NEW INSIGHTS INTO *SCHISTOSOMA MANSONI* PURINE NUCLEOSIDE PHOSPHORYLASE GATE MOVEMENT

Pereira, H.M[1], Castilho, M.S[2], Garratt, R.C[1], Oliva, G[1].

[1]Instituto de Física de São Carlos-USP, [2]Faculdade de Farmácia-UFBA.

Purine nucleoside phosphorylase is a key enzyme of purine salvage pathway of *Schistoma mansoni* and is an attractive target for drug discovery and development. We solved 5 crystal structures of SmPNP in complex with substrates (guanosine, inosine, ribose-1-phosphate, hypoxanthine) and in the apo form. The structures of the complexes were obtained by soaking and the data collection was performed at beamlines MX1 and MX2 of LNLS. The resolution of the structures was: inosine 1.9Å, hypoxanthine 1.75Å, ribose-1-phosphate 2.1Å, guanosine 2.0Å and apo 1.65Å. The structures were solved by molecular replacement using the previously solved SmPNP structure. Refinement was performed employing the programs Refmac and Phenix, and Coot was used for model building and ligand placement. PNPs have been described as presenting a gate movement involving residues 250-266, whose conformation is alleged to be dependent on ligand binding. The conformational change tends to increase the secondary structure content via a coil to helix transition. Indeed, several authors have described that when the base-binding site is occupied, the C-terminal helix is extended by more than one turn at its N-terminus. Our observations derived from the above complexes, show that only nucleosides are able to induce conformational changes in the gate region. For example, the binding of hypoxanthine to the base binding site alone or of ribose-1-phosphate to both the ribose and phosphate binding sites does not induce the rearrangement of gate region. It would appear that both contributions from the sugar- and base-binding sites are necessary for inducing the conformational change associated with gate movement. Furthermore, to our surprise the apo structure shows part of gate region (residues 261-267) to be completely extended in a way never previously described. The structures of these complexes also clarify the mode of substrate binding in SmPNP and will help in the search and design of inhibitors of this important parasite enzyme.

Supported by FAPESP