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REVIEW

Novel and emerging concepts in the role of steroids in thyroid cancer promotion and progression

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ABSTRACT
Thyroid cancer (TC) is becoming more common all over the world. It is, however, frequently neglected from a scientific standpoint, as they rarely result in a fatal conclusion. The female gender is disproportionately affected, with a frequency of 3 to 5 times higher depending on the severity of the condition, which may or may not cause severe physical discomfort but has a significant influence on life quality. The breakdown of equilibrium between the multiple components that maintain cellular homeostasis may be the cause of the illnesses. On the contrary, excessive or uncontrolled exposure to different hormones, particularly steroids, has been shown to impact the development of thyroid illnesses. The goal of this review is to look at the function of steroids in the expansion and progression of thyroid malignancy *(Ref. 54)*. Text in PDF *www.elis.sk*
KEY WORDS: thyroid cancer, signaling, steroid hormone.

Introduction

According to Global Cancer 2020 data, thyroid cancer accounted for approximately 3.0% of all malignant tumors, ranking ninth, with thyroid cancer ranking fifth among female malignancies with a 4.9 percent incidence. Thyroid carcinoma is the most widespread endocrine system cancer. Its prevalence has grown in current decades. It is categorized into three chief histologic types: differentiated (comprising papillary, follicular and hurthle), medullary, and anaplastic (aggressive undifferentiated tumor). Papillary thyroid carcinomas (PTC) account for over 80 percent of malignant endocrine tumors and about 65 percent of malignant thyroid tumors (Eldien et al, 2017; Jalali-Nadoushan et al, 2016). With an indolent course, localized lymph node metastases, and long-term survival, PTC has a favorable prognosis (Jalali-Nadoushan et al, 2016). Thyroid cancer is not substantially different in males and females in childhood. Gender disparities in the incidence of thyroid cancer increase progressively with age, notably in reproductive age, where females are affected roughly 3 to 5 times more likely than men. This issue may be due to hormone levels in women, particularly at reproductive age, when sex hormone levels are at their maximum in the body (Rahbari, Zhang, and Kebebew 2010; Zhang et al, n.d.). Furthermore, the presence of estrogen and progesterone receptors (ER and PR) in normal thyroid gland tissue may play a part in the development of neoplastic lesions (Jalali-Nadoushan et al, 2016) , implying that estrogen and progesterone may show essential roles in the molecular pathogenesis of thyroid malignancies (Eldien et al, 2017). On the other hand, menopausal women were shown to have a lower risk of thyroid cancer (Caini et al, 2015). Experiments have shown that estrogens contribute to the development of papillary carcinoma by boosting cell proliferation and invasion of mutant epithelial follicular cells (Huang et al, 2014, 2015). Furthermore, research has shown that long-term exposure to exogenous estrogens is linked to the development of TC (Ahmed and Aboelnaga 2015; Caini et al, 2015; Sungwalee et al, 2013). It seems that female hormones can directly influence the thyroid cancer promotion and progression. In the current review, we aim to elucidate the role of these hormones in Thyroid cancer promotion and progression.

Steroids signaling in cancers

SHs, or steroid hormones, are a kind of cell regulator. In this line, Sex hormones, which comprise androgen as male hormones, estrogen and progesterone as female hormones, and corticosteroids, glucocorticoids and mineralocorticoids, may be easily distinguished (Simoncini and Genazzani 2003). Their biological effects are mediated by a diverse set of ligand-dependent intracellular transcription factors known as SH receptors (SHRs), which are divided into five categories: estrogen receptors (ERs), progesterone receptors (PRs), androgen receptors (ARs), glucocorticoid receptors (GRs), and mineralocorticoid receptors (MCRs) (Chen et al, 2020; Simoncini and Genazzani 2003; Stanišić et al, 2010). SHs have been found to have a role in the genesis and progression of

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human malignancy, with each SH being engaged in a subset of neoplasms including colon, lung, and thyroid cancers (Ahmad and Kumar 2011; Magri et al, 2012). The ER protein is divided into two isoforms: ER and ER and PR A and PR B are two isoforms of PR protein (Kansakar et al, 2009). On cell survival and proliferation, the estrogen receptor and its antagonist have conflicting effects. The proliferative and anti-apoptotic activity of the estrogen receptor is contrasted by the differentiated and pro-apoptotic actions of the estrogen receptor (Speirs and Walker 2007). The formation, growth, and advancement of breast cancer are influenced by cumulative estrogen exposure, whereas androgens are required for the beginning and progression of prostate cancer. Steroid hormones, such as corticosteroids and sex steroids, are necessary for the homeostatic regulation of critical different systems like metabolism, immunity, stress response, fluid equilibrium, and development. Signaling disruption of canonical hormone causes a wide range of diseases and can promote cancer-linked behaviors at the cellular level, such as proliferation, migration, invasion, and metastasis (Yen 2015). In current years, it has become apparent that steroid hormone signaling affects the genome's stability, hence cancer initiation and development, in direct and indirect ways. Augmented oxidative stress (Ganguly et al, 2021; Ide et al, 2012), triggering of DNA double-stranded breaks (DSBs), boost of DNA-protein adduct construction, and the beginning of gene rearrangement actions are all examples of how steroid hormone signaling affects genomic stability (Ganguly et al, 2021). Thyroid hormone and steroids have two separate signaling pathways: an outside-the-nucleus nongenomic transcription-independent mechanism and an inside-the-nucleus genomic transcription-dependent channel. Thyroid hormones and steroid hormones, on the other hand, have been discovered to exploit boundaries or relations between their genomic and nongenomic mechanisms of action in the last decade, implying that genomic and nongenomic signaling is not permanently equivalent but frequently sequential processes. Thyroid and steroid hormone signaling seem to overlap in some cases. Nongenomic thyroid hormone signaling, for example, has been shown to stimulate the nuclear estrogen receptor (ERa) in breast and lung cancer cells, and ERa up regulation by thyroid carcinoma has been shown to modify the disease course (Hammes and Davis 2015).

Estrogen receptor in various types of thyroid cancer

Estrogen, a low-molecular-weight lipophilic hormone, plays a role in cellular processes like proliferation, cell motility, and organ function (Dong et al, 2013). Estradiol (E2) is the most effective type of estrogen because it binds to the soluble intracellular nuclear receptors ERa, ERb, and GPER1 with the highest affinity (Arciuch and Di Cristofano 2012; Santin and Furlanetto 2011). Following E2 binding, ER makes a constant dimer that cooperates with estrogen response elements (EREs) to activate the transcription of desired genes. Ligand-bound ERs can also cooperate with other transcription factor compounds, influencing gene transcription that does not include EREs. Non-genomic and independent ligand pathways are the third and fourth modes of ER regulatory activity, respectively (Juvenal et al, 2011). Thyroid follicular cells, both regular and cancerous, express ER protein and ER mRNA. ERa promotes proliferation while inhibiting apoptosis, whereas ERb promotes apoptosis and growth inhibition (Santin and Furlanetto 2011). The stimulation of signal-transducing pathways is responsible for some of E2's activities in thyroid cell proliferation. In follicular thyroid cancer cells, E2 may activate phosphatidylinositol 3-kinase (PI3K) and phosphorylate extracellular signal-regulated kinase 1/2 (ERK1/2) owing to contact via membrane-associated ER. By stimulating the expression of essential genes, PI3K and Erk1/2 signaling may show a significant part in avoiding apoptosis and promoting cell cycle progression (Antico-Arciuch et al, 2010; Saji and Ringel 2010). Various experts have begun to investigate the function of estrogen in the development of thyroid illnesses in recent years (Derwahl and Nicula 2014; Zane et al, 2014). Estrogen receptors located on chromosomes 6 and 14 and polymorphisms in these genes have been implicated in the oncogenesis of cancers in a variety of organs. They may modify the tissue's susceptibility to estrogens (Zane et al, 2017). According to a growing number of studies, estrogen may directly influence carcinogenesis in human thyroid cells via ER-dependent or ER-independent processes such as cell proliferation, sodium iodide symporter modulation, and thyroglobulin gene expression (Eldien et al, 2017). 17-estradiol's proliferative effects in thyroid carcinoma were discovered to be facilitated via the modulation of growth control genes such as BCL-2, Bax, and c-fos (Vivacqua et al, 2006; Zeng et al, 2007). ER-agonists increased cell proliferation, whereas ER-antagonists inhibited cell growth (Chen et al, 2008). Several studies have looked into the involvement of estrogens in the development and progress of DTC. According to a new meta-analysis involving over 5,000 patients, postmenopausal women had a lower risk of thyroid cancer. However, increasing age at first pregnancy/birth was linked to greater cancer risk. Like other epithelial cancers, DTC displays both ER isoforms, with ER activation linked to enhanced estrogen-dependent cell proliferation. In thyroid tumors, ER presumably favors apoptotic activities and other suppressive effects. Overall, there is evidence that ER-expression is higher in tumors than in normal thyroid tissues. ER-expression is lower in neoplastic thyroid tissue than in nonneoplastic thyroid tissue (Sturniolo et al, 2016).

Papillary thyroid cancer

Further research revealed that ER expression had been linked to well-differentiated thyroid follicular tumors and a lower risk of disease recurrence in differentiated thyroid follicular tumors (Kavanagh et al, 2010). Vannucchi et al (2015) discovered that tumors expressing ER and PR had a higher incidence of local metastasis. Many studies have discovered that E2 can increase the metastatic potential of numerous PTC cell lines by increasing cell adhesion, motility, and invasion(Ahmad and Kumar 2011; Dong et al, 2013). Cancer cells must leave the initial tumor and develop migratory and invasive capacities in the metastatic phase. Several distinct mechanisms are implicated in cancer cells, including epithelial to mesenchymal transition (EMT), downregulation of adhesion mo-

lecules, and overexpression of matrix metalloproteinases (MMPs). Loss of the epithelial protein marker E-cadherin, concurrent overexpression of the mesenchymal protein markers vimentin, and expression of MMP-9 play essential roles in the metastatic procedure in various malignancies, such as breast cancer, ovarian, colon, and lung cancers, and may be regulated by E2 (Hsu et al, 2012; Zheng et al, 2011). Endothelial proliferation and migration are induced by estradiol through the traditional estrogen receptor, expressed by endothelial cells. This action might be a contributing factor to estradiol's angiogenic properties (Mylonas, 2010). This might be one reason for the increased expression of ER- in metastatic patients. Immunohistochemical evaluation of ER-expression in individuals with PTC may exert a potential prognostic marker (Chen et al, 2015) and possibly indicate more aggressive behavior, which is consistent with our restricted follow-up, where the individuals displayed recurrence and lymph node metastasis were initially positive for ER. Furthermore, it will have significant biological and therapeutic consequences and potentially change follow-up, especially for infertile women with chronic illness (Dong et al, 2013; Vannucchi et al, 2015). The presence of inflammatory cells in thyroid tissue distant from the tumor was linked to ER expression to a substantial degree. This observation might be explained by the supposed relationship between E2 and the inflammatory response. Inflammation: estradiol has a complicated immunomodulatory impact. Estradiol affects vascular cell adhesion molecules and proinflammatory mediators, decreasing acute lung inflammatory responses in mice (Speyer et al, 2005). Nonetheless, E2 has been shown to have a pro-inflammatory effect (Straub 2007). T-cell-dependent immunological responses can be stimulated by estradiol (Adori et al, 2010). These data also imply that ER may mediate estrogen's cancer-promoting impact in PTC patients, suggesting it may be employed as a cancer marker. Estrogen-induced increases in ER production rather than ER in PTC cells might be an effective mechanism by which estrogen promotes tumor formation (Zeng et al, 2008). Although its splice variants were not studied separately, their findings recommend that ER may have inhibitory effects on development and progression (Magri et al, 2012). Expression patterns of ER1 and ER2 varied between PTC lesions and NTG tissue in a prior preliminary investigation, suggesting that distinct ER splice variants may play diverse roles in the etiology of PTC (Dong et al, 2012). As a result, the effects of the two ER subtypes and their splice variants on PTC development must be explored and examined independently to offer a foundation for ER agonists or antagonists in therapeutic and preventative approaches to PTC.

Follicular thyroid cancer

In human medullary thyroid cancer, the expression of ER and ER was found, with an elevated ratio of ER/ER, indicating a probable involvement in tumor development and progression (Juvenal et al, 2011). It was recently discovered that ER is expressed substantially more in follicular thyroid adenoma than in follicular thyroid carcinoma (FTC). It is a better differential diagnostic marker than Ki-67 in follicular thyroid adenoma (Heikkilä et al, 2013). In FTC, low ER expression seems to be linked to poor survival (Heikkilä et al, 2013). In another investigation, malignancies acquired ER expression and reduced ER expression compared to normal thyroid parenchyma (Magri et al, 2012). ER-positive tumors had greater postsurgical serum thyroglobulin levels than ER-negative tumors, whereas ER-negative tumors had more vascular invasion than ER-positive tumors (Magri et al, 2012).

Progesterone receptor in various types of thyroid cancer

PR has been found in a variety of human organs, including reproductive as well as non-reproductive tissues. On the other hand, PR isoforms (PRA and PRB) influence cells in various ways (Asavasupreechar et al, 2020). In terms of PR, most of the few studies that have examined its expression in thyroid malignancies thus far have done so in conjunction with ER (Sturniolo et al, 2016). In papillary thyroid cancer, the traditional nuclear PR may play a role. According to a recent investigation, the PR was discovered in 75.8% of these instances. In ER+ and PR+ papillary thyroid cancers, there was a non-significant trend toward a greater rate of local metastases. As a result, anti-estrogen medication may be beneficial for certain thyroid cancers. Some women may benefit from anti-progesterone receptor treatment (Check 2017). In the case of PR, its presence shortens the length of PTC-free survival throughout the patients' whole follow-up period, indicating that PR may have prognostic significance in predicting active illness. The mechanism through which PR contributes to PTC advancement, however, is yet unknown. Progesterone can increase thyrotropin-mediated transcription actions in the thyroid, which might be essential in PTC advancement (de Castro et al, 2019).

Mechanisms of steroids action

Estradiol (E2) and progesterone (P) are steroid hormones that govern critical physiological processes in diverse species, including development, differentiation, metabolism, reproduction, learning, and memory. E 2 and P's biological effects are primarily facilitated by binding to their classical intranuclear receptors, estrogen (ERs) and progestin receptors (PRs), which act as ligand-inducible transcription factors and interact with steroid receptor coregulators to modulate target gene expression and function (Mani et al, 2012).

The role of steroids in thyroid carcinogenesis

The following are the mechanisms through which estrogen and progesterone participate in DTC pathogenesis via ER and PR: (1) Estrogen and progesterone connect to their receptors, triggering the mitogen-activated protein kinase (MAPK) signaling cascade, which promotes mitosis. (2) Estrogen and progesterone signal the nucleus via ER and PR, upregulate cyclin D1 expression and promote the growth of thyroid tumor tissue. (3) Estrogen and progesterone activate the Ras-Raf-MAPK signaling pathway. The current study found that the favorable rates of ER and PR expression were significantly higher in DTC thyroid cancer tissue with a diameter greater than or equal to 1 cm than in tissue with a diameter less

than or equal to 1 cm and that ER and PR expression levels were linked with tumor size, lymph node metastasis, and capsular invasion. On the other hand, ER and PR expression levels were unrelated to histological type, gender, or age. It seems that estrogen and progesterone have a role in DTC pathogenesis through the ER and PR pathways. Estrogen and progesterone bind to ER and PR, activate downstream signaling pathways, and imitate thyroid cancer cell proliferation and growth by decreasing G0/G1 phase cells and increasing S phase cells, resulting in tumor cell proliferation and tumor formation. Furthermore, ER and PR expression levels and favorable rates rose (Zhang et al, 2014).

Diagnosis

A serum thyroid-stimulating hormone (TSH) level should be included in the first workup for any newly detected thyroid nodule. The anterior pituitary releases TSH, which instructs the thyroid gland to produce thyroid hormone as needed. TSH rises in response to low thyroid hormone levels and falls in response to high thyroid hormone levels. Consequently, assessing a TSH level allows distinguishing between functional and nonfunctional nodules. Because hyperfunctioning nodules are seldom malignant, this is an essential trait. A nuclear medicine imaging investigation (thyroid uptake and scan) should be undertaken if the TSH is subnormal, suggesting a hyperactive gland, to determine whether the nodule is hyperfunctioning (hot), functioning (warm), or nonfunctioning (excellent) relative to the surrounding thyroid tissue. No cytologic test is required if the nodule is hot or warm; however, if the patient is symptomatic, additional assessment is essential to rule out other causes, such as Graves' disease, and offer suitable therapy.

Fine-needle aspiration (FNA) will be required for cytologic examination of nonfunctioning nodules. Malignancy is likely greater with nonfunctioning nodules and glands damaged by Hashimoto's thyroiditis, a common autoimmune hypothyroid illness. Hence, an FNA is advised whether the TSH is normal or raised, even within the upper ranges of normal.

A diagnostic neck ultrasound should be conducted on all suspected nodules in addition to serum TSH to confirm the presence of a nodule and look for any worrisome characteristics. However, no single ultrasound characteristic, or combination of ultrasound features, is sensitive enough to detect cancer independently. Microcalcifications in papillary thyroid cancer and their absence in follicular thyroid cancer are two ultrasonography findings that have a higher correlation with various types of cancer. Furthermore, some sonographic characteristics, such as exclusively cystic nodules and nodules with a spongiform appearance greater than 50% of the time, are significantly predictive of benign nodules (aggregation of multiple microcystic components). It should be noted that regular measures of blood thyroglobulin and calcitonin are not advised for the first diagnosis of thyroid cancer (Nguyen et al, 2015).

Prognosis

Patients with PTC have a better prognosis than those with other types of cancer. However, many patients with PTC develop local and distant metastases, and the recurrence rate remains as high as 30%. Traditional anti-tumor treatments have a good impact, but they are not perfect. However, a small minority of PTC patients remain resistant to standard treatment, particularly those unable to be operated on or who suffer recurrence after surgery and do not respond to iodine therapy. Traditional anti-cancer treatments are unable to address all of the issues that PTC patients face (George et al, 2018; Ho et al, 2015). As a result, novel molecular targets must be developed to monitor the treatment efficacy and forecast the evolution of PTC to enhance patient care (Qin et al, 2021).

Treatment

Treatment Surgery, radioactive iodine (131I) therapy, and molecular-targeted treatments using various tyrosine kinase inhibitors are alternatives for thyroid cancer treatment (TKIs). The typical treatment choices differ based on the cancer type and stage. Different oncology groups have different treatment choices for thyroid cancer (Nguyen et al, 2015).

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