ANTICANCER RESEARCH *39*: 3353-3363 (2019)
doi:10.21873/anticanres.13478

Review

Potential Molecular Mechanisms of the Anti-cancer Activity of Vitamin D

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Abstract. *Vitamin D, or more precisely its active metabolite calcitriol (1,25-$(OH)_2D_3$), plays a fundamental role in bone metabolism and differentiation as well as in intestinal absorption of calcium and regulation of calcium-phosphate metabolism. Recent decades have brought about the discovery of the role of calcitriol in processes regulating cell differentiation, proliferation, angiogenesis and apoptosis. This creates the potential for numerous therapeutic applications of vitamin D in diseases associated with autoaggressive immune responses or in cancer. This study presents selected issues regarding current knowledge of the anti-cancer mechanisms of vitamin D.*

The discovery that most tissues have receptors for vitamin D was a breakthrough in understanding its role in cancer development. A long-term vitamin D deficiency probably increases the risk of cancer (1-5). The hypothesis that vitamin D_3 deficiency is linked to cancer development is supported by the results of experiments on animal models as well as epidemiological studies investigating the relationship between exposure to UVB radiation and cancer survival (6-8). Vitamin D protects the genome against the accumulation of mutations underlying neoplastic transformation and cancer progression. At the same time, owing to the anti-tumour activity of calcitriol and its analogues, these compounds can be used alone (promyelocytic leukaemia) or in synergy with other anticancer drugs, mainly cytostatics (9, 10). This means that the dose of cytostatics can be reduced, thereby reducing the risk of side effects following chemotherapy. For example, treatment with calcitriol in combination with carboplatin, dexamethasone or paclitaxel has been proven effective against both androgen-dependent and androgen-independent prostate cancer (10, 11). As in the case of prostate cancer (PCa), the therapeutic efficacy of calcitriol has also been confirmed in both hormone-dependent (oestrogen-receptor-positive) and oestrogen-receptor-negative breast cancer (12), as well as colorectal and head and neck cancer (13-17). The mechanism of the anti-neoplastic activity of vitamin D and its derivatives may vary depending on the type of cells and tissues. The excessive supply of calvium is itself considered by some researchers to be a PCa risk factor, and a low concentration of vitamin D may additionally increase the risk of prostate cancer by reducing production of 1,25-$(OH)_2D_3$. Moreover, a high concentration of Ca may inhibit the release of PTH (parathyroid hormone), which regulates the conversion of $25(OH)D_3$ to 1,25-$(OH)_2D_3$ in the kidneys (18).

Thus, there is a clear dependency between calcium supply and the concentration of $25(OH)D_3$ (19, 20). The mechanism of the biological activity of calcitriol is still quite difficult to explain, because the degree of inhibition of proliferation, apoptosis and cell cycle arrest depends on many different factors, primarily the degree of cell differentiation, the occurrence of growth factors, the dosage of vitamin D, and calcium concentrations in the intra- and extracellular environment.

Vitamin D – Cell Cycle Regulation

The growth and proliferation of hormone-dependent epithelial cells in health and disease depend on many intracellular signal transmission pathways. The signalling pathways may be activated by insulin-like growth factor 1 or 2 (IGF-1, IGF-2) or epidermal growth factor (EGF) and by pro-inflammatory cytokines such as tumour necrosis factor (TNF), interleukin-2 (IL-2) or granulocyte-macrophage colony-stimulating factor (GM-CSF). There are also pathways specific for tumours, called proliferative signalling pathways (21). The activation of transcription signalling pathways results in the modulation of numerous target genes which regulate proliferation of cells and genes influencing processes which mediate cell transformation

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Key Words: Vitamin D, nVDR receptor, antitumor effect, review.

in normal and proliferative tissues, such as inflammation, angiogenesis, cell mobility, and the ability to metastasize. These may lead to cell transformation and tumour formation. Vitamin D, primarily, influences calcium and phosphate balance, but in recent years a number of publications have highlighted its multi-faceted activity associated with the presence of the vitamin D receptor (VDR), including an anti-tumour effect (22). Although several mechanisms have been suggested to explain the inhibitory effect of $1,25(OH)_2D_3$ on the cell cycle, no convincing data have been presented on the primary mechanism of the regulation of cell division. The most commonly mentioned mechanisms of cell cycle regulation by vitamin D are presented below.

In order for the cell to pass from phase G_1 to phase S, in which DNA synthesis takes place, retinoblastoma (Rb) protein phosphorylation is required to activate transcription factors of the E2F family, which activate transcription of many genes, including cyclins E and A. Rb phosphorylation is catalysed by specific cyclin-dependent kinases (CDKs), whose activity is inhibited by p21 and p27 proteins. The complex of $1,25(OH)_2D_3$ and VDR binds to the regulatory site in the promoter region of the p21 and p27 genes, intensifying their expression, which leads to inhibition of CDKs, lack of Rb phosphorylation, and cell-cycle arrest in the G_1 phase (23, 24). The antiproliferative effect of vitamin D also involves modulation of intracellular kinase pathways (p38 MAPK – P38 mitogen-activated protein kinases, ERK – extracellular signal-regulated kinases, and PI3K – phosphoinositide 3-kinase) and repression of the proto-oncogene Myc, which plays the key role in cell proliferation (24).

$1,25(OH)_2D_3$ and its analogues are known to cause rapid and concentration-dependent (10^{-10}–10^{-8} M) activation of phospholipase C, which is responsible for the hydrolysis of inositol lipids. This results in activation of protein kinase C (PKC) which plays an important regulatory in the control of gene expression; activates expression of the gene encoding Raf1 – a kinase of mitogen-activated kinase (MAPK). This is followed by an increase in the activity and phosphorylation of two members of the kinase family, MAPK-1 and MAPK-2, associated with regulation of the growth of many cells (25). In the context of long-term processes, PKC plays a significant role in cell differentiation, mobility and metastasis (2, 12).

The anti-proliferative effects of $25(OH)D_3$ correlate with the expression of endogenous 1-α-hydroxylase, whose activity is reduced in cancer cells compared to healthy prostate cells (5, 26, 27). The discovery of reduced activity of 1-α-hydroxylase in prostate cancer (PCa) epithelial cells provided an explanation for the locally reduced production of $1,25(OH)_2D_3$, which results in the inhibition of cell differentiation and an increase in cancer invasiveness (27).

Another type of interaction of regulatory pathways caused by activation of the EGF (epidermal growth factor) receptor is the induction of other biological processes (apart from proliferation) in tumour transformation, such as inflammation, tumour angiogenesis, and infiltration, through stimulation of cyclooxygenase 2 (COX-2) and production of prostaglandin PGE2 (28, 29). It has been demonstrated that calcitriol may also inhibit the activity of cellular growth stimulators – prostaglandins. It has been shown that treatment of theprostate cancer cell line LNCaP with $1,25(OH)_2D_3$ limits PGE2 synthesis (through inhibition of COX-2) and increases its inactivation (by stimulating prostaglandin dehydrogenase (15-PGDH), which transforms prostaglandins into ketone derivatives) (29).

Other mechanisms of cell cycle regulation by $1,25(OH)_2D_3$ involve inhibition of mitogenic signals transmitted by growth factors such as EGF and stimulation of the pathways of transforming growth factor β (TGF-β) and insulin-like growth factor-binding proteins (IGF-BP), *e.g.* IGF-BP3 (30), as well as the aforementioned reduction of the expression of *c-Myc* gene, which plays a significant role in cell proliferation. In normal cells, the expression of c-Myc gene is correlated with an increase in the concentration of the c-Myc protein. This leads to metabolic disorders and tumour formation. Abnormal oncogene structure has been observed in many tumours.

Moreover, in cells exposed to calcitriol analogues, a reduction has been observed in the activity of ornithine decarboxylase, an enzyme necessary for DNA synthesis, as well as a decrease in the secretion of IL-6 (interleukin-2) and IL-8 (interleukin-8), which are known mitogens for keratinocytes (31).

One of the characteristic features of tumour cells is increased activity of telomerase. The enzyme is active in about 80-90% of all tumours and is responsible for the reconstruction of telomeres. It is a specialized DNA polymerase with reverse activity to that of transcriptase, which synthesises telomeric repetitions *de novo* (32, 33). The enzyme is composed of two key sub-units: a sub-unit consisting of an RNA chain (reverse transcriptase, RT) and the equally important sub-unit telomerase reverse transcriptase (TERT) (33-35). TERT has the ability to elongate telomeres in order to maintain the integrity of chromosomes, and in some sense regulates cell life span (34). It plays a significant role in proliferation, differentiation, carcinogenesis and ageing of cells (35). The RT and TERT sub-units together make up the enzyme core. Calcitriol and its analogues inhibit the high telomerase activity seen in human cancer cells by decreasing TERT mRNA expression. Induction of miR 498 gene by calcitriol is implicated in the down-regulation of TERT mRNA in some cancer cells (24).

Nuclear Vitamin D Receptor (nVDR)

Vitamin D initiates or suppresses the transcription of genes after binding to its receptor, VDR, which belongs to the nuclear receptor superfamily and acts as a ligand-activated transcription

factor (1, 5). It is composed of the conserved N-terminal DNA-binding domain and an α-helical C-terminal ligand-binding domain. Binding of calcitriol to the ligand-binding domain causes heterodimerization of VDR with retinoid X receptor (RXR). This is necessary for binding to a DNA sequence known as the vitamin D response element (VDrE), located in the promoter region of the $1,25(OH)_2D_3$ target genes (36, 37). These include the genes for amphiregulin – an epithelial growth factor stimulating the development of head and neck, and breast cancer (15, 38), the cell cycle inhibitor protein p21, apoptosis regulator protein bcl-2, and p53, a protein suppressing oncogenes that control cell growth, such as c-fos (39). Following binding to certain VDrE sequences and activating proteins, VDR acts as a transcription factor, inducing cell growth and proliferation as well as apoptosis (5). A significant discovery was the presence of VDR in cancerous cells, including breast cancer cells (40), which suggests that these cells may be susceptible to the effects of vitamin D. Advanced research is currently underway to introduce calcitriol and especially its analogues in the treatment of patients with breast, prostate, colorectal and head and neck cancer, as well as in combination therapy that is already used for acute promyelocytic leukaemia (9, 13, 15, 41-45). On the other hand, subtle allelic variations of the VDR gene located on chromosome 12 (12q13.1) are relatively common in the population (46). It has been demonstrated that polymorphisms in the VDR gene can play a significant role in the formation of cancers (47-49). Thus far, over 60 different polymorphisms localized in the promoter region, the region of exons 2-9, and the 3'UTR region have been detected. These can be single nucleotide polymorphisms (SNP) or functional polymorphisms, but also repeats (*e.g.* BsmI (G/A) (rs1544410), ApaI (G/T) (rs7975232), TaqI (T/C) (rs731236), Fok1 or Poly (A) in the 3'UTR region) (50). All changes in VDR can affect mRNA stability, and hence the translation of VDR mRNA. For example, the GG genotype of the ApaI (G/T) polymorphism influences the efficacy of chemotherapy in patients with non-small cell lung cancer (NSCLC). The authors of the study even suggested that the ApaI polymorphism in the VDR gene may prove to be a good marker for the use of individualized chemotherapy for NSCLC (51).

Thus, both normal and mutant VDR receptors are very important factors in the activity of vitamin D and its analogues in the process of tumorigenesis.

Vitamin D – Apoptosis Induction

Another possible pathway of the anti-tumour function of calcitriol is apoptosis induction, which has been demonstrated in tumour cells of the prostate, breast and large intestine (22, 52). However, the exact mechanism of this activity has not yet been identified. During apoptosis, the cell undergoes biochemical changes involving expression of specific genes (bax, bcl-2, TRPM-2/clusterin, cathepsin B) as well as morphological changes (cytoplasm condensation, DNA fragmentation or the formation of apoptotic bodies) (39, 53). Vitamin D treatment of colon cancer cells activates the expression of cystatins, endogenous inhibitors of cysteine proteases of the cathepsin family (54). Cathepsin B participates in the carcinogenesis process on many levels of tumour transformation, invasion and metastasis. Cathepsin B has been shown to enter into the cell nucleus and activate apoptosis (55). Most research studies have confirmed that the activity of cysteine endopeptidases can be measured as marker of tumour aggressiveness and their inhibitors as markers in diagnosis and monitoring of cancer therapy (56-58). In prostate epithelial cells, clusterin expression increases immediately after castration, reaching its maximum level in rat prostate cells 3-4 days after the procedure, which is associated with the beginning of mass cell death. At the same time, clusterin may be a marker of cell death and an apoptosis promoter. According to Zhu *et al*. (59), vitamin D may express its antitumoral effect by mediating the MEG3/clusterin signaling pathway. Proteins belonging to the bcl-2 family (B-cell CLL/lymphoma 2) play the key role in apoptosis regulation. Despite the similarity in their structure, different proteins in this family play opposite roles in the regulation of apoptosis. They may block apoptotic signals or cause an increase in the permeability of the external mitochondrial membrane to release of cytochrome c and activate caspases and cell death (60-62). Moreover, in the early stages of carcinogenesis, over-expression of protein bcl-2 protects cells with lethal mutations and contributes to genetic destabilization, a characteristic of tumours (62). The reduced efficiency of apoptosis in tumour cells may also be linked with mutations in the *bax* gene, one of the main effectors of p53-induced apoptosis (63). The co-dependency between the occurrence of *TP53* gene mutations in cancers and disordered balance of the expression of bcl-2-bax is very often observed (64). Calcitriol has been found to decrease Bcl-2 expression in breast cancer cell lines (65). Ohnishi *et al*. have shown that vitamin D-induced cell-cycle arrest is mediated by inhibition of several key proteins which regulate the G_1/S phase and by up-regulating TP53 expression (66).

Vitamin D – Inhibition of Invasiveness and Metastasis of Tumours

The colonization of tissues by tumour cells does not seem to be accidental. Tumour cells show some preferences for settling in a given organ (67). This probably takes place due to chemotaxis of tumour cells in connection with the level of cytokines produced by the cells, due to exceptionally favourable environmental conditions in the organ or to selective adhesion of tumour cells into the endothelial cells of the vessels in the organ. The over-expression of some

integrins suggests that integrins are the main molecules involved in selective adhesion (68). *In vivo* research on animal models of prostate and bladder tumours has shown that $1,25(OH)_2D_3$ reduces the invasiveness of tumours (69-71). Suggested mechanisms of the 'anti-invasive' function of vitamin D include inhibition of metalloproteinase and serine protease activity and increase E-cadherin expression, as well as reduction of the expression of integrins a6 and b4. E-cadherin belongs to the superfamily of calcium-dependent adhesion molecules. Changes in the expression and regulation of these proteins are strictly linked to tumour invasiveness. The loss of E-cadherin activity has been correlated with the clinical level of prostate cancer malignancy and the capacity to metastasize, as well as with poor overall survival of patients (72-74).

Vitamin D – Angiogenesis Inhibition

Another anti-tumour mechanism that has been described for $1,25(OH)_2D_3$ is the inhibition of angiogenesis, *e.g.* in prostate cancer, both directly through the impact of tumour endothelial cells and indirectly through a reduction in the amount of COX-2-generated prostaglandin E2 (PGE2) (24, 31). One of the factors which induce angiogenesis is IL-8. The main functions of IL-8 are chemotactic attraction of neutrophils to the site of inflammation and stimulation of their bactericidal properties. Moreover, IL-8 plays a crucial role as an agent stimulating the formation of new blood vessels. In prostate cancer cells, $1,25(OH)_2D_3$ has been shown to inhibit the activation of *IL-8* gene transcription, most likely through interaction with the p65 subunit of nuclear factor kB (NF-kB). Other mechanisms of action of calcitriol through VDR include suppression of the expression of vascular endothelial growth factor (VEGF), angiopoietin 1 and platelet-derived growth factor (PDGF) and transcriptional repression of hypoxia-inducible factor 1 alpha (HIF1α) (75).

It is also worth noting that the presence of a physiological concentration of calcitriol is essential for a normal T lymphocyte-dependent immune response, which has been shown to depend on the presence of VDR (increased risk of infectious diseases with vitamin D insufficiency) (76).

Inhibition of Hedgehog (Hh) Signaling by Vitamin D

The Hh signaling begins with the attachment of the Hh peptide to the Patched (Ptch) receptor. The free form of Ptch inhibits Smoothened (Smo) protein. However, after Hh is attached, activation of Smo occurs, which induces the transport of GLI proteins to the cell nucleus followed by attachment to DNA and induction of transcription of target genes (77, 78). Deregulation of Hh signaling can lead both to stimulation and progression of cancer (79, 80). Four different types of human cancer, related to the Hh pathway, have been described: basal cell carcinoma, medulloblastoma, rhabdomyosarcoma and meningiomas (81). These can occur *via* mutations in the genes encoding components of the pathway (*e.g.*, *PTH1, CLI1, HIP* or *SFRP1*) or by excess production of the Hh ligand by the tumor or stromal cells (80, 81). The drugs blocking the Hh pathway are relatively new in oncological medicine (82, 83). The first human inhibitor of Hh signaling, GDC- 0449, is now in clinical trials for at least 8 human cancers, and several other Hh inhibitors are in varying stages of clinical development. As early as in 2006, the inhibition of Hh signaling by vitamin D *in vitro* was described (84). The effect of Hh signaling on the growth of basal cell carcinoma (BCC) is particularly well documented (82, 85). Tang *et al.* (82) claimed that Vitamin D inhibits both Hh proliferation and signaling, on the basis of mRNA expression of the Hh *GLI1* target gene. Moreover, it was emphasized that this effect was independent of the VDR receptor. Abert *et al.* (86) have shown that in Ptch mutant mice with basal cell carcinoma and in BCC cell lines, both Vitamin D and its active metabolite calcitriol ($1,25(OH)_2D_3$) exhibit an anticancer effect, mainly, by inhibiting Hh signaling.

Interaction of p53 and VDR Signaling

The p53 protein protects cells against changes in the genome due to DNA damage by inducing apoptosis, halting cell cycle progression or cellular aging (87). This protein undergoes inactivation in over 50% of cancer cases because of increased proteasomal degradation, or the presence of inactivating checkpoint mutations in its gene (88). This results, among other, in the formation of a transcriptionally inactive protein, hyperproduction of the mutant p53 protein or disturbance of p53 regulation by the chief negative regulators in the cell (by way of overexpression of binding factors – MDM2 and MDM4 (murine double minute 2 and 4) and the inhibition of transcription activity of the p53 protein (mainly MDM4) (89-92). Mutated p53 not only loses its tumor suppressor activity, but can also acquire oncogenic functions which are defined as gain-of-function (GOF) (93, 94). The introduction of the *TP53* gene allele with null mutation to the stem cells of mice by way of homologous recombination, resulted in a spontaneous development of cancer in 75% of mice with the p53 phenotype (–/–) before they were 6 months old (95). On the other hand, the introduction of the gene encoding the wild type p53 (wtp53) to the cell line of mouse myeloid leukemia, devoid of the active p53 protein, resulted in a drastic reduction of cell viability and of apoptosis markers including chromatin condensation, nucleus fragmentation and DNA fragmentation (96).

Thus, restoration of the tumor suppressor function of the p53 protein in cancer cells could lead to cancer remission (97). Attempts have been made to design non-protein low-

molecular mass inhibitors of MDM2-p53 interaction, and also of MDM4-p53, that will reactivate p53 and will have potential of being anticancer drugs (98), such as for example actinomycin D (99).

Vitamin D and its analogs are also considered to be potential antineoplastic agents. The active form of vitamin D, $1,25(OH)_2D_3$, is capable of initiating or terminating gene transcription after binding to VDR which belongs to the nuclear receptor superfamily and functions of a ligand-activated transcription factor. Maruyama *et al*. (100) have confirmed that expression of the VDR gene is directly regulated by p53 protein. Overexpression of VDR increased the response to vitamin D treatment and inhibited the growth of colon cancer. The VDR gene is a transcription target of wtp53 and also of p63 and p73 (100-103). It is particularly interesting, that VDR is increased in several types of cancer, including breast and ovarian cancer (104, 105). A mutated p53 can cause deregulation of the anticancer activity of the VDR pathway. Stambolsky *et al*. (106) have described the mechanism of mutp53 GOF (gain-of-function), based on the interaction between p53 and VDR. It was shown that VDR and mutp53 (and also wtp53) interact with each other and this interaction increases as a result of vitamin D_3 supplementation (106). The existence of an interaction between mutp53 and the regulation of transcription by calcitriol is probably due to the fact that mutp53 is bound to chromosome regions containing VDRE elements, probably *via* binding to VDR. Moreover, mutp53 increases nuclear accumulation of VDR which in some cases correlates with tumor stage (107, 108). In order to inhibit apoptosis, high endogenous levels of mutp53 in cancer cells probably cooperate with vitamin D, which is additionally enhanced by supplementation. The mutp53-dependent antiapoptotic activity of vitamin D has also been observed in breast cancer MDA-MB-231 and ovarian cancer OVCAR3 cell lines (106, 109). Moreover, increased VDR nuclear accumulation due to the activity of mutp53 can occur even without the supply of calcitriol, indicating that the mutant p53 protein changes the conformation of the receptor in a way that imitates the activity of vitamin D. It has been emphasized that the increased nuclear accumulation of VDR is probably not the only explanation of the effect of mutp53 (106). In the case of transactivation, VDR recruits mutp53 to VDRE in target genes, whereas mutp53 increases VDR-dependent transcription, thus stimulating the recruitment of additional transcription co-activators such as p300 (p300/cyclic AMP-response-element binding protein). The conversion of the VDR pathway from proapoptotic to antiapoptotic can occur due to a mutation in p53 GOF, at least in the cell lines which are protected by vitamin D. Undoubtedly, this discovery should be taken into account while deciding to apply therapies with vitamin D analogs for cancer. This means that apart from its well-documented proapoptotic activity, vitamin D can also have an antiapoptotic effect, and thus the VDR pathway can lead either to the patient's death or survival, depending on the presence of a *TP53* mutation (106).

Vitamin D – Interaction of Photocarcinogenesis

Over 90% of vitamin D in the human body is produced in the skin in response to sun exposure. Human epithelial cells (keratinocytes) possess a complete system for the synthesis and metabolism of vitamin D. They have receptors for vitamin D (VDR) which are responsible for inducing gene expression. Both 25-hydroxylation and 1-hydroxylation lead to the formation of a biologically active form of vitamin D known as calcitriol ($1,25(OH)_2D_3$) and 24-hydroxylation leads to catabolism of vitamin D. Moreover, fibroblasts of the dermis possess a mechanism that allows the formation of $25(OH)D_3$, yet they do not have 1-hydroxylase and hence are unable to produce calcitriol (110). The application of vitamin D in dermatology is mainly due to its immunomodulatory properties, as well as its effect on the regulation of cell proliferation and differentiation. Vitamin D is formed in the epidermis and, together with calcium, it participates in the process of regeneration of the epidermal barrier (which is important for the treatment of various skin disorders such as psoriasis, photodermatoses, xeroderma pigmentosum and cancers) (111). Unfortunately, the increased incidence of skin cancers is largely the effect of increased exposure to ultraviolet radiation; UVB (which penetrates through the epidermis) and UVA (which penetrates into the dermis). The effects of excessive UV exposure include erythema, sunburns and dysfunction of Langerhans cells which are a part of the immune system of the skin. On the molecular level, exposure of DNA molecules to UV radiation leads to their damage, which in the absence of efficient repair systems can result in mutations and subsequently the initiation of neoplastic processes (112, 113). The potential anticancer activity of calcitriol in the case of malignant melanoma have been examined in many experimental and epidemiological studies, but contrary results have also been obtained (114-120). Sunburns in childhood (before the age of 15) are the most significant risk factor, regardless of the latitude of the children's locations (120). The systemic or local administration of $1,25(OH)_2D_3$ immediately after excessive exposure to UV radiation was found to reduce sunburns in both humans and mice (121, 122). Besides, the presence of at least one actinic keratosis lesion also increases the risk of melanoma development (123). However, there is no unequivalent answer to the question concerning the relationship between the risk of melanoma and taking vitamin D either in the diet or in the form of supplements (124). Similarly, no relationship was found between the risk of developing melanoma and the concentration of vitamin D in serum (125). An attempt has been made to examine the effect of vitamin D used locally on

the skin after exposure to UV radiation. It was found that tumor development was inhibited due to a strengthening of the repair mechanisms (126, 127). Makarova *et al*. (128) found that vitamin D synthetized in the skin by UVR protects the organism against oncogenic activity by inhibiting Hh signaling, whereas vitamin D taken in the diet does not exhibit such a protective mechanism, probably due to the rapid hydroxylation reaction accompanying oral intake (129).

UV radiation induces a number of changes in the skin by generating reactive oxygen species (ROS) and nitric oxide (NO) which can provoke DNA oxidative damage and lipid peroxidation. Promutagenic pyrimidine dimers and 8-hydroxy-2'deoxyguanosine are the major forms of DNA damage produced directly by UV radiation (122, 130-132). Vitamin D analogs were found to decrease the levels of thymine dimers which are formed after UV exposure (133) and the frequency of occurrence of oxidative and nitration DNA damage by reducing the production of NO and other toxic reactive forms of nitrogen (127, 133, 134). A decrease in DNA damage after exposure to UV radiation in the presence of $1,25(OH)_2D_3$ has been observed in keratinocytes (127, 133), fibroblasts (135) and melanocytes (136). The protective activity of vitamin D against the sun's damaging effects to the skin also includes increase in the levels of p53 protein and metallothionein in the presence of calcitriol (127, 133, 134). A multifactorial effect of vitamin D to skin damage due to UV exposure is also related to the immune functions of the skin (among other things by its influence on maturation of the Langerhans cells presenting the antigen, NF-κB, T lymphocytes, IL-10, monocytes, macrophages) (122).

It seems that in the case of malignant melanoma the protective activity of sunrays through the synthesis of vitamin D is less important than its carcinogenic activity (regardless of the amount of time spent in the sun) (137, 138). The relationship between melanoma and sun radiation is very complicated and involves both the slow genome pathways (via the VDR receptor) and the rapid non-genome responses. Further investigations are required in this respect that would take into account not only the promising aspects of vitamin D anticancer effect, but its "dark" side as well.

Conclusion

On the basis of current data, it cannot be stated conclusively whether intake of vitamin D may offer protection against cancer. The presence of the VDR throughout the body and the effect of vitamin D on the cell cycle, apoptosis, angiogenesis, Hh signaling, interaction of p53 and photocarcinogenesis unquestionably suggest such a potential. However, further research is required, first to fully elucidate the mechanisms of action of this vitamin, and secondly to determine a specific dose and time of intake necessary to achieve an anticancer effect.

Conflicts of Interest

The Authors declare no conflict of interest.

Authors' Contributions

Conception and drafting of the manuscript: Dorota Skrajnowska; Critical revision of the manuscript for important intellectual content: Barbara Bobrowska – Korczak. All Authors gave approval of the final version for submission.

Acknowledgements

None declared.

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Received March 15, 2019
Revised May 21, 2019
Accepted May 23, 2019