Peptides modulators of malate synthase of *Paracoccidioides brasiliensis* obtained from Protein-Protein interactions and docking simulations

Raisa Melo Lima, Luciane Sussuchi, Gabriela Lima de Menezes, Célia Maria de Almeida Soares, Maristela Pereira and Roosevelt Alves da Silva

Universidade Federal de Goiás

Paracoccidioidomycosis (PCM) is a systemic mycosis endemic in Brazil, where are recorded about 80% of cases worldwide, and It has Paracoccidioides sp. as the etiologic agent. Malate synthase of Paracoccidioides species (*Pb*MLS) is an important enzyme related to the fungal metabolism, once it is essential in the glyoxylate cycle, a secondary metabolic pathway of the citric acid cycle exclusive to microorganisms and plants. Its absence in humans makes this enzyme an interesting subject to study, mainly in rational drug design. From recent in vitro studies, several interacting proteins of *Pb*MLS were classified, but the modes of interaction and key regions involved in protein-protein interfaces (PPIs) have not been described yet. In this work, six (6) binding proteins (BPs) were selected to describe the PPI's of MLS. Their 3D structures, as well as *Pb*MLS, were predicted by homology modeling using I-TASSER server, and subsequent molecular dynamics simulations (MD). The most common conformational modes of each protein were obtained by cluster analysis of the trajectories generated by MD. Molecular docking simulations using Gramm-X were then performed for the conformational modes of *Pb*MLS against the BPs, resulting in a total of 36 complexes. Based on the higher frequency of some small fragments of proteins observed in the IPP's, 57 peptides with sizes between 5 and 20 residues, were initially selected from five regions of *Pb*MLS, those considered more frequent in the protein-protein interactions. FlexPepDock simulations were performed to optimize the atomic coordinates of the peptide complexed with *Pb*MLS, and concomitantly, PepFOLD simulations were performed to evaluate the stability of each peptide in solution. Based on the lower energy of peptides linked to *Pb*MLS, as well as the stability of their structures in solution, six (6) peptides were selected as promising ligands to *Pb*MLS. The stability and patterns of interactions of these peptides are showed in detail.

Supported by CNPq, FINEP, CAPES and FAPEG