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REVIEW

A new insight into GH regulation and its disturbance from nutrition and autoimmune perspectives

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Abstract. GH activates GH receptors, which activates IGF-1 in the liver through a cascade of processes. The GH/IGF-1 axis plays an important role in the regulation of metabolism. Insufficient GH secretion results in short stature in childhood, while adult GH deficiency (AGHD) is observed in adulthood. The early diagnosis of AGHD is important for early initiation of GH replacement therapy. This review described the regulatory mechanisms of GH signaling based on nutritional status and a novel disease concept pathogenesis that causes AGHD. GH-dependent IGF-1 production in the liver is regulated by a complex interplay between nutritional status, hormones, and growth factors. GH resistance is an adaptive response that enhances survival during starvation and malnutrition. Sirtuin 1 (SIRT1) negatively regulates GH-induced IGF-I production in the liver by directly inhibiting STAT5 activation, which causes GH resistance under starvation and malnutrition. The presence of autoantibodies is strongly associated with the disruption of immune tolerance in pituitary cells. Pituitary-specific transcription factors (PIT-1) are essential for the development, differentiation, and maintenance of GH, PRL, and TSH producing cells. However, the underlying mechanism that causes immune intolerance to PIT-1 remain unclear. The GH-IGF-1 system plays a pivotal role in growth, and the involvement of SIRT1 in this regulatory mechanism presents an intriguing perspective on the interplay between nutrient metabolism and lifespan. The discovery of the anti-PIT-1 pituitary antibody, a novel disease concept associated with AGHD, has provided valuable insights, which serves as a significant milestone towards unraveling the complete pathogenesis of the disease.

Key words: Growth hormone, Insulin-like growth factor 1, Sirtuin 1, Pituitary-specific positive transcription factor 1

Introduction

GH, a 191-amino-acid polypeptide, is secreted by the somatotroph cells of the anterior pituitary gland. GH receptor (GHR), a class I cytokine receptor, exists in a constitutively dimeric form and is present in various tissues, including the liver, cartilage, muscle, adipose tissue, and kidney [1]. Upon binding of GH to GHR, GHR is activated and triggers the activation of JAK2, leading to its phosphorylation and recruitment of STAT5 through the interaction between the STAT5 SH2 domain and phosphorylated tyrosine (Tyr) in GHR. JAK2 then phosphorylates STAT5, causing its dimerization and translocation to the nucleus, which in turn activates target genes, mainly IGF-1, in the liver [2]. In addition, GH signaling modulates the activity of other hormones and signaling pathways, including the insulin, glucocorticoid, and mitogen-activated protein kinase pathways [3]. IGF-1 mediates its effects by binding to the IGF-1 receptor (IGF-1R), a tyrosine kinase receptor. When IGF-I binds to IGF-1R, it induces receptor autophosphorylation and activation of intracellular signaling pathways, mainly the PI3K-Akt and the Ras-Raf-MAPK pathways [4].

GH and IGF-1 are integral to growth and metabolism, yet their functions are distinct. GH directly modulates glucose, lipid, and bone metabolism as well as immune function and cognition *via* the widely distributed GHR [4]. More specifically, GH stimulates growth and cell reproduction, influencing prechondrocytes in the growth plate to stimulate longitudinal bone growth, fat cells to stimulate lipolysis, and liver cells to promote IGF-1 production [5]. The indirect effects of GH are primarily mediated through IGF-1, which facilitates growth and development in various tissues by promoting cell proliferation and differentiation, crucially impacting skeletal muscle, bone, and cartilage growth. Additionally, IGF-1 plays a key role in metabolic regulation with insulin-like

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effects on glucose and lipid metabolism, promoting glucose uptake and utilization by cells. IGF-1 also exhibits anti-apoptotic effects, fostering cell survival under conditions of tissue injury or stress [4] (Fig. 1).

GH and IGF-1 exhibit feedback mechanisms that regulate GH secretion in the pituitary gland, which includes stimulation of growth, anabolic activities, and body maintenance. During periods of energy deprivation, these promote catabolic feedback mechanisms that shift carbohydrate oxidation to lipolysis, which preserves protein stores and ensures survival [6]. Nutrients play a critical role in modifying the GH/IGF-1 axis, and these hormones govern the intricate coordination of nutrient utilization in cells and tissues. Collectively, the GH-IGF-1 system plays an important role in the regulation of metabolism, especially in living organisms.

Therefore, insufficient GH secretion results in short stature in childhood, while a variety of symptoms due to the deficiency of GH physiology, namely adult GH deficiency (AGHD), are observed in adulthood. The subjective symptoms include fatigue, low stamina, poor concentration, low energy intake, depression, and low libido. In addition, increased body and visceral fat, decreased lean body mass, muscle mass, and bone mineral density, abnormal lipid metabolism, glucose tolerance, and fatty liver were observed. Although the early diagnosis of AGHD is important because many of these symptoms can be ameliorated by GH replacement therapy, the underlying pathogenesis of AGHD is variable [7]. In particular, GH replacement therapy should be administered with caution to patients with malignant tumors or glucose intolerance; thus, appropriate evaluation of its pathogenesis is important [8].

This review described the regulatory mechanisms of GH signaling based on nutritional status and a novel disease concept pathogenesis that causes AGHD.

Chapter 1

GH signaling and its regulatory mechanisms based on nutritional status

GH signaling is a complex and dynamic process regulated by multiple factors including age, sex, and disease state [9]. IGF-1 production is also influenced by factors such as nutritional status, cytokines, sex steroids, and thyroid hormones. Also, insulin-like growth factor binding proteins control the biological activity and half-life of IGF-1 in the bloodstream [9]. In particular, GH-dependent IGF-1 production in the liver is regulated by a complex interplay between nutritional status, hormones, and growth factors [10]. During feeding, insulin stimulates IGF-1 production in the liver, whereas GH secretion is suppressed [11]. In contrast, IGF-1 production in the liver does not increase even though GH secretion increases due to decreased insulin and increased glucagon concentrations during fasting periods, which is commonly referred to as GH resistance [12]. In fact, administration of GH to fasting rats does not elevate circulating IGF-1 levels [13]. Administration of exogenous GH to fasting patients with GH deficiency only leads to a 2-fold increase in serum IGF-1 concentrations compared to a 10-fold increase in patients with GH deficiency on a normal diet [14]. Nutritional deficiencies such as protein malnutrition can impair IGF-1 production in the liver, leading to growth retardation and other developmental disorders [15]. GH resistance is an adaptive response that enhances survival during starvation and malnutrition conditions. This response is triggered by the inhibition of growth due to a decrease in IGF-1 levels and an increase in GH levels, which leads to insulin resistance and the mobilization of free fatty acids to prevent hypoglycemia (Fig. 2).

Mechanisms of GH resistance and sirtuin 1 (SIRT1)

Several studies have investigated the mechanisms

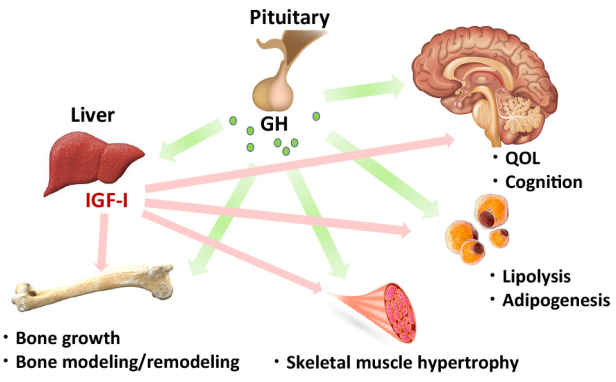

Fig. 1 Physiological role of the GH/IGF-1 system

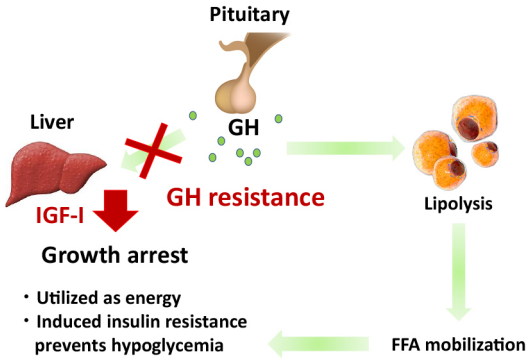

Fig. 2 Physiological relevance of GH resistance as an adaptive response to starvation

underlying GH resistance. Insulin positively modulates GHR expression in the liver, and lower insulin concentrations are present in the portal vein during fasting, which reduces GHR expression and translocation to the hepatocytes [16, 17]. In another study, fibroblast growth factor 21, an adaptive hormone for fasting, was shown to cause GH resistance by decreasing phosphorylated STAT5 levels, resulting in suppressed growth to conserve energy during starvation [18]. These data suggest that GH resistance during fasting may arise through several underlying mechanisms. However, the extent to which these mechanisms account for GH resistance observed in the physiological context remains uncertain. SIRT1 is a member of the sirtuin family of NAD^+-dependent deacetylases, which plays important roles in regulating a wide range of cellular processes, including metabolism, stress responses, DNA repair, and aging. In mammals, SIRT1 is widely expressed in various tissues and organs, including the brain, liver, skeletal muscle, and adipose tissue, and has been implicated in the pathogenesis of various age-related diseases such as cancer, neurodegeneration, and metabolic disorders [19]. The expression and function of SIRT1 are enhanced by caloric restriction (CR), which helps maintain normal blood glucose levels and promotes efficient energy utilization [20]. SIRT1 plays a crucial role in regulating glucose metabolism by inhibiting the gluconeogenic activity of the transducer of regulated cAMP response element binding protein 2 through deacetylation and degradation, and promotes gluconeogenesis by activating the deacetylation of peroxisome proliferator-activated receptor gamma coactivator 1 and forkhead box protein O1 [21-23]. In addition, SIRT1 promotes gluconeogenesis by inhibiting the activity of STAT3 *via* deacetylation [24].

We hypothesized that SIRT1 might negatively affect GH-induced IGF-1 production in the liver during starvation. We conducted *in vivo* and *in vitro* experiments and found that SIRT1 interacts directly with STAT5 and suppresses GH-dependent IGF-1 expression by decreasing Tyr phosphorylation of STAT5. Furthermore, when lysine residues adjacent to the SH2 domain of STAT5 are mutated, STAT5 acetylation and transcriptional activity decrease. Knockdown of SIRT1, on the other hand, enhanced the acetylation of STAT5 and GH-induced Tyr phosphorylation of STAT5 as well as the GH-induced interaction between the GHR and STAT5. The results suggest that SIRT1 negatively regulates GH-induced STAT5 phosphorylation and IGF-1 production through STAT5 deacetylation in the liver (Fig. 3) [25, 26].

While the somatotropic axis requires energy to promote growth, SIRT1 uses energy to increase survival during CR. In conclusion, SIRT1 plays a crucial role in the switch from growth to survival in response to malnutrition by regulating the somatotropic axis at multiple levels.

Chapter 2

AGHD and autoimmune diseases

AGHD is caused by pituitary and peripituitary tumors, autoimmunity, inflammatory disease, infection, trauma, cerebrovascular disease, and radiation therapy, which often results in nonspecific impairment of pituitary hormone secretion [27]. Although autoimmunity is believed to be the major cause, its pathophysiology remains unclear.

Autoimmune polyglandular syndrome (APS) is an autoimmune disease, wherein more than two endocrine

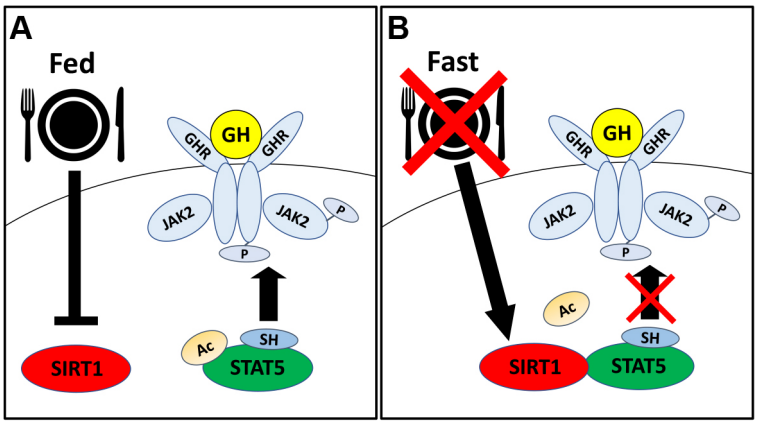

Fig. 3 The mechanisms through which sirtuin 1 (SIRT1) regulates STAT5 activation through GH

(A) In the state of nutrient intake, the SH2 domain of STAT5 selectively identifies and binds to GHR that has undergone phosphorylation on tyrosine residues, leading to the activation of JAK2 and subsequent phosphorylation of STAT5.

(B) Conversely, during fasting, the activation of SIRT1 facilitates its interaction with STAT5, resulting in the deacetylation of adjacent lysine residues near the SH2 domain of STAT5. This deacetylation process impairs the ability of STAT5 to effectively bind to GHR that has been phosphorylated on tyrosine residues, thereby inhibiting the activation of STAT5.

organs are impaired [28]. Multiple classifications have been proposed. Eisenbarth *et al.* classified the disease into three types: APS-I, APS-II, and IPEX. APS-I is a very rare congenital autoimmune disease, wherein mutations in the *AIRE* gene cause chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency [29]. In contrast, APS-II is a heterogeneous group of diseases strongly associated with *HLA* gene polymorphisms, wherein various autoimmune diseases, including type 1 diabetes, autoimmune thyroid diseases, Addison's disease, and pituitary inflammation, are observed, and autoantibodies against target organs are often detected in the blood [30]. Autoantibodies against GH and α-enolase [31, 32], as well as anti-pituitary antibodies, have been reported in patients with autoimmune hypophysitis. However, their pathophysiological significance is unclear, and they are thought to be produced as a result of the inflammation-induced destruction of the pituitary tissue. Some autoantibodies were closely associated with impaired hormone-producing cells, suggesting a pathogenic connection. Representative examples include the identification of autoantibodies against gonadotrophs in patients with undescended testes and undescended testicular hypogonadism [33], autoantibodies against lactotrophs in cases of postpartum milk dyssecretion [34], anti-GH antibodies in GH dyssecretion [35, 36], and anti-corticotroph antibodies in patients with ACTH deficiency alone [37, 38]. The presence of autoantibodies is strongly associated with the disruption of immune tolerance in pituitary cells; however, the pathogenesis of the disease has not yet been elucidated.

Pituitary-specific transcription factors (PIT-1) are expressed in the anterior pituitary gland and are essential for the development, differentiation, and maintenance of GH, PRL, and TSH producing cells [39]. Congenital disorders of these three hormone production systems are typical in PIT-1 gene disorders [40].

In this chapter, we described the process from the discovery of the novel disease concept to the elucidation of the mechanism of acquired GH, PRL and TSH specific deficiencies resulting from the breakdown of immune tolerance to PIT-1.

Case presentations

In 2003, Takeno and Iguchi *et al.* reported the first case of acquired GH, TSH, and PRL deficiency in a 44-year-old male who presented to our department with peripheral edema that had persisted for 2 years [41]. The patient showed intact growth and pubertal development. Endocrinological findings revealed low TSH and free T4 levels, which suggested central hypothyroidism. In addition, the serum GH and PRL levels were extremely low and completely unresponsive to hormone stimulation tests. ACTH, LH, and FSH secretions were normal. These results suggest the acquired disruption of GH, TSH, and PRL. Magnetic resonance imaging (MRI) showed mildly atrophic pituitary glands. The symptoms and quality of life improved dramatically after replacement therapy with levothyroxine and GH. Although the patient's endocrinological phenotype was compatible a *PIT-1* gene mutation, his clinical symptoms developed in adulthood, which was unlikely to be congenital combined pituitary hormone deficiency (CPHD). No mutations in *PIT-1*, *PROP1*, and *HesX1* genes that were related to CPHD were detected in this patient. Because autoimmunity is known to be involved in the pathogenesis of acquired hypopituitarism, the presence of autoantibodies against the pituitary gland in the sera derived from the patient was investigated. Surprisingly, autoantibodies from the patient's sera recognized a 33 kDa protein extracted from the pituitary tissues. Further investigation revealed that the 33 kDa protein that was recognized was PIT-1 [42].

The second case was reported by Tokyo Jikei University, wherein the patient was a 75-year-old male who suffered from slowly progressive insulin-dependent diabetes mellitus with anti-glutamic acid decarboxylase (GAD) antibodies, exhibiting low levels of GH, PRL, and TSH. These three pituitary hormones did not respond to GRH or TRH. The secretory capacities for corticotropin and gonadotropin were also conserved. MRI showed no morphological abnormalities [43]. After the patient died during the accident, an autopsy was performed, wherein pathological findings of the pituitary gland revealed infiltration of lymphocytic and plasma cells. Moreover, GH, PRL, TSH and PIT-1 positive cells were all absent [44]. In the third case from Kanto Rosai Hospital, a 78-year-old male who complained of prolonged eyelid and leg edema exhibited GH, PRL, and TSH specific deficiencies with a normal pituitary size [45].

All three cases had an acquired GH, PRL, and TSH specific deficiency without morphological abnormalities in the pituitary gland. In the subsequent analysis of the second and third cases, circulating PIT-1-specific autoantibodies were identified in the sera of the patient, indicating that this antibody was strongly associated with the pathogenesis. We previously described this novel clinical entity as anti-PIT-1 antibody syndrome [44].

Pathophysiology

Antibodies are involved in the pathogenesis of autoimmune diseases. For example, anti-TSH receptor stimulating antibodies cause Graves' disease [46] and anti-acetylcholine receptor (AChR) antibodies cause myasthenia gravis (MG) [47]. Furthermore, acquired hypocalciuric hypercalcemia is associated with the

stimulation of antibodies against calcium-sensing receptors [20], and autoantibodies against Nax were detected in idiopathic hypernatremia [48]. However, anti-GAD antibodies in type 1 diabetes and anti-thyroid peroxidase antibodies or anti-thyroglobulin antibodies in Hashimoto's thyroiditis were the result, not the cause, and are the only diagnostic markers used in clinical practice. In our subsequent study, the potential pathogenic role of the autoantibodies was examined. However, these findings did not reveal any complement-dependent cytotoxicity associated with anti-PIT-1 antibodies. Instead, an enzyme-linked immunospot assay revealed that PIT-1-reactive cytotoxic T cells were responsible for the specific disruption of PIT-1-positive cells [49]. Despite these observations, the underlying mechanism that causes immune intolerance to PIT-1 remained unclear.

Anti-PIT-1 hypophysitis as a thymoma-associated disease

Subsequently, we encountered three cases of anti-PIT-1 hypophysitis with thymoma. After thymectomy, PIT-1-reactive cytotoxic T lymphocytes (CTLs) decreased and anti-PIT-1 antibody titers decreased, suggesting that thymoma may be a part of the cause of this disease [50]. Thymomas are closely associated with various autoimmune diseases such as MG, hypogammaglobulinemia, erythroblastoma, autoimmune thyroid disease, and type 1 diabetes mellitus [51]. Thymoma-associated multiorgan autoimmunity (TAMA) is a tumor-associated syndrome reported in patients [52]. The etiology of TAMA is unknown, but its clinical features, which may occur before, after, or simultaneously with the diagnosis of thymoma, suggest that TAMA may be a part of the pathophysiology of anti-PIT-1 hypophysitis. In the thymus, bone marrow hematopoietic progenitor cells proliferate and differentiate into mature T cells *via* positive and negative selection in the thymic cortex and medulla, and thymic dysfunction, such as APS-I, causes a variety of autoimmune diseases [53]. As an example of a possible mechanism of autoimmune disease pathogenesis in thymomas, an association between the ectopic expression of AChR in thymomas and the development of MG has been suggested [54]. In an autopsy case, the ectopic expression of PIT-1 was observed in thymic epithelial tumor cells, suggesting that PIT-1-reactive T cells were not eliminated, leading to the development of this disease [50].

Mechanisms of ectopic PIT-1 expression in thymoma

Mutations in tumor suppressor gene *TP53*, histone modification genes (*BAP1*, *SETD2*, *and ASLX1*), chromatin remodeling genes (*SMARCA4*), and DNA methylation modification genes (*DNMT3A*, *TET2*, *and WT1*) have been reported [55]. Since many genes in thymic carcinomas undergo DNA methylation due to *TET2* mutations [56], it is possible that PIT-1 is ectopically expressed in thymoma tissues due to epigenetic abnormalities. However, the detailed underlying mechanisms remain unclear.

Anti-PIT-1 hypophysitis as a tumor-associated syndrome

Since our first report, we have encountered four additional patients who exhibited acquired and specific defects in GH, PRL, and TSH, completely phenocopying the first three patients (Table 1). Three patients were diagnosed with thymoma, whereas the other four patients were not. Three patients without thymoma had concomitant malignancies (B-cell lymphoma and multiple metastatic carcinomas of unknown primary origin), which may have occurred as tumor-associated syndromes; hence, ectopic PIT-1 expression in tumor tissue may have developed as a result of its presentation as an antigen. Interestingly, PIT-1 is expressed not only in the pituitary gland, but also in human breast tissue, and its overexpression promotes tumor growth and metastasis

Table 1 A summary of clinical characteristics found in anti-PIT-1 hypophysitis

Case No.	1	2	3	4	5	6	7
Sex	Male	Male	Male	Male	Female	Male	Male
Age	44	75	78	85	79	70	85
Pituitary hormone deficiency	GH + PRL + TSH	GH + PRL + TSH	GH + PRL + TSH	GH + PRL + TSH	GH + PRL + TSH	GH + PRL + TSH	GH + PRL + TSH
PIT-1 antibody	Positive	Positive	Positive	Positive	Positive	Negative	Positive
Pituitary MRI	Atrophic	Normal	Normal	Normal	Normal	Normal	Normal
Neoplasm	Thymoma	Thymoma	Thymoma	Unknown origin with multiple hepatic metastasis	Bladder lymphoma	ND	Unknown origin with multiple metastasis

Abbreviations: PIT-1, pituitary-specific positive transcription factor 1; MRI, magnetic resonance imaging; ND, not detected.

Table 2 Diagnostic criteria for anti-PIT-1 hypophysitis (Adapted from reference [33]).

Criterion 1. Acquired specific GH, PRL, and TSH deficiency.
1. Endocrine findings include undetectable GH and PRL levels and low TSH, IGF-1, and free T4 levels, wherein the responses of these hormones in provocative tests are blunted. Provocation tests are required, particularly for the diagnosis of GH deficiency.
2. Secretion of other pituitary hormones is not impaired.
3. Patients are frequently diagnosed with central hypothyroidism of unknown etiology because pituitary MRI does not reveal obvious abnormalities. However, enhanced MRI techniques have revealed slightly atrophied anterior pituitary glands with heterogeneous enhancement in some patients.
4. Some patients may present with other autoimmune conditions such as Hashimoto's thyroiditis or type 1 diabetes.
Criterion 2. Presence of circulating anti-PIT-1 antibody or PIT-1-reactive T cells
1. Anti-PIT-1 antibody is a specific disease marker that is measured by immunoblotting analysis or a specific enzyme-linked immunosorbent assay.
2. PIT-1-reactive T cells play a pivotal role in disease development and can be measured using an enzyme-linked immunospot assay.
Criterion 3. Coexistence of thymoma or malignant neoplasm.
1. Most patients also harbor thymomas or malignant neoplasms.
2. Endocrine abnormalities generally precede a neoplasm diagnosis.

Probable diagnosis: Fulfills criterion 1
Definite diagnosis: Fulfills criteria 1 and 2
Note: Criterion 3 may help in the diagnosis and clarification of pathogenesis, but may not necessarily be obvious at the time of diagnosis based on endocrine abnormalities.
Abbreviations: PIT-1, pituitary-specific positive transcription factor 1; MRI, magnetic resonance imaging.

[57], suggesting that PIT-1 is ectopically expressed in various tumor tissues.

Disruption of immune tolerance to PIT-1

Since PIT-1 is a transcription factor localized in the nucleus, it is unlikely to be targeted as an antigen under the existing conditions. In general, antigen epitopes are presented by HLA class I and recognized by T cell receptors on CTLs; therefore, the antigenicity of the presented antigen epitope is constrained by patient-specific HLA. Recently, we confirmed that patient-specific HLA is conserved in the anterior pituitary tissue induced from patient-derived iPS cells and that PIT-1 is presented as an epitope on HLA class I *via* the epitope presentation pathway [58]. These results suggest that PIT-1-expressing cells express PIT-1 as an epitope of HLA class I and can be a target of CTLs. However, as iPS cells derived from healthy individuals also express the PIT-1 epitope on HLA class I, similar to patient-derived iPS cells, the primary cause of this disease may be the presence or absence of PIT-1-reactive CTLs caused by thymomas or other conditions.

Shift from Anti-PIT-1 antibody syndrome to Anti-PIT-1 hypophysitis

The first three of seven cases were initially named "anti-PIT-1 antibody syndrome" because of the acquired specific deficiency of GH, PRL, and TSH with circulating anti-PIT-1 antibody, however, it became clear that the anti-PIT-1 antibody was a disease marker rather than a cause of this disease [49]. Furthermore, subsequent studies identified cytotoxic T cells that react to PIT-1 protein as the cause, and since the pituitary histopathology of the disease was consistent with hypophysitis, we proposed the name change to "anti-PIT-1 hypophysitis," which more accurately describes the pathogenesis of the disease. Based on the characteristics and pathophysiology of the cases reported thus far, we developed a diagnostic criteria found in Table 2 [59].

Conclusions

The GH-IGF-1 system plays a pivotal role in growth, necessitating a close interaction with nutrient metabolism. This system is subject to regulation based on nutritional status. The involvement of SIRT1 in this regulatory mechanism presents an intriguing perspective on the interplay between nutrient metabolism and lifespan. Furthermore, the discovery of the anti-PIT-1 pituitary antibody, a novel disease concept associated with AGHD, has provided valuable insights. The unforeseen identification of ectopic PIT-1 expression in thymomas or malignant tumors disrupting immune tolerance as a tumor-associated syndrome has unveiled a novel pathophysiology of autoimmune hypopituitarism.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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