REVIEW ARTICLE

Reconstitution of the immunological defence and *Candida albicans* infection in oral mucosa of HIV+ patients under HAART

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Abstract:

The HIV infection is a worldwide spread disease which with the HAART (highly active antiretroviral therapy) application has became a chronicle disease. The HAART promotes the reduction of the HIV viral load and partial and temporary reconstitution of the immunological defence system of the HIV-infected subject, although for that its toxicity and patient adherence to the treatment might be well monitored. With the HAART, the past high prevalence of oral and oropharyngeal lesions decreased significantly, although in a non-homogeneous pattern. The fungus *Candida albicans* is a commensal microorganism of the human gut tract which provokes an opportunistic infection, when there is an imbalance between its virulence and the defence conditions of the host. The pathogenicity of the *Candida albicans* influences the degree of opportunistic infection; however, the fungical colonization is mainly dependent of the current immunological status of the patient. The host defence against *Candida albicans* is also provided by non-immunological barriers, physical as the keratinocytes of the oral epithelium, serological as the neutrophils, polymorphonuclear leukocytes and macrophages or humoral as the saliva, although the role of the salivary immunoglobulins is still unclear. Independently of the immunosuppression, the sensitive control to balance immunological innate and immunological acquired actions is complex and it prevents against an indiscriminate immunological acquired response. Dendritic cells and lymphocytes are the main defensive immunological cells of the oral mucosa. The dendritic cells phagocytise and deplete microorganisms, presenting the products of such depletion as antigens to the T lymphocytes, which provide acquired immunological defence for excellence. Specific Th1 type provides cell-mediated immunological protection against *Candida albicans* and other pathogens. Moreover, Th2 type cells provide immunological tolerance against external and auto-antigens. Treg and Th17 cells are actors of vital importance in the switching between Th1 type and Th2 type responses, although the complete understanding of their roles in this balance is still an ongoing process.

Keywords: candida albicans; HAART; HIV+ patients; immunological defence; oral mucosa.

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INTRODUCTION

The HIV infection is a devastating epidemic, with serious socio-economical and population reduction consequences. The main strain of the virus which causes acquired immunodeficiency syndrome is the HIV1, in this present paper called HIV. Few HIV+ patients do not present oral lesions during some phase of the disease progress, presenting pathological signals and symptoms mainly in oral mucosa and salivary glands[131].

It is known that the mucosa of HIV+ patients are vulnerable to the incidence of opportunistic fungical infections, as candidiasis, cryptococcosis, invasive aspergillosis, disseminated histoplasmosis and disseminated coccidioidomycosis[146,285]. However, the compromising of oral defence in HIV+ patients occurs even before the incidence of opportunistic infections. It has been mentioned, as examples, the occurrence of salivary glands dysfunctions[201] and the presence of yeasts and hyphae of *Candida albicans* in oral mucosa[345,316] before significant decrease in the number of $CD4^+$ cells in the blood stream and in the IgA concentration of the saliva of infected patients[316].

Therefore, the current research in the oral aspects of HIV+ patients highlights a broader approach, involving not only the classical deficiency of $CD4^+$ cells but especially the innate and acquired attributes of the immunological system of such subjects. Researchers investigate in special the defensive role of cells Th1 and Th2 and the regulatory role of cells Treg and Th17, contextualized in the complex control of the interactions between microorganisms and host.

In such contextualized approach, it is mandatory to consider the proofed partial and temporary reconstitution of the immunological system of HIV+ patients under HAART (highly active antiretroviral therapy), with important reduction of the prevalence of opportunist infection by *Candida albicans* in oral mucosa.

HAART: HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

With HAART application, the immunological system of the HIV patient is partially and temporarily reconstituted[27], due to the decrease of the viral load and the enhanced response of the defensive cells, in adults[19,83,9,332] and children[335]. More than the increase in number of the defensive cells, with increase of the hematopoietic activity[332], there is a functional recovery of immunodepressed cells[232,332].

Under HAART, the enhanced reactivity of cells $CD4^+$[19,20,83,232,89,90], and other effects imply in significant decrease of the morbidity and mortality of HIV+ patients[231,74]. The positive effects of HAART may be also of non-immunological nature[50], as a worst fungical adherence to epithelial cells[28].

Moreover, it has been suggested that HAART could act directly as anti-fungical drug, especially over the virulence factor Sap (secretory aspartyl proteinase) of *Candida albicans*[48,49,216]. Microbiologically, certain fungical strains may respond differently to HAART. It was verified an increase of *Candida spp.* (*no-albicans*) in the oral microbiota, as examples, *C. tropicalis* e *C. parapsilosis*; however, there were rare assessments of *C. dubliniensis*, *C. norvegensis*, C. *humicola* and *C. rugosa*[207].

Classically, HAART includes at least two inhibitor drugs of reverse transcriptase of nucleoside (RTI) plus a protease inhibitor (PI) or a reverse transcriptase inhibitor of no-nucleoside[226]. In regard to the risk-benefit of its composition, toxicity is the main cause to avoid certain regimens; therefore the clinical protocols must always evaluate the side effects simultaneous to the viral load reduction[88].

In theory, reduction of the antiretroviral drugs included in the medication could be worth, since it implies in lower toxicity and better adherence of the patient to the treatment. However, simplified regimens carry a significant higher risk of resistance and consequent loss of the power of viral suppression[271]. In HIV+ patients the resistance to HAART may be due to the high rate of viral mutations, since the applied drugs have selective effects[226,241].

In opposite, very "efficient" medications, there is a high risk of substantial side effects, what may provoke important lack of commitment of the patient with the treatment; what also significantly diminish its efficacy[320,325]. As consensual rule, the therapeutic prescriptions, if working well, must be preserved, unless a change is clinically necessary[271].

The IRIS (Immunologic Reconstitution Inflammatory Syndrome) occurs days or weeks after the beginning of the antiretroviral therapy, as an organic response to the drugs which compose HAART[27]. The hypertrophy of the parotid gland is suggested as a possible oral manifestation of IRIS in patients under HAART[229].

With HAART, the HIV infection has became a chronicle disease and it presents a different scenario. One of the features of this new scenario is the expressive reduction of the incidence and prevalence of opportunistic oral lesions[19,83,9,199,286,20,15,172,278,86,317].

Epidemiologically, studies confirm such reduction as definitive trend in the USA[160,142], in Mexico[252], in general industrialized countries[142], and in Brazil[109,137,243]. However, in England there is no evidence that it has happen a significant difference in the reduction of the incidence of oral candidiasis with the HAART introduction, substituting no-HART (antiretroviral therapy not highly active), according to Ives et al[152].

It is important to highlight that cohorts which follow patients submitted to HAART for a long period of time, the immunological reconstitution might be much more expressive[334],

although such recovery is slow and incomplete in immunological very compromised patients[209,310]. In these patients, the re-incidence of oral lesions, especially candidiasis, may be an indicator of HAART failure[142,253,211].

Besides that, the reduction of the incidence of oral manifestations in HIV+ patients was not homogeneous for all lesions[235], being hard to distinguish the oral manifestations of the HIV infection from the side effects of HAART[142]. As an example, HAART significantly increased the presence of oral warts[129,142,109].

Other factors must also be considered in this new scenario. Co-infections may in smaller decrease of incidence of oral lesions[122] and socio-demographic factors may also influence, since there is a trend for the decrease to be smaller in HIV+ patients under HAART Who present a lower scholar level[75].

FUNGUS *CANDIDA ALBICANS*

Candida albicans is an imperfect diploid dimorphic fungus, with phenotypic flexibility, which resides in a commensal way in the human gut in 40% of healthy subjects, usually without potential to overwhelm the host immunological defence[14]. The possibility of *Candida albicans* colonize, penetrate and damage the host tissues depend basically of the unbalance between the fungical virulence and the defence conditions of the host, immunological[148,111,112,84] or no-immunological, as the pH of the anatomic site colonized by *Candida albicans*[76] and the possibility of formation of a shelter niche, a biofilm for homing and resistance of the microorganisms[59]. In this case, the fungus *Candida albicans* does not present the commensal status anymore and provokes an opportunistic infection called candidiasis.

Candidiasis can be a light opportunist infection or up to a live-threading disease in seriously immunodepressed patients. To achieve such level of severity, the fungical infection, of species *C. albicans* and *no-albicans*, occurs through the mucosa and gain the blood stream leading to a generalized systemic candidiasis[82]. That is a potentially lethal complication in AIDS patients in advanced stage of the disease[171,315,240].

The pathogenicity of the fungus *Candida albicans* is complex and multifactorial. The secretion of hydrolytic enzymes aspartyl proteinases (Saps) promotes a virulence potential well descried in the pertinent literature[70,149,78]. The enzymes Saps are codified by at least tem genes Sap (Sap1 a Sap10), identified by mDNA sequences[148,264], which roles in the colonization and invasion of the host tissues are distinct[148,213]. The phenotype of the opportunistic fungus *Candida albicans* influences the cytokines production and the response of the host to the infection[328]. First, a fungical aggression stimulates an innate response, constituted by phagocytosis, generation of pro-inflammatory mediators, traffic of inflammatory cells to the injury site and the beginning of an acquired immunological response[145].

The pattern of adherence and fungical colonization of the epithelial cells of the oral mucosa reflects its pathogenicity, mainly because of the expression of Saps by different strains and biotypes of *Candida*[39]. In HIV+ patients, the higher adherence of *Candida albicans* to the oral mucosa, independently of lower levels of antibodies against *Candida* in saliva and of potential lower salivary secretion, is simultaneous with the Sap production[305]. Such results suggest that there is a selective colonization of *Candida albicans* strains which present better adherence to the oral mucosa[228,76,343]. Other enzyme secreted by *Candida albicans* which plays a pathogenic role is the B phospholipase[151,123], that can kill or damage the host cells[123].

Ultra-structural studies showed that the tissue response in oral mucosa of HIV+ patients is different in the pseudomembranous candidiasis when compared to the erythematous candidiasis. In the pseudomembranous form, the cellular immunological compromising, especially of dendritic cells and lymphocytes, is proportionally more severe than in the erythematous form[268]. In the pseudomembranous form, the fungical hyphae are abundant and extend up to the spinous layer (*stratum spinosum*) of the oral epithelium, with simultaneous parakeratosis, acanthosis and spongiosis of the infected epithelium. The hyphae penetrate in inter-cellular spaces, suggesting that *Candida albicans* may present thigmotropism (guide by contact), observed in vegetal fungi and recognized in fungical proliferation *in vitro*[287]. The inter-cellular fungical penetration is facilitated by the detachment of epithelial desmosomes, probably caused by Saps and/or phospholipases produced by *Candida*[259], also observed in HIV- patients[212]. It is interesting to observe that in the HIV+ patient the immunological cellular reaction against fungical hyphae seems to be minimal; although, possibly, because of the ongoing immunodepression[259]. In the erythematous form, hyphae are rare[259,104,258].

There is important variation of strains of *Candida albicans* and other species, which colonize the oral cavity of HIV+ patients[87]. The great majority of HIV+ patients who present oral candidiasis are mainly infected by the endogenous *Candida albicans*, already present as a commensal microorganism f the oral flora of the patient. However, part of the patients presents new *Candida albicans* strains[275,189,23] or other *Candida no-albicans* species[170,326], as *Candida dubliniensis*[64,303,206,280] and *Candida glabrata*[114]. Different strains and species may be transmitted between subjects[275], what may contribute for episodes of fungical resistance to therapeutic drugs.

Overall, there is significant genetic diversity[72] and the degree of fungical colonization increases proportionally to the disease advancement[246,326], depending directly upon of the

individual response in each anatomical infected site[289,113,115,111,112]. Therefore, occurrence of oropharyngeal candidiasis and vaginal candidiasis are not associated[72].

The individual resistance to drugs as fluconazole may occur because of the use in different episodes of candidiasis or prolonged use[193,110], and contributes for the diversity of strains and species presented by the patients[275,255,23,170]. Moreover, interactions between the HIV virus and *Candida albicans* may change the virulence potential of the fungus[136].

ORAL INFECTION BY *CANDIDA ALBICANS* IN HIV+ PATIENT

The earliest and significant incidence of oral and oropharyngeal lesions in HIV+ patients was presented in the 1980's[126,1,132,164] as a predictive signal of the HIV infection[132,164,308,272,162,222,237,46,67].

In 90% of the HIV infected individuals, in some stage of the disease, it occur one or more episodes of *Candida albicans* infection[112], which can affect either the oropharyngeal region as the oesophagus[91,120]. In 75% of the cases of oropharyngeal candidiasis, it also occur esophagical candidiasis or significant risk of its occurrence[3].

Esophagical *candidiasis* is only confirmed by endoscopic biopsy[256], and part of the patients positive for that (30 to 43%) do not present symptoms, as pain and burning sensation[116]. If they do, they must receive the prescribed anti-fungical therapy even without diagnosis confirmation by endoscopic exam[250,12]. With HAART, episodes of opportunistic oropharyngeal infections, sometimes called "AIDS predictors", decrease significantly[44].

The resistance of the oral mucosa to candidiasis in a health subject is the sum of the redundant mechanisms which include salivary anti-candidiasis proteins, inhibition of the growth of *Candida albicans* by oral keratinocytes and the acquired immunological response provided by T lymphocytes[84]. The protection of the salivary proteins and the action of the oral keratinocytes against *Candida albicans* was evidenced *in vitro*. Experimental models of oropharyngeal candidiasis have detected that the mechanisms and the role of mediators in the acquired immunological response against *Candida albicans*, with presentation of antigens by the dendritic cells to $CD4^+$ T lymphocytes[84]. However, the presentation of antigens by keratinocytes is uncertain, since these cells are located in the superficial layer of the epithelium and the $CD4^+$ cells are located in the basal layer[292], although such presentation may be stimulated by *Candida* infection[16].

As a model to study the evolution of the incidence of candidiasis, it has been suggested that the debility and immaturity of the dendritic cells may interfere in the presentation of *Candida albicans* antigens to the $CD4^+$ cells, which are debilitated by the HIV infection. HIV virus may also prejudice the phagocytary activity in the oral mucosa against *Candida albicans*, leading to clinical infection. However, such debilities may be partially compensated by the defence mechanisms still preserved (physical barrier of the keratinocytes, citotoxic activity of the $CD8^+$ lymphocytes and partial phagocytary activity). Such remaining mechanisms may limited the candidiasis proliferation in the oral mucosa and prevent its systemic dissemination[84].

Moreover, dendritic cells, T lymphocytes and macrophages of the oral mucosa may be the entrance door for the HIV viral infection[58], although the transmission of the HIV virus by oral mucosa is unexpected[150].

In general, oral lesions in HIV+ patients have been extensively categorized[2,130,337,67] and directly correlated with the decrease of the $CD4^+$ lymphocytes number[108,270,200,124,163,166,181] and with the HIV viral load[197,133]. Different opportunist infections are associated with the viral load, but not with the number of $CD4^+$ cells[43], although the number of $CD4^+$ cells is indicative of the stage of evolution of the HIV infection and the baseline for therapeutic decisions[294].

Among the detected oral lesions, candidiasis is the one with greater prevalence and incidence, although the epidemiological data is very heterogeneous. There are some reasons for such heterogeneity: a) differences among the assessed samples and the stage of the HIV infection in the included research subjects; b) concomitant prevalence of other oral lesions, which may difficult the differential diagnosis of candidiasis[124]; c) significant influence of covariants as smoking habit[233,266], use of alcohol[236], use of heroin/methadone[133] and oral hygiene and; d) prevalence of co-infections potentially facilitators of the fungical colonization, as the *Herpes simplex* virus (HSV) and the Epstein-Barr-EBV virus[288].

Oral candidiasis may be presented in the pseudomembranous form, erythematous form, angular cheilitis[128] and hyperplasic[258]. The pseudomembranous and erythematous forms are the most common[260]. The pseudomembranous form is characterized by the presence of white papular multifocal lesions. The diagnosis is mainly clinical but the diagnosis confirmation is made by microbiological culture of clinical collection, what leaves a reddish surface. Fungical hyphae are pathognomonic. It practically does not present associated inflammation and rarely presents micro-abscess, even though the colonization area is broad[104,258].

The erythematous form provokes multiple micro-abscesses in the epithelium[260,104] and diffused erythemae in the palate, oropharynge and tongue dorsum. In general, fungical hyphae are absent. The erythematous form demands biopsy for diagnosis confirmation. In the hyperplasic form, a superficial cellular reaction occurs against the pathogen, depending upon the degree of its virulence[258].

Signs of oropharyngeal fungical infection vary from light to generalized thrush[326]. The esophagical candidiasis can also be light or generalized, depending upon the stage of AIDS, or can be associated with an acute HIV infection[55,239]. The patient may present hyperplasic palatal papillae[260] or exfoliated cheilitis, mainly in the lower lip[261].

In regard to the symptoms, the patient with oropharyngeal candidiasis presents burning feeling, pain, taste change and difficult to swallow liquid and solid food[128]. Esophagical candidiasis may lead to dysphagia, odynophagia, fever and nausea/vomiting[308,60]. Because of painful swallowing, the limited intake of food and liquid may provoke expressive weight loss, which is very common in HIV+ patients[308].

SALIVA

The salivary flow and its aggregating properties provide a dynamic balance between *Candida albicans* and other commensal microorganisms of the oral microbiota, protecting against the establishment of oral candidiasis in a healthy subject[26,196,140]. However, such salivary mucine properties may also facilitate the *Candida albicans* adherence to the oral mucosa[101,143].

Some salivary proteins present fungicidal effects. Lysozyme and lactoferrin are two proteins of the innate defence, no-immunological and no-specific against *Candida albicans*; however, with potential fungicidal properties[141,290,223,344,274,139].

Histatins are other salivary proteins which may contribute to the non-immunological innate defence of the oral mucosa[254,100,314,139], as the antileukoprotease[312].

In HIV+ patients, the salivary antifungicidal effect is controversial. It is lower for a group of researchers[183]; however, for others, the salivary lysozyme concentration is greater[345,18,195] and the lactoferrin production is not definitively associated to the limited proliferation of *Candida albicans*[84].

Candidiasis and salivary flow may also be associated. Subjects with Sjögren syndrome present reduced salivary flow and higher incidence of candidiasis.[263] The same occurs with HIV+ patients in advanced stage, in which the salivary flow is reduced in 40%[183] and in patients with oral acid pH, in which the virulence of *Candida albicans* is enhanced[273,176,77].

The detection of specific IgA antibodies against *Candida* suggests that there is a specific humoral response against *Candida albicans* that inhibits the adherence and colonization of such fungus in the oral epithelium; however, such hypothesis was confirmed *in vitro* only[103,330] and the fact that subjects with deficient salivary IgA production do not present significant increase in the incidence of candidiasis[7] makes such hypothesis vulnerable.

HIV infection produces direct and indirect effects in the humoral and cellular immunity of the oral mucosa, innate or acquired[57], with consequent increase in the incidence of opportunist infections; however, conclusions in regard to the humoral immunity of HIV+ patients, especially about salivary flow and salivary IgA concentration, are controversial[56,111].

For some authors, there is no significant alteration in the salivary flow, although there is a tendency for flow reduction[195]. For others, the reduction is certain and consequently its antimicrobial effect too[183]. According to some authors, it occur significant reduction in the IgA production and consequent reduction in the antimicrobial effect[215,306]. However, for others, there is no change[29] or the IgA anti-*Candida* production increases[18,66], simultaneously with the increase of the production of anti-microorganism proteins as lactoferrin, lysozyme and histadine; independently of the decrease in the salivary flow[68,99].

The change in the profile of the immunological response from Th1 to Th2 might be critical in the immunological unbalance in HIV+ patients[62]. Healthy subjects present in the saliva cytokines of Th1 and Th2 immunological responses. However, in HIV+ patients, the profile of salivary cytokines is clearly of Th2 response but not Th1 response[175].

IMMUNOLOGICAL DEFENCE

Immunologically, the host defence can be divided in innate and acquired. The innate defence is congenital and DNA oriented and the acquired defence is basically organized by T and B lymphocytes with structurally unique receptors. The lymphocyte receptors are random generated, and provide an extremely diverse repertoire of defence. Then, there is a great probability that a lymphocyte recognizes an antigen and, consequently, to be activated and proliferate in cloned expansion. Such process is absolutely necessary for an efficient immunological response[204]. The effector mechanisms of the innate immunity, including macrophages, phagocytes and complement system, are immediately activated when an antigen is presented to the host, while the cloned expansion delays in average from 3 to 5 days[205].

The activation of the acquired immunological system can be triggered not only by infectious microbial antigens, but also by environmental innocuous antigens and self-antigens, generating allergic and auto-immune diseases[205]. So, how the immunological system can identify the origin of the antigen? And when the immunological response must be activated? The connections among some components of the immunological system are not well understood yet, however, recent progresses allow a contextualized view of the defence system[204] and its failure substantially collaborates for the susceptibility of the oral mucosa to candidiasis in HIV+ patients[125].

The innate immunity is fundamental in the host defence against pathogenic antigens. It is mediated by many genetically pre-determined receptors, which specificity is molded by natural selection. The issue is that the genome can codify only

a limited number of gens, for example, the human genome contains only 75,000 to 100,000 gens, which, in the most cases, are not related to the immunological recognition[205]. In opposite, the acquired defence system presents approximately 10^{14} receptors for immunoglobulins and 10^{18} limphocytary receptors, developed in a clonal basis. With such defence *armamentarium*, even though the microorganisms being extremely heterogeneous and suffering periodic mutations, the acquired defence can potentially recognize ever possible antigen. However, the trade off of such diversity is the lack of ability to distinguish pathogenic external antigens from innocuous external antigens and from self-antigens.

The strategy of innate defence is not clonal as the acquired one and it does not recognize ever antigen *per se*, however, be triggered by few molecular standard structures present in large groups of pathogenic microorganisms, as example, bacterial lipopolysaccharides, peptidoglycans, lypoteichoic acids, mannans, bacterial DNA, double-stranded RNA and glucans[154]. For example, lipopolysaccharide is synthesized only by bacteria, and the receptors for such molecules alert the host to the presence of an infection by bacteria. Such "sensitive" and sophisticated balance can prevent the invasion of pathogens and, at the same time, preserve the symbiotic interaction with the commensal flora[21,276,97].

However, other important effect of the innate immunologic defence is the professional antigen-presentation, especially by dendritic cells, macrophages and B lymphocytes. In general, when a molecular pattern in a pathogenic microbe is recognized, antigen-presenting cells (APCs) process it and present part of that, as example, MHC (major histocompatibility complex) class II segments.

In order to trigger the acquired immunological system, beside MHC class II presentation, co-stimulatory signals as CD80 and CD86 molecules are necessary. The induction of expression of such molecules is also controlled by the innate immunological system, throughout the activation of toll-like receptors (TLR) in an infectious scenario. The recognition of an antigen by a T cell in the absence of CD80 or CD86 molecules promotes its permanent inactivation. Then, the combined activation of different receptors, TLR or non-TLR, results in complementary effects, synergic or antagonic, which modulate the innate and acquired immunity[313,97] and protect against an indiscriminate acquired immunological stimulation[63].

Systems of receptors may modulate the antigenic specificity of the response, as T helper 1 (Th1) or T helper 2 (Th2), throughout the feedback of the effect cells to the dendritic cells and not throughout the instructions provided by the pathogens, therefore, an experience-based criteria, inducing and maintaining an appropriated polarized response[159].

ORAL MUCOSA INVASION

Histologically, the oral mucosa presents in 60% of its surface similar characteristics to the esophagic and vaginal mucosa. The stratified squamous epithelium and the lamina propria of the connective tissue, mainly formed by dense collagen fibers, are separated by a basal membrane. One difference between the oral epithelium and the esophagus/vagina epithelium is the oral keratinized epithelium, which is similar to the skin epithelium, is found in the gingiva and hard palate and represents 25% of the oral mucosa. Other difference is the dorsal tongue epithelium, which presents a large number of sensorial gustative papillae, representing 15% of the oral mucosa surface.

Keratinocytes are cells of the oral epithelium adjacent to the basal membrane, which united by desmosomes (in larger number and better attached in the external region of the epithelium) provide the main physical barrier against pathogenic agents invasion. The oral epithelium turnover (approximately 14-20 days) occurs due to the lost of the protein integrin of the keratinocytes. Such process is fundamental for the homeostasis of the oral mucosa, limiting for example, the colonization and infection by *Candida albicans* fungus[274].

Epithelial cells invade the lamina propria, allowing that dendritic cells present antigens to lymphoid tissue nodes, which contain lymphocytes as host defence agents. Keratinocytes are HIV infectable cells[249], with potential risk that their action to be diminished, although such hypothesis has not been clinically proofed[291]. The calprotection production in keratinocytes, preserved in HIV+ patients, is a physical barrier against the penetration of *Candida albicans* hyphae[104].

In the skin, infected keratinocytes by *Candida albicans* produce specific cytokines which collaborate to the immunological response regulation[11,295,277], as in the oral mucosa[179,117,292,95,96,214,94], thru the activation of innate recognition mechanisms by toll-like receptors (TLR). Furthermore, epithelial cells might secrete antimicrobial peptides as beta-defensins, which prevent the installation of the infectious process in the oral mucosa[335].

Neutrophils offer innate protection, mainly phagocytizing and digesting bacteria and fungi, and also producing cytokines which attract and stimulate other immunological actions, instructing and modulating dendritic cells[282,321].

The local response against *Candida albicans* is mediated by macrophages and polymorphonuclear leukocytes, which are more potent that the dendritic cells to kill *Candida albicans*[220] and play an important role in the innate immunological response[205]. Further, they stimulate the lymphocytary proliferation and the synthesis of related cytokines[17,336,125].

Macrophages are physiologically located in the lamina propria and produce peroxynitrite, an *anti-Candida* product[327]. They present a repertoire of receptors which promote the ho-

meostasis, defence and immunological induction[309,198]. When they are activated by cytokines as interferon-gamma, they differentiate and participate of the acquired immunological response against *Candida*[327].

Polymorphonuclear leukocytes are present in the blood stream, providing protection against systemic infections[338,112], and are also in the lamina propria and in the epithelium by inflammatory induction[205].

In HIV+ persons, the phagocytary function of the macrophages is not affected[225,125]. Macrophages may also produce nitric acid, an *anti-Candida* product. Such production may be regulated by T gamma-delta cells[155], and is not compromised in HIV+ patient[125]. However, cytokines as IL4 e IL10 may compromise the antifungical action of the polymorphonuclear leukocytes, increasing the susceptibility of the host to opportunist infections[307].

Dendritic cells and lymphocytes are the main acquired immunologic cells *anti-Candida* of the oral epithelium[221]. Dendritic cells phagocytose *Candida*, presenting the products as antigens to the T lymphocytes, which are the immune cells by excellence. The proliferation of specific lymphocytes against *Candida* is stimulated by cytokines produced by dendritic cells[221].

Dendritic Cells

Dendritic cell had its identity and function clarified in the 1970's[297,298,300,296,299]. Langerhans cells are a sub-population of the dendritic cells[22,251], a type which presents certain features, as example, $CD1a^+$ identification, Birbeck granules, Lag antigens and E-cadherin[53,52].

Dendritic cells are located in the basal and supra basal layers of the epithelium of the oral mucosa[40,73,5,257,69,323,185,24,283,284,71,158], architecturing the MALT (mucosal associated lymphoid tissue) as primary lymphatic tissue. In oral mucosa, the dendritic cells and other antigen-presenting cells must quickly respond against intrusion pathogens[220]. Similarly, in the gut the dendritic cells architecture the GALT (gut associated lymphoid tissue)[186]; however, there they are considered secondary lymphatic tissue[40]. Anyway, in both anatomic sites they are fundamental for the acquired immunological protection[248]. Furthermore, in the oral mucosa they might be more efficient in the antigen-presentation process to T lymphocytes than the skin dendritic cells[138].

Dendritic cells are specialized in the antigen capture, migration and presentation to T lymphocytes[346,54,340,22,158], performing a crucial defence against pathogens[322,324]. Furthermore, the dendritic cells might collaborate to the immunological tolerance of the subject against self-antigens, minimizing auto--immune response[22]. In a broader view, dendritic cells also perform diverse roles in the mobilization of the immunological response, innate or acquired, working simultaneously in the homeostasis and host protection[153].

The functional properties of the dendritic cells are related to their state of maturation[238]. Different lineages and phenotypes of dendritic cells have being identified and there are signals that the Langerhans cells come from the same linage of lymphocytes $CD8^{+10}$. Mature dendritic cells induce T helper 1 (Th1) response and immature dendritic cells inhibit the proliferation of Th1 and induce T $CD4^+$ regulatory cells (Treg) and the IL-10 production[156].

Treg cells stimulate the CTLA-4 production, which negatively regulate T citotoxic cells. Interferon-gamma, IL4 e IL12[102] are required to induce $CD4^+$ lymphocytes and Th response, possibly by combined innate and acquired immunological mechanisms[208,98]. The IL18 cytokine has a similar action to the IL12 cytokine and stimulate Th1 response; however, it could also stimulate the tolerance response of the Th2 type, becoming an example that the immunological protection is heterogeneous and complicated[218].

The fundamental question in the ontogenesis of diverse lineages of dendritic cells is if they are cells originally autonomous or hold common cellular background and differentiate according to the functional environmental inputs[248]. Studies with rats[165,41], with mice[297] and humans[51] support the existence of diverse lineages of dendritic cells.

Dendritic cells may come from myeloid cells[98], plasmocytoid cells[135,13], monocytes[339], macrophages[269,187,34] or germinative blood cells[269,302]. Some specific dendritic cells lineages hold better functional plasticity than others[184,82,289,348] and such plasticity is exemplified by the differentiation in interdigital cells[341]. Furthermore, such plasticity facilitates its collaboration in the orquestration of the immunological response[161], presenting antigens to the T cells in a Th1 response type or inducing the host tolerance to the antigen in a Th2 response type[194,289].

Myeloid dendritic cells phagocytose quickly and efficiently fungus in the yeast and hyphae forms[98]. Functionally, myeloid dendritic cells tend to polarize to Th1 response and are called e dendritic cells 1 (DC1). Plasmocytoid dendritic cells tend to polarize to Th2 response tolerance response, and are called dendritic cells 2 - DC2[265]. Other authors show that dendritic cells 1 may also provide Th2 responses[247,157], depending upon the type of the endotoxin or lypopolysaccharide as antigen and of the cytokines involved, being they type Th1 or Th2[265,98,247,218,192].

The acquired immunological response is triggered by the recognition of pathogens and activation of cascade events for specific inflammatory start, evolving in special toll-like receptors - TLR[180], considered the link between the innate and acquired immunological systems[177]. TLR receptors are able to induce the maturation of dendritic cells and address Th1 cells responses[318,322,167,219]; and, among such cells, the Th17 cells[6].

MHC class II molecules of the dendritic cells, in the presence of IL18 and IL12 cytokines, induce T CD4+ cells to Th1 acquired immunological response[22,291]. In the absence of IL12 cytokine, the antigen presentation might induce the Th2 tolerance response[218].

The dendritic cells are helped by T CD4+ helper in order to present antigens to the cytotoxic CD8+ lymphocytes. Such help is mediated by CD40 and CD40L molecules, in the surface of T CD4+ helper lymphocytes. The CD40 and CD40L molecules may also be linked to other antigen-presenting cells, as macrophages and B lymphocytes[279].

It is important to highlight that dendritic cells do not need to interact with T lymphocytes to mature[79]. However, naive Th1 cells, when stimulated by DC1, present good proliferative potential and good cytolitic power, performing important role in the acquired immunological response. Such cells produce good amount of interferon-gamma, IL2[17,291] and IL12[98,291]. In opposite, the naive Th2 cells, when stimulated by DC2 cells, present poor proliferative potential and poor cytolitic power, i.e., a poor acquired immunological response. They produce good amount of IL10, TGF-beta and lower amount of interferon--gamma, do not producing IL4 or IL5. They are regulatory cells which play the immunological tolerance, expressing the role of the DC2 cells[121,291].

DENDRITIC CELLS AND HIV VIRUS

The HIV virus infects and replicates in dendritic cells[42]; however, these cells maintain their capability to present antigens to T CD4+ cells, although such capability is depressed[38]. Furthermore, the dendritic cells function as a vector of HIV virus infection proliferation[119,118,245,244,61,81,319] even though they are more important as antigen-presenting cells than vectors of infection proliferation[144].

The infection of dendritic cells in oral mucosa of HIV+ patients might contribute to its weakness or death,[61] reducing its number[234]. Such process also occurs in the spleen[203] and in the blood[191,127,92,230,25].

HIV virus may also subvert the immunological system to escape its surveillance, targeting specifically C-lectin DC-SIGN receptors (DC-specific intercellular adhesion molecule-grabbing nonintegrin) of the dendritic cells[322], though interference in their intracellular signilling or their maturation inhibition and cytokines production decrease, necessary to trigger the acquired immunological response.

The dendritic cells infected by HIV virus present defect in the MHC class II molecules (as macrophages infected y HIV virus as well), that may change its ability to present antigen to CD4+ cells[242].

LYMPHOCYTES

The oral mucosa, as the skin, does not have B lymphocytes, but only T lymphocytes, grouped in small niches random distributed in both sides of the basal membrane and rarely in a superficial position[323]. The oral epithelium presents approximately 37 times more T lymphocytes than the skin epithelium[323] and the rate of lymphocytes CD4+/lymphocytes CD8+ in the oral mucosa is 1:2; in the skin is 1:4[323], indicating that in the oral mucosa there is significantly more differentiation of CD4+ cells than in the skin.

The vast majority of these lymphocytes express the memory phenotype CD45RO+[63]. The lymphocytes of the oral epithelium are not activated (CD25-), differently than the CD25+ lymphocytes of the adjacent connective tissue[63]. The conversion from naive CD45A+ lymphocytes to memory CD45RO+ lymphocytes requires antigenic stimulation, suggesting that intra-epithelium apoptotic CD25-/CD45+ lymphocytes degenerate if the antigen-presentating process does not occur[63]. CD4+ cells when activated differentiate in some lineages of T helper cells[93].

The role of CD4+ cells in the oral mucosa against *Candida albicans* is fundamental, although the importance of their products IL2 and interferon-gamma has not been confirmed[47,106,105]. Other cytokines involved in such primary immunological response are IL-6 e TNF (tumor necrosis factor)-alpha[107]. It is also possible that to occur direct antimicrobial action of T lymphocytes against *Candida* and other microorganisms[178].

Regulatory T cells (Treg) operate a fundamental role in the homeostasis of the immunological system[202,30]. Basically, they control the balance between the activation and the suppression of the immunological responses, although, with such control, they limit the antipathogenic action of the host[210,32,342,33]. The function of the Tregs is controlled by cytokines, antigen-presenting cells or directly, thru TLRs (toll-like receptors) by pathogens[304] or dendritic cells[31] and its migration from the inflammatory site to the lymphoid site[347]. Immunoregulatory cytokines as IL10 e TGFβ, produced by innate immunological cells in response to the molecules derived from the pathogens, can be also produced by Tregs[30]. The reduced number of Tregs in HIV+ patients suggests that such cells are lost with the HIV infection as the T conventional cells as well. However, Tregs can be preserved in lymphoid sites, and do not be infected by HIV virus, providing a partial regulatory immunological control in such different scenario[8,224].

T LYMPHOCYTES AND HIV VIRUS

The Th1 type acquired immunological response provided by CD4+ is considered the *premium* defence of the HIV+ patient against oral and vulvovaginal *candidiasis*, although the

immunological *armamentarium* against such fungical infection are complex and not totally clarified[174]. The number of $CD4^+$ lymphocytes is certainly reduced in the oral mucosa of HIV+ patients who present candidiasis[268,112], what is also confirmed in their periodontal tissues[293,227].

As alternative defence system, the epithelium of the oral mucosa induces response of the T $CD8^+$ cytotoxic lymphocytes[147], independently of the situation of the $CD4^+$ lymphocytes[85]. Such $CD8^+$ cells, important actors in the resistance of the oral mucosa to infections[58], are attracted to the oral epithelium[182] by cytokines IL1, IL6, IL8, TNF-alpha and TGF-beta, produced by oral keratinocytes of the oral epithelium[323,188].

The $CD8^+$ cells when activated by IL12 cytokine may inhibit the *Candida albicans* hyphae[35]; however, it is not commonly near to the fungical hyphae because the hyphae are usually superficially located in the oral epithelium[260,104]. The apoptosis of the $CD8^+$ cells in HIV+ patients is, in general, mediated by macrophages, although $CD8^+$ cells might be recruited by the oral mucosa in response to candidiasis, especially when the $CD4^+$ cell number is low[268,217].

T lymphocytes specific for *Candida albicans*, developed by the antigenic stimulation and IL12 are eliminated in HIV+ patients, independently of its affinity degree[169]. Furthermore, in HIV+ patients specific T lymphocytes for *Candida albicans* produce low amount of interferon-gamma, and possibly inuce, by negative feedback, a Th2 tolerance response[331]. Then, the HIV viral infection is associated to T regulatory cells (Tres) and decrease of the primary immunological response. It occurs decrease of the naive cells ($CD45RO^-$) and of the memory cells ($CD45RO^+$), both direct mediators of the acquired immunological response[311].

In response to oral candidiasis in HIV+ patients, Th17 and IL17 cytokine are essential, offering innate and acquired immunological response throughout neutrophils and anti-microbial factors[65]. T helper responses may occur throughout 03 cellular types: Th1, Th2 or Th17[36,168]. Th17 cells come from $CD4^+$ cells, and different of Th1, Th2 and Tregs cells[301] e produce the IL17 cytokine. They have become the focus of the applied Immunology, because they present special functions[93]. The role of the Th17 cells has been extensively studied *in vitro*; however, few details are known about its proprieties and its role in human immunological response[37].

In humans, Th17 cells hold distinct migratory qualities and antigenic specificity[4]. In the specific case of candidiasis, the action of Th17 cells and the cytokine IL17 have been presented of crucial importance[190]. In the other hand, the fungical pathogenic process also holds an important role in the cellular polarization. Fungical hyphae promote the differentiation of Th17 cells and the cells Th23/cytokine IL23; however, fungical yeasts promote the differentiation of Th1 cells ant the IL12 cytokine[4]. The role of TGFβ in modulating the activation of Th17 cells is critical. Cytokines IL23, IL1 and IL6 are also involved in the antifungical defence; although their participation is not completely clear[329].

In such defence, the pathogens are recognized by PRRs (pattern recognition receptors), which trigger the beginning of the immunological response to the infection[267]. The most studied way for fungus is the receptor *Dectin-1*, thru *Syk kinase* (*spleen tyrosine kinase*), *CARD9* e Raf-1[134], being critical in the induction of the Th17 cells[267]. The receptor *Dectin-1* is *C-type lectin* and is present in the NK (*natural killers*) cells, promoters of the innate response[45,262]. In the same way, *Dectin-2*, throughout *Syk kinase* e *CARD9*, contributes for the activation of the dendritic cells and the regulation of the acquired antifungical immunological[173,267].

CONCLUSIONS

Oral lesions, in special the oropharyngeal opportunistic fungical infection by *Candida albicans*, have been part of the clinical evaluation of HIV+ patients and have stimulated extensive research. In such circumstances, the incidence of oral candidiasis must consider many different factors, about the fungus and about the host patient.

Currently, the main discussion in the specialized literature involves the modulation of the immunological defence in immunodepressed HIV+ patients under antiretroviral coverage. However, many aspects of the possible vulnerability of the oral mucosa and the circumstances of its breakage and the fungical colonization and invasion are not clear enough. The interaction between the host and the commensal fungus *Candida albicans* in HIV+ patients must be further explored.

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