Comparative Murine Infection by Paracoccidioides lutzii and Paracoccidioides brasiliensis Reveals Distinct Polymorphonuclear Cell Activation and Cytokine Profiles

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Introduction: Paracoccidioidomycosis (PCM) is a major systemic and endemic mycosis prevalent in Latin America, primarily caused by the thermodimorphic fungi *Paracoccidioides brasiliensis* (specifically the virulent Pb18 strain) and the distinct species *Paracoccidioides lutzii* (Pl). Although these species share overlapping clinical manifestations, their interaction with the host immune system and their susceptibility to antifungal therapies differ significantly. **Objectives:** This study investigated and compared the early innate immune parameters induced by these two distinct etiological agents using a well-established murine air-pouch model, which mimics a localized inflammatory microenvironment. **Methods:** Following a ten-day infection period, several critical immunological markers were rigorously evaluated, including local cellular recruitment, oxidative metabolism, cytokine profiles, and the overall fungal load within the cavity. Mice infected with the Pb18 strain of *P. brasiliensis* exhibited a markedly higher absolute number of polymorphonuclear neutrophils (PMNs) and monocytes recruited to the infection site compared to those infected with *P. lutzii*. **Results:** Furthermore, significant differences were observed regarding oxidative stress and antioxidant defenses, specifically in the production of Reactive Oxygen Species (ROS), catalase, and peroxidase activity between the two fungal strains. In terms of soluble inflammatory mediators, while the levels of GM-CSF, IL-4, IL-12, and IL-17 remained statistically similar between the experimental groups, the Pb18 infection induced substantially higher levels of pro-inflammatory cytokines, namely TNF-α and IL-1β. Conversely, *P. lutzii* infection elicited lower levels of these cytokines but led to a significantly higher production of IL-10, KC, IFN-γ, and Nitric Oxide (NO) than Pb18. Additionally, animals infected with the Pb18 strain showed a slightly higher index of fungal viability and burden at the end of the experimental period. Taken together, these findings clearly demonstrate that *P. brasiliensis* (Pb18) and *P. lutzii* elicit distinct innate immune profiles, characterized by divergent neutrophilic activity, microbicide mechanisms, and inflammatory mediators. **Conclusion:** Understanding these strain-specific responses is fundamental for clinical management and targeted antifungal therapy, including predicting Fluconazole efficacy, as host-pathogen interactions vary dramatically between species. Consequently, identifying the specific etiological agent in clinical practice is a crucial step for predicting disease progression, managing tissue damage, and optimizing therapeutic outcomes in Paracoccidioidomycosis.

Agradecimentos: This work was supported by Fundação de Amparo à Pesquisa do Estado de Minas Gerais - FAPEMIG-BPD-00341-22 and APQ 01878/24 and Conselho Nacional de Desenvolvimento- CNPQ (CNPq-309917/2020-4).