TITLE: INVOLVEMENT OF TOLL-LIKE RECEPTORS AND INTEGRINS IN IL-8 SECRETION BY EPITHELIAL CELLS DURING INTERACTION WITH *Paracoccidioides brasiliensis*

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ABSTRACT: Paracoccidioidomycosis is one of the most relevant systemic human mycoses that is endemic in Latin America, and it is caused by fungi of the genus *Paracoccidioides*. Once in the lungs, *Paracoccidioides* interacts with epithelial cells, which in addition to forming a structural barrier, they also promote an innate immune response through the secretion of inflammatory mediators that recruit immune cells. Over the years, our research group has been dedicated to studying cellular signaling mechanisms involved in the secretion of the proinflammatory cytokines IL-6 and IL-8, induced by *Paracoccidioides,* in the human lung epithelial A549 cell lineage, and recently, we demonstrated that integrins participate in this event. In this work, we verified that *P. brasiliensis* yeasts differently modulate α3 integrin protein levels during the 24 h-infection of A549 epithelial cells. By Western blot, we demonstrate that although *P. brasiliensis* induces an increase of the α3 integrin expression in the first 5 hours of A549 cell infection, the fungus promotes almost the total absence of this integrin protein levels in later times of infection (24 h), which may be due to the fungal inducement of α3 integrin degradation in epithelial cells. Regarding α5 integrin, *P. brasiliensis* increases this receptor protein levels even after 24 h of interaction with A549 cells. Moreover, by coimmunoprecipitation, we observed that *P. brasiliensis* promotes the interaction of α3 (in the first hours of infection) and α5 integrins with TLR2. Using siRNA to silence TLR2 expression, we found that the decrease of α3 integrin protein levels occurs in a TLR2-dependent manner, which in turn is involved in the secretion of IL-8 levels by the epithelial cells infected with *P. brasiliensis* yeasts. On the other hand, we found that the secretion of IL-8 in infected cells is independent of TLR4. Thus, these results indicate that *P. brasiliensis* may modulate receptor activity in the host cell differently during infection.

Keywords: *Paracoccidioides*, Epithelial Cells, Alpha 3 Integrin, Interleukin-8, Toll-like Receptor 2.

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