T Helper Cell Dichotomy to *Candida albicans*: Implications for Pathology, Therapy, and Vaccine Design

**Abstract**

Acquired immunity to *Candida albicans* is believed to prevent mucosal colonization of adult immunocompetent individuals from progressing to symptomatic infection. Resistance to disease appears to correlate with the detection of delayed-type hypersensitivity responses in vivo and a T helper type 1 (Th1) cytokine secretion profile in vitro. Cellular immunodeficiency, particularly HIV infection, greatly increases the risk of mucosal infection, confirming that CD4+-cell-directed immunity is effective locally in controlling infectivity of the yeast. While Th1-type CD4+ cell activation resulting in phagocyte-dependent immunity clearly represents an important mechanism of antifungal resistance, clinical observations suggest that Th2-type CD4+ cell reactivity may be triggered by *Candida* antigens in several disease states, including symptomatic infections and immunopathology. This may imply that a Th1-type pattern of reactivity characterizes the saprophytic yeast carriage and resistance to disease by healthy humans, whereas Th2-type responses would be mostly associated with pathology. Moreover, *Candida*-specific T helper responses, namely humoral and cell-mediated immunity, appear to be reciprocally regulated, as typically occurs in experimental models of parasitic and retroviral infection, where the Th1/Th2 paradigm of acquired immunity has been best characterized. Recent studies, besides providing direct evidence for the occurrence of cross-regulatory Th1 and Th2 responses in mice with candidiasis, emphasize the potential of cytokine/anticytokine therapy for recruiting *Candida*-specific responses toward protective, Th1-type CD4+ cell reactivity. At the same time, these studies call attention to the possible consequences of *C. albicans* infection for immunopathology, allergy, and coinfection.
Introduction

Although the status of the yeast Candida albicans as a commensal in the human digestive tract is universally acknowledged, and it often colonizes the buccal cavity and vagina without causing overt symptomatology, the complex relationship that affects the balance between the status of the organism as a 'commensal' or 'pathogen' has not been adequately delineated [1]. On the one hand, altering the microbial environment and impairment of the host defense mechanisms by either underlying pathology or breakdown of anatomical barriers definitely contribute to increased infectivity and dissemination of the yeast. On the other, a newly emerging concept in microbial pathogenesis is that organisms causing chronic infection have evolved mechanisms to evade the immune responses resolving the acute stage of infection and favor their own persistence [2, 3]. Chronicity may then develop, or disease can be exacerbated via an increased infectivity of the pathogen, despite the fact that the down-regulation of a strong, potentially immunopathological reaction may be beneficial to the host [4, 5]. If the suppressed response is phagocyte-dependent [i.e., cell-mediated or T helper type 1 (Th1)] immunity, the Th1/Th2 paradigm of acquired immunity predicts that Th2-dependent immunity will become a prominent characteristic of the response, with implications not only for persistence of the organism or progression of infection, but also for the onset of immunopathology and autoimmunity [6].

A good example might be candidal infection in mice, where local control of infectivity in colonized mucosal tissue (but also yeast eradication in deep-seated foci of infection) is effected by phagocyte-dependent immunity, yet candidal antigens activate Th2 cells as an evasive strategy. As Th1 responses are in general more protective than Th2 responses against most infectious agents, particularly intracellular parasites, experimental models of C. albicans infection may be very useful to gain insight into the general immunoregulatory pathways, to facilitate vaccine development in infection, and to devise strategies for promoting the preferential activation of Th1 cells. This could be most helpful in a variety of disease states in which an inappropriate Th2 response mediates immunopathology or disease is best controlled by cell-mediated immunity.

T Helper Cells in Candidiasis

Patterns of susceptibility and resistance to protozoan, helminthic, and retroviral infections in experimental models have been associated with distinct, mutually exclusive profiles of cytokine production [2, 3]. For example, genetically susceptible mice have relatively high levels of interleukin (IL)-4 (Th2 associated), and low levels of interferon (IFN)-γ (Th1-associated) in their lymphoid tissue during infection with Leishmania major, whereas the opposite pattern is observed in genetically resistant mice with healing infections of the parasite. This dichotomy of responses implies that protective immunity depends on the activation of the appropriate CD4+ Th cell subset but can be down-regulated via inhibitory cytokines produced by the other subset as well as by a number of other cell types. The best characterized of these regulatory cytokines are IL-12 and IFN-γ on one side, and IL-4 and IL-10 on the other. Th1 cells, whose expansion requires the presence of IL-12 and IFN-γ, trigger phagocyte-mediated intracellular or extracellular killing of the pathogen (via IFN-γ) and are the principal mediators of delayed-type hypersensitivity (DTH). Th2 cells induce the production of IgG1 and IgE (via IL-4), favor the growth of mast cells (via IL-3, IL-4,