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Research Progress on the Mechanism of Correlation Between Vitamin D and Thyroid Cancer

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Abstract: Vitamin D is a kind of fat-soluble vitamin, which is mainly involved in the metabolism of calcium and bone in the human body. As a metabolic substance, it also has a certain impact on the cellular microenvironment, and vitamin D also inhibits the proliferation of tumor cells. 25(OH)D is considered the best index to evaluate the vitamin D level in the human body because of its relatively stable characteristics in the circulation. Thyroid cancer is a common malignant tumor that develops from malignant thyroid nodules. A large number of studies have found that the lower the serum 25(OH)D level, the higher the risk of thyroid nodules. A large number of studies have found that the lower the serum 25(OH)D level, the higher the risk of thyroid nodules.

Keywords: Thyroid cancer; Vitamin D; Wnt/β-catenin signaling pathway; EGFR gene polymorphism

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1. Introduction

Thyroid cancer (TC) is a common endocrine tumor, and its incidence has increased gradually and annually in the past two decades [1]. In 2020, TC has become the ninth most common cancer in the world [2]. At present, most TC clinicians use surgical resection and radioactive iodine 131 therapy. Whether it is surgical resection or radiotherapy, thyroid hormone replacement therapy should be used. Secondly, it can inhibit the recurrence and growth of thyroid tumors by reducing the secretion of thyroid-stimulating hormone. There are many pathogenesis of thyroid tumors. With the continuous development of molecular biology, the molecular biological mechanisms of thyroid carcinogenesis and evolution mainly include the following aspects:

(1) The rearrangement of RET/PTC and TRK in thyroid follicular epithelial cells is based on the mutation of *Ras* gene, which leads to the formation of thyroid papillary carcinoma [3];

(2) Vascular endothelial growth factor (VEGF) is an important pro-angiogenic factor, which can promote the division of vascular endothelial cells and neovascularization and participate in the pathological process of malignant tumor lymphangiogenesis, promote the proliferation and metastasis of malignant tumors, and

the high expression of serum VEGF is closely related to the metastasis of thyroid tumor cells [4,5].

At present, a large number of studies have shown that vitamin D not only has the common function of regulating calcium and phosphorus metabolism but also has the function of inhibiting the occurrence and development of tumors. In-depth exploration of the role and mechanism of vitamin D in the occurrence and development of TC will help to detect, prevent, and treat TC. From the perspective of the regulatory mechanism of vitamin D in the process of TC, this paper summarizes the mechanism of vitamin D in the occurrence and development of TC from multiple dimensions such as vitamin D and Wnt/β-catenin signaling pathway, microRNA (miRNA), *VEGF*, *EGFR*, and vitamin D receptor (*VDR*) gene polymorphism and thyroid cancer. It is expected to provide new ideas for the clinical detection and treatment of thyroid cancer.

2. Synthesis and function of vitamin D

Vitamin D is a fat-soluble vitamin. Its active forms include 25-hydroxyvitamin D_3, 1,25-dihydroxyvitamin D_3, 24,25-dihydroxyvitamin D_3, etc. Among them, $1,25(OH)_2D$ is the most active metabolite of vitamin D and can exert the greatest physiological effect. However, 25-hydroxyvitamin D_3 is the main form of vitamin D in blood circulation and is a commonly used clinical detection index. Generally, the nutritional status of vitamin D refers to the blood 25(OH)D level. The main functions of vitamin D at present are as follows:

(1) Promoting the absorption of calcium and phosphorus in the intestine;
(2) It participates in bone metabolism;
(3) Regulating the synthesis and secretion of insulin, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and other hormones;
(4) Inhibit the formation and metastasis of tumor cells;
(5) Regulate the body's immune system;
(6) It can regulate the regeneration, proliferation, and differentiation of various cells in the body;
(7) It has a certain preventive effect on cardiovascular diseases [6]. $1,25(OH)_2D_3$ exerts anti-tumor proliferation, differentiation, and immunomodulatory effects by binding to VDR mainly through genomic and non-genomic pathways [7].

The anti-tumor mechanisms of vitamin D include:

(1) Inhibition of abnormal proliferation and differentiation of tumor cells;
(2) Inhibit the migration and metastasis of tumor cells;
(3) Regulate the immune function of the body;
(4) Promote the apoptosis of tumor cells.

3. The mechanism of vitamin D in the occurrence and development of thyroid cancer

3.1. Correlation between vitamin D and Wnt/β-catenin signaling pathway

The anti-tumor effect of vitamin D can be achieved through the Wnt/β-catenin signaling pathway. The Wnt pathway is important for the body to regulate cell differentiation, proliferation, and growth and plays an important role in the occurrence and development of thyroid cancer. The classical Wnt signaling is called the Wnt/β-catenin signaling pathway, which is triggered by the key effector β-catenin controlled by the Wnt protein [8]. When the Wnt pathway is activated, the phosphorylation inactivation effect of β-catenin is inhibited, resulting in the increase of β-catenin in vivo. The β-catenin protein entering the nucleus binds to TCF/LEF, activates the transcription of Wnt target genes, and eventually promotes cell differentiation, proliferation, growth, and migration [9,10]. The downstream target genes of the Wnt/β-catenin signaling pathway include cyclinD1 and

c-myc, which are common proto-oncogenes and often play a regulatory role in the growth and proliferation of cancer cells [11]. When activated, they can promote cell carcinogenesis [12]. When the Wnt signaling pathway is activated, the abnormal expression of cyclinD1 and c-myc leads to the abnormal proliferation of tumor cells. Wnt3a, the most common Wnt family ligand, has been shown to inhibit the activity of GSK-3β by binding to its receptor, thereby inhibiting the phosphorylation of snails by GSK-3β. After entering the nucleus, the snail binds to the promoter region of E-cadherin and inhibits the expression of E-cadherin, leading to the destruction of the junction between cells, which makes cancer cells more likely to migrate and metastasis [13-15]. When the Wnt pathway is activated, the inhibition of E-cadherin expression accelerates the spread of tumor cells. SFRP2 is a protein encoded by the SFRP2 gene, which can compete with the Wnt3A for cell surface receptor binding sites to inhibit Wnt signaling, thereby inhibiting tumor cell proliferation [16,17]. Studies have shown that $1,25(OH)_2D_3$ May play an anti-tumor role by promoting the demethylation of SFRP2 [18]. However, the specific mechanism is still unclear and needs further study.

3.2. Correlation between vitamin D and miRNA

Studies have shown that vitamin D also regulates miRNA expression [19]. microRNA (miRNA) is a class of non-coding single-stranded RNA molecules with a length of about 20–24 nucleotides encoded by endogenous genes, which is involved in regulating gene expression after transcription [20]. The expression of miRNAs *in vivo* is closely related to TC. A large number of studies have shown that miR-146b-5p, miR-222-3p, and Ex-miRNA423-5p are significantly highly expressed in TC [21-23]. Some studies have shown that miR-21, miR-181a, etc., such as miR-26, miR-125, etc. [24-26], can also help to identify the type of TC and the degree of disease deterioration [27,28]. miRNAs may be associated with *BRAF* V600E mutation, which is the most common genetic alteration in *PTC* [29]. Lv M *et al.* (2013) showed that high expression of miRNA-146b-5p in PTC was associated with *BRAF* gene mutation in high-risk PTC [30]. Geraldo MV *et al.* (2012) also showed that RET/PTC3 and BRAF activation upregulate miRNA-146b-5p expression [31]. Some microRNAs are regulated by the VD/VDR complex. When vitamin D binds to the VDR, it will form transcriptional regulators, which act on the vitamin D response element (VDRE) in the promoter region of target genes to regulate the expression of microRNA at the transcriptional level [32].

3.3. Correlation between vitamin D and VEGF

The growth and metastasis of malignant tumors are often closely related to the blood supply. When many tumor cells grow rapidly, new microvessels will be generated in the malignant tumor tissue under hypoxic conditions to ensure that the tumor tissue can have sufficient blood and continue to grow. Some studies have shown that vitamin D maintains VEGF concentration in the body and induces endothelial cell function [33]. VEGF, which acts on vascular endothelial cells, can promote angiogenesis and angiogenesis, increase vascular permeability, and maintain blood vessels. Under hypoxic conditions, the level of VEGF mRNA in cells is significantly increased [34]. It has been reported that VEGF may be involved in the evolution of TC and is closely related to tumor metastasis and growth [35]. There are many theories about vitamin D and VEGF. For example, Palmer HG *et al.* pointed out that $1,25(OH)_2D_3$ can reduce the expression of VEGF by up-regulating the mRNA level of thrombospondin 1 (THBS1) in cells [36]. However, after the combination of vitamin D and VDR, vitamin D regulates the expression of genes in the body, thus negatively regulating the expression of VEGF.

3.4. Correlation between vitamin D and EGFR

EGFR is a kind of epidermal growth factor receptor that exists on the surface of various cells in the body. Its

overexpression plays an important role in the evolution of malignant tumor cells. When the ligand binds to EGFR, it activates the downstream phosphatidylinositol kinase through dimerization and phosphorylation to participate in mitosis and then regulates the proliferation and differentiation of tumor cells [37]. Studies have shown that the high expression of EGFR is closely related to the degree of differentiation, invasion, and lymph node metastasis of TC [38]. Relevant studies have also shown that the positive expression of EGFR in local invasion tissues of TC is higher than that in thyroid cancer without invasion and thyroid adenoma [37]. Studies have shown that vitamin D can inhibit the RAS cascade, thereby restricting the EGFR signaling pathway [39].

3.5. Correlation between VDR gene polymorphism and TC

VDR gene has obvious polymorphism, among which *BsmI* (rs1544410), *ApaI* (rs7975232), *TaqI* (rs731236), and *FokI* (rs2228570) have been studied more frequently. In recent years, a large number of studies have found that *VDR* gene polymorphism is associated with various cancers. Penna-Martinez *et al.* (2009) linked *VDR* gene polymorphism with thyroid cancer. They showed that the alleles AA and FF of *ApaI*, *FokI*, and haplotype *tABF* were protective factors for follicular thyroid cancer [40]. Haplotype *tABF* is a risk factor for thyroid follicular carcinoma. Some studies have also found that the distribution of *VDR* gene polymorphisms varies to varying degrees among different races, ethnicities, and regions, and *rs10783219* was found to be associated with 25(OH)D levels in the Hispanic population [41].

4. Summary

Nowadays, a large number of studies have shown that vitamin D is closely related to thyroid cancer, and there are many related mechanisms. Peng W *et al.* (2016) found that $1,25(OH)_2D_3$ can inhibit the proliferation of cancer stem cells derived from thyroid cancer cells, thereby inhibiting the occurrence of TC [42]. Li B *et al.* (2020) found that $1,25(OH)_2D_3$ can inhibit the activity of human papilloma-like thyroid cells (TPC-1) by inhibiting the Ras-MEK-ERK signaling pathway, thereby promoting cell apoptosis [43]. However, Kuang J *et al.* (2012) showed that serum 25(OH)D level was not related to the occurrence, tumor size, and invasiveness of thyroid cancer [44]. Although there are many studies on the relationship between vitamin D and various cancers such as colon cancer, cervical cancer, breast cancer, etc., there is no direct and specific statement on the relationship between vitamin D and TC. Moreover, due to the wide range of effects and numerous mechanisms in the body, the clinical application of vitamin D is also limited, and it needs to be explored and evaluated in various aspects. Therefore, it can provide a safer and more effective treatment plan for clinical practice and realize the transformation from basic research to clinical application.

Disclosure statement

The author declares no conflict of interest.

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