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Vitamin D in thyroid tumorigenesis and development

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Abstract

Besides its classical role in bone and calcium homeostasis, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), the active form of vitamin D, has many non-classical effects; antiproliferative, anti-apoptotic and prodifferentiating effects of $1,25(OH)_2D_3$ have been described in several tumour types in preclinical models. This review focuses on the insights gained in the elucidation of the role of

Abbreviations: $1,25(OH)_2D_3$, 1α,25-dihydroxyvitamin D_3; $25\text{-}OHD_3$, 25-hydroxyvitamin D_3; ATC, anaplastic thyroid cancer; CDK, cyclin-dependent kinase; CDKI, cyclin-dependent kinase inhibitor; CEA, carcinoembryogenic antigen; CT, calcitonin; CYP24A1, 24-hydroxylase; CYP27B1, 1α-hydroxylase; DBP, vitamin D binding protein; DC, dendritic cells; DIT, diiodotyrosine; DTC, differentiated thyroid cancer; Duox, dual oxidase; ER, estrogen receptor; FA, follicular adenoma; FGF23, fibroblast growth factor-23; FNAC, fine needle aspiration cytology; FTC, follicular thyroid cancer; GPCR, G-protein coupled receptor; H&E, haematoxylin and eosin; H_20_2, hydrogen peroxide; HAT, histone acetyltransferase; HDAC, histone deacetylase; HDACI, histone deacetylase inhibitor; HPT, hypothalamic-pituitary-thyroid; KO, knockout; MIT, monoiodotyrosine; MTC, medullary thyroid cancer; NIS, sodium iodide symporter; PDS, pendrin; PDTC, poorly differentiated thyroid cancer; PMCA, plasma membrane calcium ATPase; PPI, proton pump inhibitor; PTC, papillary thyroid cancer; PTH, parathormone; Rb, retinoblastoma; RT-PCR, reverse transcriptase–polymerase chain reaction; RXR, retinoid X receptor; SAHA, suberoylanilide hydroxamic acid; T3, tri-iodothyronine; T4, thyroxine; Tg, thyroglobulin; I-Tg, iodinated thyroglobulin; TH, thyroid hormone; TKI, tyrosine kinase inhibitor; TPO, thyroid peroxidase; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone; TSHR, thyroid stimulating hormone receptor; US, ultrasound; VDR, vitamin D receptor; VDRE, vitamin D responsive element; VEGF, vascular endothelial growth factor; WT, wild type.

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$1,25(OH)_2D_3$ in the normal thyroid and in the pathogenesis, progression and treatment of thyroid cancer, the most common endocrine malignancy. An increasing amount of observations points towards a role for impaired $1,25(OH)_2D_3$-VDR signalling in the occurrence and progression of thyroid cancer, and a potential for structural analogues in the multimodal treatment of dedifferentiated iodine-resistant thyroid cancer. A role for vitamin D in thyroid-related autoimmunity is less convincing and needs further study. Altered $1,25(OH)_2D_3$-VDR signalling does not influence normal thyroid development nor thyrocyte function, but does affect C-cell function, at least in rodents. If these findings also apply to humans deserves further study.

1. Introduction

1.1. The thyroid

1.1.1. The thyroid as an endocrine gland

The main function of the thyroid consists in the synthesis, storage and secretion of thyroid hormone (TH), thyroxin (T4) and tri-iodothyronin (T3). TH has biological effects on virtually every tissue and cell type, affecting growth, development and metabolism, and is indispensible for normal life, from intra-uterine to older age, affecting cellular respiration, oxygen consumption, regulation of intermediary metabolism (carbohydrates, lipids, proteins), maturation and differentiation. As such, TH is required for normal growth and development of the foetal and neonatal brain, myelination, cell differentiation, migration and signalling (Bernal J, 2005; Werner et al., 2005).

THs are amino acid (tyrosine) derivative iodine-containing hormones (Fig. 1). T4 and T3 represent respectively 80% and 20% of the secreted TH. In the blood circulation the majority of TH is bound to proteins (thyroxin binding globulin and (pre)albumin). Only a very small proportion (0.03% for T4 and 0.3% for T3) is unbound and physiologically active. T3 exhibits the highest affinity for the TH receptor, in contrast to T4 which is therefore considered a pro-hormone. TH exerts its effect through binding to the nuclear TH receptor. Following homodimerisation or heterodimerisation with retinoic X receptors (RXR), the complex binds to thyroid response elements (TREs) in the regulatory regions of target genes. In the presence of T3, corepressors are released and coactivators are recruited, assisting in the transcription of the target genes.

Calcitonin is a 32-amino acid hormone and acts through binding to the calcitonin receptor, a G-protein coupled receptor (GPCR). It is involved in the reduction of serum calcium levels by increasing renal calcium excretion and by inhibiting osteoclast-mediated bone resorption (Zaidi et al., 2002). In human physiology calcitonin is probably redundant, as acquired deficiency (e.g. after thyroidectomy) or excess (e.g. in case of medullary thyroid cancer) does not give rise to changes in the calcium-phosphate homeostasis. However, calcitonin plays an important role in daily clinical endocrine practice, as it used as a sensitive tumour marker for the diagnosis and follow-up of medullary thyroid cancer (Costante et al., 2009).