Molecular models of enzymes of the oxidative pentose phosphate pathway from *Mycobacterium tuberculosis*


The World Health Organization reports that two million people are dying each year from tuberculosis, and one-third of the world’s population is infected with the causative bacterium, *Mycobacterium tuberculosis*. Metabolic pathways that are common to other organisms frequently have aspects that are peculiar to *M. tuberculosis*. Such is the case for ribose metabolism. Ribose, particularly in the form of ribose-5-phosphate, is essential to the synthesis of nucleotides and a number of important cofactors such as ATP and NAD$^+$. Additionally, this pathway oxidizes glucose and under certain conditions can completely oxidize glucose to CO$_2$ and water. Enzymes that function primarily in the reductive direction utilize the NADP$^+$/NADPH cofactor pair as co-factors as opposed to oxidative enzymes that utilize the NAD$^+$/NADH cofactor pair. The pentose phosphate pathway has both an oxidative and a non-oxidative arm. The oxidation steps, utilizing glucose-6-phosphate as the substrate, occur at the beginning of the pathway and are the reactions that generate NADPH. Model building of the enzymes of oxidative arm, glucose-6-phosphate dehydrogenase, 6-phosphogluconolactonase and 6-phosphogluconate dehydrogenase were carried out using the program Parmodel, which is a web server for automated modeling and protein structural assessment. Parmodel runs a parallelized version of MODELLER. We have constructed three-dimensional models by comparative molecular modeling, and these models are further assessed by Procheck and Verify-3D. The models present good correlations with its templates, and the possible interactions between the structural NADP$^+$ and substrate in glucose-6-phosphate dehydrogenase, and in 6-phosphogluconate dehydrogenase are considered. In glucose-6-phosphate dehydrogenase, the first enzyme, the tetramer interface remains the flexibility in the predominantly hydrophilic dimer-dimer interactions, as observed in the template. In 6-phosphogluconate dehydrogenase, the third enzyme, each subunit of the dimer conserves the three domains: the domain of NADP$^+$, the domain of the dimer interface and the C-terminal domain. These three-dimensional structures can help in the understanding of the action mechanisms of this essential pathway in *M. tuberculosis*. 