TITLE: TWO-CARBON METABOLISM ACROSS MEMBERS OF THE *Paracoccidioides* GENUS

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ABSTRACT:

Paracoccidioides is the etiological agent of paracoccidioidomycosis (PCM), one of the most prevalent systemic mycosis in Latin America. Phylogenetic analyzes revealed that the genus *Paracoccidioides* comprises two species: *P. brasiliensis* and *P. lutzii*. In addition, *P. brasiliensis* was classified in different phylogenetic lineages [S1 (divided into S1a and S1b), PS2, PS3 and PS4], that can potentially differ in their biochemical and molecular characteristics, virulence and immune response in the host. To grow, a pathogen has to assimilate carbon and must have a metabolic flexibility in order to assimilate available nutrients in different niches of the host. Acetate is a two-carbon compound and important source of acetyl-CoA. Its use requires the tricarboxylic acid (TCA) shunting through the glyoxylate cycle. We evaluated proteomic profiles in different isolates, members of distinct phylogenetic species, [*Pb*01, *Pb*339, *Pb*03, and *Pb*EPM*83*] in sodium acetate as the carbon source, using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). A total of 1280, 1211, 1462 and 1160 proteins were reproducibly identified, and relatively quantified in *P. brasiliensis* members *Pb*339, *Pb*03, *Pb*EPM*83,* and *P. lutzii*, respectively, totalizing 5113 proteins. Notably, a total of 744, 442, 569 and 526 proteins were differentially expressed in the isolates mentioned above, respectively, considering the proteins that presented 50% difference in expression values, comparing the ratios between sodium acetate and glucose. The analysis revealed the induction of proteins related to gluconeogenesis, glyoxalate cycle, response to stress and degradation of amino acids in the four evaluated isolates. Differences between the isolates were observed as higher increases in the expression levels of proteins belonging to the TCA and respiratory chain in *Pb*EPM83 and *Pb*01. The ethanol production, β-oxidation and the methylcytrate cycle showed high expression in *Pb*01and *Pb*EPM83. The proteomic profile indicates that the four isolates reorganize the metabolism for the use of the acetate as carbon source, with metabolic differences among the members of the phylogenetic species evaluated.

Keywords: *Paracoccidioides* spp.; phylogenetic species; two-carbon source; sodium acetate; proteomics.

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