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Trypanosoma cruzi: Treatment with the iron chelator desferrioxamine reduces parasitemia and mortality in experimentally infected mice

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Abstract

The effects of prolonged treatment with iron chelator (desferrioxamine) on the development of infection in mice inoculated with Y *Trypanosoma cruzi* were determined. Infected/treated mice presented lower levels of parasitemia and reduced mortality rate compared with infected/non-treated animals. The five out of twenty infected/treated mice that survived the acute phase of infection showed negative hemoculture and positive ELISA in the acute and chronic phases and positive PCR in the acute phase: in the chronic phase, three of the animals presented negative PCR. The single surviving infected/non-treated animal exhibited positive hemoculture, PCR and ELISA in both phases of infection. Infected groups presented lower levels of iron in the liver compared with treated/non-infected or non-treated/non-infected animals. The serum iron levels of the infected/non-treated group were higher on the 21st day post-infection in comparison with control and infected/treated groups. These results suggest that decrease of iron in the host leads to *T. cruzi* infection attenuation.
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Index Descriptors and Abbreviations: Trypanosoma cruzi; ANOVA, analysis of variance; DNA, deoxyribonucleic acid; DFO, desferrioxamine; d.p.i., day post-infection; ELISA, enzyme-linked immunosorbent assay; EDTA, ethylenediamine tetraacetic acid; i.p., intraperitoneal; LIT, live infusion tryptose medium; PCR, polymerase chain reaction; IT, treatment groups—infected with *T. cruzi* and treated with DFO; INT, infected with *T. cruzi* but not treated with DFO; NIT, DFO-treated/non-infected control; NINT, non-treated/non-infected control; Mice; Iron chelator

1. Introduction

Iron is the most abundant of the heavy metal micronutrients in body fluids and tissues (Crichton and Ward, 1992), and is essential for the continued growth and proliferation of almost all living cells. Moreover, iron homeostasis is fundamental in the regulation of the human immune system (Weinberg, 1984; Kent et al., 1990), affecting both humoral and cellular immunity (Blakley and Hamilton, 1988; Galan et al., 1988). Modulation of the availability of iron represents, therefore, a potential strategy for augmenting host defence levels and restricting the development of disease.

In relation to the immune system, it has been demonstrated that the iron chelator desferrioxamine (DFO) blocks expression of the IL-12 receptor in human T cells, inhibits DNA synthesis through the inactivation of ribonucleotide reductase (Carotenuto et al., 1986), and

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up-regulates the expression of cyclooxygenase-2 and prostaglandin in human macrophages (Tanjii et al., 2001). *In vitro* and *in vivo* studies have demonstrated that various malignant human and experimental animals tumours are sensitive to therapies that include DFO (Wolfe et al., 1988; Hann et al., 1992; DonFrancesco et al., 1996; Richardson, 1997; Wang et al., 1999). DFO also exhibits a significant *in vitro* antiviral effect against cytomegalovirus (Cinatl et al., 1994, 1995; Martelius et al., 1999) and is effective in reducing trauma injuries mediated by free radicals (Shadid et al., 1998).

Parasitic protozoa also depend on iron for their survival, and iron chelators have been employed in various studies aimed to evaluating the relationship between the iron status of the host and the development of infection (Dhur et al., 1989). Studies in human malaria have shown that treatment with DFO, either alone or in combination with standard therapies, enhanced parasite clearance in asymptomatic and in severe malaria (Traore et al., 1991; Gordeuk et al., 1992; Mabeza et al., 1996). DFO has also been shown to inhibit the growth of *Plasmodium falciparum* (Hershko and Peto, 1988) and of bloodstream forms of *Trypanosoma brucei* (Breidbach et al., 2002) and this chelator was considered to be a promising drug against *Toxoplasma gondii* (Mahmoud, 1999).

The first reports of a correlation between iron levels and the development of infection by *Trypanosoma cruzi* were published by Lalonde and Holbein (1984) and Loo and Lalonde (1984). These authors observed that the depletion of iron stores in mice that had been treated with DFO or maintained on an iron-deficient diet, reduced the parasitemia and mortality of the infection. Subsequently, Pedrosa et al. (1990) evaluated the effects of iron deficiency on the evolution of experimental *T. cruzi* infection in mice and observed a strain-dependency. Compared with the control group, mice infected with the YuYu strain developed a less severe form of the disease when treated with DFO at a dose of 10 mg/mouse in the 5th d.p.i., but no differences were observed in mice infected with Y and CL strains. Lima and Villalta (1989) showed that amastigote forms of *T. cruzi* possess receptors for human transferrin, the major iron transport protein in mammalian plasma. It would thus appear that the iron essential for amastigote growth is delivered by receptor-mediated transferrin endocytosis.

Previous studies concerning the effect of DFO on the development of *T. cruzi* infection have typically involved short-term treatments, i.e. up to the 5th (Pedrosa et al., 1990) or 5th and 6th (Lalonde and Holbein, 1984) d.p.i. Considering that DFO is rapidly cleared from the circulation (Brittenham, 1988), it is suggested that a longer period of treatment with this chelator could give rise to a more pronounced effect on the development of *T. cruzi* infection. In order to test this hypothesis, mice were experimentally infected with *T. cruzi* Y strain that not affect the course of infection when used a single dose of DFO (Pedrosa et al., 1990), herein we used a daily treatment with a dose (5 mg/mouse) of DFO from 14 days before infection up until the 14th or 21st d.p.i. The effect of the iron chelator on parasite virulence and host survival was determined during the acute phase of the infection. Our results clarify that this DFO prolonged treatment resulting in powerful protection of infection with *T. cruzi* Y leading attenuation of parasitemia and mortality in infected mice.

2. Materials and methods

2.1. Animals and experimental design

All animal procedures were approved by the Committee on Ethics in Research of the Universidade Federal de Ouro Preto, MG, Brazil, and followed the guidelines for the use and care of animals for research published by the Canadian Council on Animal Care (1980, 1984).

Eighty Swiss male mice, each *ca.* 30 days old, were fed throughout the 45 days of the study on a commercial non-purified diet consisting of Purina Rodent Chow (Purina, São Paulo, Brazil) provided in pellet form. Forty mice received a daily dose (5 mg; 0.05 ml) of DFO (Desferal®, Novartis, Basel, Switzerland) by i.p. injection during a period commencing 14 days prior to infection and continuing up to 14 or 21 d.p.i. The second set of 40 animals received a daily i.p. injection of 0.05 ml of sterile water. On day 14 of the study period, 20 animals that had been receiving the DFO treatment were infected with *T. cruzi* Y strain (Silva and Nussenzweig, 1953) by i.p. injection of 500 bloodstream forms, thus forming the infected/treated (IT) group. Twenty animals that had not received DFO treatment were similarly infected with *T. cruzi* Y strain forming the infected/non-treated (INT) group. The remaining 40 mice were not infected with *T. cruzi* and formed the non-infected/treated (NIT) and the non-infected/non-treated (NINT) groups, respectively.

2.2. Parameters evaluated

Levels of hemoglobin and of iron in the liver and serum were evaluated in mice from all four groups on the 14th and 21st d.p.i. as appropriate. In all infected animals (i.e. those in groups IT and INT), parasitemia was measured on the 4th d.p.i. and daily thereafter according to the method of Brener (1962): the prepatent period, the patent period, the maximum parasitemia, and the day of maximum parasitemia were thus determined. Mortalities were recorded on a daily basis and expressed as a cumulative percentage up to the 32nd d.p.i. In the case of animals that survived the acute phase of the infection, blood samples were collected in the acute (60th d.p.i.) and chronic (240th d.p.i.) phases and submitted to parasitological (hemoculture and PCR) and serological (ELISA) tests.

2.3. Hemoculture

Hemocultures were carried out according to the method of Filardi and Brener (1987). Blood collected from the orbi-

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