

SITUAÇÃO ATUAL DOS ESTUDOS SOBRE A IMUNOPATOLOGIA DA DOENÇA DE CHAGAS

CH4-1

MECHANISMS OF HEART TISSUE DAMAGE IN CHAGASIC MICE: PATHOGENICITY INDUCED BY AUTOREACTIVE T-CELL LINES AND MODULATION BY INTERLEUKIN-4. Ribeiro-dos-Santos R. Centro de Pesquisas Gonçalo Moniz, FIOCRUZ-BA. rrsantos@e-net.com.br

To study the role of autoreactivity in the pathogenesis of myocardium heart lesions in Chagas' disease, we generated CD4+ T cell lines from chronically *T.cruzi*-infected mice by stimulation with myocardium or *T.cruzi* antigens. After repeated *in vitro* stimulation with syngeneic heart antigen, an anti-heart cell line showed reactivity *in vitro* to *T.cruzi* lysates, in addition to different heart antigen preparations. This cell line also destroyed fetal heart cell clusters *in vitro* when co-cultured with feeder cells, caused heart graft rejection and induced carditis and mortality when transferred in BALB/c nude mice. The T-cell lines obtained by stimulation with heart antigen showed a Th1 cytokine profile, with high production of IFN-gamma. In contrast, some anti-*T.cruzi* T-cell lines also responded to heart antigens, but had a predominant Th2 cytokine production and were unable to induce carditis or mortality of BALB/c nude mice. To investigate the role of Type 1 and Type 2 responses in the development of carditis in the experimental Chagas' disease, we studied the model of infection with 100 Colombian strain *T.cruzi* in IL-4 -/- BALB/c mice. Infected IL-4 +/- BALB/c mice had higher parasitemia and a mortality than IL-4 -/- BALB/c mice in the acute phase. Histopathology of hearts from IL-4 +/- mice revealed the presence of multifocal inflammatory infiltrate by mononuclear cells and intense tissue parasitism 30 days post-infection (dpi). In contrast, hearts of IL-4 -/- mice had carditis 2-3 fold more intense and lower tissue parasitism than wild-type mice. Although a significant splenic hyperplasia was observed in both groups of mice at 30dpi, spleens of IL-4 +/- mice were twice as large as spleens obtained from IL-4 -/- mice. Interestingly, hearts obtained from IL-4 +/- mice after 3 months post-infection presented discrete and focal carditis, whereas in IL-4 -/- mice carditis was intense. Parasitemia and tissue parasitism in the heart sections examined were negative in both groups at this timepoint of infection. We next analyzed the immune response of IL-4 -/- mice in acute and chronic phases of infection. In the acute phase, splenocytes from IL-4 +/- mice showed suppressed IL-2 production and proliferative responses to concanavalin A (Con A). In contrast, splenocytes obtained from IL-4 -/- mice showed higher proliferative response and IL-2 production after stimulation with Con A or *T.cruzi* antigen. IL-4 -/- BALB/c mice also presented higher levels of IFN-gamma than wild-type mice in response to *T.cruzi* antigen in the acute phase. In the chronic phase, splenocytes from both groups of mice showed IL-2 production and proliferative and response to Con A similar to non-infected mice. Anti-*T.cruzi* IgG titers were higher for IgG1 and IgG3 in sera from IL-4 +/- mice, whereas IL-4 -/- mice produced higher levels of IgG2a and IgG2b anti-*T.cruzi* antibodies. Although no significant DTH responses against *T.cruzi* antigen were observed comparing both groups of mice, IL-4 -/- mice strongly rejected syngeneic heart transplants in the acute phase of infection, different from IL-4 +/- mice. These results demonstrate the presence of autoreactive CD4+ T cells in *T.cruzi*-infected mice and the important role of IL-4 in the modulation of *T.cruzi*-induced carditis.