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LITERATURE REVIEW

Understanding Thyroid Autoimmunity: A Mini Review on the Role of Stress and Immune Activation

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ABSTRACT

Background: The theory that stress plays a critical role in the pathogenesis of autoimmune thyroid diseases (AITDs) has been proposed for at least a century. However, evidence supporting this hypothesis has only recently come to surface. AITDs, including Hashimoto's thyroiditis and Graves' disease, result from immune system infiltration, with stress significantly modulating neuro-immune-endocrine responses.

Methods: This literature review examines the impact of stress-related immune activation in AITD. It explores how triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), thyroid peroxidase (TPO), and thyroglobulin (Tg) are affected by T and B cell behaviors, cytokine production, sympathetic nervous system (SNS) functions, hypothalamic-pituitary-adrenal (HPA) axis activity, glucocorticoid signaling pathways, glucocorticoid-induced tumor-necrosis-factor-receptor (GITR) proteins, and the Th17/Treg ratio.

Results: Sensory stimuli (stress, exercise, and diet) trigger HPA axis and SNS altering cortisol levels affecting TSH signaling and immune responses. Glucocorticoid and catecholamine stimulation impacts immune cell activity by acting on IL-6, IL-10, and IL-17 and other proinflammatory cytokines. Th17/Treg ratio imbalances are exerted by FoxP3 transcription factors and GITR protein expression heightening cytokine behavior and activating B10 cells, driving autoimmunity. $CD4^+$, $CD8^+$, and B10 cells to elicit attacks on thyroid hormones, receptors, TPO, and Tg proteins.

Conclusion: Stress influences AITD development and progression through complex immune pathways. Auto reactivity attacks on thyroid cells may occur as a memory mechanism to chronic stress episodes and desperate measures to reduce intracellular stress. Future research should explore stress questionnaires related to AITD onset and develop integrative body-mind-spirit interventions to mitigate stress-related immune activation.

Introduction

Autoimmune thyroid diseases (AITDs), such as Hashimoto's thyroiditis (HT) and Graves' disease (GD) are conditions where the immune system attacks thyroid tissues.[1–7] These diseases are influenced by various external environmental factors, including alcohol,[1,2] exercise,[8,9] diet,[2,5,6,9] smoking,[1,2,5,6] or stress,[1,2,6,8,9] with stress being the significant modulator of immune responses.[2,6,8,9] As such, stress-induced glucocorticoids, including cortisol produced during sympathetic nervous system (SNS) activation of the hypothalamic-pituitary-adrenal (HPA) axis, contribute to altered immune cell behavior and cytokine production.[5,6,8–10] Particularly, proinflammatory cytokine interleukin-6 (IL-6), is a critical factor in the pathogenesis of AITD.[2–9] Acute stress-induced cytokine activation[6,8,9,11] impacts the balance between thymus-derived (T) cells (both T helper [Th] and regulatory T [Tregs] lymphocyte subsets), influencing disease progression through Th17/Treg ratio imbalances.[2–7] Possessing a clear understanding of how these mechanisms affect leukocyte activity is crucial for a comprehensive view of AITD pathology. Therefore, this literature review focuses on elucidating how stress-related factors impact immune function leading to AITD.

Objective

This review aimed to examine the impact of psychological stress-related immune activation in AITD with the purpose of informing the development of integrative body-mind-spirit interventions. The initial section provides a comprehensive understanding, which is essential for the readers to grasp the

subsequent mechanisms in question. The focus then shifts to how sensory stimuli related to development of PTSD activates sympathoadrenal and neuro-immune-endocrine pathways involved with AITD phenomena. The review does not extend into specific details of other environmental factors, such as alcohol, exercise, diet, or smoking. While these factors are important in stress-induced immune modulation, they are mentioned only as additional environmental components that can trigger similar immune responses through the same mechanisms.

Methods

The author explored peer-reviewed research on how triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), thyroid peroxidase (TPO), and thyroglobulin (Tg) are affected by T cells and bone marrow-derived (B) cell responses, cytokine production, SNS functions, HPA axis activity, glucocorticoid signaling pathways, glucocorticoid-induced tumor-necrosis-factor-receptor (GITR) proteins, and the Th17/Treg ratio. Articles were selected based on their relevance to the pathogenesis of AITD (GD and HT) and the impact of psychological stress on cellular processes. The synthesis presented is based on a critical review of regulatory T and B cell responses in AITD patients, GITR profiles, thyroid responses to HPA axis activity, basic endocrine physiology and pathophysiology, and hypothalamus mechanisms related to PTSD.

Understanding Thyroid Autoimmunity

Leukocyte and Cytokine Activity

Autoimmune thyroid diseases primarily involves activity from lymphocytes, monocytes, and to some extent, neighboring neutrophils.[2–4] Lymphocytes include destructive T cells and auto-antibody producing B cells.[2–4] Monocytes function as antigen-presenting cells (APC) processing endocytosed protein antigen-derived peptides onto major histocompatibility complex (MHC) class I and II molecules. T cells, including Th cells and Treg, express specific surface antigen proteins known as cluster of differentiation (CD), commonly referred to as $CD4^+$ and $CD8^+$.[4] Cluster of differentiation 4^+ surface antigen proteins are predominantly found on Th cells, which interact with MHC class II molecules,[2,4] whereas $CD8^+$ present on cytotoxic T cells, recognizing MHC class I molecules.[4] Cluster of differentiation 4^+ and $CD8^+$ launch immune responses accordingly.[4] Notably, within the T cell group, $CD4^+$ Th cells are the predominant cells in the pathogenesis of AITD.[2–4,7] Naive Th cells produce cytokines in response to stimuli, and its milieu determines whether a Th0 will differentiate into Th1, Th2, or Th17.[2,3,7] Th1 cells produce interferon-gamma (IFN-γ),[2–4,6,9] transforming growth factor-beta (TGF-β),[3] tumor necrosis factor-alpha (TNF-α),[2,4,6,9] IL-1,[3] IL-2,[2–4,9] IL-10,[4,6] and IL-12.[3,6,9] Th2 cells are known to secrete IL-4,[2–4,6,9] IL5,[2–4] IL-6,[3–5] IL-10,[2,3,9] and IL-13.[2–4,9] Whereas, Th17 cells release IL-17 (IL-17A and IL-17F),[2,4,9] IL-21,[2,4] and IL-22.[2–4] In addition, some studies report mobilization of cytotoxic natural killer (NK) cells,[9,11] T and B cells,[9,11] and elevated IFN-γ[9] IL-1,[8,9] IL-6,[8,9,11] and transcriptional nuclear factor kappa-beta (NF-kβ) by TNF-α[8,9] activity during high-stress or high intensity physical activity (PA).[8,11]

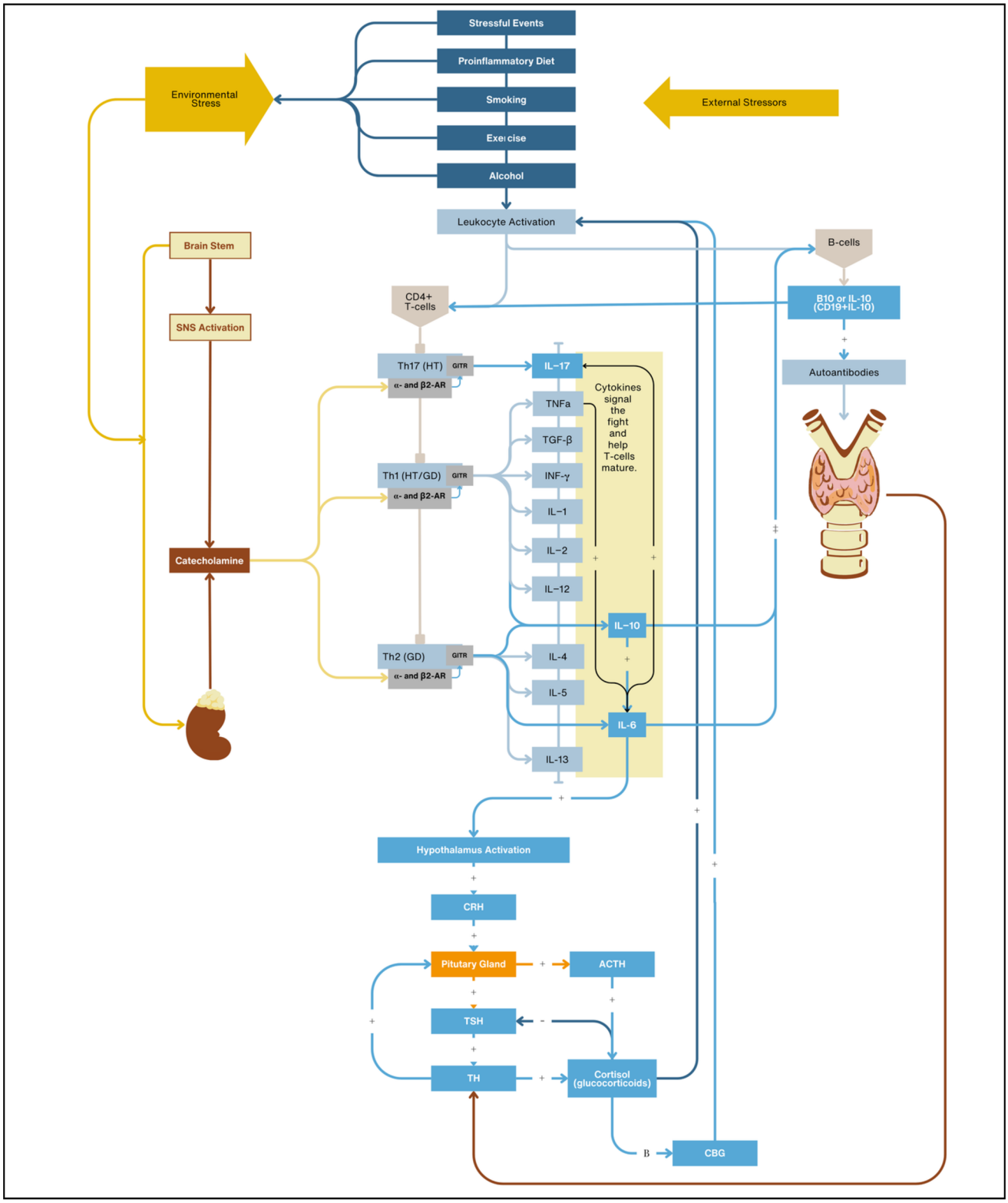
Auto-Reactive B Lymphocyte Activity

Recent developments have linked auto-reactive B cells to the pathogenesis of AITD.[2,4] These cells secrete a specific type of IL-10 cytokines referred to as $CD19^+$IL-10 (B10).[2,4] It is important to note that some activated B cells can convert to memory B cells to sustain the adaptive immune response, the major player in autoimmunity. In HT and GD the thyroid gland is infiltrated with auto-reactive B10 cells in addition to $CD4^+$ Th cells and cytotoxic $CD8^+$ T cells.[2] B cells in general, are reported to also drive IL-4,[6] IL-17,[6] and IL-6[2] proinflammatory cytokines. In HT, B10 cells may serve as the primary origin of auto-antibodies targeting thyroglobulin (Tg) and thyroid peroxidase (TPO) proteins.[2] These conclusions are evidenced by significantly reduced $CD19^+CD24hiCD27^+IL\text{-}10^+$ Breg cells and B10 cells,[4] as well as similar frequencies of B10 cells[2] in AITD patients. Research has also demonstrated that independent IL-10 cytokines have stimulatory effects on B cells, preventing apoptosis and enhancing antigen presentation, thereby increasing proliferation.[2] Particularly, the Tg self-antigen protein can activate this process, as Tg is more relevant in the pathogenesis of AITD.[2] Tg-pulsed B cells increase the production of IL-6, IL-10, and TNF-α in both $CD4^+$ Th cells and B cells.[2] Furthermore, B cells are reported to act on thyroid stimulating hormone receptors (TSHR),[4] are upregulated by Th cells,[4,6] and are further increased by chronic mild stress.[6]

The Interplay of IL-6, Th17/Treg Ratio, and FoxP3 Transcription Factor

The activity of AITD is coupled with increased Th17[2,6,7] and Treg cells expressing the forkhead box P3 (FoxP3) transcription factor.[2–4,7] Specifically, Th17 is a principal character in promoting pathogenesis of autoimmunity.[4,7] In the presence of TGF-β, IL-6 promotes expression of the retinoic acid-related orphan receptor C (ROR-C) human ortholog,[2,4,6,7] which is critical for Th17 cell differentiation.[2,7] This process is influenced by B cells, as B10 cells are

Figure 1. Environmental Factors Inducing Cytokine Activity in AITD Patients



Schematic representation of the interactions of various environmental factors that play a role in stress-induced physiological activity. External stressor, such as isolated stress, exercise, alcohol, smoking, or proinflammatory diet activate leukocyte activity, the sympathetic nervous system (SNS), and adrenal system. Cascades of reactions occur within the immune system through cytokine reactions (primarily IL-6) initiated by activation of β2-adrenergic receptors (β2-AR) and expression of glucocorticoid-induced tumor-necrosis-factor-receptor (GITR) impacting hypothalamic-pituitary-adrenal (HPA) axis. Alterations in thyroid hormone feedback and circulating glucocorticoid activity perpetuate this cycle by acting on T and B lymphocytes. Activation is represented by forward arrows (→) and plus (+) symbols; **B** = binding.

reported to drive release of IL-17,[6] from Th17 cells.[3,4,9] In contrast, Treg cells are reported to control and maintain self-tolerance.[2,7] In mouse studies examining immunity mechanisms in AITD, Treg cells concurrently express ROR-γt mouse orthologs of human ROR-C and FoxP3 transcription factors.[2] Thus, the Th17/Treg ratio has shown a pivotal role in the development of AITD.[2,4,5,7] Withal, Tg is observed to stimulate IL-6 and B10 cells in both HT and GD patients.[2] Whereas, TPO prompts a higher frequency of Th17 in HT.[2] Interleukin-17 is reported to stimulate production of IL-6, while IL-6 might potentiate IL-17 production from FoxP3$^+$ Tregs,[2] evidenced by elevated levels of IL-6[2,4,5,7] and increased expression of FoxP3.[2] Furthermore, ROR-α is documented to play a role in the hypothalamic, peripheral components of the circadian clock system during episodes of stress.[9] Refer to Figure 1 for a schematic representation of the stress-induced immune process.

Link Between Stress and Thyroid Autoimmunity

Glucocorticoid Activity in AITD

Th17 cells[4,5,9] and Treg cells expressing FoxP3[2–5] are positively correlated with increased glucocorticoid-induced tumor-necrosis-factor-receptor (GITR) related proteins.[2,4,5] Cortisol is a major glucocorticoid altered during periods of stress,[6,8,9,11] including stress-induced activities, such as exercise,[8,11] diet,[6,9,] and smoking;[6] and, a primary factor in the biochemical-related changes in AITD.[5] Coherently, the understanding is that the GITR ligand (GITRL) is predominantly expressed by APCs.[7] Findings of GITR-induced cytokines are evidenced by the high plasticity of Th17/Treg ratio,[2,4,7] positive analogues between Tg and Th17/Treg ratio,[7] and higher occurrence of CD4$^+$GITR$^+$ and CD4$^+$FoxP3$^+$ in individuals with AITD.[2,5] While type 1 transmembrane protein GITR expression levels vary in CD4$^+$ and CD8$^+$ T cells after induction, CD4$^+$CD25$^+$Tregs have high expression of GITR.[7] TGF-β can also encourage CD4$^+$CD25$^-$ T cells to develop into CD4$^+$CD25$^+$ cytotoxic lymphocyte associated protein 4$^+$ (CTLA-4$^+$), GITR$^+$, FoxP3$^+$ cells.[5] However, exposure to IL-6 redeploys cell development back into Th17 cells.[2,5] In addition, monocytes and lymphocytes are highly reactive to glucocorticoids.[11] Hence, understanding the role of GITR on immune complexes is crucial to evaluating the evidence of stress-related activities in AITD pathogenesis.

Sympathetic Nervous System and Adrenal Activation

Whether increased or decreased,[8] IL-6 is reported to be generated from skeletal muscle during exercise[11] and from the adrenal glands during periods of acute or severe stress.[6,8] The activation of the SNS terminates signals from the locus coeruleus in the brainstem[6,8–10] and subsequently the adrenomedullary system releases catecholamine neurotransmitters[6,9] inducing IL-6 secretion[6,8,9] and altering Th cell regulation. Interleukin-6 acts through signal transduction of beta-2-adrenergic receptors (β2-AR),[6,8,11] which are known to exclusively rest on Th APCs.[6] Catecholamine neurotransmitters additionally alter IFN-γ, IL-2, IL-4, and IL-10 activity,[9] and thyroid releasing hormone (TRH) via the α-AR.[8] In response to leukocyte activity,[6,8,11] hypothalamic paraventricular nucleus production of corticotropin-releasing hormone (CRH) signals the pituitary gland subsequently discharging adrenocorticotropic hormone (ACTH) and concomitantly altering TSH activity[6,8–10] (Figure 1). Thyroid hormones and ACTH simultaneously signal the secretion of cortisol, ultimately increasing levels of corticosteroid binding globulin (CBG),[6,8,9] reducing freely available glucocorticoids.[6] The "treatment of stress with cortisol significantly reduces frequency of AITD,"[6] indicating that, under normal stress conditions reduction of cortisol glucocorticoids frees up CBG, thus increasing the levels of unbound CBG in the bloodstream. Additionally, a neuroendocrine immune feedback loop allows signaling to the central nervous system (CNS), communicating a direct influence from peripheral immune activation, reactivating stress-related function allowing the CNS to modulate inflammation activity.[9] Furthermore, glucocorticoids suppress TSH secretion,[6,8] affect the activity of Th1 cytokines,[6,9] enhance Th2 pathways,[6,9] and reduce glucocorticoid sensitivity in monocytes.[6] The aforementioned evidence suggests stress-induced glucocorticoids trigger GITR and GITRL[7] activity. These proteins thereby modulate the production of autoantibodies by activating cytokines,[6,9] regulating leukocyte proliferation[7,9] and affecting leukocyte polarization and relocation[6,8,9] in patients with AITD. Stress-induced autoimmunity is further corroborated by: 1) the evidence of athletes partaking in stressful exercise routines with lower leukocyte counts and impairments in adaptive immunity (altered T and B cells synthesis);[11] 2) the altered TPO and Tg activity in AITD patients during exercise;[1] 3) increased activity of TRH, TSH, and thyroid hormones T3 and T4 in connection with traumatic stress; and 4) altered TSHR,[3,5] TPO,[2,4] and Tg[4] activity by cytokine-induced IgG action as a result of diet-induced Th1 and Th2 cell responses.[2–4]

Expanding on AITD and PTSD:
A Stress Stimuli Perspective

Post Traumatic stress disorder (PTSD) is common among individuals with AITD, as confirmed by strong correlations between PTSD and increase thyroid

hormones (T3, T4, TRH and TSH), glucocorticoid increases in individuals with thyroid dysfunction,[2,3,5–10] and elevated lymphocyte counts in those who experience negative life events.[6,10] Although PTSD is not the focus of this review, its components provide insights into how stress-related mechanisms in AITD patients unfold. When the arcuate nucleus releases hormones to regulate the HPA axis, the human body is able to respond to physiological and psychological stressors.[9,10] Psychological stress is positively correlated with increased IL-1,[9] IL-6,[6,8,9] IL-10,[6] IFN-γ,[6] and TNF-α[6,9] proinflammatory cytokines[6,10] and increased T3[8] via hypothalamic stimulation[6,8] in various autoimmune diseases.[6] This may be due to reduced hippocampal volume,[9] however other biochemical pathways should be considered. As well, it is common knowledge that people can acquire PTSD and various autoimmune diseases[6,9,10] from witnessing (seeing and hearing) and physically experiencing traumatic events, including thyroid disorders.[5,6,9,10]

In evidencing such a theoretical framework, one might argue, how can stress that is seeable or heard elicit the same immune responses as physical stress? Does stress only work through one pathway? Particularly, non-physical forms of stimuli, such as experiencing negative emotional stress, seeing adverse events, or hearing verbal threats involve the hypothalamic integrations of autonomic and neuroendocrine responses.[10] Human sensory systems detecting external stimuli send signals to the amygdala, prefrontal cortex, and hippocampal brain regions to determine how stressful the situation may be.[6,9,10] The amygdala is key in emotional response and threat detection, the prefrontal cortex is responsible for higher-level thinking and decision-making, and the hippocampus helps relate the current experience to past events. The brain converts light and soundwaves into electrical signals via medial forebrain cortical sensory perceptions and suprachiasmatic nucleus via the retinohypothalamic tract.[9,10] Therefore, in response to negative life events that may be perceived, the suprachiasmatic nucleus regulates hormone secretion leading to increases in cortisol.[9,10] Essentially, there are various mechanisms and pathways. Yet, such anomalies are induced simultaneously to engage the body's appropriate responses to various sensory-induced responses to threats. The mechanisms for psychological and physiological stimuli are indistinguishable. In addition, CRH receptor-1 (CRH-R1) projecting cells are primarily expressed in the adrenal gland, gastrointestinal tract, skin, anterior pituitary, neocortex, and cerebellum.[9,10] Whereas, CRH receptor-2 (CRH-R2) are primarily distributed in the hypothalamus, amygdala, lateral septum, brain stem skeletal muscles, peripheral vasculature, and heart.[9,10] Inevitably, sensory-initiated communication between neighboring organ networks reinforces how stress-related factors impact immunity through neuro-immune-endocrine and sympathoadrenal systems.

Conclusion

The research demonstrates that stress significantly influences the development and progression of AITD through complex immune pathways and protein gene regulation originating from sensory stimuli. Both T and B cells, including B10 cells drive autoimmune responses as a reaction to stress-induced leukocyte activity and negative feedback involving thyroid hormone influx of cortisol and CBG. Biochemical pathways utilizing glucocorticoids and catecholamines through sympathoadrenal and neuro-immune-endocrine systems impact the activity of Th17 and Treg cells via imbalances in the Th17/Treg ratio exerted by IL-6, FoxP3 transcription factor, and GITR related protein expression. Ultimately, understanding these pathways and their influences in individuals with AITD may shed light into why certain stress-like activities, such as intense exercise, alcohol, and diet hypersensitivities play roles in modulating AITD development and progression. Evenmore, future research should dive into providing stress questionnaires outlining onset of AITD diagnoses in relation to traumatic events and how stress initiation affects corticospinal signaling on sympathoadrenal pathways. These innovative approaches may lead to new developments in designing ‘specific stress-reduction interventions’ for AITD patients. Suggestions for intervention starting points should be related to integrative body-mind-spirit approaches, as stress can be both physiological and psychological. As such, individuals with AITD may benefit from reducing exposure to negative life events, adverse environments, alcohol and proinflammatory foods, and pessimistic occupations; and incorporating healthier sleep routines, stress-free exercises, mindfulness thought patterns and nuanced perspectives, forgiveness and conflict resolution tactics, and spiritual practice strategies.

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