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Dosreis, George A.

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## Susceptible Hosts: a Resort for Parasites Right in the Eye of the Immune Response\*

GEORGE A. DOSREIS\*\*

Laboratório de Biologia Imunitária, Instituto de Biofísica Carlos Chagas Filho,  
Federal University of Rio de Janeiro, Cidade Universitária,  
Ilha do Fundão – 21944-970 Rio de Janeiro, Brasil

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### ABSTRACT

Trypanosomatid protozoan parasites express an aggressive strategy of parasitism by infecting host macrophages and inducing extensive T-lymphocyte activation. One goal of such strategy is to drive the immune response of genetically susceptible hosts to a state of unresponsiveness regarding parasite killing. Unresponsiveness is achieved through different mechanisms, depending on the parasite species. In this brief review, recent findings on the molecular and cellular bases of the parasites' exploitation of host immune responses are discussed.

**Key words:** *Trypanosoma cruzi*, *Leishmania chagasi*, T lymphocytes, CTLA-4, apoptosis, transforming growth factor.

Trypanosomatid protozoan parasites, such as *Trypanosoma cruzi* (the agent of Chagas disease) and *Leishmania chagasi* (the agent of Visceral Leishmaniasis, or kala-azar in the New World), induce chronic infection and consequent disease in genetically susceptible hosts, that can persist for life if left untreated. Persistence of intracellular pathogens must be associated with efficient mechanisms of immune evasion, since they mobilize intense innate and acquired immune responses in the infected hosts (Dos-Reis 1997). However, the nature of genetic differences between resistant and susceptible hosts, and how these differences are exploited by parasites, remain to be defined. Previous studies demonstrated a deleterious role for the suppressive cytokine Transforming Growth Factor (TGF- $\beta$ ) in infection of

susceptible mice with both *T. cruzi* (Silva *et al.* 1991) and *L. chagasi* (Wilson *et al.* 1998). In addition, TGF- $\beta$  plays a virulence-determinant role in murine infection by *L. amazonensis* and *L. braziliensis*, causative of cutaneous leishmaniasis (Barral-Netto *et al.* 1992). Currently, the nature of cellular immune mechanisms regulating TGF- $\beta$  secretion in infections by trypanosomatid parasites is unknown.

Working with a model of murine infection by *T. cruzi*, we demonstrated intense spontaneous lymphocyte apoptosis, and also activation-induced cell death (AICD) by apoptosis of CD4<sup>+</sup> T cells in the course of acute infection (Lopes *et al.* 1995), the first demonstration in a parasitic disease. The Fas-Fas Ligand (FasL) death pathway has been characterized as the major pathway for host CD4<sup>+</sup> T cell apoptosis following vigorous immune responses (Van Parijs & Abbas 1996). Fas is a surface receptor that

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\*\*Member of the Academia Brasileira de Ciências  
E-mail: gdosreis@biof.ufrj.br

expresses a caspase-activating death domain in its cytoplasmic tail, and belongs to the TNF Receptor Superfamily (Baker & Reddy 1998). FasL is surface protein trimer induced in the cell membrane following T-cell activation through the T-cell receptor for antigen (TCR) (Van Parijs & Abbas 1996). FasL is a member of the TNF superfamily (Baker & Reddy 1998). We have characterized that Fas-FasL interactions mediate CD4<sup>+</sup> T cell apoptosis that follows *T. cruzi* infection (Lopes *et al.* 1999). We have also investigated the pathogenic role of CD4<sup>+</sup> T cell AICD in the control of *T. cruzi* replication within host macrophages (M $\phi$ ). The onset of CD4<sup>+</sup> T cell AICD greatly exacerbates the growth of infective forms of *T. cruzi* within cocultured M $\phi$  (Nunes *et al.* 1998). The deleterious effect was mediated by Fas-FasL interactions since: i) an agonist anti-Fas monoclonal antibody induced T-cell death and *T. cruzi* growth within M $\phi$  (Nunes *et al.* 1998); ii) a neutralizing anti-FasL monoclonal antibody blocked both T-cell death and *T. cruzi* replication within M $\phi$  (Nunes *et al.* 1998); iii) CD4<sup>+</sup> T cells from infected, FasL-mutant *gld* mice were unable to increase *T. cruzi* growth in wild-type M $\phi$  (Lopes *et al.* 1999). How do apoptotic lymphocytes exacerbate *T. cruzi* replication? One intriguing possibility was that dead, but not alive T lymphocytes were partially responsible for the increased growth of the parasite. Uptake of apoptotic cells by M $\phi$  triggers the autocrine and paracrine secretion of immunosuppressive mediators such as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and TGF- $\beta$  (Fadok *et al.* 1998), that functionally inactivate M $\phi$ . Uptake of apoptotic cells by M $\phi$  is mediated by a multifunctional receptor that includes CD36 and the integrin Vitronectin Receptor (VnR); the receptor binds thrombospondin attached to the apoptotic cells (Savill 1998). Based on these new concepts, we recently identified one mechanism driving the intracellular growth of *T. cruzi* in M $\phi$ . We found that apoptotic, but not necrotic or viable T cells, inactivate macrophages by blocking nitric oxide production, and exacerbate *T. cruzi* replication (Freire-de-Lima *et al.* 2000). Adhesion of apoptotic cells to

macrophages engages the VnR, and VnR crosslinkage triggers intense PGE<sub>2</sub> and subsequent TGF- $\beta$  production; TGF- $\beta$  secretion is required for parasite growth (Freire-de-Lima *et al.* 2000). Through engagement of VnR and autocrine TGF- $\beta$  secretion, apoptotic cells induce marked *de novo* ornithine decarboxylase (ODC) activity and polyamine (mainly putrescine) synthesis in M $\phi$  (Freire-de-Lima *et al.* 2000). Parasitemia can be exacerbated *in vivo* by injection of apoptotic cells. Interestingly, blockers of polyamine synthesis inhibit *T. cruzi* growth induced by apoptotic cells *in vitro*, suggesting that the parasite uses this source of putrescine to replicate inside M $\phi$ . Pharmacological blockers of PGE<sub>2</sub> secretion also prevent parasite replication *in vitro* and control parasitemia *in vivo* (Freire-de-Lima *et al.* 2000), suggesting that the phenomenon is immunopathogenic for *T. cruzi* infection. Thus, the onset of host lymphocyte apoptosis is beneficial to the parasite, as it triggers intense TGF- $\beta$  secretion and therefore, polyamine synthesis by infected M $\phi$ , driving parasite growth.

In a second model of chronic parasitic disease, susceptible mice were infected with *L. chagasi* (a model of murine kala-azar). In this disease, the splenic load of *L. chagasi* increases indefinitely, and local CD4<sup>+</sup> T cells are unresponsive to mitogen or leishmanial antigen stimulation, but do not undergo AICD (Gomes *et al.* 1998). Recently, the negative costimulatory T-cell receptor CTLA-4 has been characterized as an important negative regulator of T-cell activation (Waterhouse *et al.* 1995). We found that antibody-mediated blockade of either CTLA-4 or its ligand B7-1, restored otherwise suppressed T-cell responses, increased IFN- $\gamma$  production, and promoted rapid killing of *L. chagasi* parasites within splenic M $\phi$  (Gomes *et al.* 1998). Although the mechanisms of CTLA-4 suppression of T-cell activation are still undefined, a recent study demonstrated that engagement of CTLA-4 promotes the production of TGF- $\beta$  by CD4<sup>+</sup> T cells, while inhibiting the production of all other cytokines tested (Chen *et al.* 1998). We found that splenic CD4<sup>+</sup>

T cells from kalazar secrete large amounts of TGF- $\beta$  when stimulated by *Leishmania* antigen or mitogens, and that TGF- $\beta$  secretion can be abolished by CTLA-4 blockade (Gomes *et al.* 2000). Moreover, we demonstrated that CTLA-4 engagement suppresses T-cell IFN- $\gamma$  production and promotes *L. chagasi* growth in cocultured M $\phi$  through secretion of TGF- $\beta$  (Gomes *et al.* 2000). These results suggest that *L. chagasi* infection induces host T cells to produce TGF- $\beta$  by driving them to a state of sustained CTLA-4 engagement. However, the cell types and mechanisms responsible for sustained CTLA-4 engagement in T cells from kalazar remain to be determined. If these results could be extended to human T cells, they would suggest a new immunotherapeutic strategy for treating patients with kalazar.

Therefore, in spite of using very distinct mechanisms, both trypanosomatid parasites induce TGF- $\beta$  production following intense mobilization of the host immune system, and TGF- $\beta$  appears to be an essential factor for parasite survival and growth. Modulation of cell interaction molecules directly or indirectly responsible for subsequent TGF- $\beta$  release, such as Fas, VnR and CTLA-4, could help in the elimination of parasites from susceptible hosts.

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