[PS2.26]

INHIBITION OF THE DNA REPAIR BER PATHWAY INCREASESTHE CYTOTOXICITY CAUSED BY OXIDATIVE DNA DAMAGE IN *Trypanosoma cruzi*

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Trypanosoma cruzi, a parasitic protozoan, is the etiological agent of Chagas' disease, an endemic pathology in Latin America. The transmission of the disease is produced by an infected triatomine insect that upon feeding on mammalian blood, deposits feces with infective parasites (trypomastigotes) which enter the mammalian body mainly through the skin wound produced by the insect. Upon entering the body, the parasites invade macrophages taking a round, replicative form, the amastigote. After replication, the amastigotes transform back to trypomastigotes that invade heart, ganglia and other tissues. Drugs used for treatment of Chagas disease are only active in acute infection and present collateral effects (1).

To establish a chronic infection some parasites must resist the oxidative damage to its DNA exerted by oxygen and nitrogen free radical (ROS/RNS) generated by the host cells (2). We propose that the DNA repair BER pathway is activated when *T. cruzi* is exposed to ROS/RNS, allowing its survival. The mechanisms responsible for the repair of the DNA damage by ROS/RNS in *T. cruzi* are unknown.

We observed that H_2O_2 and NOO^- induce DNA damage in *T. cruzi* (Fig 1). Metoxiamine (MX), an inhibitor of the AP enzymes of the BER pathway, decreases parasite viability (Fig. 2) and increases apoptosis induced by oxidative agents (Fig. 3), suggesting that the BER pathway is active in *T. cruzi.*

We have cloned, expressed and identified by amino acid sequencing three recombinant *T. cruzi* DNA repair enzymes (TcAP1, TcAP2 and NI1Tc). As analyzed by modeling, these enzymes present structural characteristics similar but not equal to mammalian ones.

Our results confirm that inhibition of DNA repair represents a possible therapeutic target for the control of *T. cruzi* infection, particularly if this target is articulated with the conventional drugs used for Chagas disease treatment.

References:

1. http://www.who.int/tdr/publications/publications/swg_chagas.htm
2. Piacenza et. al. Curr Opin Microbiol. 2009 (4):415-21.

Key words: *Trypanosoma cruzi*, resistance to oxidative damage

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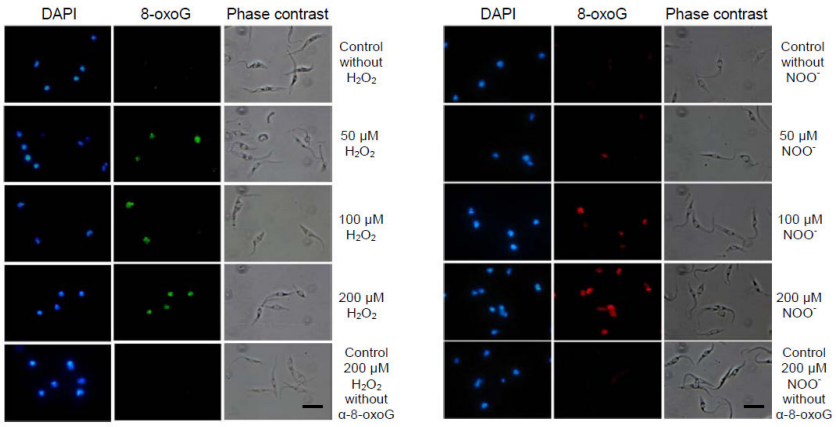


Figure 1. Oxidative DNA damage detection in *T. cruzi* epimastigotes.

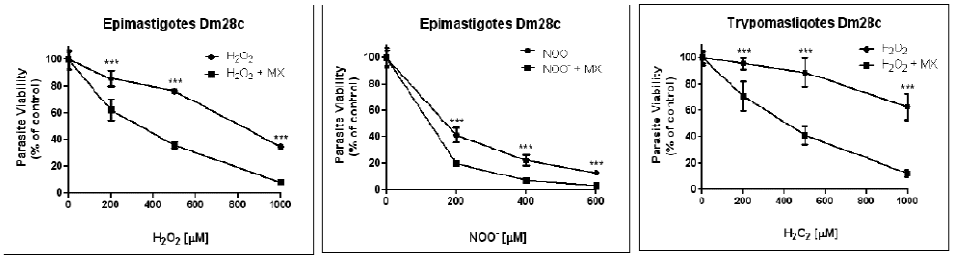
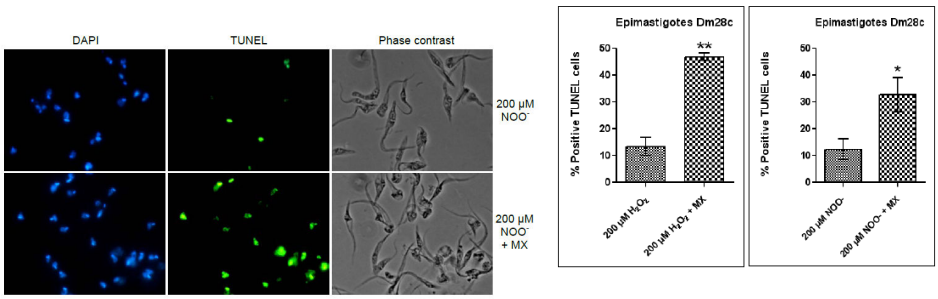


Figure 2. Viability of *T. cruzi* epimastigotes and trypomastigotes in the presence of H_2O_2 or NOO^- alone or combined with MX.



A. **B.**

Fig 3A and B. Apoptosis induced by NOO^- is enhanced by methoxyamine (MX)

Bars 10µm.

Keywords: Trypanosoma cruzi, resistance, oxidative damage

200 µM

NOO^-