* colonization or infection of the oral mucosa remains to be determined. (iii) Human oral keratinocytes directly inhibit the growth of blastoconidia and/or hyphae of *Candida* species in vitro, with a strict requirement for cell contact (411). Growth inhibition appears to involve a carbohydrate moiety on the surface of the keratinocytes but is not mediated by phagocytosis, nitric oxide, superoxide-hydrogen peroxide pathways, or defensin and calprotectin antimicrobial peptides (412). Direct growth inhibition of *Candida* by oral keratinocytes appears to occur through a novel and distinct mechanism, complementary to other components of the antimicrobial armamentarium of oral keratinocytes. Oral epithelial keratinocytes are thus equipped with numerous redundant defense mechanisms, acting either directly or indirectly against the continuous microbial challenge at the oral mucosal surface. The role of keratinocytes in host protection against *Candida* at mucosal surfaces appears likely, since *C. albicans* hyphae are restricted to the upper layers of the oral epithelium in OPC and are some distance away from lymphocytes and Langerhans' cells located in deeper layers.

Macrophages and PMNs. Macrophages and PMNs originate from monoblasts and myeloblasts, distinct populations of myeloid stem cells which differentiate into monocytes and neutrophils in the bloodstream. In the normal uninfected host, circulating monocytes differentiate into resident tissue macrophages, in contrast to PMNs, which are retained almost exclusively within the circulation. Because of their key role in the innate immune response (289), these two cell populations are critical effectors in the first line of defense against oral microbial pathogens. In the normal human oral mucosa, macrophages are located mainly in the lamina propria (86) while PMNs appear in the lamina propria and epithelium only in response to inflammation (268). Macrophages are not a homogeneous cell population but can be separated into biologically active subpopulations which appear at early, intermediate, or late stages of inflammation (185).

Oral mucosal resident macrophages express MHC class II molecules and CD11b, as well as Fc receptors that bind IgG (FcγR) (31). Like Langerhans' cells, macrophages present antigenic peptides to $CD4^+$ T cells after induction of CD86 costimulatory molecules (112, 113). Th1 $CD4^+$ T cells secrete IFN-γ and IL-2, which activate both macrophages (97) and $CD8^+$ cytotoxic T cells to kill intracellular pathogens (113). After activation, macrophages produce TNF-α, which activates PMNs, further amplifying the innate immune response (19). For this reason, macrophages play a critical dual role at the crossroads of innate and acquired cell-mediated immunity. Indeed, activation of a specific T-cell response to *C. albicans* antigens in vitro has been found to require macrophages expressing MHC class II molecules (314).

To date, Langerhans' cells, monocytes, macrophages, and PMNs are the only cells that have been reported to be candidacidal (132a, 213, 310). Macrophages and PMNs have the ability to kill both *C. albicans* blastoconidia and hyphae by both oxygen-dependent and -independent mechanisms (446). Oxy-

gen-dependent killing by PMNs is mediated by superoxide anion and the myeloperoxidase-hydrogen peroxide-halide system, with the added participation of reactive nitrogen intermediates including NO and peroxynitrite in the candidacidal activity of macrophages which lack myeloperoxidase (446). Production of IFN-γ by γδ T cells augments NO production by macrophages and enhances resistance to orogastric candidiasis, indicating that γδ T cells indirectly contribute to macrophage killing of *C. albicans* (213). Macrophages and PMNs are also equipped with oxygen-independent mechanisms including the cationic protein defensins (446) and calprotectin (54, 73, 403), demonstrating the use of an extensive array of oxidative and nonoxidative mechanisms to kill *C. albicans* blastoconidia and hyphae (446).

In experimental OPC in the mouse model, the early inflammatory response 24 to 48 h postinfection is composed of large numbers of PMNs migrating from the lamina propria to accumulate in the superficial epithelial layers (242). During recovery from primary infection, at 5 to 6 days postinfection, the initial influx of PMNs is replaced by a massive recruitment of macrophages in the lamina propria (71). The presence of both macrophages and PMNs in experimental candidiasis concurs with similar histologic findings in HIV-infected patients with OPC, suggesting a major role for these professional phagocytes in mucosal containment of *C. albicans*.

Mechanisms of Protective Cellular Immunity to *C. albicans* in the Oral Mucosa

A foundation for understanding the complex mechanisms critical to host defense against *C. albicans* at mucosal sites was provided by a large body of work conducted with experimentally infected, congenitally immunodeficient mice (26, 27, 63, 64, 209, 210, 309, 446), as well as in intact (94) or knockout (28) mice depleted of specific factors ($CD4^+$ cells or IFN-γ). These studies demonstrated that functional T cells play a role in resistance to *C. albicans* colonizing or infecting mucosal surfaces and that an added defect of phagocytes is required to produce dissemination of *C. albicans* from the gastrointestinal tract (63, 209). Further investigation showed that, although Th1 and Th2 $CD4^+$ cells are involved in recovery from primary gastrointestinal candidiasis in immunocompetent mice, activation of a Th1 response occurs in animals that show delayed-type hypersensitivity to *Candida* and protection after a second gastrointestinal inoculation (70). Studies of B-cell knockout mice demonstrated that antibodies do not play a role in protection against mucosal candidiasis or dissemination from the gastrointestinal tract (449). However, a protective role of antimannan antibodies has been demonstrated in experimental vaginal candidiasis (106, 184). Overall, these investigations have produced the current paradigm of a central role for a Th1 $CD4^+$ response in host defense against mucosal candidiasis (42, 70, 211, 406).

In contrast to gastrointestinal and vaginal candidiasis, relatively few hypothesis-driven, cause-and-effect investigations have been conducted to specifically elucidate the mechanisms of host defense against *C. albicans* in the oral mucosa (157). The accumulated evidence indicates that normal host defense against OPC is the sum of individual redundant mechanisms which include several salivary anticandidal proteins, growth inhibition of *C. albicans* by oral keratinocytes, and the presence of T-cell-mediated delayed-type hypersensitivity to *C. albicans*. The evidence implicating anticandidal proteins and oral keratinocytes, described in previous sections of this review, has so far been derived solely from observations of in vitro activity against *C. albicans*. Although their role in host defense appears likely, no direct demonstration has been presented using compelling approaches such as their depletion, augmentation, or transfer in an experimental model of OPC. Consequently, mechanistic investigations of host defense in experimental OPC have been focused almost entirely on dissecting the precise role of an acquired cell-mediated immune response to *C. albicans*.

Although this has not yet been directly studied in experimental OPC, oral mucosal Langerhans' cells are most probably involved in the initiation of an acquired cell-mediated immune response to *C. albicans*. Both human (310) and murine (132a) DCs recognize *C. albicans* by the mannose-fucose receptor, can phagocytose and degrade *Candida*, and can subsequently present *Candida* antigens to T cells. Interestingly, the yeast and hyphal forms of *Candida* are ingested by different mechanisms and receptors. Phagocytosis of the yeast cells by DCs occurs by coiling phagocytosis, characterized by the presence of overlapping bilateral pseudopods, whereas ingestion of hyphae occurs through a more conventional zipper-type phagocytosis (132a). Human DCs kill *Candida* as efficiently as human monocyte-derived macrophages do, and killing appears to be mainly oxygen independent, possibly via lysosomal hydrolases (310). In contrast, killing of *C. albicans* yeast cells or hyphae by murine DCs is correlated with the production of NO (132a). The T-cell proliferation observed with a mixture of human DCs, *Candida*, and T cells most probably represents a secondary immune response, since *C. albicans* is a commensal in humans (310). However, analogous experiments conducted using murine DCs required the presence of IL-2 to elicit a priming response since *C. albicans* is not a commensal organism in mice (132a). In vitro, ingestion of the yeast form of *C. albicans* activated DCs for IL-12 production and priming of Th1 cells whereas ingestion of hyphae inhibited IL-12 and Th1 priming and induced IL-4 production (132a). The pivotal role of DCs in initiating the immune response to *C. albicans* was elegantly demonstrated by the generation of protective immunity against intravenous infection after injection of DCs ex vivo pulsed with *C. albicans* yeasts but not hyphae (132a). Yeast-pulsed DCs from IL-12 knockout mice primed lymphocytes for IL-4 production in vitro and were unable to confer resistance to candidiasis (132a), consistent with the lack of Th1 response development (272). Finally, work from the same group showed that murine DCs pulsed with yeast but not hyphal RNA induce protective immunity to *C. albicans* in allogeneic bone marrow-transplanted mice (24).

In addition to Langerhans' cells, macrophages and keratinocytes could be potentially involved in the processing and presentation of *Candida* antigens to $CD4^+$ cells and could therefore also participate in the induction of an adaptive immune response to *C. albicans* in the oral cavity. Keratinocytes of the reproductive tract express MHC class II molecules and can function as APCs (459). In addition, expression of MHC class II molecules by epithelial keratinocytes is enhanced in patients with angular cheilitis (320) or OPC (214), possibly in response

to IFN-γ produced by infiltrating T lymphocytes (18, 448). However, the ability of oral keratinocytes to engage in presentation of *Candida* antigens is uncertain, since these cells do not appear to have the capacity to engulf *C. albicans* (412), and the epithelial $CD4^+$ cells are located above the basement membrane and therefore not in proximity to the superficial keratinocyte layer where *C. albicans* is localized. Although not formally demonstrated in OPC, the participation of macrophages in *Candida* antigen presentation is more likely, since these cells are a prominent component of the innate immune response to *C. albicans* and fulfill all the requirements for engulfment, killing, and presentation of *C. albicans* antigens to $CD4^+$ cells (18, 173, 314). Of direct relevance to this process, the ability of human monocytes to phagocytose the yeast but not the hyphal form of *C. albicans* is correlated with enhanced induction of IL-12, again indicating that *C. albicans* yeasts are specifically involved in promoting Th1 protective immunity (79).

The initiation of the mucosal immune response to *C. albicans* in OPC requires the maturation and mobilization of the Langerhans' cells (30) resulting either directly from exposure to *C. albicans* or from cytokines produced by the T-cell response to infection (30). Maturation of DCs, including mucosal Langerhans' cells, is characterized by a strong up-regulation of MHC class II expression, secretion of IL-12, and expression of the adhesion molecules CD54, CD58 and CD86 (30). Enhancement of MHC class II expression on APCs by coculture with *C. albicans* or exposure to *C. albicans* antigens has been demonstrated in vitro (18), in accordance with the ability of microbial pathogens and their products to directly induce the maturation of DCs (30, 458). Cytokines such as IL-1, GM-CSF, and TNF-α, as well as the T-cell ligand CD40L, which binds CD40 on dendritic cells, may also contribute to maturation of Langerhans' cells in mucosal candidiasis (30). MHC class II alloantigens (173, 314, 433) and the adhesion molecules CD54 and CD58 (433) are all directly involved in *Candida*-specific T-cell activation by APCs and therefore most probably participate in this critical step in the afferent limb of the specific immune response in OPC.

Several lines of evidence in support of the protective role of acquired cell-mediated immunity in OPC have been presented by Ashman and colleagues, using experimentally infected mice (142, 149, 150). The differences between the colonization patterns of *C. albicans* in infection-resistant BALB/c mice and infection-prone DBA/2 mice following oral inoculation correlated with both *Candida* antigen-specific T-cell proliferation and early expression of IL-4, IFN-γ, and IL-12 in cervical lymph nodes, supporting the concept of a balanced Th1 and Th2 response in clearing OPC (142). A constitutive mixed Th1/Th2 cytokine expression (Th0) was also found in whole saliva of healthy HIV-negative individuals with (251) or without (252) *Candida*-associated denture stomatitis. Although associated with a Th2 response, IL-4-enhanced resistance to OPC may be mediated by the promotion of a protective Th1 response (291) and by enhanced killing of *Candida* by both PMNs (46) and macrophages (153). Although systemic depletion of $CD4^+$ cells alone did not increase the severity of oral infection in immunocompetent BALB/c and CBA/CaH mice (150), reconstitution of immunodeficient BALB/c and CBA/CaH *nu*/*nu* mice with naive $CD4^+$ but not $CD8^+$ T cells significantly decreased oral colonization compared to that in controls and was correlated with expression of IL-12 and IFN-γ in cervical lymph nodes (149), demonstrating the direct requirement for T lymphocytes in recovery from OPC. The depletion of PMNs and the inactivation of monocytes/macrophages increased the severity of infection in immunocompetent BALB/c and CBA/CaH mice, clearly demonstrating the critical role of these professional phagocytes in the efferent limb of the immune response (150). It thus appears that the clearance of OPC is dependent on $CD4^+$ T-cell augmentation of monocyte/macrophage and PMN functions exerted by Th1-type cytokines such as IL-12 and IFN-γ (150). A significant expansion of γ/δ T cells in the cervical lymph nodes was demonstrated after oral inoculation of *C. albicans* (142), and these cells may also augment the function of phagocytes by their production of IFN-γ and indirectly contribute to clearing OPC, as previously demonstrated in experimental gastrointestinal candidiasis (213).

PATHOGENESIS OF OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASES IN HIV/AIDS

Evidence Implicating *C. albicans* Virulence Factors

The ability of *C. albicans* to colonize, penetrate, and damage host tissues depends on imbalances between *Candida* virulence attributes and specific defects in host immune defenses. *C. albicans* possesses a multiplicity of properties, including adhesins, dimorphism, phenotypic switching, molecular mimicry of mammalian integrins, and secretion of hydrolytic enzymes, each with a low propensity for enhancing fungal infection and none necessarily dominant, and all, even in combination, unable to fully overcome intact host defenses (319). Hydrolytic enzymes are probable virulence factors in pathogenic *Candida* species (reviewed in references 87, 100, 109, 202, 203 and 456). Among these, *C. albicans* Saps, under the control of a multigene family (*SAP1* to *SAP10*) expressing distinct isoenzymes that are regulated differentially at the mRNA level in vitro (204, 295, 456), are implicated in the breakdown of several host substrates (202). Evidence has been presented that phospholipase B, expressed by at least two genes (*PLB1* and *PLB2*) (249, 421), also contributes to the pathogenesis of candidiasis by the degradation of host tissues (172, 205).

Several lines of evidence implicate Saps in the pathogenesis of OPC in the setting of HIV infection. Sap antigens have been detected on the surface of blastoconidia and hyphae adhering to human oral mucosa (48), and *C. albicans* isolates from HIV-infected patients with OPC not only exhibited enhanced adherence to buccal epithelial cells (423) but also produced higher Sap levels in vitro than did strains isolated from an HIV-negative control group (107, 321, 462). In addition, in vivo expression of individual members of the *C. albicans SAP* gene family was found to be differentially regulated in a murine model of esophageal candidiasis (409), during oral infection in intact and HIV-1 Tg mice (363), and in HIV-positive and -negative patients with OPC (307). Specifically, assessment of the expression of the *SAP1* to *SAP6* genes by in vivo expression technology revealed that the *SAP5* and *SAP6* genes were strongly activated at a single time point examined during infection of the esophageal mucosa in experimentally infected, immunocompromised mice whereas only low-level expression

of *SAP1* to *SAP4* occurred (409). A controlled sequential reverse transcription-PCR analysis of the temporal expression of individual members of the *SAP* gene family was conducted in a model of OPC in intact and transgenic mice that expressed HIV-1 and developed an AIDS-like disease (363). In contrast to the sustained expression of other *SAP* genes, *SAP7* and *SAP8* were conspicuously distinguished by their transient expression in both intact and transgenic mice. *SAP5* and *SAP9* were most strongly expressed throughout the course of infection in the transgenic mice (363). In accordance with these findings, reverse transcription-PCR analysis of the in vivo expression of the *SAP1* to *SAP7* genes on single samples of saliva, collected from a limited number of HIV-positive and -negative patients with OPC, revealed that *SAP2* and *SAP4* to *SAP6* were uniformly expressed and that all seven *SAP* genes were simultaneously expressed in some patients (307). Expression of specific *SAP* genes was comparable in HIV-positive and -negative patients with OPC (307) and in immunocompetent C3H and DBA/2 mice, non-Tg controls, and HIV-1 transgenic mice (363), indicating that the HIV status does not in itself alter *SAP* expression. Finally, a temporal progression of *SAP* expression in the order *SAP1* and *SAP3*, *SAP6*, and *SAP2* and *SAP8* was observed in an in vitro model of OPC that made use of reconstituted human epithelium (384). Taken together, these results suggest that some *SAP* gene products may be involved in specific steps in the onset, progression, and maintenance of OPC in HIV infection by their ability to degrade particular host substrates. This possibility is supported by the observation that although recombinant Sap1p, Sap2p, Sap3p, and Sap6p cleave peptide bonds between larger hydrophobic amino acids, substrate specificities differ among the four Sap proteins (236). Evidence implicating *C. albicans* Saps in the pathogenesis of OPC in HIV infection was further strengthened by studies demonstrating that the decreased prevalence of OPC in patients treated with HIV-1 protease inhibitors results not only from immune reconstitution but also from inhibition of Sap activity (65, 67, 128, 238, 304). The requirement for specific *SAP* genes in the pathogenesis of mucosal candidiasis may differ according to the microenvironment at individual anatomic sites, as exemplified by the loss of virulence of null *sap1* to *sap3* but not *sap4* to *sap6* mutants in an estrogen-dependent rat vaginitis model (105). In this regard, a direct role for individual *C. albicans SAPs* in the pathogenesis of OPC will require assessment of the virulence of targeted null mutants at this specific mucosal site.

In contrast to the substantial evidence implicating *SAP* genes in the pathogenesis of OPC in HIV infection, the potential role of *C. albicans* phospholipase at this specific mucosal site has received less attention. *PLB1* mRNA transcripts were detected during the entire course of OPC, with the exception of primary infection, in Tg mice expressing HIV-1 (363). This was the first report of *PLB1* expression at the mRNA level in vivo and corroborated the finding of caPlb1p secretion in the stomach (172) and kidneys (249) of experimentally infected mice. In vitro, blastoconidia, pseudohyphae, and hyphae of *C. albicans* expressed higher levels of *PLB1* mRNA than did germ tube-forming cells, suggesting that expression of ca*PLB1* is regulated as a function of morphogenic transition (200). The presence of both blastoconidia and hyphae in the oral cavities of the Tg mice was therefore consistent with detection of expression of *PLB1*. In addition, the optimal activity of caPlb1 at pH 6.0 (172) makes it likely that the enzyme is functional in oral candidiasis. The attenuated virulence of *plb1* null mutants in a hematogenous-dissemination murine model (249) and an oral-intragastric infant mouse model (172), combined with the involvement of *PLB1* in the penetration and damage of host tissues (172, 249), indicates that *C. albicans* phospholipases also contribute to fungal virulence. However, determination of the precise role of *PLB* gene products in the pathogenesis of OPC in HIV-infected patients will require further analysis, including but not limited to the demonstration of attenuated virulence of *plb1* null mutants in a clinically relevant model of OPC and an assessment of *C. albicans* phospholipase gene expression in HIV-infected patients with OPC.

Perturbed Mucosal Immune Defense Mechanisms against *C. albicans* in HIV-Infected Patients

Humoral immune response. Secretory immunoglobulin A (sIgA) constitutes the predominant immunoglobulin isotype in secretions, including saliva, and is considered to be the first line of defense of the host against pathogens which colonize or invade surfaces bathed by external secretions (275). Salivary sIgA binds to a group of polydispersed heat shock mannoproteins expressed on *C. albicans* yeast cells and germ tubes grown at 37°C, and the highest reactivity is observed with yeast grown at pH values between 5.9 and 7.5, a range similar to that found in normal saliva (41). The possibility that specific anti-*Candida* sIgA antibodies may be protective was suggested by their higher concentrations in patients with oral candidiasis than in controls (144), as well as their ability to quantitatively inhibit the adherence of *C. albicans* to buccal epithelial cells in vitro (144, 447). However, a primary role for sIgA in protection against mucosal candidiasis remains inconsistent with the rarity of oral candidiasis in patients with selective IgA deficiency (8). In HIV infection, salivary concentrations and secretion rates of total sIgA and its subclasses have been found to be unchanged (274), increased (20, 258), or decreased (299, 425), with a lower avidity of sIgA antibodies (73, 91). In contrast, the concentration of *Candida*-specific salivary sIgA has been repeatedly found to be increased in HIV-infected patients despite the decreased salivary flow rate (92, 133). Furthermore, *Candida*-specific salivary IgA production significantly correlated with the salivary *Candida* load (92), suggesting that an adequate mucosal humoral immune response to *C. albicans* is maintained in HIV infection. It was further suggested that increased salivary *C. albicans*-specific sIgA antibody concentrations may be a consequence of infection instead of playing a protective role (92). In support of this interpretation, increased salivary sIgA concentrations were correlated with decreased salivary anticandidal activity in HIV-infected patients (258). More recently, a comprehensive analysis of *Candida*-specific antibodies in the saliva of HIV-positive patients revealed that despite changes in total immunoglobulin levels, when levels of *Candida*-specific antibodies were normalized to total protein or total immunoglobulin levels of the corresponding isotype, no distinct differences in IgA or sIgA were seen, regardless of the OPC status or $CD4^+$ cell count (461). Therefore, there is no evidence of appreciable changes in levels of *Candida*-specific

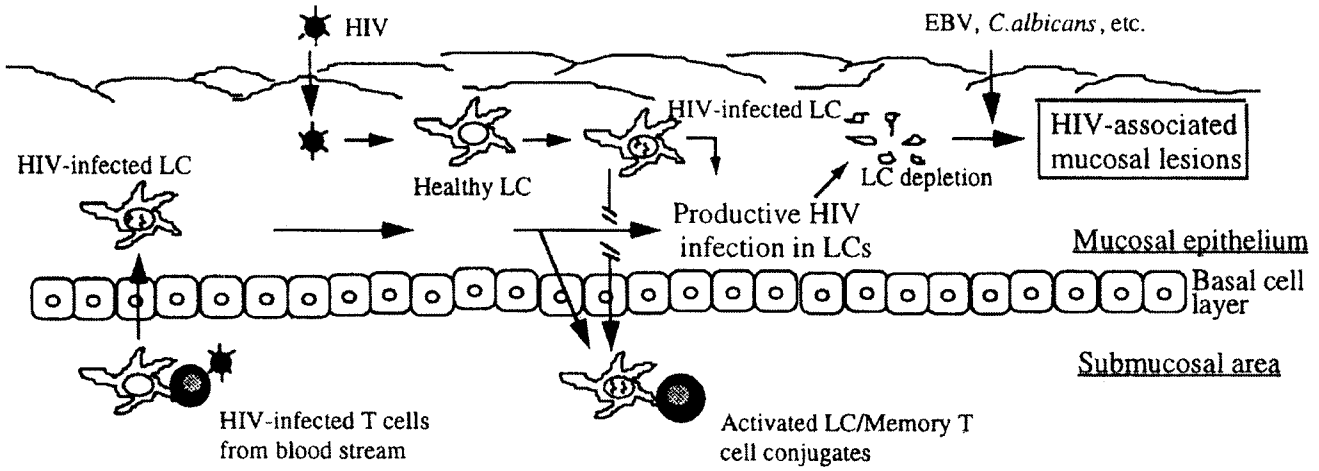


FIG. 1. Hypothetical model of the role of mucosal Langerhans' cells (LC) in HIV infection. Oral mucosal Langerhans' cells serve as an initial target for HIV infection. The cytopathic changes of Langerhans' cells with a productive HIV infection contribute to selective depletion of Langerhans' cells, which may impair mucosal immunologic protection against colonization by microorganisms causing HIV-associated oral mucosal lesions. Reprinted from reference 81 with permission of the publisher.

IgA in saliva that would account for the prevalence of OPC among patients infected with HIV.

Cellular immune response. The devastating impact of HIV infection on mucosal cell populations is most probably central to the pathogenesis of mucosal candidiasis in HIV-infected patients. In several investigations, possible defects of cells with immune potential against *Candida* were specifically examined in the HIV setting of infection.

Oral epithelial keratinocytes play a critical role in the pathogenesis of OPC because of their close interaction with *C. albicans* in the superficial epithelium. Because oral epithelial keratinocytes from HIV-infected patients contain integrated HIV proviral DNA and HIV Tat/Rev RNA (347, 348), possibly acquired through contact with submucosal HIV-positive lymphocytes and/or Langerhans' cells, the anticandidal properties of these cells could be potentially impaired. However, although HIV-positive patients with OPC had a significant decrease in oral epithelial cell-mediated growth inhibition of *C. albicans* in vitro compared to those without OPC, there was no difference in epithelial cell activity between HIV-noninfected and -infected persons without OPC (411). Expression of IL-1 and IL-8 by keratinocytes was equivalent in HIV-positive and -negative patients with OPC, and no constitutive expression of either cytokine was found in control patients without OPC (147). As mentioned above, expression of calprotectin by keratinocytes was preserved in HIV-infected patients with OPC and appeared to serve as a keratinocyte barrier to hyphal penetration (147). Consequently, further investigation is required to firmly establish whether defects in the anticandidal mechanisms of keratinocytes contribute to the predisposition to OPC in HIV infection.

Mucosal Langerhans' cells are the initial target cells after primary mucosal contact with the virus, facilitating the transfer of HIV to $CD4^+$ cells (81, 340, 341). Tonsils and adenoids from HIV-infected patients contain multinucleated syncytia expressing high levels of intracellular HIV Gag protein in the DC- and T-cell-rich crypt lymphoepithelium (164, 165). DCs within these areas express the viral coreceptors CD4 and CCR5 required for cell entry (217) and are selectively infected by R5 (macrophage-tropic) strains, promoting vigorous replication of HIV. DCs play two critical roles in the pathogenesis of HIV infection, first by spreading infection to and then by inducing virus-specific immune responses in draining lymph nodes (217, 340, 341). Despite being infected by HIV, oral mucosal Langerhans' cells are challenged to perform a vital task: the uptake of *Candida* antigens in the mucosa and their presentation to $CD4^+$ T cells in draining lymph nodes. Several lines of evidence have now clearly demonstrated multiple defects of oral Langerhans' cells, which probably contribute to a progressive loss of protective acquired cell-mediated immune responses to *C. albicans* antigens in HIV infection. Numbers of both oral (81) and esophageal (78) Langerhans' cells are depleted in HIV infection, congruent with decreased numbers of cervical (368), splenic (286), and blood (36, 130, 175, 271, 322) DCs (Fig. 1). It remains unclear whether decreased DC populations result from cytopathic changes caused by productive HIV infection, cytotoxic T-cell responses resulting in lysis of targeted DCs, migration to lymph nodes where active viral replication occurs, or down-regulation of DC surface markers (36, 81). In addition, impairment of terminal differentiation of Langerhans' cells was demonstrated by decreased expression of MHC class II antigens (338, 367), as well as the presence of blunt dendrites, very limited development of organelles, and lack of Birbeck granules (367). In contrast, however, increased expression of CD40 and CD86 costimulatory molecules was observed on blood DCs from HIV-infected patients (36). HIV and its transcriptional transactivator (Tat) block the expression of MHC class II genes in HIV infection by competing with the class II transactivator (218). Expression of MHC class I antigens in APCs is also down-regulated, but to a lesser degree than expression of MHC class II molecules (218), and results from a combination of their transcriptional blockade by Tat (56, 201) and intracytoplasmic sequestration by the HIV Nef protein (176, 248). Several of the defects identified in Langerhans' cells are also present in monocytes and macrophages, including reduced expression of MHC class II and formation of

MHC class II-antigen complexes (339) and altered capacity to stimulate and present antigen to $CD4^+$ T cells (265). In addition to these defects, expression of HIV gp120 in APCs and impaired CD40L induction on $CD4^+$ cells activated by antigens contribute to impaired IL-12 and IFN-γ production by APCs, thus preventing a protective $CD4^+$ Th1 response as well as differentiation of $CD8^+$ cells into cytotoxic lymphocytes (335, 420).

Progressive depletion of $CD8^+$ cells in HIV infection results from apoptosis mediated by macrophages through interaction of HIV gp120 with the chemokine receptor CXCR4 (195). Despite a progressive diminution in absolute numbers, remaining $CD8^+$ T cells nevertheless successfully accumulate in the basal epithelial layer of the oral mucosa in HIV-infected patients with OPC, demonstrating that these cells can be actively recruited to the mucosa in response to candidiasis (305, 367). However, the precise role of $CD8^+$ cells in mucosal containment of *C. albicans* in HIV infection, either by direct growth inhibition of *Candida* or, more likely, by an indirect mechanism, remains to be determined (157, 305).

Numbers of $CD4^+$ T cells are strikingly reduced in the oral mucosae of HIV-infected patients with or without OPC (318, 367, 413). In addition, *C. albicans*-specific peripheral $CD4^+$ cells become depleted with HIV disease progression in patients with concurrent OPC (240), but these findings have not yet been demonstrated for $CD4^+$ cells isolated from cervical lymph nodes draining the mucosal surface. HIV-infected patients have a Th2 cytokine profile in saliva (252) consistent with the well-documented switch from Th1 to Th2 in HIV infection (83), which correlates with a loss of lymphocyte proliferation in response to *Candida* antigens in patients with advanced HIV infection (252, 346). However, deficiencies in *Candida*-specific systemic cell-mediated immunity do not solely account for susceptibility to OPC in HIV-infected patients (250). The overall evidence nevertheless suggests that the depletion and immaturity of oral Langerhans' cells may interfere with normal processing and presentation of *C. albicans* antigens to $CD4^+$ cells, which are themselves depleted in HIV infection, and that perturbation of these protective mechanisms probably plays a preponderant role in the pathogenesis of OPC in HIV infection.

Potential defects of phagocytes could also predispose to OPC in patients HIV with infection. HIV-infected patients with chronically inflamed gingivae have increased numbers of mucosal macrophages and PMNs, demonstrating that HIV infection does not prevent a normal innate mucosal immune response by these cells (306). Although recruitment of phagocytes to the oral epithelium does not appear to be perturbed by HIV infection, their anticandidal properties could be impaired either directly by HIV infection or by altered stimulation by cytokines. In several investigations yielding conflicting results, phagocytosis of *C. albicans* by blood monocyte-derived macrophages from HIV-infected patients has been found to be either normal (312, 315) or reduced (95), possibly by HIV Nef (345). Likewise, although HIV gp41 suppresses the reduction of nitroblue tetrazolium by PMNs in vitro (168), growth inhibition of *C. albicans* and IL-1 and IL-6 production by PMNs were found to be preserved in HIV infection (66), while in other studies phagocytosis (143) and killing (454) of *C. albicans* by PMNs were impaired but without altered production of reactive oxygen intermediates (454). Interestingly, the candidacidal activity of PMNs from healthy subjects and HIV-infected patients is impaired by the Th2 cytokines IL-4 and IL-10, suggesting a role for these cytokines in mediating increased susceptibility to OPC in HIV infection (427).

In conclusion, HIV infection severely perturbs APCs and $CD4^+$ cells, and may also reduce the function of phagocytes against *C. albicans* in the oral mucosa, leading to the onset of OPC. However, these critical defects may be partly compensated by preserved host defense mechanisms (calprotectin, keratinocytes, $CD8^+$ T cells, and some activity of phagocytes), which individually or together may limit *C. albicans* proliferation to the superficial mucosa and prevent systemic dissemination in HIV infection.

AIDS-Like Disease in Transgenic Mice Expressing HIV-1

The above description of the numerous manifestations of HIV infection, including multiple perturbations of immune cells which express HIV as well as of the immune response to *C. albicans*, highlights the difficulties in studying and understanding the pathogenesis of candidiasis in the context of HIV infection. Undoubtedly, the availability of an adequate animal model would facilitate this task enormously. Unfortunately, there is no animal species in which HIV-1 can replicate and induce an AIDS-like disease. The most widely used model for AIDS remains the rhesus macaque infected with simian immunodeficiency virus (SIV) (117, 118). These primates are not widely available to researchers, the model requires the use of a virus different from HIV-1, and the tools to probe the macaque immune system, especially at the genetic level, are very limited. For studies of the immune system, the mouse has been the species of choice. Decades of research have provided a panoply of biological and molecular reagents to study virtually any cell population of the immune system. More recent advances in transgenesis and in embryonic stem cell technology, coupled with the development of efficient homologous recombination, have allowed the generation of Tg and gene-deficient mice. These technologies have been used largely for the investigation of the immune system.

Early attempts to express HIV-1 gene products in Tg mice were not totally successful in initiating an AIDS-like disease (52, 122–124, 254, 259, 381, 401, 434; for reviews, see references 51 and 232). Novel phenotypes not usually seen in HIV-1-infected individuals were observed in some of these Tg mice, while others showed either minimal or no permanent perturbation of immune cell populations, or severe immune defects, distinct from those usually associated with HIV-1 infection in human individuals. However, more recent attempts to generate a mouse model of AIDS were more successful, and the CD4C/HIV Tg mice were found to develop an AIDS-like disease very similar in its manifestations to human AIDS (186, 187).

Structure and expression of HIV-1 in CD4C/HIV Tg mice. A key feature of the CD4C/HIV transgene is the nature of its regulatory elements (CD4C) allowing the expression of HIV-1 in a selected subset of immune cells: thymic immature $CD4^+$ $CD8^+$ and mature $CD4^+$ $CD8^-$ T cells, peripheral mature $CD4^+$ T cells, and cells of the myeloid lineage such as macrophages, DCs, and Kupffer cells. These cells represent the ma-

jority of the natural cell populations found to be infected with HIV-1 in humans (325). The CD4C regulatory elements were indeed chosen to target as faithfully as possible the expression of HIV-1 in the same cell populations as those infected in humans.

It was initially thought that the best way to achieve this selected cell tropism was to use the regulatory elements of the CD4 gene itself, which codes for the receptor of HIV-1. The human CD4 (hCD4) gene was chosen, since expression of the mouse CD4 gene is absent in most myeloid cell populations, including macrophages, while several subsets of human myeloid cells, including macrophages and DCs, express CD4 at their surface (228, 460). Using a reporter gene, the cell surface hCD4 itself and the hCD4 regulatory elements were dissected (first by generating the CD4A, CD4B, and CD4C constructs) in order to identify which sequences were required to drive expression in $CD4^+$ T cells and macrophages and at the same time to silence the expression in $CD8^+$ T cells, B cells, and other nonhematopoietic cells (189). An in vivo (Tg) approach was used, since initial experiments with established human cell lines in vitro appeared unreliable. Among the DNA constructs tested, the CD4C regulatory elements were found to drive the expression of the reporter gene most faithfully (Fig. 2A). These CD4C elements represent a human/mouse chimeric construct (14.4 kbp) containing the murine T-cell-specific enhancer (1.9 kbp) (382) fused to human genomic elements (12.5 kbp) representing 4.5 kbp of sequences upstream of the first noncoding exon (exon 1), intron 1 (9.9 kbp), exon 2, and part of exon 3 (189). Further work has now confirmed that intron 1 contains a silencer (repressing expression in $CD8^+$ T cells, B cells, and nonlymphoid cells [426]) and DNA elements necessary for macrophage expression (188).

The CD4C regulatory elements have been used in Tg mice to express the genome of wild-type HIV-1 (186), of point and deletion mutants of HIV-1 (187, 190) (Fig. 2A), of natural HIV-1 variants, of an experimental variant of HIV-1 encoding green fluorescent protein (Z. Hanna, C. Simard, and P. Jolicoeur, unpublished data), and of the wild-type SIV genome (400). They have also been used to express other nonviral genes, such as Notch1 (IC) (X. Zang, Z. Hanna, J. Poudrier, D. G. Kay, and P. Jolicoeur, unpublished data). In each case, the expression of the transgene, assessed with a very large number of Tg founder lines, has been remarkably reproducible and faithful, the major differences between lines being the levels of expression, most probably reflecting the distinct sites of transgene integration within the host genome. A variety of techniques were used to identify the cells expressing the transgene: immunohistochemistry with cell-specific markers coupled with in situ hybridization (ISH) with transgene-specific probes, cell sorting of specific populations followed by ISH or Western blot analysis, and fluorescence-activated cell sorter (FACS) analysis on cells expressing a cell surface reporter (CD4C/hCD4 Tg mice) or expressing a fluorescent reporter ($CD4C/HIV^{GFP}$ Tg mice). The consensus emerging from these studies is that the transgene is expressed in the same murine cell populations which have been found to express the cell surface CD4 molecules in human cells, i.e., thymic immature $CD4^+$ $CD8^+$ T cells and mature $CD4^+$ $CD8^-$ T cells, peripheral $CD4^+$ T cells, and cells of the myeloid lineage (peripheral macrophages, Kupffer cells, DCs, and microglial cells). Expression was not detectable in many cell populations which are not thought to express hCD4, notably hepatocytes, kidney epithelial cells, lung epithelial cells, cardiomyocytes, endothelial cells, intestinal epithelial cells, muscle cells, neurons, oligodendrocytes, and astrocytes.

It therefore seems that HIV-1 gene products are expressed in CD4C/HIV Tg mice in the same cell populations which are thought to be infected with HIV-1 in human individuals. This specific targeted expression of HIV-1 genes is thought to be critical for the development of the AIDS-like disease observed in these Tg mice (186, 187). However, the latency of disease was found to correlate very closely with the levels of transgene expression (187). Indeed, Tg mice from very-high-expressor lines died within weeks after birth, and these lines could not be maintained. Tg mice from medium-expressor lines survived 4 to 6 months, while Tg mice expressing low levels of HIV-1 Nef survived as long as 1 year but still developed essentially the same multiorgan phenotypes as Tg mice dying early (Fig. 2B). This feature of fast and slow disease progression in Tg mice is reminiscent of the human clinical situation.

To determine whether all or only a subset of the HIV-1 gene products were required to induce this AIDS-like disease in mice, various mutated forms of the HIV-1 genome were constructed and assessed in Tg mice (Fig. 2). It was found that only Tg mice expressing Nef developed disease, while Tg mice expressing all other HIV-1 genes or a subset of them did not develop apparent phenotypes and apparently led a disease-free life (187). This mutational analysis established that Nef was the major determinant of this AIDS-like disease in Tg mice.

Clinical and pathological features of AIDS-like disease in CD4C/HIV Tg mice. The CD4C/HIV Tg mice, even those expressing only Nef, develop a severe AIDS-like disease whose latency correlated with the levels of Tg expression (186, 187). Clinically, these Tg mice show wasting, failure to thrive and/or weight loss, premature and sudden death, and sometimes edema and diarrhea. Wasting is a known consequence of human AIDS (90, 181, 270). The early death and edema are most probably caused by a severe renal disease (see below). The sudden deaths are probably due to a cardiac disease (see below). The Tg mice are fragile: often minor manipulations such as preparation for echocardiography will precipitate an early death. They also appear to survive better in a specific-pathogen-free environment than in non-specific-pathogen-free animal rooms. Tg females have lower fertility than non-Tg female littermates and typically give birth to fewer pups per litter. Tg males also show lower fertility, although this is not as apparent as with females. This lower fertility may reflect a general disease state or more specific problems of the autonomic nervous system.

A more detailed macroscopic and histological examination of these CD4C/HIV Tg mice showed multiorgan AIDS-like disease.

(i) Kidneys. Smaller, atrophic, and pale kidneys with an irregular surface are the most macroscopically visible manifestation of the disease. This phenotype also has the highest penetrance (in virtually 100% of Tg mice), at least for Tg mice bred on the C3H/HeN background. This kidney disease represents a tubulointerstitial nephritis associated with tubular atrophy, interstitial mononuclear cell infiltration, and fibrosis, as well as with lumen dilatation forming cysts. In addition,

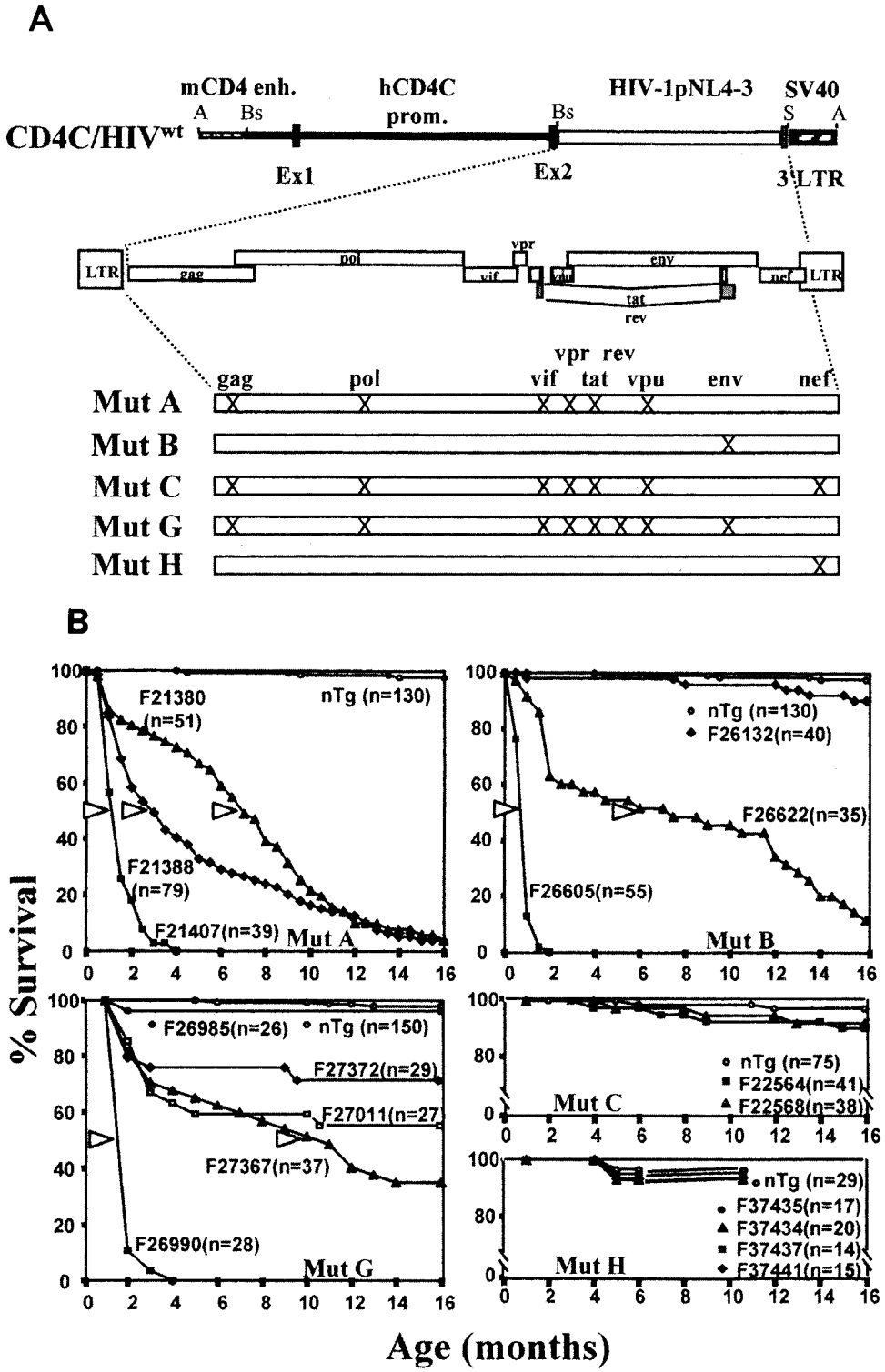
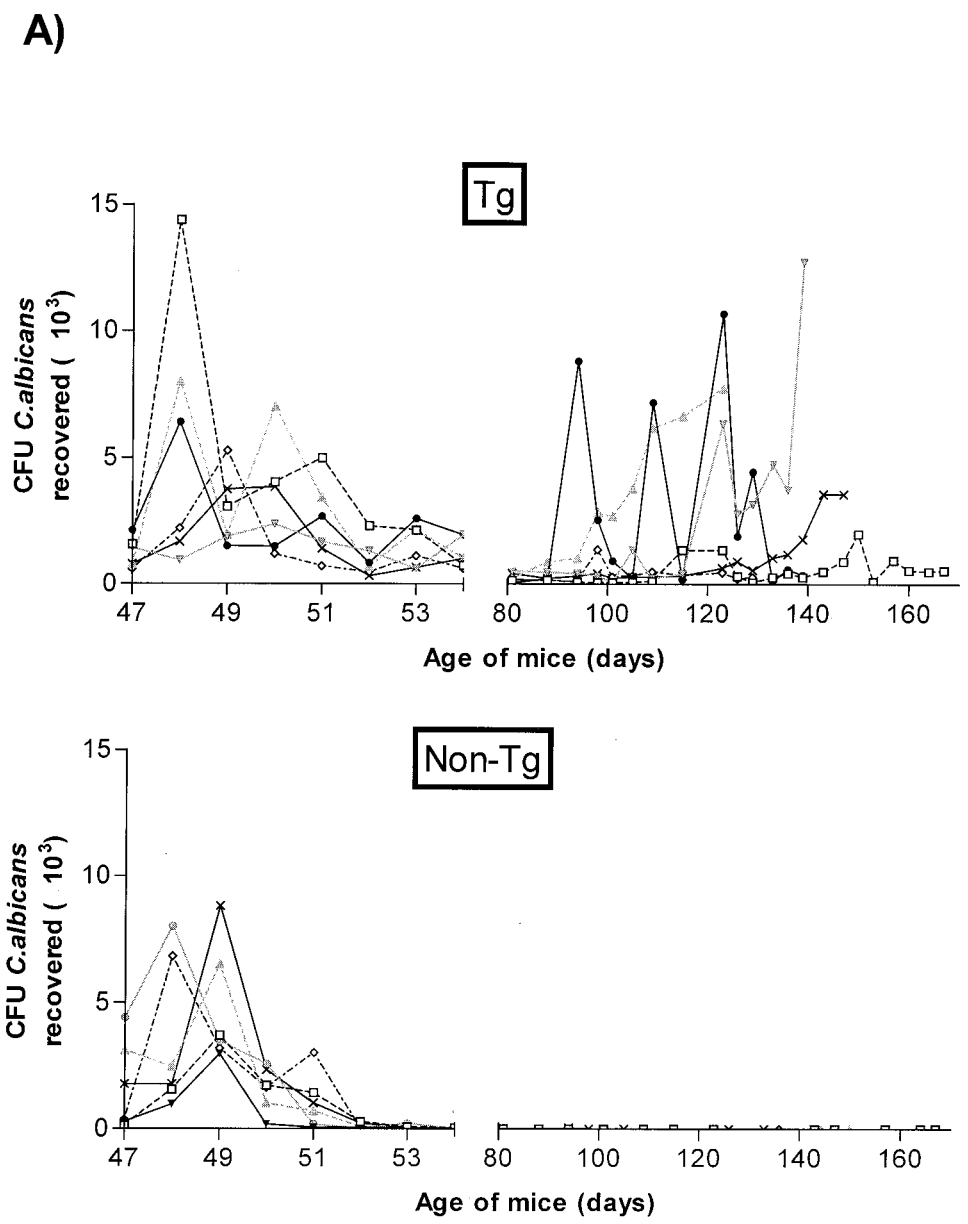


FIG. 2. Incidence of death in CD4C/HIV^{Mut} Tg mice. (A) Structure of the CD4C/HIV^{Mut} transgenes. The mouse CD4 enhancer (mCD4enh.), the human CD4 promoter (hCD4C prom.), each of the HIV-1^{NL4-3} mutant genomes, and the polyadenylation sequences from simian virus 40 (SV40) were ligated. Ex1 and Ex2 are the first two untranslated exons of the hCD4 gene; 3′ LTR is part of the 3′ long terminal repeat of the HIV-1 genome. The symbol × means that the open reading frame of the indicated HIV gene was interrupted. Restriction sites: A, AatII; B_s, BssHII; S, SstI. (B) Cumulative incidence of death in non-Tg and CD4C/HIV^{Mut} Tg mice. The arrows show the time of death of 50% (TD_{50}) of the Tg mice from different founders (F) for each mutant. Each point represents the death of a mouse. Symbols: n, number of animals observed. Reprinted from reference 187 with permission of the publisher.



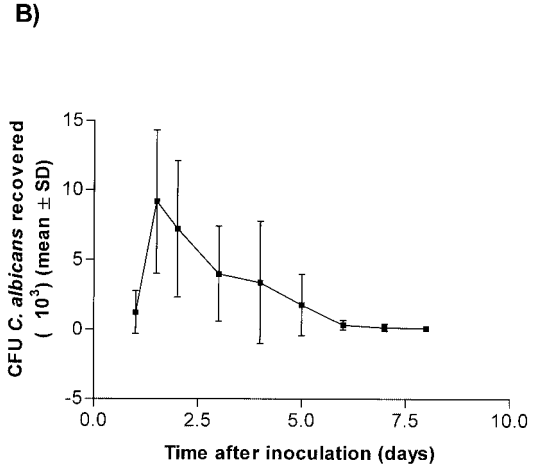


FIG. 3. Oral burdens of *C. albicans* in CD4C/HIV^{MutA} Tg mice and non-Tg controls. Mice were inoculated intraorally with 10^8 CFU of *C. albicans* LAM-1, and burdens were assessed longitudinally by sampling the oral cavity. Oral burdens were strikingly elevated in Tg mice compared to control non-Tg mice during primary infection, the 6- to 10-week carrier state, and marked terminal outgrowth preceding death. In contrast, *C. albicans* was rapidly cleared from oral cavities of non-Tg mice immediately after primary infection. Oral burdens during primary infection in control non-Tg (A) and intact C3H mice (B; mean and standard deviation [SD]) were not significantly different ($P > 0.05$). There were six Tg and six non-Tg mice in the experiment in panel A and 42 C3H mice in the experiment in panel B. Adapted from reference 116 with permission of the publisher.

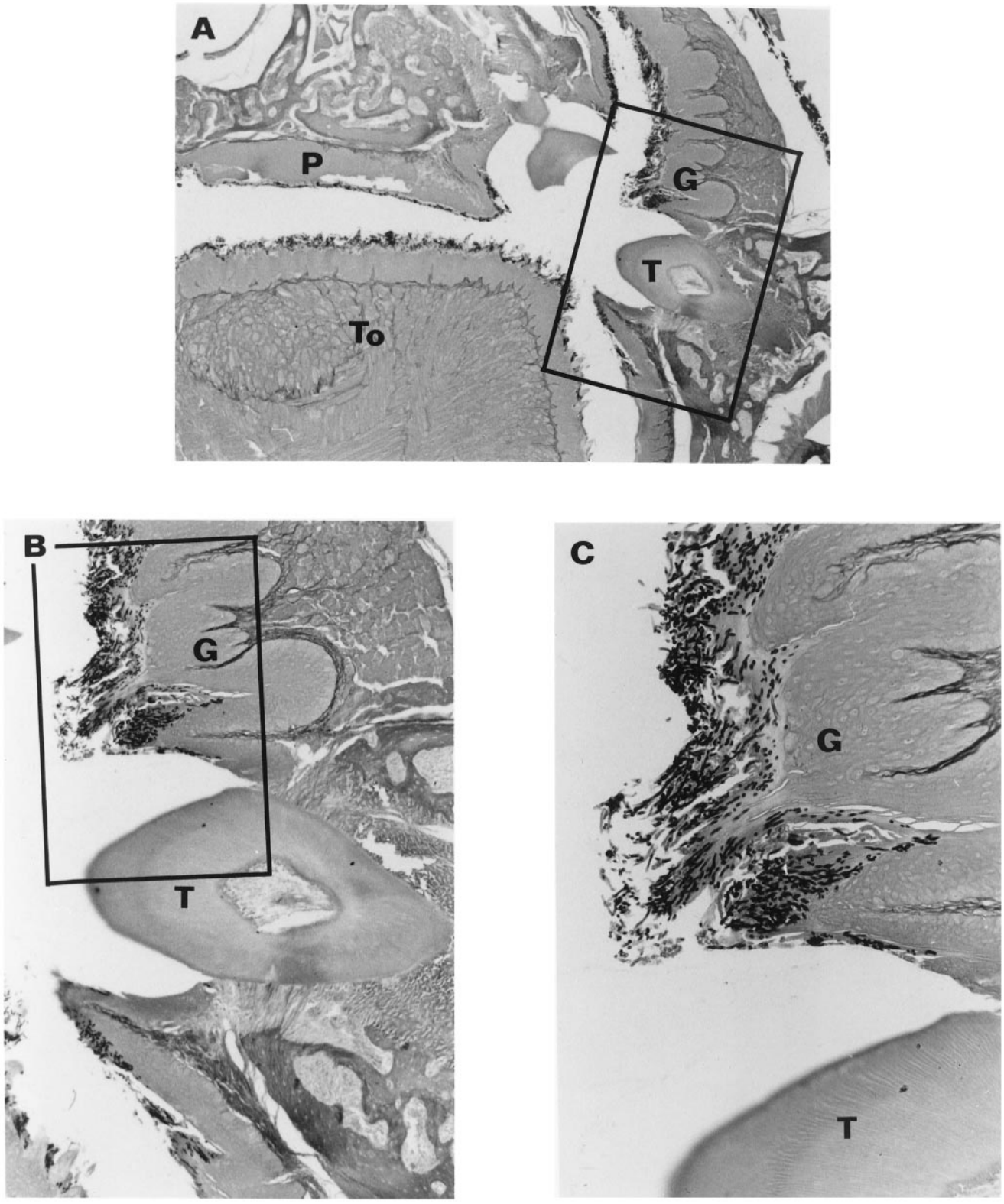


FIG. 4. Histopathology of oral candidiasis in CD4C/HIV^{MutA} Tg mice. *Candida* hyphae penetrate the superficial keratin layer of the stratified squamous epithelium of the tongue (To), palate (P), and gingiva (G) surrounding the tooth (T). Stain, Gomori-Grocott methenamine silver. Magnifications: A, ×100; B, ×250; C, ×500. Adapted from reference 116 with permission of the publisher.

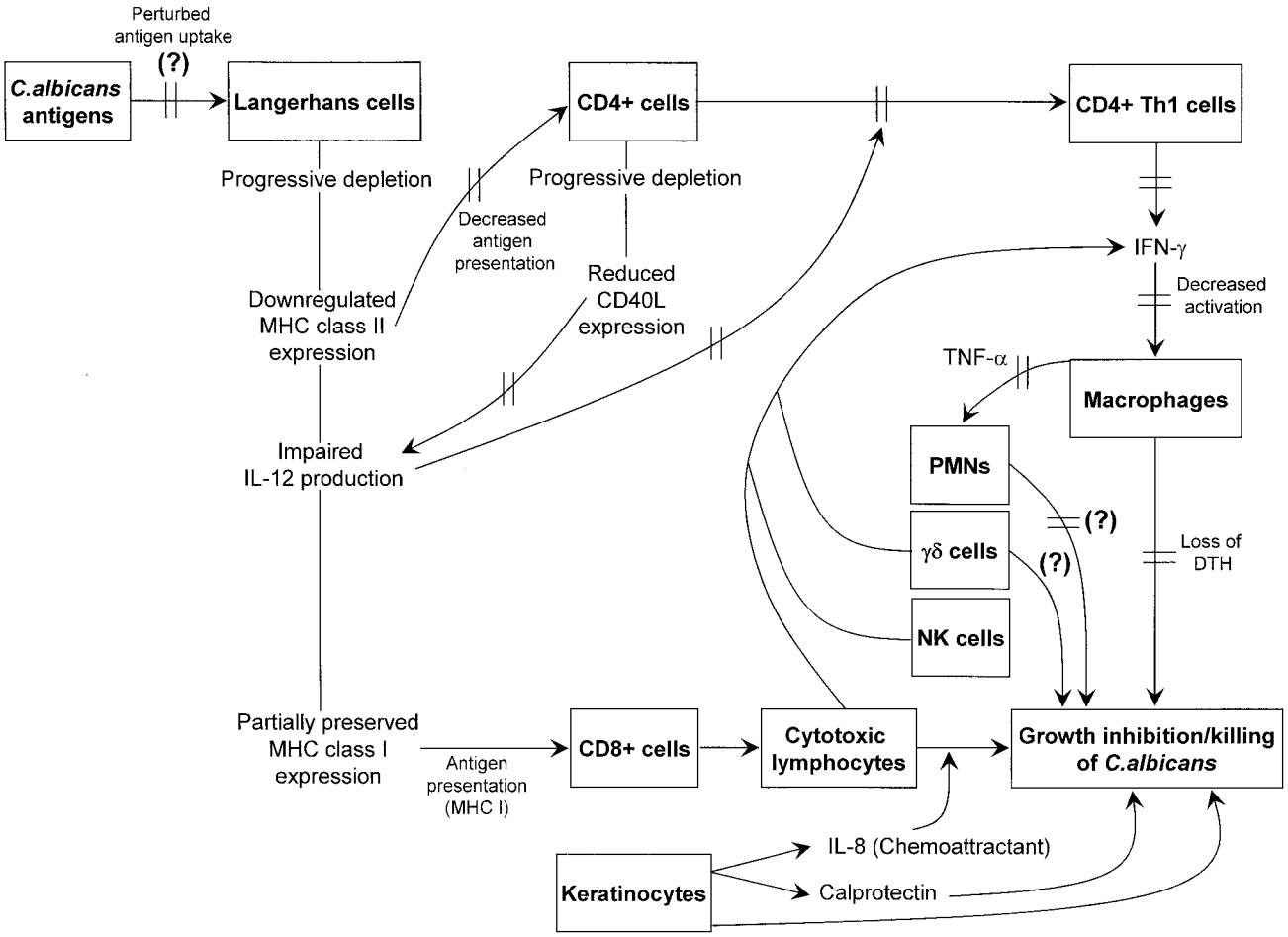


FIG. 5. Hypothetical defects in host defenses against oroesophageal candidiasis in HIV infection. Progressive depletion and functional dysregulation of mucosal Langerhans' cells alters normal processing and presentation of *C. albicans* antigens to $CD4^+$ cells, which are themselves depleted in HIV infection, resulting in diminished numbers of $CD4^+$ Th1 cells and perturbed adaptive immunity to *C. albicans.* However, substantially preserved innate defense mechanisms (calprotectin, PMNs, and γδ T cells) and cytotoxic T lymphocytes prevent systemic dissemination.

glomerular changes are observed and often represent segmental glomerulosclerosis. Kidney disease such as tubulointerstitial nephritis and focal and segmental glomerulosclerosis are relatively frequent in SIV-infected macaques (417) and in AIDS patients, especially in children (352, 394, 418). The early expression of the Tg along with the specific C3H/HeN background may explain the high penetrance of this phenotype in the CD4C/HIV Tg mice.

(ii) Lungs. A lymphocytic interstitial pneumonitis (LIP) (thickening of alveolar walls caused by infiltrating mononuclear cells) was observed in a high proportion of Tg mice bred on a mixed C3H-C57BL/6 background. The incidence of LIP decreased somewhat after inbreeding within the C3H background. LIP also develops in SIV-infected macaques (23) and is most often observed in human pediatric AIDS and constitutes an AIDS-defining condition (4, 5, 60, 215, 288). Since the CD4C/HIV transgene is expressed early in life, it is therefore not surprising to observe this phenotype in these Tg mice.

(iii) Heart. The sudden deaths observed in these Tg mice prompted a detailed analysis of the heart. Noninvasive echocardiography revealed signs of depressed cardiac functions (increased systolic left ventricular internal dimension and decreased fractional shortening, ejection fraction, stroke volume, and cardiac output) compared to those of their non-Tg littermates (227). Cardiac disease was also observed very frequently at autopsy, especially when the animals were bred on a C3H-C57BL/6 mixed background. The hearts often appeared enlarged and dilated. After exsanguination, they become smaller, suggesting dilated cardiomyopathy. Histologically, multifocal lesions representing focal areas of myocytolysis, sometimes associated with infiltrating mononuclear cells and fibrosis, were observed. In addition, a more diffuse interstitial fibrosis compared to that in non-Tg mouse hearts was revealed by Sirius red staining. This was not always associated with focal lesions. More recently, evidence of disturbances of the cardiac rhythm was found (D. G. Kay and P. Jolicoeur, unpublished data). Analysis by ISH with HIV-1-specific probes revealed no detectable expression in cardiomyocytes of Tg mice (227), suggesting that the pathogenesis of this cardiomyopathy is indirect and reflects abnormal functions of immune cells, some of them most probably expressing the transgene. Interestingly, cardiac disease is a relatively frequent manifestation of simian (396,

397) and human (3, 9, 84, 154, 196, 225, 260, 293) AIDS, and the cardiac lesions of the CD4C/HIV Tg mice are similar to those found in individuals with AIDS.

(iv) Bones. Often, the bones of CD4C/HIV Tg mice have a white appearance and are more fragile than those of non-Tg mice. Again the severity and penetrance of this phenotype was more apparent when these Tg mice were bred on a C3H-C57BL/6 background. These two phenotypes suggest the presence of a myelodysplasia and of osteoporosis. These phenotypes have not been extensively investigated, but preliminary FACS and X-ray analyses conducted on bone marrow cells and bones, respectively, are consistent with such anomalies (J. Caceres-Cortes, C. Simard, and P. Jolicoeur, unpublished data). Hematological abnormalities have been described in AIDS (93, 169, 297, 353).

Immune defects in CD4C/HIV Tg mice. In addition to the various organ diseases described above, the CD4C/HIV Tg mice developed several phenotypes of the immune system involving many cell populations and structures, which are very similar to those found in human AIDS.

(i) Thymus. The most striking macroscopic feature of the immune system is a severe thymic atrophy (186, 187). Histologically, loss of the normal thymus architecture is noted, with the cortical and medullary regions being poorly defined in contrast to the well-defined structures observed in non-Tg mice. In addition, the thymuses of the Tg mice are hypocellular. Thymocyte cell counts are close to normal at birth and during the first few weeks of life, but thereafter they progressively decrease to reach very small numbers, with loss of more than 90% of thymocytes. FACS analysis data show that the relative proportion of thymocytes is often almost normal, except for a lower proportion of mature $CD4^+$ $CD8^-$ cells (P. Chrobak, M. C. Simard, T. Ndolo, Z. Hanna, and P. Jolicoeur, Abstr. 10th Conf. Retroviruses Opportunistic Infect., 2003). This appears to reflect a block in differentiation at the transition stage of double-positive (DP) $CD4^+$ $CD8^+$ to single-positive $CD4^+$ $CD8^-$ T cells (Chrobak et al., Abstr. 10th Conf. Retroviruses Opportunistic Infect, abstr. 210, 2003). This thymic depletion appears to be cell autonomous and independent of stromal epithelial cells. It can indeed be reproduced in lethally irradiated normal non-Tg mice transplanted with bone marrow or fetal liver cells from Tg mice. Depletion of thymic cell populations is a feature of human AIDS, in both children and adults (171, 215, 229).

Phenotypically, these Tg DP $CD4^+$ $CD8^+$ T cells are abnormal and show a significant downregulation of the cell surface CD4 molecule (186, 187), also a characteristic of Nef-expressing human cells. In addition, DP cells from Tg mice show dysregulation of development marker expression (Chrobak et al., Abstr. 10th Conf. Retroviruses Opportunistic Infect., 2003), suggesting an impaired differentiation. Moreover, biochemical studies revealed constitutively enhanced levels of phosphotyrosine-containing proteins and further enhancement of tyrosine phosphorylation of several protein species, notably lysophospholipid:acyl-CoA acyltransferase and mitogen-activated protein kinases (ERK 1/2), on in vitro stimulation with anti-CD3 (187) compared to the situation for DP cells from non-Tg mice.

(ii) Peripheral lymphoid organs. Macroscopic and microscopic examination of peripheral lymphoid organs (lymph nodes [LN] and spleen) from CD4C/HIV Tg mice showed that they were atrophic, in contrast to organs from control non-Tg mice (186, 187). They had lost their normal architecture and were hypocellular and often fibrotic. On stimulation with an antigen (ovalbumin), the CD4C/HIV Tg mice produced a significantly smaller number of germinal centers (GC) in their LN (342). In spleens of Tg mice, the T-cell zone was markedly decreased and the marginal zone (MZ) appeared larger and contained numerous Mac-1^+ and $CD11c^+$ cells, likely to represent macrophages and DCs (342). In addition, the follicular DC network was found to be markedly reduced in Tg mice compared to non-Tg mice (342). An atrophic follicular DC network and smaller numbers of GC were observed early during the course of the AIDS pandemic and were considered one of the pathological hallmarks of the disease (326, 336, 430, 431). The CD4C/HIV Tg mice show this phenotype. Such a phenotype, reminiscent of that found in CD40- or CD40L-deficient mice (226, 463), is likely to reflect a lack of $CD4^+$ T-cell help (342).

(iii) $CD4^+$ T cells. Peripheral $CD4^+$ T cells are present in smaller numbers in Tg mice than in non-Tg mice (186, 187, 342). At later stages of the disease, they often almost totally disappear from peripheral organs. They also show a downregulation of the cell surface CD4 molecule. Therefore, the loss of this population is best assessed by quantitating the $TcR\alpha\beta^+$ $CD8^-$ T-cell population, which essentially represents the entire $CD4^+$ T-cell population, including the subpopulation which expresses no or very low levels of CD4. FACS analysis of $CD4^+$ T cells from Tg mice revealed a lower expression of CD40L than that in cells from non-Tg mice (342). Also, an increased population of $CD4^+$ T cells in Tg mice, compared to that in non-Tg mice, exhibit an activated/memory phenotype ($CD69^{Hi}$, $CD44^{Hi}$, $CD25^{Hi}$, $CD45RB^{Low}$, $CD62L^{Low}$) (342; X. Weng, E. Priceputu, J. Poudrier, D. G. Kay, Z. Hanna, T. W. Mak, and P. Jolicoeur, unpublished data). Assessment of the division capacity of these cells carried out by in vivo bromodeoxyuridine labeling showed that a higher proportion of these $CD4^+$ T cells from Tg mice than from non-Tg mice divided in vivo. However, in vitro, the purified $CD4^+$ T cells appear to be restricted in their ability to divide. They also appear to die by apoptosis at a higher rate. Finally, in a mixed leukocyte reaction, they performed poorly compared to cells from non-Tg mice (Weng et al., unpublished). It therefore appears that the peripheral $CD4^+$ T cells are functionally impaired, especially in their helper function, despite being in a state of activation.

(iv) $CD8^+$ T cells. The numbers of peripheral $CD8^+$ T cells of CD4C/HIV Tg mice are proportionally increased, as in human AIDS (186, 187). At later stages of the disease, these cells are lost, along with the $CD4^+$ T cells, as occurs in human AIDS (151, 327). Coupled with the smaller $CD4^+$ T-cell numbers, this leads to a lower CD4/CD8 ratio, also a characteristic of human AIDS.

(v) B cells. The proportion of B cells in lymphoid organs of CD4C/HIV Tg mice is increased compared to that in non-Tg mice (186, 187, 342). The presence of hyperglobulinemia is associated with this peripheral B-cell expansion in Tg mice. Most of the immunoglobulins are of the IgM isotype because of a failure to class switch (342). After ovalbumin immuniza-

tion, most of the ova-specific antibodies (Ab) were of the IgM isotype (342). Interestingly, these Tg mice also appear to exhibit signs of autoimmunity, producing autoantibodies, notably anti-DNA Ab (342) and anti-heart Ab (227).

(vi) Macrophages. The macrophages from the Tg mice seem to have a constitutively activated phenotype. Preliminary experiments also indicate that they can produce higher levels of NO and TNF-α on stimulation than those from non-Tg control littermates (D. Jovanovic, P. Vincent, and P. Jolicoeur, unpublished data). In addition, they were found to be more numerous in the spleen MZ (342).

(vii) Dendritic cells. DCs express the transgene and are abnormal in CD4C/HIV Tg mice (342a). In LN, the total number of DC were found to progressively decrease and to express lower levels of MHC class II, CD40, and CD86 cell surface markers, suggesting an immature phenotype. Interestingly, a subpopulation of $CD11b^{Hi}$ DC was found to accumulate in these lymphoid organs. LN DC also show a reduced capacity to deliver costimulatory signals to syngeneic $CD4^+$ T cells in the presence of anti-CD3 and to stimulate a mixed leukocyte reaction in coculture with allogeneic $CD4^+$ T cells from non-Tg mice. In addition, LN DC exhibit an impaired capacity to present antigen, both as proteins (pigeon cytochrome *c* [Pcc]) and as Pcc peptides. In contrast, in the spleen, DC were present in large numbers, especially in the MZ. In the thymus of Tg mice, recovery of $CD8\alpha^+$ DCs tended to be low compared to that in non-Tg control mice. Consistent with these findings, maturation of bone marrow-derived DCs from Tg mice was impaired and expression of MHC class II, CD86, and MHC class I cell surface proteins was lower than on DCs from non-Tg mice. Therefore, it appears that DCs from Tg mice fail to undergo full maturation. This may well affect their capacity to fully activate T cells. Also, the abnormal DC phenotypes and functions may contribute to the expanded B-cell compartment described above and the Ab production found in these Tg mice.

The number of DCs in HIV-infected individuals has been reported by some investigators to be small in the blood (130, 148, 175, 271, 322, 328), skin (302), lymphoid tissues (264), and oral mucosa (407). Also, DCs with an immature phenotype have been observed in some HIV-infected patients (137, 286, 338). In addition, reduced DC function has been detected in AIDS patients (reviewed in references 233 and 234). Although the benefit for the virus to elicit such a phenotype is unclear, it may favor viral replication. Indeed, it has been reported that HIV-1 replicates preferentially in immature DCs (25, 62, 163, 174).

This brief summary highlights the main features of the AIDS-like disease which develops in this CD4C/HIV Tg mouse model. All of the immune and organ disease phenotypes studied to date appear to be similar to human AIDS, not only pathologically but also at the cellular and molecular levels. In addition, no major phenotypes which are absent in human AIDS arise in the Tg mice. Conversely, almost all of the phenotypes found in human AIDS develop in these Tg mice. This strong similarity suggests that this murine AIDS model is relevant to the human disease and may be instrumental in understanding several manifestations of AIDS, in particular, opportunistic infections with pathogens such as *C. albicans*.

Oroesophageal Candidiasis in CD4C/HIV Transgenic Mice: a New Tool To Study Pathogenesis

Controlled studies of the pathogenesis of mucosal candidiasis in HIV infection have been hampered by the lack of a relevant animal model. The availability of CD4C/HIV Tg mice expressing HIV-1 in immune cells and developing an AIDS-like disease has recently provided a unique opportunity to devise a novel model of mucosal candidiasis that closely mimics the clinical and pathological features of candidal infection in human HIV infection (116). The following features of mucosal candidiasis in the Tg mice were found to be identical to those in patients with HIV infection: a sustained enhancement of oral burdens of *C. albicans*, becoming more manifest in the later stage of HIV disease (161, 439, 467) (Fig. 3); penetration by *Candida* hyphae of the stratified squamous epithelium of the oral cavity and esophagus, limited to the superficial epithelial layer (147, 357, 367) (Fig. 4); a low incidence of systemic dissemination of *C. albicans* (219, 296, 438); and a mononuclear inflammatory cell infiltrate of the mucosa (147, 367). In addition to closely mimicking the features of mucosal candidiasis in patients infected with HIV, the model obviates the problematic procurement of tissue samples from human patients; avoids the potentially confounding effects of antiretroviral therapy and of mixed infection by different strains of *C. albicans* or different *Candida* species, often found in HIV-infected patients (344); and allows for longitudinal observations at fixed times during the progression of HIV infection by direct comparison with non-Tg littermates. The Tg mice thus provide a novel opportunity to study the pathogenesis of mucosal candidiasis in HIV infection under controlled conditions in a small laboratory animal.

In accordance with the findings in humans with advanced HIV infection, the frequencies of cells expressing MHC class II antigen and $CD4^+$ cells were markedly reduced in the oral mucosa of the Tg compared to the non-Tg mice at the time of marked terminal outgrowth of *C. albicans* preceding death (116). However, in the Tg mice, infection with *C. albicans* also resulted in a substantial increase in the frequencies of mucosal cells expressing MHC class II and a more modest enhancement in the frequencies of $CD4^+$ cells, demonstrating the ability of the Tg mice to partially respond to mucosal infection despite the reduction in these cell populations (116).

Continuing investigation using this novel model in Tg mice is under way and is allowing, for the first time, a precise cause-and-effect analysis of the immunopathogenesis of mucosal candidiasis in HIV infection.

FUTURE DIRECTIONS AND CONCLUSION

The accumulated evidence presented in this review suggests a number of hypothetical defects which may underlie the susceptibility to mucosal candidiasis in HIV-infection (Fig. 5). Depletion of Langerhans' cells and their reduced expression of MHC class II molecules and IL-12 probably perturb the development of *Candida*-specific $CD4^+$ Th1 cells which are instrumental in orchestrating a protective adaptive cell-mediated immune response to *C. albicans* in the oral and esophageal mucosa. The depletion of $CD4^+$ cells and a shift in expression from Th1 to Th2 cytokines may reduce the anticandidal activity

of macrophages and PMNs and thus trigger the onset of OPC. Partly preserved expression of MHC class I antigens on Langerhans' cells may allow the recruitment of a compensatory protective $CD8^+$ T-cell response to *C. albicans* in the mucosa despite HIV infection; this, combined with the anticandidal activity of preserved innate defense mechanisms (calprotectin and keratinocytes), may limit the proliferation of *C. albicans* to the mucosa and prevent systemic dissemination to deep organs.

Oral biopsy material from HIV-infected patients will continue to provide clinically relevant, descriptive information about critical alterations in mucosal host defense mechanisms which may predispose to mucosal candidiasis in HIV-infection and may also suggest a protective role for cell populations which appear in the mucosa in response to candidiasis. The specificity of these identified alterations will be strengthened by examining tissue samples from normal and infected areas of the oral cavity in HIV-infected patients with OPC in comparison to HIV- and non-HIV-infected patients without OPC. Complementary to these investigations, the novel model of mucosal candidiasis in CD4C/HIV Tg mice will for the first time allow a longitudinal assessment of the alterations in oral mucosal and cervical lymph node cell populations and their production of cytokines at the single-cell level under controlled conditions. New Tg mouse constructs and replenishment with specific cell populations and cytokines should provide the opportunity to achieve a precise cause-and-effect analysis of the immunopathogenesis of mucosal candidiasis in HIV infection. The new knowledge gained is a prerequisite to designing novel approaches to immune reconstitution.

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