

The Role of Tissue-infiltrating T cells in Immunopathology of Chagas Disease

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In chronic Chagas disease, a heterogeneous set of inflammatory T cells infiltrates the heart tissue. However, little is known about the specificities they recognize and about their functional status. Recent studies indicate that tissue-infiltrating T cells are antigen-unresponsive and bear additional defects in function, yet they can sustain local production of inflammatory cytokines. Studying these unusual T cells might help understanding the nature of the immunologic attack in chronic Chagas disease.

Little is known about the molecular and cellular events discriminating the host immune response in the indeterminate and progressive forms of chronic Chagas disease. We are left with the impression that something big is missing: something that is going on only in a proportion of patients and that is associated with the surge of a second wave of immune injury to the host heart tissue. A precise knowledge of such big immunological event is also missing in other chronic inflammatory diseases, such as the most common human autoimmune diseases. Even though autoreactive T cell clones can be demonstrated, the behavior of effector cells, the time course and the sudden qualitative changes in the inflammatory attack are not easily predictable. Progressive steps towards derangement of homeostasis of cell-mediated immunity are noted, yet we miss the driving force behind this behavior. Among the classical autoimmune diseases, "epitope spreading" (Lehmann et al. 1992) has been one of the few immune phenomena precisely defined at the molecular and T-cell clonal levels, and associated with the horror of an autotoxic state in the immune system. Recent work in murine models of autoimmunity identified the B7-1 costimulatory molecule, and its negative counterreceptor CTLA-4 on T cells as key molecular signals preventing epitope spreading (Karandikar et al. 1996). However, the changes in

immune environment leading to loss of control and to epitope spreading are unknown. A provocative study identified dominant T-cell clones in several patients at the early stage of multiple sclerosis (Tuohy et al. 1997). The autoantigenic peptides recognized were mapped. Clearly, no single target epitope was dominant, both within and between patients. Many autoreactive clones and their cognate peptides transiently dominated the response, but suddenly were replaced by new ones, and simply disappeared (Tuohy et al. 1997). These studies suggest that the search for dominant epitopes with therapeutic value might be meaningless. Alternatively, the search for the origins of epitope spreading, and for common molecules able to block it, now appears to be of more general interest in the management of autoimmune diseases.

Also of general interest is the management of cell-bound and soluble molecules that effect cytotoxicity. Thus, mechanisms based on the perforin or the Fas/FasL pathways, applying to CD8⁺ and CD4⁺ effector T lymphocytes, were defined as essential for many autoimmune reactions. These mechanisms are amplified or modulated by inflammatory cytokines, such as TNF- α and IFN- γ . Studies in gene knockout mice demonstrated that, besides B7 expression, locally expressed cytokines greatly influence the ability to initiate autoimmune reactions (Grewal et al. 1998). Yet, we don't know why autoreactive T cells start the autoimmune attack in susceptible hosts only at a certain age. We are also ignorant of the reason many autoimmune diseases first progress with relatively benign inflammation, long before generation of destructive T cells able to kill the parenchyma (Lenschow et al. 1995).

The inflammatory setting where chronic Chagas disease evolves has received little attention. Proliferating CD4⁺ T cell clones were isolated from fragments of human heart tissue (Cunha-Neto et al. 1996), contrasting with *in situ* studies showing a predominance of activated CD8⁺ T cells (Reis et al. 1993), and the presence of CD8⁺ T cells geographically associated with *T. cruzi* antigens (Higuchi et al. 1997). The different immunopathogenic roles of the two subsets are still undefined. Studies in human autoimmune and inflammatory diseases show

that, although expressing markers of memory and recent activation, tissue-infiltrating T cells are unresponsive to antigen stimulation, are defective in signal transduction, and susceptible to spontaneous apoptosis if removed from their habitat (Salmon et al. 1997, Agrawal et al. 1998). Therefore, the majority of inflammatory T cells cannot be cloned. Recently, a provocative hypothesis suggested that autoimmunity results from functionally abnormal T cells (Salojin et al. 1998). It was suggested that defects in signal transduction and in expression of certain surface molecules in regulatory T cells could help autoimmune T cells to evade mechanisms of suppression and apoptosis, leading to tissue injury (Salojin et al. 1998). A role for regulatory T cells was also suggested in rheumatoid arthritis. A doubled-blinded clinical trial indicates that treatment with a nondepleting humanized anti-CD4 antibody induces marked clinical benefit and reduces proinflammatory cytokine production in rheumatoid arthritis (Lipsky & Davis 1998). These findings indicate that, although unresponsive, tissue-infiltrating T cells in rheumatoid arthritis are not simply effete cells programmed to die, but are actively driving local inflammation. In fact, although impaired in proliferative capacity, these T cells provide help for B cells and macrophages (Lipsky & Davis 1998). It has been suggested that CD4⁺ T cells do not initiate, but rather perpetuate synovial inflammation by recognizing an endogenous, MHC-derived self peptide, which crossreacts with some peptides expressed by microorganisms, the so-called "shared epitope", continuously presented in the context of other, unrelated MHC molecules (Lipsky & Davis 1998). Again, a major role for a regulatory T cell is being suggested, instead of a simple and classical role played by autoreactive T cells.

As deduced from several independent studies, the chronic stage of cardiac aggression in Chagas disease is carried out by a heterogeneous set of T cells bearing receptors for parasite antigens, crossreactive receptors for self antigens, and probably purely autoreactive receptors as well. However, T cells recognizing endogenous MHC-derived peptides were not identified. Parasites are required for the continuous supply of "danger" signals that break self tolerance through local induction of costimulatory molecules. At the effector side, Fas/FasL, the perforin pathway and inflammatory cytokines such as IFN- γ , could play an important role in myocyte death induced by lymphocytes (DosReis et al. 1995) or even by other myocytes. It is difficult to imagine how patients with different forms of Chagas disease would differ in terms of the overall sets of antigens being recognized by T cells in the heart tissue. One possibility would be the presence of a shared regulatory epitope, similar to the one proposed in rheumatoid arthritis. Another possibility would be a

polymorphism controlling the local parasite burden in the heart. Perhaps, one key to the nature of immune attack in Chagas disease resides in functional studies of the epitopes recognized and the biological functions of the non-proliferating, primary tissue-infiltrating T cells, an advance that still waits for further technical improvement.

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