Immunology of oral candidiasis

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Received : 30-03-14
Review completed : 30-03-14
Accepted : 09-04-14

ABSTRACT

A successful pathogen is one that is able to effectively survive and evade detection by the host immune defense. Oral candidiasis has adopted strategies, which evade host defense and eventually cause disease in at-risk patients. Host defense against infections with *Candida* spp. depends on rapid activation of an acute inflammatory response by innate immunity, followed by an incremental stimulation of specific immune responses mediated by T-cells (cellular immunity) or B-cells (humoral immunity). Understanding these complex pathways of immune evasion can potentially contribute to the development of novel therapeutic strategies against oral candidiasis.

KEY WORDS: Cellular immunity, humoral immunity, oral candidiasis

In a day, today life people are affected by so many systemic diseases such as diabetics, hypertension, etc., Many systemic diseases and treatment for numerous conditions can predispose the individual to many bacterial and fungal infections. Those bacteria and yeast form a complex bio layer covering the mucosal membrane of the body. Among this candidiasis is considered to be important opportunistic pathogens due to increasing frequency of this infection in compromised patient groups such as those who on cancer chemotherapy, broad-spectrum antibiotic and human immunodeficiency virus (HIV)-infected individuals.[1]

Candida albicans is a unique human parasite capable of colonizes, infect, and persist on mucosal surfaces, and stimulate mucosal immune responses. *Candida* may seek to induce a protective host immune response that permits its own survival. Underlying acquired immunity to the fungus is usually present in immunocompetent adults, and is presumed to prevent progression from mucosal colonization to symptomatic infection.[2] Oral health is dependent on the integrity of the mucosa, which normally prevents the penetration of microorganisms as well as macromolecules, which might be antigenic.[3] Combination of recent knowledge and increasingly sophisticated technology, the future for *Candida* research will doubtless be fruitful, exciting, and highly rewarding.

Access this article online

Quick Response Code:

Website: www.jpbsonline.org

DOI: 10.4103/0975-7406.137251

The mucosa is also protected by two independent immune systems

- The systemic immune system and
- The secretory immune system.

The oral cavity is part of the secretory or mucosal immune system which can be stimulated locally or systemically. Diseases such as candidiasis are of particular interest because potentially

How to cite this article: Dineshshankar J, Sivakumar M, Karthikeyan M, Udayakumar P, Shanmugam KT, Kesavan G. Immunology of oral candidiasis. J Pharm Bioall Sci 2014;6:S9-12.

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both the secretory and systemic immune systems may be involved in the maintenance of oral health.[3]

Host defense mechanism against *Candida* infection

Host defense against infections with *Candida* spp. depends on rapid activation of an acute inflammatory response by innate immunity, followed by an incremental stimulation of specific immune responses mediated by T-cells (cellular immunity) or B-cells (humoral immunity). The first step in initiating an immune response during infection is represented by recognition of conserved chemical structures named pathogen-associated molecular patterns (PAMPs) of the invading pathogen by pattern recognition receptor (PRRs). It is now clear that PRR engagement by PAMPs is a crucial event coordinating the succession of processes leading to pathogen elimination. In the case of *Candida* infection, these events start with *Candida* sensing, followed by phagocytosis, killing, stimulation of cytokines, and the induction of adaptive specific immune responses. Phagocytosis of *Candida* is mediated by the concerted action of humoral and cellular components of the immune system. The most important cells involved in the phagocytosis (and subsequent killing) of *Candida* are neutrophils and macrophages. In addition, macrophages together with the monocytes are the major producers of proinflammatory cytokines. These innate immune cells are important cellular components of host defense against disseminated *Candida* infections. Following uptake by neutrophils and mononuclear phagocytes, killing of *Candida* occurs through both oxidative, and nonoxidative mechanisms.[4]

Candida cells as immunogens

Once the framework in which *Candida* immunogens and potentially protective antigens should be placed is established, it may be easier to say that the most potent *Candida* immunogen is the whole *Candida* cell itself.[5]

Heat-inactivated cells, and even more so, a living attenuated *Candida* vaccine, induce in animals not colonized by *C. albicans*, a highly protective response against a virulent fungal challenge both in mucosal infection models and in systemic ones. The role of early involvement of natural immunity, in particular interleukin (IL)-4, IL-12, and IL-6 dependent on the activation of the protective type 1 $CD4^+$ T-cell response has also been recently emphasized.[6]

In systemic *Candida* infection by parenteral challenge, the fungus disseminates through blood and lymphatics and induces a strong inflammatory response, mostly in the target organs, of which the kidney seems the principal one. The abscessual action is typical of this infection and hyphae of *C. albicans* are seen surrounded by polymorphonucleate cells and macrophages at the site of infection.[7]

Inflammation is the mandatory source and mediators of cytokines such as IL-6 and also tumor necrosis factor-α (TNF-α), whose critical role for induction of the protective axis natural immunity. The mechanisms of immunoregulation and effector activity, in both mucosal and systemic infections, major protective antigens have been actively sought for with only limited success.[8]

Interaction of *Candida albicans* with the host immune system

Innate primary defense mechanisms play key roles in preventing yeast colonization of the oral cavity.

These primary defenses include

- The physical barrier of the epithelia
- Lingual antimicrobial peptide, a defensin with broad-spectrum antimicrobial activity that is expressed in epithelia surrounding oral lesions
- Secretory IgA, which aggregates yeasts and assists in clearance, and
- Salivary factors.

Saliva flow rate affects microbial clearance, and specific salivary molecules-such as lysozyme, histatins, and lactoferrin have candidacidal properties.[9]

Phagocytes provide the second line of defense against invasive *Candida* infection. In the immunocompetent host, neutrophils, eosinophils, and monocytes phagocytose yeast and hyphal forms of *C. albicans* that gain access to deeper tissues. During acute inflammatory responses to *Candida* infection, neutrophils predominate numerically and in candidacidal activity. Both oxidative and nonoxidative mechanisms are involved in the intracellular killing of *Candida*, but these are not always effective. For maximum killing efficiency, granulocytes and macrophages require augmentation by cytokines such as interferon-gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor (CSF), and IL-1 and IL-2, produced by T-cells.[10]

A significant factor in the pathogencity of *C. albicans* is the ability of surface molecules, such as mannoproteins and complement receptor to modulate phagocyte responses.[11]

The importance of cell-mediated immunity in resistance to *Candida* infection is illustrated by the severe mucosal candidiasis seen as a result of T-cell dysfunction in AIDS patients and in many people with chronic mucocutaneous candidiasis (CMC). This contrasts with neutropenic patients, who are at greater risk of disseminated infection. Humoral immunity, in the form of serum antibodies, plays a lesser role in the defense against infection.[9]

Host defense immune factors against *Candida*

Granulocytes

Bone marrow-derived cells, probably neutrophils, are crucial to the natural resistance to *C. albicans*. Individual granulocytes can phagocytose up to 10 yeast, but the proportion killed remains constant at about 20-30% regardless of the number ingested. The myeloperoxidase (MPO)-hydrogen peroxide-halide system

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appears to play a major role in the intracellular killing of *Candida*. Susceptibility to candidal and staphylococcal infection has been the chief problem resulting from MPO deficiency. Okuda *et al*. (1991) reported a case of alveolar pyogenic granuloma in the maxilla caused by infection with *C. albicans* in a patient with MPO deficiency.[12]

The candidacidal activity of human neutrophils has been shown to be enhanced independently by immune IFN-α and TNF. In the presence of sub-optimal levels of IFN-α, TNF acts synergistically to increase neutrophil effector function. Cytokines such as granulocyte CSF can increase production of neutrophils by bone marrow and increase resistance to *C. albicans*. Granulocytes can also kill the mycelial elements of *Candida*, and the capacity to bind and to generate microbicidal oxidants is augmented by serum opsonins.[13]

Cell-mediated immunity

Although phagocytosis represents the prime mechanism by which *C. albicans* is controlled, the intrinsic candidacidal abilities of both granulocytes and macrophages are quite limited, and full expression of their effect is dependent on augmentation by cytokines synthesized or induced by T-cells. *Candida* infections are consistently seen when cell-mediated immunity is depressed. Lymphokine production by T-cells is initiated by an antigen-specific interaction. This process involves antigen processing and presentation by macrophages or other accessory cells that carry appropriate (compatible) Class 1 and Class 2 major histocompatibility complex antigens on their surface.[13]

In this context, it is significant that human *Candida*-specific T-cells require human leukocyte antigen-DR (HLA-DR)-compatible macrophages for their activation, and that *Candida* infection markedly increases the expression of HLA-DR and HLA-DQ antigens on the surface membranes of epithelial cells.[14]

Activation of T-cells produces a wide range of lymphokines that can, in turn, modulate the functions of macrophages and other leukocytes. IFN-γ is the only lymphokine known to increase the microbicidal activities of macrophages: it also initiates TNF synthesis by them. In the presence of suboptimal levels of IFN-γ, *Candida* killing by neutrophils is markedly enhanced by TNF. Unfortunately, the cytokines produced as a result of T-cell/macrophage interactions have the potential to exacerbate symptoms of illness as well as enhancing clearance of the infection.[13]

Polysaccharide antigens of *C. albicans* may generate a complex series of interactions that suppress both T- and B-cell responses. These effects may eventually block the synthesis of both IL-2 and IFN-γ, as well as the expression of the Tac antigen (the IL-2 receptor) by normal T-cells; antigen presentation and IL-1 production by monocytes may also be affected.[15]

Humoral immunity

Serum antibodies can affect the growth of *C. albicans*. The major specific immunologic factor in saliva is sIgA, which may be a primary defense against oral candidiasis by aggregating the organisms and by preventing their adherence to mucosal epithelium.[16]

Humoral and cell-mediated immunity to *C. albicans* may comprise a second line of defense when penetration of mucosa or systemic infection occurs. Both mucocutaneous and systemic candidiasis are typically associated with defects in the cell-mediated immune response. These can be caused by deliberate immunosuppression (as in transplant patients) or in cancer patients treated with cytotoxic drugs; they can be associated with some underlying disease, such as the HIV infection, or they may reflect specific deficiencies in the cell-mediated immune response, as in CMC.[13]

Immunological aspect of candidiasis

As far as specific immunity against oral candidiasis is concerned, both secretory IgA and cellular immunity might play a role in the protection of the oral mucosal surfaces against candidal infection. Indeed, a markedly increased prevalence of candidal infection can be seen in IgA-deficient individuals. Among patients with CMC, which is a systemic disease with widespread chronic hyperplastic candidiasis lesions, over 50% appear to have reduced IgA antibodies.[17]

In CMC, a wide spectrum of immune abnormalities has been reported, and these range from lowered serum lgM and IgG antibodies to defects in lymphocyte transformation and mitogen stimulation in the most severe types of CMC. It is not clear, however, whether these immune defects are primarily due to the disease or a consequence of it. A number of studies have shown restoration of immune functions once *Candida* has been cleared by antifungal therapy. There is considerable evidence to suggest that cell-mediated immune response is impaired in patients with CMC.[3]

It has been suggested that patients with CMC can be characterized into four groups

- Group 1 who have depressed delayed hypersensitivity (DH) abnormal macrophage migration inhibition factor (MIF) but normal lymphocyte proliferative response to *Candida* (lymphozytentransformations test [LTT]).
- Group 2 with no DH but normal MIF and LTT
- Group 3 with defects in all three cellular response and possibly in neutrophil chemotaxis also
- Group 4 with especially normal response.

As far as detected, humoral response were normal in all the groups.[3]

Budtz-Jörgensen demonstrated the role of cellular immunity in resisting chronic candidal infections in the rhesus monkey. Evidence for the significant role played by cellular immunity against *Candida* infection can be found in the observation that infection by the fungus is a widespread problem among patients with severe T-cell defects and not in those with B-cell defects, unless the latter also have concomitant T-cell defects.[18]

Williams *et al*., who characterized the inflammatory cell infiltrate in CHC using immunocytochemical techniques, concluded, on the basis of their finding that mucosal defense against *Candida* infection involves a cell-mediated reaction. This consists of recruitment of macrophages and local production of immunoglobulin with a prominent IgA component.[19]

Candida appears to vary between patients with different types of candidiasis. In some studies, it was shown that antibody titers in chronic hyperplastic candidiasis patients were not as high as in patients with *Candida*-associated denture stomatitis. It had been suggested that this observation perhaps reflects the greater mucosal area involved in the latter condition with the concurrent transmucosal penetration of antigens compared with most cases of chronic hyperplastic candidiasis.[17]

Conclusion

Although considerable progress has been made in the understanding of *Candida* and oral candidiasis during the last few decades, much remains to be done. Understanding the pathogenesis of fungal diseases from the perspectives of immunology, it is hoped that this knowledge will help direct the development of future therapeutics and minimize risk of disease in the ever-increasing population of immunocompromised patients seen in day today practice.

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Source of Support: Nil, **Conflict of Interest:** None declared.

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