

## SUMMARY OF THESIS\*

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BILATE, A.M.B. - **Expressão de mediadores inflamatórios e progressão diferencial de miocardite aguda e cardiomiopatia chagásica crônica experimental em hamster sírio infectado por *Trypanosoma cruzi***. São Paulo, 2006. (Tese de Doutorado - Instituto de Ciências Biomédicas da Universidade de São Paulo).

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### EXPRESSION OF INFLAMMATORY MEDIATORS AND DIFFERENTIAL PROGRESSION OF ACUTE MYOCARDITIS AND CHRONIC EXPERIMENTAL CHAGASIC CARDIOMYOPATHY IN SYRIAN HAMSTERS INFECTED WITH *Trypanosoma cruzi*

Chagas' disease, caused by protozoan *Trypanosoma cruzi*, is a significant cause of mortality and morbidity in many Latin-American countries, where it is estimated that 13 million people may be infected. Previous results from our group show that, with a single combination of parasite (Strain Y) and genetically heterogeneous host (Syrian hamster), it is possible to reproduce the range of different outcomes of human Chagas' disease. In the present study, we tested the hypothesis that the inflammatory infiltrate and its locally produced mediators may be related to morbidity and mortality in the acute phase and with the severity of chronic cardiomyopathy in the Syrian hamster model of *T. cruzi* infection using Strain Y. Like humans, hamsters infected by *T. cruzi* Strain Y show different patterns of evolution in both the acute and chronic phases. In the acute phase, 30-50% of animals showed symptoms such as cachexia, lethargy, vomiting, and diarrhea, which were related with mortality during this stage. The presence of circulating parasites on the 13th day post-infection (PI) was associated with intense cardiac parasitism on the date spontaneous death during the acute phase. High cardiac parasitism, in addition to its association with symptoms, was also associated with high expression of mRNA for IL-10, TNF- $\alpha$ , and genes activated by inflammatory cytokines (A20 and iNOS) in the myocardium. During the acute phase, blockade of TNF- $\alpha$  with Etanercept lead to increased parasitism in blood and heart and to increased expression of IL-10 in the myocardium of asymptomatic animals. In the chronic phase of infection, although the intensity of myocarditis was positively correlated with macroscopic dilation of the left ventricle, none of these variables were associated with death during the chronic phase. In this phase, there was a predominance of expression

of mRNA for IFN- $\gamma$  in the myocardium over that of TNF- $\alpha$  and IL-10, although the latter two were also detected at increased levels. Death during the chronic phase was associated only with the expression of A20. In the chronic phase, treatment with Etanercept worsened post-*T. cruzi* infection chronic cardiomyopathy, as measured by ventricular dysfunction and left ventricle dilation, and lead to increased expression of IL-10 and decreased expression of iNOS mRNAs in the myocardium. Overall, cardiac parasitism in the acute phase seems to determine the levels of expression of cytokines - such as TNF- $\alpha$  and IFN- $\gamma$  - and genes activated by TNF- $\alpha$  and IFN- $\gamma$  - such as iNOS. The low parasitism and cytokines in the myocardium of asymptomatic animals suggests that these animals were able to control parasitism before its dissemination to the tissues during the acute phase. In the chronic phase, although significant levels of cytokines were present in the myocardium and the intensity local inflammation is involved in the progression of Chagas disease cardiomyopathy to the dilated form, these factors seem not to be determinants of mortality in chronically infected animals. This indicates that inflammatory mechanisms play an important pathogenic role in the evolution of *T. cruzi* chronic cardiomyopathy, but are not sufficient to lead to death.

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