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# EVALUATION OF MACROPHAGES AND T CELLS ACTIVITY IN MURINE EXPERIMENTAL MODELS OF HIGH AND LOW ANTIBODY-PRODUCERS (SELECTION IV-A) INFECTED WITH *Paracoccidioides brasiliensis*

**THESIS.** C. C. Pedigone submitted this thesis for her Masters in Tropical Diseases at Botucatu School of Medicine, São Paulo State University, UNESP, Botucatu, São Paulo, Brazil, 1998.

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**ABSTRACT:** The goal of this work was to evaluate the activity of macrophages and T cells in murine experimental models of paracoccidioidomycosis using High (H) and Low (L) antibody-producer mice of the IV-A selection, and to explain the differences in the pattern of pulmonary lesions showed by both strains. Animals were intravenously infected with 18 strains of *P. brasiliensis* (2.0 x 105 yeast/animal) and sacrificed after 3 days, and 1, 2, and 4 weeks. The following parameters were observed: recovery of viable fungi from pulmonary lesions; lymphocytes proliferative response to Concanavalin A (Con A); INF-$\gamma$ determination in the serum and in the supernatant of spleen cells culture; and $H_2O_2$, NO, and TNF-$\alpha$ release by peritoneal macrophages. $H_{IV-A}$ mice had a higher recovery of viable fungi from the lung in the beginning of the infection (3 days and 1 week) when compared with $L_{IV-A}$. This was inverted in the last periods of time, and $L_{IV-A}$ showed a higher recovery of fungi. With regards to the lymphocytes proliferative response, there was a positive association between the higher recovery of fungi in the $H_{IV-A}$ strain and the lower proliferative response only after 3 days and 1 week. Higher levels of INF-$\gamma$ were remarkably related to lower recovery of fungi in the $H_{IV-A}$ animals. With respect to the activation state of macrophages, the higher production of $H_2O_2$ in the $H_{IV-A}$ strain after 3 days was associated to a control of the fungi multiplication in the lung. On the other hand, the decrease in this metabolite production in the $L_{IV-A}$ strain was associated to an increase in the recovery of fungi. NO production was increased in $H_{IV-A}$ strain when these animals showed lower recovery of fungi, but this association cannot be made in the $L_{IV-A}$. Another indicative of macrophage activation was TNF-$\alpha$ production. This cytokine level was high in the beginning of the infection in both strains. However, this increase cannot be associated to a possible control of fungi multiplication, mainly in the $H_{IV-A}$ strain, when the increase of this cytokine was associated to a higher fungi recovery. Thus, the higher levels of TNF-$\alpha$ showed by the infected animals, when compared to controls, were considered as a parameter of macrophage activation and not as a regulatory cytokine involved in fungi multiplication. Our results show the important role of INF-$\gamma$ in the defense mechanisms against *P. brasiliensis*.

**KEY WORDS:** *Paracoccidioides brasiliensis*, Biozzi mice, immune response.

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