Investigating the redox cycle of tryparedoxin at ultra-high resolution

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Tryparedoxins are critical regulators of the redox metabolism in parasitic protozoa such as trypanosomones and leishmania, which cause the neglected tropical diseases sleeping sickness and leishmaniosis, respectively. Although tryparedoxins belong to the thioredoxin superfamily, they differ in their substrate specificity for the low molecular weight redox carrier, utilizing trypanothione, a spermidine-linked di-glutathione instead of glutathione. The unique nature of the redox carrier opens avenues for the targeted interference in the protozoan redox metabolism which hold potential for future therapeutic intervention.

We were able to obtain crystals of a tryparedoxin which have the potential to diffract to ultra-high resolution. Crystals of the oxidized protein diffract to well below 1 Å with our current highest resolution data set extending to 0.75 Å/0.85 Å resolution in the best/worst direction. Preliminary refinement indicated a mixture of oxidized and reduced states in the Cys-Pro-Pro-Cys active site with photoreduction of the disulfide bond being the reason for the appearance of the reduced state. Subsequent efforts resulted in crystal structures of the oxidized and reduced states, which at present extend to a more limited resolution in the 1 to 1.1 Å range. An analysis of the two redox states defines the redox linked conformational changes in the tryparedoxin family.

Keywords: **Photoreduction, Thioredoxin, Tryparedoxin, Ultra-high resolution**