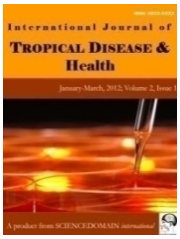

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Thymic Atrophy during Infection as a Host Response to Avoid Tolerance to Persistent Pathogens

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Authors' contributions

This work was carried out in collaboration between all authors. Authors LS, ETG, LC and AFN managed the literature searches. Author AM wrote the manuscript. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

The immune system consists in part of a functionally competent T-cell repertoire that is reactive to foreign antigens but tolerant to self-antigens. The repertoire of T cells is primarily formed in the thymus through positive and negative selection of developing thymocytes that are critical for establishing central tolerance. One of the features of the thymus is to sense stress hormones produced in pathophysiological conditions. Increased levels of these hormones are associated with infections and are able to induce thymic atrophy. We have shown that in acute *Trypanosoma cruzi* infections, the atrophic thymus is a consequence of increased thymocyte apoptosis and premature export of immature thymocytes to secondary lymph nodes. This atrophy does not necessarily result in dysfunction of the thymus since the organ micro architecture is preserved and maintains negative selection, thus avoiding the development of tolerance to the pathogen during the establishment of protective immunity. However, in chronic infections, the dissemination of invading pathogens able to target the thymus interferes with T cell differentiation,

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generating T cells that are tolerant to pathogen-specific antigens. In what follows we propose to describe what is known about thymic atrophy induced by infectious pathogens in the context of host-pathogen interactions.

Keywords: Chagas disease; Trypanosoma cruzi; thymus; central tolerance; T cells.

1. INTRODUCTION

Infectious pathogens interfere with host physiological homeostasis at several levels. One of the first systemic sensors that identify the danger of invasion is the stress system consisting of a number of responses involving all three regulatory systems, neural, endocrine and immune [1]. In most vertebrates the acute short-term stress signals are responsible for inducing host responses that enhance innate defense mechanisms [2]. However, when stress signals persist chronically the host immune response can be suppressed, a scenario that favors the infection [3,4]. Chronic stress is known to cause a shift from T helper 1-mediated cellular immunity towards T helper 2-mediated humoral immunity and this can influence the course of an infection and the susceptibility to microorganisms [5,6].

In general, stress signals result from release of neurotransmitters, hormones and cytokines into the circulation or locally within tissues [7]. The major mediators of stress effects are norepinephrine and epinephrine, which are released by the sympathetic nervous system, and corticotropin-releasing hormone, adrenocorticotropin (ACTH) and cortisol, which make up the hypothalamic-pituitary-adrenal (HPA) axis [8,9]. All vertebrate cells have receptors for one or more of these factors, allowing them to signal threats from pathogens in response to changes induced by infection [5].

Critical synergistic interactions occur between cytokines and stress hormones in inducing the effects of the stress circuits on the immune system [7]. For example, acute psychological stress has been shown to increase circulating IL-1β levels in both humans and rodents [10,11] and stress hormones are able to induce similar biological responses to those produced by inflammatory cytokines. This is well demonstrated in the case of glucocorticoids, whose levels increase in response to a variety of infections [5,11-13]. It has been shown in various systems that glucocorticoids synergize with IL-1, IL-6 and other cytokines such as IL-2, IFN-β, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, and oncostatin M in inducing acute phase proteins [14]. Some of the interactions between glucocorticoids and cytokines may involve glucocorticoid induced downregulation of cytokine receptors on target cells, as shown by decreased cytokine binding or cytokine receptor mRNA levels [7]. For example, there are reports that glucocorticoids inhibit the expression of IL-2 and its receptor (IL-2R) in leukocytes [15]. This effect accounts for the important role of endogenous glucocorticoids in preventing ongoing immune responses from reaching damaging levels. These observations point to the existence of a negative feedback loop between the immune system and the HPA axis, such that proinflammatory mediators arising in an ongoing immune response stimulate the HPA axis, which in turn results in the secretion of corticosterone and prevents the immune response from reaching level that could damage the host [3,16].

In infections caused by *T. cruzi* parasite, the causative agent of Chagas disease, the inflammatory syndrome induced by TNF-α in the acute phase of infection activates the hypothalamus-pituitary-adrenal (HPA) axis leading to release of corticosterone and the latter appears to be responsible for changes in both lymphoid and non-lymphoid compartments of

the thymus and for disease outcomes [17,18]. The protective effects of immune suppression by endogenous glucocorticoids also have an impact on the thymus, the central lymphoid organ controlling the formation of T cells, which constitute the peripheral host immunological repertoire [19].

2. THE STRESS HORMONE CIRCUIT AS A SYSTEMIC HOST SENSOR FOR PATHOGEN INFECTIONS: SENSING OF GLUCOCORTICOIDS LEADS TO ATROPHY OF THE THYMUS

The thymus is the primary lymphoid organ, located in the thoracic cavity, where T cells are continuously generated and released to the periphery [20]. The complex developmental process responsible for generating T cells within the thymus depends on signals from stromal cells that direct the maturation, clonal expansion and selection of T cell precursors [21]. Defects in the thymic microenvironment can prevent the development of the adaptive immune system, cause severe immune deficiencies and inhibit immunological surveillance, which is essential for recognizing and removing pathogens and malignant cells in vertebrates [22].

All T cell lineages are derived from hematopoietic precursor cells recruited from the blood [23,24]. The recruited cells have a triple negative $CD3^-CD4^-CD8^-$ phenotype and penetrate the vascularized microenvironment of the thymus at the boundary between the two major thymic compartments, the cortex and medulla. Early T lineage progenitors enter the thymus and form cell-to-cell contacts with cortical thymic epithelial cells. The engagement between Notch1 receptors on progenitor T cells and their ligand Delta-4-like, expressed by thymic epithelial cells, result in proliferation of the cells and their commitment to the T cell lineage [20]. In subsequent developmental steps, these cells expose both CD4 and CD8 antigens to the clones of antigen-specific T cell receptors (TCR) generated by somatic rearrangement of the variable germinal TCR genes. At this stage the maturing T cells are referred to as double-positive (DP) thymocytes, and these cells must be able to bind self major histocompatibility complex (MHC) molecules, otherwise they die within the first 4 days after the appearance of T cell receptors [25,26].

In this scenario, the initial selection process in the thymus will only retain those T cells that bear a αβ TCR that is able to recognize self MHC. This process is referred as positive selection and occurs when the T cells bind cortical epithelial cells expressing Class I or Class II MHC plus self-peptides with sufficiently high affinity to receive a survival signal. The maturing cells that are not positively selected are committed to “death by neglect” [27]. The remained thymocytes undergo in the thymic medulla a second selection process known as negative selection, which leads to programmed cell death of T cell clones that by chance express T cell receptors (TCRs) with above-threshold affinities for self-peptide/MHC complexes [25,28]. Thus, thymocytes capable of generating autoimmune responses are removed and only T cells able to recognize non-self antigens in the context of self MHC molecules are released into the periphery [29]. Upon maturation, thymocytes that express a TCR restricted to class I MHC molecules have the $CD4^-CD8^+$ phenotype while those with an MHC class II-restricted TCR specificity become $CD4^+CD8^-$ cells [27]. After a time required for maturation, these naïve single-positive (SP) T cells exit the thymic medulla and migrate to the periphery in a process that requires signaling via sphingosine 1-phosphate receptor type 1 [26,30].

Thymic homeostasis can be severely affected by infection. It has been shown that several infectious pathogens (bacteria, virus, parasites and fungi) can cause atrophy of the organ [31,32]. It is not completely understood how this atrophy occurs and the mechanism may vary. In most infectious diseases causing thymic atrophy, the major biological event associated with thymocyte loss is cell death by apoptosis [32]. This is seen for example, in experimental models of *Trypanosoma cruzi* infection [33] and malaria in rodents caused by *Plasmodium berghei* [34]. Most of the cells that die are $CD4^+CD8^+$ thymocytes but other sub-types such as double-negative (DN) T cells and SP cells are also reduced in number. Glucocorticoid hormones appear to be responsible for the thymus atrophy and thymocyte death during parasitic infections. In acute *Trypanosoma cruzi* infections, atrophy is associated with a rise in serum glucocorticoid levels and activation of thymocyte caspases-8 and -9, which promote cell death by apoptosis [33]. Elevated levels of serum glucocorticoids have also been found in other infections: experimentally-induced malaria, African trypanosomiases, also known as sleeping sickness, toxoplasmosis and leishmaniasis, parasitic diseases caused respectively by the protozoan *Toxoplasma gondii* and *Leishmania* parasites, as well as schistosomiasis, a parasitic disease caused by several species of trematodes belonging to the genus *Schistosoma* [35].

3. THYMIC ATROPHY DURING TRYPANOSOMA INFECTIONS DOES NOT INTERFERE WITH NEGATIVE SELECTION

The primary event in thymic atrophy is a severe reduction in thymic cell numbers, which is reflected in an equally dramatic reduction in thymic output, potentially reducing peripheral T cell numbers [31] . Although the induction of thymic atrophy is considered a virulence trait shared by many pathogens, until recently it was not clear whether intrathymic negative selection was affected by the alterations in the thymic microenvironment. During thymopoiesis, clonal deletion appears to occur normally late in thymocyte development at the transition from DP to SP cells, and happens at the junction between cortex and medulla [36,37]. Thymic metallophilic macrophages have been shown to be involved in thymocyte maturation at this interface. Like cortical macrophages and medullary interdigitating cells, metallophilic macrophages contain large endocytic compartments devoted to processing and presentation of antigens by MHC class II molecules [38,39]. Interestingly, we have shown that the distribution of these metallophilic macrophages is altered by infection: their number increases, and while some remain in the cortico-medullary region many more are spread throughout the cortex. The thymic distribution of these cells may indicate that clonal selection switches from the cortico-medullary junction to the cortex [40].

It has been consistently shown that thymopoiesis requires sustained interactions between thymic epithelial cells (TEC) and thymocytes [21]. When the thymic architecture is disturbed, thymic function is severely compromised, since the pattern of expression of autoantigens by TECs is altered [41,42]. In an experimental murine model of *T. cruzi* infection, we detected similar expression levels of Aire and highly selective tissue-restricted antigens in whole thymuses of *T. cruzi*-infected mice and non-infected control mice [40]. These findings suggest that the expression of peripheral antigens in the infected thymuses is sufficient to modulate the induction of tolerance by negative selection.

In *T. cruzi*-infected mice, thymic atrophy becomes apparent after a rise in the number of apoptotic intrathymic DP T cells caused at least in part by increased systemic glucocorticoid levels [33,43]. We found that expression of Bim, a pro-apoptotic factor essential for negative selection [44], was maintained while the number of DPs declined [40]. Furthermore, using

the OTII TCR transgenic system specific for a $CD4^+$-epitope of the chicken ovalbumin (OVA) protein, in which all the T cells are OVA-specific, we observed that apoptosis of TCR-stimulated immature thymocytes was promoted when the cognate OVA peptide was *in vivo* administred to acutely infected mice undergoing thymic atrophy [40]. These data provide evidence that DP T cells can be negatively selected during thymic atrophy, suggesting that negative selection operates normally during infection. This is consistent with the finding that mature single-positive $CD4^+$ and $CD8^+$ T cells within the thymus do not harbor forbidden TCR genes, unlike their DP counterparts, indicating that immature thymocytes bearing auto-specific TCR continue to be negatively selected in the thymus [40,45].

4. CHRONIC PERSISTENT INFECTIONS OF PATHOGENS TARGETING THE THYMUS SUBVERT CENTRAL TOLERANCE

Thymic atrophy in pathogen infections has been explained as a host response aimed at controlling thymopoiesis in order to prevent tolerance to the colonizing pathogen [31,46,47]. The severe loss of thymic cell numbers reduces thymic output [46]. However pathogens such as *M. avium* that target the thymus are able to induce the production of new T cells to the host repertoire, but these T cells are unable to mount a protective response against the pathogen in the periphery [48]. In this study, it was shown that T cells from *M. avium* infected animals are deficient in producing IFN-γ in response to mycobacterial antigens, and are therefore unable to control bacterial growth [48].

Interestingly, *M. avium* was found to be present inside macrophages and dendritic cells (DCs) in the medulla as well as in the cortico-medullary thymic regions [48]. Since DCs are considered key players in the negative selection of specific-T cell [49], presentation of mycobacterial antigens by thymic DCs would be able to induce clonal deletion of *M. avium*–specific T cells. This event is thought to be responsible for the observed host tolerance to *M. avium*[48] . However, since there is also a pathway in the thymus leading to the development of regulatory T cell recognizing specific antigens with high affinity [50,51], the generation of mycobacteria-specific regulatory T cells could not be discarded in the tolerance to *M. avium*. Furthermore, these studies show that infection of the thymus by mycobacteria targets T cell recirculation from the periphery to the thymus, which guarantees that the immune system can respond to thymic infection [33]. The *M. avium*-infected thymus increases the production of chemokines, such as CXCL9 and CXCL10, known to recruit $CXCR3^+$ peripheral T cells involved in the control of bacterial infections [52]. As these cells recycle into the thymus, they may become susceptible to clonal deletion through negative selection. These findings together indicate that *M. avium* infection of the thymus promotes the loss of *M. avium*-specific T cells, resulting in host tolerance to the pathogen and favoring chronic infection [48,52]. This process is an important aspect of the host-pathogen interplay in infections that target the thymus.

5. FIGURE LEGEND

The hypothalamic-pituitary-adrenal (HPA) axis originates in the brain and is involved in recognizing signal stressors from infections, such as IL1, IL6 and TNF-α. After a pathogen infection, the hypothalamus releases corticotropin-releasing factor (CRF) to the pituitary gland, which is rich in CRF type 1 receptors (CRFR-1). In response, the pituitary releases adrenocorticotropic hormone (ACTH) into the bloodstream. This hormone targets the adrenal glands, located atop the kidneys. These glands then release the glucocorticoid (GC) hormone cortisol, which causes thymic atrophy. In the atrophic thymus there is a reduced

output of recent-thymic emigrants. T cells to the periphery, which guarantees that normal thymopoiesis is accompanied by negative selection of T cells bearing undesired TCR specificities. However in chronic infections some pathogens can colonize the thymus persistently; as a result their antigens are presented in the context of negative selection and can induce central tolerance to the corresponding organism.

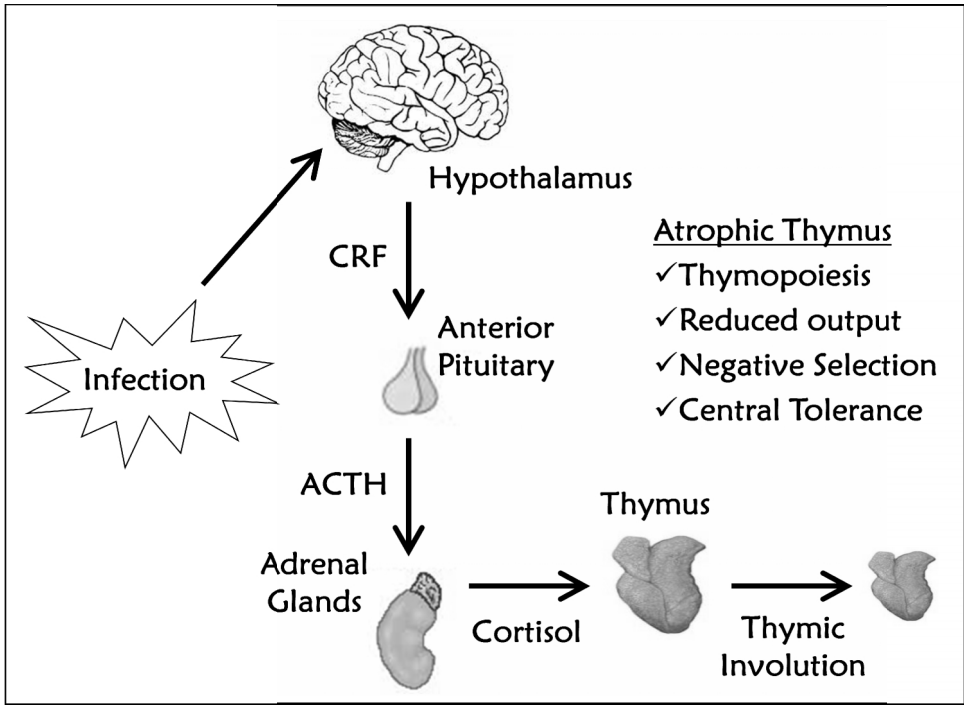

Fig. 1. Stress hormones induced during infection promote atrophy of the thymus.

6. CONCLUDING REMARKS

Infectious thymic atrophy is a consequence of host colonization by bacteria, viruses, and parasites and is considered a common response to pathogens. Various hypotheses have been proposed to explain this atrophy, including increased apoptosis of developing thymocytes, premature egress of immature thymocytes bearing undesired TCR specificities, and thymic hibernation inhibiting the thymocyte selection process and preventing the establishment of central tolerance to pathogen antigens that may access the thymic tissues. The latter hypothesis is relevant to host-pathogen interplay in many chronic infections. It has gained strength from the recent demonstration of pathogen-induced tolerance in thymic infections by *M. avium*. Those studies have demonstrated that pathogen-derived antigens present in the thymus of infected mice seem to interfere with the capacity of pathogen-specific activated T cells to respond to the invading organism. This is highly relevant to our understanding of the development of host immunity during persistent pathogen infections. The presence of pathogen antigens in the thymus may in fact promote the recirculation of activated T cells from the periphery to the thymus resulting either in clonal deletion of pathogen-specific T cells or possible in the generation of pathogen-specific regulatory T cells that induce tolerance to a persistent infection. These concepts are important for our

understanding of the stablishment of T cell protective immunity in the host and its ability to control chronic persistent pathogen infections.

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CONSENT

Not applicable.

COMPETING INTEREST

The authors have declared that no competing interests exist.

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