Structural studies of two novel peroxidases from the protozoan parasite *Trypanosoma cruzi*

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Abstract:

The protozoan parasite *Trypanosoma cruzi* is the causative agent of Chagas' disease. In Latin America, 16-18 million people are infected by the parasite creating a major health problem. The disease is fatal in 15-30% of those infected while others are inflicted by serious disabilities. Drugs currently used in the treatment of Chagas' disease often have toxic side effects and fail to clear parasitaemia and their mode of action is unknown. One of these drugs, nifurtimox, undergoes redox cycling with the parasite.

Reactive oxygen species (ROS), such as hydroperoxides, are the unwanted by-products of aerobic metabolism. To protect cells against their potentially lethal effects a series of pathways have evolved that are collectively called the oxidative defence system. Uniquely, trypanosmatidae contain several enzyme-mediated pathways for the removal of hydroperoxides that are centred upon the unusual thiol trypanothione and are potential therapeutic targets.

Work presented here aims to characterise two enzymatic pathways involved in the pathway of hydroperoxide metabolism by *T. cruzi* through functional and structural studies. The enzymes Ascorbate peroxidase (APX) and Glutathione Peroxidase (GPX) reduce hydroperoxides by utilising ascorbate and gluthathione/tryparodoxin as electron donors, respectively. Protein constructs have been generated for APX and GPX allowing large scale over-expression for structural studies. Here we report, for both enzymes, the purification and structural information using X-ray crystallography and NMR spectroscopy.