

TITLE: HEMOGLOBIN INDUCES THE EXPRESSION OF ADHESINS AND ENZYMES RELATED TO DEFENSE AGAINST OXIDATIVE STRESS IN *Paracoccidioides lutzii* CELL WALL

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ABSTRACT:

Paracoccidioides spp. is a genus of pathogenic fungi, which are the etiological agents of paracoccidioidomycosis, an endemic disease in Latin America. In the infection scenario, the fungus undergoes iron (Fe) deprivation promoted by the nutritional immunity of the host. As a way to counteract this mechanism, the pathogen employs systems with high affinity and specificity for uptake of Fe from host sources. In the human organism, about 60 to 70% of Fe is associated with the heme cofactor present in the oxygen carrier protein hemoglobin. A recent study demonstrated the ability of *Paracoccidioides* spp. lysate erythrocytes and use hemoglobin as Fe sources through a receptor (*PbRbt5*)-dependent process present on the cell wall. However, more detailed information on the process is scarce. In this view, the objective of this work was to investigate additional mechanisms that *Paracoccidioides lutzii* employs for the use of hemoglobin. For this, we subjected yeast cells of *P. lutzii* to Fe deprivation for 36 h in MMcM medium and then, the cells were transferred to MMcM without Fe (control) or MMcM containing 10 μ M of bovine hemoglobin (treatment). After 48 h, cell wall extraction was performed and the obtained extracts were submitted to nanoUPLC-MS^E to investigate the cell wall proteome of *P. lutzii* after the fungus exposure to hemoglobin. The data obtained demonstrated that, when in the presence of hemoglobin, *P. lutzii* expresses a high number of adhesins in the cell wall, such as EF-Tu, recently described in the literature as adhesin in *Paracoccidioides brasiliensis*. In addition, other proteins identified in the cell wall were predicted as potential adhesins, through the online adhesin predictor FaaPred (<http://bioinfo.icgeb.res.in/faap/>). Enzymes related to ROS detoxification, such as catalase, have also been identified in the cell wall. The present findings allow us to infer that *in vivo* *P. lutzii* uses these molecules to adhere and lyse erythrocytes. Lysis of erythrocytes causes the release of heme/hemoglobin, which may promote the generation of ROS. The induction of enzymes related to defense against oxidative stress in *P. lutzii* cell wall indicates that the fungus counteracts the toxicity generated by heme/hemoglobin, which allows the absorption and use of these molecules. Our data also highlight interesting targets for future studies, which may contribute to the understanding of the mechanisms employed by *Paracoccidioides* spp. for hemoglobin utilization.

Keywords: Paracoccidioidomycosis, PCM, nanoUPLC-MS^E, Iron, Host-pathogen interactions

Development Agencies: INCT-IPH, CNPq, CAPES, FAPEG