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Review

Modulating the function of the immune system by thyroid hormones and thyrotropin

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ABSTRACT

Accumulating evidence suggests a close bidirectional communication and regulation between the neuroendocrine and immune systems. Thyroid hormones (THs) can exert responses in various immune cells, e.g., monocytes, macrophages, natural killer cells, and lymphocytes, affecting several inflammation-related processes (such as, chemotaxis, phagocytosis, reactive oxygen species generation, and cytokines production). The interactions between the endocrine and immune systems have been shown to contribute to pathophysiological conditions, including sepsis, inflammation, autoimmune diseases and viral infections. Under these conditions, TH therapy could contribute to restoring normal physiological functions. Here we discuss the effects of THs and thyroid stimulating hormone (TSH) on the immune system and the contribution to inflammation and pathogen clearance, as well as the consequences of thyroid pathologies over the function of the immune system.

Contents

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1. THs and TSH: background

Thyroxine (T_4) and 3,5,3'-triiodo-L-thyronine (T_3), two thyroid hormones (THs), regulate numerous mammalian metabolic processes [1]. Blood TH levels are finely regulated by the hypothalamus-pituitary-thyroid axis, which secretes the thyrotropin-releasing hormone to maintain adequate blood TH levels. In turn, pituitary-gland secretion of the thyroid-stimulating hormone (TSH) is triggered with this hormone, then activating its receptor (TSHR) in the thyroid gland to stimulate TH synthesis and secretion [2].

The effects of TSH are mediated by TSHR, a seven-transmembrane domain G-protein coupled receptor expressed by the thyroid gland [3]. This receptor is also expressed by a variety of external thyroid tissues, including the anterior pituitary, hypothalamus, ovary, testis, skin, kidney, immune cells, bone marrow, peripheral blood cells, white and brown adipose tissue, preadipocytes, fibroblasts and bone [4]. While TSHR expression is low outside the thyroid gland, the binding affinity for TSH and the ability to produce cAMP in response to TSH stimulation has a Kd $\approx$ 0.3 nM and an EC50 $\approx$ 3 nM. Therefore, TSHR could function and activate a cellular response even at low TSH levels [5]. Although currently there is no evidence for other receptor(s) acting in the extra thyroidal effects of TSH, this possibility cannot be definitively excluded.

TSHRs couple to $G\alpha_s$ and $G\alpha_q$, which work as signaling transducing molecules. $G\alpha_s$ activation triggers the cAMP-protein kinase A signal transduction pathway [6] and together with adenylate cyclase stimulates iodine uptake, thyroglobulin transcription, thyroid peroxidase activity and the sodium-iodine symporter in the thyroid cell [6,7]. The activation of phosphoinositide phospholipase C increases intracellular Ca^{2+} and regulates iodide efflux, H_2O_2 production and thyroglobulin iodination. Despite that, analyses using TSHR photoaffinity labelling with azido-GTP and subsequent immunoprecipitation have suggested that Gα, Gαi/o, Gαq/11 and Gα12/13 can interact with TSHR, only $G\alpha_s$ and $G\alpha_q$ are known to contribute to TSHR signaling [8].

An alternative ligand for TSHR is thyrostimulin, that binds to TSHR with an affinity similar to TSH, in addition to presenting thyroid-stimulating activity *in vivo* [9]. This ligand is present in the anterior pituitary gland, an area known to express TSHR, suggesting a paracrine action mechanism [10]. The effects of thyrostimulin on immune cells remain unknown. Then further research is needed to define a potential modulatory effect by this molecule over the immune response.

T_4 and T_3 derived from the blood are incorporated into cells via TH-specific transporters [11]. There are several transporter families, but only the monocarboxylate transporters MCT8 and MCT10 and the organic anion-transporting polypeptide OATP1C1 are highly specific for THs [12]. At the cytoplasm, T_4 is converted into T_3 by deiodinases located in the endoplasmic reticulum or the plasma membrane [13,14]. Among these enzymes, the most significant are the iodothyronine deiodinases types I, II and III (D1, D2 and D3 respectively) [15]. While D2 is located at the endoplasmic reticulum membrane, D1 and D3 are found in the plasma membrane [16]. In addition to T_4 to T_3 conversion, D1 and D3 can also inactivate T_4 through conversion to reverse T_3 (rT_3) [15].

In humans, approximately 20% of circulating T_3 originates from thyroidal production, while the remaining 80% derives from a peripheral conversion of T_4 to T_3 through D1 and D2 activities [15]. In rodents, the contribution of peripheral conversion is approximately 60%, with the remaining 40% secreted by the thyroid gland [15]. In macrophages, inflammation-induced D2 expression in the liver occurs in conjunction with expression of the selective thyroid hormone transporter MCT10 [17].

TH effects are mainly mediated by genomic mechanisms, however there is a growing body of experimental evidence indicating that THs can also function through non-genomic mechanisms [18]. The genomic actions of THs are mainly carried out by T_3, TH considered biologically active. Specifically, T_3 binds thyroid hormone receptors (THRs) of nuclear hormone receptor superfamily, which includes receptors for steroids, retinoids and the vitamin D3 [19]. These receptors are transcription factors that positively or negatively regulate target gene expression [20,21]. For example, the expressions of genes encoding for TSHB and TRH (thyrotropin-releasing hormone) are negatively regulated by T_3 [22].

The human TRα and TRβ proteins are transcribed from two separate genes, THRA and THRB, each of which has a homologue gene in the mouse, known as *Thra* and *Thrb*, respectively. Three mRNA species are transcribed from the THRA gene located at human chromosome 17 (TRα1, TRα2 and TRα3 mRNAs). TRα1 protein binds T_3 and can form dimers with the truncated THRA gene products, the TRα2 and TRα3 proteins. Meanwhile, TRα2 and TRα3 proteins can not bind this hormone [13]. Although the exact physiological importance of these truncated proteins remains unknown, heterodimerization of these isoforms with full-length TRα1 protein *in vitro* antagonizes the transcriptional activation induced by T_3 [23,24]. On the other hand, the THRB gene is located at the human chromosome 3 and expresses two protein isoforms, TRβ1 and TRβ2 proteins, which bind T_3. TRβ3, a third protein isoform is found only in rats [25]. The expression of these THR isoforms is tissue-dependent and developmentally regulated [26–28]. While TRα1 mRNA is constitutively expressed during embryonic development, TRβ1 mRNA is preferentially expressed at later developmental stages [27]. TRβ1 protein is widely expressed; TRβ2 protein is expressed in the retina, brain and inner ear [25,29] and TRβ3 protein, a functional receptor is expressed in the kidney, the liver and the lung. Finally, the TRα1 and TRα2 protein isoforms are highly expressed in the brain and, to a lesser extent, in the kidneys, skeletal muscle, lungs, bone, heart, testes and liver [25]. It is noteworthy that TRβ1 protein can be expressed by dendritic cells (DCs) [30] and other antigen-presenting cells, such as macrophages [31], an observation reported by scientists from the Nuclear Receptor Signaling Atlas research program.

Clinical research and animal-model studies have provided support to the notion of a close communication between the neuroendocrine and the immune system [2,32]. Of note, homeostatic regulation of the immune system involves several factors, including hormones [33]. Indeed, thyroid activity and the hypothalamic-pituitary-thyroid axis play pivotal roles at modulating the function of the immune system [33].

In this article we have focused on the contribution of THs to the regulation of immune cell functions, as well as on the importance of THs for the control of sepsis, inflammation, autoimmunity and viral infection.

2. Effects of thyroid hormones on immune system cells

Previous reports indicate that alterations in TH levels can affect the immune system [34]. Patients with hyperthyroidism frequently manifest unbalanced immune responses, including abnormal antibody production (either increased or decreased) [35], increased migration of polymorphonuclear leukocytes [36], lymphocyte proliferation [37] and increased reactive oxygen species (ROS) production by macrophages, specifically hydrogen peroxide and superoxide [38,39]. Additionally, these patients may show reduced levels of pro-inflammatory markers and lower antioxidant enzyme activity. In contrast, patients with hypothyroidism display an opposite phenotype [40,41]. However, in some cases, contrasting results have been reported and therefore it is difficult to establish a clear

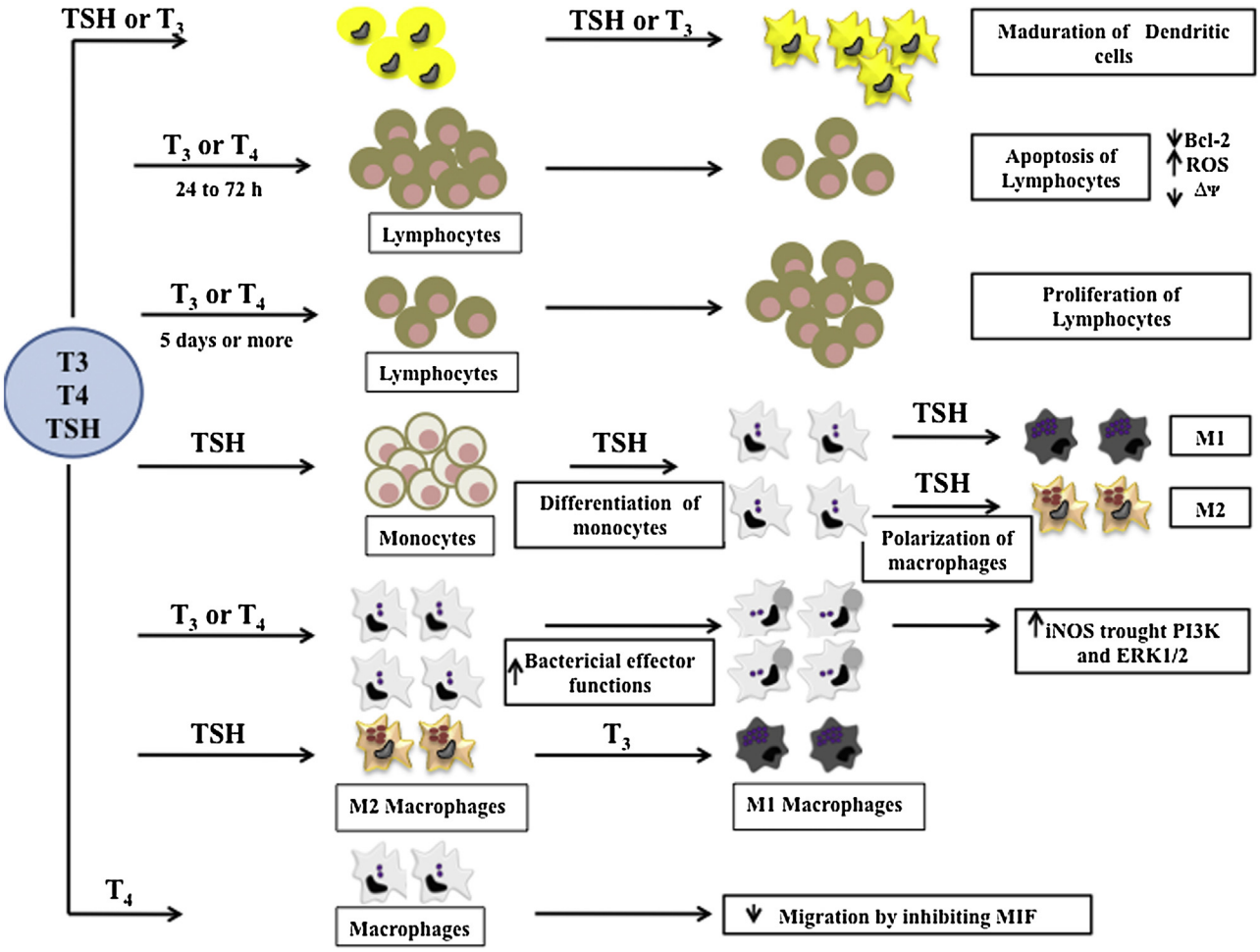

Fig. 1. Actions of the thyroid hormones over immune system cells. Thyroid hormones can act through non-genomic and genomic mechanisms. In immune system cells such as monocytes, macrophages, and lymphocytes, thyroid hormones can exert effects over various processes such as chemotaxis, phagocytosis, generation of reactive oxygen species (ROS) and the induction and release of cytokines. Hormones, such as TSH induce the maduration of DCs, differentiation of monocytes into macrophages and the polarization of macrophages. On the other hand, T_3 increases the apoptosis of lymphocytes through a decrease in Bcl-2 expression, ROS production and a decrease in mitochondrial potential. Also, T_3 contributes to the maturation of DCs. In addition, T_3 promotes the generation of M1 macrophages even after the differentiation and activation of monocytes into M2 macrophages. Finally, T_4 can also induce apoptosis in lymphocytes and increases the bactericidal effector functions in macrophages.

correlation between immune function and hyper- or hypo-thyroid conditions [35,42,43].

Patients with hypothyroidism show immune deficits and significantly increase susceptibility to infections [44–47]. For example, Ho et al. reported that patients with severe sepsis, septic shock and hemorrhagic shock had a 12.0% incidence of concurrent hypothyroidism [48]. Furthermore it has been described that in HIV-infected patients there is an increase in the prevalence of hypothyroidism [49]

To provide detailed insights into the effects of THs and TSH on immune system functions, the next sections describe the effects of T_3, T_4 and TSH on various immune cell types, such as lymphocytes, macrophages and DCs.

2.1. Lymphocytes

The effects of THs observed in lymphocytes depend on the time of exposure to these hormones. In cultures *in vitro* of BW5147 T-lymphoma mouse cell line, the incubation with THs for 24–72 h induces cell proliferation [50]. The increase in proliferation shown by this T cell lymphoma line is mediated by the atypical ζ isoform of protein kinase C (PKCζ) and involves activation of the inducible nitric oxide synthase (iNOS) [50]. Additionally, the effects of TH-induced T cell proliferation have been studied via free and noncell permeable THs coupled to agarose in cultures *in vitro* (TH-ag) [18]. Interestingly, agarose-coupled THs induced less T cell proliferation than did free THs. The authors of these studies also reported that the THs rapidly induce various events through non-genomic mechanisms, including: PKCζ translocation to cell membrane, extracellular-signal-regulated kinase (ERK1/2) phosphorylation and nuclear factor-κB (NF-κB) activation [18]. Cell proliferation in cultures *in vitro* of the T lymphoma cell line is also mediated through a genomic mechanism that involves the engagement of the TRα1, increasing the transcription of the iNOS gene [18]. These data suggest that THs can enhance T lymphocyte proliferation by non-genomic signaling (e.g. PKCζ activation) and genomic mechanisms (e.g. increased transcription of iNOS gene) [18]. Meanwhile, T cells cultured *in vitro* with T_3 (10^{-9}–10^{-7} mol/L) and T_4 (10^{-9}–10^{-7} mol/L) undergo enhanced apoptosis, as measured by DNA fragmentation and other morphological characteristics related to programmed cell death. However, this effect is not observed when TSH or the thyrotropin-releasing hormones are added to the T cell cultures *in vitro* [51] In turn, *in vitro* splenic T cells treated with THs by more than 5 days showed reduced B-cell lymphoma 2 (Bcl-2) expression, increased reactive oxygen species production and reduced mitochondrial membrane potential ($\Delta\Psi$), all conditions that contribute to the induction of apoptosis [51] (Fig. 1).

B cells can also be regulated by THs, as suggested by the observation that THs positively regulate primary B cell lymphopoiesis [52,53]. This supposition is based on B lymphopoiesis *in vivo* studies performed in mouse strains deficient in the production of anterior pituitary-derived hormones due to naturally occurring or induced genetic defects [53,54]. More specifically, the frequency and absolute number of B lineage cells (i.e. pro-B and B cells) showed a significantly decreases in TH-deficient mice. In hyt/hyt mice, which display an extensive hypothyroidism and homozygous expression for the inactivation of TSH receptor mutations, THs are produced at ≤ 10% of normal levels [55–57]. *In vivo* treatment of these mice with T_4 increases both the frequency and total number of cycling pro-B cells (B cell precursors negative for cell-surface immunoglobulin but positive for the B cell lineage marker B220). The results, suggest that THs can regulate the proliferative potential of developing B cell precursors [58].

2.2. Macrophages

Macrophages are key immune system cells derived from monocytes in response to infections or to the accumulation of damaged or dead cells [59]. Two distinct polarized activation states have been defined for macrophages – the classically activated (M1) macrophage phenotype and the alternatively activated (M2) macrophage phenotype. Classically activated (M1) macrophages act as effector cells in the T_H1 cellular immune response, whereas alternatively activated (M2) macrophages appear involved in immunosuppression and tissue repair [60].

THs positively affect macrophage bactericidal effector functions, consequently improving wild-type mouse survival in a number of disease models, such as meningococcal infection [61]. Specifically, when the RAW264.7 macrophage cell line is treated *in vitro* with T_3 or T_4 for 24 h before *Neisseria meningitidis* infection, this cell line can capture significantly more bacteria than untreated macrophages [61]. Here, THs enhance iNOS-mediated nitric oxide production in a membrane receptor integrin αvβ3-dependent manner (i.e. via non-genomic stimulation) through pathways involving PI3K and ERK1/2 [61].

Mouse and human studies suggest that a T_4-induced inhibition of the macrophage migration inhibitory factor (MIF) could improve the treatment of sepsis treatment [62,63]. In greater detail, the MIF molecule contains a hydrophobic pocket important for many proinflammatory activities. Several small molecules can inhibit the catalytic activity of this pocket, thereby reducing MIF activity. The dose-dependent inhibitory effects of T_4 on MIF and subsequently improved survival rates suggest a clinically relevant interaction between T_4 and MIF [63]

Macrophages significantly contribute to immune system surveillance by sensing and adapting to local stimuli and microenvironment signals [64]. Regarding macrophage differentiation, T_3 was recently shown *in vitro* to negatively contribute to the differentiation of bone marrow-derived monocytes into non-polarized macrophages [65]. T_3 promotes the generation of M1 macrophages, even after the differentiation and activation of monocytes into M2 macrophages [65]. Nevertheless, while T_3 increases the number of resident macrophages in the peritoneal cavity, the THs can also reduce monocyte-derived cell recruitment [65]. In an *in vivo* model of endotoxemia, as induced by intraperitoneal lipopolysaccharide injection, T_3 protects mice from developing endotoxic shock [65]. While low T_3 levels increase inflammatory cell recruitment into tissues, an opposite phenomenon occurs when T_3 levels are restored [64,65].

Microglia is another cell type with innate immune properties in central nervous system (CNS), which also can be modulated by THs [66]. It has been reported that hypotiroid rat pups present defects in the morphology, microglial process formation and diminution in the number of these cells until the 3rd week after birth, as compared to controls. However, these defects could be reverted by the administration of T_3 [66]. In addition, *in vitro* microglial cultures showed that T_3 can promote the survival and growth of the culture. In addition to modulating the microglial phenotype, the lack of T_3 also affects the phagocytic capacity of these cells *in vitro* and *in vivo*, which is one of the principal functions of microglia in the CNS [67]. Taking into account the microglial function modulation by THs, Perotta et al. recently reported the role of T_3 inducing the proliferation of malignant glioma cell line GL261, only through microglial cocultures. The cellular changes observed in microglia after stimulation with T_3 [68] were an increase in the levels of pSTAT3 pathway and the induction of *cxcl9* and *cxcl10* chemokine expression, which directly impacted on glioma cell line proliferation [68]. These data suggest a novel homeostatic link between THs and the pathophysiological role of macrophages, thus providing new perspectives on interactions between the endocrine and immune systems.

2.3. Dendritic cells

Dendritic cells are highly specialized cells that recognize, process and present antigens to naive T cells to induce antigen-specific immune responses [69]. Recent studies propose that THs can influence the phenotype and function of human peripheral blood DCs. Thus, these hormones can significantly influence the homeostasis of the immune response as well as contribute to the pathogenesis of immune and endocrine disorders. Blood samples obtained from hypothyroid/thyroid carcinoma patients prior to and after thyroidectomy revealed a higher percentage of peripheral blood plasmacytoid and myeloid DCs in individuals that received L-T_4 administration up to two months after surgery, as compared to a pretreatment group [70] and the expression of CD86 on both DC subtypes is higher in L-T_4 treated than in untreated hypothyroid patients. Likewise, T_3 stimulation of DCs *in vitro* with T_3 increases surface expression of CD86 expression. Although these studies are very informative, further research is required to clearly define the effects of THs on DCs. Due to the various capacities of DCs to modulate the function of other immune cells during healthy and disease conditions, THs could be important at regulating the onset of an immune response. More studies could contribute to understand the influence of thyrometabolic status on the phenotype and function of human peripheral blood DCs. It is important to take into account that these cells express receptors for T_3 and T_4, specifically $TR\beta_1$ [30].

3. Thyroid-stimulating hormone-mediated effects of thyroid hormones on immune cells

The TSH influences immune cell frequency and functions in a number of ways. The immune cell distribution of TSHRs has been studied *in vitro* and in an *in vivo* animal model using immunoprecipitation and flow cytometry analyses with highly enriched B cells, T cells and DC populations [71]. However, the extent to which TSH modulates the immune response in TSHR-expressing lymph node T cells remains only partially understood.

3.1. Lymphocytes

Flow cytometry analyses of splenocytes and lymph node T cells reveal important differences between the lymphoid organs. In *in vitro* cultures, only 2–3% of splenic T cells are TSHR-positive, whereas 10–20% of $CD4^+$ and $CD8^+$ lymph node T cells express this receptor [71]. Remarkably, TSHR expression is exclusively associated with $CD45RB^{high}$ cells and is not observed during or after the activation of these cells [71]. In this case, CD45RB expression determines pathogenic potential [72]. For example, $CD45RB^{high}$ T cells

present in patients during inflammatory bowel disease produce more proinflammatory cytokines than do CD45RB^{low} T cells, indicating an importance for pathogenesis [72]. Therefore, this receptor could play a key role in inflammatory bowel disease development and progress.

In turn, purified murine splenic T cells can produce TSH in response to the superantigen staphylococcal enterotoxin A [73]. In *in vitro* models using sheep red blood cells and trinitrophenylated *Brucella abortus*, TSH production by T cells enhances the production of antibodies by B cells for T cell-dependent and −independent antigens [74]. Thus, TH therapy could be a viable alternative treatment for patients with a depressed immune system, particularly in cases where immunoglobulin production is decreased. However, this aspect remains to be assessed. In *in vitro* cultures of mouse lymphocytes, TSH significantly increases the proliferative response to both concanavalin A and phytohemagglutinin [75]. Subsequently, this increase can be associated with a higher lymphocyte secretion of interleukin (IL)-2.

In vivo models, such as in hyt/hyt mice resistant to TSH due to a TSHR-inactivating mutation [76], show increased numbers of peripheral CD4$^+$ T cells and few developing CD8$^+$ T thymocytes [77]. These mice also display a skewed distribution of thymus-derived CD8$^+$ T cell subsets in the gut epithelium [78], suggesting that CD8$^+$ T cells are particularly susceptible to the effects of TSH. Another effect of THs on lymphocytes in TSHR-defective hyt/hyt mice is a significantly reduced frequency of pro-B cells in the S-G2/M phase as compared to wild-type mice [79]. These data demonstrate that THs regulate pro-B cell proliferation and are consequently required for normal bone marrow B cell production. This regulation establishes a role for the hypothalamus-pituitary-thyroid axis in B cell development that could later influence the humoral immune response. Conversely, specific increases for the amount of cycling pro-B cells and bone marrow B cell lineages occur in hypothyroid mice treated *in vivo* with T_4, specifically. This situation naturally lends to the conclusion that TH deficiency would be responsible for proliferating the B cell defect in hyt/hyt mice [79]. These data also suggest that TSH can indirectly act on the immune system by modulating T_3 and T_4 release.

Mice harboring gene deletions for the T_3 receptors $\alpha1$ and $\alpha2$ show a reduced number of lymphocytes in the bone marrow, thymus and spleen. Of these, splenic leukocyte populations are the most affected[80]. Similarly, lymphoid and myeloid cells express TSHR to modulate lymphocyte functions. This is supported by studies showing the expression of TSHR in lymphoid and myeloid cells [81,82] and by studies demonstrating the ability of TSH to influence the functional behavior of lymphocytes[83]. In *in vitro* plaque assays, TSH elicits elevated antibody responses [84,85] and potentiates the effects of concanavalin A- and phytohemagglutinin-induced T cell proliferation [75]. Furthermore, TSH possesses a co-stimulatory activity for natural killer cells combined with IL-2 in *in vitro* assays [75].

3.2. Dendritic cells

In secondary lymphoid tissues, splenic DCs have been shown to be a significant source of TSH. Following *in vitro* culture in medium without stimulation, or when cultured with staphylococcus enterotoxin B, DCs produced 3–6 times more TSH than did purified B cells or T cells [86]. Here, the capacity of DCs to produce TSH was confirmed *in vivo* by immunofluorescence staining of splenic tissues from normal mice, revealing that the majority of TSH-producing cells were localized in the marginal zones surrounding T cell areas and in germinal centers where DCs are enriched [87].

On the other hand, in peripheral blood, the percentage of plasmacytoid DCs is not significantly affected in patients with complete thyroidectomy by TSH administration [88]. The lack of significant differentiations also applies to the percentages of the two main myeloid DC subpopulations, CD1c/BDCA1$^+$ and CD141/BDCA3$^+$. Administration of TSH had no effect on the surface expression of CD86 in either a whole peripheral blood mononuclear cell fraction or in particular DC subtypes in these patients [88].

4. Thyroid hormone in inflammation, autoimmunity and pathogen clearance

THs and TSH seem to affect immune functions during several pathological states, including inflammation, autoimmunity and pathogen clearance. Indeed, healthy human subjects (aged 55–70) show positive correlations between the following: THs, inflammation markers, natural killer T cell quantities, monocyte-activated IL-6 expression, memory T cell percentages, quantities of CD3$^+$/CD4$^+$/CD45RO$^+$ memory T helper cells and more IL-2 receptors in CD3$^+$ T cells [89]. The concentration of THs can also be inversely related to early lymphocyte death and to the ratio of naïve:cytotoxic CD3$^+$CD8$^+$CD45RO$^+$ memory T cells [89]. These data suggest that THs stimulate the immune system to strongly react to infection. In fact, increased TH levels are associated with decreased septic shock symptoms in major trauma patients with poor prognoses. Furthermore, TH supplements can reduce mortality in *in vivo* animal models affected by sepsis induced through cecal ligation and puncture [90].

Nevertheless, sufficient evidence has not been provided for a direct beneficial role of THs in specific immune cells and subsequently, in counteracting infectious diseases. However, indirect evidence suggests that these hormones play positive roles in the immune system.

It has been reported that THs, also contribute to the immune response against viral infections [91]. Hyperthyroid mice lymphocytes, as compared to euthyroid counterparts, show increased proliferation and interferon-gamma production in response to herpes simplex virus-1 infection in *in vitro* cultures [91]. Treatment of euthyroid mice with T_4 increases *in vitro* the proliferative capacity of lymphocytes but does not increase interferon-gamma production, which remains antigen-specific. Furthermore, the hyperthyroid state significantly attenuates concanavalin A-induced IL-10 release as compared to the euthyroid state [91]. Given that IL-10 is an anti-inflammatory cytokine that inhibits during infection the activities of T_H1, natural killer and macrophage cells, all of which are required for optimal pathogen clearance, it is possible that THs could be used to treat viral infections by activating the T_H1 over the T_H2 immune response.

In vitro studies show that THs can regulate herpes simplex virus gene expression and modulate the latency/reactivation of this virus in the host [91]. In *in vitro* virus-susceptible cell line cultures (Vero cells), splenic viral loads in hyperthyroid rats are significantly lower than in euthyroid rats [91]. Remarkably, hypothyroid rats also show significantly increased splenic viral loads as compared to euthyroid controls [91]. These data clearly indicate that herpes simplex virus-1 infectivity is affected by THs, suggesting that THs or TH analogs may have potential applications for the prevention and/or treatment of viral infections.

While there is a clear relationship between THs and autoimmune thyroiditis, little is known about the effects of these hormones on other autoimmune pathologies. During inflammatory end-stage renal disease, alterations occur for total and free form THs. More specifically, both free T_3 and total T_3 levels are often reduced in end-stage renal disease. This alteration seems attributable to an impaired extra-thyroidal conversion of T_4 into T_3. Indeed, free T_4 and total T_4 less frequently decrease in end-stage renal disease patients [92]. Another study observed inverse associations between IL-6, the C-reactive protein, and vascular cell

adhesion molecule 1, which is an indicator of endothelial activation/dysfunction [93]. Furthermore, free T_3 was found significantly reduced during the inflammatory process, with a reversal of this alteration occurring post-inflammation [93].

THs also alter the distribution and number of T cells in mucosal tissues. For example, human autoimmune gastritis is characterized by the inflammation and atrophy of the gastric mucosa, the loss of parietal cells, and the presence of parietal autoantibodies to H1K1-ATPase [94]. This disorder is associated with achlorhydria, vitamin B12 deficiency, and megaloblastic anemia [94]. Autoimmune gastritis is an organ-specific autoimmune disease, the experimental model of which involves T cell responses and auto-antibodies that can be elicited in mice following a thymectomy performed one to three days after birth [94]. In this model, the administration of T_4 in young neonatal thymectomy mice during an active phase of disease drastically reduces the incidence and overall severity of gastritis [94]. Remarkably, T_4 treatment also lowers the levels of anti-parietal cell antibodies [94]. In contrast, the treatment of young, neonatal thymectomy mice with T_4 prior to disease onset had no beneficial effect on gastritis, but T_4 pre-treatment did result in significantly higher anti-parietal cell antibody levels as compared to non-pretreatment and adult-treated neonatal thymectomy mice [95]. These results suggest that THs could play a role in controlling the development of autoimmune gastritis. This is important because autoimmune gastritis has been associated with other autoimmune diseases, particularly thyroiditis [96]. In subjects with hypothyroidism, the occurrence of these disorders may be associated with higher doses of levothyroxine [97].

Regarding other autoimmune diseases, there is a higher incidence of thyroid dysfunction in systemic lupus erythematosus and rheumatoid arthritis patients (52.5% and 17.5%, respectively), as compared to healthy patients (10%). Worth highlighting, the incidence of thyroid dysfunction in rheumatoid arthritis patients is less than in systemic lupus erythematosus patients [98]. These results are similar to other reports finding subclinical hypothyroidism to be the most common abnormality present in systemic lupus erythematosus and rheumatoid arthritis patients (35% and 10%, respectively), followed by clinical hypothyroidism (15% and 5%, respectively) and euthyroid sick syndrome (2.5% and 2.5%, respectively) [99]. This latter study did not detect subclinical or clinical hyperthyroidism in any systemic lupus erythematosus, rheumatoid arthritis, or control patients [99].

Although the contribution of thyroid hormones has been reported in the above-described conditions (i.e. inflammation, autoimmunity, and pathogen clearance), the mechanisms by which these contributions occur remain to be determined. In autoimmune processes, the exact role of thyroid hormones remains to be studied, particularly since autoimmune diseases are associated with thyroid abnormalities. So far, existing reports only indicate correlations between TH levels and autoimmune diseases.

5. Conclusions

The accumulated evidence strongly supports the notion that THs exert a modulatory role on immune cells and in establishing immune responses. Indeed, it is widely accepted that THs regulate the immune response by affecting phagocytosis, chemotaxis, the generation of reactive oxygen species and cytokine secretion (Fig. 1). In the practice, the role of THs as a modulators of immune cells are described during infectious and inflammatory conditions, however current knowledge have transforming the measurement of THs levels as indicators of disease progression. For example, clinical observation in sepsis patients have suggested a direct association between fT3 levels and the patient outcome, indicating that significant decreased levels of fT3 during the sepsis evolution could be used as a prognostic and mortality marker, together with IL6 and CRP [104]. In the same lines, studies made in newly diagnosed HIV patients to evaluate a potential correlation with the development of thyroid disorders, mainly subclinical hypothyroidism and hypothyroidism are growing in the field. In these patients a positive correlation has been described between the levels of fT3 and fT4 and the numbers of circulating CD4+ T cells [100]. Then this ratio could be useful as potential marker for disease activity, which could be improved by adding information such as viral load and IFN-γ production of these patients.

As mentioned above, a link between THs modulation and the onset of autoimmune disorders also has been reported. As in sepsis or HIV infection, the most prevalent THs dysfunction is related with subclinical hypothyroidism, but the cellular mechanism triggered by these concomitant diseases are more difficult to establish.

On the other hand, THs not only are associated with potentially detrimental effects. Research in animal models has allowed to propose some possible exploitation of the modulation of immunity by THs, as for example during vaccination. Consistently with this notion, Klecha et al. [41], showed that the levels of T_3 and T_4 in mice increased after immunization with allogeneic lymphoid cells and *in vivo* treatment with T_4 increased alloreactive antibody titers at early after immunization. Furthermore, T_4 enhances lymphoid proliferation *in vitro* in a mixed lymphocyte reaction[41]. In addition, it was shown that hyperthyroid state potentiates humoral response and activates NF-κB signaling pathway in lymphocytes [102]. These results suggest that the measurement of THs levels before vaccination or the use of THs to enhance the immunity induced during the immunization schedules. This notion was also recently explored in immunotherapy against cancer [103]. However, further research is required to clearly establish the relationship between immune function and THs, as some controversy in the literature. Further the potential use of THs as markers of disease prognosis has been proposed for human diseases. Therefore, further studies are needed in healthy individuals to clarify and better characterize the relationship between THs and the immune system.

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