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Thesis Abstract

Biochemical and molecular studies of copper metabolism during the infection process of the human pathogenic fungus *Paracoccidioides brasiliensis*

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The fungus *Paracoccidioides brasiliensis* is a human pathogen with a wide distribution in Latin America. The fungus causes paracoccidioidomycosis when mycelia reach the lungs. The success of the infection depends on the acquisition of essential micronutrients such as copper, which is required as a cofactor for a variety of enzymes important in several biological processes, such as respiration, growth and iron uptake. Previous studies of the Laboratory of Molecular Biology showed that a high-affinity copper transporter (*Pb*CTR3) is a molecule that is highly expressed and probably necessary for the establishment of infection by *P. brasiliensis*. In the present study, the genomic and cDNA sequences encoding *Pb*CTR3 of *P. brasiliensis* were isolated and characterized. The cDNA consists of 582 bp and encodes a protein of 193 amino acids, with a predicted molecular mass of 21.5 kDa and pI of 8.6. The genomic sequence has four exons interrupted by three introns. *In silico* analysis was performed on the database of the structural genome of *P. brasiliensis* (http://www.broad.mit.edu/annotation/genome/paracoccidioides_brasiliensisMultiHome.html), where genes involved in maintaining the homeostasis of copper have been identified and used to design a model of copper homeostasis in *P. brasiliensis*. The transcriptional behavior of *Pbctr3* and genes involved in copper homeostasis were examined during exposure of yeast cells of *P. brasiliensis* to conditions of copper and iron depletion, by real time qRT-PCR. A significant change was found in the transcription level of these genes in the absence of copper, as well as in the combined absence of both metals. qRT-PCR was used to analyze the expression of *Pbctr3* and *Pbcrp* (which encodes a protein responsive to copper) in yeast cells of *P. brasiliensis* derived from infected lungs and spleen at different times of infection. *Pbctr3* and *Pbcrp* were super-regulated during experimental infection. Taken together, these data suggest the importance of *Pb*CTR3 and of copper/iron uptake during the infection process.

Key words: Copper; *Paracoccidioides brasiliensis*; Gene expression and infection

