Early expression of local cytokines during systemic *Candida albicans* infection in a murine intravenous challenge model

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Abstract. Local cytokine production is a significant indicator for disease pathogenesis or progression. Previous studies on cytokine production during systemic *Candida albicans* (*C. albicans*) infection were solely on kidney or single cell type interaction with *C. albicans*. Therefore, the present study aimed to assess the early cytokine expression of various target organs (kidney, spleen and brain) over a 72-h time course during systemic *C. albicans* infection. The local cytokine profiles of the target organs during systemic *C. albicans* infection were measured by cytometric bead array and ELISA analysis. The results demonstrated that interleukin-6 (IL-6) and IL-2 were statistically significant ($P<0.05$) in the spleen at 24 and 72 h post-infection, whereas in the kidney, IL-6 and tumor necrosis factor-α (TNF-α) were statistically significant ($P<0.05$) at 24 and 72 h post-infection and CXCL-1 and transforming growth factor-β (TGF-β) were statistically significant ($P<0.05$) at 72 h post-infection. In the brain, IL-6 and TNF-α were statistically significant ($P<0.05$) at 24 and 72 h post-infection, whereas TGF-β was statistically significant ($P<0.05$) at 72 h post-infection. These findings demonstrate that host immune responses were varied among target organs during systemic *C. albicans* infection. This could be important for designing targeted immunotherapy against this pathogen through immunomodulatory approaches in future exploratory research.

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Introduction

Cytokines are a group of low molecular weight proteins that act as a mediator between cells. They are produced by leukocytes and a variety of non-immune cells in the body in response to stimuli. Cytokines are messengers of the immune system and play critical roles in regulating the immune response, hematopoietic development and cell-to-cell communication, as well as host responses to infectious agents and inflammatory stimuli (1,2).

Cytokines are not typically stored as preformed proteins. They are only produced when required in immune responses. Therefore, under normal circumstances, cytokines are not detectable or are present at low levels in body fluids or tissues. Their syntheses are initiated by gene transcription and their mRNAs are short lived. Fundamentally, their presence at elevated levels of expression or dysregulated production may associate with inflammation or disease pathogenesis (3).

Candida bloodstream infections remain the most frequent life-threatening fungal disease with *Candida albicans* (*C. albicans*) accounting for 70-80% of the *Candida* isolates recovered from infected patients. Previously, life-threatening *Candida* infection continues to increase due to the existence of drug resistance in *Candida*, inefficacy of the available antifungal drugs, diagnostic procedures and a steady increase of immunocompromised patients (4).

Systemic infection with *C. albicans* often results in high mortality and morbidity rate in immunocompromised patients. During systemic candidiasis, *C. albicans* is carried by the bloodstream to almost all the organs of the body, with the immune responses occurring in the kidney influencing the *C. albicans* infection outcome (5-7). The brain is the second most affected organ. However, its immunopathogenesis remains incomplete and requires further study. The spleen is a primary lymphoid organ that may possess specific protective mechanisms to confer it from infection by *C. albicans*. In addition, previous studies have mostly centred on investigating the responses on kidney or a single host cell type, such as monocytes and neutrophiles, which do not reflect the real