

## IS THE THYMUS A TARGET ORGAN IN INFECTIOUS DISEASES?

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*The thymus is a central lymphoid organ, in which T cell precursors differentiate and generate most of the so-called T cell repertoire. Along with a variety of acute infectious diseases, we and others determined important changes in both microenvironmental and lymphoid compartments of the organ. For example, one major and common feature observed in acute viral, bacterial and parasitic diseases, is a depletion of cortical thymocytes, mostly those bearing the CD4-CD8 double positive phenotype. This occurs simultaneously to the relative enrichment in medullary CD4 or CD8 single positive cells, expressing high densities of the CD3 complex.*

*Additionally we noticed a variety of changes in the thymic microenvironment (and particularly its epithelial component), comprising abnormal location of thymic epithelial cell subsets as well as a denser Ia-bearing cellular network. Moreover, the extracellular matrix network was altered with an intralobular increase of basement membrane proteins that positively correlated with the degree of thymocyte death.*

*Lastly, anti-thymic cell antibodies were detected in both human and animal models of infectious diseases, and in some of them a phenomenon of molecular mimicry could be evidenced.*

*Taken together, the data reviewed herein clearly show that the thymus should be regarded as a target in infectious diseases.*

Key words: thymus – thymic microenvironment – thymocytes – infectious diseases – Chagas' disease – schistosomiasis – AIDS

The involvement of T cells in the course of a variety of infectious diseases has been demonstrated by several lines of evidence. For example, the evolution of the schistosomal granuloma can be prevented by *in vivo* treatment with anti-CD4 monoclonal antibody (Mathew & Boros, 1986). Moreover, CD4-bearing T lymphocytes are responsible for the anti-cardiac muscle autorreactivity occurring in Chagas' disease (Hontebeyrie-Joskowicz, 1991; Ribeiro dos Santos et al., 1992), whereas CD8<sup>+</sup> cells are involved in protective mechanisms (Tarleton, 1991). Furthermore, distinct T cell

subsets are relevant in the delayed-type hypersensitivity occurring in leprosy and leishmaniasis (Modlin et al., 1988; Pirmez et al., 1990).

In this respect, although peripheral T lymphocytes are largely recognized as playing a key role in the immunopathology of infectious diseases, much less data are available concerning putative alterations of intrathymic T cells. In the present work, we shall review a number of findings recently come out from our and other laboratories, concerning the thymus in murine or human models of some parasitic, bacterial or viral diseases. Nonetheless, before going into the specific data obtained on this subject, we think it is worthwhile to briefly discuss some general features regarding thymic lymphocytes and microenvironmental components.

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## INTRA-THYMIC T CELL DIFFERENTIATION: GENERAL COMMENTS

The thymus gland is a central lymphoid organ, in which bone marrow-derived T cell precursors, undergo a complex process of maturation, eventually leading to the migration of positively selected thymocytes to the T-dependent areas of peripheral lymphoid organs. This differentiation process, that involves a positive selection of some thymocytes and negative selection of many others (the latter accompanied by programmed cell death), allows T lymphocytes to distinguish self from nonself proteins, representing the vast majority of the so-called T cell repertoire. Along with intrathymic T cell differentiation, lymphocytes modulate the expression of a number of membrane proteins. For instance, the molecule named CD1, typical of immature cortical thymocytes is lost along with differentiation. Conversely, CD4 and CD8 proteins, absent in the most immature thymocytes, are simultaneously expressed in the majority of cortical (still rather immature) thymocytes, being then further modulated, so that the mature medullary subsets are either CD4 or CD8 single positive cells. Lastly, the CD3/Ti complex, in the context of which the antigen recognition will take place, is expressed in low densities in cortical lymphocytes whereas their density increases when cells further differentiate acquiring the medullary phenotype (see review Boyd & Hugo, 1991). Expression of other differentiation markers is modulated along with maturation of thymic lymphocytes, but a detailed discussion of them is beyond the scope of this review.

It should be pointed out that key events of intra-thymic T cell differentiation are driven by influence of the *thymic microenvironment*. This later actually corresponds to a tridimensional network composed of distinct cell types, such as epithelial cells, macrophages and dendritic cells, as well as extracellular matrix elements.

The thymic epithelium is the major component of the thymic microenvironment and plays important and multifaceted influences in early events of T cell differentiation. This is accomplished by at least two distinct ways: (a) secretion of a variety of polypeptides as thymic hormones (see review Bach, 1983), interleukins 1 and 6 (Le et al., 1988a) and granulocyte-macrophage colony stimulator factor (Le et al., 1988b), and (b) cell-cell con-

tacts, including those occurring through classical adhesion molecules (Nonoyama et al., 1989) and, most importantly, the paramount interactions with differentiating thymocytes that are mediated by the major histocompatibility complex products, highly expressed on thymic epithelial cell membranes (Janossy et al., 1980; Jenkinson et al., 1981; Savino et al., 1985; van Ewijk et al., 1988). Thus, MHC class I proteins interact with the CD8 molecule whereas MHC class II binds the CD4 complex. These interactions are determinant in defining the positive versus negative selection of thymocytes bearing the distinct T cell receptor rearrangements.

Although thymic epithelial cells (TEC) can be generally characterized by the presence of cytokeratin-containing intermediate filaments and desmosomes (Singh, 1986), the epithelial reticulum is a heterogeneous tissue in which morphological and antigenic differences are detected. Regarding the latter, several laboratories produced anti-TEC monoclonal antibodies (MAb), able to define cells in different regions of the thymic lobules (see review van Ewijk, 1991). Moreover, we and other used MAb specific for distinct cytokeratins, that were proved to be differentially expressed throughout the intralobular parenchyma (Savino & Dardenne, 1988a, b; Colic et al., 1990; Meireles de Souza et al., 1993). Nonetheless, in spite of the large variety of available reagents for defining TEC, the physiological significance of such heterogeneity remains unknown. In any case, the use of a panel of antibodies, originally raised against either thymic fragments or cytokeratins, can be considered as relevant tools in the study of thymic pathology.

Besides the above discussed phenotypically-defined TEC heterogeneity, a particular TEC-containing structure has been isolated, namely the so-called thymic nurse cell complexes (TNC). These are lymphoepithelial multicellular structures formed by one TEC harbouring 20-200 thymocytes (Wekerle & Ketelson, 1980). Interestingly, a number of experimental arguments show that thymocytes do undergo initial differentiation steps within TNC (Le et al., 1992).

## CHANGES OF THE THYMIC LYMPHOID COMPARTMENT IN INFECTIOUS DISEASES

One of the common features occurring in acute infectious diseases is a thymic atrophy defined by loss of thymus weight and cellular-

ity. This feature can be seen in both human and experimental infectious diseases (Savino et al., 1989; Fonseca, 1991; Cardenas, 1992; Silva Barbosa et al., 1990). In several animal models, the degree of thymic atrophy positively correlates with the dose of the given infectious agent applied.

The decrease in cell numbers essentially corresponds to a cortical thymocyte depletion, so that in animals or patients severely affected, the cortical region of the thymic lobules virtually disappears. In keeping with this, a consistent decrease in the percentage of CD4/CD8 double positive cells (normally located in the cortex) is observed. Furthermore, it is frequently seen an augmentation in the percentage values of double negative as well as CD4 and CD8 single positive thymocytes. Moreover, the proportion of thymic lymphocytes expressing high densities of the CD3 complex was enhanced along with infections.

One might argue that, in both human and animals models, these thymocyte alterations occurring in acutely-infected individuals are stress-associated, since similar findings can be induced by injection of glucocorticoid hormones. In fact, high levels of circulating corticosterone can be detected in acute *Trypanosoma cruzi* infection. Nonetheless, adrenalectomy did not alter the thymic atrophy and thymocyte subset changes seen in the murine acute Chagas' disease (Leite de Moraes et al., 1992). Moreover, in the case of murine schistosomiasis, glucocorticoid hormone levels did not significantly vary during the infection period (Silva Barbosa et al., 1990). Lastly, in human syphilis, that courses with rather low levels serum cortisol, cortical thymocyte depletion is clearly detected (Fonseca, 1991). Thus, if stress is associated to the infectious disease-related thymic atrophy, it does not seem to occur via the hypothalamus/pituitary-adrenal axis.

Besides the phenotypic differences observed in thymocyte subsets, these cells may be also functionally affected in infectious diseases. Thus, low numbers of cycling cells are detected in *S. mansoni*-infected animals (Silva Barbosa et al., 1990). Moreover, in murine Chagas' disease, lymphokine production by thymocytes is clearly changed (manuscript in preparation).

Regarding chronic infections, much less data is so far available. Yet, we have shown

that in *T. cruzi* chronically-infected mice, the thymus weight, cellularity and CD4/CD8-defined subsets, progressively returns to values similar to those of age-matched control animals (Leite de Moraes et al., 1992). However, an important aspect yet to be determined concerns whether the intrathymically generated T cell repertoire is changed or not after infection.

#### THE THYMIC MICROENVIRONMENT IN INFECTIOUS DISEASES

In addition to the thymocyte changes summarized above, several infectious diseases promote alterations in the thymic microenvironment. For example, epithelial cells recognized by the MAb ER-TR.5 (normally restricted to the thymic medulla) could be detected in both inner and subcapsullary cortex, following infection by *T. cruzi*. Conversely, the expression of cytokeratins 8 and 18, restricted to cortical TEC in normal conditions, was also found as medullary clusters or isolated cells (Savino et al., 1989). Interestingly, similar changes were seen in animals developing experimental schistosomiasis (Silva Barbosa et al., 1990).

The studies carried out on AIDS thymuses (Savino et al., 1986) also revealed changes in TEC phenotype, as demonstrated by the decreased in the numbers of cells reactive with the monoclonal antibodies anti-p19 and TE-4, that define in the normal thymus TEC located in the medulla and subcapsullary cortex (Haynes et al., 1983, 1984).

Thymic nurse cells can also be affected in infectious diseases. Thus in the Radiation Leukemia Virus infection, TNC are very early infected (Houben-Defresne et al., 1982). Moreover, preliminary data in our laboratory suggest that the total TNC numbers as well as TNC-derived extracellular matrix production, are altered in acute *T. cruzi* infection. Besides the phenotypic changes in epithelial cells located in different areas of the thymic lobules, alterations in the expression of functional molecules could already be evidenced in infectious diseases. Thus, the serum levels of one chemically-defined thymic hormone namely thymulin, were found to be decreased in AIDS patients (Dardenne et al., 1983). These findings were further confirmed when we detected a decreased immunohistochemical labeling of thymulin in thymus frozen sections from AIDS subjects (Savino et al., 1986). We



also studied thymulin production in mice acutely infected with *Trypanosoma cruzi*. Nonetheless, in contrast to what was found in acquired immunodeficiency syndrome, only a minor decrease of thymulin was detected in parasite-infected animals, even in late acute infection stages (Savino et al., 1989).

As regards the expression of class II MHC gene products, we showed that, contrasting to the normal positive cellular framework, HLA-DR expression in AIDS thymuses was decreased (or even absent) in some epithelial regions, where only dendritic non-epithelial (keratin-negative) cells were labeled (Savino et al., 1986). This pattern was however not detected in mouse models of viral or parasitic diseases we analysed so far. In *T. cruzi* acutely infected animals, the Ia-bearing cellular network was rather denser as compared to control non-infected mice (Savino et al., 1989). Similar was seen, in rabies virus-infected mice, as well as in schistosomotic animals, in which the Ia-positive framework remained strongly labeled (Savino et al., 1987; Silva Barbosa et al., 1990). Taking into account the importance of intrathymic MHC expression for normal thymocyte differentiation, it is possible that abnormal MHC distribution in the thymus from infected subjects affects the physiological generation of the T cell repertoire.

Lastly, we should discuss the modulation of extracellular matrix (ECM) components of the thymic microenvironment in infectious diseases, and its parallelism with thymocyte death. In the last few years we cumulated evidence showing that the expression of basement membrane proteins, namely type IV collagen, laminin and fibronectin, is dramatically increased in atrophic thymuses (see review, Savino & Lannes-Vieira, 1991). In acutely-infected animals, we evidenced a progressive increase in intra-lobular ECM expression. In fact, kinetic analysis of rabies virus, *T. cruzi* or *S. mansoni* infections, showed that such process precedes thymocyte depletion (Savino et al., 1987, 1989; Silva Barbosa et al., 1990). Moreover, in neonatal human infections, such as measles, siphylis or cytomegalia, a positive correlation between the atrophy degree and extracellular matrix enhancement was clearly observed (Fonseca, 1991). These data together with our preliminary findings evidencing that, at least *in vitro* fibronectin enhances thymocyte death, suggest the existence of a cause-effect relationship between the infectious dis-

ease-related increase in thymic extracellular matrix and thymocyte death.

#### ANTI-THYMIC CELL AUTOANTIBODIES IN INFECTIOUS DISEASES

Anti-self reactivity, involving both B and T cell autoimmune responses, appears to be a common finding in infectious diseases. As regards anti-TEC autoreactivity, we noticed that *T. cruzi* acutely infected mice develop circulating anti-TEC antibodies (Savino et al., 1989). Interestingly, during the chronic phase of both human and murine Chagas' disease, anti-thymocyte antibodies with cytotoxic properties were detected in the sera (Savino et al., 1990). In AIDS thymuses, we and others reported the presence of immunoglobulins and complement components bound to epithelial cells (Savino et al., 1986; Pekovic et al., 1987). More recently, Ig-binding sites were also evidenced in thymuses from *Schistosoma mansoni* infected animals (manuscript in preparation).

One interesting question raised from these data refers to the triggering mechanisms yielding clonal expansion. As recently revealed by Minoprio et al. (1988), most of the MAb obtained by fusing myeloma cells with splenocytes from *T. cruzi*-infected mice do not recognize parasite epitopes. Nonetheless, in other examples the epitope recognized is shared by molecules of the host and the infectious agent. Thus, *T. cruzi* and astrocytes bear common MAb-defined epitopes in a ganglioside (Petri et al., 1988). Moreover in chronic *T. cruzi* infection, anti-thymocyte antibodies cross-react with parasite antigens (Savino et al., 1990).

Specifically concerning the thymic epithelium, it was showed that a MAb directed against the p. 19 protein of the HTLV-1 (human T cell leukemia virus type 1) also recognized a cytoplasm epitope of the normal human thymic epithelium (Haynes et al., 1983). Similar findings were reported in terms of epitopes shared by the thymic epithelium and distinct components of HIV, including thymic hormones (Naylor et al., 1987; Wu et al., 1988; Parravicini et al., 1988). Particularly in respect to thymosin  $\alpha$ -1, an aminoacid homology with the HIV peptide T was demonstrated (Nguyen & Scheving, 1987). In addition to these findings, we recently observed that sera from rabbits immunized with a saline extract derived from adult *S. mansoni*, were able to decorate

the epithelial network when applied on thymus frozen sections (manuscript in preparation).

This series of data drives us to the hypothesis that the so-called *molecular mimicry* between viral- or parasite-derived proteins and molecules of the normal thymic cells may be a rather common phenomenon. In this respect, it should be mentioned that consequence(s) of this particular molecular mimicry in terms of the host's immune response represent(s) a completely open avenue for investigation.

#### CONCLUSIONS AND PERSPECTIVES

The data above reviewed provide a strong evidence that both the lymphoid and microenvironmental compartments of the thymus are significantly affected as a consequence of infection. It appears that changes in the thymocyte subsets, the thymic epithelial cell network pattern, together with an increase in thymic extracellular matrix production, might be considered as general features in individuals undergoing acute infections. On the other hand, it is also apparent that much more results should come out before we can conceive more precisely whether common or specific mechanisms are involved in generating such thymic abnormalities in distinct viral or parasitic diseases.

Finally, an important question to be further addressed concerns the putative influences of these alterations in modulating the host's immune system. In this respect, the analysis of T cell receptor gene rearrangements within the thymus and in the peripheral lymphoid organs, following infection, may bring valuable information regarding a possible plasticity of the T cell repertoire.

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