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Cellular and humoral immune responses during intrathoracic paracoccidioidomycosis in BALB/c mice

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Abstract

Paracoccidioidomycosis is a chronic infection that primarily affects the lungs. Here we investigated cellular and humoral immune responses after intrathoracic *Paracoccidioides brasiliensis* infection in BALB/c mice. *P. brasiliensis*-colony-forming units (CFUs), fungal DNA and granulomas in lungs increased progressively, peaking at day 90 postinfection (p.i.). IFN-γ production was highest on day 15 p.i., declining thereafter. The kinetics of the NO production was similar to that described for IFN-γ. In contrast, IL-10 increased from day 45 p.i. reaching a peak at day 90. Levels of serum IgG1 were higher than IgG2a between days 30 and 90 p.i. 30% of mice died by day 90 p.i. These data indicate that infection with *P. brasiliensis* by the intrathoracic route shows high IFN-γ and NO production at day 15 p.i., unable to control multiplication of fungi, which appears to be associated with a progressive increase in IL-10 and in the number and complexity of granulomas.

Keywords: *Paracoccidioides brasiliensis*; Paracoccidioidomycosis; IFN-γ; IL-10; Antibody response; Intrathoracic route

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Résumé

La paracoccidioïdomycose est une infection chronique qui affecte principalement les poumons. Nous avons réalisé une étude chez des souris BALB/c sur la réponse immunitaire cellulaire et humorale après une infection intrathoracique par *Paracoccidioides brasiliensis*. Nous avons constaté une augmentation progressive d'ADN de *P. brasiliensis* et de granulomes dans les poumons pour culminer au 90^{e} jour après l'infection. La production d'IFN-γ était plus élevée le 15^{e} jour après l'infection, pour décroître ensuite. La cinétique de la production de NO était similaire à celle décrite pour l'IFN-γ. En revanche, l'IL-10 a augmenté après le 45^{e} jour, pour atteindre un pic au 90^{e} jour après l'infection. Les niveaux d'IgG1 étaient supérieurs à IgG2a entre le 30^{e} et le 90^{e} jour après l'infection dans les sérum. 30% des souris sont mortes sur les 90 jours de l'expérimentation. Ces données indiquent que l'infection intrathoracique par *P. brasiliensis* montre une haute production d'IFN-γ et de NO après quinze jours, n'entraînant aucun contrôle de la multiplication fongique qui semble être associée à une augmentation progressive de IL-10, au nombre et à la complexité des granulomes.

Mots clés : Paracoccidioides brasiliensis ; Paracoccidioïdomycose ; IFN-γ ; IL-10 ; Réponse anticorps ; Infection intrathoracique

1. Introduction

Paracoccidioidomycosis, or South American blastomycosis, is a chronic granulomatous infection caused by the dimorphic fungus *Paracoccidioides brasiliensis* [1]. The lung is the organ of entry of *P. brasiliensis*, through the inhalation of fungal conidia, which can reach the pulmonary alveolar epithelium and differentiate into the pathogenic yeast form [2]. The spectrum of paracoccidioidomycosis ranges from benign and localized to severe and disseminated forms. The acute form affects young patients of both sexes and involves mainly the reticuloendothelial system, whereas the chronic form is most prevalent in adult males and has a predominant pulmonary and/or mucocutaneous involvement that is often fatal [3].

Cellular immune response is markedly involved in host defense against *P. brasiliensis* infection, determining the severity of the disease and its clinical form [4]. High levels of specific antibodies are proved in the serum of infected individuals, but it has been almost definite that these antibodies have no direct connection with the defense mechanism of the host [3]. There are significant differences in susceptibility among inbred strains of mice, resistant mice exhibited low fungal load in many organs and the infection trends to resolution through a response mediated by a dominant T-helper 1 (Th1) cell phenotype with prominent IFN-γ production [5]. This cytokine appears to be a major mediator of resistance against *P. brasiliensis* infection in mice, as it promotes the antifungal activity of the macrophages in part through NO production. Although iNOS-derived NO appears to be essential for resistance to paracoccidioidomycosis, the high and continued NO production was associated with susceptibility [6–8]. Susceptible mice develop a progressive disease, which seems to result mainly from T cell dysfunction and unbalanced activation of Th1 and Th2 cells with high IL-4 and IL-10 production [9] and [10]. The granuloma formation plays