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The Thyrotropin Receptor and The Regulation of Thyrocyte Activity and Proliferation

Dorendra Deshmukh[1]*, Nisar Anjum[2], Bholenath Sahu[1], Neeraj Deshmukh[1]

[1]SOP, Shri Shankaracharya Professional University, Bhilai, Chhattisgarh, India

[2]KIPS, Shri Shankaracharya Professional University, Bhilai, Chhattisgarh, India

***Corresponding Author E-mail:** dorendradeshmukh7741@gmail.com

Abstract:

The thyrotropin receptor (TSHR), a G protein-coupled receptor (GPCR) family member, is the key controller of thyroid gland physiology, translating thyroid-stimulating hormone (TSH) signals into modulation of thyrocyte activity. Upon binding with a ligand, TSHR initiates a set of intracellular signaling pathways, ranging from the conventional cAMP/PKA cascade to non-conventional pathways like PLC, PI3K/AKT, and MAPK, all of which cumulatively orchestrate thyroid hormone production, release, proliferation, differentiation of thyrocytes, and overall glandular homeostasis. This review offers a detailed overview of the molecular structure of TSHR, its expression in thyroidal and extrathyroidal tissues, and its function in physiological and pathological processes. Special attention is given to TSHR dysregulation and its role in a variety of thyroid diseases, such as autoimmune hyperthyroidism (Graves' disease), toxic adenomas, thyroid carcinomas, and congenital hypothyroidism due to receptor mutations. The extrathyroidal expression of TSHR, particularly in orbital fibroblasts and fat tissue, broadens its clinical relevance to diseases like Graves' orbitopathy and metabolic regulation. In addition, the review discusses existing and new therapeutic options focused on the targeting of TSHR and its downstream pathways, emphasizing the receptor's biomarker and drug target potential in precision endocrinology. In spite of advances, substantial gaps persist concerning the roles of non-cAMP signaling and the safety profile of long-term TSHR-targeted interventions. Filling these gaps through multi-disciplinary research is important for creating innovative and personalized therapies to treat and prevent complex thyroid pathologies.

Keywords:TSHR, thyroid-stimulating hormone, thyrocyte proliferation, GPCR signaling, cAMP/PKA, PLC, PI3K/AKT, MAPK, thyroid disorders, Graves' disease, thyroid cancer, congenital hypothyroidism, precision medicine

1. INTRODUCTION

The thyrotropin receptor (TSHR) is the central regulator of thyroid function through mediating the action of thyroid-stimulating hormone (TSH) for the synthesis and secretion of thyroid hormones [1]. The TSHR, as

a G protein-coupled receptor (GPCR), triggers intricate intracellular signaling cascades upon binding with TSH, such as the activation of cAMP/PKA, PLC, and PI3K/AKT pathways. These pathways as a whole control crucial processes like production of thyroid hormone, thyrocyte differentiation, and cellular growth. Upon its activation, TSHR helps ensure the synthesis of thyroid hormones, i.e., thyroxine (T4) and triiodothyronine (T3), in adequate amounts to help drive metabolic processes, growth, and general body homeostasis.

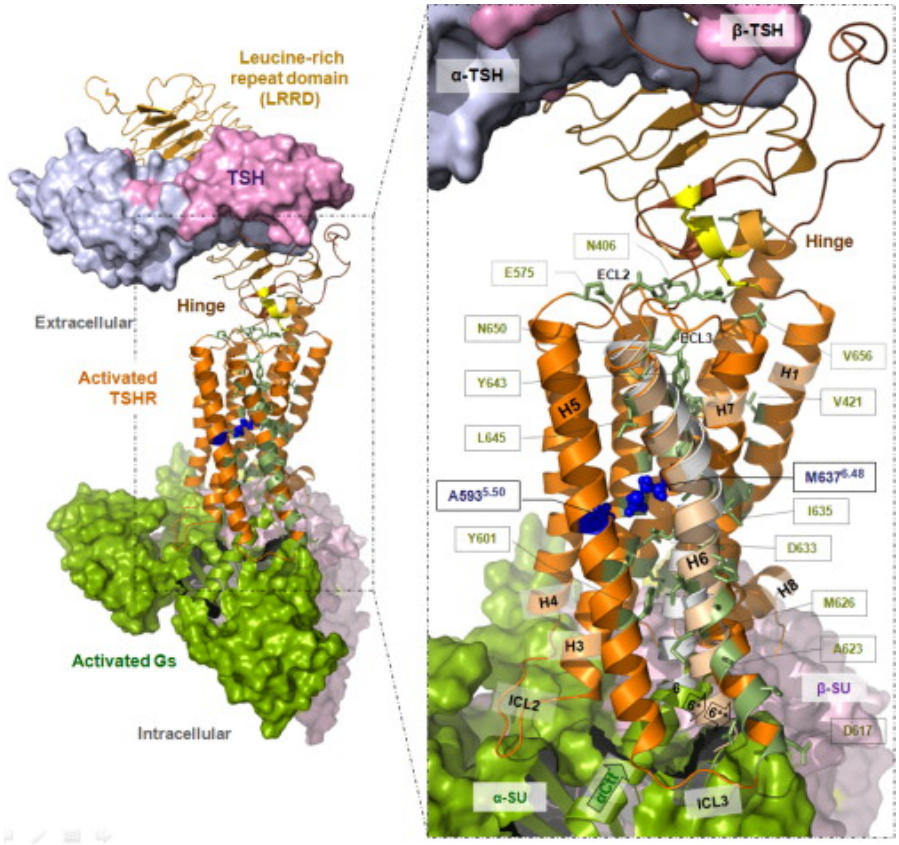

Figure 1: Thyrotropin Receptor (TSHR) [2]

In addition to the synthesis of hormone, TSHR has also a role to play in the thyrocyte's cell proliferation. Activating TSHR stimulates regular cell growth and differentiation and promotes the overall healthy functioning of the thyroid gland structurally as well as functionally. But prolonged or excessive stimulation of TSHR may cause abnormal thyrocyte proliferation, which leads to the pathogenesis of thyroid diseases like goiters, thyroid cancer, and hyperthyroidism. It is essential to know the molecular mechanisms of how TSHR controls thyroid hormone production and cell growth to develop targeted therapy for thyroid diseases.

1.1.Background and Context

The thyroid gland plays a central role in the regulation of metabolic functions, growth, and development by the synthesis and secretion of thyroid hormones, T4 and T3. The hormones affect many aspects of physiology, such as thermogenesis,

cardiovascular function, and neural growth. Thyroid activity is largely controlled by thyroid-stimulating hormone (TSH), released from the anterior pituitary. TSH's action is brought about through the binding of thyrotropin receptor (TSHR), a G protein-coupled receptor (GPCR) present on the cell surface of thyrocytes. This binding triggers a intricate cascade of intracellular signaling reactions, stimulating numerous downstream pathways like the cAMP/PKA pathway, which is involved in the regulation of hormone production, the PLC pathway, which influences calcium mobilization and cell growth, the PI3K pathway, which is implicated in cell survival and metabolism, and the MAPK pathway, which is implicated in cell growth and differentiation. All of these signaling pathways play a role in the regulation of thyroid hormone production, thyrocyte proliferation, and the function of the thyroid gland overall, maintaining the proper operation of metabolism and development within the body.

1.2.Objectives of the Review

This review aims to provide a comprehensive exploration of the following:

- The molecular architecture of TSHR and its functional domains.
- The complex signaling networks activated by TSHR and their contribution to thyroid function and disease.
- The role of TSHR in regulating thyrocyte proliferation and differentiation.
- Pathophysiological alterations in TSHR function, especially in thyroid diseases.
- The emerging therapeutic strategies targeting TSHR and potential future directions for clinical interventions.

1.3.Importance of the Topic

An understanding of the molecular basis of thyrotropin receptor (TSHR) function is fundamental to the improvement of our knowledge of thyroid physiology and the pathophysiology of a range of thyroid disorders. TSHR-related diseases characterized by dysregulation of TSHR signaling, including autoimmune thyroiditis, hyperthyroidism, and thyroid cancers, are not only common but have major clinical and public health concerns [3]. These states tend to lead to thyroid hormone production disturbances, causing metabolic dysregulation, autoimmune dysregulation, and aberrant cell proliferation. With TSHR's pivotal role in controlling thyroid function, targeting TSHR and the related signaling pathways has significant potential for creating new therapeutic approaches. This encompasses the promise of precision medicine, which may provide individualized interventions for a variety of thyroid diseases, both benign (e.g., goiter or Hashimoto's thyroiditis) and malignant (e.g., thyroid carcinomas). Through the modulation of TSHR activity, physicians can potentially better treat thyroid dysfunction, halt disease progression, and even enhance the prognosis for patients with thyroid cancers.

2. THYROTROPIN RECEPTOR (TSHR): STRUCTURE, SIGNALING, AND PATHOPHYSIOLOGY

The thyrotropin receptor (TSHR) is a key G protein-coupled receptor in thyroid physiology, controlling hormone production and thyrocyte growth. Its structure consists of

extracellular, transmembrane, and intracellular domains, which facilitate multiple signaling pathways such as cAMP/PKA, PLC, and PI3K/AKT. Mutations or dysregulation of TSHR are associated with thyroid diseases like Graves' disease, toxic adenomas, thyroid cancer, and congenital hypothyroidism, which underscores its function in normal thyroid physiology and pathology.

2.1. Molecular Structure and Expression of TSHR

Thyrotropin receptor (TSHR) is an integral part of regulation of thyroid functioning and metabolism. Being a paradigm G protein-coupled receptor (GPCR), TSHR functions in a very complicated signalling mechanism enabling the synthesis as well as release of thyroid hormones. The TSHR comprises three major domains, each serving a crucial purpose in its role [4].

1. **Extracellular Domain (ECD)**: The extracellular domain of TSHR is defined by a big leucine-rich repeat (LRR) motif. This motif is critical to the receptor's high-affinity binding of thyroid-stimulating hormone (TSH). The LRR region provides a structural scaffold that enables the receptor to bind TSH in a very specific way. Binding of TSH to this domain induces conformational changes in the receptor, which play an important role in its activation. This interaction is crucial in initiating the downstream signaling events that control thyroid hormone synthesis and secretion, which are required for normal metabolism.
2. **Transmembrane Domain (TMD)**: The transmembrane region of TSHR is composed of seven α-helical segments that traverse the lipid bilayer of the cell membrane. These helices are typical of all GPCRs and are important for the transmission of conformational changes from the extracellular space to the intracellular signaling apparatus. When TSH binds to the ECD, these helical segments change their structure to allow the receptor to bind to G proteins within the cell. This signal transduction from the extracellular to the intracellular space is crucial for initiating different cellular activities such as thyroid hormone production and cell growth.
3. **Intracellular Domain (ICD)**: The intracellular domain of TSHR also interacts with numerous G proteins, mainly Gs and Gi, that mediate the activation of several intracellular signaling pathways. Activation of Gs generally activates adenylate cyclase, which increases the levels of cyclic AMP (cAMP). The increase in cAMP activates protein kinase A (PKA), which also activates transcription factors like CREB (cAMP response element-binding protein). These signal cascades eventually lead to the expression of thyroid-specific genes that are involved in synthesizing major thyroid hormones. Interaction with Gi proteins can stimulate other pathways, including the phospholipase C (PLC) pathway, which includes the production of inositol triphosphate (IP3) and diacylglycerol (DAG) to regulate cellular activities such as growth and differentiation.

The thyroid-specific receptor TSHR functions mainly within thyrocytes which represent specialized thyroid gland cells dedicated to thyroid hormone synthesis of T4 and T3. The

TSHR protein exists outside of the thyroid gland where it can be detected in adipose tissue as well as orbital fibroblasts that play a part in Graves' disease and thyroid-related eye disease and the thymus tissue. Additional TSHR functions exist outside thyroid hormone production since the receptor has been detected in locations beyond the thyroid gland. The TSHR receptor found in adipose tissue controls metabolism by influencing energy regulation together with fat cell transformation. The TSHR molecule within the thymus affects how immune cells function thus influencing both autoimmune reactions and immune response mechanisms. The presence of TSHR in orbital fibroblasts during Graves' disease contributes to thyroid-associated ophthalmopathy by making the cells vulnerable to immune system attacks which leads to eye swelling known as exophthalmos [5].

The thyrotropin receptor controls more than thyroid hormone synthesis because it influences broader physiological mechanisms including metabolism and immune responses and cellular proliferation. The receptor's widespread expression and diverse functions demonstrate its central role in regular thyroid operations and medical conditions which exhibit its complex relationship with body tissues.

2.2.TSHR Signaling Pathways

The cAMP/PKA signaling pathway functions as the primary regulatory mechanism for thyroid function following TSHR binding to TSH. The extracellular domain of TSHR activates Gs protein when TSH binds to this domain which leads to adenylate cyclase activation and the production of cyclic AMP (cAMP). An increase in cAMP functions as the second messenger to activate protein kinase A (PKA). The key transcription factor CREB (cAMP response element-binding protein) gets phosphorylated by PKA after activation. CREB phosphorylation enables the transcription of essential thyroid-specific genes that consist of thyroglobulin (Tg) and thyroid peroxidase (TPO) together with the sodium/iodide symporter (NIS). The proteins are vital components that enable thyroid hormone synthesis and hormone secretion of T3 and T4 which control metabolism and growth along with developmental processes. The pathway serves as an essential mechanism to sustain thyroid health because it affects both hormone production and thyrocyte development and maturation [6].

In addition to the canonical cAMP/PKA pathway, TSHR also triggers several non-canonical signaling pathways that further contribute to thyroid cell function and growth. The activation of Gq proteins leads to the initiation of the Phospholipase C (PLC) signaling pathway. Gq proteins activation stimulates phospholipase C which results in the production of inositol triphosphate (IP3) and diacylglycerol (DAG). The cellular release of IP3 results in calcium ion liberation while the DAG substance activates protein kinase C (PKC). The elevated calcium levels within the cell together with PKC activation trigger different cellular responses that lead to cell proliferation and differentiation. The signaling pathway works as a critical mechanism for thyroid gland formation and enables thyroid cells to multiply and adjust their functions during hypothyroidism or goiter development [7].

The cell survival and differentiation together with proliferation processes heavily depend on the PI3K/AKT signaling pathway as a critical non-canonical pathway. When TSHR

becomes active it activates the PI3K/AKT pathway that supports several cellular growth processes and defends cells from apoptosis. The pathway emerges as crucial when thyroid cells must increase their number and expand to replace lost thyroid hormones due to hypothyroidism-induced thyroid enlargement. Through TSHR signaling the MAPK/ERK pathway gets activated to manage cell cycle advancement and generate mitogenic responses. A malfunctioning MAPK/ERK pathway creates conditions for thyroid neoplasia that may develop into thyroid cancer because this pathway maintains fundamental control over cell proliferation and differentiation processes. TSHR signaling uses alternative signaling mechanisms to regulate thyroid function while controlling thyroid cell growth in different physiological and pathophysiological conditions.

2.3.Regulation of Thyrocyte Proliferation

The Thyrotropin Receptor TSHR has dual functions by regulating thyroid hormone production through its essential role and controlling thyrocyte proliferation for thyroid gland normal development and maintenance. TSHR interaction with TSH enables thyrocyte growth and differentiation when functioning normally to preserve thyroid hormone production of T3 and T4. The hormones perform critical roles in managing metabolic processes and energy system activities and they control complete body expansion. Through its signaling pathways TSHR controls a balanced mechanism that links thyroid hormone production to cellular expansion to maintain proper thyroid function and structure according to body requirements. The proper balance between thyroid hormone levels is fundamental for maintaining thyroid stability because it prevents both hormone excess and deficiency states [8].

The prolonged activation of TSHR results in abnormal cell growth that will ultimately damage thyroid function and disrupt its normal structure. Overexpression of the receptor or mutant TSHR that results in constant activation will lead to thyroid hyperplasia which refers to an abnormal growth of thyroid cells. Thyroid gland enlargement produces goiters through this mechanism. Graves' disease and toxic adenomas result in uncontrolled cell proliferation with excessive hormone production because of persistent TSHR stimulation. Animal models with constitutively active TSHR exhibit thyroid hyperplasia thus demonstrating that the receptor serves as an essential control mechanism for thyroid cell development and growth as well as hormone synthesis [9].

2.4.TSHR in Thyroid Pathophysiology

Graves' disease and toxic thyroid adenomas and thyroid cancer together with congenital hypothyroidism result from defective functions of the thyrotropin receptor (TSHR). The autoimmune response in Graves' disease creates TSH-resembling antibodies that activate TSHR excessively thus resulting in hyperthyroidism with goiter development and ophthalmopathy appearance. Mutations in TSHR that produce gain-of-function effects cause toxic thyroid adenomas to generate excessive hormones without TSH control. TSHR loss or reduced expression in thyroid cancer cells promotes tumor aggression as well as tumor progression. The development of thyroid glands and hormone production gets impaired when TSHR undergoes inactivating mutations resulting in congenital hypothyroidism. Research into the molecular

processes of these conditions creates new prospects for specific treatment approaches.

2.4.1. Graves' Disease

The immune system in Graves' disease compounds thyroid-stimulating immunoglobulins (TSIs) that act as autoantibodies which attach to thyroid-stimulating hormone receptor (TSHR) on thyrocytes and then activate them. The TSIs function as surrogate TSH to repeatedly activate the TSHR leading to an excessive secretion of thyroid hormones namely T4 and T3. Unregulated hormone release from the thyroid gland results in hyperthyroidism which manifests as weight loss and anxiety together with tachycardia and elevated metabolism levels. The persistent TSHR stimulation from TSIs leads to both therapeutic gland enlargement referred to as diffuse goiter and Graves' orbitopathy (ophthalmopathy) marked by inflammatory eye tissue swelling. Studying the complex molecular bonding mechanisms between TSHR and TSIs will help create new therapeutic approaches to block the autoimmune attack on Graves' disease while providing better alternatives for antithyroid drug treatment without radioactivity and surgery operation [10].

2.4.2. Thyroid Nodules and Adenomas

The process of toxic thyroid adenomas formation depends heavily on TSHR gene activating mutations because these mutations help develop benign autonomous thyroid nodules that overproduce thyroid hormones without normal TSH regulatory control. Activating mutations convert the TSH receptor into an unregulated device which remains activated throughout TSH shortage. Inside the adenoma thyroid cells keep producing thyroid hormones which results in hyperthyroidism that appears as weight loss combined with tachycardia and increased metabolic effects. These mutations affect the structural components of the receptor by modifying its extracellular domain or intracellular signaling parts to stop the standard receptor activity reductions. αράble insights come from molecular pathophysiological investigations of toxic thyroid adenomas while establishing therapeutic possibilities as targets **[12]**. A targeted approach to treating hyperthyroidism in patients with these adenomas could be achieved through drug development that blocks mutated TSHR receptors or their downstream signaling pathways.

2.4.3. Thyroid Cancer

Well-differentiated thyroid carcinomas depend on TSHR expression to keep their cells with hormonal production abilities in addition to their TSH sensitivity status. A deficiency or reduced activity level of TSHR leads thyroid cancers to exhibit dedifferentiation which coincides with more intense malignancy behavior resulting in worse patient outcomes. The development and progression of thyroid cancer start through faulty TSHR signaling pathways either caused by receptor mutations or breakdowns within signaling chains that include the MAPK and PI3K/Akt pathways. This disruption encourages thyroid cells to proliferate uncontrollably and invade neighboring tissue. Well-differentiated tumors undergo a transformation into more anaplastic or poorly differentiated forms due to these alterations which present a highly resistant condition to conventional therapies. TSHR plays a pivotal role in thyroid cancer progression thus making receptor or signaling

pathway targeting a significant therapeutic possibility. The management of thyroid cancer will benefit from therapies designed to restore TSHR functionality or block aberrant signaling because they will cause tumor cell differentiation while inhibiting growth and enhancing the effectiveness of radioactive iodine therapy.

2.4.4. Congenital Hypothyroidism

The TSHR gene mutations that decrease its function serve as one of the main causes of congenital hypothyroidism through thyroid hormone production problems at birth. Underdevelopment of thyroid gland due to thyroid hypoplasia and abnormal development because of dysgenesis results from these mutations in TSHR. The severe impairment of thyroid hormone production results in hypothyroidism of varying severity that expresses as developmental problems and mental impairment when patients fail to get proper treatment. The exact level of hypothyroidism develops from combined factors that include how much the receptors fail and what state the thyroid gland has achieved development-wise. The diagnosis of congenital thyroid disorders depends on genetic screening which enables doctors to start thyroid hormone replacement treatment promptly [13]. Early care before TSHR-related genetic mutations progress proves vital since it stops permanent developmental and intellectual disabilities from affecting patients. Therefore clinical practice must focus on TSHR-related genetic mutation knowledge. The discovery of TSHR mutations enables healthcare professionals to provide important genetic counsel about inherited risks to affected families.

3. SIGNALING PATHWAYS AND MECHANISMS MODULATING THYROCYTE FUNCTION AND GROWTH

The complex molecular signals and cellular processes through signaling pathways and mechanisms control how thyrocytes (thyroid cells) operate and multiply in size and function. The pathways sustain thyroid operations and thyroid gland expansion while enabling thyroid hormones (T3 and T4) production for normal thyroid function [14].

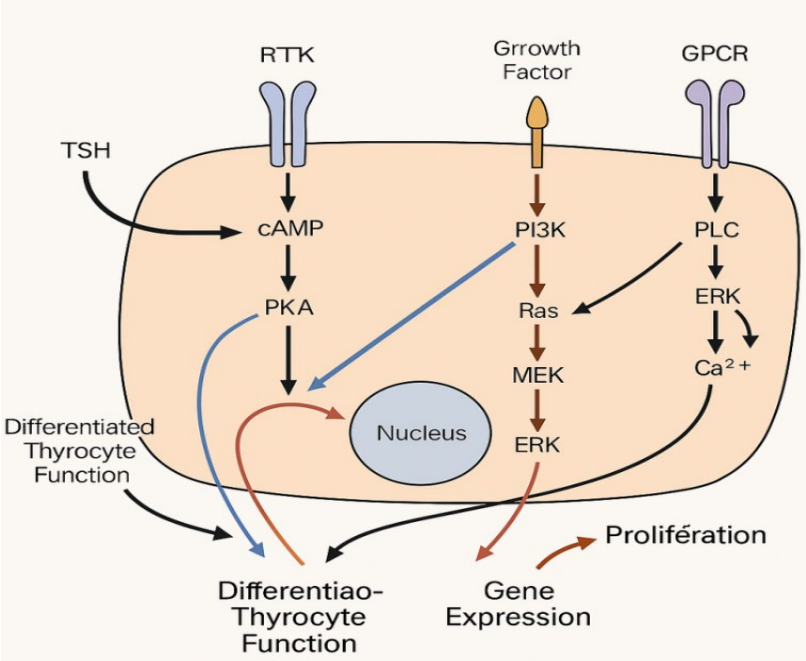

Figure 2: Signaling Pathways Regulating Thyrocyte Function and Growth [15]

1. **Thyrotropin Receptor (TSHR) Signaling:** The thyrocyte function and growth regulation depends on the activation of the thyrotropin receptor (TSHR) by thyroid-stimulating hormone (TSH). Thyrocytes experience signaling pathway activation due to the binding of TSH to TSHR receptors at their surface:

- **Canonical cAMP/PKA pathway**: TSH activates the Gs protein when it binds to TSHR which activates adenylate cyclase through stimulation and results in cyclic AMP (cAMP) production elevation. High levels of cyclic AMP activate protein kinase A (PKA) which starts multiple transcription factors that regulate the expression of thyroid-specific genes essential for thyroid hormone synthesis.
- **Non-canonical pathways**: Signals from TSHR lead to multiple signaling pathways including cAMP/PKA but also activate the PI3K/AKT pathway and the MAPK/ERK pathway responsible for cell survival, differentiation and growth and cell cycle progression and mitogenesis respectively [16].

2. **Regulation of Thyrocyte Proliferation:** The signaling pathways function as regulators to control thyroid tissue growth together with cell multiplication. The thyroid gland cells respond to TSH by producing thyroid hormones while simultaneously performing cell population growth and cell specialization to support thyroid tissue health. Paternal TSH stimulation that continues for an extended period or exceeds normal levels leads to unfavorable changes such as goiter development along with thyroid cell multiplication known as thyroid hyperplasia. The activated TSHR signals

together with growth factors control the precise relationship between thyroid hormone synthesis and cellular multiplication.

3. **Feedback Mechanisms and Homeostasis:** The thyroid axis functions through feedback control systems to preserve stable conditions in the body. High levels of thyroid hormones (T3 and T4) lead to decreased production of TSH by both hypothalamus and pituitary gland through negative feedback. The feedback loops control thyroid hormone levels to stay within a restricted range which prevents both overgrowth and overactivity of thyrocytes. A malfunction in this regular feedback mechanism between body systems can result in either hyperthyroidism or hypothyroidism disorder.
4. **Pathophysiology of Thyrocyte Dysfunction:** The signals that control thyroid advancement might become irregular which results in thyroid disorders. The autoantibodies in Graves' disease imitate TSH signals that activate TSHR and produce additional thyroid hormones and cellular enlargement [17]. The pathways drive thyrocyte uncontrolled proliferation which results in tumor formation whenever they experience mutations or alterations. The development of congenital hypothyroidism with TSHR mutations impairs thyroid function as well as growth which leads to complications during development.

Table 1: Studies on Thyroid Signaling and Therapeutics

Authors	Study	Focus Area	Method	Findings
Kang et al. (2022) [18]	Role of GLIS3 in TSH/TSHR signaling	Thyroid hormone biosynthesis and follicular proliferation	Knockout mouse models, cellular assays	GLIS3 is crucial for expression of thyroid-specific genes and hormone production
Lacheta et al. (2019) [19]	Immunological mechanisms in Gravesâ€™ ophthalmopathy	Autoantibodies, TSHR, IGF-1R interaction in GO	Literature review and immunological analysis	Autoimmune response plays a central role in GO via TSHR and IGF-1R
Lanzolla et al. (2024) [20]	Pathogenesis and treatment of Gravesâ€™ disease	Autoimmune basis and immunotherapy in Gravesâ€™ disease	Review of recent literature and clinical trials	Gravesâ€™ disease involves genetic and environmental factors; new therapies are emerging
Latif et al. (2020) [21]	Gq-biased small molecule targeting TSHR	Pharmacological modulation of TSHR signaling	Experimental pharmacological evaluation	Gq-biased molecule selectively modulates TSHR activity with fewer side effects

Luffy et al. (2024) [22]	Effects of linsitinib on IGF-1R and TSHR expressing cells	Therapeutic targeting in thyroid and orbital fibroblasts	Cell culture studies on proliferation and apoptosis	Linsitinib inhibits proliferation and inflammation in IGF-1R/TSHR co-expressing cells

4. DISCUSSION

TSHR plays a fundamental role in thyroid regulation as it controls thyroid hormone and cell multiplication processes along with hormone secretion functions. Any malfunction in TSHR signaling results in several thyroid disorders which include hyperthyroidism and thyroid cancer alongside goiter [23]. The clinical applications include the creation of TSHR antagonist drugs for autoimmune disorders and MAPK or PI3K inhibitor medications for thyroid cancer management. The discovery of TSHR outside thyroid cells creates new potential for treating Graves' orbitopathy as well as other conditions. Research must continue because three important gaps exist: scientists need to understand alternative signaling pathways to cAMP and molecular mechanisms of TSHR-linked cancer development as well as the lasting effects of TSHR-targeted medical approaches [24].

4.1.Interpretation and Analysis of Findings

This review identifies the thyrotropin receptor (TSHR) as the key element which controls thyroid gland operations [25]. The Thyroid-Stimulating Hormone (TSH) action gets mediated through the principal protein TSHR which directs multiple vital physiological processes that include thyroid hormone synthesis as well as secretion and thyrocyte growth. TSHR controls both thyrocyte metabolic processes and cell growth by using cAMP/PKA and phospholipase C (PLC) and PI3K/AKT and MAPK signaling pathways. Any type of dysregulation affecting this receptor from autoimmunity, activating mutations or loss-of-function variants results in multiple devastating diseases including hyperthyroidism, goiter, thyroid cancer and congenital hypothyroidism [26]. The receptor guides tissue functions in non-thyroid organs such as adipose and orbital fibroblasts thus extending its effects outside thyroid territories which may explain Graves' orbitopathy development.

4.2.Implications and Significance

The TSHR receptor's regulatory capacity in thyroid functions creates many significant clinical consequences [27]. Targeted therapies become possible because of the improved knowledge about receptor signaling mechanisms that exist during thyroid pathologies. A treatment method for hyperthyroidism would benefit from TSHR-specific compounds to block or enhance receptor activity since these substances could help treat autoimmune diseases triggered by thyroid-stimulating immunoglobulins. Therapeutic potential exists for thyroid cancer treatment when researchers focus on blocking TSHR signaling mechanisms including MAPK and PI3K/AKT pathways because these pathways develop mutations in thyroid cancer tumors. The presence of TSH receptors in locations outside the thyroid creates promising prospects to treat diseases apart from thyroid disorders mainly through

targeting the receptor in orbital fibroblasts to manage autoimmune orbital disease [28].

4.3.Highlighting Gaps and Future Research Directions

The literature currently shows major progress in understanding TSHR but multiple essential knowledge gaps continue to persist [29]. The specific functions of alternative signaling pathways other than the cAMP pathway which involve PLC, PI3K/AKT and MAPK must be better understood in terms of their impact on thyrocyte growth and thyroid tumorigenesis. Researchers need to investigate the complete molecular pathways between TSHR mutations and throat cancer development in thyroid cancers. Further research into the long-term effects of TSHR pharmacological targeting must be performed to determine safety and efficiency against side effects as well as their impact on thyroid hormone regulation. Researchers need to develop enhanced diagnostic techniques for identifying TSHR-related genetic mutations mainly in cases involving congenital hypothyroidism. A combination of endocrinology with immunology and oncology disciplines should develop comprehensive therapeutic approaches while long-term assessments through continuous research must measure TSHR stimulation effects on thyroid health together with cancer risks [30].

5. CONCLUSION

The review demonstrates how the thyrotropin receptor (TSHR) controls thyroid hormone production as well as controls thyrocyte growth while sustaining thyroid gland equilibrium through multiple complex signaling pathways that include cAMP/PKA, PI3K/AKT, PLC and MAPK activities. The thyrotropin receptor function as the signaling intermediary for thyroid-stimulating hormone (TSH) by converting external hormone signals to activate coordinated cellular events which control genetic processes and cellular growth and differentiation while governing cellular metabolism. Evidence indicates that pathologies such as Graves' disease and toxic adenomas and thyroid cancers and congenital hypothyroidism develop from TSHR dysregulation caused by autoimmune mechanisms and by activating or inactivating mutations as well as altered TSHR expression. The widespread expression of this receptor in extrathyroidal tissue shows its broad systemic influence by connecting to metabolic and immunological functions as well as disorders that affect Graves' orbitopathy. The review integrates information about TSHR structural domains together with signaling paths to reveal their physiological and pathophysiological effects. Research demonstrates how TSHR and its linked pathways represent promising targets for precise medical treatments of thyroid diseases. tátes o acesso crítico à compreensão das vias de sinalização não-concorrentes além do segurança de aplicar estratégias farmacológicas que manipulam TSHR no tempo longo. Future thyroid research demands integrated knowledge from molecular biology and endocrinology with immunology and clinical pharmacology to develop better diagnostic tools together with personalized treatments for managing various thyroid diseases with prevention potential.

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