DIFFUSION AND CYTOTOXICITY OF MACROPHAGE-DERIVED OXIDANTS

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Macrophage-derived radicals generated by the enzymes NADPH oxidase and inducible nitric oxide synthase (iNOS) are cytotoxic for a variety of phylogenetically diverse microorganisms such as viruses, bacteria, protozoa and fungi. Nitric oxide ($^{\bullet}NO$) plays a central role in the control of acute Chagas infection either directly or through derived species such as peroxynitrite, arising from the reaction of $^{\bullet}NO$ with superoxide radical ($O_2^{\bullet-}$). As an obligate intracellular parasite *Trypanosoma cruzi* has a series of antioxidant enzymes, including cytosolic tryparedoxin peroxidase (*Tc*CPX), that protects it from oxidant-mediated killing catalyzing the reduction of peroxides. Our experimental model evaluates the infecting capacity of wild type and *Tc*CPX *T.cruzi* overexpressers against macrophages activated for the production of $^{\bullet}NO$, $O_2^{\bullet-}$ or both, and hence, peroxynitrite. Also, we explore the ability of *T.cruzi* metacyclic trypomastigotes to activate NADPH oxidase and modulate $^{\bullet}NO$ production during the infection process. Our results show that: i) trypomastigotes of *T.cruzi* are capable of triggering the assembly of NADPH oxidase and $O_2^{\bullet-}$ production and do not interfere with IFN-?-dependent induction of iNOS, ii) peroxynitrite formation inside the phagocytic vacuole limits the progression of the infection, achieving an inhibition of parasite growth by 60% compared to the infection in unelicited macrophages or macrophages producing $O_2^{\bullet-}$ or $^{\bullet}NO$ only, and iii) peroxynitrite cytotoxicity is reverted by the overexpression of *Tc*CPX that readily detoxifies peroxynitrite and permits proliferation and development of the infection process in macrophages.