Review Article

Thyroid Hormones and Immune Regulation: Molecular Mechanisms and Clinical Implications of Endocrine–Immune Cross-Talk

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Submission: March 7, 2026 Accepted: June 26, 2026 Published: June 30, 2026

Abstract

The immune and endocrine systems function together to keep the body in balance through regulating mechanisms alongside the body's capacity to respond to both internal and external stressors. The two principal thyroid hormones are T4 (thyroxine) and T3 (triiodothyronine); both are widely recognized as having critical roles in managing an individual's metabolism, growth, and energy levels. Current literature indicates that thyroid hormones are also important regulators of the immune system. Thyroid hormones play a role in the development, differentiation, and function of immune cells. Investigating the molecular pathways that inform the relationship between thyroid hormones and the immune system will provide insight into the etiology of immune-mediated diseases and other systemic/pathophysiological processes. The aim of the current narrative review is to determine what is known based on the scientific literature regarding how thyroid hormones impact the immune system on a molecular level, as well as how these effects could influence the clinical presentation of immune-mediated and systemic disease. A narrative review of the literature was performed using PubMed, Scopus, Web of Science, and Google Scholar to identify relevant publications. This review summarizes current evidence regarding the molecular mechanisms through which thyroid hormones regulate immune function and how immune activation influences thyroid physiology. Evidence from experimental and clinical studies indicates that thyroid hormones modulate innate and adaptive immunity through genomic and non-genomic pathways involving thyroid hormone receptors, MAPK, PI3K/Akt, and NF-κB signaling. Conversely, inflammatory cytokines alter thyroid hormone metabolism and contribute to non-thyroidal illness syndrome. These interactions are implicated in autoimmune thyroid disease, infection, sepsis, cancer progression, and responses to immunotherapy. Understanding endocrine–immune cross-talk may improve diagnostic strategies and support the development of targeted therapeutic approaches

Keyword: Thyroid hormones, Immune regulation, Endocrine–immune crosstalk, Autoimmune thyroid disease, Non-thyroidal illness syndrome

Introduction

The immune and endocrine systems function as highly integrated regulatory networks that regulate host defense, metabolic homeostasis, and adaptation to stress. Traditional concepts of hormonal regulation have been challenged by the growing understanding of neuroendocrine–immune interactions in traditional theories, which shows that endocrine mediators actively contribute to immune modulation [1]. Thyroid gland secretes the hormones thyroxine (T4) and triiodothyronine (T3). These hormones play a crucial role in regulating cellular bioenergetics and systemic metabolism. In addition to their metabolic functions, thyroid hormones are important for immune cell development, differentiation, and effector responses in addition to their main roles in body's metabolism [2]. Thyroid hormones have both genomic and non-genomic effects at the molecular level. From a genetic standpoint, T3 attaches to nuclear thyroid hormone receptors (TRα and TRβ). These recep-

tors are ligand-dependent transcription factors that control the expression of certain genes that have to do with oxidative metabolism, apoptosis, cellular proliferation, and inflammatory signaling. Integrin αvβ3, a membrane-associated receptor, starts intracellular signalling cascades like nuclear factor kappa B (NF-κB), phosphatidylinositol 3-kinase (PI3K)/Akt, and mitogen-activated protein kinase (MAPK) to carry out non-genomic actions. There is a mechanical basis for the cross-regulation of thyroid hormones and the immune system because these pathways are necessary for activating the immune system and making cytokines [3]. Immune cells have receptors for thyroid hormones and enzymes that break down those hormones. These cells macrophages, dendritic cells, neutrophils, natural killer cells, and lymphocytes help to control the supply of T3 inside cells. This particular regulation in tissues suggests that thyroid hormones influence immune responses at both the microenvironmental and organ system levels [35]. An experimental study investigated immune dysregulation. It determined that the expression of PD-1 and the suppressive function of regulatory T cells (Tregs) were markedly reduced in patients with Graves' disease compared to healthy controls. When human peripheral blood mononuclear cells were treated with T3 in vitro, PD-1 expression in Tregs decreased in a concentration- and time-dependent manner. These findings suggest that elevated T3 levels may impair Treg function by diminishing PD-1 expression [4]. Conversely, clinical studies have demonstrated that pro-inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) are associated with decreased levels of free T3 and thyroid-stimulating hormone (TSH) in euthyroid individuals, indicating that inflammation affects thyroid hormone homeostasis. Cytokines significantly contribute to the non-thyroidal illness syndrome (NTIS) by affecting thyroid hormone metabolism and deiodinase activity. Two pro-inflammatory cytokines which are tumor necrosis factor-α (TNF-α) and IL-6, also increased in autoimmune thyroid diseases. This provides evidence that inflammatory mediators play a part in disturbing thyroid regulation [5-7]. These mechanisms play a role in the developpment of NTIS. This syndrome is characterized by altered peripheral hormone metabolism and decreased circulating T3 levels, when systemic inflammation and critical illness occur. The dynamic feedback, between immune signaling and thyroid regulation, is highlighted by this adaptive or maladaptive endocrine response [8]. Hashimoto thyroiditis and Graves' disease are autoimmune thyroid conditions. In those conditions, loss of immune tolerance results in autoreactive lymphocyte infiltration and targeting of thyroid-specific antigens. This highlights the clinical significance of thyroid–immune cross talk clear. Transcriptomic evidence supports the role of immune-mediated mechanisms in disease pathogenesis, by showing immune cell dysregulation within thyroid tissue [9]. Additionally, the development of cancer, chronic inflammatory conditions, infectious diseases, and metabolic syndromes have all been linked to thyroid-immune cross-talk [2]. Although research is increasing, some molecular mechanisms and mechanistic processes are not fully understood. According to a study conducted by Montesinos and Pellizas [10] , there are many unanswered questions regarding the local regulatory mechanisms and how immune cells respond to thyroid hormones [23]. In contrast to the evidence outlined by Wenzek, Boelen [2], who demonstrated the expression of thyroid hormone transporters, receptors, and deiodinases in immune cells [37], limited research has examined how these thyroid-related interact with

distinct immune cell types. Despite growing evidence supporting thyroid hormone involvement in immune regulation, several important questions remain unresolved. The precise mechanisms through which thyroid hormone receptor signaling influences distinct immune-cell subsets, including regulatory T cells, macrophages, and dendritic cells, are incompletely understood. Furthermore, findings from in vitro studies and animal models are not always consistent with observations in human clinical research. Considerable uncertainty also exists regarding the clinical significance of thyroid hormone alterations during critical illness and whether therapeutic modulation of thyroid hormones can improve patient outcomes. Although previous reviews have described individual aspects of thyroid–immune interact-tions, recent advances in molecular immunology, deiodinase biology, immune checkpoint regula-tion, and cancer immunotherapy justify an updated synthesis of current evidence. The objective of this review is to analyze the molecular and cellular mechanisms that underline the bidirectional relationship between thyroid hormones and the immune system. Additionally, the review provides clinical/ contextual considerations of the relationship between thyroid hormones and the immune system in terms of various disease processes (autoimmune, inflammatory, infectious and neoplastic). A deeper understanding of this relationship may lead to the development of novel therapeutics and better management of the disease.

Review Methodology

This manuscript was conducted as a narrative review. Relevant literature was identified through searches of PubMed, Scopus, Web of Science, and Google Scholar using combinations of keywords related to thyroid hormones, immune regulation, inflammation, autoimmune disease, and endocrine–immune interactions. The search was intended to provide a broad overview of current evidence rather than to follow formal systematic review methodology.

Physiology and Molecular Biology of Thyroid Hormones

A. Regulation of Thyroid Hormone Synthesis

Thyroid hormones (T3 & T4) are iodine containing hormones. They are produced inside thyroid follicles. thyrocytes absorb iodide from the blood through sodium-iodide cotransporter at the basolateral membrane. The thyrocytes produce and release thyroglobulin (TG) that provides structural framework for hormone synthesis. At the apical membrane, oxidation of iodide occurs and binds to tyrosine residue through thyroid peroxidase (TPO) and hydrogen peroxide actions. This process leads to the formation of T3 and T4. The entire process is regulated by TSH, also iodide recycling is necessary for normal production of thyroid hormones [11].

B. Thyroid Hormone Receptors and Genomic Actions

Triiodothyronine exerts its biological effects mainly through two nuclear receptors (TRα and TRβ). these receptors function as transcription factors that are activated when they bind to thyroid hormone response elements (TREs), this occur in the promoter regions of target genes [12]. When T3 is not present, thyroid hormone receptors interact with co-repressor proteins that inhibit gene transcription. Once T3 binds to the receptor, the receptor undergoes structural modification and recruits co-activator proteins. this process results in chromatin remodeling and activates transcription of genes that involved in mitochondrial activity, metabolism, cell proliferation, and differentiation. [13].

C. Non-Genomic Signaling Pathways

Thyroid hormones have non-genomic action in addition to nuclear receptor effects. These rapid effects occur through receptors located on the cell membrane. An important receptor that binds T3 and T4 at the cell surface is Integrin αvβ3. Activation of this receptor triggers intracellular signaling pathways notably MAPK and PI3K/Akt signaling mechanisms [14]. These signaling pathways interact with key inflammatory regulators including NF-κB. This point to an interaction between thyroid hormone signaling and the immune response. Such rapid signaling may explain the rapid changes in immune cell function that documented in experimental studies (Fig. 1) [10].

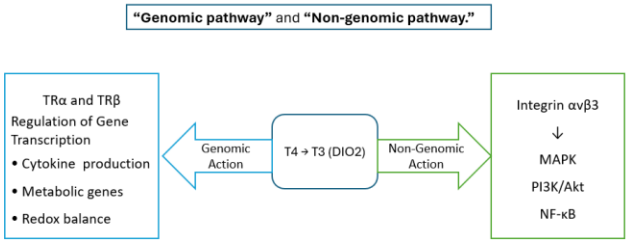

Figure 1: Genomic and non-genomic mechanisms of thyroid hormone signaling in immune regulation.

Genomic and non-genomic mechanisms of thyroid hormone signaling in immune regulation. T3 binds nuclear thyroid hormone receptors (TRα and TRβ) and regulates transcription of genes involved in metabolism, cell proliferation, differentiation, and inflammatory responses. Thyroid hormones also activate non-genomic signaling through integrin αvβ3 on the plasma membrane, triggering MAPK, PI3K/Akt, and NF-κB pathways that influence immune-cell activation and cytokine production.

D. Tissue-Specific Regulation and Immune Relevance

Immune cells express thyroid hormone receptors as well as deiodinase enzymes. They are allowing regulation of intracellular T3 levels. When inflammation process occurs, it can change deiodinase expression that alters the availability of thyroid hormone locally. This localized regulation is considered an important mechanism regardless of systemic thyroid hormone levels [15].

Effects of Thyroid Hormones on the Immune System

A. Differential Effects on Innate and Adaptive Immunity

Thyroid hormones have effect on innate immune cells. They regulate neutrophils, macrophages, and neutral killer (NK) cells. These hormones also promote the proliferation and maturation of dendritic cells that lead to improvement in antigen presentation. in the adaptive immune system, hyperthyroidism is associated with increased lymphocyte activation through pathways such as NF-κB and protein kinase C (PKC) while hypothyroidism is associated with reduced immune response by decreasing lymphocyte activation . That means immune activity depends on thyroid hormone levels. collectively, These mechanisms highlight the important role of thyroid hormones in regulating both innate and adaptive immunity (Fig. 2) [16].

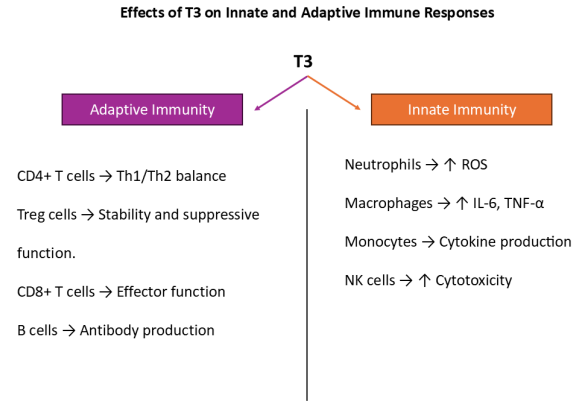

Figure 2: Differential effects of T3 on innate and adaptive immune responses.

Differential effects of thyroid hormones on innate and adaptive immunity. Thyroid

hormones regulate neutrophils, macrophages, dendritic cells, and natural killer cells within the innate immune system while influencing T- and B-lymphocyte activation in adaptive immunity. Alterations in thyroid hormone levels may enhance or suppress immune responses through modulation of cytokine production and intracellular signaling pathways.

B. Effects on Innate Immunity

Thyroid hormones regulate innate immune responses by modulating the function of macrophages, neutrophils, and dendritic cells. These cells express thyroid hormone receptors and deiodinases [10]. During inflammatory stimulation, optimal macrophage phagocytosis and cytokine production depend on intracellular T3 availability, especially through D2 activity [17]. Furthermore, T3 supports a direct role of thyroid hormones in innate immune defense by influencing neutrophil antimicrobial activity and promoting macrophage polarization [10, 17].

C. Effects on Adaptive Immunity

A hyperthyroid condition increases lymphocyte activation in the adaptive immune system. Numerous mechanisms, including as the β-adrenergic receptor and the NF-κB and protein kinase C signaling pathways, mediate this impact of thyroid hormone. Immune system activation is generally higher in hyperthyroidism and lower in hypothyroidism [16].

Effects of Immune Activation on Thyroid Function

Immune activation significantly alters thyroid physiology at multiple regulatory levels, including hypothalamic–pituitary signaling, thyroid hormone synthesis, peripheral metabolism, and autoimmunity [18]. Pro-inflammatory cytokines and immune mediators can directly interfere with thyroid function and systemic hormone homeostasis [19].

Autoimmune thyroid disease (AITD) results from a dysregulation of the immune system that leads to loss of tolerance to thyroid antigens and to an autoimmune attack on the thyroid gland [20].

A. Cytokine-Mediated Suppression of the Hypothalamic–Pituitary–Thyroid (HPT) Axis

During systemic inflammation and critical illness, cytokines suppress TSH secretion and alter hypothalamic thyrotropin-releasing hormone (TRH) expression, contributing to reduced circulating thyroid hormone levels [21]. Interleukin-6 in particular has been associated with decreased TSH secretion and impaired thyroid hormone production during inflammatory states [22]. These mechanisms are central to the pathogenesis of non-thyroidal illness syndrome (NTIS) which is mediated by cytokines such as interleukin-1, interleukin-6, tumor necrosis factor-α, and interferon-β. These cytokines affect the hypothalamus and pituitary gland. They inhibit TSH and TRH secretion, and alter thyroglobulin (TG), T3, and thyroid-binding globulin (TBG) production. They were also thought to reduce the activity of type 1 deiodinase and decrease the binding capacity of the T3 nuclear receptors [23].

B. Effects on Thyroid Hormone Synthesis and Thyrocyte Function

Pro-inflammatory cytokines directly impair thyroid hormone synthesis by inhibiting key thyroidal proteins. Interferon-γ (IFN-γ) and TNF-α reduce expression of sodium-iodide symporter (NIS), thyroglobulin (TG), and thyroid peroxidase (TPO) in thyrocytes [24]. Cytokine-induced oxidative stress also alters iodide organification and thyroid follicular integrity [25].

Clinical Implications

Increasing research about the relationship between thyroid immune systems has important clinical consequences across critical illness, autoimmunity, infection, and oncology. Understanding these interactions may improve diagnostic interpretation and guide therapeutic strategies.

A. NTIS in Critical and Inflammatory States

Recent clinical studies highlight that changed metabolism of intracellular TH has role in the pathophysiology of (NTIS) during critical illness. A recent cohort study included 96 patients who admitted to intensive care unit (ICU). The investigators observed Different expression patterns and localization of type 2 deiodinase (DIO2) and type 3 deiodinase (DIO3) in neutrophils and monocytes. Patients were observed at two different times, at admission and after 7 days. The study found that oxidative stress markers were increased. These markers involve elevated carbonyl protein and reduced sulfhydryl groups and glutathione (GSH) in all patients. These findings suggest the presence of redox imbalance. Notably, D3 protein levels were different between survivors and non-survivors. Also, intracellular T3 concentrations in immune cells have associated with patient outcomes. These findings suggest that thyroid hormone metabolism in specific immune cells and redox alterations contribute to NTIS pathogenesis and may have prognostic value in critically ill patients (Fig. 3) [26].

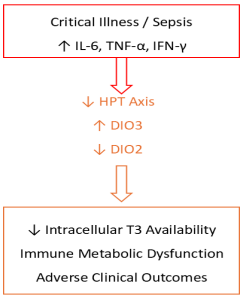

Figure 3: Cytokine-mediated dysregulation of thyroid hormone metabolism during critical illness and sepsis.

Cytokine-mediated dysregulation of thyroid hormone metabolism during critical illness and sepsis. Pro-inflammatory cytokines including IL-6, TNF-α, and IFN-γ suppress hypothalamic pituitary thyroid axis activity, alter deiodinase expression, and reduce intracellular T3 availability. These changes contribute to non-thyroidal illness syndrome and may influence disease severity and clinical outcomes.

B. Autoimmune Thyroid Disease and Immune Dysregulation

A clinical study observed patients who were diagnosed with Graves' disease. The study demonstrated that elevated T3 levels result in reduced expression of PD-1 on regulatory T cells (Tregs) and reduced immunosuppressive ability. In vitro treatment of human peripheral blood mononuclear cells (PBMCs) with T3 lowered PD-1 expression on Tregs depending on hormone concentration and exposure time. These changes were also associated with alteration in T-helper cells balance [4]. In addition, thyroid function (fT4 and TSH levels) is strongly associated with homeostasis of lymphocyte subsets, including effector and regulatory T cells, underscoring a link between thyroid hormone status and adaptive immune regulation [27].

C. Infection and Sepsis

Clinical data demonstrate that thyroid hormone levels are associated with the severity of infection and the inflammatory burden. A recent observational study involved sixty-two patients with sepsis and septic shock. They found that serum free (fT3) levels were significantly lower in patients with septic shock compared to those with sepsis. Lower fT3 levels were associated with higher Sequential Organ Failure

Assessment (SOFA) scores, greater disease severity, and higher risk of death. These findings support the clinical relevance of thyroid hormone alterations as a marker of disease outcome in sepsis [28]. A retrospective cohort study evaluated 186 patients with septic shock. Serum T3 and fT3 levels were lower in some patients. This was significantly associated with patients' death during ICU stay. Patients with higher T3 levels demonstrated better survival rates. Although, T3 was identified as an independent prognostic marker for short-term outcomes. This result suggests that decreased T3 levels are associated with more severe illness [29].

D. Cancer and Immunotherapy

Thyroid hormones have been associated with tumor growth (proliferation). Although involved in angiogenesis (formation of new blood vessels). These hormones have also been reported to influence and modify the tumors immune environment [30]. Thyroid hormone signaling stimulates angiogenesis and tumor growth in squamous cell carcinoma by upregulating important proangiogenic and metabolic pathways, according to a translational study. It has been demonstrated that thyroid hormone (TH) coordinates metabolic reprogrammming and increases the transcription of vascular endothelial growth factor A (VEGF-A), which increases endothelial cell proliferation and metabolic adaptations linked to the Warburg effect. This indicates a TH–VEGF-A-HIF1α regulatory axis that is important for the development of cancer [31]. Patients with advanced urothelial cancer receiving immune checkpoint inhibitors (ICIs) were enrolled in a clinical cohort trial. The fT3/fT4 ratio was used to evaluate thyroid hormone abnormalities. A low fT3/fT4 ratio was found to be an independent predictive factor. This study also found that patients with higher fT3/fT4 ratios had longer progression-free survival and overall survival. These findingss suggest that TH status has influence on cancer immunotherapy outcomes [32].

E. Translational and Therapeutic Considerations

Experimental studies support interaction between THs and immune system. However, therapeutic use of THs in clinical practice remains debated. Randomized controlled trials about thyroid hormone replacement in NTIS have produced inconsistent results. These trials did not clearly improve mortality or major outcomes in very sick patients, particularly those with low THs levels, but the evidence remains uncertain. Collectively, this highlights the difficulty of translating hormonal interventions into improved clinical outcomes [33]. Similar to this, studies comparing levothyroxine (T4) plus liothyronine (T3) versus T4 monotherapy in hypothyroid patients have not consistently shown improvements in quality of life or symptoms, which reflect the continuous discussion about the best thyroid hormone therapy, even in cases of established endocrine disease [34].

Discussion

Interactions between thyroid hormones and the immune system are increasingly recognized in recent literature, but their cellular and molecular mechanisms are not fully understood [35]. Future research should utilize advanced techniques, including single-cell transcriptomics and epigenomic profiling. These approaches can help in identifying TRα and TRβ signaling pathways in specific immune cell subsets such as T helper cells, regulatory T cells and macrophages [36]. Thyroid hormones' function in immunological polarization will become clearer if we comprehend how they control transcription factors. One major limitation of the

current evidence is the predominance of experimental and observational studies. Many mechanistic findings have been generated from in vitro models or animal studies, which provide important biological insights but may not fully reflect human immune physiology. Consequently, direct translation of these findings into clinical practice remains challenging. Differences in study design, patient populations, and methods used to assess thyroid function further contribute to variability among reported results. Non-genomic TH signaling occurs through integrin αvβ3. This signaling activates intracellular pathways, including MAPK/ERK and PI3K/Akt. These pathways may affect cytokine production and macrophage phenotype, but more research is needed [37]. Additionally, Inflammation can change the expression of deiodinase. It may create local T3 gradients that influence immune–metabolic reprogramming, mitochondrial function and redox balance [38].

Evidence across autoimmune disease, infection, sepsis, and cancer consistently demonstrates an association between thyroid hormone status and immune function; however, causality remains difficult to establish. In autoimmune thyroid diseases, thyroid hormones may influence immune tolerance and regulatory T-cell function, whereas inflammatory cytokines simultaneously alter thyroid hormone metabolism. This bidirectional relationship complicates interpretation of whether thyroid dysfunction is a cause, consequence, or adaptive response to immune activation. Thyroid hormones control immunological checkpoint mechanisms and angiogenesis in oncology. Prospective immunotherapy trials with endocrine biomarkers should investigate these impacts. Additionally, tissue-specific deiodinases or particular TR isoforms may be the focus of therapeutic approaches. Compared to systemic thyroid hormone replacement, this method might have more targeted effects [39].

From a clinical perspective, thyroid hormone measurements may have diagnostic and prognostic value in several immune-related conditions. Reduced serum T3 levels have been associated with disease severity and mortality in critically ill and septic patients, while alterations in thyroid hormone profiles may predict responses to cancer immunotherapy. Nevertheless, current evidence is insufficient to support routine therapeutic manipulation of thyroid hormones solely for immune modulation. Future studies should focus on identifying patient subgroups that may benefit from personalized endocrine-based interventions.

Conclusion

The interaction between thyroid hormones and the immune system represents a complex endocrine–immune network with important implications for human health and disease. Current evidence demonstrates that thyroid hormones regulate immune-cell development, activation, and inflammatory signaling through both genomic and non-genomic mechanisms, while immune-mediated cytokine responses significantly influence thyroid hormone metabolism and function. These interactions contribute to the pathogenesis of autoimmune thyroid disease, infection, sepsis, cancer progression, and non-thyroidal illness syndrome. Beyond their biological significance, thyroid hormone alterations may provide valuable diagnostic and prognostic biomarkers in several immune-related disorders. Although therapeutic targeting of thyroid–immune pathways remains challenging, emerging evidence suggests potential opportunities for personalized medicine and the development of novel endocrine-based immunomodulatory strategies. Future research using advanced molecular and translational approaches is needed to clarify unresolved mechanisms and facilitate clinical application.

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