TITLE: COMPARATIVE PROTEOMIC ANALYSIS OF THE CELL DIFFERENTIATION PROCESS IN *Paracoccidioides brasiliensis.*

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ABSTRACT:
Paracoccidioides sp. is a dimorphic pathogenic fungus and causative agent of paracoccidioidomycosis (PCM). The fungus is found as mycelium in the soil at temperatures below 25ºC, while in host tissues, and at 36-37ºC it takes the yeast form. The ability to switch between multicellular hypha and unicellular yeast is essential for pathogenicity, virulence and lifecycle of this pathogen and this aspect of morphogenesis is essential to the establishment of infection. Proteomic approach using (NanoUPLC-MS^E) was applied to evaluate the differential proteomic profile of *P. brasiliensis* (Pb18, phylogenetic lineage S1) in the mycelium and yeast fungal phases and during an early stage in the mycelia-to-yeast transition. The yeast and mycelia phases were maintained by 7 and 15 days, at 22 °C and 36 °C, respectively. For the transition form, the mycelia phase was grown in liquid medium for 16 h at 22 °C followed by incubation for 22 h at 36 °C. The differences in protein expression levels among the three conditions were tested using the one-way ANOVA and Tukey's test. The statistical analyses were performed using R software. A *p*-value equal to or less than 0.05 was considered statistically significant. A total of 726, 585 and 635 proteins were identified, and relatively quantified in mycelia, transition and yeast, respectively, totalizing 1946 proteins. From those 200, 177 and 210 proteins were upregulated in the different forms of the fungus mentioned above, respectively, and the same protein could be regulated in more than one condition. Analyses of functional categories to which those proteins belong provided us a comprehension of the metabolic reprogramming that occurs during the cell differentiation process. During the transition and in the yeast phase, beta-oxidation and glycolysis were induced. Surprisingly the fermentation process was activated in mycelia along with ATP production by the respiratory chain. Some proteins related to virulence, were accumulated in the dimorphic transition and yeast cells, as superoxide dismutases, immunodominant antigen gp43, enolase and aqualysin, showing that in the early stages of the cell differentiation process, occurs the induction of proteins associated with cell adhesion and invasion, important for establishing the PCM. The obtained data can be relevant to the understanding of the thermal dimorphism and to the fungal establishment in the host.

Keywords: *Paracoccidioides* sp.; dimorphism; proteomic analysis.

Development Agencies: INCT-IPH, CNPq, CAPES/PNPD and FAPEG.