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## Thyroid Growth Factors

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### 1. Introduction

The effect of exogenous and endogenous factors on the thyroid is manifested as stimulation or inhibition of the gland's excretory activity and growth regulation of the thyroid tissue itself. External factors affecting thyroid enlargement were known as early as approximately 2000 years B.C. in ancient China, where marine products were administered to inhabitants of the central part of the country. This specific supplementation of iodine-rich products prevented goiter development. [1,2] In modern times, the first country to introduce iodine prophylaxis was Switzerland, followed by the United States. Poland has been implementing a program of common salt iodization since 1986, albeit with an interruption of less than a score of years. We presently know that apart from iodine, there are numerous factors that affect regulation of thyroid secretion and growth. Thyroid homeostasis is thus controlled by several different substances acting on various levels: directly and indirectly by thyrotropin TSH (thyroid stimulating hormone); locally by other growth stimulators, such as the epidermal growth factor (EGF), transforming growth factor alpha (TGF- $\alpha$ ), insulin growth factors (IGFs), fibroblast growth factors (FGFs), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF- $\beta$ ), as well as through programmed cell death in the mechanism of apoptosis. Hence, changes in thyroid size and hormone demand occur mostly through TSH and complex interactions of local growth factors with expression of specific receptors. It has been also observed recently that para- and autocrine effects of growth factors are also associated with expression of particular oncogenes. Except the embryonal and adolescent periods, the volume of a normal thyroid gland does not increase. Each thyroid follicular cell is programmed to undergo five mitotic cycles during adult life and the final population of thyrocytes demonstrates specific differentiation, manifested by hormone secretion in response to thyrotropin via the mechanism of negative feedback. Thus, participation of the thyroid gland in hemostasis is regulated via hormonal, neural and immune pathways. The first level of thyroid growth and function control occurs via the effect of thyrotropin (TSH). The second level of tissue hemostasis is controlled by local factors. The third level consists of interactions between thyroid cells and connective tissue stroma, while the fourth level includes genetic factors with programmed death cell (apoptosis).

## 2. Regulation of growth and hormonal secretion – Mitogenic pathways

### 2.1 Role of TSH

#### Mechanism of activation via a receptor (types of receptors)

Thyrotropin (TSH) is traditionally believed to be the principal stimulator of growth, differentiation and maturation of thyroid follicular cells and connective tissue stroma. It is a 28 kD glycoprotein. Its level is among major parameters describing thyroid function and playing a decisive role in the clinical status of a patient. As early as in mid-thirties (1935 Kippen; Loeb; 1937 Dunhill), observations were made on the effect of TSH on thyroid follicular cells. Both a stimulatory and inhibitory effect of thyrotropin on thyroid follicular cells was described in cells cultured *in vitro*; attempts were undertaken at explaining the role of suppression therapy in preventing thyroid cancer development. For decades, particular research teams obtained contrary results of investigations on the proliferogenic effect on growth and differentiation of thyroid follicular cells. The effect on thyroid function and hormonal secretion has remained unquestioned [3,4]. In the last decade, numerous reports were published that discussed the complex regulation system of thyroid cell growth and proliferation, where thyrotropin alone may play an important role, but is not a prerequisite. Thus, TSH administration to rats resulted in thyroid enlargement both via cell hypertrophy and hyperplasia [5]. TSH-induced thyrocyte proliferation was triggered by human thyroid tissue implantation to mice (thymus-deficient nu/nu mice). In another study, thyrotropin was not necessary for compensatory thyroid growth following hemithyroidectomies, what suggested the effect of other factors that also play a role in the gland's growth [6,7]. Recently, attention has been also focused on the role of cAMP in thyroid growth-associated processes. Numerous reports on the proliferogenic effect of cAMP on thyroid follicular cells point to three pathways of activating growth and proliferation of thyroid cells:

1. first - activation of the adenyl cyclase-cAMP system, stimulated by TSH;
2. second - the phosphatidylinositol-Ca ion system,
3. third - most likely independent of cAMP - protein phosphorylation of tyrosine.

An increase of cAMP level in the majority of differentiated thyroid tumors (in contrast to normal tissue collected from the same patient) was interpreted as a result of an increased response to TSH stimulation. In numerous differentiated thyroid cancers, the functional TSH-cAMP-thyroid follicular cell growth system was noted; nevertheless, the question on intercorrelations of the above factors continue to remain open (Table 1.). Numerous authors have also pointed to a double effect of TSH depending on activation of other transmitters. Thus, 1) thyroid follicular cell growth is stimulated via activation of phosphatidylinositol and protein kinase C, while 2) the function of thyroid follicular cells is regulated by cAMP and protein kinase A (Figure 1). The two alternative pathways may explain diversified effects of thyrotropin in cancerous thyroid tissue [2]. The turning point in explaining many growth-associated phenomena within the thyroid gland was determination of the receptor structure on the molecular level and demonstration of intracellular interactions via activation of other transmitters. The thyrotropin receptor itself belongs to the family of G protein-coupled receptors (similarly as FSH, LH, estrogens, hCG or other steroid receptors). The predominant property of all the above receptors is the presence of a transmembrane domain that crosses the lipid layer (Figure 2.). The N-terminal region of the receptors is the so-called ectodomain situated on cell surface. The C-terminal region, situated within the cell,

is much shorter. The TSH receptor, in contrast to other receptors from this family, is modified post-translationally. Approximately 75% of the monomeric, membrane receptor is proteolyzed. In consequence of proteolysis, the so-called peptide C is released, while the generated subunits A and B are linked by disulfide bridges. Both forms of the receptor - monomeric and dimeric - actively bind TSH. In the cell membrane of thyrocytes, the TSH receptor is found in two forms: active, which binds Gs protein, and inactive, which is prevalent. Both TSH and stimulating autoantibodies bind to the active form of the receptor and stabilize it. In turn, inhibiting antibodies stabilize the inactive ("closed") form of the receptor and thus, the genuine receptor agonist seems to be the active ("open") form of the receptor rather than the thyrotropin (TSH) molecule itself [8,9,10,11].

### **3. Vascular endothelial growth factor (VEGF), epidermal growth factors (EGFs) and transforming growth factor alpha (TGF- $\alpha$ )**

Neoangiogenesis is a process consisting of numerous paracrine and endocrine interactions between cancer cells and vascular endothelial cells, connective tissue stromal cells and some morphotic blood elements, such as macrophages or mastocytes. The result of such interactions is a change in the microenvironment of a tumor that allows for its further uncontrollable growth and progression. A prerequisite for initiation of angiogenic phenomena is disturbance of balance between the system of pro- and anti-angiogenic factors. Not each of the proangiogenic factors that have been described to date (VEGF; bFGF; aFGF; PDGF; TGF- $\alpha$ ; TGF- $\beta$ ; EGF; IGF-1) meets all the three characteristic criteria: exerting a specific effect on endothelium, possessing a system of specific cell receptors and manifesting fluctuations that inhibit or induce angiogenesis. Many of such factors, acting in conjunction with mediators secreted by other cells (e.g. macrophages - TNF), induce and promote development of cancer. In keeping with the presently accepted assumptions, angiogenesis is initiated via hypoxia of cancer cells that are situated at the highest distance from the lumen of a blood vessel, as well as via a defect of the genetic apparatus, the consequence of which is formation of the so-called angiogenic phenotype. This term denotes a state of permanent, constitutive activation of growth factors-encoding genes. An additional loss of function of suppressor genes (e.g. the p53 gene) favors the process of neoangiogenesis. One of the relatively well-understood epithelial growth factors is VEGF. This specific protein, defined and named in late eighties, is assumed to play a key role in vascularization of solid tumors, including thyroid tumors. At present, the VEGF group is believed to include six proteins: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and PlGF (Placenta Growth Factor). They act through binding to receptors: VEGFR1, VEGFR2 - on vascular endothelial cells, and VGFR3 - on lymphatic endothelium cells (Figure 3). The necessary cofactors for the VEGF receptor are neuropilins 1 and 2 (Nrp-1,2), which are indispensable for proper activation of the receptor by a ligand. Synthesis of the vascular growth factor is induced by numerous other substances, such as nitrogen oxide, insulin, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), tumor necrotic factor (TNF- $\alpha$ ), transforming growth factor (TGF- $\beta$ ), IL-1,2. In keeping with the theory of Folkman, which states that tumor growth is limited by its vascularization, attempts have been made to demonstrated higher VEGF expression in cancer tissues as compared to normal cell populations. Similarly as in the case of cancer of the stomach, colon, uterus, breast and ovary, also in thyroid tumors a key role in neoangiogenesis is played by VEGF. As it has been already mentioned, not only thyroid

epithelial cells, but also stromal cells are capable of producing and secreting VEGF. The above described results have allowed for formulating a hypothesis that VEGF participates in initiation of neoangiogenesis, yet further tumor development and progression most likely depend on the effect of other chemokines secreted both by tumor cells, its stroma and macrophages migrating to the neoplastic lesion [12,13,14]. In turn, epidermal growth factor EGF is one of the most potent stimulators of thyroid growth and its multiple effect is determined by its binding to specific EGF receptors. *In vitro*, it is a factor that stimulates proliferation of thyroid follicular cells. A factor that increases EGF binding to receptors is thyrotropin (TSH), which - stimulating the increase of the number of EGF receptors - enhances its effect. Yet, in contrast to the above-mentioned TSH, to reveal its mitogenic effect, EGF does not require the presence of other chemokines. In subsequent studies, investigators attempted to determine the effect of positive EGF receptors expression in thyroid cancer tissue on the clinical course of the disease. A comparison was made between the presence of EGF receptors in various types of thyroid cancer, finding their highest expression in anaplastic and medullary carcinoma of the thyroid. Also adenomas demonstrated considerable expression of EGF receptors, but only in some limited areas within the tumor. EGF-R was also noted to bind not only to EGF - $\alpha$  1, but also to the transforming growth factor alpha (TGF- $\alpha$ ). The autocrine mechanism of activating EGF receptors both by the epidermal growth factor molecule and by TGF $\alpha$  was seen in thyroid cancers (papillary carcinoma and its nodal metastases) [15].

#### **4. Insulin growth factors and their receptors (IGFs)**

Growth hormone (GH) affects growth processes in tissues and organs through specific substances called the insulin growth factors (IGF-I; IGF-II). IGF-I, termed somatomedin C, and IGF-II affect growth regulation of thyroid endothelial cells. In turn, thyroid follicular cells show high expression of specialized IGF-I and IGF-II receptors. The IGF-I receptor, as a member of the family of receptors that act via tyrosine kinase, is a mediator of the effect of IGF-I on stimulation and growth of thyroid follicular cells. IGF-I has been proven to strongly stimulate growth of the FRTL-5 line cells and to synergistically enhance the mitogenic effect of thyrotropin (TSH). In turn, the IGF-II receptor plays no significant role in thyroid growth stimulation. Autocrine secretion of IGF-I, IGF-II and expression of the IGF-I-Rs receptor were demonstrated in primary cultures of thyroid follicular cells, as well as in adenomas and thyroid papillary carcinoma cell lines [16,17,18].

#### **5. Fibroblast growth factor (FGFs), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF)**

To date, nine subtypes of the fibroblast growth factor belonging to a single family (the "FGF family") have been determined. The FGF factor itself is known as a stimulator of proliferation, differentiation and functioning of various diverse cells of human body. FGF also plays a significant role in neoangiogenesis. The cell response to FGF effect is mediated by its four receptors (FGF-R 1-4) that belong to the family of tyrosine kinases. Thyroid endothelial cells show expression of FGF-R receptors, while the basement membrane of thyroid follicular cells is capable of producing the factor itself. Based on numerous observations *in vitro* and *in vivo* in rat thyroid follicular cells, an autocrine, stimulatory effect of FGF-2 ("basic FGF") on thyroid growth processes has been demonstrated. In turn, a

paracrine effect has been manifested in neovascularization seen in nodular goiter. Similarly as EGF, FGF has an inhibitory effect on thyroid function. The effect of FGF consists in inhibition of cAMP activation and weakening of TSH activity. FGF-1 administration to rats leads to development of colloid goiter, most likely through inhibition of TSH-dependent colloid transport from the lumen of thyroid follicles (Figure 4.).

The hepatocyte growth factor (HGF) is also a potent myogen for numerous diversified cell types in human body, especially these of epithelial origin. It operates through its receptor that is encoded by the c-met proto-oncogene and belongs to the family of tyrosine kinase receptors. HGF-R expression has been noted both in normal and cancer tissue, with the factor being present in papillary and follicular carcinoma, but absent in anaplastic carcinoma tissue. Some importance in neoplastic proliferation is also ascribed to the platelet-derived growth factor (PDGF), the presence of which has been noted in the papillary carcinoma cell line.

## 6. Interactions between stimulatory growth factors and their inhibitors

A group of factors that inhibit thyroid growth is the family of the thyroid growth inhibiting factor -  $\beta$  (TGF-  $\beta$ ). Through their receptors TGF-  $\beta$ -R I to TGF-  $\beta$ -R III, the factors TGF-  $\beta$ 1 to TGF-  $\beta$ 3 affect inhibition of thyroid follicular cell growth in vitro; their role has also been implicated in development of benign lesions. A drop in TGF production has been observed in thyroid follicular cells of patients with non-toxic goiter.

Stimulation of thyroid tissue growth occurs through an increased frequency of signals reaching the gland from the surrounding structures, resulting in sensitization of follicular cells to normal external stimuli. Such stimuli may be the afore-mentioned growth factors or antibodies or else dietary iodine deficit. A notion of the so-called "grey zone" has become popular in thyrology, to denote a population of cells with a high internal growth potential, which, in consequence of single or multiple genetic damage, change their growth potential (in hyperplastic tumors) towards cancer, yet without obvious neoplastic transformation. The effect on cell cycle, manifested as for example the shortened G0 phase or limitation of apoptosis may lead to an increase in the number of cell divisions prior to programmed cell death.

Within the past decade, development of modern research methods, molecular biology and genetics has allowed for gradual understanding of molecular foundations of thyroid cancers. It is presently known that activation of certain oncogenes and inactivation of suppressor genes may lead to tumor development. Of 35 proto-oncogenes determined in neoplastic transformation of thyroid follicular cells, the following have their effect proven:

1. c-erb encodes the EGF (endothelial growth factor) receptor;
2. flg, bek encodes the FGF receptor type 1 and 2 (fibroblast growth factor);
3. c-met encodes the HGF (hepatocyte growth factor) receptor;
4. c-sis encodes the PDGF (platelet-derived growth factor) receptor;
5. Ras is characteristic of follicular carcinoma, adenoma, anaplastic carcinoma;
6. PTC/ret, TPC - characteristic of papillary carcinoma;
7. Trk encodes NGF (nerve growth factor) characteristic of papillary carcinoma and detected in nodular goiter.

As it follows from the presented data, they play a key role in encoding growth factors and/or their receptors production

Summing up, it should be stressed that the theories presented in the chapter constitute only a very narrow fragment of the bulk of knowledge on the subject. An extensive presentation of the topic is possible only in a monograph, yet the above provided examples help in understanding the foundations of contemporary knowledge on the effect of external factors on cancer development.

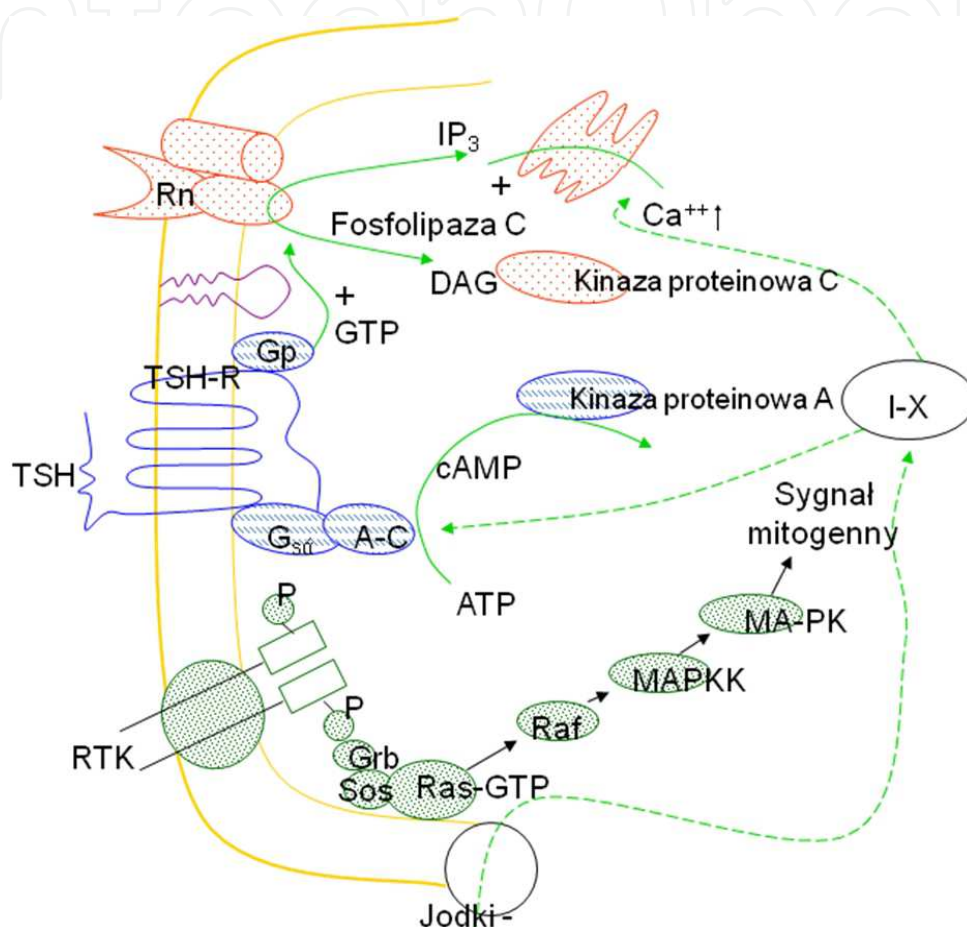


Fig. 1. Mitogenic pathways in regulation of thyroid function and growth. The scheme present the main pathways that participate in regulation of thyroid function and growth.

1. The AC/cAMP/PKA pathway: The main factor that stimulates the pathway in thyrocytes is thyrotropic hormone (TSH), which interacts with the TSH receptor (TSH-R). Stimulation of the TSH-R receptor leads to activations that bind guanosine triphosphate (GTP) of regulatory proteins; Ga protein in the plasma membrane activates adenylyl cyclase (AC) that synthesizes cyclic adenosine monophosphate (cAMP), which activates protein kinase A (PKA), and phospholipase C (PLC)-associated Gp protein, which stimulates phosphatidylinositol (PI) metabolism.
2. The PI-PKC-Ca<sup>2+</sup> pathway: In addition to TSH-R, the cascade of signal transmission is activated through numerous diversified receptors (marked as Rn in the scheme). Stimulation of TSH and other receptors leads to an increased PLC activity; in consequence, 1,4,5-inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG) are formed with

- a resultant increase of intracellular level of calcium (Ca<sup>2+</sup>) and PKC activity. Both PKA and PKC are serine-threonine kinases and they phosphorylate several different proteins.
- The receptor tyrosine kinase pathway (RTK): Binding of a ligand to RTK leads to phosphorylation of tyrosine residues in the receptor molecule. The stimulated phosphorylated receptors connect to numerous different signaling pathways (the scheme does not show all the pathways) through direct binding of signaling proteins that contain a homology domain with Src proteins (SH2). Nevertheless, the main mitogenic pathway of numerous receptors tyrosine kinase (RTK) includes activation of a chain of events on the *ras* pathway (see the scheme). In brief, phosphorylated RTK interacts with Grb2 adaptor protein. Grb2 binds to a protein called Sos ("son of sevenless"), resulting in activation of the *ras* pathway. The activated form of *ras* GTP protein triggers increased activity of raf protein, with a resultant sequential activation of MAPK cascade proteins (mitogen-activated kinases), what ultimately leads to an increased transcriptional activity (MAPKK kinase, MAPK). The scheme also shows a negative effect of organic forms of iodine (I-X) on various pathways. ATP = adenosine triphosphate.

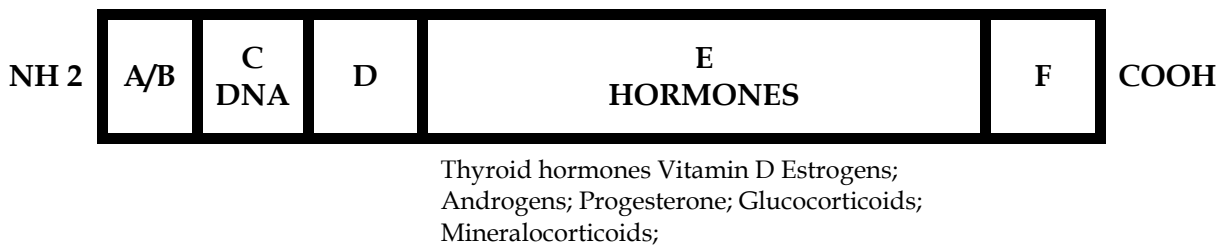


Fig. 2. The family of steroid/thyroid receptors. The marked receptors have similar structure. The C domain consists of DBD domains.

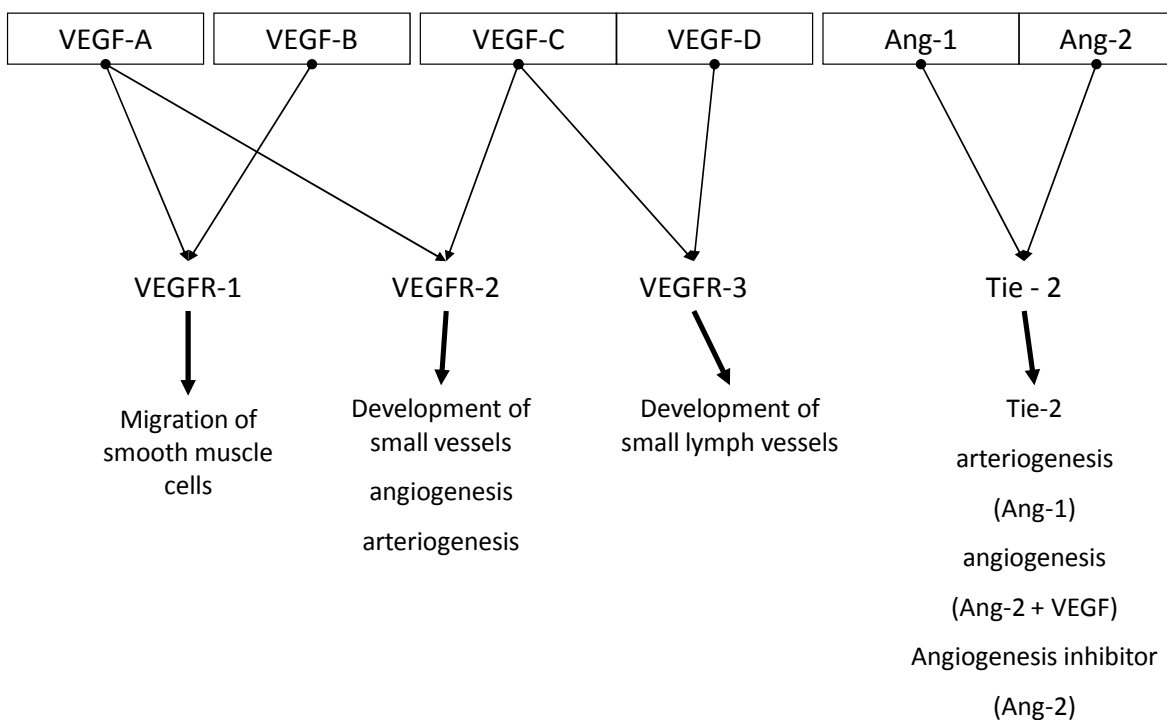


Fig. 3. Vascular growth factors and the effects of their acting through receptors.



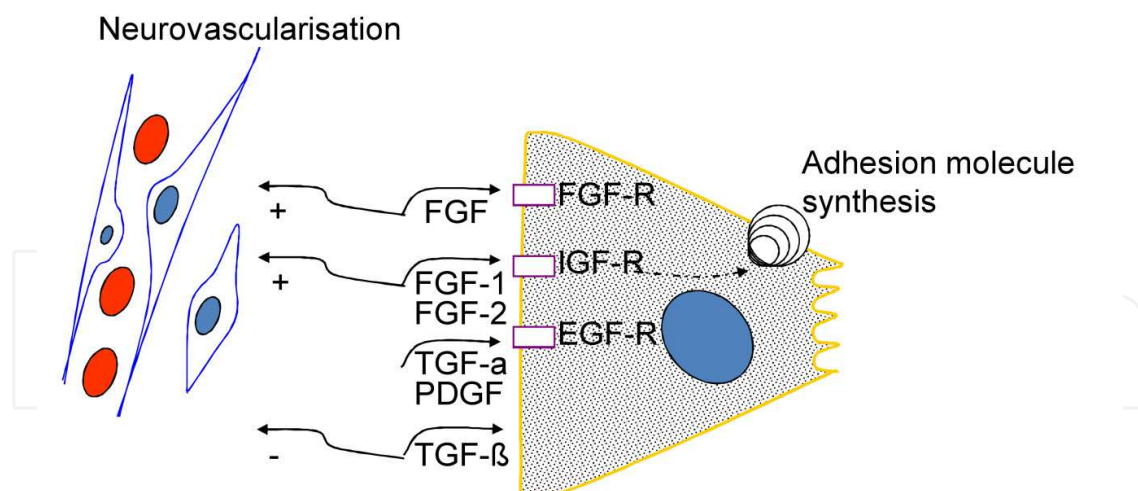


Fig. 4. Autocrine and paracrine regulation of growth and inhibition of thyrocytes via growth factors and their receptors. The factors may be also secreted by the surrounding stromal tissue, thus giving rise to proliferation of endothelial cells and fibroblasts. IGF-insulin growth factor; TGF – transforming growth factor; EGF – epidermal growth factor; FGF – fibroblast growth factor; PDGF – platelet-derived growth factor.

Activation pathway (other transmitter)	Factors	Receptor	Effect	"Related" proto-oncogene
AC-cAMP-PKA	TSH	TSH-R	Stimulatory and inhibitory	
	Iodides (inhibition of cAMP)		Stimulatory	
	Epinephrine (inhibition of cAMP)		Stimulatory	
Receptor tyrosine kinases	EGF	EGF-R	Stimulatory	<i>c-erb B</i> (EGF-R)
	TGF-α	EGF-R	Stimulatory	
	FGFs	FGF-Rs (1-4)	Stimulatory	<i>flg, bek</i> (FGF-R-1, FGF-R-2)
	Insulin	(ffi) IGF-I-R	Stimulatory (via IGF-I-R)	
	IGF-I	IGF-I-R	Stimulatory	
	IGF -n	(IGF-n-R) IGF-I-R	Stimulatory (via IGF-I-R)	
	HGF	HGF-R	Stimulatory	<i>c-met</i> (HGF-R)
Phosphatidylinositol cascade	PDGFs (AA, AB, BB)	PDGF-Rs (a, )	Stimulatory	<i>c-sis</i> (PDGF-BB)
	TSH	TSH-R	Stimulatory	
	Esters	PKC	Stimulatory	
	TGF -β1	TGF--Rs (1-3)	Inhibitory	
	Iodides		Inhibitory	

Table 1. Major factors with stimulatory and inhibitory effect on growth of thyroid follicular cells.

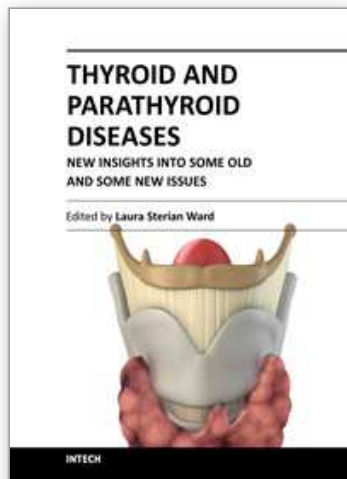
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## **Thyroid and Parathyroid Diseases - New Insights into Some Old and Some New Issues**

Edited by Dr. Laura Ward

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This book was designed to meet the requirements of all who wish to acquire profound knowledge of basic, clinical, psychiatric and laboratory concepts as well as surgical techniques regarding thyroid and parathyroid glands. It was divided into three main sections: 1. Evaluating the Thyroid Gland and its Diseases includes basic and clinical information on the most novel and quivering issues in the area. 2. Psychiatric Disturbances Associated to Thyroid Diseases addresses common psychiatric disturbances commonly encountered in the clinical practice. 3. Treatment of Thyroid and Parathyroid Diseases discusses the management of thyroid and parathyroid diseases including new technologies.

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