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Review

The Role of Vitamin D in Cancer Prevention: A Review of Molecular Mechanisms

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ABSTRACT

Vitamin D, also known as the sunshine vitamin, is produced in the body by exposure to sunlight. The most well-known function of vitamin D is its effects on bone health, and bone problems are the most common disease caused by vitamin D deficiency. However, recent studies have shown that vitamin D is involved in many different cellular mechanisms, and its deficiency influences a variety of diseases. One of these important diseases in which the effects of vitamin D are being investigated is cancer. Many studies have revealed tumor inhibitory properties of vitamin D. It triggers different pathways in different cancer types to inhibit the progression of the disease. There are strong suggestions that vitamin D can be used in the prevention of cancer, and can be used as a therapeutic agent in the treatment of cancer. In this review, the anti-cancer properties of vitamin D for cancer types were examined.

Keywords: Calcitriol, cancer, vitamin D, vitamin D receptor

Vitamin D is one of the essential elements for a healthy body. The body's vitamin D needs are provided either through nutrition or directly through the skin.[1] Although it can be taken into the body through nutrients, as in most vitamins, it is known that vitamin D is mainly produced in the skin through ultraviolet radiation. The main function of vitamin D in the body is known as the absorption of calcium and phosphorus, which promotes bone growth. However, in addition to calcium homeostasis, recent studies have revealed many different mechanisms in the body in which vitamin D is involved. It can be said that the studies investigating the different roles of vitamin D in cell functioning are based on the discovery of the nuclear vitamin D receptor (VDR), which is the steroid hormone.[2,3] It has been shown that the VDR-mediated action of vitamin D is at the transcriptional level, which means it plays a role in controlling hundreds of genes.[4,5] Since the introduction of the nuclear receptor for vitamin D, it has been revealed that vitamin D plays a role in cell proliferation, differentiation, and apoptosis in different cell types. The protective and preventive roles of vitamin D against different health problems, especially cancer, are being investigated. Cancer is known to be one of the most important health problems in our era.[6] The role of 1,25-$(OH)_2$D-VDR complexes at the transcriptional level are described as activation of tumor-suppressor genes and repression of many proto-oncogenes. In this review, the anti-proliferation, pro-apoptosis, and pro-differentiation effects of vitamin D on different cancer types were examined.

VITAMIN D METABOLISM AND MECHANISM OF ACTION

There are two forms of vitamin D: vitamin D_2 and vitamin D_3. Vitamin D_2, also known as ergocalciferol, is found in plants, while vitamin D_3, also known as cholecalciferol, is found in animals and is also produced in human skin.[1] Normally, vitamins are the nutrients that cannot be produced in the body, so they must be taken through food. However, the form of vitamin D_2 is not sufficient for human metabolism. The primary source of vitamin D for the human body is vitamin D_3, which is synthesized in the epidermis.[7] The biosynthesis of D_3 begins with the

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photoisomerization of 7-dehydrocholesterol (7-DHC), a molecule found abundantly in the epidermis, by exposure to ultraviolet-B (UV-B) radiation.[7,8] UV-B radiation (280-320 nm) breaks the β-ring of 7-DHC, which results in the formation of previtamin D_3, which is a biologically inert molecule.[4] After this process, D_3 is hydroxylated to 25-hydroxycholecalciferol [(25(OH) D (calcitriol)] in the liver by the 25-hydroxylase enzymes found in the liver. Then, 25(OH)D is converted into 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) by 1-alpha-hydroxylase (1α-hydroxylase) in the kidneys, which is the active form of vitamin D.[4,7–9] Although the biologically most active form is $1,25(OH)_2D$, the form of 25(OH)D is used to test vitamin D levels in the body. This is because serum 25(OH)D has a higher circulating level as a result of its more stable structure and much longer half-life.[10]

It has been shown that an active form of vitamin D, $1,25\text{-}(OH)_2D$, stimulates both genomic and nongenomic signaling pathways to regulate different metabolisms in the body.[2,8] Nongenomic activity of $1,25\text{-}(OH)_2D$ is not related to the transcription and it is mediated by the membrane vitamin D receptor (m-VDR).[8] Binding of $1,25\text{-}(OH)_2D$ to m-VDR triggers various signaling cascades. The most well-known effect of the $1,25\text{-}(OH)_2D$-mVDR complex is rapid Ca^{2+} transport in the intestine, which can occur with the activation of protein kinase C, a signaling pathway. As a result of this activation, voltage-gated Ca^{2+} channels begin to open rapidly, and intracellular Ca^{2+} increases.[11] The process, movement of Ca^{2+}, balances the level of Ca^{2+} in the body and so enhances bone health, which is a leading role of vitamin D in the body. The other pathway that vitamin D follows is the genomic way mediated by VDR which belongs to the nuclear hormone receptor superfamily of a transcription factor.[2] This receptor, which is in the steroid form, plays a role in the regulation of many different gene expressions, as a result of interaction with $1,25\text{-}(OH)_2D$.[2] This ligand-dependent interaction of $1,25\text{-}(OH)_2D$-VDR causes a conformational change on the surface of VDR to the following interactions. One of them is the association with retinoid X receptor (RXR).[12] It is known that the VDR building complex with RXR specifically binds to different regions in DNA known as vitamin D response elements (VDREs) located in the promoter region of target genes.[2,4] Thereafter, co-modulators are involved in the process to induce or inhibit gene expression. The co-modulator that will interact with the VDR/RXR complex is determined depending on the target gene; it can be either co-activator or co-repressor. All of this VDR-regulated transcription mechanism in which hundreds of genes are regulated is dependent on cell-specific cellular action of $1,25\text{-}(OH)_2D$. It has been observed that the metabolic pathway of vitamin D in the manner of transcription is involved in many different mechanisms in the body; proliferation, apoptosis, differentiation, anti-inflammatory, and immunomodulatory actions. A study on mice has revealed that VDR function plays a role in cancer progression. In the study, VDR was knocked out in tumor cells in one group of mice, while the other group was left as a wild-type. As a result of the study, it was observed that tumors in knockout mice progressed much faster than in wild-type groups.[13]

ANTI-CANCER ACTIONS OF VITAMIN D

Cancer is one of the major diseases in the world that humanity suffers from. Cancer is described as a disease in which cells grow and divide uncontrollably in the simplest term. Mutations in the DNA structure that trigger the cell cycle progression defects are known as the main cause of cancer. Mutagens in the environment such as chemicals, and UV lights cause damage to the DNA structure, which results in disorders in many different mechanisms involved in cell progression such as cell cycle checkpoints, and translocation in DNA. These abnormal cancerous cells can grow and divide without any signal from the environment which is necessary for normal. In addition to this, cells do not undergo apoptosis when it is necessary, although there is a signal. There have been numerous studies on potential agents that inhibit the proliferation of cancer cells or stimulate apoptosis to prevent the growth of cancer. Vitamin D is considered one of these potential agents in cancer treatment. Preclinical studies have proposed the effective role of vitamin D in different cancer types. Epidemiological studies have shown that sunlight exposure adversely affects the progression of breast cancer.[2,12,14] In addition, there are studies on colorectal cancer in animal models that have revealed that sufficient levels of vitamin D decrease the incidence of colon cancer.[15]

There are three important pathways in that vitamin D plays a role in these effects; proliferation, apoptosis, and differentiation.

Cell Proliferation

Anti-proliferative activity of calcitriol on cells has been revealed. The mechanism of calcitriol that prevents the proliferation of tumor cells is based on interfering with the cell cycle.[16,17] The regulatory mechanisms of cell cycles are controlled

by cyclins, cyclin-dependent kinases (CDKs), and cyclin-dependent kinases inhibitors (CKIs). Cyclins are the protein molecules that activate the pathway of CDKs and form a complex with them. This cyclin-CDK complex regulates transitions between different cell cycle phases through phosphorylation.[18] These cell cycle mechanisms are one of the targets of calcitriol when inhibiting growth. As a result of the functioning of calcitriol, it was observed that cells are arrested in the G_1/G_0 phase, and cannot pass through the S phase. This is because calcitriol can reduce or increase the activity of CDKs, especially decreasing CDK2 activity.[16,19] As mentioned earlier, the regulatory effect of vitamin D on genes has been demonstrated by many studies. Again, the other pathway that vitamin D follows to prevent proliferation is the expression of CKIs, p21, and p27.[2,20] Expression of these two genes blocks the transition to the S phase, which again causes the accumulation in the G_1 phase.[21] This pathway is accepted as major vitamin D-mediated cell-cycle arrest. The other important action of calcitriol is known as the trigger for phosphorylation of retinoblastoma protein (Rb), which is responsible for the G_1 checkpoint.[19,22] The key function of pRb in cell progression is the negative regulation of the cell cycle by repression of gene transcription required for the process.[23] Phosphorylation mediated by calcitriol activates pRb protein which results in arrest at the G_1 phase.

Apoptosis

Apoptosis, also known as programmed cell death, is the process of self-destruction of cells. Studies on cancer biology have revealed that defects in the apoptosis mechanism bring about tumor initiation, progression, and metastasis. The most prominent regulators of apoptosis pathways are known as the anti-apoptotic gene *Bcl_2*, and the pro-apoptotic gene *Bax*, which influence the activity of intracellular proteases (caspases).[2,24,25] The results of the research have revealed strong evidence that calcitriol induces apoptosis through these regulators. Different studies on breast cancer have reported that MCF-7 cells, one of the breast cancer cell lines, treated with calcitriol showed cytoplasmic disruption, mitochondrial fragmentation, and hyperchromatic, irreversible condensation of chromatin, called pyknotic nuclei [20,27], which are the basic apoptosis morphologies. It has been shown that this vitamin D-mediated apoptosis in MCF-7 cells is the result of suppression of the *Bcl_2* expression.[2,26,27] Another study in which the growth of MCF-7 human breast cancer cells was stimulated by insulin-like growth factor-I (IGF-I) showed the anti-apoptotic property of IGF-I was blocked by treatment with vitamin D analogs.[28] Moreover, higher levels of apoptosis were observed when vitamin D was combined with other molecules. For example, it has been shown that the combined treatment with melatonin and vitamin D increased the Bax/BCL-2 ratio significantly, by up-regulation of Bax and down-regulation of BCL-2.[29] Antiestrogen 4-hydroxytamoxifen is another molecule that potentiates the apoptotic effect of vitamin D in MCF-7 cells.[30] In addition to them, the effect of calcitriol on caspase activity is also being examined. Studies suggest that vitamin D-mediated apoptosis in MCF-7 cells is independent of the caspase. However, some sources propound the Ca^{2+} regulation of vitamin D is associated with proteases.[31] Consequently, there is no definite conclusion on this issue, it remains ambiguous.[2,26,27]

Differentiation

Cell differentiation can be described as a specialization of cells. When cells differentiate they gain more specific functions and properties. In the case of cancer, with the development of stem cells, studies on the differentiation of cancerous cells came into prominence. It has been indicated that the differentiation status of tumor cells is associated with the aggressiveness of the tumor, that is so, tumor cells obtained by biopsy are assessed for anaplasia, a term for poorly differentiated or undifferentiated cells, to grade cancer.[32,33,34] The grading is based on whether the cancer cells resemble normal cells. If the tumor cells are well-differentiated, they behave like normal cells more. Poorly differentiated tumor cells, on the other hand, are more aggressive and tend to grow and spread more rapidly.[35] Studies on vitamin D have shown the pro-differentiation effects of calcitriol. It promotes a variety of tumor cells to differentiate in different ways. One study on human myelomonocytic leukemia cell lines has revealed that calcitriol induces the differentiation of myeloid leukemic cells into monocytes/macrophage by the transcriptional activation of the Cdk inhibitor p21. Firstly it has been revealed that calcitriol induces the p21 gene transcriptionally in the VDR-dependent manner, which facilitates the differentiation of cell lines.[36] For colon cancer, the Wnt/ß-catenin signaling pathway comes forward in the differentiation induced by calcitriol. In colon cancer, the Wnt/ß-catenin signaling pathway is abnormally activated by the mutations in different genes, which is responsible for the initiation and progression of cancer via the loss of differentiation properties. Studies have

demonstrated that calcitriol has an antagonistic effect on the Wnt/ß-catenin signaling pathway. VDR as a transcriptional factor binds to the ß-catenin protein and blocks their function, which is the gene expression. It has been also shown that calcitriol induces the expression of the gene that encodes the inhibitor of Wnt/ß-catenin signaling.[37] In the differentiation action of vitamin D, there are different pathways for various cancer types, as shown in the examples.

In conclusion, epidemiological studies indicate that inadequate levels of vitamin D are associated with an increased level of a variety of cancer, while a high level of vitamin D provides a better prognosis. Extensive research has emphasized the anti-proliferative, pro-apoptosis, and pro-differentiation properties of calcitriol as mentioned in the article. The data described above clearly shows the importance of vitamin D for the body as well as cancerous tissue. Researchers provide evidence about the tumor-inhibitory effects of vitamin D by stimulating different cellular mechanisms in different cancer types. It can be said that vitamin D has a grand potential as a therapeutic agent in the treatment of cancer. The precise effect of this potential needs further studies. Combining different molecules with vitamin D or its analogs to be used as a drug in cancer treatment can yield successful results.

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