REVIEW

Vitamin D Receptor Gene and Vitamin D Binding Protein Gene Polymorphisms in Differentiated Thyroid Carcinoma – Still an Issue

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Abstract

A deficient vitamin D status has been associated with various diseases but its correlation with different types of cancer remains of interest. Thyroid cancer is the most frequent endocrine malignancy and despite the fact that differentiated thyroid carcinoma (DTC) has an excellent survival rate (>90% 10-year survival), persistent and recurrent disease is still an issue nowadays. Epidemiological studies confirmed lower levels of vitamin D in patients with DTC and correlation of 25-hydroxy vitamin D3 [25(OH)D3] status with clinicopathologic features and poor prognosis, being considered a biomarker for aggressiveness.Vitamin D, through it active form 1α,25-dihydoxyvitamin D3 [1,25(OH)2D3] and its receptor (VDR) exerts genetic changes to both healthy and neoplastic cells thus controlling their proliferation, differentiation and apoptosis. Also, vitamin D binding protein (DBP) has been recently discovered to have many different biological functions. This review is an update on molecular mechanisms of vitamin D signaling and its association with thyroid cancer prevention, treatment and prognosis.

Keywords: thyroid cancer, 25-hydroxy vitamin D, prognosis, vitamin D receptor, VDR

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INTRODUCTION

Epidemiological studies suggest that vitamin D may have protective benefits against different types of cancer, including thyroid cancer and particularly against the differentiated subtype[1]. DTC is proved to be one of the most common endocrine cancers worldwide with an increasing incidence and an excellent prognosis with a 90% 10-year survival rate but the risk of persistent or recurrent disease urges more molecular studies[2]. The genetic basis of cancer consists of accumulation of point mutations and copy number variations which can either stimulate oncogenes activity and inhibit tumor suppressor genes[3]. Studies confirmed that epigenetic changes can have both negative as well as positive effects on cancer onset, evolution and prognosis [1, 3]. Regarding vitamin D, in addition to its classical roles on bone homeostasis, cellular research revealed that vitamin D has many extra-skeletal effects, data suggesting that its metabolism and roles are dysregulated in different types of cancer thus confirming its antitumorigenic effects[4]. Important trials such as VITAL, RECORD and ViDa randomized a large number of participants and studied prevention of cancer, cardiovascular disease, fragility fractures and were associated with a reduction in cancer incidence but none of these trials confirmed a real benefit of vitamin D supplementation on overall mortality[4,5].

In this review, we overview the genetic and molecular mechanisms through which vitamin D can exert antitumorigenic effects in thyroid cancer and underline prognostic modifications due to vitamin D supplementation. In addition to that, we discuss possible future directions for vitamin D as a adjuvant therapy in cancer patients.

MATERIAL AND METHOD

We conducted a review of literature using online databases PubMed and Embase using the search criteria: differentiated thyroid cancer, papillary, follicular, vitamin D receptor, VDR polymorphism, vitamin D binding protein.

RESULTS AND DISCUSSIONS

Vitamin D physiology

Vitamin D is a prohormone synthesized in the skin due to solar ultraviolet B photons exposure (290-315 nm). Its main forms are ergocalciferol and cholecalciferol[4,6]. Ergocalciferol (vitamin D_2) is produced from ergosterol by UVB radiation in plants. Vitamin D_3 is synthesized from 7-dehydrocholesterol (7-DHC) also by UVB radiation in the epidermis. During sunlight exposure, 7-DHC is converted into pre-vitamin D_3 which is isomerized to vitamin D_3 in the cell membrane[6,7]. Vitamin D_3 reaches extracellular space and binds to vitamin D-binding protein being first delivered to the liver. In the liver, it is converted by the enzyme vitamin D 25-hydroxylase (CYP2R1 and CYP27A1) into the major circulating metabolite, 25-hydroxyvitamin D_3 [$25(OH)D_3$][6,8]. The next step is the renal hydroxylation by the enzyme 25-hydroxyvitamin D 1-alpha-hydroxylase (CYP27B1) in the proximal tubule of the kidney to generate the active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$] or calcitriol[4,9]. Calcitriol enters bloodstream and after binding to DBP, it is delivered to target tissues where vitamin D exerts its classical actions on calcium and phosphate metabolism [10, 11]. After their production, vitamin D levels are regulated by 25(OH)D 24-hydroxylase (CYP24A1), the main inactivating enzyme producing calcitroic acid and 1,25-26,23 lactone thus closing the metabolism circle[4,10,11].

$1,25(OH)_2D_3$ exerts its activity through binding to VDR which is a nuclear receptor which mediates genomic and non-genomic effects of vitamin D[7]. The presence of VDR in all tissues explains the variety of vitamin D effects, calcitriol regulating the expression of nearly 200 genes including those involved in proliferation, differentiation, apoptosis and angiogenesis[9]. The genomic pathway consists of calcitriol binding to cytosolic VDR with further heterodimerization with retinoid-X receptor (RXR) and nuclear translocation. This complex binds to vitamin D response element (VDRE) and regulates gene expression[12]. The non-genomic pathway calcitriol binds to 1,25D-membrane-associated rapid response steroid-binding protein (1,25D-MARRS) with secondary signaling alterations[13].

VDR polymorphisms

VDR is a member of the nuclear receptors superfamily and is the exclusive mediator of the effects of calcitriol[1]. The VDR gene is located on chromosome 12q12-14 and contains two promoter regions and eight exons[13, 14]. The most studied single-nucleotide polymorphisms (SNPs) of the VDR gene are: BsmI (rs1544410 G>A) and ApaI (rs7975232 G>T) located in intron 8, FokI (rs10735810 C>T in exon 2) and TaqI (rs731236 T>C)

in exon 9. FokI is located at the 5'end of VDR gene and the rest of SNPs are at the 3'end[14]. According to data, the VDR polymorphisms are associated with a variety of diseases and have a real impact on health with a possible increase of risk to develop different types of cancer, including thyroid cancer[14]. Calcitriol shows anti-tumoral properties by enhancing cellular differentiation and apoptosis[15]. It also inhibits proliferation, inflammation, angiogenesis and invasion through VDR-mediated pathways[16,17]. Regarding VDR polymorphisms correlation with DTC, studies are still controversial. The ApaI CC and FokI TT subtypes were associated with a lower risk of follicular thyroid cancer but haplotype Tabf was associated with a higher risk for it[18]. FokI may be associated with papillary thyroid cancer (PTC) occurrence with an increased susceptibility of the variant allele (T). FokI genotype TT was also correlated with more aggressive forms of thyroid cancer (T3/T4, stage III/IV and distant invasion of PTC). Same study reveals that FokI CT/TT or TT genotype patients developed more frequently N1 staging, multifocality or tumor size ≥10 mm in PTC but with no differences in follow-up regarding persistence or recurrence rate[16]. There are of course studies that prove the opposite, VDR gene polymorphisms not being correlated with a high risk of papillary thyroid cancer in certain populations like German and Iranian[18,19]. These differences are due to the fact that ApaI and BsmI are considered to be silent SNPs since they do not change the amino acid sequence of the encoded protein and studies confirmed that the only polymorphism that can alter VDR structure and function is FokI being the only one located in a coding sequence[20]. Since FokI is incriminated in thymine to cytosine substitution (T/C) in exon 2, two different VDR isoforms are coded: the C/C allele codes the 424-amino acid isoform and the T/T allele codes the 427-amino acid protein. Accordingly, the longer VDR protein is, the lower transcription and activity in target cells it has[16,20]. $1,25(OH)_2D_3$ signaling through VDR is demonstrated to be decreased in primary thyroid cancer with metastasis and even more lost in metastatic anaplastic thyroid carcinoma thus confirming that the anti-tumoral effects of vitamin D requires the presence of VDR[18,21].

DBP polymorphisms

Vitamin D binding protein is a α2-globulin initially called „group-specific component" - Gc globulin and it transports 85-90% of vitamin D metabolites but also contributes to binding of fatty acids and to proteoglycans of lecocytes and activation of complement C5 system[22]. The DBP gene is located on chromosome 4q12-q13, encodes 474 amino acids and consists of 13 exons and 12 introns[23]. The most common SNPs are rs7041 and rs4588 located in exon 11 and correspond to the three DBP subtypes (DBP1F, DBP1S, DBP2). Gc1f and Gc1s are defined by an amino acid substitution in position 416 with substitution of aspartic acid by glutaminic acid and Gc2 is defined by threonine to lysine substitution[23]. These polymorphisms have been associated with a variety of disorders including lower levels of vitamin D[24,25]. Considering that more than 90% of bloodstream vitamin D is bound to DBP and that only free $25(OH)D_3$ can enter cells for conversion to the active form, its gene polymorphisms may influence seric levels of vitamin D. Studies correlated rs7041 and rs4588 polymorphisms with lower levels of $25(OH)D_3$ especially in subjects with Gc2 allele[26-28]. The rarest alleles of DBP (rs4588, rs2282679, rs1155563) were correlated with higher vitamin D levels thus confirming that genetic differences have an impact on vitamin D variations[23].

Regarding vitamin D binding protein association with cancer, studies confirmed that $25(OH)D_3$ and DBP polymorphisms influence the risk of breast cancer, particularly the Gc2 allele[29]. Mechanisms in cancer are based on the fact that DBP is required for macrophage activation and in the presence of tumoral tissue, Gc-globulin is hydrolyzed and activated with the sialidase of T lymphocytes and β-galactosidase to yield a powerful MAF. The conversion of Gc-globulin to Gc-MAF makes the phagocytosis of cancer cells by macrophages possible [30]. In terms with that, studies reveal that immunotherapy with GcMAF can be useful in breast cancer therapy because the macrophages ability to infiltrate tumors and the GcMAF potential to recognize, internalize and eliminate cancerous cells[31]. DBP may also act more through actin scaveging to protect tissues from the negative effects like ischemia, inflammation or mechanical injury, DBP blocking actin released from damaged cells and thus inhibiting outcomes of tissue injury[31,32]. Similar correlation have been made for prostate cancer[33], pancreatic cancer[34], lung and colorectal cancer[35]. Another study showed that DBP polymorphisms can contribute to autoimmune thyroid disease development, being correlated with Graves disease in Polish population[36]. Since thyroid cancer is considered one of the most frequent endocrine cancers with a rising incidence, it is expected

that new risk factors to be discovered. The correlation with the prognosis of thyroid cancer is based on the fact that DBP has anti-inflammatory, immunoregulatory functions and it is also involved in apoptosis and angiogenesis. The prognosis is better when DBP levels are higher[37]. A different research determined an inverse correlation between DBP expression and thyroid cancer staging. Lower or negative DBP staining was associated with a more aggressive staging and phenotype [37]. DBP has been demonstrated to lower thyroid cancer growth and higher DBP levels correlated with a better prognosis[38,39,40,41]. Also, when DBP was overexpressed in papillary thyroid cancer cell lines, n important reduction in cell proliferation and migration was noticed[37].

Studies confirmed multiple biological functions of DBP but its major role is that of regulating free and total levels of vitamin D. According to the free hormone hypothesis, only free $25(OH)D_3$ can enter cells but in some tissues, the system based on megalin/cubilin takes up $25(OH)D_3$ bound to DBP [42]. The actual function of DBP has been confirmed using knockout mice. In these mice vitamin D metabolites are normal, they do not show signs of vitamin D deficiency unless started on a vitamin D deficient diet and have normal $1,25(OH)_2 D_3$ tissue levels as well as markers of vitamin D function (TRPV6, calbindin 9k, PMCA1b, TRPV5). In terms with that, DBP does not appear to be essential for getting vitamin D into cells but it represents a reservoir for the vitamin D metabolites thus lowering the vitamin D deficiency risk when skin synthesis is compromised[42,43]. Regarding supplementation, it was shown that $25(OH)D_3$ levels were higher in subjects with the major homozygous rs7041 genotype and after supplementation, the $25(OH)D_3$ concentration was higher in people with homozygous major genotype rs4588 and rs7041 by comparison to other genotypes[44].

These results clearly indicate that DBP and VDR genetic variability is essential in determining vitamin D status which in turn is an important prognosis factor in differentiated thyroid cancer.

Although trials suggest that the use of vitamin D in thyroid cancer prevention and for a better prognosis is promising, in practice there is a long way to go since there are some therapeutic limitations in using large doses of vitamin D. One of the main inconveniant is the high risk of hypercalcemia and research is directed towards developing agonists of VDR that do not induce this side effect but keeps its anticancer properties[45]. Some of this potential analogs are metabolites of CYP11A1-driven alternative pathway which can exert similar anti-proliferative effects with less calcemic properties[46]. Another mechanism to avoid hypercalcemia is to increase calcitriol levels in cancer cells since CYP24A1 enzyme which degradates calcitriol into inactive calcitroic acid is frequently overexpressed in many cancers thus inhibiting it might lead to higher calcitriol levels in tumor cells[47]. Also, studies confirm that levels of CYP27B!, VDR, CYP11A1 in cancer cells slowly decline with cancer progression and the eficiency of vitamin D could be limited to the early stages only[45-47].

CONCLUSIONS

Thyroid cancer has experienced a continuous rising incidence but with a relatively constant mortality rate. This could be secondary to extensive ultrasound screening and increased adresability but this could be the result of genetic variability in VDR and DBP genes which can alter proliferation, survival, differentiation and apoptosis in cancer cells. Vitamin D showed protective antineoplastic effects in cultured cells and animal model studies thus future directions are oriented towards a vitamin D based therapy as an adjuvant treatment in order to prevent or improve prognosis of thyroid cancer. Literature is still studying vitamin D based pathways in thyroid cancer but data is inconclusive needing further evaluation since vitamin D supplementation is simple and inexpensive. There is growing evidence that DBP and VDR play an important roles in cancer, directly through its polymorphisms or indirectly altering vitamin D status. Therefore analysis of SNPs panel could be important in order to establish subjects with high risk of thyroid cancer and thereby prevent, treat and improve prognosis at an early stage.

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