

Immunological regulation of metabolism—a novel quintessential role for the immune system in health and disease

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ABSTRACT The hypothalamus-pituitary-thyroid (HPT) axis is an integrated hormone network that is essential for maintaining metabolic homeostasis. It has long been known that thyroid stimulating hormone (TSH), a central component of the HPT axis, can be made by cells of the immune system; however, the role of immune system TSH remains enigmatic and most studies have viewed it as a cytokine used to regulate immune function. Recent studies now indicate that immune system-derived TSH, in particular, a splice variant of TSH β that is preferentially made by cells of the immune system, is produced by a subset of hematopoietic cells that traffic to the thyroid. On the basis of these and other findings, we propose the novel hypothesis that the immune system is an active participant in the regulation of basal metabolism. We further speculate that this process plays a critical role during acute and chronic infections and that it contributes to a wide range of chronic inflammatory conditions with links to thyroid dysregulation. This hypothesis, which is amenable to empirical analysis, defines a previously unknown role for the immune system in health and disease, and it provides a dynamic connection between immune-endocrine interactions at the organismic level.—Schaefer, J. S., Klein, J. R. Immunological regulation of metabolism—a novel quintessential role for the immune system in health and disease. *FASEB J.* 25, 29–34 (2011). www.fasebj.org

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THE HYPOTHALAMUS-PITUITARY-THYROID (HPT) axis is an integrated hormone network that is essential for maintaining metabolic activity. Thyrotropin-releasing hormone (TRH) is produced in the hypothalamus and transported to the anterior pituitary *via* the superior hypophyseal artery, where it induces the release of thyroid-stimulating hormone (TSH). TSH travels *via* the circulation to the thyroid, where it binds to TSH receptors on thyroid follicular cells. Binding of TSH induces the secretion of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Although T4 is the predominant thyroid hormone in the circulation, it is

principally a prohormone for the more biologically active T3 form following conversion in tissues of T4 to T3 by deiodinases. Feedback mechanisms (in particular, the levels of circulating TSH, T4, and T3) control TRH and TSH output. Thyroid hormones drive and sustain essentially every aspect of mammalian physiology, including basal metabolism, growth, development, mood, and cognition.

TSH is a glycoprotein hormone consisting of α and β subunits. The α subunit, which is shared with luteinizing hormone, follicle stimulating hormone, and chorionic gonadotropin, stabilizes the TSH α/β complex and facilitates TSH receptor (TSHR) binding. The TSH β subunit confers hormone specificity on TSH. Both human and mouse TSH β molecules consist of 138 aa, 118 of which comprise the native TSH β protein with a 20-aa signal peptide. The human TSH β gene consists of 3 exons and 2 introns; the coding regions being located in portions of exons 2 and 3. The mouse TSH β gene consists of 5 exons; the coding region being located in portions of exons 4 and 5.

EVIDENCE FOR IMMUNE SYSTEM TSH

Early studies demonstrated that TSH is produced by human peripheral blood leukocytes (PBLs) following stimulation with *Staphylococcus* enterotoxin A or with TRH, that TSH can have diverse effects on lymphocyte function, and that leukocyte TSH can be inhibited by thyroid hormones or TRH (1–6). TSH can be produced by dendritic cells (DCs) following stimulation with *Staphylococcus* enterotoxin B (7, 8). A variety of cells in the small intestine also has been shown to produce TSH, including intestinal intraepithelial lymphocytes (IELs; ref. 9), IL-7+ cryptopatch-like cells in submucosal regions, and by intestinal epithelial cells (10, 11). Intestinal TSH may contribute to IEL maturation

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(12, 13), particularly during viral or bacterial infection (10, 11).

TSH-PRODUCING LEUKOCYTES TRAFFIC TO THE THYROID

Hematopoietic cells in the bone marrow (BM), in particular, a CD11b⁺ cell subset, have been shown to spontaneously produce TSH (14). Moreover, the thyroid possesses large numbers of cells that bear similarities to the myeloid population of TSH-producing BM cells (7, 14). Those cells express the CD45 leukocyte-common antigen and CD11b but do not express CD80, CD40, CD19, CD3, CD8 α , Gr-1, or F4/80, suggesting they may be a specialized group of BM cells dedicated to intrathyroidal TSH production. Following adoptive transfer of total BM cells, or CD11b-enriched BM cells from green fluorescent protein transgenic mice, cells trafficked to the thyroid, where they produced TSH locally (7).

The finding that TSH-producing leukocytes are present in the thyroid established two important points. First, it suggested that TSH can be produced locally within the thyroid. Because endocrine TSH is produced in thyrotrophs in the adenohypophysis—the anterior lobe of the pituitary—TSH gene expression in the thyroid was strong evidence for an extrapituitary source of TSH. Second, the presence of TSH-producing leukocytes in the thyroid placed them directly in the tissue where TSH would be most needed.

A NOVEL TSH β SPLICE VARIANT IS PREFERENTIALLY EXPRESSED IN BM HEMATOPOIETIC CELLS, THE THYROID, AND PERIPHERAL BLOOD LEUKOCYTES

Analysis of TSH β gene expression in the mouse pituitary, the BM, and the thyroid revealed several unexpected findings. Using primer sets targeted to sites surrounding exons 4 and 5, *i.e.*, the coding region for the full-length native TSH β polypeptide, gene expression was dramatically higher in the pituitary than the BM (26,987-fold greater; ref. 15), suggesting that the native form of TSH β is rare in the BM. Unex-

A

MSAAVLLSVLFALACGQAASFCIPTEYTMVDRRECAVCLTINTTICAGYCMTR
DINGKLFLPKYALSQDVCTYRDFIYRTVEIPGCPHVTVPYFSPVAISCKCGKCN
TDNSDCIHEAVRTNYCTKPQSFYLGGSFV

B

MLRSLFFPQDINGKLFLPKYALSQDVCTYRDFIYRTVEIPGCPHVTVPYFSPVA
ISCKCGKCN TDNSDCIHEAVRTNYCTKPQSFYLGGSFV

Figure 2. Comparison of mouse TSH β full-length (A) and splice-variant (B) amino acids. Red amino acids are signal peptides; black amino acids are coded for by exon 4; blue amino acids are coded for by exon 5.

pectedly, when primers were used that targeted sites exclusive to exon 5, the ratio of pituitary:BM expression, though still higher for the pituitary, was far more similar (~500-fold greater; ref. 15). Those differences implied that the TSH β molecule produced by the BM was substantially different from that produced by the pituitary, possibly reflecting an alternatively spliced form of TSH β that utilized exon 5 but not exon 4.

To explore this possibility, 5' rapid amplification of cDNA ends (5' RACE) was done using mouse BM cDNA to generate nucleotide sequences in the 5' region of the BM TSH β transcript (15). Surprisingly, sequence analyses of 5' RACE products revealed that BM TSH β incorporated a section of intron 4 that was contiguous with and included all of exon 5. The portion of intron 4 that immediately preceded exon 5 included a 27-nt section that began with an ATG methionine start codon (Fig. 1) and coded for 8 additional amino acids that were in frame with exon 5 (Figs. 1 and 2). On the basis of the high transmembrane helix preference and the high hydrophobic moment index (15), the 9 aa coded by mouse intron 4 appeared to function as a signal peptide—albeit a short one. CHO cells transfected with a TSH β splice-variant construct secreted an 8-kDa TSH β protein, the correct size for the splice variant, compared to a 17-kDa TSH β product obtained from CHO cells transfected with a native TSH β construct (15). The TSH β splice-variant protein comprised 71.2% of the native TSH β molecule (Fig. 2). Notably, the TSH β splice-variant gene expression in mice was also abundant in the thyroid relative to native TSH β expression (15). Moreover, when mice were infected with reovirus, gene expression of the splice variant but not the native form of TSH β was elevated in the thyroid, suggesting that intrathyroidal

H5' -ATGCTCTCTTTTCTGTTCTTTCCCGAGATATCAATGGCAAACGTGTTCTTCCCAAATATGCTC 64
M5' -ATGTTAAGATCTCTTTCTTTCCACAGGATATCAATGGCAAACGTGTTCTTCCCAAATATGAC 64

TGTCCAGGATGTTTGCACATATAGAGACTTCATCTACAGGACTGTAGAAATACCAGGATGCCACT 131
TCTCTCAGGATGTCTGTACATACAGAGACTTCATCTACAGAACGGTGAAATACCAGGATGCCCGCA 131

CCATGTTGCTCCCTATTTTCTCTATCCTGTTGCTTTAAGCTGTAAGTGTGGCAAGTGCAATACTGAC 198
CCATGTTACTCTTATTTCTCTTCCCTGTCGCCATAAGCTGCAAGTGTGGCAAGTGTAAATACTGAC 198

TATAGTGACTGCATACATGAAGCCATCAAGACAACTACTGTACCAAACTCAGAAGTCTTATCTGG 265
AACAGTGACTGCATACACGAGGCTGTGAGAACCACTACTGCACCAAGCCGAGTCTTCTATCTGG 265

TAGGATTTTCTGTCTAA-3' 282

GGGGATTTTCTGTCTAA-3' 282

Figure 1. Comparison of human (top lines) and mouse (bottom lines) TSH β splice-variant nucleotide sequence as reported by our laboratory (16). Green nucleotides are from intron regions that are contiguous with exons 5 and 3 for mouse and human TSH β , respectively. Red nucleotides are from exons 5 and 3. Black nucleotides differ in mouse compared to human TSH β .

A

MLRSLFFPQDINGKLFLPKYALSQDVCTYRDFIYRTVEIPGCPHHVT
PYFSFPVALSCKCGKCNNTDSDCIHEAVRTNYCTKPQSFYLVGGFSV

B

MLSFLFFPQDINGKLFLPKYALSQDVCTYRDFIYRTVEIPGCPLHVA
PYFSYPVALSCKCGKCNNTDYSDCIHEAIAKTNCTKPQKSYLVGGFSV

Figure 3. Comparison of mouse (A) and human (B) TSH β splice-variant amino acid sequence. Red amino acids are the putative signal peptides coded for by the intronal region. Black amino acids are coded for by mouse exon 5 and human exon 3, respectively. The green residues amino acids represent the “seat-belt” region of the TSH β polypeptide used to dimerize with TSH α .

use of the splice variant may be important during times of immune stress. This was consistent with a system in which hematopoietic cells traffic to the thyroid (7), where they preferentially produce the TSH β splice variant (15).

Studies using RNA from human tissues revealed an expression pattern for a TSH β splice-variant gene with similarities, and some differences, to that of the mouse TSH β splice variant (16). As with mouse TSH β , the splice variant consisted of a 27-nt region from intron 2 (the equivalent of intron 4 in mice) that preceded exon 3 (the equivalent of exon 5 in mice) that began with an ATG codon. Seven of the remaining 8 aa coded for by intron 2 of human TSH β were identical to mouse intron 4. The 2 unique amino acids coded for by intron 2 in the human splice variant retained hydrophobic or uncharged polar properties, thus supporting its potential as a transmembrane signal peptide (Fig. 3).

In humans, the TSH β splice-variant gene, but not the native form of TSH β , was expressed in the thyroid and PBL (16). The TSH α gene also was expressed in those tissues, suggesting that the TSH β splice variant may dimerize with the TSH α subunit. The extent to which this occurs remains an open question given that optimal binding of TSH β to TSH α involves some portions of the β -subunit that are not present in the splice-variant molecule (17), although the TSH β splice vari-

ant retains an 18-aa “seat-belt” region (Fig. 3) that is reported to noncovalently dimerize to TSH α (17, 18). Thus, it is possible that the TSH β splice variant weakly associates with TSH α .

Although the TSH β splice-variant gene is expressed in mouse BM, in the one study done to date, it was not detected in human BM (16). Unpublished studies from our laboratory point to variations in levels of splice-variant TSH-production by human BM cells, suggesting that expression in the BM may occur in a regulated manner as needed to seed peripheral immunological compartments with a source of those cells. Additional work will be required to address this. Finally, it is interesting that the TSH β gene of 7 of 9 species examined, including several nonhuman primates, retained an in-frame 27-nt sequence in the intron prior to the last TSH β exon, suggesting that the splice variant may be a common feature of the TSH β molecule (Fig. 4).

THE IMMUNE SYSTEM AS A REGULATOR OF METABOLISM IN HEALTH AND DISEASE

Clearly, the question remains as to why the immune system would need to be involved in metabolic regulation. For the answer to this question, we point to an inherent component of immunological function that is not an integral aspect of endocrine function: namely, the capacity of the immune system to sense the presence of biological threats and to mount a defense against those. There are several ways this could occur. The possibility exists that the splice-variant form of TSH interferes with native TSH β binding or that it delivers a functionally unique signal to thyrocytes that disrupts the natural process of thyroid hormone synthesis. Thus, the involvement of immune system TSH, in particular, the TSH β splice-variant isoform, in the regulation of host metabolism could occur through a network of TSH β -sensing (14, 19, 20) and TSH β -producing (15, 16) leukocytes that normally seed the thyroid, or that traffic to the thyroid under special

In frame

Homo sapiens	CCTGTCACATTATGCTCTCTTTTCTGTTCTTTCCCCAGGATATCAATGGCAAACGTGTTCTTCCCAA
Pan troglodytes	CCTGTCACATTATGCTCTCTTTTCTGTTCTTTCCCCAGGATATCAATGGCAAACGTGTTCTTCCCAA
Gorilla gorilla	CCTGTCACATTATGCTCTCTTTTCTGTTCTTTCCCCAGGATATCAATGGCAAACGTGTTCTTCCCAA
Pongo pygmaeus	CCTGTCACATTATGCTCTCTTTTCTGTTCTTTCCCCAGGATATCAATGGCAAACGTGTTCTTCCCAA
Macaca mulatta	CCTGTCACATTATGTTCTCTTTTCTGTTCTTTCCCTCAGGATATCAATGGCAAACGTGTTCTTCCCAA
Callithrix jacchus	CCTGTCACATTATGGTCTTTTTTTGTTCTTTCTTCAGGATATCAACGGCAAACGTGTTCTTCCCAA
Mus musculus	TGGAGTTTATCATGTTAAGATCTCTTTTCTTTCCACAGGATATCAATGGCAAACGTGTTCTTCCCAA

Out-of-frame

Rattus norvegicus	ATGCAGTTTATCATGTTAAGATCTCTTTTCTTCCACAGGATATCAATGGCAAACGTGTTCTTCCCAA
Bos taurus	TCCTATCGCATTATGCTCCTTTTAAATTCTTTCTTCAGGATGTCAACGGCAAGCTGTTCTTCCCAA

Figure 4. Comparison of TSH β sequences for *Homo sapiens* (human), *Pan troglodytes* (chimpanzee), *Gorilla gorilla* (gorilla), *Pongo pygmaeus* (orangutan), *Macaca mulatta* (Rhesus monkey), *Callithrix jacchus* (marmoset), *Mus musculus* (mouse), *Rattus norvegicus* (rat), and *Bos taurus* (bull). Black and green nucleotides designate intron components prior to the beginning of the last exon (red nucleotides; exon truncated) coding for the TSH β open-reading frame.

circumstances during or after antigenic challenge. Intrathyroidal synthesis of the TSH β splice variant may block the binding of the native form of pituitary-derived TSH β . Recent studies in our laboratory support this scenario, as seen by an *in vivo* suppressive effect of the TSH β splice-variant recombinant protein on circulating thyroid hormone levels (unpublished results). Physiologically, this would curtail thyroid hormone secretion and lower host metabolic activity. Suppression of metabolic activity would promote energy conservation, suppress the desire to overexert, encourage rest, and may account for the sense of malaise and lethargy that frequently occur during the early stages of many infections.

Besides the potential involvement of immune system TSH during infection, there are a large number of human disease conditions with links to thyroid dysregulation that have yet to be fully understood, many of which have notable inflammatory components. These include Graves' disease and Hashimoto's thyroiditis (21), Graves' ophthalmopathy (22, 23), Pendred's syndrome (24), post-traumatic stress disorder (13), Lyme disease (25), and inflammatory bowel syndrome (26). TSH-related disorders also are present in osteoporosis (27), obesity (28), infertility (29), rheumatoid arthritis (30), system lupus erythematosus (31, 32), psoriasis (33), inflammation in the respiratory tract and sinus associated with asthma (34), chronic obstructive pulmonary disease (35), and emphysema (36), as well as inflammation associated with single-organ or multiorgan failure or sepsis (37–39). Inflammation associated with nonalcoholic fatty liver disease (40) may have underlying etiologies associated with TSH dysregulation. Given the relationship of the immune system with the inflammatory effects of those conditions, a direct link between the TSH β

splice-variant isoform produced by leukocytes could provide a new way of understanding how those diseases are perpetuated.

A model of how the immune system contributes to host regulation of metabolism during infection is presented in **Fig. 5**. Under normal conditions (Fig. 5, left panel), TSH produced by the pituitary would be the primary mechanism for regulating thyroid hormone output and maintaining homeostatic control of metabolism. Production of the TSH β splice-variant isoform by intrathyroidal leukocytes would have minor effects on thyroid hormone regulation in this scenario. During acute infection due to virus or bacteria, in particular, systemic infection or potentially debilitating infection, such as that caused by influenza virus, increased intrathyroidal production of TSH β by leukocytes would interfere with the binding of pituitary-derived TSH β (Fig. 5, right panel). This could occur as a consequence of increased trafficking of TSH-producing leukocytes to the thyroid, or increased production of TSH β by leukocytes already present in the thyroid. The primary advantage of this system would be the regulation of basal metabolism under the control, at least in part, by the immune system during a critical period of immunological stress. This hypothesis is amenable to empirical analysis in mice following experimental infection, and using mouse models of chronic immunologically based disorders, such as autoimmunity and inflammatory bowel disease.

In the context of autoimmune disorders, the delicate balance between splice-variant and native TSH β may be undermined. In Hashimoto's thyroiditis, autoantibodies against thyroid peroxidase and/or thyroglobulin lead to the destruction of thyroid follicles, resulting in decreased T3 and T4 levels. We speculate that under normal conditions, expression of im-

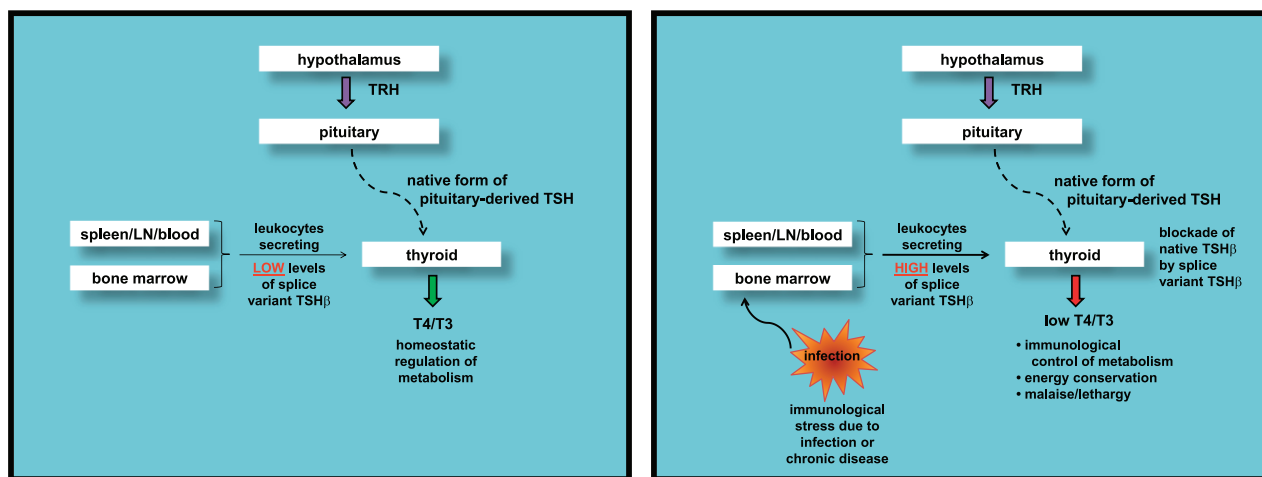


Figure 5. Model of role for leukocyte-derived TSH β splice variant in the regulation of metabolism. Under normal homeostatic conditions (left panel), thyroid hormone output is regulated by the native form of TSH β produced by the pituitary. Some splice-variant TSH β may be produced by the pituitary, though its overall significance may be minimal if produced in low levels. In that situation, the contribution of leukocyte-derived TSH also would be expected to be minimal. Under periods of immunological stress, such as during infection (right panel), leukocytes would contribute heavily to the regulation of thyroid hormone output and metabolic regulation by producing high levels of the TSH β splice variant that compete for binding of the native form of TSH β . The net effect would be suppressed levels of circulating thyroid hormones and lower metabolic activity.

mune-derived TSH β may be negatively regulated by T3 and T4. Thus, in response to low levels of T3 and T4 in the circulation, increased numbers of TSH-producing leukocytes would be recruited to the thyroid. The continual presence of TSH β -producing leukocytes in the thyroid would further avail the destruction of thyroid follicles. Conversely, in Graves' disease, TSHR activation by autoantibodies would lead to excessive thyroid hormone production, thus disrupting the natural balance between splice-variant TSH β and native TSH β as regulators of thyroid hormone synthesis.

Finally, it will be of interest to understand the molecular mechanisms that control the expression of the TSH β splice variant. A recent study of thymostimulin, a molecule with TSH-like activity, described the presence of several binding motifs for the NF κ B transcription factor in the 5' flanking region of the β 5 subunit of thymostimulin (41). Using a Web-based promoter-predicting program, we have identified two putative NF- κ B binding sites in mouse TSH β intron 4, implying that regulation of the TSH β splice variant may be under control of immunologically mediated transcriptional signals. **[F]**

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