Área: MED

Molecular Modeling and Structural Comparison of *Leishmania* Sirtuin 2 Enzymes, an Epigenetic Target in Drug Discovery

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Highlights

Sirtuin 2 models from species of *Leishmania* and the human homolog were built by Comparative Modeling. Molecular Dynamics were employed to evaluate the residues involved in their substrates' binding.

Resumo/Abstract

Leishmaniasis are neglected diseases that affect a large part of the world's population, mainly in developing countries, causing major socioeconomic impacts. The medications available to treat these diseases are ineffective and have serious adverse effects. The process of researching new drugs involves, among other things, a selection of biochemical targets essential for the survival and development of the causative agent. In this sense, Sirtuin 2, an epigenetic enzyme with hydrolase activity essential for the survival of parasites of the genus *Leishmania*, presents itself as an interesting target in the search for new drugs against these parasites. Structure-Based Drug Design requires knowledge of the three-dimensional structure of the target protein. Therefore, the structural elucidation and a detailed study of Sirtuins from various species of the genus *Leishmania* presents itself as an important approach in the application of this strategy in the search for chemotherapeutic agents. To date, in the *Trypanosomatidae* family, the only experimentally resolved three-dimensional structure of a Sirtuin 2 enzyme is that of the *Leishmania infantum* species Sirtuin 2-related protein 1 (Protein Data Bank accession code 5OL0). Thus, this work applied the Comparative Modeling approach using the software Modeller in the construction of Sirtuin 2-related protein 1 (Sir2rp1) models of the species *L. infantum*, *L. major*, and *L. braziliensis*, whose amino acid sequences were retrieved from the UNIProt database. The constructed models were validated by means of the Modeller's DOPE score function and the servers PROCHECK, MolProbity and QMEAN, evaluating their stereochemical quality and their folding. The Sirtuin 2 natural ligands were superimposed in the built models using the PyMol software and the validated complexes were submitted to Molecular Dynamics simulations through the GROMACS package. The refined complexes were then analyzed by means of the softwares PyMol and LigPlotPlus and the packages GROMACS and gmx_MMPBSA, and the substrates' binding sites and the relevant amino acid residues involved in their binding and recognition were studied. The application of Molecular Modeling is an alternative for the structural study of homologous enzymes, making it possible to elucidate the points of interaction and the selectivity for substrates and modulators of these parasitic hydrolases. A comparative study between these enzymes expressed by different parasitic species provided us with an understanding of structural differences between them and in relation to the human homologous protein. The Comparative Modeling of the human Sirtuin 2 and its homologues from the species *L. infantum*, *L. major*, and *L. braziliensis*, the Molecular Dynamics simulations conducted with the constructed and validated enzymatic models complexed with their natural ligands, the calculations of the energy of interaction between the models and their substrates and the comparative structural study carried out between them provides us with a theoretical basis for the search for novel Sirtuin 2 inhibitors that are more selective and potent against the parasitic enzymes, paving the way for the development of safer and more effective leishmanicidal drug candidates.

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