CRYSTAL STRUCTURE OF ADENYLOSUCCINATE LYASE APO FORM FROM Schistosoma mansoni: A POTENTIAL CHEMOTHERAPEUTIC TARGET


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Schistosomiasis is a disease that affects about 207 million people worldwide, Schistosoma mansoni is the parasite responsible for it and does not have the purine “de novo” pathway, depending entirely on the purine salvage pathway to supply its purines demands. The purine salvage pathway has been reported as a potential target for developing new drugs against schistosomiasis. Adenylosuccinate lyase (SmADSL) is an enzyme in this pathway, that cleaves adenylosuccinate into adenosine 5'-monophosphate and fumarate. This project is part of a project aimed obtaining the structures three-dimensional of all enzymes of purine salvage pathway from the parasite. ADSL was amplified, cloned, expressed and purified at the Oxford Protein Production Facility (OPPF) in Harwell - UK. Robotic crystallization trials were performed and SmADSL APO crystallized in several conditions of the Morpheus crystallization kit. Several crystals were screened with x-rays and one dataset was collected for a crystal grown in the condition F2 (0,12M of monosacharides, 0,1M of MES/imidazole pH6.5, 30% of Ethylene glycol and PEG8000), on the macromolecular crystallography beamline I04-1 at Diamond up to 2.14 Å resolution. The crystal belongs to the P2_12_1 space group, with two monomer in the ASU. The structure was solved by the program Phaser using SmADSL with AMP previously solved in our group as a search model. The refinement is currently by program Phenix and Coot. The structure consists almost entirely of α-helices and only 2 β-sheet, divided into 3 domains and this is the only enzyme in this pathway to catalyze two separate reactions, both reactions catalyzed by adenylosuccinate lyase involve the beta-elimination of fumarate. Enzymes that catalyze this type of reaction belong to a superfamily, the members of which are homotetramers. This structure will increase the structural information available about the Schistosoma mansoni purine salvage pathway.

Key-words: Adenylosuccinate Lyase; Schistosoma mansoni; purine salvage pathway.