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*Research Article*

# Impact of *Paracoccidioides brasiliensis* Coinfection on the Evolution of *Schistosoma mansoni*-Induced Granulomatous Liver Injury in Mice

**Matheus Pereira de Araújo,[1] Eva Burger,[1] Rômulo Dias Novaes,[1] Amanda Ami Akatuti,[1] Maria Ângela Rodrigues,[1] Ana Carolina Silvério Cerqueira Mendes,[1] Giulia Maria de Castro Bani,[1] Eliziária Cardoso Santos,[2] Andréia Aparecida Santos Mendonça,[2] and Raquel Lopes Martins Souza[1]**

[1]*Instituto de Ciências Biomédicas, Universidade Federal de Alfenas (UNIFAL-MG), Alfenas, Minas Gerais, Brazil*
[2]*School of Medicine, Universidade Federal dos Vales do Jequitionhonha e Mucuri (UFVJM), Diamantina, Minas Gerais, Brazil*

Correspondence should be addressed to Raquel Lopes Martins Souza; souzaraquel807@gmail.com

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The pathogens *Schistosoma mansoni* and *Paracoccidioides brasiliensis* share common geographic areas, determining infectious diseases with high mortality rates worldwide. Histopathological and immunological changes induced by each pathogen are well understood; however, the host responses to *S. mansoni* and *P. brasiliensis* coinfection are still unknown. Thus, we investigated liver damage and cytokines production in a murine model acutely and chronically coinfected with these pathogens. Fourty male Swiss mice were infected with *S. mansoni* and *P. brasiliensis* alone or coinfected. The animals were euthanized with 50 (acute infection) and 120 (chronic infection) days of infection. All infected animals exhibited liver inflammation. Intense granulomatous inflammation was detected in animals infected with *S. mansoni* alone and those coinfected. Productive and involutive granulomas were clearly observed in acute and chronic infections, respectively. Granuloma size was reduced in the acute phase and increased in the chronic phase of *S. mansoni* and *P. brasiliensis* coinfection, compared with animals infected only with *S. mansoni*. In the chronic phase of infection, the granulomatous inflammation in coinfected animals was characterized by intense neutrophils accumulation and reduced eosinophils number. IFN-$\gamma$, IL-2, IL-4, and IL-5 circulating levels were increased in all infected groups. Coinfected animals presented attenuated IFN-$\gamma$ and IL-4 production in the acute and chronic infections. Taken together, our findings indicate that coinfected animals exhibited a differential modulation of granulomatous inflammation during the acute and chronic phases of infection, which was potentially associated with a divergent profile of cytokines production and migration of neutrophils and eosinophils in response to *S. mansoni* and *P. brasiliensis* antigenic stimulation.

## 1. Introduction

The development of infectious diseases is deeply influenced by the interaction between pathogen phenotype (i.e., infectivity, pathogenicity, and virulence) and host conditions, such as immunological health and presence of comorbidities, including coinfections [1–3]. Although coinfections are often neglected, these diseases are highly prevalent worldwide, especially in developing countries [4, 5]. Coinfections are more dangerous than infections induced by a single pathogen [3, 6], especially considering that divergent (i.e., cellular *vs.* humoral, or Th1 *vs.* Th2 *vs.* Th17) and unbalanced immunological phenotypes simultaneously are required to combat two or more parasite species can compromise the infection resolution [3, 7, 8]. In general, coinfections are typically determined by pathogens that share common endemic areas [9], such *Schistosoma mansoni* that causes schistosomiasis in Latin America [10] and the fungus *Paracoccidioides brasiliensis,* the etiological agent of paracoccidioidomycosis [11].