

**TITLE:** CELL WALL MODULATION OF *Paracoccidioides brasiliensis* IN RESPONSE TO HYPOXIA

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**ABSTRACT:**

Thermomimorphic fungi of the *Paracoccidioides* genus are the etiological agents of paracoccidioidomycosis (PCM), a systemic mycosis in Latin America. The interaction between *Paracoccidioides* spp. and its extracellular environment are important for the successful establishment of the fungus in the host. Although pathogenic fungi respond to different stresses such as: high temperatures, ROS/RNS, pH changes, and macro and micronutrient limitation, little is known about how pathogenic fungi respond to oxygen limitation, mainly hypoxic conditions are encountered in the host tissue. In this sense, this work aims to evaluate the modulation of cell wall components of *Paracoccidioides brasiliensis* in response to environments with low oxygen concentrations. Therefore, the fungus was subjected to hypoxia (approximately 1% of O<sub>2</sub>) in an anaerobic jar, and then cell viability, RT-qPCR, flow cytometry, phagocytosis, cAMP/PKA dosage, and antifungal susceptibility assay were performed. The results demonstrate increased viability of *P. brasiliensis* when incubated at low oxygen concentrations for 24 hours. Furthermore, genes involved in  $\alpha$ -glucan synthesis increased while that related to  $\beta$ -glucan synthesis reduced their relative expression in response to hypoxia. Assay of interaction between  $\beta$ -glucan and Dectin-1 by flow cytometry demonstrated that there is a reduction in the interaction between  $\beta$ -glucan and its receptor at low oxygen concentrations. Moreover, *P. brasiliensis* yeasts are resistant to phagocytosis when previously subjected to hypoxia. In addition, the cAMP-PKA pathway does not appear to be involved in the cell wall modulation of *P. brasiliensis* yeast under low oxygen concentrations. Finally, the yeasts submitted to hypoxia showed lower susceptibility to the antifungal fluconazole. Together, the results found in this work suggest a cell wall modulation of the pathogenic fungi *P. brasiliensis* in response to hypoxia.

**KEY-WORDS:** *Paracoccidioides brasiliensis*, Hypoxia, Cell Wall,  $\beta$ -glucan.

**DEVELOPMENT AGENCY:** FAPESP, CNPq and Capes.